Kathirvel Subramaniam
Tetsuro Sakai
Editors

Anesthesia and Perioperative Care for Organ Transplantation

Springer

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To my daughters, Nozomi and Inori, and my son, Hibiki. Especially to my wife, Sonomi, who has made our journey so special.

Tetsuro Sakai

I dedicate this work to my parents (Subramaniam & Palaniammal), my wife (Dalia), my children (Manav, Manas & Milan) and all my teachers.

Kathirvel Subramaniam

Foreword I

This book aims to summarize the progress in organ transplantation medicine, surgery, anesthesiology, and critical care medicine of the last 20 years and serves as the core reference to those who care for patients undergoing organ transplantation. The authors are the national and international leaders in each field of organ transplantation. The foundation of this book is the deep understanding of the specialty each author has accumulated through clinical and basic research, as well as through the extensive clinical experience. Now these authors are very happy to share the pearls with the readers.

This comprehensive textbook provides the necessary background to understand the complexity of organ transplantation. In the first part, ethics of organ transplantation, organ distribution network, immunology, and infection control are discussed. Also, various donor managements including donation after cardiac death, live donor, and multiorgan brain-dead donor are detailed. In the following parts of the book, perioperative management of the thoracic organ transplantation (heart and lung), the abdominal organ transplantation (kidney, pancreas, liver, small intestine, and multivisceral organs), and the composite tissue transplantation are discussed. Each section contains pre-transplantation recipient management and summary of transplant surgical techniques. These components, along with the anesthetic and post-transplant management components, will help those involved in anesthesiology and critical care medicine understand all facets of organ transplantation.

Because this unique book summarizes the current knowledge of perioperative organ transplantation (transplant medicine, surgery, anesthesiology, and critical care medicine), it will serve as a reference for those who routinely care for patients with end-stage organ dysfunction. Those new to these exciting fields will gain sufficient knowledge to successfully address many of the complex issues that may arise during organ transplantation anesthesiology and critical care medicine. To those who already may have extensive experience in the care of the patients undergoing organ transplantation surgery, this book will serve as an authentic reference and may open the opportunity to further understanding of this exciting field of transplantation anesthesiology and critical care medicine.

Thomas E. Starzl
Pittsburgh, PA, USA

Foreword II

I am honored to be invited to write the foreword for the textbook entitled, *Anesthesia and Perioperative Care for Organ Transplantation* .

I first met Ted Sakai when he arrived in Pittsburgh in 1999 as a surgical fellow in heart and lung transplantation. He impressed me as an earnest young surgeon eager to operate and learn the nuances of postoperative care. I remember him spending many hours in observation of our work before he was given the opportunity to become more hands on. At the same time, Ted brought his remarkable tissue engineering interest to us, and we were so enthusiastic about a rodent-functional, right ventricular outflow myopathy that it helped to secure NIH funding.

His transition to anesthesiology was natural for him. I am not at all surprised to find him and his coeditor, Kathirvel Subramaniam, at the hub of this encyclopedic text oriented toward anesthetic and critical care of the heart, lung, kidney, and pancreas plus liver transplantation. The work product calls upon the editors' broad personal experience, hard-earned in the operating rooms and ICUs at the University of Pittsburgh Medical Center. Specific chapters have been contributed by acknowledged specialty leaders. The impact of this comprehensive book on modern operative and perioperative care is in its unique coming together of information and a recipe for success in the multiorgan transplant setting. I know of no other text that rivals it and, rest assured, it will become a required reference source for our own surgical trainees and, of course, our broader and enabling anesthesiology plus critical care teams.

Bartley P. Griffith

Preface

Research on organ transplantation dates back to the eighteenth century. By the mid-twentieth century, the tireless efforts of eminent researchers and expert clinicians made solid organ transplantation a reality. Advances in immunosuppressive therapy and tissue typing processes facilitated the success of solid organ transplants. The first successful kidney transplantation was performed by Dr. Joseph E. Murray at Brigham and Women's Hospital in Boston, MA, in 1954. The first successful pancreas/kidney transplant was performed by Drs. Richard Lillehei and William Kelly at the University of Minnesota in Minneapolis in 1966. In 1967, Dr. Thomas Starzl performed the first successful liver transplantation at the University of Colorado Health Sciences Center in Denver. These successes in the field of abdominal organ transplantation were immediately followed by initiatives in thoracic organ transplantation. Dr. Norman Shumway performed the first successful human heart transplant at Stanford University Hospital in Stanford, CA, in 1968, and Dr. Bruce Reitz at the same university successfully performed the first heart-lung transplant in 1981. Dr. Joel Cooper of the Toronto Lung Transplant Group performed successful single lung and double lung transplantations for the first time at Toronto General Hospital in Toronto, Canada, in 1983 and in 1986, respectively. Transplantations of kidneys, livers, hearts, pancreases, intestines, lungs, and heart-lungs are now considered routine medical treatments for each end-stage organ dysfunction. Composite tissue transplantations, including hand and face transplants, have also become a reality.

We could never sufficiently thank the above-mentioned innovative leaders who brought these challenging transplantations to clinical practice. At the same time, however, we are fully aware that these clinical successes were only possible with advances in the fields of perioperative medical, anesthesia, and critical care, which parallel developments in surgical care. Complexity and unique challenges in the perioperative care of patients undergoing organ transplantation demand these perioperative physicians and all the other healthcare team members have a wider and more in-depth understanding of transplantation medicine for end-stage organ diseases, including pre-transplant preparation and optimization, intraoperative surgical and anesthesia management, and postoperative intensive care. How to care for organ transplantation patients undergoing non-transplant surgeries is also a challenging matter for all healthcare professionals who devote themselves to transplantation medicine.

This textbook, entitled *Anesthesia and Perioperative Care for Organ Transplantation* , represents our best attempt to bring together these components that need to be understood in order to properly meet the perioperative challenges of caring for patients with end-stage organ disease. We designed this textbook as a comprehensive reference featuring thoracic, abdominal, and composite tissue

transplantation. This textbook is unique in describing recent developments in organ transplantation medicine such as living donor transplants, donation after cardiac death, perioperative echocardiography, newer organ preservation methods, extracorporeal life support, multiorgan donor management, and simulation education for transplant anesthesiology.

This book is intended for all healthcare professionals who are involved in the care of transplant patients: anesthesiologists, surgeons, intensivists, internal medicine physicians, resident and fellow physicians, medical students, certified registered nurse anesthetists, perioperative care nurses, student nurses, and other healthcare professionals and trainees. We identified the top experts in their respective fields of transplantation medicine as chapter authors. We thank all of the contributing authors for their generosity in sharing their wisdom and for their commitment to completing the chapters in a timely manner despite their busy clinical work schedules.

This textbook would not have been possible without the tireless support from the editorial team at Springer publishers, Ms. Shelley Reinhardt and Ms. Georgette Forgione, for whom we are most grateful. We also thank Ms. Christine Heiner (Scientific writer, Department of Anesthesiology, University of Pittsburgh) for her help proofreading several chapters.

We sincerely hope that this textbook provides readers with the knowledge base to help improve their clinical practice and ultimately patient outcomes. As we always believe in the scope for further improvement, we sincerely look forward to receiving your comments and criticisms regarding this textbook.

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Part I
General Topics

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1. Ethical Considerations for Organ Transplantation

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Introduction

Despite extensive surgical training, many transplant team members including surgeons may feel ill prepared in the area of medical ethics. The breadth of transplant surgery, including the need to balance the needs of multiple patients, and the frequent interaction with issues surrounding death, expose the transplant team members to a variety of ethical concerns. The practicing transplant team members should be prepared to deal with the ethical issues that are integral to this broad spectrum of clinical encounters. Certainly no text or course of study could prepare one for each possible clinical scenario and its associated ethical concerns. This chapter will provide a framework for understanding and addressing the ethical issues that arise daily with patients and families. It is anticipated that this discussion will include some familiar as well as new perspectives on medical decision-making. As transplant team members considering ethical issues in organ donation it may help to adopt the understanding that donation may best be viewed as a voluntary act that has the potential to morally elevate mankind,

rather than seeing the human body as a repository of parts.

What Is *Ethics*?

In general, ethics is a term for understanding the moral life. In considering medical ethics, we most commonly think of normative ethics that attempts to define a set of general moral norms, which can be broadly accepted as a guide to conduct. This can be an increasingly difficult task, especially in our multicultural society with a vast array of cultural and religious backgrounds, but the identification of a shared moral ground is critical to discussing and resolving difficult ethical issues. This is a significant issue in transplant surgery, as different cultures often have different fundamental beliefs regarding the definition of death. Practical or applied ethics refers to the application of these moral norms or ethical theories to the resolution of ethical dilemmas. This common morality contains moral norms, the core dimension of morality that binds all persons in a community, although they may come from diverse backgrounds. In this manner, the common morality can be seen as normative, describing and establishing moral standards and obligations for the broad community, with further moral virtues and obligations specific for physicians as described in a professional morality. These special role-related moral norms for medical professionals are rooted in and developed from the common morality. True ethical dilemmas are difficult because the conflict is generally between moral principles pertinent to the problem at hand. A background in medical ethics provides the tools to balance these conflicting moral principles to reach an ethically acceptable solution.

Frameworks for Medical Ethics

A commonly utilized framework of moral principles reflecting the common morality is principle-based ethics as described by Beauchamp and Childress [1]. This account identifies four moral principles that can function as guidelines in considering options in patient care and professional behavior. These principles include respect for autonomy, nonmaleficence, beneficence, and justice. Nonmaleficence (avoiding harm) and beneficence (providing benefit and balancing benefit against harm) reflect values stated in the Hippocratic Oath. Historically, these values have been viewed as the physician's primary obligation, as suggested by the statement *primum non nocere*. Respect for autonomy is a more modern concept and is derived from Kantian moral philosophy. Key elements are liberty, defined as the capacity to live life according to one's own reasons and motives, and agency, defined as the rational capacity for intentional action. The principle of justice can be understood as fairness. Justice can be viewed as equals being treated equally. Distributive justice is reflected by fair, equitable, and appropriate distribution of goods and risks, an important consideration in the allocation of organs

for transplantation.

While the principle-based approach to medical ethics has been widely utilized for several decades, other frameworks have been recently developed. There has been significant recent interest in virtue ethics. Virtue ethics can be derived from Aristotle's account of the virtues in the Nicomachean Ethics [2]. Virtues are understood as dispositions not only to act in a particular way, but also to feel in a particular way. Rather than focusing on the rightness or wrongness of an action, virtue ethics focuses on the nature or character of the agent. In this manner, virtue ethics has contributed significantly to the current work on professionalism. Many professional codes stress the importance of these virtues, and the development of the moral character of the professional. Pellegrino has written extensively on the nature of medicine as a moral enterprise [3]. While not suggesting that virtue ethics can provide a foundation for all medical ethics, he is persuasive in suggesting that the physician's character and virtues are at the heart of moral choice and ethical actions. While this framework is helpful in teaching and evaluating professionalism, it clearly has limitations in addressing all the ethical concerns that may arise during the practice of transplant surgery.

A relatively new framework for analysis of ethical concerns has been developed in significant part from feminist writings and theory. This framework is most commonly referred to as an ethics of care . Gilligan developed the theory that due to social roles and expectations, men and women develop different conceptions of moral problem solving [4]. Women more often take a contextual approach to what they view as conflicting responsibilities, while men may take a more formal or abstract approach to what may be seen as competing rights. This focus on relationships, interconnectedness, and caring contributes to the notion of caring as primary in the ethics of care. Rather than focusing on the protection of autonomy, an ethic of care provides an opportunity to assess the problem in terms of responsibilities within relationships. Rather than seeing autonomy in decision-making as an ideal, an ethic of care places the patient within a web of relationships, providing a very different orientation to the discussion of ethical concerns.

The development of this framework of an ethics of care provides another alternative to principle-based ethics in resolving ethical dilemmas. Although both are valid, an ethics of care may prove helpful in facing ethical concerns that arise in transplant surgery where often the needs of two patients, donor and recipient, and their interpersonal relationship, must be addressed. It is very clear that all these patients reside within interdependent webs of relationships. Although an ethics of care is often portrayed as being in conflict with a principle-based ethical framework, these systems should be viewed as complementary to allow a more robust evaluation of moral problems in clinical care. A quote demonstrating this balance between these frameworks is provided by Dietrich Bonheoffer: "An essential perspective in assessing a moral question is the 'view from below' … which is the perspective of 'those who

suffer' and which those who seek to 'do justice to life in its entire dimension' can learn to appreciate" [5].

With this background in ethical theory, several of the ethical issues faced by transplant surgeons will be addressed. As it would clearly be impossible to address all the ethical challenges a transplant surgeon may face in the course of their career, I have chosen to highlight several current concerns or points of debate, including organ trafficking/transplant tourism, incentives for donors of organs for transplantation, the altruistic donor, donation after circulatory determination of death, and the allocation of organs for transplant.

Organ Trafficking and Transplant Tourism

Although "medical tourism ," travel abroad to another country is increasingly common in the Unites States due to rising health care costs, in this discussion I am solely focused on travel abroad to allow purchase of organs for transplant. The mismatch between available donor kidneys and the growing population of recipients in need of a transplant, along with the widening gap in income seen in many populations, continues to fuel this market. As would be anticipated, there is a wide gulf between sellers and buyers of trafficked kidneys, but both groups are vulnerable and are exposed to poorly communicated risks. The limited data available on sellers demonstrates that they are often illiterate, and almost universally poor, commonly saddled with significant debt, often still paying off the debt accumulated by a previous generation. Unfortunately, despite undergoing nephrectomy for transplant as a relatively desperate measure to address their poverty, most sellers state that over time there was no significant improvement in their lives, and they either remained in debt or had not met their financial goals. A majority also felt that their health deteriorated after the nephrectomy [6]. Data on the recipients of trafficked kidneys is more difficult to collect, but suggests a poorer outcome as compared with transplant recipients in the U.S., with transplant tourists having a higher incidence of acute rejection, lower graft survival, and more severe infections. While there is clearly adequate medical evidence to make a case against supporting transplant tourism, there are also well developed ethical arguments against this practice. Poor sellers are often coerced into this activity due to limited economic alternatives, and the buying and selling of the kidney in these circumstances can be seen as a very clear example of commodification, with the seller seen not as a fellow human with all the attributes of personhood, but as merely a collection of parts, more valuable than the whole [7]. In terms of basic ethical theory, this is a violation of a commonly acknowledged version of Kant's categorical imperative, which asks that others not be treated as means or goods, but rather as ends in themselves, valuing their intrinsic personhood. There are obviously other ethical issues to consider in this sort of transaction including but not limited to the nature of the consent obtained from both the

buyer and the seller.

The Declaration of Istanbul on Organ Trafficking and Transplant Tourism was published in 2008 and reflects the work of an international summit convened by the Transplantation Society and the International Society of Nephrology. This document describes organ trafficking and transplant tourism as violating the principles of equity, justice, and respect for human dignity and should be prohibited. In its' principles, the Declaration states "Because transplant commercialism targets impoverished and otherwise vulnerable donors, it leads inexorably to inequity and injustice and should be prohibited" [8]. This statement would appear to be a reasonable practical realization of the categorical imperative speaking against the commodification of people and their organs. The Declaration goes on to make several suggestions to eliminate the practice of organ trafficking, taking a very holistic view of the transplant "business." In addition to prohibiting this practice, and asking for oversight, transparency, and accountability in the practice of organ donation and transplantation, the Declaration urges development of comprehensive programs for preventing and treating organ failure and actions to increase deceased organ donation with a goal of maximizing this potential. While this document does not carry the power of enforcement, it can be hoped that the broad international input into its development can help the transplant surgeon, a critical player in this process, understand the deep ethical concerns raised by organ trafficking, and by speaking to professional responsibilities, minimize if not eliminate this practice. The American Society of Transplant Surgeons (ASTS) raised specific concerns in response to the Declaration. Their response notes that in the U.S. the National Organ Transplant Act (NOTA) specifically prohibits receiving "valuable consideration" for providing a human organ for transplant, and they ask if the requirement to provide health, life, and disability insurance related to the donation would be a violation of the Act. Additionally, the ASTS questions whether limited controlled trials of donor incentives in the well regulated U.S. environment would be in violation of the Declaration [9].

Incentives for Organ Donors

As noted in the section above, the development of limited, controlled trials of incentives for organ donors to improve organ donation rates have been of interest to a majority of the ASTS membership. This would require an amendment to NOTA, as was done to allow participation in paired donor kidney exchanges. While it is clear that unregulated, illegal markets are often dependent on unethical practices and are associated with adverse consequences for both donors and recipients, it has been suggested by some that the harms associated with organ trafficking are due to its underground, illicit features with lack of control, regulation, or oversight. Many professionals in the transplant field question if a regulated system of incentives could be developed that would bypass these concerns. In support of a system of incentives, many have noted that payment for

donation of other bodily material, such as human oocytes, sperm, and blood, is legal in the U.S. and that everyone other than the donor receives tangible benefits from organ transplantation [10]. There are certainly many disincentives associated with serving as a living organ donor, including but not limited to financial and personal costs associated with the work up, surgery and recovery, fear of difficulty in obtaining health, life, and disability insurance following organ donation, and the lost opportunity to provide an organ for transplant to a family member, especially a child, in the future.

Historically, there has been an idealized vision of organ donation, with a belief held by many, both in and outside the transplant community, that donation must be in the spirit of pure altruism, a "gift-of-life" [11]. This insistence on pure altruism fails to recognize that everyone, including living organ donors, generally act in response to a number of internal and external pressures. These pressures may well result in a sense of obligation to donate, although without associated coercion or force. In light of these various factors, altruistic behavior can perhaps be seen as a continuum, with few of us having no other internal or external pressures motivating our behavior. Despite this deeply rooted belief in organ donation provided solely on an altruistic basis, there is limited data available suggesting that regulated, limited incentives for either living or deceased donation would either decrease or increase donation rates [12].

There have been many suggestions of options that would reduce disincentives, and provide limited incentives for organ donation. The removal of disincentives would include reimbursement of any expenses and lost income for living donors, along with the provision of disability insurance, life insurance, and care of donation related illnesses/complications health insurance. Incentives for both deceased and living donation would need to be both carefully regulated and limited in scope to allow room for true donor, or family autonomy in decision making without the fear of excessive or coercive inducements while still being of meaningful value and potentially able to improve the donor's circumstances. Despite the provision of incentives, it is important that there is continued respect for the donor, and there should be no diminution in the information provided the donor, or the support for their health. Perhaps most importantly, in maintaining the culture of organ transplantation and society's support of this practice, there must be gratitude expressed for the act of donation, acknowledging that the incentive(s) are not in payment for the organ, and cannot by themselves provide adequate compensation for the donation. With care, a system can be fashioned where organ donation maintains its significant moral value. The system for removing disincentives and providing incentives would need to be provided by a professionally or government regulated third party, and payments should never flow from recipient to donor. Obviously there would need to be very tight control and oversight of such a system, with civil or criminal sanctions in place for violations. It would be extremely important to prospectively embed research protocols into the development of a system of incentives to allow for data collection on donor and recipient outcomes and to track

any increase (or decrease) in organ donation, with donors and recipients aware of and consenting to this research registry participation.

Altruistic Organ Donation

The internet and social media are increasingly being used to solicit living organ donation to facilitate organ transplantation. MatchingDonors.com even states on its website that many patients will get their transplant within 6 months of signing up [13]. Although this site stresses that they are seeking purely altruistic donors, and note that it is illegal to receive financial benefit from organ donation, as with much of the internet, it is unclear what regulatory authority or oversight is in place. Both the use of emotionally or biologically unrelated purely altruistic donors and the use of the internet to solicit these living donors are relatively new in the world of organ transplantation. The internet has widened everyone's ability to search out and form new relationships without some of the safety nets we might have become accustomed to in the past, such as a tie linking a new acquaintance to established friends or family. Although neither society, nor transplant centers can regulate how people establish relationships, the combination of the reach and the anonymity of the internet and social media raise the concern for a need for closer scrutiny when assessing altruistic donors identified via the internet. It is critical to have a multidisciplinary approach when assessing all potential living donors, but particularly so for those identified through internet solicitation. It is very important to invest the time and effort in working to discern truly altruistic from self-serving motivations such as positive publicity or monetary reward [14].

While assessing the motivation of the potential donor is often a primary concern, there are other ethical issues raised by the solicitation of donors through the internet. A concern that was widely expressed when internet solicitation first started was the potential for different opportunities to access living organ donation based on access to the internet or other forms of publicity, often a proxy for income or educational level [15]. The potential for socioeconomic or educational discrimination persists, and extends beyond society's current digital divide. Most commonly, cadaveric organs are offered to the next medically appropriate patient on the waiting list, without consideration of the various social factors that may influence a living donor solicited via an internet website. While directed donation of a cadaveric organ to family or friends is permissible, discrimination, and exclusion of candidates based on race, ethnicity, or socioeconomic status is not allowed. While there are altruistic donors, and transplant programs that accept the donation, with the understanding that the organ will go to the next medically appropriate person on the wait list, the potential for discrimination in the search for the attractive or worthy recipient is high. This risk is present with both internet and more broad based media solicitation. The ability to access and manipulate the media to solicit living unrelated donors highlights the issue of

a great divide between those relatively few who may have this opportunity based on income or social standing, and the majority of the population awaiting organ transplantation, raising serious justice concerns. Importantly, while the potential for abuse should always be considered with the presentation of the altruistic donor, there is also the potential for good, by providing the opportunity to start in motion a chain of multiple transplants by providing an organ to someone with a willing but incompatible donor. A reasonable argument can be raised that much as we have UNOS/OPTN to oversee an equitable system of cadaveric organ allocation, there should be consideration of a similar mechanism to provide oversight and equitable distribution of living, not emotionally related, altruistic organ donations. Some have voiced an opposing opinion, suggesting that partiality and personal relationships help shape who we are, and color our decisions, certainly often providing the motivation for donation, and clearly also have a place in directed altruistic organ donation just as they do in living emotionally related organ donation [16]. These are critical issues for transplant surgeons to consider, as they are actively participating as moral agents in facilitating the transplant, and they should find their actions morally justifiable.

Donation After Circulatory Determination of Death

The recovery of organs after circulatory determination of death (DCDD) had been the original source of cadaveric organs until the development of criteria for the determination of death by neurologic criteria, or brain death, by an ad hoc committee at the Harvard Medical School in 1968 [17]. With the publication of a 1981 report on a whole brain determination of death by the Presidential Commission, and the passage of the Uniform Determination of Death Act [18], determination of death by neurologic criteria became widely accepted, and patients meeting those criteria became the most utilized source for cadaveric organ recovery. Both the increasing disparity between the number of patients awaiting organ transplantation and the organs available for transplant, and increased understanding of the need to include the opportunity for organ recovery in discussions on end of life care have focused attention on DCDD. While an opportunity to provide organs for transplant may offer comfort to a family grieving the death of their loved one, it is extremely important to be clear with families regarding the differences in the process of organ recovery between patients who are dead by neurologic criteria and those anticipated to undergo DCDD following withdrawal of life sustaining medical therapy (LSMT).

There are several ethical concerns that arise in the consideration of DCDD. The process for recovery is significantly different from that with the more common cadaveric donor who has met brain death criteria. A critical difference is that the decision to withdraw LSMT must be made prior to and separate from the decision to proceed with DCDD. The family must be provided the opportunity to make this decision

without pressure or coercion, and the decision to proceed with withdrawal of LSMT should be made to further the patient's best interests, and not to serve a utilitarian goal of organ recovery. Additionally, families should understand that depending on the individual hospital's protocol, they may not be able to be with their loved one at the time of death, or that their time together will be extremely brief, to allow for the expeditious recovery of organs and the minimization of warm ischemic time. While it is anticipated that asystole will occur shortly after withdrawal of LSMT, allowing the determination of death and the recovery of organs, families should be made aware that it is possible that the patient may not die, and may return to the patient care unit, or that the progression to death may be so delayed that the patient will no longer be a candidate for organ recovery. Finally families must be made aware that there may be limitations on what organs can be recovered in the setting of DCDD, due to varying response to warm ischemia time. All these factors must be discussed when approaching the family for consent for DCDD as they may affect their willingness to proceed [19].

There are additional ethical issues concerning DCDD that significantly impact the health care provider. Support for DCDD is dependent on an understanding that the patient is dead at the time of the organ recovery so as not to violate the dead donor rule: organ recovery must not cause the donor's death and the donor must be dead prior to proceeding with the recovery of organs [20]. Given the relatively short period of time between the onset of asystole and the determination of death (generally 2–5 min) some health care providers are concerned that these patients are in the process of dying, but not yet dead at the time of organ recovery. While there has been general acceptance by the Institute of Medicine, critical care societies, and UNOS/OPTN regarding the determination of death under DCDD criteria, individual practitioners may have valid concerns about this practice [21]. Hospitals should have a process that allows for individual practitioners to decline to support DCDD, as a matter of conscientious objection, while still providing this service to families that request it [22]. A related concern is the need for the physicians involved to avoid a conflict of interest in the patient's care. Those caring for a patient undergoing removal of LSMT and proceeding with DCDD should not be involved in the organ recovery process or transplantation. The transplant surgeon/organ recovery team should have no contact with the patient until after the determination of death. Further ethical concerns surrounding DCDD include the place for extracorporeal membrane oxygenation in stabilization for DCDD, the use of uncontrolled DCDD, and the continued need for the dead donor rule, but these go beyond the scope of this chapter.

Allocation of Organs

Although the previous sections of this chapter focus on organ donation/acquisition, there is clearly a interrelatedness between the limits of organ donation and the decisions that

need to be made regarding organ allocation [23]. As the gap between the supply and demand of transplantable organs continues to grow, it has been recognized that there is a need to improve the allocation system to maximize the "life" of the transplanted organs while maintaining a just system that allows all patients an opportunity to receive a cadaveric organ [24]. The issues of designing the optimal allocation system relates to cadaveric kidney transplant, as liver and hearts for transplantation are allocated on the basis of medical urgency, and lungs by a system that is a mixture of medical urgency and expected survival [25]. The system for kidney allocation had been based primarily on time on the waiting list, with patients receiving one point for each year on the list, with a small number of organs allocated for simultaneous transplantation with a lifesaving organ and for those patients with zero antigen mismatches. In addition to these standard criteria donor kidneys (SCD), 15 % of donor kidneys were designated as from expanded criteria donors (ECD, older or less healthy donors) and these were allocated based on wait list time to those patients who had consented to receive such an organ, in anticipation that they would have a reduced waiting time to transplantation. After several years of consideration, including an opportunity for public comment, which included a great deal of discussion in the ethics literature, a new allocation algorithm will now be utilized. The National Organ Transplant Act requires that organ allocation decisions must take into account both efficiency (graft and patient survival) and equity (fair distribution of organs), and there is significant discussion in the literature as to whether these changes comply with the regulation.

The new kidney allocation system was developed to hopefully increase the life years of transplanted kidneys, decrease the retransplant rate, and minimize the discard rate for donor kidneys. The major changes included in this new system include: refinement of the current kidney donor quality metric beyond SCD or ECD, determination of an expected post transplant survival (EPTS) score for all adult patients on the waiting list, utilize the quality metric and the EPTS to allow for longevity matching between donor kidneys and recipients, dialysis time will be included in the waiting time, and a change in how pediatric priority will be assessed. It is anticipated that these changes will account for differences in potential survival of recipients and donated organs, something that was not possible in the current system, and hopefully minimize the rate of repeat transplantation by better matching the anticipated recipient and donor kidney life spans.

Although this new allocation algorithm anticipates meeting the utilitarian goal of increasing the efficiency of kidney allocation and transplantation, many have raised other ethical concerns regarding its implementation, specifically its impact on equity in the allocation of organs. Many have voiced concerns regarding age discrimination under the new allocation system, with the potential for decreased availability of organs for older recipients. Some have commented on the limitations, and probability of error, in using population derived prognostic tools for the purpose of prospective individualized

risk stratification regarding both donor kidneys and recipients. Errors in prognostication may result in reduced opportunity for transplantation for those thought to have poor long-term survival. It will be important to follow both graft and recipient outcomes prospectively to document the accuracy of the new allocation algorithm, being open to the need for further change should the outcomes differ significantly from what is predicted in the modeling [26, 27]. Another important consideration is the impact of changes in the allocation of deceased organs on the number of living donor kidneys available for transplantation. There is evidence that with changes in allocation resulting in more rapid transplantation of pediatric patients with deceased donor kidneys there was a temporally related decrease in living donor kidneys transplanted in pediatric patients. As with all significant changes in process, it is important to be alert to unintended outcomes [28].

There were equity concerns in the previous system that the new allocation system should address. An important change incorporated into the new system is the use of dialysis time rather than just waitlist time in the allocation of deceased organs. This change was made to address the inequity resulting from racial and socioeconomic disparities in being placed on the transplant waiting list and provides a more balanced view of the patient's burden from ESRD. A disparity that will still not be addressed in the new system is the issue of differences in availability of deceased donor organs based on geographic area, resulting in regional differences in the balance between patients listed for transplant and the availability of organs. These geographic disparities have persisted over time, and while there are many criteria that may reasonably play a part in determining the waiting time for organ transplant, there is no ethical support for place of residence being a significant factor [29].

Conclusion

Although I have chosen just a few areas to highlight in this chapter, the field of transplantation ethics is quite broad, and extends beyond the topics I have included here. Other areas of significant interest include the concept of ones interests surviving ones death, and the increasingly common practice of informing families of the deceased's wish to donate organs, rather than requesting permission [30], the limits of parental refusal of transplant for end stage disease, acceptable risks to the donor in liver transplant, and the concept of a communal approach to organ donation with presumed consent legislation. An important ongoing discussion in the ethics literature that is beyond the scope of this chapter, but which the transplant community should be aware of addressed the interrelated issues of the true nature of death by neurologic criteria and the need for the dead donor rule versus the primacy of autonomy and consent. Just as there are exciting developments in transplant surgery and immunology, pushing the field forward, transplantation ethics is also a vibrant, exciting specialty.

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2. Prevention of Perioperative Infections in Organ Transplant Recipients

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Introduction

SOT recipients are at high risk for infections due to the complexity of surgical procedures combined with the impact of immunosuppression. The sources of infections basically originate from the recipient prior to or during transplant, the donor organ, and environment exposures [1]. In general, the major types of infection are predicted by the timing of infections after transplant [1].

First Month After Transplant

Three factors are important in determining the risk of infections during this period. First, as after any surgical procedures, *surgical site infections* (SSIs) are the most important. This in turn is influenced by the organs being transplanted, the surgical techniques and technical difficulties. A good understanding of the surgical aspects of transplantation

and their complications is very important in caring for recipients after transplantation. Along these lines, specific organ transplant predispose patients to unique spectrums of infection: urinary tract among renal transplant recipients, intra-abdominal infection among liver, small bowel, or multivisceral transplant recipients, and pneumonia among lung transplant recipients. Second, *nosocomial infections* such as hospital-acquired or ventilator-associated pneumonia, catheter-related blood stream infections, antibiotic-associated diarrhea, and catheter-related urinary tract infections are also important and related to the duration of hospitalization. Lastly, *donor-derived infections* from bacteria, viruses (i.e. West Nile Virus, Lymphocytic Choriomeningitis Virus, Rabies, Human Immunodeficiency Virus, etc.) or parasites (*Trypasonoma cruzi*) and *recipient-derived infections* can also contribute to these early onset infections. At this stage, the net state of immunosuppression has not been prolonged enough to predispose to opportunistic infections. The only virus that might cause significant morbidity and mortality early after transplant is *Herpes simplex virus* (HSV) , which usually reactivates in the recipient; the routine use of acyclovir or anti-cytomegalovirus (CMV) prophylaxis has significantly reduced its incidence.

Between the Second and Sixth Months After Transplant

This is the peaked time for opportunistic infections due to: *CMV*, *Aspergillus*, *Pneumocystis*, *Toxoplasma*, *Nocardia,* and *Listeria*. Chronic or latent infections preexisted before transplant such as tuberculosis, endemic fungi due to *Histoplasma*, *Coccidioides*, *and Blastomycosis*, or viral infections due to HBV and HCV might reactivate during this period. Lastly, late manifestations of donor-derived infections (*Strongyloides*, *Toxoplasma gondii*, *Leishmania*, *T. cruzi*) might also occur.

From 6 Months After Transplantation and Beyond

Most transplant recipients return to full-life in the community. They experience typical infections that nontransplant patients get, including respiratory virus infection, community-acquired bacterial infection, or endemic fungal infections. The clinical manifestations might be more severe than experienced by non-transplant patients. Furthermore, the patients remain at risk for opportunistic infections due to *Nocardia, Listeria, pathogenic moulds, Cryptococcus neoformans, and endemic fungi*. Patients who receive anti-CMV prophylaxis might manifest late onset CMV infection during this stage. Reactivation of *Varicella Zoster Virus* might cause devastating disease during this stage.

At any of these stages, if the patients develop acute rejection requiring immunosuppression, the above timetable might be altered, and the clock of infectious complications is reset.

In this chapter, we will focus on organ transplant-related infections during the early

period after transplant, and discuss means to prevent them.

Surgical-Related Infections

The most common infections encountered within 30–90 days after transplant are surgically related, and their rates depend on the types of organ transplanted. For the past decade, advances in surgical techniques, knowledge and refinement of immunosuppression strategy, and the use of antibiotic prophylaxis have significantly reduced SSI rate, and the most SSIs are now superficial rather than deep. Despite this improvement, SSIs remain a problem within 90 days of transplant, and when occur, are associated with prolonged hospitalization stay and cost, as well as graft loss. SSIs are classified as superficial (limited to skin and subcutaneous tissue), deep (affecting fascial, or muscular layers) and organ or organ space that is manipulated during transplant procedure [http://www.cdc.gov/HAI/ssi/ssi.html. Accessed December 19, 2011]. Cellulitis also occurs, and diagnosed by erythema, tenderness, swelling, and warmth of skin surrounding the wound. The general risk factors for SSIs are those observed with nontransplant general surgery, which include recipient's age, nutritional status, underlying diseases, diabetes mellitus, obesity, and site/complexity of the procedure. The risk of SSI also directly correlates with the dose and virulence of the affected pathogen; certain organ transplant, such as intestinal or lungs, involve a higher burden of microbial colonization or contamination than others [2]. Lastly, each type of organ transplantation is associated with a set of technical and medical problems which predispose to a unique set of infectious complications. These organ-specific infections are discussed below.

Kidney Transplantation

SSIs

Kidney transplant is considered a clean-contaminated procedure since it involves bladder opening which might cause urine spillage into the operative field [3]. The SSI rate is now ~5 %, a rate consistent with the nontransplant urologic procedures [3]. Older donor age, and surgical transplant complications such as vein or artery thrombosis/stenosis, perigraft hematoma, urinomas, urinary leaks, and lymphoceles might predispose to SSIs. Fortunately, most SSIs are superficial and mainly related to contamination from the skin organisms or from urine spillage during bladder opening and anastomosis. Opening the wound and enabling it to heal by secondary intention are usually adequate as treatment of superficial SSIs, but antibacterial agents should be considered in the presence of cellulitis and/or systemic symptoms [3]. Deep infections are generally related to complications such as urinary leaks, and generally require

drainage and antimicrobial agents; surgical repair might also be required.

Most SSIs are caused by bacteria, with aerobic Gram positive cocci (*Staphylococcus aureus*, *S. epidermidis*, *Enterococcus* spp.) and Gram negative bacilli (enteric organisms, and less commonly *Pseudomonas aeruginosa*) predominate. Fungal infections, mostly due to *Candida* spp., affect ~1 in 1000 kidney transplant [4], and manifest as surgical site infection, infected urinoma, graft abscess, and arteritis [4]. Positive blood culture for Candida early after kidney transplant should prompt the diagnosis of *Candida* arteritis since this is associated with very poor outcome and often requires nephrectomy [4–6].

Urinary Tract Infection (UTI)

UTI is the most common infection after kidney transplant , affecting 23–75 % of recipients [7]. It mostly occurs within the first 3–6 months after transplant [8]. These early onset UTIs are associated with a higher rate of pyelonephritis, septicemia, and recurrence or relapse than later onset UTIs. Of note, 60 % of bacteremia after transplant is related to the urinary tract, and 50 % of the bacteremic UTIs are associated with technical complications such as ureteral leaks or stricture, or with perinephric infection. UTIs, especially pyelonephritis, are associated with long-term graft function and outcomes [9–11].

Risk factors for UTI can be divided into recipient- and donor-specific, transplant procedure-specific, and posttransplant factors.

Recipient-Specific Factors

Risk factors that predispose to posttransplant UTI are similar to those in the general population and include old age, female sex, diabetes mellitus, pretransplant need of immunosuppression, urinary abnormality including vesicoureteral reflux, and history of UTIs. Prolonged dialysis pretransplant and presence of polycystic kidney disease (especially when this was associated with pretransplant upper tract infection) are also at higher risk for UTIs after transplantation.

Donor Allograft-Specific Factors

Cadaveric allografts have been associated with higher rates of UTI and other complications than living donor allograft, as they are subjected to longer ischemic time, more severe ischemia-reperfusion injury and higher rate of delayed graft function. In addition, infected donor kidney, infected organ storage perfusate, and allograft trauma also predispose recipients to UTI.

Transplant Procedure-Related Factors

Retransplantation and transplant techniques also predispose to UTIs after transplant [12]. Renal transplants are generally performed in a heterotopic position, and the transplant ureter is anastomosed via an extravesical technique that may have a short anti-reflux tunnel [13]. Unfortunately, this does not eliminate vesicoureteric reflux and the subsequent risk of UTI. Intraoperative ureteral stents are being used at many centers to prevent urinary leakage and ureteral obstruction; this leads to an increase risk of UTI, especially when remains in place for more than 30 days. Lastly, an indwelling urinary catheter is routinely inserted during transplant surgery; the duration of indwelling catheter is directly related to the risk of UTI after transplant.

Posttransplant Factors

Graft dysfunction or rejection and excessive immunosuppression predispose to UTIs. Among the immunosuppressive agents, depleting antibodies like antithymocyte globulin and antimetabolites like azathioprine and mycophenolate mofetil have been associated with a higher risk of UTI.

UTI can present as asymptomatic bacteriuria, pyuria, acute cystitis, pyelonephritis, and septicemia [4, 10, 11, 13–15]. The diagnosis of UTI posttransplant might be difficult, since immunosuppression and the denervated allograft might mask clinical signs and symptoms of infection.

Pathogens causing UTIs in the kidney transplant recipients are similar to those from the general population, with *E. coli* as the most common. Other uropathogens include members of the *Enterobacteriaceae* group, *Pseudomonas aeruginosa*, *Enterococcus* spp., coagulase-negative *Staphylococcus,* and *Corynebacterium urealyticum*. Unusual bacteria with unknown virulence potential such as *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *Lactobacillus* spp. can cause invasive infection in kidney transplant recipients. Over the past decade, there has been increasing reports of antimicrobial resistance among the uropathogens recovered from kidney transplant recipients. Indeed, trimethoprim-sulfamethoxazole and fluoroquinolone-resistant uropathgens have been linked with prophylactic use of these agents [16]. More concerning, however, is the finding of multiple-drug-resistant organisms such as extended spectrum β lactamase-producing *Enterobacteriaceae* and vancomycin-resistant *Enterococcus* spp. in the urine of patients within 1 month of kidney transplantation [17].

Candida is the most common fungal pathogen causing UTI and affect ~11 % of kidney transplant recipients. Diabetes mellitus appears to be the risk factor. Most of the patients with candiduria are asymptomatic, and to date, there have not been any reliable diagnostic tests that can differentiate colonization from true infection. *Candida* and *Aspergillus* are rarely associated with devastating complications such as pyelonephritis, candidemia, obstructing fungal ball at the ureterovesical junction and arteritis [18, 19].

The management of UTI relies on the clinical manifestations and onset from

transplant (Table 2.1). All symptomatic UTIs should be treated, and the duration of treatment is dictated by the presence of upper tract disease, severity of infection or septicemia (Table 2.1). For asymptomatic bacteriuria during the first 1–3 months after transplant, although there have not been any controlled trials to influence treatment decision, most centers recommend antibiotic treatment, since this is the period when the allograft is particularly prone to injury, which adversely affects long-term allograft function [12], and UTI might not be clinically apparent due to denervation of the allograft and effect of immunosuppression. For late onset asymptomatic bacteriuria, treatment is recommended only for those with associated worsening renal function.

Table 2.1 Management of UTI in kidney transplant recipients

	Recommendations	**Note**
Asymptomatic bacteriuria	There is no consensus recommendation on therapy for this category.	
Early (within 1–3 months of transplant)	Consider treatment based on culture and sensitivity. Duration: 5–7 days.	Because most UTIs are asymptomatic, a routine screening strategy of urine analysis and culture is performed at many transplant centers during the first 1–3 months after transplant.
Late (after 3 months)	No data to support antimicrobial therapy, but many centers prefer to treat patients with associated worsening in renal function.	Antimicrobial therapy beyond 1 month of transplant does not sustain sterilization of urine, prevent subsequent UTIs or improve graft function.
Symptomatic UTI		
	– Empiric treatment with broad spectrum antibiotic (based on patient's previous UTI history and local antibiogram), which can be tailored based on culture and sensitivity. – Consider removing ureteric stent. Duration: 7–10 days for lower tract infection, and 14–21 days for upper tract infection and septicemia.	If patient does not respond, consider renal or perinephric abscess or emphysematous pyelonephritis.
Recurrent symptomatic UTI	Consider imaging (CT scan of kidney, cystoscopy, etc.). If no abnormality identified, consider treatment to 6 weeks	
Candiduria	Remove urinary catheter, stent. Treat with an antifungal agent (preferably an azole if susceptible) for symptomatic infection, persistent candiduria, neutropenia, or impending urologic procedure.	

Antibiotic Prophylaxis

Several studies have clearly shown that antimicrobial prophylaxis significantly reduces the posttransplant infection rates for both living donor and cadaveric renal transplant [20]. The regimen used for prophylaxis, however, has not been well defined. Single

drug regimen is as effective as multidrug regimens, and cefazolin is as effective as ceftriaxone in preventing SSIs. Based on data to date, the American Society of Health-System Pharmacists (ASHP) recommends cefazolin for renal transplant prophylaxis [20] (Table 2.2). For patients with β-lactam allergy, an agent effective against Gram positive cocci (clindamycin or vancomycin) given in combination with an agent effective against Gram negative rods (aztreonam or fluoroquinolone) are reasonable alternatives. The duration of prophylaxis is restricted to 24 h. Gentamicin might enhance the nephrotoxicity of other drugs used in transplant, and should be avoided.

Table 2.2 Antimicrobial prophylaxis recommendations for specific solid organ transplant organs

Organ transplant	**ASHP recommendation (agents, duration)**	**Common practices at various transplant centers[a]**	**Notes**
Kidney			
Antibacterial	Cefazolin[a] Duration: <24 h	Ampicillin-sulbactam 3 g IV Duration: <24 h	
Antifungal	Not recommended	Not recommended	
Pancreas or kidney-pancreas			
Antibacterial	Cefazolin[a] Duration: <24 h	Ampicillin-sulbactam 3 g IV or piperacillin-tazobactam 4.5 g IV Duration: 24–48 h	
Antifungal [98]	Fluconazole for patients at high risk for fungal infection[c]	Fluconazole 400 mg daily 2 weeks (1–4 weeks)[c]	Risk factor for candida infection: enteric drainage of the pancreas.[c] There have not been any controlled trials to support antifungal prophylaxis practice.
Liver			
Antibacterial	Piperacillin-tazobactam or cefotaxime plus ampicillin Duration: <24 h	Ampicillin-sulbactam 3 g IV	
Antifungal [98, 99]	Targeted prophylaxis: For patients at high risk for *Candida* infections: fluconazole Duration: up to 4 weeks	Fluconazole 400 mg daily or echinocandin or a lipid formulation of amphotericin B Duration: up to 4 weeks or during initial hospital stay	*Risk factors for candida infections*: prolonged or repeat operation, retransplantation, renal failure, choledochojejunostomy, Candida colonization, requirement for transfusion of >40 units of blood products. *Risk factors for mould infections*: retransplantation, renal failure requiring renal replacement therapy, reoperation involving thoracic or abdominal cavity. There have not been any controlled trials to support antifungal

	For patients at high risk for mould infections: Liposomal amphotericin B (3–5 mg/kg/day) or an echinocandin Duration: up to 4 weeks or during initial hospital stay		prophylaxis practice.
Heart			
Antibacterial	Cefazolin <24 h	Cefazolin 1 g IV (or 2 g for weight >80 kg)	Patients with indwelling VAD might benefit from coverage of the infected microorganisms.
Antifungal	Not addressed	Some centers offer targeted anti-mould prophylaxis: voriconazole or itraconazole 200 mg bid 50–150 days, or until risk factors resolve	Antifungal prophylaxis is recommended for the followings: isolation of *Aspergillus* species in respiratory tract cultures, reoperation, CMV disease, posttransplant hemodialysis, and existence of an episode of invasive aspergillosis in program 2 months before or after heart transplant. There have not been any controlled trials to support antifungal prophylaxis practice.
Lung			
Antibacterial	Cefazolin Duration: <24 h Regimen should be modified to cover for potential pathogens, pre- and posttransplant cultures from the recipients, as well as donor culture	Cefepime 2 g IV q12h or Aztreonam 2 g IV q8h + Vancomycin 1 g IV q12h Duration: 48–96 h (if sterility cultures are negative)b Regimen should be modified to cover for potential pathogens, pre- and posttransplant cultures from the recipients, as well as donor culture	If sterility cultures are positive for pathogenic bacteria, the duration of antimicrobial prophylaxis is extended to 7–10 days.
Antifungal	Targeted prophylaxis according to local fungal epidemiology, and risk factors for fungal infections	Voriconazole or itraconazole 200 mg BID or inhaled amphotericin B Duration: not known (up to 4 months)	Optimal antifungal prophylaxis is not known. AST Infectious Diseases Community of Practice recommends targeted prophylaxis for the following risk factors: (1) Pre, peri- or posttransplant colonization with *Aspergillus*; or (2) ≥1 of the followings: induction with thymoglobulin or alemtuzumab, single lung transplant, acquired hypogammaglobulinemia. To date, there have not been any studies validating the efficacy of this approach.

Small bowel			
	Not discussed	Aztreonam 2 g IV q8h + vancomycin 1 g IV q12h + metronidazole 500 mg IV q8h or piperacillin-tazobactam 4.5 g IV q8h or a carbapenem Duration: 48–96 h or until surveillance enteroscopy demonstrates integrity of the intestinal allograft	
		Fluconazole 400 mg daily Duration: until surveillance enteroscopy demonstrates integrity of the intestinal allograft [98]	In some centers, anti-mould prophylaxis are targeted for: multivisceral transplant, abdominal reoperation, anastomotic site disruption, graft rejection, augmentation of immunosuppression

[a]Commonly used at various transplant centers

[b]For patients with b-lactam allergy, a combination of either vancomycin 1 g IV or clindamycin 600 mg IV with either aztreonam 2 g IV or a fluoroquinolone is an effective alternative

[c]In the settings of high rates of non-*C. albicans* infection, either an echinocandin or a lipid formulation of amphotericin B is recommended

Pancreas or Kidney–Pancreas Transplant

Pancreas transplantation is considered a clean-contaminated surgery. Several factors predispose pancreas and kidney–pancreas transplant recipients to infections. First, individual's diabetes mellitus might be complicated by vascular insufficiency that leads to poor vascular flow and impaired wound healing after transplant. Second, renal failure pretransplant is a risk factor for infection. Third, during transplant, spillage from the contaminated donor duodenum, which is used in the anastomosis between the pancreatic graft and either the intestine (enteric drainage) or bladder (bladder drainage) can contaminate the abdominal cavity. Lastly, anastomotic leaks leading to intra-abdominal infection can occur after pancreas transplant. In general, the site of drainage

of pancreas transplant has important implications for infectious complications: enteric drainage poses a risk of abdominal and graft infections, whereas bladder drainage poses a high risk for urinary tract infections.

SSIs

SSIs occur in 7–35 % of pancreas transplant recipients, and are more common after kidney–pancreas transplantation than kidney transplant alone [21]. Similar to kidney transplantation, superficial wound infections after kidney–pancreas transplantation are often caused by Gram positive cocci. Deep wound infections are more severe, and usually associated with intra-abdominal infections, and involve polymicrobial organisms of bacteria and *Candida* in ~50 % of the cases [22]. Donor's duodenum contamination, diabetes mellitus, and recipient's obesity predispose to SSIs [21, 23–25].

Intra-abdominal Infections

Intra-abdominal infections are among the most serious complications after pancreas transplant, occurring in ~5–10 % of patients. It is associated with graft loss and can be life threatening. Sources of infection includes donor duodenum duodenal leaks associated with enteric drainage, and graft inflammation or pancreatitis. The risk factors include donor age, obesity, and recipient's need for peritoneal dialysis and duration of dialysis pretransplant. Similar to SSIs, intra-abdominal infections after pancreas transplant are polymicrobial with bacteria and yeasts. Common organisms are *Enterococcus* spp., *Escherichia coli*, *Klebsiella* spp., and *Pseudomonas* spp. [22, 26]. ESBL-producing and carbapenem-resistant Gram negative rods have recently been reported [27]. Polymicrobial and fungal infections are associated with a higher mortality rate than monomicrobial bacterial infections. Fungal infection can lead to iliac artery mycotic aneurysm that might rupture [28]. Intra-abdominal infection is associated with a poor graft survival at 1-year, a high rate of graft removal at 50 % [26], and a mortality rate of 6–20 % [26, 29, 30].

UTIs

UTIs develop in a very high percentage of patients after pancreas or kidney–pancreas transplant, and 10–20 % of these have recurrent infections. Risk factors for UTI in pancreas transplant recipients are related to neurogenic bladder as a complication of diabetes mellitus, alkalization of the urine from bicarbonate in the pancreatic secretions among patients with bladder drainage, indwelling Foley catheters, and contamination from the donor's duodenum [31, 32]. The most common isolated organisms are *Enterococcus*, *Candida* spp., and *Pseudomonas aeruginosa* [17, 22, 31, 32].

Bacteremias

Bacteremias affect ~26 % of pancreas transplant patients, and are common within the first 3 weeks after transplant, especially among patients with enteric drainage [33]. Overall, bacteremia is associated with a higher mortality and graft loss, as well as higher rate of rejection [33].

Antimicrobial Prophylaxis

Due to the high rates of SSIs after pancreas transplant and their association with poor outcome, antimicrobial prophylaxis has become routine for pancreas transplant despite the lack of placebo-controlled studies. A single dose of cefazolin to donors and recipients appears effective in one nonrandomized study [34]. Another small randomized trial showed no significant impact of vancomycin given in conjunction with another antibacterial agent on infections due to Gram positive bacteria [35]. Given these findings, the ASHP recommend a single dose of cefazolin, or in the event of β-lactam allergy, combination of clindamycin or vancomycin with either aztreonam or a fluoroquinolone (Table 2.3). For patients with VRE colonization, an effective anti-VRE agent should be used (linezolid or tigecycline). Due to the high rate of candida infection in SSI, ASHP also recommends fluconazole prophylaxis for pancreatic transplant patients, especially those undergoing enteric drainage [20]. In settings of high prevalence of infections due to non-*C. albicans* spp., amphotericin B or caspofungin is a reasonable alternative antifungal agent.

Table 2.3 Prophylaxis against opportunistic infection

	Agent	Alternative	Note
Pneumocystis jerovicii	Trimethoprim (TMP)/sulfamethoxazole (SMX) 1 single strength (80 mg TMP) daily or 1 double strength (160 mg TMP) three times a week Duration: 6 months to 1 year. The duration is usually extended to beyond 1 year for lung transplant recipients (lifelong prophylaxis), patients receiving higher degrees of immunosuppression, or those with chronic viral infections	Aerosolized pentamidine 300 mg once a month Dapsone 100 mg daily[a] Atovaquone 1500 mg daily	TMP-SMX may also provide protection against *Toxoplasma* and *Listeria* species.
Toxoplasma gondii	For heart transplant, donor serology+/recipient serology−: TMP-SMX 1 single strength (80 mg TMP) daily or 1 double strength (160 mg TMP) three	Prophylactic regimen for high-risk patients is not known – Clindamycin-	Patients at highest risk for toxoplasmosis are heart transplant recipients with pretransplant Toxoplasma serology negative who receive an organ from a donor with positive serology.

	times a week Duration: Lifelong For recipient serology +: TMP/SMX as for PJP prophylaxis	pyrimethamine has been used successfully – Other potential regimens include: sulfadiazine, dapsone, atovaquone, clindamycin in combination with pyrimethamine or primaquine	
Cytomegalovirus [100]	Universal prophylaxis or preemptive therapy *Universal prophylaxis*: valganciclovir 900 mg PO daily Or ganciclovir 5 mg/kg IV daily IV Duration: 1. CMV D+/R−: 3–6 months for all organs except for lungs (12 months) 2. CMV R+: 3 months for all organs except for lungs (6 months) *Preemptive therapy*: weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation. For positive CMV threshold: treat with valganciclovir 900 mg PO BID or IV ganciclovir 5-mg/kg IV q12h until negative test		Patients at highest risk for CMV disease are those recipients with pretransplant CMV serology negative who receive an organ from a donor with positive serology (D+/R−); those with latent CMV infection who require treatment with antilymphocyte antibodies as a part of induction therapy or for graft rejection.
Herpes simplex (HSV) infection [101]	Acyclovir 400–800 mg PO BID or valacyclovir 500 PO BID for ≥1 month (Ganciclovir or valganciclovir is effective for HSV prophylaxis)		

Both universal prophylaxis and preemptive therapy strategies are equally effective in preventing CMV disease [102], but only universal prophylaxis reduces CMV organ disease among patients at highest risk (CMV D+/R− and induction with anti-lymphocyte antibodies), reduces rate of allograft rejection, bacterial and fungal infections, and death [103]

[a]Screen for glucose 6-phosphatase dehydrogenase deficiency before prescribing this drug

Liver Transplant

Liver transplantation is a long and complex procedure, and at best, a clean-contaminated surgery. The most consistently identified risk factors for infections after liver transplantation are duration of surgery and retransplantation [36–38]. Other surgical risk predisposing to infections are previous hepatobiliary surgeries, intraoperative blood transfusions of >4 units, intra-peritoneal blood, and prolonged total ischemia time [36, 37, 39]. Roux-en-Y choledochojejunostomy is also a risk factor for transplant-related infections, as it predisposes to reflux of bowel flora into the biliary system. Lastly, complications from liver transplant, such as portal vein thrombosis, hepatic artery thrombosis, biliary leaks or stricture, affect 54–67 % of patients [38, 40–42], and predispose to infections.

SSIs

SSIs affect 4–48 % despite prophylaxis [43], and the majority of these are related to transplant technical problems. Peritonitis, bilomas, intra-hepatic abscesses, and cholangitis are most common infections, accounting for 27–48 % of all bacterial infections early after transplant [44]. Peritonitis and abscesses may complicate biliary anastomotic leaks, which are especially common after living donor transplant. Other risk factors include Roux-en-Y choledochojejunostomy, prolonged intraoperative time, human leukocyte antigen mismatches, low serum albumin levels, ascites, increased transfusion requirements, and severe obesity. *Bilomas* occurs in 12 % of patients after liver transplant in one study [45]. These are intrahepatic or perihepatic fluid collections that develop as complications of hepatic artery thrombosis or stenosis, and biliary necrosis, stricture, or leaks [40, 45, 46]. Broad-spectrum antibiotics and percutaneous drainage have varying degrees of success. If bilomas are associated with hepatic artery thrombosis, retransplantation is generally required.

SSIs are largely due to organisms colonizing the recipients' intestinal tract or skin pretransplant. MDR enteric Gram negative bacteria and *Enterococcus* (including vancomycin-resistant *E. feacium*), and *Candida* spp. are common infections in liver transplant recipients, especially in transplant centers using selective bowel decontamination [47]. *Candida* affects 53–68 % of liver recipients [48, 49], and manifests as intra-abdominal abscess, peritonitis, or candidemia. Risk factors for invasive candidiasis includes Roux-en-Y choledochojejunostomy, prolonged operative time (≥11 h) requiring >40 units of blood product, and *Candida* colonization or infection within 3 months of transplantation.

Antimicrobial Prophylaxis

As for pancreas transplant, due the high complexity of surgical procedure and high rates

of infection, antibiotic prophylaxis has been a standard approach for liver transplantation despite the lack of controlled studies. ASHP recommends piperacillin-tazobactam or cefotaxime plus ampicillin [20], but many centers, including ours, use ampicillin-sulbactam (Table 2.2). For patients colonized with VRE, tigecycline is a reasonable alternative; some other centers add linezolid to the standard antibiotic regimen. For patients at high risk for Candida infection (choledochojejunostomy, known Candida colonization, and transfusion of >40 units of blood products), fluconazole may be considered for prophylaxis after transplant. Since invasive aspergillosis has the highest mortality in liver transplant recipients compared to other SOT recipients [50], some but not all transplant centers also consider an anti-mould prophylaxis with an echinocandin or an amphotericin B product for patients at high risk for mould infection (retransplantation, renal failure requiring renal replacement therapy, fulminant hepatic failure as indication for transplant, and intra-abdominal or thoracic reexploration within the first month after transplantation) [51].

Intestine or Multivisceral Transplant

Intestine or multivisceral transplantation is a complicated and difficult surgery that takes at least 8–10 h. It is considered as a contaminated, and sometime even dirty surgery. As a consequence, the rates of infections associated with intestinal transplantation are higher than those reported with other organ transplant. Isolated intestinal transplant is associated with the lowest risk of infections, whereas multivisceral transplant is associated with the highest risk [52–56]. Indeed, over 90 % of multivisceral transplant patients have at least an infection after transplant, with the median of 5 infections per patient [54, 57–59]. This can be explained by pre-, peri-, and posttransplant risk factors. Pretransplant risk factors include patients' poor nutritional status (with associated secondary immunodeficiency), chronic total parenteral nutrition dependence (with associated risk for blood stream infection), underlying intra-abdominal anatomic abnormalities (with associated infections and translocation of bacteria), and presence of enterocutaneous fistula (with associated intra-abdominal infection and sepsis). Peritransplant factors include complexity of the surgical techniques in the setting of extensive intra-abdominal dissection, adhesions from previous abdominal surgery, potential intraoperative spillage, and the necessity of an intestinal anastomosis. In addition, complications and requirement for reoperation is high due to postoperative hemorrhage, vascular and biliary leaks, vascular and biliary obstructions, and intestinal perforation [53]. Intestinal allograft is an immunogenic organ which requires intensive immunosuppressive therapy [60]. Posttransplant risk factors include need for indwelling vascular catheters for temporary total parenteral nutrition, bacterial translocation arising from ischemia and reperfusion injury during the early transplant period, or from episodes of rejection. All these factors predispose to intra-abdominal abscess,

peritonitis, and bacteremia [53]. The epidemiology and types of infections after intestinal and multivisceral transplantation are not as well described as for other organ transplant. Overall, bacteremia is the most common, followed by SSIs and intra-abdominal infections.

Bacteremia

Bacteremia occurs in >60 % of intestinal transplant patients [61, 62], and is more common in patients receiving a concomitant liver transplantation [63]. The sources of bacteremia are from indwelling vascular catheters and translocation of organisms from the GI tract in ~65 %. Bacteremia also originates from an infection from a deep-seated site or from other nosocomial infection. Bacteremia was polymicrobial in ~50 % of the cases [59], and the most common organisms were *Enteroccocus* and *Staphylococcus* spp., followed by enteric Gram negative rods. *Candida* sp. accounted for ~3 % of bacteremia.

SSIs

SSIs, mostly intra-abdominal abscess and peritonitis, are the second most common infection after intestinal and multivisceral transplantation. *Staphylococcus* spp., *Enterococcus* spp., *Pseudomonas aeruginosa*, and members of the *Enterobacteriaceae* group are the most common causative agents. *Candida*, both *C. albicans* and non-*C. albicans* spp., are also important pathogens, affecting ~25 % of patients [64]. The risk factors of deep-seated candida infections include use of broad spectrum antibiotics, use of induction immunosuppression for transplant, anastomotic leaks or intra-abdominal collections, the need for multiple abdominal surgical procedures, and the presence of a multivisceral graft [55]. Abscesses are not always accessible to percutaneous drainage and may require laparotomy. In multivisceral transplant recipients, graft pancreatitis with bacterial or candida superinfection might also occur, in which case, the mortality rate is high.

Antimicrobial Prophylaxis

Since small bowel or multivisceral transplantation is a contaminated procedure, all patients should receive antimicrobial prophylaxis. There has not been any ASHP recommendation specifically for small bowel transplant (Table 2.3). The prophylaxis regimen should cover for the intestinal enteric flora; commonly used antimicrobial prophylaxis regimens include piperacillin-tazobactam, ampicillin-sulbactam, and aztreonam + vancomycin with or without metronidazole. Candida prophylaxis with either fluconazole, an echinocandin, or an amphotericin B product should also be in the prophylaxis regimen. The duration of prophylaxis is not known, and is center-specific.

Duration of 3–7 days is likely adequate, although many centers maintain antimicrobial prophylaxis until surveillance enteroscopy demonstrates integrity of the intestinal allograft (Table 2.3).

Heart Transplant

Heart transplant is considered a clean surgical procedure. However, the SSI rates after heart transplant are higher than those of other general cardiac surgeries, with the rates of superficial and deep SSIs after heart transplant ranging from 4 to 16 % and 2 to 35 %, respectively, compared with those of general cardiac surgeries of 8 % and 2 %, respectively [20, 65]. Even with antimicrobial prophylaxis, the rates of SSI remains at 5.8–8.8 %. Risk factors associated with SSI include: recipient age, BMI > 30 kg/m^2, female sex, previous cardiac procedure, receipt of ciprofloxacin as a single antibiotic prophylactic agent [66], and hemodynamic instability requiring inotropic support [20]. In addition, ventricular assist devices (VADs) , especially when associated with infection, have been identified as risk factor for post-heart transplant SSI in several reports. Importantly, patients with device infection have significantly worse outcome in term of survival at 1 and 10 years after transplant. Although superficial SSIs are relatively easy to treat, deep SSIs such as mediastinitis and sternal wound infection, which affect 3–10 % of heart transplant recipients, are difficult to diagnose and treat, and prognosis is poor [67, 68]. Unlike in non-immunosuppressed patients, heart transplant patients with mediastinitis may not present with signs and symptoms of infection. For example, in one study, fever, chest wall erythema, or purulent discharge were present in only 30 % of patients, and leukocytosis in only 40 % of patients. Chest wall pain, in disproportion to sternotomy, appears to be the most common symptoms. Chest CT is sensitive in depicting mediastinal fluid collection or air. Once diagnosis is made, aggressive surgical debridement and appropriate antibiotic [69], followed by placement of vacuum-assisted drainage have been effective in controlling infections.

As with other cardiac surgeries, Gram positive organisms such as *S. aureus* and *Enterococcus faecalis* are primary causes of SSI after heart transplant. Gram negative bacilli, especially *E. coli* and *Acinetobacter*, have also been reported. Lastly, fungi, such as *Candida* and *Aspergillus*, occur much more commonly in heart transplant than other cardiac procedures. The rates of invasive aspergillosis range from 1 to 14 % [70, 71], and depend on whether or not the center employ antifungal prophylaxis.

Toxoplasmosis is a preventable, uncommon but fatal infection. Toxoplasmosis can occur after any organ transplant [72], but is most important after heart transplant because the *Toxoplasma* cysts are commonly found in muscle tissues. The highest risk group is transplanting a donor with *Toxoplasma* seropositivity into a seronegative recipient; the risk in this setting in the absence of prophylaxis is as high as 75 % [73]. The most common manifestations after transplant are myocarditis, brain abscess,

pneumonia, empyema, or disseminated infection. Toxoplasmosis typically occurs between 25 and 195 days posttransplant. Primary infection transmitted by the donor organ is generally more severe than that due to reactivation of latent infection in the recipient [74].

Antimicrobial Prophylaxis

Although there has not been any randomized controlled trial to assess the need of antimicrobial prophylaxis, based on data of other types of cardiac procedures, antimicrobial prophylaxis is considered standard practice. ASHP recommends a single dose of cefazolin for all patients undergoing heart transplantation. For patients with a history of MRSA colonization or infection, vancomycin should be considered. For patients with a β-lactam allergy, vancomycin or clindamycin are reasonable alternatives. ASHP recommends <24 h of prophylaxis but many centers are given for 24–48 h. The duration of antimicrobial prophylaxis for patients who do not have their chest primarily closed is unclear; many centers continue prophylaxis until the chest is closed, but there is no evidence to support this practice.

Patients with an indwelling VAD or Extracorporeal Membrane Oxygenation (ECMO) and no history of device-related infections should receive the standard antimicrobial prophylaxis as patients with no devices. For those patients with previous history of device-related infections, antimicrobial prophylaxis should be effective against these organisms. The duration of antimicrobial prophylaxis might be longer than 24–48 h, based on the presence or absence of retained infections at the time of transplant.

Antifungal prophylaxis in heart transplant is a controversial issue. Although universal antifungal prophylaxis with either itraconazole or inhaled amphotericin B during the first 3 months of transplant is safe and effective, considering the low incidence of invasive aspergillosis after heart transplant recipients, targeted prophylaxis is widely preferred [75]. The major indications for targeted antifungal prophylaxis are: retransplantation, reoperation, end-stage renal disease requiring hemodialysis, Cytomegalovirus disease and existence of another patient with invasive aspergillosis in the heart transplant program within 3 months of the transplant procedure [76]. The typical recommended duration of antifungal prophylaxis is 3 weeks after the resolution of the risk factors.

Lung Transplant

Lung transplant is considered a clean-contaminated surgery . Infections are the most common complications after lung transplant, and account for ~25 % of death within the first year. Lung transplant is particularly at risk for respiratory tract infection because of

the blunted cough from allograft denervation, impaired mucociliary clearance due to ischemic reperfusion injury to the bronchial mucosa, and exposure of the allograft to the external environment. In addition, since there is no direct blood supply to the donor bronchus and bronchial anastomosis, and circulation to this area depends on collateral circulation from the pulmonary arteries, airway ischemia is a serious problem early after lung transplantation, leading to airway complications such as bronchial stenosis, dehiscence, malacia, and necrosis; these may in turn facilitate colonization with subsequent infection by bacterial or fungal pathogens.

Tracheobronchitis and Endobronchial Infection

Tracheobronchitis and endobronchial infection are unique forms of airway infections that typically develop within the first 3 months of lung transplantation. The diagnosis is suggested by bronchoscopic findings of airway purulence, pseudomembrane, endobronchial plaques with or without necrosis or dehiscence, and confirmed by culture and histopathology. The actual rate of airway infection is not known, because it is often incorporated under "lung infection." Both bacteria (like *S. aureus*, *P. aeruginosa*, and *Burkholderia* spp.) and fungi (*Candida* spp. and pathogenic moulds) have been implicated in airway infections.

Pneumonia

Pneumonia is by far the leading cause of pulmonary infection, and affects 10–20 % of patients within the first 30 days of lung transplantation despite antibiotic prophylaxis [77]. Organisms causing pneumonia arise either from the recipient's or donor's respiratory tract, or the hospital environment. Even after the source of infection in the native lungs is removed during lung transplantation, the patients might continue to be colonized with their endogenous flora, since the organisms can persist in the native upper airways and/or sinuses. Patients with cystic fibrosis are at particular risk for severe pneumonia, because they are chronically colonized and/or infected with multiple-drug-resistant bacteria such as *Pseudomonas aeruginosa*, *Burkholderia* spp., *Achromobacter*, and *Alcaligenes*, as well as methicillin-resistant *Staphylococcus aureus*. *Burkholderia cenocepacia* causes significant problems and leads to very poor outcome among cystic fibrosis patients posttransplant due its unique multidrug-resistant patterns; for this reason, colonization or infection due to this specific organism is considered a strong relative contraindication for lung transplant at many centers. It is important to note that although ~60 % of donor respiratory tracts are colonized with organisms, the presence of these organisms does not necessarily predict pneumonia in lung transplant recipients. Several studies have shown that, in the setting of appropriate antibiotic prophylaxis, 6–12 % of lung recipients develop pneumonia from organisms transmitted from the donor [77, 78].

Lung transplant recipients have a higher rate of invasive fungal infections than other organ transplant recipients. *Aspergillus* (*A. fumigatus* most common, followed by *A. flavus*, *A. terreus*) is the most common cause of fungal infection following lung transplantation [79]. Pretransplant colonization or a positive intraoperative culture with *Aspergillus* increases risk of invasive Aspergillus infection after transplant [80]. Other risk factors predisposing to invasive fungal infection include airway ischemia, receipt of a single lung transplant, fungal sinusitis, neutropenia, hypogammaglobulinemia, receipt of thymoglobulin or augmentation of immunosuppression for cellular rejection, intercurrent viral infections (CMC, respiratory viruses, etc.), renal failure requiring hemodialysis, and mechanical intervention of the airway (such as airway stenting or ballooning) [81].

In the early period after lung transplant, airway disease due to *Aspergillus* (tracheobronchial aspergillosis) is more common than parenchymal disease (pneumonia) [82, 83]. Tracheobronchial aspergillosis occurs in ~5 % of all lung transplant patients. Cystic fibrosis patients with pretransplant *Aspergillus* colonization are at risk for developing tracheobronchial aspergillosis and anastomotic complications despite antifungal prophylaxis [84–86]. Airway aspergillosis has a wide spectrum of clinical manifestations, ranging from simple tracheobronchitis, plaque-like necrotic endobronchial lesions, to ulcerative tracheobronchitis and to necrotizing pseudomembranous formation. Tracheobronchial aspergillosis can occur alone, or in conjunction with parenchymal disease. It is sometimes difficult to differentiate from ischemic reperfusion injury, and the diagnosis relies on histopathology and microbiology for differentiation. Treatment of tracheobronchial aspergillosis involves systemic antifungal therapy in conjunction with inhaled antifungal with or without debridement and stent placement [87–90]. In this early transplant period when the anastomotic site is devascularized, adjunctive inhaled antifungal agent might be valuable since parenteral therapy might not achieve therapeutic concentrations. Duration of therapy is not known, but the typical approach is to continue antifungal therapy until the lesions are cleared on bronchoscopy, or for at least 3 months. In general, *Aspergillus* tracheobronchitis has a better response rate to antifungal therapy (71–82 %) than pulmonary disease (26–41 %) [87].

Fungi other than *Aspergillus* spp. such as *Scedosporium*, *Fusarium*, and the agents of mucormycosis and phaeohyphomycosis have been increasingly recognized as important pathogens in lung transplantation, causing both airway and pulmonary disease [91]. Diseases due to these non-*Aspergillus* moulds are associated with mortality rate up to 80 %.

SSIs

SSIs affect 5–11 % of lung transplant recipients, rates which are higher than the 1–2 %

rate reported for cardiothoracic surgery. Superficial SSI is of minor clinical significance. Deep SSIs, on the other hand, have been linked with prolonged hospitalization stay, high cost, and poor long-term outcome [86, 92]. Pleural empyema is the most common, followed by surgical wound infections; mediastinitis, sternal osteomyelitis, and pericardis are rare. Of note, mediastinitis and sternal infections were not observed among patients undergoing minimally invasive lung transplantation [92].

Empyema occurs in 3–8 % of patients after lung transplantation [86, 93, 94]. Lung transplant recipients are at risk for empyema because the organisms within the infected native lungs (as in cases of cystic fibrosis or bronchiectasis) can spill into the chest cavity during lung explantation. Second, development of pleural effusion is almost universal after lung transplant due to increased alveolar capillary permeability and disruption of lymphatic channel, and the effusion might get infected. Lastly, indwelling chest tubes might also predispose to infection. Empyema usually occurs within the first 6 months following transplant [86]. Earlier series associated empyema with increased patient mortality [86]. In our more recent series, however, empyema is associated with less morbidity and mortality than other SSIs [92]. Management requires surgical drainage or placement of a chest tube drain in conjunction with effective antibiotic. In some cases, empyema may result in significant scarring which requires decortication [95].

The microbiology is diverse. Gram-positive (*S. aureus*) and Gram-negative (*P. aeruginosa*, *E. coli*, *Klebsiella* spp., and *Acinetobacter*) are the predominant pathogens, but other atypical pathogens including *Mycobacterium abscessus*, *Mycoplasma hominis,* and *Lactobacillus* sp. have also been reported. Importantly, in one study, 23 % of SSIs were due to pathogens colonizing recipients' native lungs at time of lung transplantation, suggesting surgical seeding as a source.

Antimicrobial Prophylaxis

Antimicrobial prophylaxis for lung transplantation is routinely administered despite the lack of randomized controlled trials. ASHP recommends a single dose of cefazolin, but this might not be sufficient, especially for patients with suppurative lung diseases or those with chronic lung infections. Lung transplant centers are using broader spectrum antimicrobial agents. The general prophylaxis regimen recommendation is based on: (1) local antibiogram of common Gram-positive and Gram-negative pathogens associated with nosocomial infection, (2) pathogens previously recovered from a given patient and their susceptibility, and (3) pathogens recently recovered from the donor's respiratory (and/or blood) culture. Many transplant centers use an anti-pseudomonal antibiotic (cefepime, ceftazidime, piperacillin-tazobactam, or aztreonam); vancomycin is added for patients known to be previously colonized or infected with MRSA. Routine respiratory tract cultures of the donor and recipient (called sterility cultures) are

performed at the time of transplant, the result of which will dictate the subsequent antimicrobial regimen. The duration of prophylaxis varies per centers. At our center, we stop antimicrobial agents after 3 days if the sterility cultures are negative. If the sterility cultures are positive, the antimicrobial agent(s) will be modified according to susceptibility data, and continue(s) for 7 days; for organisms such as *Pseudomonas aeruginosa* or MRSA, the antibiotics are continued for 14 days. The duration of antibiotics prophylaxis for patients with cystic fibrosis might be longer. Although the role of inhaled aminoglycosides has not been systematically studied, its use has become popular among lung transplant recipients with cystic fibrosis or purulent lung disease due to multidrug-resistant Gram-negative bacteria prior to transplant.

Although there are no randomized controlled trials to advocate the use of antifungal prophylaxis in lung transplantation, this practice is commonly used among lung transplant centers [96], as evidence exists that antifungal prophylaxis decreased the incidence of invasive aspergillosis [79]. Common prophylaxis regimens include a systemic antifungal agent (voriconazole or itraconazole) or inhaled amphotericin. Inhaled amphotericin B has the advantage of direct delivery to the at-risk anastomotic site. The oral suspension of posaconazole is not commonly used because of problems with absorption after transplant (protein pump inhibitor use, requirement for nasogastric tube feeding, poor appetite after transplant, etc.); the delayed-release tablet provides better bioavailability than the suspension and might become a preferred option if posaconazole is considered. The optimal duration of prophylaxis is not known. Although prophylaxis is efficacious in preventing invasive fungal infections, late onset fungal disease might occur after the antifungal is stopped. The safety of prolonged duration of antifungal prophylaxis is not known, and there have been links between prolonged voriconazole use and the development of squamous cell skin cancer [97]. Clearly randomized controlled trials are needed to define optimal regimens for efficacy and safety.

Standard Prophylaxis Against Opportunistic Pathogens

In addition to specific organ transplant perioperative prophylaxis, all solid organ transplant recipients need to receive prophylaxis against opportunistic infections. Please refer to Table 2.3 for specific recommendations.

In conclusion, infections occurring after solid organ transplantation reflect the intricate relationship between the net state of immunosuppression and environmental exposure. Familiarity with the epidemiology, risk factors, and time line of posttransplant infections, and surgical techniques and complications is necessary to design appropriate antimicrobial prophylaxis. Preventing infections is the most important method for improving both short-term and long-term morbidity and mortality of organ transplant recipients.

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3. Donation After Cardiac Death

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Introduction

With the increasing success of transplantation as life-saving therapy, the waitlist continues to grow disproportionately to the number of available donor organs. In the United States, 18 people die every day while waiting for a life-saving organ. The majority of those who are fortunate to receive a transplant receive organs from brain dead (BD) donors. To overcome this disparity, alternate organ donors are increasingly sought. These include live donor lung transplants, marginal or extended criteria donors, and donation after cardiac death.

Prior to the adoption of brain death criteria in 1968, most cases of organ donation were primarily from non-heart-beating donors [1]. However, after the definition of brain death was established by the Harvard group, there was a shift towards utilization of primarily brain dead or living donors. In the early 1990s, with the persistent shortage of organs and continuing wait-list deaths, there was a renewed interest in non-heart-

beating donors. This has become known as donation after cardiac death (DCD) and has contributed to a steady increase in organs available for transplantation. Kidneys, livers, pancreata, and lungs have been transplanted from donors after cardiac death with reasonable outcomes [2, 3]. However, donation after cardiac death is not without risk; and higher numbers of complications compared to brain dead donors are reported and vary by the type of organ. This review will address transplantation of organs from DCD donors.

The critical issue in DCD donation has been that of warm ischemia. The consequences of circulatory dysfunction, arrest and rapid perfusion and cooling at the time of recovery affect the outcomes of organs and overall graft function. However, there is mounting evidence that brain death might have its own deleterious effect on the quality of organs as a consequence of inflammatory cascades. It is speculated that organs recovered from a DCD donor might not be subjected to the same processes [4].

Definitions

DCD donors are patients who have suffered catastrophic and irreversible neurologic damage, but do not meet criteria for brain death. Since 1995, donors after circulatory death have been classified into different categories known as the Maastricht categories (Table 3.1) [5]. By in large, DCD donors across the United States come from Maastricht category III donors. These donors are stable and expected to expire after planned withdrawal of life support. This most often occurs in the operating room, but on occasion, withdrawal occurs in the intensive care unit. In Europe; however, utilization of DCD donors from all Maastricht categories are more often being considered for transplantation.

Table 3.1 Maastricht categories of DCD donors

I	Uncontrolled	Brought to hospital dead
II	Uncontrolled	Unsuccessful resuscitation leading to death
III	Controlled	Awaiting cardiac arrest
IV	Controlled	Cardiac arrest after brain death
V	Uncontrolled	Unplanned cardiac arrest in a hospitalized patient

The DCD Process and Donor Management

Hospital Relations

Presently, all hospitals that have potential for DCD are required to have policies and protocols in place by JCAHO. Furthermore, UNOS has a set of guidelines that must be followed in DCD donor cases. Due to these processes that must be communicated and

strictly followed, DCD donor cases are more labor-intensive and require more organ procurement organization (OPO) resources than brain dead donors. Specifically, this involves a clear delineation in roles and responsibilities in a patient who has not yet been declared dead. This typically involves multiple OPO coordinators on DCD cases to be sure all protocols are being followed, that families' needs are being met, and that all personnel in the OPO and donor hospital understand their roles and responsibilities.

Donor Assessment

All patients where a decision has been made to withdraw life support are referred to the OPO. These are typically patients who have suffered catastrophic brain injury though have not met brain death criteria. Such patients have been determined to have no meaningful recovery by their medical team. It is important to emphasize that the patient who is a potential candidate for a DCD is not legally dead and thereby considered a donor until he/she has been declared dead following withdrawal of support. It is essential that the transplant and organ recovery team have no involvement in these medical decisions and the declaration of death.

Crucial to a successful DCD recovery is the ability to predict if clinical death will occur within an acceptable time frame. These predictions are often difficult to make and families are always informed that there is a possibility that the donation may not occur. The University of Wisconsin has developed a DCD assessment tool (Table 3.2) in an attempt to predict if the patient will expire within 2 h, thus making him/her a DCD donor [6]. A score is calculated based on the following: patient's age, BMI, oxygen saturation, method of intubation, level of spontaneous respiration, and vasopressor requirements. The higher the tool score, greater the likelihood that the patient will expire. If a patient unstable or on maximum ventilation support, the tool is not performed. Utilization of this tool in deciding whether to proceed with a DCD donor has led to an organ recovery rate of approximately 80 %.

Table 3.2 The UW DCD tool

Criterion	Assigned points	Patient score
Spontaneous respirations after 10 min		
Rate >12	1	
Rate <12	3	
TV >200 mL	1	
TV <200 mL	3	
NIF >20	1	
NIF <20	3	
No spontaneous respirations	9	
Body mass index		

<25	1	
25–29	2	
>30	3	
Vasopressors		
No vasopressors	1	
Single vasopressor	2	
Multiple vasopressors	3	
Patient age (years)		
0–30	1	
31–50	2	
51+	3	
Intubation		
Endotracheal tube	3	
Tracheostomy	1	
Oxygenation after 10 min		
O_2 saturation >90 %	1	
O_2 saturation 80–89 %	2	
O_2 saturation <79 %	3	
Final score		
Date of extubation/time of extubation		
Date of expiration/time of expiration		
Total time		

NIF negative inspiratory force, *TV* tidal volume
Scoring: 8–12: High risk for continuing to breathe after extubation; 13–18: Moderate risk for continuing to breathe after extubation; 19–24: Low risk for continuing to breathe after extubation

Consents

Once the patient is deemed to be a donor, detailed consents are obtained. Although the details may vary between institutions and OPOs, the consent process may include placement of femoral artery and vein catheters in the operating room prior to withdrawal of life support. Consent may also obtained for administration of medications such as heparin, vasodilators such as phentolamine, amphotericin B, *N*-Acetyl cysteine (mucomyst), vitamin E, steroids, etc. [7].

Families are assured that organ donation will not occur until the patient has expired and has been declared dead by a physician caring for the patient. This physician must be independent of the organ recovery and transplant team. It is important to explain to

families the possibility of the patient not expiring within a set amount of time, usually 2 h, which would preclude the patient from being an organ donor. If this were to happen, the patient would be taken back to the ICU where he or she would expire without organ donation.

Surgical Technique

Pre-mortem Administration of Pharmacologic Agents

Specific consents are obtained from the patient's family for administration of medications prior to withdrawal of support. These medications may minimize the ischemia/reperfusion injury and may improve organ function after implantation through protective effects on the vascular endothelium, thereby having a beneficial effect on the transplanted organ [8].

Heparin is often administered prior to withdrawal along with vasodilators and reactive oxygen scavengers. Heparin is used to prevent the risk of thrombi in the recovered organ, which would negatively affect function after implantation. There is a theoretical risk that heparin might hasten death, but there is no evidence that heparin causes enough bleeding to result in the demise of the patient. Vasodilator agents, such as phentolamine (10–20 mg) may also be administered in order to prevent vasospasm and facilitate an adequate organ flush. This may result in a transient drop in blood pressure in the donor; however, this is usually short-lived and blood pressure returns to baseline prior to withdrawal. Mannitol (12.5–25 mg) is also often given to protect against reactive oxygen species and for osmotic diuresis.

Operative Procedure

It is paramount that DCD recovery is a rapid procurement of organs, done safely to ensure organs are not injured while minimizing ischemic time. Clear communication between the surgical recovery team and the donor hospital operating room team is crucial. Different methods of rapid procurement have been described previously in the literature [7, 9].

Once the patient has been brought to the OR, he or she is prepped and draped from chin to proximal thigh. If consent was obtained for medication administration and femoral artery/vein cut down and cannulation, this is done prior to withdrawal of support. Local anesthesia is administered and the femoral artery and vein are exposed to prepare it for cannulation. Typically, an 18 or 20 Fr catheter is sufficient for femoral artery cannulation. These catheters are kept ready for cannulation, which is not actually done until after death has been declared. Similarly, the chilled preservation solution is kept ready with the tubing primed for rapid infusion.

Once the pre-mortem interventions as described above are performed, members of

the surgical recovery team leave the operating room. All maneuvers pertaining to withdrawal of life support are entirely the discretion of the physician responsible for care of the patient. The surgical recovery team may not be involved in these decisions. The physician responsible for the care of the patient withdraws support and monitors the patient, noting the time of cessation of cardio-respiratory function. Once the patient is declared dead by the physician, there is an additional waiting period prior to beginning the procurement and infusing the flush solution. The purpose of this waiting period is to assure that there is no auto-resuscitation after cardio-respiratory arrest has occurred. This issue, however, has been under debate. In a review by DeVita et al. of published case reports on 108 patients from 1912 to 1970 who expired while their vital signs were monitored, there was no evidence of auto-resuscitation 65 s after cardiopulmonary arrest was noted [10]. The Society of Critical Care Medicine has thus endorsed a 2 min waiting period [11]. The Institute of Medicine has recommended a 5 min waiting period [12]. A member of the OPO is usually present in the operating room during the withdrawal process in order to record hemodynamic measurements during the withdrawal process along with times of declaration of death, the prescribed waiting period, when the recovery was begun and the times when the organs were flushed. These data are crucial for the transplant team to decide if the organs are transplantable.

After death has been declared and the prescribed waiting period has elapsed, the surgical recovery team returns to the operating room. If the femoral vessels were previously exposed, the femoral artery is cannulated with the pre-selected cannula, which is inserted approximately at the aorto-iliac junction, and a rapid flush with cold UW solution is begun. Concurrently, a median sternotomy is performed and the abdomen is opened sharply from the xiphoid to the pubic symphysis. If pre-mortem exposure of the femoral vessels was not obtained, direct cannulation of the distal aorta is performed immediately after entry of abdomen and cold flush is begun. The pericardium is opened and the right atrium is incised. This serves a vent to blood and the flush solution. Alternative means to vent include incision of the femoral vein while the chest and abdomen are being opened. The thoracic aorta is then identified and a large clamp placed across it. This ensures that the abdominal organs get the majority of the cold flush. Two to three liters of UW solution is infused. The abdomen is then filled with ice; ensuring most of the liver is covered with it.

Once the flush is complete and the effluent is clear, recovery of abdominal organs is begun. Different techniques have been described. To expedite recovery, an en bloc abdominal organ recovery technique will be described (Fig. 3.1) [7]. The esophagus is divided using a GIA stapler load in the chest. A large clamp is placed in the thoracic aorta, which serves as a useful retraction tool. Dissection starts at the level of the right atrium and all retroperitoneal attachments are divided along with the diaphragm. Care is taken to remain anterior to the vertebral bodies and posterior to the aorta and the vena cava. All posterior muscular attachments are divided with a curved Mayo staying

posterior to the aorta, vena cava, and abdominal organs. This dissection plane is carried down inferior to the level of the aortic bifurcation.

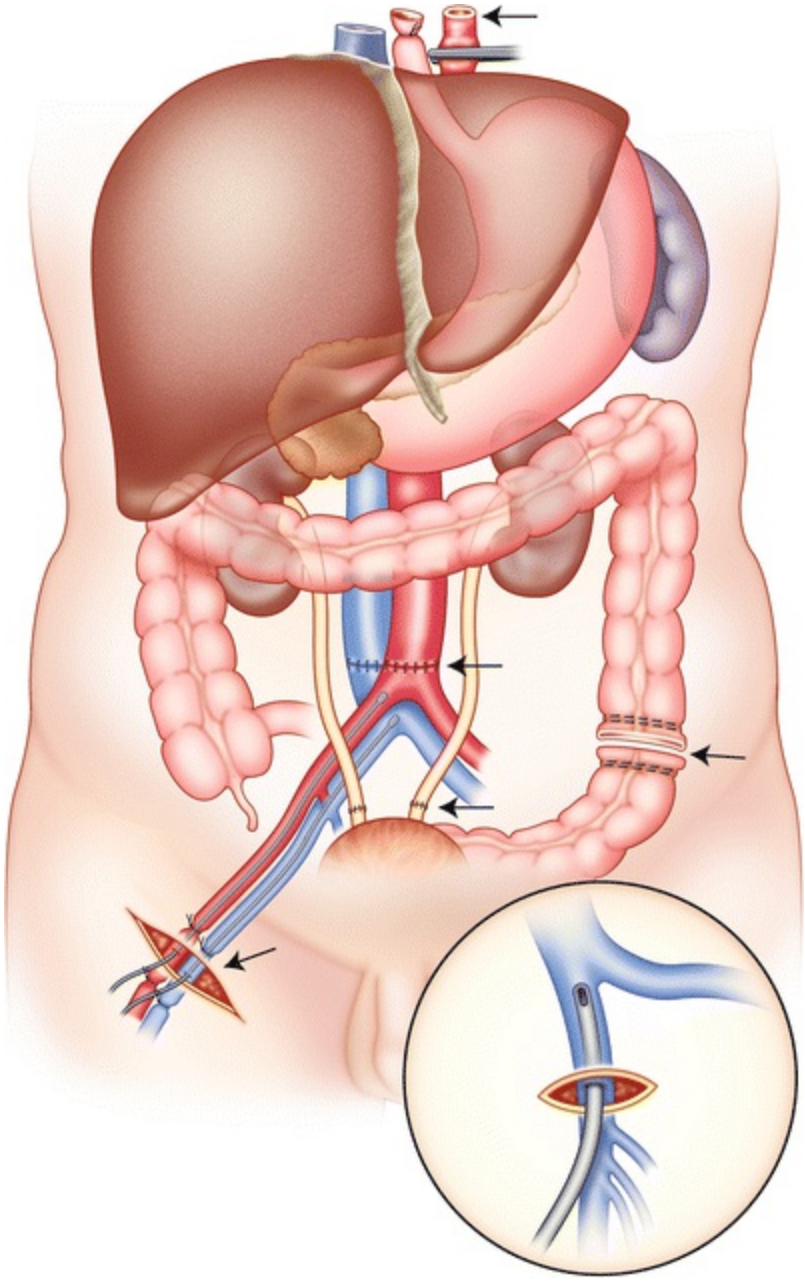

Fig. 3.1 Technique of rapid en bloc removal of all intra-abdominal organs . The *arrows* indicate the major steps, and the *inset* shows ex vivo superior mesenteric/portal vein flush-out

The organs are then returned to their anatomic position. The lateral attachments of the left and right colon are taken down. The ureters are identified and divided near the bladder. Hemostats are placed on the ureters for ease of identification and retraction. The ureters are then mobilized to a level just above the aortic bifurcation and retracted cephalad. The distal aorta and cava are divided right above the bifurcation. The sigmoid colon is then identified and divided using an appropriate GIA stapler load. Any

remaining retroperitoneal attachments are divided. The abdominal viscera are then removed en bloc and placed in a large basin with ice. The usual operative time for this portion of the procedure is less than 15–20 min.

Upon en bloc removal , either the inferior mesenteric vein or a branch of the superior mesenteric vein is identified and cannulated and 1 L of cold flush solution is flushed through the portal system. The common bile is also identified and divided at the level of the duodenum. The biliary system is flushed with 50 mL of solution. The gall bladder is also opened, its contents emptied, and then flushed with cold saline. The posterior wall of the aorta is opened longitudinally, revealing the celiac, SMA, and renal artery orifices. These are all flushed with 500 mL of UW solution each. The entire en bloc of organs is then stored in UW solution at 4 °C and transported to the transplant center where additional back table dissection and separation of organs is performed. This usually takes about 60–90 min. Prior to concluding the donor operation, the bilateral iliac arteries and veins are procured for possible vascular reconstructions.

Another technique is described as the “super rapid recovery technique ” [9, 13]. In this technique, the abdomen is opened from the xiphoid to the pubic symphysis. The distal aorta is identified and is cannulated. Perfusion of the organs with cold preservation solution is initiated. Simultaneously, the chest is opened via a median sternotomy, the thoracic aorta is cross-clamped and the vena cava is opened to vent. The inferior mesenteric vein is then cannulated to perfuse the portal system. Once the organs have been flushed and cooled adequately, a rapid hepatectomy is performed. This is followed by en bloc nephrectomies. Caution must be taken when using this technique if recovery of the pancreas is intended, weighing the risk of injuring a possible replaced or accessory right hepatic artery. In such cases, the liver is procured along with the head of the pancreas. An alternative is to recover the liver and pancreas en bloc.

DCD Abdominal Organ Utilization

DCD Liver Transplantation

Criteria for Acceptance

Selection criteria fo r DCD liver donors vary between centers. In general, they are more stringent than selection criteria for BD livers. Most require a heparinized flush at cross clamp or, preferably systemic heparinization with high doses of IV heparin prior to withdrawal of life support. However, this practice depends on variations of the law in each donor service area or country. A 30–60 min warm ischemic time is generally considered the upper limit; with the most common definition of warm ischemic time being from withdrawal of all life support to cold flush or cross clamp. However, there has been a movement to use hemodynamic parameters to define an agonal phase, which is used to define warm ischemic time (Functional warm ischemic time.) [14]. Generally,

this is defined as the point at which systolic blood pressure drops below 70 mmHg or the oxygen saturation drops below 70 %. A conservative maximum donor age for DCD donation ranges between 40 and 50 years old; however, there are reports of a few programs successfully transplanting livers from DCD donors up to 65 years old [14–16]. There should be a history of hemodynamic stability and normal or near normal, liver function tests [17]. Ideally, DCD liver donors are lean, with a body-mass index (BMI) less than 28–30, or a body weight of less than 100 kg. Some programs prefer a history of a short hospital stay prior to donation [17–19]. Gross inspection plus biopsy for hepatocyte viability and macrosteatosis or fibrosis is routinely required in some [2, 14] but not all institutions [16, 17]. Aggressive use of extended criteria DCD livers has been reported [20]. These were defined as having one or more of the following criteria: warm ischemic time over 30 min (but under 60 min from systolic blood pressure less than 50 mmHg to flush, or from oxygen saturation less than 80 % to flush), donor age over 60 years, donor BMI over 30, or cold ischemic time over 8 h. Acceptable outcomes can be achieved with graft survivals at 1 year similar to nonextended criteria DCD donors, when carefully selected.

Risk factors for post-transplant graft loss, primary nonfunction, biliary complications, and recipient death include donor age over 40–50 years, donor weight exceeding 100 kg, donor warm ischemic time greater than 35 min, or prolonged donor hypotension [16, 18, 21]. Prolonged cold ischemic time also adversely affects outcomes [21], with each hour of cold ischemic time increasing the chance of allograft loss by 6 % [16, 18]. Furthermore, recipient mortality is increased by increased donor weight and cold ischemic time [18]. As such, cold ischemic time of less than 8 h is required by many centers [16, 17]. Broader organ sharing is associated with increased cold ischemic time and has been shown to correlate with worse outcomes after DCD transplantation. Recipient age over 60 years, renal dysfunction at transplant, and donor hepatitis C positivity also worsen outcomes after DCD transplantation [21].

Recipient selection for DCD donor livers is also critical to optimize outcomes. The literature to support use of DCD liver transplantation in pediatrics is sparse. However, Gozzini et al. report successful transplantation of two full size and two reduced size (segment II–III) DCD liver grafts in children [19]. Recipients older than 55 years have 26 % higher graft failure than younger adult recipients. Male recipients and African American recipients also fare worse with DCD livers than their female and non-African American counterparts. Also, recipients with metabolic liver disease have a higher graft failure risk. There is a 45 % higher rate of graft failure in retransplant recipients compared to primary DCD liver transplant recipients. Patients with MELD scores greater than 35 have a 47 % higher rate of graft failure than recipients with MELD scores of 15–25. Therefore, liver transplant candidates older than 55 years, retransplants, or high MELD score patients need to carefully consider the risk of waiting for a DBD liver versus accepting the increased risk of graft loss after DCD

transplantation [18].

Risks and Benefits of DCD Liver Transplantation

The primary benefit of using DCD livers for transplantation is that it ameliorates the growing waitlist and allows patients faster access to transplantation. Thus, by adding livers from the DCD donor pool, waitlist deaths are reduced and many patients can be transplanted in a less morbid condition. However, this is not without risk and compared to BD liver transplantation, DCD liver transplantation carries with it significantly increased risk for primary nonfunction, biliary complications, hepatic artery thrombosis, and shortened graft survival. Large database studies have reviewed outcomes after DCD liver transplantation in the United States. Specifically, SRTR data from 1996 to 2007 show worse patient survival in the DCD group, which did not improve with increasing experience in DCD transplantation. Retransplantation is twice as common for DCD recipients (14.7 % vs. 6.8 %); and patient survival after retransplantation is less than survival after primary liver transplantation [21]. These continue to remain barriers to achieving similar outcomes after DCD and BD liver transplantation. Furthermore, due to higher rates of complications after DCD transplantation, the costs for DCD liver transplantation exceed those of DBD liver transplantation by approximately 25 %. This is attributable to higher numbers of retransplants (21 % vs. 7 %) and higher rates of biliary complications (58 % vs. 21 %) [22]. Several risk factors for poor outcomes after DCD liver transplantation have been identified and include long donor warm ischemic time (less than 20–30 min), long cold ischemic time (exceeding 8–10 h), and older donor age (greater than 40–60 years), and geographic sharing of organs [23, 24]. Similarly, recipient age over 60 years, renal insufficiency at the time of transplant, and donor HCV status exacerbate the risk for poor outcome after DCD transplantation [23, 24].

Primary Nonfunction

Primary nonfunction (PNF) after liver transplantation is defined as severe hepatocyte injury (AST $\geq$ 3000) and the failure to synthesize clotting factors (INR > 2.5) or clear lactate (lactate $\geq$ 4 mMol/L). PNF occurs 3.6 times more frequently after liver transplantation from DCD donors versus BD donors [25]. The literature reports incidence of PNF after DCD liver transplantation ranges between 0 and 12 % compared to 1.4 and 3 % after BD transplantation [16, 26]. In larger studies, the risk appears to be somewhat lower with rates of PNF around 2.5–3 % [23, 26, 27]. A survey of Europe has shown similar rates of primary nonfunction between controlled and uncontrolled DCD donors [28]. Risk factors for primary nonfunction include transplanting a male liver into a female recipient, older recipient age (over 60 years old), and higher recipient BMI (over 30) [16].

Hepatic Artery Thrombosis

Hepatic artery thrombosis (HAT) is an uncommon, but devastating complication after liver transplantation. The incidence of HAT varies from 0 to 33 % after DCD liver transplantation, with larger studies reporting lower rates (0–6 %) [16, 23, 26, 27]. A large SRTR database review reported a similar incidence of HAT comparing DCD and BD liver transplantation [25], similarly supported by previous reports [16, 27, 29]. It has been reported that hepatic artery stenosis is more common after DCD liver transplantation [29]. Moreover, biliary stricture as a consequence of hepatic artery stenosis was more frequent in recipients of DCD versus BD liver transplantation [29]. Treatment for HAT after DCD liver transplantation frequently requires retransplantation [14, 30].

Biliary Complications

Biliary complications are more common after DCD liver transplantation than after BD transplantation [29]. This is likely related to sensitivity of the biliary tree to the effects of warm ischemia during the donation process. The overall incidence of biliary complications after DCD liver transplantation is between 15 and 58 % compared to much lower rates of 6 and 21 % seen in BD liver transplantation [14, 16, 17, 19, 22, 23, 25–27, 29–31]. In a multinational meta-analysis, the odds of biliary complications are 2.4 times higher after DCD than after DBD liver transplantation [25].

It is generally felt that minimizing ischemic time is critical in preventing biliary complications. Others have attributed biliary ischemia to microthrombotic events during donation and have attempted to mitigate this by infusing TPA in the hepatic artery during implantation [32]. Additional risk factors for biliary complications after DCD liver transplantation include donor age over 40 years and higher donor BMI [29]. The spectrum of biliary complications seen in DCD liver transplantation include anastomotic and non-anastomotic biliary strictures, bile leaks, bile casts, biliary sludge, bilomas, biliary abscesses, and ischemic cholangiopathy, among others. Many of these biliary complications can be managed endoscopically, while others require operative intervention. In a subset, retransplantation will be required [23, 26].

One subset of biliary complications is ischemic cholangiopathy, which is difficult to treat, often associated with intrahepatic bilomas or biliary sepsis, and not infrequently leads to repeat transplantation. Ischemic cholangiopathy manifests itself as non-anastomotic biliary strictures, either in isolation or with diffuse involvement. Most ischemic cholangiopathy manifests within the first 4 months post-transplant [29]. Some cases can be managed percutaneously with dilations via ERCP or PTC, but it can lead to graft failure and up to 50 % eventually require retransplantation [17, 27, 29, 31]. Like all biliary complications, it is significantly more common after DCD than after DBD liver transplantation with reported rates of up to 10.8 times higher odds than DBD liver

transplantation [25]. The incidence of ischemic cholangiopathy has been reported anywhere between 0 and 44 % after DCD transplantation, versus around 3 % after BD transplantation [22, 25–27, 31]. Predictors of ischemic cholangiopathy include a longer time from asystole to cross-clamp, with every additional minute associated with a 16 % increased risk [27, 33]. Further risk factors for ischemic cholangiopathy include cold ischemic time over 8 h, donor age over 40 years, and African American recipients [27, 29].

Other Risks

Ischemia-reperfusion injury is exacerbated after DCD liver transplantation, as manifested by laboratory parameters such as a higher peak AST and INR after DCD transplantation [16, 23]. A post post-reperfusion syndrome during the DCD liver transplant operation has been described with a high likelihood of requiring transient vasopressor support at reperfusion and afterwards [14]. Overall, postoperative recovery after DCD liver transplantation is similar to that of BD liver transplantation. Length of stay post-transplant is similar to BD transplantation, although ICU length of stay is longer in DCD recipients in one study [16, 26].

Outcomes of DCD Liver Transplantation

Graft Survival and Retransplantation

Overall graft survival after DCD liver transplantation is inferior compared to BD liver transplantation. Although some studies report short-term graft survival after DCD liver transplantation similar to that seen with BD liver transplantation [26, 27], others do not. Twofold higher graft failure rates after DCD liver transplantation at 1 and 3 years were seen in a meta-analysis of DCD and BD liver transplantation [25]. At 5 years, DCD liver graft survival is 43–53 % compared to 51–68 % BD liver graft survival [15–17, 29]. Only one report describes similar graft survival at 5 years around 69 % in both DCD and DBD groups [27]. Long-term outcomes appear, ultimately, to be similar at 37.5 % at 10 years in both groups and 29 % and 25 % at 20 years in DCD and BD groups, respectively [30].

Retransplantation is more common after DCD liver transplantation, with rates as high as 19 % for DCD liver transplantation compared to only 5–7 % for BD transplantation [24, 29]. Retransplantation rates are highest in older DCD donors to older recipient pairs [16]. Causes for retransplantation include ischemic cholangiopathy in 81 %, primary nonfunction in 13 %, and vascular complications in 6 % [29].

Patient Survival

Patient survival after DCD transplantation is similar or slightly less than after DBD

transplantation, depending on the study. In one study, an increase in 1 year patient mortality is reported after DCD transplantation, but overall, 3 year survival appears to be comparable [25]. Conversely, another large study reports a decreased DCD liver transplantation patient survival of 82 % and 71 % at 1 and 3 years, compared to 86 % and 77 % at 1 and 3 years after DBD liver transplantation, respectively. Again, this bore out at 5 years, with patient survival after DCD and BD liver transplantation ranging between 68–77 % and 62–81 %, respectively [15, 16, 24, 27, 29]. Looking at long-term outcomes, patient survival after DCD transplantation lies between 43 and 57 % at 10 years, approximately 54 % at 15 years, and at 20 years around 38 %. This compares to BD liver transplantation survival rates of 64–67 % at 10 years and 58 % after 15 years [16, 29, 30]. The mortality for retransplant recipients is significantly worse; however, the 1 and 3 year survival after retransplantation with DCD livers (71 % and 59 %, respectively) versus BD livers (68 % and 60 %, respectively) is overall comparable.

Rejection and Other Complications

No differences exist in long-term complications, including acute or chronic rejection [29]. Rejection occurs with similar frequency by 90 days and 1 year post-transplant [26, 29]. Interestingly, recurrent hepatitis C is seen with the same or higher frequency after DCD liver transplantation compared to after BD liver transplantation [16].

DCD Pancreas Transplantation

Criteria for Acceptance

Utilization of DCD pancreas transplantation for the treatment of severe type 1 diabetes, with or without simultaneous kidney transplantation, remains a relatively uncommon practice. Only select centers will choose to transplant pancreata recovered from donation after circulatory death [28, 34]. In experienced centers, DCD pancreas transplant has been successful [34–36]. However, selection criteria for DCD pancreata though overall similar to those required of BD pancreata, are more stringent.

Donor age ranges from 3 to 60 years, though most centers will only accept organs from adult DCD donors [2, 34, 36]. There must be no history of diabetes or pancreatitis. Other exclusion criteria include intra-abdominal sepsis, pancreatic malignancy, prior pancreatic surgery, or pancreatic trauma [37]. The presence of hyperglycemia or mild hyperamylasemia at the time of organ donation may be acceptable [36]. Preferably, young donors with a low BMI who are hemodynamically stable are ideal for DCD pancreas utilization. Other factors that may affect outcomes include whether the donor operation is performed in the local donor service area, whether the anticipated cold ischemic time is short, whether an experienced team is available for recovery, whether

the quality of the flush and gross visualization of the organ is good, and whether there is a possibility of pumping an accompanying kidney in the case of simultaneous pancreas-kidney transplant [34]. The ideal warm ischemic time limit varies, with most adhering to a range between 20 and 45 min, depending somewhat on the course after withdrawal of support [34, 36].

Risks and Benefits of DCD Pancreas Transplantation

Overall, complication rates after DCD and BD pancreas transplantation are similar. Hospital length of stay is identical [2, 36, 38]. With regards to technical complications, pancreas graft thrombosis occurs with slightly higher frequency in DCD compared to BD pancreas transplantation, 13 % vs. 6 %, respectively [2, 36]. Enteric conversion, if performing bladder drainage, is necessary slightly more often with DCD pancreas (17 % vs. 8 % at 1 year and 28 % vs. 15 % at 5 years). Although enzyme leaks occur in 4 % of patients within the first year post-transplantation, it is not significantly higher over the subsequent 5 years. This compares to BD pancreas transplantation, where enzyme leaks are slightly higher at 9 % in the first year and 10 % over a 5-year period. The rates of pancreatitis at 1 and 5 years post-transplant are similar after DCD (9 % and 9 %, respectively) and DBD transplantation (9 % and 14 %, respectively). Pancreatic pseudocysts and pancreatic necrosis occur infrequently (<1 %) in both groups. The frequency of peri-pancreatic abscesses is also similar in both groups, with a rate of 8–10 % up to 5 years post-transplant.

Function of DCD Pancreas Transplants

Glycemic control after whole organ pancreas transplantation is similar at discharge and long-term comparing DCD and BD pancreata [2, 36, 38]. Moreover, fasting blood glucose and hemoglobin A1C are nearly identical. The vast majority of patients (93 %) are free from hypoglycemia at 1 year, which is the same regardless of donor type [2]. Nine percent of patients in each group develop post-transplant diabetes mellitus [2]. One year post transplant, hemoglobin A1C is 5.63 ± 0.57 after DCD pancreas transplantation and 5.43 ± 0.75 after BD [2, 36, 38].

Long-Term Outcomes of the DCD Pancreas Transplants

Long-term data on outcomes after DCD pancreas transplantation are lacking. Patient and graft survival are also comparable after solitary pancreas transplantation as well as after simultaneous pancreas-kidney transplantation from DCD donors. Overall, DCD pancreas graft survival is similar to BD pancreas transplantation, with 1 and 5 year survival rates being 83 % and 72 % versus 89 % and 79 %, respectively [36, 38]. For simultaneous pancreas-kidney transplantation, pancreas graft survival is 85 %, 80 %,

and 74 % at 1, 3, and 5 years after DCD transplantation [34]. Patient survival is 98 %, 93 %, and 89 % at 1, 3, and 5 years after DCD transplantation [34].

Acute rejection rates after DCD pancreas transplantation at 1 and 5 years post-transplant are 14 % and 19 %, respectively. This is in comparison to 13 % and 15 %, respectively for BD pancreas transplantation. Acute and chronic rejections remain a common cause of long-term graft loss. For DCD pancreas transplantation, leading causes of pancreatic graft loss include acute rejection (9 %), chronic rejection (9 %), as well as bleeding (18 %), and graft thrombosis (13 %) [2, 36, 38].

DCD Kidney Transplantation

Criteria for Acceptance

Of all organs, kidneys are the most frequently transplanted organ from DCD donors. Thus, we have more experience with, and therefore more data for DCD kidneys than with any other DCD organs. Furthermore, DCD kidneys are also most often considered for multiorgan transplants, including simultaneous kidney-pancreas transplants and simultaneous liver-kidney transplants [2, 3, 38].

In addition to the usual kidney acceptance criteria, transplant centers have varying criteria for DCD kidney acceptance, and some of these are delineated here. If uncontrolled DCD donors are to be considered, they should be reasonably young patients (under 60–65 years old), have no history of renal impairment, cancer, sepsis, or advanced diabetes. Furthermore, warm ischemic time limits should be confined to 40–120 min [39, 40].

In one large, single center study by Farney et al. [41], they described their optimal conditions for a DCD donor as a standard criteria donor, with a cold ischemic time under 30 h, transplanted into a recipient under 60 years of age. They report contraindications to DCD donation that include a GFR less than 70 mL/min on admission, a history of cancer, cold ischemic time over 45 h, and warm ischemic time over 90 min for SCD donors and over 60 min for ECD donors. Also, when machine perfusion criteria were used, flows under 60 mL/min or resistance over 0.4 mmHg/mL/min were contraindications to transplantation of adult DCD kidneys [41].

Studies out of the University of Wisconsin report more liberal criteria for DCD kidney donation [2, 38]. This includes a warm ischemia time of up to 120 min. In all cases, DCD kidneys are biopsied for scoring according to Remuzzi criteria as well as analysis for fibrin thrombi. Initially, a maximum age was 65 years; however, more recent experience argues against utilization of the DCD/ECD donor unless the creatinine, creatinine clearance, and medical history are all optimal.

Risks and Benefits of DCD Kidney Transplantation

DCD kidneys, like DBD kidneys, provide life-saving organs to patients. Waitlist mortality is significantly reduced by using DCD kidneys for transplantation [42]. The primary risk in DCD kidney transplantation is delayed graft function (DGF), often defined as the need for dialysis within 1 week after kidney transplantation. DGF is more common after DCD kidney transplantation than after DBD transplantation. Even with relatively short cold ischemic times (13 ± 5 h), DGF occurs in 28–57 % of patients after DCD kidney transplantation versus 19–21 % after DBD kidney transplantation [2, 38, 41, 43–47]. If uncontrolled DCD donors are used, DGF rates of 93 % have been reported [28]. Overall, the average duration of DGF after DCD kidney transplantation is 13 ± 8 days [43]. Several risk factors for DGF have been identified and include donor systolic blood pressure less than 60 mmHg for over 20 min and donor age over 50 years [43, 44]. Additionally, cold ischemic times over 30 h may also increase the incidence of DGF [41]. The consequences of DGF often are prolonged hospital stay and more procedures [41, 46, 48]; however, DGF does not have a negative effect on long-term outcomes, nor does the duration of DGF affect graft survival [41, 49]. DGF may be reduced by utilization of pulsatile perfusion preservation, though the data are not conclusive [48, 50]. In a multicenter Eurotransplant study of paired DCD kidneys, pulsatile perfusion preserved kidneys had a shorter period of DGF than cold stored DCD kidneys, although 1-year graft survival is the same at 94 % vs. 95 % [48].

Primary nonfunction is uncommon, 1–5 %, after kidney transplantation, and the risk is similar comparing DCD and DBD donors [38–41, 43, 44, 47]. Lower intraoperative blood pressure (<110/80) and central venous pressure (<6 cmH_2O) are risk factors for primary nonfunction [42]. Rejection occurs with slightly higher rates [1, 44] after DCD than BD kidney transplantation. Acute rejection occurs in 19–29 % of patients after DCD and 10 % after DBD transplantation [41, 45]. Other complications, including renal artery stenosis or thrombosis (<2 %), ureteral complications (<5 %), or lymphoceles (<10 %) are not different between DCD and DBD kidneys [2, 36, 38, 47].

Function of DCD Kidney Transplants

The overall function of DCD and B D kidneys are equivalent. As a consequence of increased rates of DGF, discharge creatinine is higher after DCD kidney transplantation than after DBD kidney transplantation (1.9 mg/dL vs. 1.7 mg/dL) [38, 47]. Additionally, creatinine on post-operative day 7 is higher in the DCD group compared to SCD or ECD kidneys [41]. However, overall, DCD kidneys had a creatinine clearance at 112 mL/min compared to SCD kidneys at 101 mL/min and ECD kidneys at 77 mL/min [41]. Furthermore, serum creatinine was similar up to 10 years after DCD and DBD kidney transplantation [40, 51].

Long-Term Outcomes of DCD Kidney Transplants

Long-term graft survival is similar for DCD and DBD kidneys [38, 45]. At 1, 3, and 10 years post-transplantation, DCD kidney graft survival is 88 %, 77 %, and 44 %, respectively, compared to 78 %, 69 %, and 42 %, respectively, after DBD kidney transplantation [13].

Graft failure is mostly due to chronic allograft nephropathy and death with function. Actuarial death censored graft survival after DCD kidney transplantation is 93 % at 1 year, 84 % at 3 years, and 84 % at 5 years [47]. Recipients over age 60 have lower 1 and 3 year graft survival at 79 % and 64 %, respectively [41]. This is similar to another report where kidney graft survival at 1, 5, and 10 years after DCD and DBD kidney transplantation is as high as 79 %, 70 %, and 62 % after DCD and 83 %, 72 %, and 62 % after DBD transplantation [40]. Others have also not found any difference in allograft survival at 5, 10, or 15 years post-transplant [47].

Patient survival is identical for DCD and DBD kidney recipients, even up to 15 years post-transplant. Actuarial patient survival is 93 % at 1 year, 91 % at 3 years, and 89 % at 5 years post renal transplant [41]. This is similar to reported rates of 1, 3, and 10-year patient survival of 92 %, 85 %, and 60 % after DCD transplantation [2]. Sepsis, cardiovascular disease, cancer, and gastrointestinal hemorrhage are common causes of death. Older recipients of DCD organs have lower patient survival than their younger counterparts (81 % vs. 98 % at 1 year, 76 % vs. 97 % at 3 years, and 69 % vs. 97 % at 5 years) [42]. Patient survival is lower in DCD-ECD recipients than in DCD-SCD recipients [42].

Lung Transplantation from DCD Donation

Limited availability of acceptable lungs for transplantation from brain dead donors lead to exploration of other options such as transplantation from marginal or extended criteria lung donors, ex-vivo perfusion, and lung transplantation from DCD donors [52]. Compared to brain dead donation, the lungs are not exposed to damage by neuroendocrine and cytokine inflammatory responses related brain death. The main insult in DCD lungs is related to the hypotension, hypoxia, and warm ischemic time during the process of withdrawal of life sustaining care in donors. Maastricht category III donors are only accepted for lung donation in United States. Explanted lungs are transported with ice to the recipient hospital and can be evaluated by extracorporeal ventilation and specific lung perfusion before they can be considered for transplantation. International Society for Heart and Lung Transplantation (ISHLT) registry compared 224 DCD lung transplantations with 2744 conventional lung transplantation from brain dead donation during the same time span [53]. Thirty-day mortality (3 % in both groups) and 1 year survival was not different in both groups. This was achieved mostly without extracorporeal pre-implantation evaluation, which could eliminate few unacceptable lung grafts and improve overall outcomes. Data from United

Kingdom and Australia have shown similar outcomes with DCD lung donation [54, 55]. Levvey et al. evaluated lung transplantation (n = 73) from DCD donors and reported 8.5 % primary graft dysfunction and 5 % chronic rejection. One and 5 year survivals were 97 % and 90 % compared to 90 % and 61 % respectively for transplantation from brain dead donors [55]. In spite of the feasibility and good outcomes, DCD lung transplantation is performed only in selective centers but definitely will gain more attention and acceptance in future. At present, the heart transplantation from DCD donors is not ethically an acceptable practice.

Conclusion

The gap between the number of patients on the waiting list and the number of organs available for transplant is continuing to widen. Along with exploring living donation, utilization of DCD donors presents an excellent source of organs and adds to the supply of organs available for transplant. Results previously mentioned have shown that kidneys and pancreata from DCD donors do equally well in the long term. The results for livers from DCD donors have a higher rate of complications, but nonetheless, have acceptable results in terms of patient and graft survival.

The operative strategy for a DCD procurement differs from that of a brain dead donor, with emphasis being placed on minimizing warm and cold ischemic times. Emphasis is on a safe, expeditious recovery once the patient has been declared dead; without undue risk of injury to the organs being procured. The techniques described above should serve as a guide in achieving this.

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4. Living-Related Organ Transplantations

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Introduction

Living-related organ transplantation (LROT) , as a treatment of end-stage organ dysfunction, has been mainly implemented due to the shortage of cadaveric donors. The increasing incidence of vital organ failure has led to the unavoidable increase in the number of patients who require organ transplantation; in contrast the number of available organs has increased only slightly. The current era's wide gap between organ availability and demand determines the existence of notably long waiting lists for cadaveric organs and elevated waiting-list death rates.

Living donor transplantation typically occurs between individuals who share an emotional bond, even if not necessarily genetically related. It is a standard practice in East Asian transplants programs, where it constitutes a strategy that sidesteps traditional beliefs on cadaveric donation, and an accepted clinical practice in various transplant centers in the United States and Western countries.

Nowadays, LROT is usually an elective procedure, where organ procurement takes place almost concurrently as the surgical intervention on the recipient.

Based on Organ Procurement and Transplantation Network (OPTN) data, from 2008 up to November 2012, a total of 30,772 living donor transplants have been performed in comparison with 108,634 deceased donor transplants [1]. Although cadaveric donors

account for more than 90 % of transplants, this source is heavily constrained by the willingness of donation. On the contrary, in recent years a steady increase of living donors has been observed, with living donor kidney transplantation taking on a more predominant role than ever. As many as nearly 40 % of all kidney transplants worldwide derive from living donors [2]. Kidneys are not the only organs that can be donated by a living donor; however, also liver, lung, pancreas segments, and intestine segments may be donated.

Living donation may be fall into one of the following categories : (a) directed to a loved one or friend, (b) nondirected, in the sense that the organ is donated to a general pool from where an organ can be transplanted into a recipient at the top of the waiting list, (c) directed to a stranger, i.e. a person with whom the donor has no prior emotional connection, and (d) directed to a blood- or emotional relative of a nonmatching blood group (complete mismatch or positive cross matching). Another category regards domino transplants, where i.e. the individual donates the organ (or part of the organ) to an unrelated person, providing another individual respectively donates to the person whom donor "A" is related. This procedure is especially important when incompatibility between donor and recipient precludes organ transplantation between the originally bound donor and recipient. A donor with a distant relationship with a specific recipient is termed a "Good Samaritan", while a nondirected donor who wishes to donate an organ to be used by any recipient who needs it, without knowledge of the recipient's need or distress is termed "nondirected Good Samaritan."

In general, better outcomes for the recipient when compared with an organ from a deceased donor, the opportunity to plan and schedule the operation in the best clinical status of the recipient, and the advantage of reducing warm ischemic time, are among the most notable benefits of this procedure. However, while the long-term functional outcome of living-related renal transplantation is markedly favorable, with 1-year graft survival ranging from 94 to 96 % in children older than 1 year, the long-term outcomes of living-donor lung, pancreas, and small intestine transplants remain not well defined.

Living-related donation is justified from both the humanistic and ethical stand-points, and it is medically acceptable, providing that a thorough medical and psychological donor evaluation is carried out and that a fully informed consent is obtained. The primary concern in living donor transplantation is donor safety, and it is well recognized that people who are willing to donate are exposed to surgical procedures that pose risks yet offer no physical benefits. Despite careful donor selection and management, mortality after living donor transplantation has occurred in Europe, USA, and Japan. For this reason, special safeguards are warranted for donors, including an advocated team,which is capable of providing the best periprocedural care.

Ethical Issues of LROT

The duty to do no harm and the duty to respect the donor's autonomy are fundamental pillars of medical ethics. In the setting of living donation, there is a need to clarify the meaning of harm, in order to properly understand the duty to do no harm. In fact, removing a part of or an entire healthy organ by invasively approaching the donor causes him/her definite though not incapacitating harm, despite good success rates, recovery rates, and postoperative functionality [3–6]. In addition, this procedure leaves the donor at risk of other surgery-related complications [7].

The biggest advantage of living donation is that by allowing the team to schedule the procedure, transplantation performed too early in the course of disease is avoided (reducing exposure times to immunosuppression), and prolonged waiting times, considering patients may become too sick to survive are also avoided.

However, as undertaking surgery on a healthy person who will not personally benefit from the procedure may not be completely devoid of complications, extensive patient information about known risks should be provided in order to aid him/her in their expression of self-determination. Although no surgical intervention is without risk, these may be minimized through careful evaluation and donor selection.

The donor must receive and understand relevant and sufficient information about the procedure, and the decision must be voluntary. He/she must be reassured that the freedom to withdraw from the donation process at any time exists, without any consequences. Furthermore, all living donors have both moral and legal rights for privacy to be guaranteed.

It is justifiable, and ethically and medically acceptable, for living-related donation to proceed in cases of emotionally related donor–recipient pairs, or in the case of altruistic living donation, only when both medical and psychological evaluations of the donor are carried out in accordance with accepted protocols, and no contraindications are identified [8]. The team that participates in the care of the donor ideally should be as independent as possible from that caring for the recipient; this can help to avoid actual or perceived conflicts of interest between donors and recipients.

Moreover, living donation should never be considered if it is reasonably not expected to yield the intended clinical benefit. That is, it must be shown that the advantages for both donor and recipient outweigh the risks associated with donation and transplantation, respectively. Albeit most donors report personal benefits from their donation experience, such as a higher self-esteem, personal growth, an increased appreciation for the value of their own life, and perceived increased respect and admiration by family and friends, others, on the contrary, report poor experiences, depression, and anxiety after donation, especially when the graft did not function as expected for the recipient [9, 10]. As psychological complications both before and after donating may affect the donor, a comprehensive psychosocial assistance, integrated into

a multidisciplinary team approach, is recommended.

Freedom from pressure and coercion should be properly investigated, as subtle coercion and pressure, though denied or remaining outside of the donor's awareness, may be rather apparent to members of the transplant team [11]. Psychological, medical, and social suitability of potential donors should be determined after complete and thorough evaluation by a team with the sufficient expertise to assess the fitness of an individual for organ donation.

Studies show that many living donors decide to donate immediately upon learning of the need for an organ, and tend not to change their minds after having received the appropriate information. However, scrupulous physicians do not perform surgery on demand, but carefully determine that living transplant surgery is in the interest of the recipient who requests it, and dutifully complete the evaluation process in the donor to prevent foreseeable harm [12].

Besides the full physical examination, laboratory testing, and "organ" specific investigations, pretransplant evaluations of the donors should include a thorough clinical interview, cognitive testing where necessary, questions about behavioral health practices such as smoking and illegal substance use, and questions about the ability and motivation to adjust to temporary changes in lifestyle that might facilitate donation.

Exceptional carefulness of the physicians involved in informing and evaluating the donor is required in case of adult to child living donation. The donation from parent to a small child is a spontaneous gift, but the donor–recipient relationship may lose its autonomy, and the tension may mount as the potential recipient's condition deteriorates, placing yet more pressure on the performance of the procedure.

The use of children for living kidney donation remains highly controversial, and in general, most transplant programs do not accept organ donation from subjects who are below 18 years of age except in very limited circumstances, such as in the case of identical twins or in the rare event of an emancipated minor donating for his or her own child.

Benefits and Disadvantages of Living Organ Donation

Living donation poses several advantages over cadaveric donation (Table 4.1). Among the most important are the following: the transplant can be planned for a time when the person waiting for the graft is in the best condition. This may greatly reduce many risks for the recipient and may positively impact the transplantation outcome. Furthermore, the time on the transplant waiting list is notably shorter [13].

Table 4.1 Advantages of living organ transplantation

Potential source to overcome cadaveric organ shortage
Avoidance of prolonged "in list" waiting time

Better matches between donors and recipients
Operation scheduled in the best clinical status of the recipient
Reduced warm and cold ischemic time
Better outcomes for the recipient when compared with an organ from a deceased donor
Need for reduced doses of immunosuppressant medications
Psychological benefit for the donor

Better matches between donors and recipients are related to the close genetic relationship, which is often the case in many donor–recipient pairs, allowing the use of reduced doses of immunosuppressant medications. Moreover, there is usually sufficient time to evaluate potential living donors, thus ensuring that they are medically and psychologically suitable. Warm and cold ischemia times are minimized, with a reduction of the potential damage to the organ. Compared to results with deceased donor transplantation, graft outcomes with live donors have been shown to be generally superior (though not always), potentially also decreasing costs. An additional psychological benefit for the donor derives from knowing that he or she has contributed to another person's life in a very meaningful way, while the recipient may experience a greater sense of responsibility to care for the donated organ, favoring compliance to adequate self and center-provided health care.

Major drawbacks are related to the perioperative risks of donors involved in this procedure (Table 4.2). In living liver, lobar lung, and pancreas, the rate of the most frequent complications such as: postoperative and chronic pain, discomfort, infections, bleeding, and potential future health status, has not been fully evaluated on large series. There are still few data on the long-term outcomes. Based upon OPTN data from 1999 through 2011, of 4069 living liver donors, at least 6 have been listed for a liver transplant. Of the 79,070 individuals who were living kidney donors from 1999 through 2011, at least 24 have been listed for a kidney transplant. However, the medical problems that caused these donors to be listed for transplant may not be connected to the donation.

Table 4.2 Major drawbacks of living organ transplantation

Donor's exposure to surgical procedures that pose risks and offer no physical benefits
Postoperative pain, bleeding, infections
Chronic pain, discomfort
Potential for subtle coercion and pressure of donor

Donors can be faced with overwhelming and complicated psychological processes linked to family pressure to donate, guilt or resentment, with no one to turn to for guidance or advice. Ethical issues are sometimes difficult to solve, and objectors to the practice of living donation may insinuate that this procedure should not only be

discouraged but abandoned altogether because of the dangers associated with donating organs [14].

Living Donor Kidney Transplantation

The total numbers of patients on the active waiting list for a kidney graft by far exceeds the number of deceased donor organs that are available each year, and waiting times are generally prolonged.

Based on OPTN data , as of January 2013, 29,537 living kidney transplants have been performed, in comparison with 52,775 deceased-donor transplants. The Eurotransplant registry reports that in 2011 and 2012, 3633 and 3472 kidney transplants from deceased donors, and 1339 and 1389 living-donor kidney transplants (LDKT) were respectively performed [15]. The rate of living-donor transplants increased from a nadir of 13.0 per 100 wait-list years in 2007 to 16.1 per 100 wait-list years in 2011.

Living-related kidney transplantation first took place in 1954 in the U.S., when one twin donated a kidney to his identical twin brother. It was the first successful original type of organ donation. Living, genetically related, donor transplantation of kidneys was later adopted by many transplantation centers in the world, until the early 1980s, when cyclosporin became available, and made kidney transplantation from cadavers more successful. However, the scarcity of cadaveric graft of the last decade has moved to reconsider the usefulness of living donation, and nowadays living kidney transplantation is increasingly practiced in many centers in Europe and USA [16]. This procedure is also very popular in countries, which lack legal and societal regulations that allow the use of organs from deceased donors.

Biologically unrelated living kidney transplants now account for 14 % of all kidney transplants in the United States, and nonspousal donations outnumber spousal donations 2 to 1.3 [17]. Although HLA matching has traditionally played an important role in choosing which living donor to evaluate, current perioperative desensitization and immunosuppression have minimized the impact of matching. Evaluation of potential living donors may consequently occur independently of the recipient's evaluation, considering motivation to be the best potential for the program, and giving donor safety the highest priority. Protocols that enable sensitized patients to receive kidneys from living donors against whom they have a positive cross-match involve pretransplant pheresis sessions to remove the offending antibodies, administration of intravenous immunoglobulin to inhibit the return of antibodies, and postoperative additional pheresis treatments and immunoglobulin infusions.

The use of living consanguineous donors has reached a large approval, as the global severe peri-operatory morbidity in this population is very low (0.2–2 %) and death is extremely rare, with death rate of 0.03 %. In addition, technical improvements such as laparoscopic nephrectomy have reduced the morbidity of donation and increased

willingness to donate a kidney.

As the presence of systemic diseases in potential donors poses ethics questions and increases perioperative risk, living donation should be reserved for healthy adults, free of overt metabolic and cardiovascular risk factors. Over the age of 45 for males and 50 for females, potential donors should also be noninvasively scrutinized to rule out coronary artery disease. However, screening tests and exclusion criteria for donors may vary among centers.

Programs of living kidney donation have recently become less strict with respect to exclusion criteria, including the acceptance of living unrelated and altruistic donors, older donors, hypertensive donors, and donors with obesity or a history of nephrolithiasis.

Procedure of Living Kidney Donation

Open living kidney donation requires a flank incision, and is often accompanied by rib resection. In recent years the introduction and the increasing practice of laparoscopic and laparoscopy-hand assisted techniques have been shown to achieve better perioperative outcomes. Detailed preoperative evaluation of renal vascular anatomy is critical for planning the operative approach in living kidney nephrectomy, and donors with serious anatomical abnormalities, such as horseshoe or ectopic kidneys, should be preferentially enrolled to "open" nephrectomy. A history of multiple intra-abdominal operations, renal vascular complexity, and kidneys with more than two arteries are additional relative contraindications to laparoscopic kidney retrieval. Hand-assisted laparoscopy offers similar advantages to open surgery because the surgeon can use his hand to help the kidney exposure and dissection and to control bleeding by finger pressure. In recent years some physicians are using robotics to perform both living-donor nephrectomies (kidney removal) and implantation of the kidney into the recipient. This advanced form of laparoscopic surgery allows surgeons to do precision work with less trauma to the patients (Table 4.3) [18]. Aggressive intraoperative volume loading may reduce pneumoperitoneum-induced renal function impairment, and laparoscopic donors should receive generous intravenous administration of crystalloid fluids, and sometimes diuretics, to significantly increase diuresis.

Table 4.3 Advantage of laparoscopic donor nephrectomy

Better donor acceptance in comparison with the open procedure
Less trauma to the patients
Significant reduction of postoperative pain
Less analgesic requirements and reduced side effects from opioids
Earlier oral food intake and ambulation
Faster and improved postoperative recovery

Shorter hospital stay

Grafts should be retrieved with adequate vessel length and with a well-preserved blood supply to the ureter. Implantation advantages associated with a longer renal vein make left kidney retrieval preferable; but the right kidney can also be taken in case of favorable renal vascular anatomy. Total ischemia time from removal of the donor kidney to restoration of blood flow in the recipient is the most notable clinical advantage of this procedure; in some instances it may be no longer than 1 h, and this sole fact can be responsible for an adequate graft function.

Benefits of laparoscopic donor nephrectomy include better donor acceptance in comparison with the open procedure, significant reduction of postoperative pain, and less analgesic requirements and reduced side effects from opioids. Earlier oral food intake and ambulation have been reported, as well as faster and improved postoperative recovery. In all studies [17–19] the mean hospital stay for patients who underwent laparoscopic kidney donation was shorter than after an open procedure.

Complications of laparoscopic surgery include trocar injuries during insertion into the abdominal cavity, penetration of blood vessels, abdominal wall hematoma, and a detrimental effect from the pneumoperitoneum on pulmonary function and renal perfusion. Vascular injuries can result in hemorrhage, while deep vein thrombosis, chest infection, umbilical hernias, and umbilical wound infection are other recognized, albeit rare, postoperative complications. Complications requiring surgical or radiologic intervention occur in <3 % of living donors, and mortality within 90 days is reportedly 0.03 %, approximately [17].

The short term consequences of kidney donation are generally not very important, and are much less relevant than the levels of risk that are regarded as acceptable for other elective surgical procedures. However, serious complications have been reported, including pulmonary emboli, pneumothorax, pneumonia, deep venous thrombosis, splenectomy, adrenalectomy, upper extremity nerve palsy, and reexploration for bleeding. Minor complications such as paralytic ileus, wound infections, wound hematomas or seromas, phlebitic intravenous sites, urinary tract infections, urethral trauma from catheter placement, femoral nerve compression, and atelectasis have been also described.

The most important long-term complications include proteinuria, and moderate reduction in glomerular filtration rate (GFR) (decrease to ≅70 % of pre-donation levels). Urinary albumin excretion is minimally increased, implying glomerular hyperfiltration and some increase in glomerular permeability to albumin in the remaining kidney. There is also a small increased risk for the development of hypertension.

Graft and Recipient Outcomes After Living Kidney

Transplantation

Over the past 15 years, for both living and deceased donor transplant recipients, 90-day, 6-month, and 1-, 3-, and 5-year results have shown ongoing improvement. Data from the United Network for Organ Sharing/Organ Procurement and Transplantation Network for the United States, and the Collaborative Transplant Study for Europe [19] demonstrated similar 1-year graft survival in Europe and the United States, whereas much higher cumulative 5- and 10-year survival estimates were found in Europe for all combinations of recipient age and donor groups. The observed differences were particularly large for children, adolescents and young adults, and African Americans. One-year graft survival in kidney transplants from both related and unrelated living donors exceeds that for deceased donor organs (94 % vs. 88 %). However, long-term graft survival rates were found substantially lower in the United States compared with Europe, independently of differences in patient characteristics. The refraining to provide health insurance coverage for immunosuppressive medication beyond 3 years after transplantation by the major insurance provider for transplant patients in the USA has been advocated as one important cause of lower survival.

The rate of late graft failure is traditionally measured by the graft half-life conditional on 1-year survival, defined as the time when half of grafts of patients surviving at least 1 year are still functioning. For living-donor transplants, the estimated 1-year conditional half-life was 15.3 years for transplants in 2011 (for deceased donor transplants 11.9 years). Unlike long-term graft survival, short-term graft survival in children is excellent. Graft failure for pediatric living-donor transplants was 1.6 % at 6 months and 2.7 % at 1 year for transplants in 2009–2010, 8.4 % at 3 years for transplants in 2007–2008, and 18.1 % at 5 years for transplants in 2005–2006 (OPTN 2011 data) [1].

Living graft survival is best for HLA identical sibling donors, with a 5-year graft survival of 87 %. In the USA, the half-life for deceased donor transplantation is quoted as half of that of living donation.

The most serious consequence of LDKT is graft loss, which is defined as the absence of kidney function, occurring any time after transplantation due to irreversible graft injury, and requiring chronic dialysis and/or retransplantation. Graft loss may be due to primary nonfunction, defined as permanent absence of kidney function within a week posttransplant, and generally due to venous or arterial thrombosis, or acute rejection. Causes leading to graft loss within months or years include graft fibrosis/atrophy, glomerular diseases, recurrent urinary tract infections, immunologic mechanisms, both cellular and antibody mediated, and chronic rejection, which is however lower in number with respect of those observed among recipients of deceased donors [20].

The 1-year patient survival rate approximates 81 % with deceased donor kidneys

and 91 % with living-donor kidneys, while expected patient survival rate and graft function at 5 years is 95 % and 80 %, respectively, in the case of living donors, and 75 and 55 % in the case of deceased donors. Preemptive transplantation is associated with better graft survival compared with patients on dialysis at the time of transplantation. Data from high volume transplant centers indicate that long term survival after transplant is more favorable, as all other outcome parameters.

Living-Donor Liver Transplantation

Living-related liver transplantation (LDLT) is a very important treatment modality for end-stage liver disease, especially in countries where programs are hindered by severe deceased donor organ shortage. The first living-donor liver transplant was performed in 1988 by a Brazilian team. The donor was a 23-year-old mother who donated her left lateral segment to her 4-year-old daughter with biliary atresia. Postoperative outcome of the donor was uneventful, but the recipient developed severe hemolysis following a blood transfusion, resulting in renal failure, and died during a hemodialysis session on the sixth postoperative day.

Right or left lobe living liver donation, a practice that has been alleviating the deceased liver shortage, still sparks considerable debate concerning the ethical aspects of exposing a healthy donor to major surgery only for the sake of the recipient [21]. Currently, the high risk associated with major hepatic resection remains a serious challenge even in the most experienced hands. The risk of donor death has been estimated to be 0.2 % for left lateral segment donation and 0.5 % for right lobe donation, so the emphasis on donor safety is of paramount importance in this procedure [22, 23]. In addition, studies have shown that the outcomes of living liver donor procedures, when applied to adult recipients with severe advanced disease, are not as good as originally expected. These disappointing results may be responsible for the decline of living liver donation in many institutions [1, 24].

Living liver donation still remains a primary source of organs for patients in Asia and in Japan. In OPTN area the number of living-donor liver transplants, which peaked in 2001 with 522, and accounted for 265 in 2005, has progressively declined to 249 in 2008 and to 230 in 2012. According to the European registry, the number of LDLT performed in 2011 and 2012 were 135 and 121, respectively, in comparison with 1770 and 1689 liver transplant from deceased donors. Pediatric living-donor liver transplantation boasts a long history and considerable success, as parents are keener to donate, a smaller volume of graft is needed, and the donor operation is relatively simpler to perform. LDLT should not be performed in patients with advanced decompensated liver disease, due to the poor posttransplantation survival, when compared with survival rates after deceased donor liver transplantation. Because of the liver's regenerattive capacity, long-term liver function is normal in both the donor and

the recipient, provided no complications arise.

Living Liver Donation: Preoperative Evaluation

One of the most important investigations prior to right lobe donation is preoperative measurement of the future liver remnant, which has to be associated with preoperative estimation of residual liver quality. The potential living donor should be extensively evaluated to determine medical and anatomic suitability, with regard to vascular and biliary anatomy, to ensure that the right and left lobes contain sufficient liver mass to sustain function in the recipient and donor, and to comprehensively assess the risks and benefits for both donor and recipient. Calculation of graft and whole liver volume is largely based upon either a helical multiphase computed tomography (CT) examination or magnetic resonance imaging (MRI), both of which can help delineate parenchymal quality and vascular anatomy. Either CT or MR cholangiography are useful in evaluating the configuration of the biliary tree.

Graft and recipient size-matching are important to achieve successful outcomes. Providing a sufficient graft size is mandatory to meet the metabolic demands of the recipient; donor's safety on the other hand, should not be compromised by excessive liver resection. For an adult-to-child liver transplant, the left lateral segments (segments 2 and 3), accounting for 20 % of the donor's liver, are most often procured, whereas segments 1–4 (left lobe, 35–40 % of the donor's liver), are being used for older children. Right hepatic lobectomy is necessary for average size adults, even though successful attempts to procure the left lobes also for adult living-donor transplantation have been made. Harvesting of the left lobe is, in fact, associated with lower morbidity for the donor than the right lobe. Guidelines have been defined to establish the minimum graft size, capable of minimizing the risk of small-for-size syndrome (SFSS) . SFSS may occur when the implanted parenchyma volume is smaller than that required for the intended recipient. Graft dysfunction during the first postoperative days, not attributable to other causes (i.e., rejection, infection, vascular complications) is the clinical picture of SFSS.

The risks to the donor include those associated with invasive testing before surgery and to the surgical procedure itself. Due to considerable reservations about subjecting a donor to major hepatic surgery, meticulous preoperative evaluation is required to identify the potential risks to donors and to exclude coexisting cardiac, pulmonary, and renal diseases. A body mass index of 30 kg/m^2 or more (27 kg/m^2 for Asians; World Health Organization, 2004) raises the concern for fatty liver and obesity-related comorbidities. Besides the recognized morbidity associated with conventional liver resections, one of the most serious potential complications of living donation is the occurrence of postoperative pulmonary embolism. For this reason, the screening of potential donors for the presence of factor V Leiden gene mutations, prothrombin gene

mutations, protein C, protein S, AT III deficiency, a factor VIII elevation, as well as the presence of antiphospholipid or cardiolipin antibodies, is recommended. Obesity, treatment with estrogens, presence of varicose veins, smoking, and a family history of thrombosis, should be also carefully evaluated for the inherent serious risk.

A multistep consent process involving different surgeons on separate occasions is preferred, during which the operative procedure and potential complications are described in detail. Preoperative donation of autologous blood is recommended to minimize the small risk of infection associated with allogeneic blood transfusion.

Living Liver Donation: Procedure

In adult-to-adult living-donor liver transplant the right hepatic lobe is often the preferred graft to assure a better graft-recipient body weight ratio. A right hepatic lobectomy usually requires a right subcostal hockey-stick incision, while left lateral allograft segmentectomy may be procured through an upper midline incision. Dissection of the suprahepatic inferior vena cava (IVC) to isolate the graft's hepatic venous outflow, mobilization of the right hepatic artery, right portal vein(s) and bile duct, temporary occlusion of the isolated hepatic artery and portal vein to delineate the appropriate plane of parenchymal transection, and cholecystectomy, are the important steps to complete the procedure.

Laparoscopic-assisted donor hepatectomies have been performed for procurement of the left lateral lobe. The larger right lobe can be mobilized laparoscopically, but a small upper midline incision may serve as the site of donor allograft removal. The use of robotic surgery has increased worldwide and is now becoming suitable for living-donor procurement as well. Robotic right lobe resection performed totally by minimally invasive approach in a living donor has been reported with successful results and outcome [25, 26].

Liver parenchyma transection is often performed under restricted fluid administration and reduced central venous pressures, and with transient interruption of blood flow as needed. This can help reduce blood loss and optimize hemostasis [27]. Intraoperative phlebotomy, acute isovolemic hemodilution and blood salvage are frequently used. Strict coordination between the donor and recipient teams ensures that the recipient hepatectomy is completed by the time the donor liver graft is available for transplantation.

Postoperative intensive care of the donor centers on ensuring hemodynamic stability, complete pain relief, preventing hemorrhage, and renal dysfunction, and frequent monitoring of coagulation profile and serum liver tests. Every effort to maintain adequate analgesia is key for both the donor's comfort and to favor a postoperative recovery, which is free of preventable nosocomial complications. Epidural analgesic delivery has proven to be very useful to improve respiratory function recovery and

mobilization [28]. Due to the rapid regeneration of liver volume, magnesium and phosphate infusion is of paramount importance in the living donor.

Some degree of hepatic insufficiency is often clinically identified immediately after surgery, presenting as transient prolonged prothrombin time and nonobstructive cholestasis. Management of biliary leakage with right hepatectomy is similar to right hepatectomy for other indications. Morbidity following liver donation can be significant, and more than 50 % of right lobe donors suffer complications. Unfortunately, an exhaustive preoperative donor assessment is not enough to guarantee a problem-free postoperative course. Right hepatectomy has been associated with higher rate of complications in comparison with left and left lateral hepatectomies (ranging from 20 to 60 %, overall approximately 35 %. Internationally reported donor morbidity rates range from 0 to 67 %, depending on the individual definition and recognition of morbidity. Annual center volume, and the percentage of liver transplants from living donors' relative to deceased donors have also been associated with donor perioperative morbidity.

In 2008, the A2ALL cohort reported an overall complication rate of 38 %. Serious postoperative complications are quite rare, however. In a recent worldwide survey, which included reports from the American Society of Transplant Surgeons, the Japanese Liver Transplant Society, and the European and Chinese liver registries, 23 donor deaths out of a total of 11,553 LDLT procedures were reported. Eighteen of the deaths were reported directly in the survey, and another five deaths were reported by the Eurotransplant Registry, for an overall mortality rate of 0.2 % [29]. Increased age of donors is associated not only with a higher rate of complications, but also a decreased and delayed capacity for liver regeneration [30]. This diminished capacity has also been shown in the old recipient population with respect to early graft regeneration and graft survival [31].

Major postoperative complications of living liver donation occur in the perioperative period and depend on many factors such as functional recovery of the remnant liver, surgical skill of the surgeons, length of procedure, presence of anatomic abnormalities, blood transfusion requirements, and level of postoperative care (Table 4.4). Postoperative bleeding requiring transfusion or relaparotomy, systemic infections, portal vein thrombosis, hepatic artery thrombosis, postoperative liver dysfunction, pleural or subphrenic effusion requiring drainage, intraabdominal abscess, and acute renal failure (requiring dialysis) are reported in 6 to >50 % of cases. Bile leaks from the cut surface of the transected liver, the formation of biliary strictures and anastomotic leaks are frequent following right lobe harvesting, ranging from 6 to 18 % of the cases. Pulmonary embolism, though rare, is extremely serious, and it is reportedly the most important cause of donor death. Deep venous thrombosis prophylaxis with heparin, sequential compression stockings, and a policy of getting the patient promptly mobilized out of bed while in hospital, are strongly recommended to prevent the potential risk of

pulmonary embolism. Approximately one third of donors encounter minor complications such as wound infection, abdominal pain, fever, gastric stasis, and nerve damage, and late complications include incisional hernia, partial fascial dehiscence, pneumonia, and partial bowel obstruction. More than 90 % of donors are able to return to their predonation occupation and to work within 2 weeks after surgery, and >80 % to their previous level of physical activity within months.

Table 4.4 Drawbacks and complications of living liver donation

Documented morbidity associated with major hepatic surgery
Risk of mild hepatic insufficiency immediately after surgery
Deep venous thrombosis
Postoperative pulmonary embolism
Chronic pain
Postoperative bleeding requiring transfusion or relaparotomy
Pneumonia and systemic infections
Portal vein thrombosis
Hepatic artery thrombosis
Pleural or subphrenic effusion requiring drainage
Intraabdominal abscess
Bile leaks from the cut surface
Biliary strictures and anastomotic leaks
Wound infection, partial bowel obstruction
Nerve damage, incisional hernia, partial fascial dehiscence

Recipient and Graft Outcomes After Living Liver Transplantation

It should be noted that when outcomes of LDLT are compared with those of deceased donor liver transplantation, various differences at the time of the procedure, for example those related to recipient selection, severity of cirrhosis, portal hypertension, renal dysfunction, malnutrition, etc., may complicate statistical interpretation, as comparisons cannot be established on the base of Model for End-stage Liver Disease (MELD) stratification . Previous retrospective reports by the Adult-to-Adult Living Donor Liver Transplantation Cohort Study identified a survival benefit for patients who received LDLT as compared to waiting for, or receiving, a deceased donor liver transplant [32].

In recent years, the survival benefit of liver transplant in candidates with MELD scores <15 has been questioned. According to the data of the Scientific Registry of Transplant Recipients (SRTR) [33], a net survival benefit is actually observed after LDLT in patients with MELD scores <15, but this benefit must be attributed largely to

reduced waitlist mortality. In fact, as of February 2010, posttransplant survival was similar in both LDLT and deceased donor liver transplant recipients in the MELD <15 group. In the current MELD era, candidates enrolled with MELD >15, who did not have HCC, and who received LDLT, had markedly lower mortality compared to those waiting for or receiving deceased donor liver transplant ($p = 0.0006$). Avoidance of waitlist deaths as a consequence of timely transplant appears to be the major contributor to favorable outcomes in both groups.

Overall, LDLT outcomes are comparable with those in deceased donor liver transplantation. Recipient outcomes in UNOS area are similar to recipients of deceased donor transplantation [34]. One year survival for recipients of living-donor grafts is 82.5 %, based on data from 1997 to 2004, compared to 82.0 % for grafts from deceased donors, while 5 year survival is 66.1 %, compared to 65.1 % for recipients of deceased donor grafts. Recipient survival rates reported from major European centers performing LDLT parallel those of large centers in USA.

Graft survival in general, in fact, has continued to improve over the past decade for recipients of both deceased donor and living-donor livers. Based on OPTN/SRTR data (may 2009), for LDLT adjusted graft survival at 3 months and 1 year, in the period 2004–2007 ranges 91.7 % to 93.6 %, and 87.5 % to 89.1 % respectively. At 3 years, graft survival rate was reportedly 82 %, and at 5 years 78 %. For deceased donor liver transplants performed in 2010 graft failure was 10.1 % at 6 months, 14.4 % at 1 year for transplants performed in 2009, 19.6 % at 3 years for transplants performed in 2008, and 25.0 % at 5 years for transplants performed in 2006 [1]. For pediatric recipients of live donor grafts, the results have been considerable, and all data from both the U.S. Scientific Registry of Transplant Recipients and various large series show that the outcomes in small children are usually better with living-donor grafts than those observed with deceased donor organs [34].

Factors influencing allograft survival include recipient age, duration of cold ischemia time, and center experience. Notably, transplants from biologically related donors have better outcomes. Neither graft size nor graft weight to recipient weight ratio (GWRWR) appear to be significantly associated with graft failure risk. Recipient medical status at time of transplant does not appear to affect graft outcome. In pediatric recipients of living-donor grafts, the incidence of hepatic arterial thrombosis has been reported to range from 7 to 20 %, and remains the most serious complications in terms of morbidity and mortality. Hepatic arterial thrombosis is the principal cause of early graft loss, manifesting as acute graft dysfunction, and represents a triggering event for biliary leak and sepsis.

Living-Donor Lobar Lung Transplant

Lung transplantation is the only therapy, which is currently available for end-stage

pulmonary disease, and it is reserved for patients who have failed maximal medical therapy. Even though the number of suitable organ donors could nowadays be increased by proper donor management, nonheart beating donor, and ex-vivo lung perfusion [35], the demand for lung grafts is ever increasing, and by far exceeds the supply. Living lung transplantation has become a realistic alternative for dealing with the staggering mortality of patients on lung transplantation waiting lists. Lobar transplantation from blood group-compatible living donors (parents or relatives) is a procedure where, in selected recipients, right and left lower lobes from two healthy donors are implanted in the recipient in place of the whole right and left lungs, respectively. The use of living-donor lung lobes for transplantation in two children with terminal pulmonary disease was first described in 1992. Since then, this program has been developed in selected centers with satisfactory intermediate survival and functional results [36].

In the OPTN registry from November 2008 to January 2013 only 3 living-donor lobar lung transplantations (LDLLT) have been performed, in comparison with 8348 deceased lung transplantations, while in the same time period, The European registry reports 4 LDLLT and 5576 lung transplantations from cadaveric donors. In Japan, where the average waiting time for a deceased donor lung is more than 2 years, lung transplants from living donors have resulted in a practical option for the treatment of end-stage pulmonary diseases. As of 2011, LDLLT has been performed in approximately 400 patients worldwide.

In general, LDLLT is reserved for candidates who urgently need transplantation and, because of their “unfavorable” place on the waiting list, seem unlikely to survive until a deceased donor becomes available. Patients being considered for living-donor lung transplantation should meet the criteria for deceased donor lung transplantation, including a progressive deterioration in clinical status and the inability to wait for a deceased organ. Cystic fibrosis represents the most common indication for living-donor lung transplantation, as these patients tend to be smaller in stature, thereby allowing two lobes from average-sized adult donors to provide sufficient pulmonary tissue and reserve. Although some ethical issues surrounding lobar lung transplantation from living donors are still under debate, recipients’ outcomes appear similar or better than those observed with deceased donor lung transplantation [37].

The most important ethical dilemma is whether two healthy family members should be risked in order to save a relative, along with the concern of unforeseen degree of permanent loss of lung function that will result from lobe resection. Despite the high risks, this procedure continues to be utilized under properly selected circumstances, as it has been life-saving in severely ill patients who would have either died or became unsuitable recipients before the availability of a deceased donor organ. The reports from various studies show that more than 80 % of living lobar recipients had cystic fibrosis, and the majority of donors are parents.

Preoperative Evaluation of Donors

As the procedure involves risks for healthy donors, a complete clinical evaluation including standard bloodwork, pulmonary function test, and chest-computed tomography scan, should be performed to properly assess family members as potential donors. Three-dimensional multidetector computed tomography angiography, which is useful to display the complex pulmonary arterial and venous anatomy, may be also necessary to evaluate and guarantee well-functioning pulmonary lobar grafts. Relatives within the third degree or a spouse, aging 20–60 years, preferably compatible in terms of blood type and organ size, may be selected as donors. Negative clinical history, no active medical problems, no significant pulmonary pathology or recent infection, no previous thoracic operation on the side to be donated, and forced expiratory volume in 1 s >85 % of predicted are among the important donor inclusion criteria. A satisfactory psychosocial evaluation should be provided, as well as the recognition of absence of coercion. All donors should be informed not only of the potential morbidity associated with donor lobectomy, but also on the potential unforeseen outcomes with regard to pulmonary function and its chronological recovery.

Living Lung Donation: Procedure

Living-donor lung transplant consists of two donor lobectomies, the recipient bilateral pneumonectomy, and lung implant. It requires three adjacent operating rooms, and careful coordination and timing of the anesthetic inductions of both the donors and the recipient. Once the recipient pneumonectomies have been completed the lobes are implanted sequentially: the right and left lower lobes of the two donors in place of the whole right and left lungs. The lower lobes are preferred because of their larger size and more suitable surgical anatomy. The recipient operation is performed under general anesthesia through a transverse thoracosternotomy (clamshell) incision, and cardiopulmonary bypass is usually needed to allow simultaneous reperfusion of both lobes. Postoperative care of both donors and recipient is similar to that instituted following “regular” lung resections and deceased donor lung transplantation.

When compared to conventional lobectomies, lobectomy in a lobar donor is associated with a greater risk of complications (Table 4.5). According to previous reports, approximately 4 % of live lung donors experienced an intraoperative complication and 5 % of donors experience complications requiring surgical or bronchoscopic intervention [38]. Overall reported complications have been described in 20–60 % of living lobar donors [37, 39]. The need for a thoracostomy tube either for persistent drainage of pleural effusions or for air leaks is quite frequent.

Table 4.5 Drawbacks and complications of living lobar lung donation

Potential risk for two healthy family members

Postoperative bleeding requiring reoperation
Persistent pleural effusions or air leaks requiring thoracostomy tube
Pulmonary artery thrombosis
Bronchopulmonary fistula, bronchial stricture necessitating dilatation
Empyema, infection
Phrenic nerve injury
Difficult breathing due to collapsed lung
Abnormal heart rhythms
Unforeseen degree of DONORS' permanent loss of lung function

A rare, though significant complication, is pulmonary artery thrombosis, while other, more unusual complications include reoperation because of bleeding, bronchopulmonary fistula, bronchial stricture necessitating dilatation, unresponsive pericaditis, empyema, infection, and phrenic nerve injury. Difficult breathing due to collapsed lung, and heart problems including abnormal heart rhythms, have also been described. Although donor morbidity can be considered relatively high, fortunately there have been no reports of donor mortality in the literature following donor lobectomy.

Previous experiences with live lung donors [40] described at 1- and 2-year postoperative pulmonary function testing an average decrease of 17 % in forced vital capacity (FVC), 15 % in forced expiratory volume in 1 s (FEV_1), and 16 % in total lung capacity (TLC) from preoperative values. Chen et al. [41], however, observed that both FVC and FEV_1 recovered constantly up to more than 90 % of the preoperative value within 1 year after donor lobectomy, and there was a significant increase in both FVC and FEV_1 12 months postoperatively.

Recipient and Graft Outcomes After Living Lung Transplantation

Given the physiology of lobar transplantation, the postoperative management of LDLLT is different from standard deceased donor lung transplantation. Since the entire cardiac output is flowing through two relatively undersized lobes, postoperative lung edema, and hemodynamic instability may be frequent. However, the reduction in pulmonary arterial pressure and pulmonary vascular resistance within the first year attests to the ability of two lobes to accept a normal cardiac output.

Other immediate postoperative complications include primary graft failure, hemorrhage requiring re-thoracotomy, cardiac tamponade, renal failure, phrenic nerve palsy, and left recurrent nerve palsy. Tracheostomy or reintubation may be required in case of delayed functional recovery of grafts. Postoperative pulmonary function testing

shows a gradual improvement in pulmonary function (FEV_1, FVC, and FEF25–75) in living lobar recipients during the first 12 months posttransplant, which is comparable to cadaveric lung transplant recipients.

The very high incidence of late lung injury, characterized histologically as obliterative bronchiolitis (OB) and physiologically as the bronchiolitis obliterans syndrome (BOS), affects also the grafts from living donors. Even though its incidence appears lower than the reported rates in cadaveric lung transplantation, it is responsible for the great majority of late deaths. The incidence of BOS is much greater in children and there is a clear relationship between the frequency of early acute rejection and the incidence of BOS. As opposed to cadaveric double lung transplantation in which rejection almost always presents in a bilateral fashion, rejection episodes in the lobar recipients are predominantly unilateral, with only 20–25 % of cases presented bilaterally. Diabetes, hypertension, and renal dysfunction are frequent complications of lung transplant that are presumed to stem from the long-term use of immunosuppressive medication.

LDLLT appears to provide similar or better survival than cadaveric lung transplantation. As reported by Bowdish et al. [37] in a cohort of 123 patients, actuarial survival with this procedure was 70 %, 54 %, and 45 % at 1, 3, and 5 years respectively, similar to the actuarial survival reported for double-lung cadaveric transplantation from the International Society for Heart and Lung Transplantation Registry (74 %, 59 %, and 49.5 % at 1, 3, and 5 years, respectively). There was no difference in actuarial survival between adult or pediatric recipients of living lobar lung transplants. The St. Louis Children's Hospital reported similar results in 38 pediatric LDLLT recipients, while in the Brazilian group experience [42] 1-year and 3-year survival was 62.5 % and 56 %, respectively.

In the 2008 official report of the Japanese Society of Lung and Heart-Lung Transplantation the 5-year survival was 74.6 %, but at the lung transplant centers at Okayama and Kyoto Universities [43] the 5-year and 10-year survival rate after LDLLT was 88.8 % and 83.1 %, respectively. Deaths occurring within 30 days of transplantation are largely due to infection or primary graft failure, while deaths occurring between 30 days and 1 year after transplantation are usually due to infectious etiologies. Infection has consistently been the major cause of mortality, which is consistent with the large percentage of cystic fibrosis patients enrolled to LDLLT.

Living-Related Pancreas Transplantation

Pancreas transplant remains a useful option for beta cell replacement in insulin-dependent type 1 diabetes mellitus. Deceased donor pancreas donation rates have been decreasing since 2005, and the number of pancreas transplants has consequently decreased every year. Based on OPTN data 227 deceased pancreas transplants have

been performed in 2012, in comparison with 433 of 2008, and 277 in the Eurotransplant area. Pancreas transplantation from living-related donors has also significantly declined in the past decade, mainly due to important postoperative morbidity of the donors, and concerns about outcomes after solitary pancreas transplant. OPTN data displays only one living-donor pancreas transplant from 2008 to 2012, and in the Eurotransplant registry there is no report of this procedure from 2008 to 2012.

Fundamental to this procedure is the proper selection of donor, which is crucial for optimizing the quality of the donated organ and for protecting the donor physically and psychologically. The donor should be younger than 45 years, with an ideal body mass index, and in excellent physical condition. Other characteristics include normal results of glucose homeostasis tests and absence of anti-insulin and anti-islet antibodies.

Procedure

Elective distal pancreatectomy in a young and fit donor can be performed with limited morbidity. Pancreas procurement is generally performed through a subcostal or midline abdominal incision.

Summarized operative steps include a gentle pancreas dissection off the splenic surface. Subsequently, the splenic vessels are identified, and the main trunks of both the splenic artery and vein are divided proximal to the splenic branches. A vascular plane between the pancreas and portal vein is bluntly dissected to define the narrowest portion of the pancreas. The pancreatic neck can then be divided, and both ends of the pancreatic duct are identified. Only a segment of the pancreas is transplanted; the vessels used for engraftment (splenic artery and vein) are shorter and smaller in diameter. Laparoscopic and robotic donor pancreatectomy for living-donor pancreas and pancreas–kidney transplantation have also been successfully performed [44]. The recipient operation is not very different from its cadaver counterpart.

Postoperative care of donors is not unlike that of any other patient undergoing a major abdominal procedure, and focus on adequate pain control and frequent monitoring of hemoglobin, blood sugar, amylase levels, and urinary output. Careful attention should be paid to “subclinical” signs of spleen infarction or injury. Surgical complications include spleen rupture, blood loss, relaparotomy, pancreatitis, pancreatic leak or fistula, pancreatic abscess and pancreatic pseudocyst, wound infection, incisional hernia, and small-bowel obstruction. The risk of becoming diabetic represents the most serious medical complication of living donation, and deterioration in insulin secretion and glucose tolerance at 1 year after donation has been frequently reported.

Recipient Outcomes After Living Donor Pancreas Transplantation

Postoperative complications for live pancreas recipients are similar to those seen for deceased donor recipients, and include bleeding, thrombosis, pancreatitis, infections, and rejection [45]. Given the small tributary vessels and the higher incidence of thrombosis, aggressive anticoagulation strategies are essential during the perioperative period, and antiplatelet drugs should be administered indefinitely. Vascular thrombosis is an important cause of segmental pancreas graft loss, while other reasons for graft loss in the early posttransplant phase include deep infections and graft pancreatitis. Rejection is less common with respect to deceased donor pancreas transplants; serum hyperglycemia is frequently the first warning signaling of pancreas allograft rejection, but by that late time, the function of the pancreas allograft has already been significantly compromised.

Overall, there are no significant differences in graft survival rates for living donor vs. deceased donor cases, with 1 year patient and graft survival rates of approximately 80 % and 90 %, respectively. Experience from a large center has shown that donor morbidity has significantly been reduced in the recent years, but the results on both graft and recipient outcome for all technically successful living donor and deceased donor are approximately equal now [46].

Conclusion

Organ transplantation, one of the most fascinating medical advances of the last 50 years, is a way of giving the gift of life to patients with end-stage organ disease. However, despite numerous educational campaigns and media promotions, the number of deceased donors has not increased in the recent years. Living-related organ transplantation represents the best resource for patients for whom cadaveric transplantation is unsuitable, or those who have deteriorated clinically to the point of transplant ineligibility while waiting for a cadaveric donor. Living organs turn out to be an established source of grafts to face a severe shortage of human organs.

However, although living-related donation has become a popular practice, and constitutes a safe and valuable option for some types of transplants, the inherent minimal, however unavoidable risk posed to the life of a healthy person who donates to save or improve the life of a patient in need, have led many physicians to be either very cautious in tapping this source or reluctant to promote it. Living donation may be a suitable feasible option for critically ill children in end-stage disease, due to both short and long-term favorable outcomes.

The willingness to invest in living transplant procedures, as well as the provision of a ‘safe’ environment through the establishment of dedicated staff for the entire process, and adequate donor/recipient perioperative care, are essential to expand the pool of living donors. Living donation should never be proposed if the best medical judgment indicates that transplantation cannot reasonably be expected to yield the intentional

clinical benefit. Careful candidate evaluation and selection, along with a periprocedural qualified expertise, are crucial to face the major concerns regarding morbidity and mortality in donors.

The future of living transplantation depends on many factors, such as the potential to improve physical and psychological outcomes of donors, better identification of outcomes for specific disease states, improvements in both graft and recipient survival rates, and financial deliberations.

Center experience leads to better outcomes, and experienced centers should assist in training the more novice centers. Given the low national volume of some living-related transplantations, it is likely preferable to concentrate these live procedures in a few excellent centers until volumes and experience increase. Successful programs of living donation will necessarily involve a multidisciplinary approach with medical, radiological, and surgical alternatives to transplantation, and a wide range of ancillary services.

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5. Intensive Care of the Deceased Multiorgan Donor: One Donor, Nine Lives

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Introduction

Solid-organ transplantation is the only definitive treatment option for individuals with end-stage organ failure. Transplantation medicine has undergone significant evolution over the past few decades with advancements in surgical techniques; improvements in immunosuppression regimens; understanding the immunologic interplay between the donor and recipients; and intensive care of donors and organ preservation techniques. Despite the dramatic success, the organ supply/demand issue remains at the crux of transplantation medicine. Leaders in transplantation have pushed the bar to include extended criteria donors, creation of novel preservation solutions to minimize injury during storage and transport, and invention of normothermic, ex-vivo organ perfusion techniques to resuscitate organs that would have otherwise been rejected.

The last and least tapped area in transplant medicine is the donor management strategies in the intensive care unit prior to organ retrieval. Only approximately 15–20 % of donors end up being suitable candidates for donation [1]. There are many factors

associated with this low figure including family refusal, technical challenges, suboptimal criteria, and logistic issues; however, adequate resuscitation of donors is key to preserve organ function and viability. Intensivist-lead donor organ donor management has been associated with increased number of organs for transplantation [2].

One of the critical challenges to organ donor management stems from the profound pathophysiologic changes associated with brain death. Brain death-induced hemodynamic instability and inflammation-mediated organ injury can render suitable organs unfavorable for transplantation. Hence central to donor management is to minimize brain death-induced and iatrogenic organ injury (e.g., Ventilator-induced lung injury).

In addition, different organs may have competing interests with respect to the optimal management therefore, balancing individual organ needs can prove to be challenging at times. In this chapter we will review the scope of pathophysiologic changes that occur during brain death, the management strategies to address these changes, organ-specific management strategies, and donation after cardiac death.

Pathophysiologic Changes During Brain Death

Hemodynamic instability and shock has the potential to complicate all brain dead donors and jeopardize the viability of organs. This is the result of a complex interplay between autonomic, hemodynamic, endocrine, immunologic, and coagulopathic changes associated with the process of brain death. Pathophysiologic changes can be divided into the three phases outlined below (Fig. 5.1):

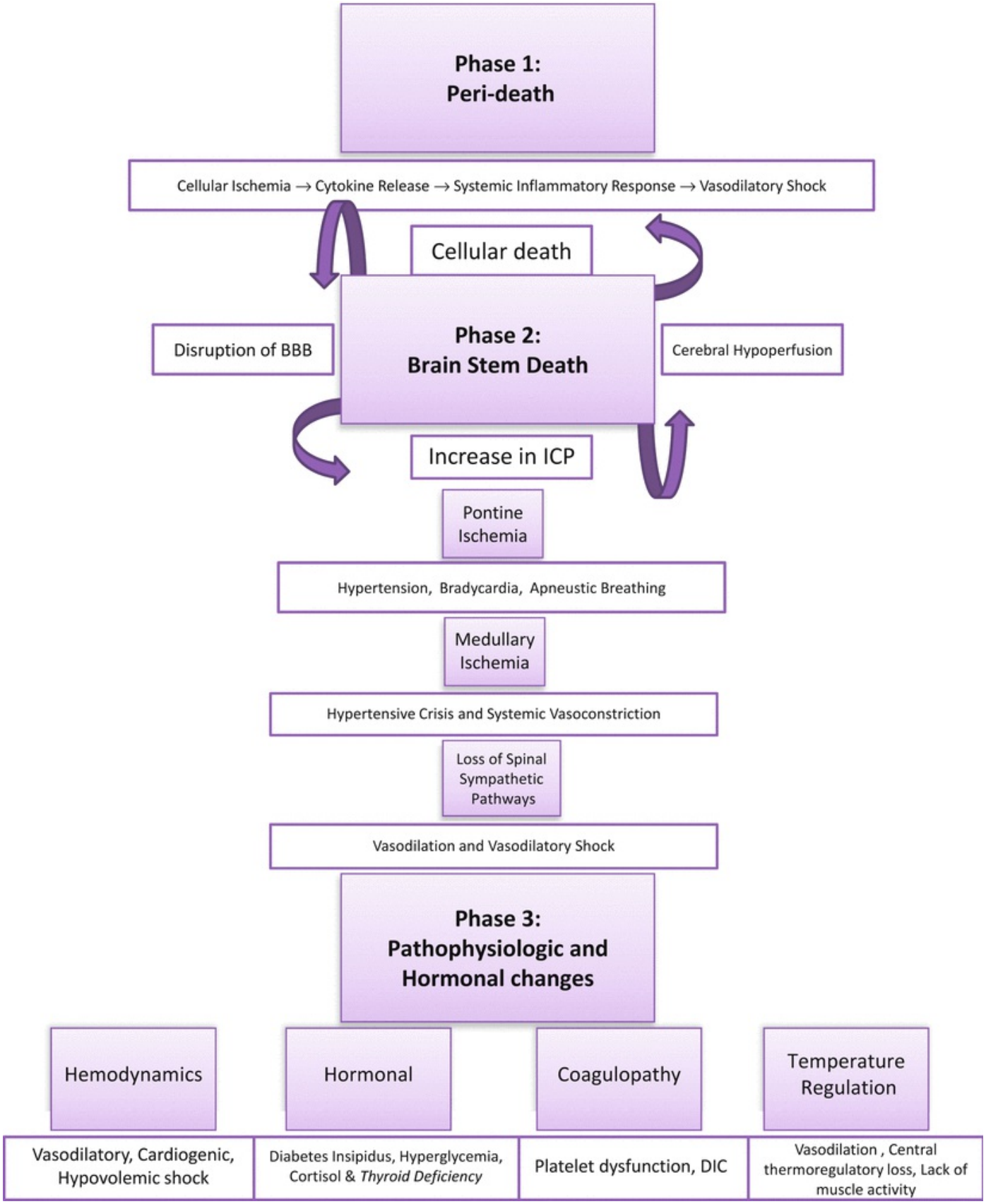

Fig. 5.1 Pathophysiologic changes during brain death. *BBB* blood brain barrier, *DI* diabetes insipidus, *DIC* disseminated intravascular coagulopathy, *ICP* intracranial pressure

First Phase: Peri-Death

Just prior to the development of brain death, it is very common to see the early development of hemodynamic instability and metabolic disruptions. The primary insult that progress to brain death often leads to cellular ischemia, disruption of the blood brain barrier, and release of cytokines resulting in a systemic inflammatory response. Systemically this could manifest early as vasodilatory shock.

Second Phase: Brain Stem Death

Once the elevated intracranial pressure (ICP) induces cerebral hypoperfusion, a vicious cycle ensues of global brain ischemia potentiating more edema, further compromising of blood flow until cessation of circulation occurs. In the last stages of this process, brain stem herniation results from mass effect and brain stem death. This occurs in a rostrocaudal direction. Pontine ischemia occurs first resulting in the classic "Cushing's response " from a mixed vagal and intense sympathetic stimulation causing bradycardia, hypertension, and an apneustic-breathing pattern. Medullary ischemia follows which is the beginning of the hypertensive and extensive systemic vasoconstrictive process given the unopposed sympathetic stimuli. This is followed by a dramatic release of catecholamines [3, 4]. Tissue hypoperfusion can develop given the systemic vasoconstriction. Finally, a sudden decrease in systemic vascular resistance manifesting as vasodilatory shock is the final step resulting in loss of spinal sympathetic pathways. The anterior and posterior pituitary gland impairment is also manifested at this stage.

Third Phase: Pathophysiologic and Homeostatic Changes After Brain Death

Hemodynamics

A complex pattern of hemodynamic changes can occur, which can rapidly progress to cardiac arrest, if untreated. Not all changes; however, are seen with every donor and factors associated with etiology of brain death, time course of the process of death and duration of support after brain death can alter the hemodynamic responses.

Cardiac Dysfunction

Cardiac dysfunction occurs after brain death due to a combination of catecholamine-mediated subendocardial ischemia during the sympathetic surge; increased intracellular calcium concentration inducing oxygen-free radicals; myocardial gene expression; and thyroid hormone depletion. Eight-nine percent of patients with no preexisting heart disease have been found to develop cardiac dysfunction following brain death [5, 6]. The role of thyroid hormone depletion remains an area of controversy; however, rapid

loss of free triiodothyronine seen after brain death has been associated with depletion of ATP, increased anaerobic metabolism, and impaired cardiac contractility.

Vasomotor Tone

Loss of spinal sympathetic tone, cytokine, and inflammatory mediator release, and cortisol deficiency contribute to vasodilatory shock following brain stem death. Circulating cytokines and inflammatory mediators are released through three mechanisms: the sympathetic outflow surge during medullary death, necrotic brain tissue and ischemia-reperfusion injury from the hypertensive-vasoconstrictive crisis followed by a loss of vasomotor tone [7–9]. Brain death has been associated with more than 100-fold increased in concentrations of IL-6 and other inflammatory markers such as TNF and IL-10. Higher concentrations of IL-6 just prior to organ procurement has been associated with lower number of organs procured for transplantation and lower six-month hospital-free survival in recipients [10].

In addition, recruitment of leukocytes, oxygen-free radicals, and capillary leak are seen [11]. Central cortisol deficiency that results from loss of adrenocroticotropic hormone release can further potentiate the loss of vasomotor tone through down-regulation of catecholamine receptors.

Volume Status

Regardless of blood pressure, patients are often volume depleted. Unrecognized intravascular volume depletion due to factors before death is not uncommon and is often not manifested until loss of vasomotor tone. Blood loss associated with trauma, hyperosmotic therapy such as mannitol and third spacing of fluid in the setting of inflammatory mediators can all contribute to volume depletion. This is further exacerbated by the development of diabetes insipidus with loss of the posterior pituitary function and is seen in over 80 % of brain dead patients [3]. To further exacerbate this, hyperglycemia (from insulin deficiency or attempts to correct hypernatremia with a dextrose solution) can also result in a free water diuresis. Careful attention to volume status during donor management is crucial.

Hormonal Changes

Anterior and posterior pituitary failure renders the clinical picture susceptible to further imbalances that potentiate instability. The degree of hormonal deficiency present has been a significant area of controversy and while largely supported in animal studies, has not consistently been seen in human studies [12–17].

Cortisol

A state of cortisol deficiency occurs after loss of release of adrenocorticotropic hormone from the anterior pituitary. Impairment in the donor's stress response and sensitivity to catecholamines ensues following brain death. Activated inflammation leads to pro-inflammatory mediators and expression of their receptors on organs which make them more susceptible to immune-mediated injury [18] putting them at higher risk of acute rejection compared to living donors. Modulation of the immune response at the level of the donor is an area of much interest [19–23].

Antidiuretic Hormone

Diabetes insipidus occurs in over 80 % of brain dead donors [24]. The resulting inappropriate diuresis, hyperosmolality, and hypernatremia can affect the viability of potential organs. If the etiology of the shock is unrecognized, aggressive resuscitation with normal saline has the potential to worsen the hypernatremic state.

Thyroid Hormone

Impaired inotropy, depletion of ATP, and the development of lactic acidosis may stem from a rapid drop in free triiodothyronine levels. Impaired secretion of thyroid stimulating hormone and loss of peripheral conversion is thought to be the mechanism for depletion of free triiodothyronine.

Insulin

A drop in insulin secretion results in systemic hyperglycemia, intracellular hypoglycemia, and a resulting energy deficit. This can result in a transition to anaerobic metabolism, further exacerbating a lactic acidosis that may be present from tissue hypoperfusion and thyroid depletion.

Coagulopathy

Disseminated intravascular coagulopathy and platelet dysfunction are common causes of coagulopathy seen after brain death. Necrotic tissue induces the release of thromboplastin and plasminogen activator leading to DIC in 28 % of donors [25]. In addition, microthrombus formation can be seen from stasis resulting from vasoconstriction during the sympathetic surge.

Temperature Regulation

Given the central role of hypothalamus in temperature regulation, this process is disrupted following brain death. In addition, the loss of muscular activity leads to an impairment in heat production and this is process is exacerbated by the vasodilated state

that ensures following spinal sympathetic outflow cessation.

Donor Management

The most significant principle behind donor management is that best practice ICU care continues beyond brain death including resuscitation end points, lung protective ventilation, and preventative infectious measures. Physicians must be cognoscenti of the fact that the care and interventions they provide during the donor management will carry over to impact graft function following transplantation.

Hemodynamics

Arterial hypertension occurs early during brain ischemia but is often self limited. Treatment with short acting agents such as sodium nitroprusside or esmolol are recommended in these cases [26] to keep systolic blood pressure <160 mmHg and mean arterial pressure <90 mmHg.

Fluid

When hemodynamic instability develops, fluid repletion is the first step to reverse tissue hypoperfusion as more than 80 % of brain-dead organ donors have shock. Careful attention to the development of diabetes insipidus and appropriate early management is crucial before a significant diuresis and hypovolemia ensues. Specific end points of fluid resuscitation include a MAP >65 mmHg; a systolic blood pressure >90 mmHg; heart rate of 60–120 min^{-1}; urine output of at least 0.5 cc/kg/h; a central venous pressure of 8–12 cm H_2O and hemoglobin of at least 10 g/dl (or hematocrit of 30) [26–28]. Early serial lactate monitoring is also recommended to evaluate success of resuscitative efforts [26, 29]. One observational study found that inadequate resuscitation of donors was associated with increased inflammatory response (IL-6 and TNF) and loss of organs for transplantation [30].

In donors with refractory hypotension or low ejection fraction more hemodynamic monitoring is recommended. Traditionally monitoring has been performed using a pulmonary artery catheter; however, given the limitations associated with the use of central venous pressure and pulmonary artery occlusion pressures to predict preload responsiveness and due to increasing availability of less invasive strategies, clinicians are moving away from placing pulmonary artery catheters to determine fluid responsiveness [31, 32]. More sensitive parameters of fluid responsiveness such as pulse pressure variability (PPV), stroke volume variability (SVV), systolic pressure variability, extravascular lung water measurements and transpulmonary thermodilution and ultrasound assessment of inferior vena cava are all minimally invasive or

noninvasive novel techniques that are increasingly being used in organ donor management.

A challenge in donor management, particularly for the multiorgan donor, stems from the fact that different organ systems have different desirable targets for fluid status with the lungs preferring a more intravascularly deplete environment; while the kidneys require more judicious fluid administration (see Table 5.1 for organ specific considerations). Use of highly sensitive and specific measures of fluid responsiveness such as PPV and SVV helps with precise volume control in multiorgan donors. A large randomized control trial is underway to examine whether protocolized donor care using PPV, CI, and MAP, targets are associated with increased organ recovery from brain dead donors (MOnIToR Trial) [33].

Table 5.1 Organ-specific considerations

Lung transplant	Judicious fluid administration Minimization of ventilator associated lung injury via lung protective ventilation Protocolized donor management strategies Consideration of ex-vivo lung perfusion for marginal lungs
Heart transplant	Serial echocardiograms if initial demonstrates impairment Minimization of high-dose beta agonists (leads to down regulation of beta receptors)
Liver transplant	Avoid excessive increase in central venous pressure (congestion) Avoid hypernatremia (aim Na <150 meq)
Kidney transplant	Euvolemia Avoid nephrotoxic insults (medications, contrast if can avoid or adequately hydrate) Lowest dose vasopressors

Traditionally during a period of instability and increased oxygen demand, a red cell transfusion to achieve hematocrit >30 % or hemoglobin >10 g/dl is recommended [34]; however, in more recent years after extrapolation from other transfusion trials in the intensive care settings and the inflammatory risks associated with older blood, more conservative thresholds are recommended (hemoglobin of 7–9 g/dl) [29, 35, 36].

Use of hydroxyethyl starches for fluid resuscitation in organ donors has been associated with increased risk of acute kidney injury, renal replacement therapy, and delayed graft function and thus should be avoided [37, 38]. While initial favorable experiences were reported with their use for liver transplant leading to less fluid administration, no outcomes of number of organs procured or organ function were reported in its initial evaluation [39]. While the use of albumin makes sense physiologically, particularly in the case of significant volume resuscitation, no good evidence to this date supports its use as initial choice for resuscitation. After significant resuscitation with crystalloid, if a patient proves to have ongoing fluid requirements, it is not unreasonable to consider albumin in the setting of low serum albumin levels [40].

Inotropes and Vasopressors

Often fluid resuscitation is inadequate to meet hemodynamic and tissue perfusion goals and therefore vasopressors and or inotropes have become the mainstay of therapy. The critical care community has been moving away from using dopamine as first line agent given the side effect profile including significant arrhythmias [41]. However, in potential kidney transplant donors, the use of low-dose dopamine was associated with the reduced need for dialysis after transplant [42]. For pure vasodilatory shock, we recommend arginine vasopressin as first line given its dual impact of blunting diabetes insipidus as well as its catecholamine sparing action by targeting vasopressin receptors. Low-dose vasopressin (<2.5 units/h) is not only sufficient to raise the mean arterial pressure but has also been found to be associated with favorable kidney, liver, and heart graft function [43]. A recent retrospective review evaluating patients managed with vasopressin compared to its absence was associated with increased graft recovery rates in the vasopressin group [44]. Finally, one study comparing vasopressin to epinephrine, demonstrated a higher incidence of cardiac arrest amongst brain dead donors in the epinephrine group compared to vasopressin [45].

Norepinephrine, epinephrine, or phenylephrine are all reasonable second agents of choices depending upon whether the predominant feature is vasodilatory shock or whether there is a lower cardiac contractility. Caution must be exercised with excessive beta agonist therapies as they lead to a down-regulation of beta receptors which has the potential to impair cardiac contractility in the recipient [27].

Regarding inotropic support, dobutamine or milrinone can be used; however, given the high likelihood of component volume depletion or the potential to develop or likely concurrent drop in the systemic vascular resistance, caution must be exercised. In shock due to impaired cardiac contractility and vasodilation, norepinephine with dobutamine or epinephrine may be reasonable choices. Avoiding or minimizing the time exposure to high dose inotropic support, if at all possible, should be strived for given its association with moderate to severe myocardial injury in heart donors [46].

Hormonal Therapy

There has been substantial debate surrounding whether hormonal dysfunction occurs during brain death, its impact on hemodynamics and whether exogenous replacement is beneficial. The largest review to date involved a retrospective analysis of hormonal resuscitation of brain dead donors that demonstrated a greater yield in suitable organs; however, results from subsequent studies and meta-analysis call into question their role [47, 48].

Cortisol

The potential role of cortisol replacement is twofold in donor management: blunting the inflammatory response and for hemodynamic support. The pro-inflammatory setting that ensues following brain death has the potential to render the organs to ischemia reperfusion injury and increased risk for allograft rejection. Early methylprednisone administration (15 mg/kg) is recommended to enhance hemodynamic stability and enhance organ function post transplant. Lower administration of steroids doses from 15 mg/kg of methylprednisone compared to hydrocortisone 300 mg has been evaluated and has been found to be noninferior with regard to pulmonary or cardiac function. In addition, less hyperglycemia was noted [49].

Antidiuretic Hormone

Diabetes insipidus is present in the majority of brain dead donors and if left untreated can induce profound hypotension and hypernatremia. Desmopressin or vasopressin can be administered to reverse the adverse effects of DI and often both agents are needed [43, 50]. Titrating the agents to a goal of 0.5–3 cc/kg/h is desirable.

Thyroid Replacement

Traditionally levothyroxine or triiodothyronine has been recommended in unstable donors, in particular for cardiac support. Conflicting results have called into question their central role in donor management. In a recent meta-analysis evaluating any randomized placebo controlled trials, the role for routine administration was not supported as no significant effect on cardiac index was noted in the pooled analysis. The major limitation of this study lies in the fact that there was only a small proportion of patients who were hemodynamically unstable. One could postulate that this underrepresented population are those ones who could have retrieved the greatest benefit [51]. A large randomized controlled trial that was recently published evaluated the role of oral vs. intravenous thyroid replacement in brain dead donors (NCT00238030, Sharpe MD*). The recently published results have shown that* orally administered T4 is well absorbed and achieves a bioavailability of approximately 91–93 % of intravenous T4 in organ donors. Inotropic/vasopressor requirements and hemodynamic responses following oral or intravenous thyroxine administration were comparable.

Hyperglycemia

Insulin administration is currently the standard of care for brain dead donors in the setting of hyperglycemia. Recommended targets vary from institution to institution with some that are more intensive than other (<180 mg/dl vs. <108 mg/dl) given the results of the more recent critical care trial evaluating intensive insulin therapy [52]. This study,

which evaluated intensive vs. conservative insulin protocol found that the intensive arm was associated with a higher mortality. Interestingly; however, the primary cause of death was cardiovascular suggesting a relationship between intensive insulin therapy and cardiovascular harm. The results of a randomized controlled trial of intensive vs. conservative insulin therapy for brain dead donors to improve renal allograft function is currently underway and could better inform the optimal threshold for the care of the brain dead donor (NCT01140035, Niemann C).

Coagulopathy

To date, no directive evidence based guidelines exist on coagulopathy management specific to donor management; however, some centers aim for a platelet count of >50,000 $\mu 1^{-1}$ and an international normalized ratio <1.5. Administration of platelets and fresh frozen plasma may be warranted prior to retrieval. Alternatively, other centers will only transfuse to reverse coagulopathy in the setting of hemorrhage given the risks associated with transfusion [26, 53].

Hypothermia

While hypothermia has the potential to be associated with adverse hemodynamic consequences including arrhythmias, myocardial suppression, cold-induced diuresis and potassium shifts, mild hypothermia may have a beneficial effect on organ preservation in the pre-retrieval phase and pilot trials are underway to examine the feasibility of therapeutic hypothermia as an-in-vivo organ preservation strategy initiated soon after brain death (NCT01680744, Niemann, C).

Ventilatory Management

Ventilatory management for the brain dead donor has undergone significant evolution over the past few years as there had been a lag in the adoption of lung protective ventilatory strategies in the management of the multiorgan donor. A landmark trial by Mascia and colleagues in 2010 demonstrated a significant increase in the number of lung eligible for donation after employment of a lung protective strategy. They ventilated brain dead donors with 6–8 cc/kg, performed recruitment maneuvers after any disconnection from the ventilator, performed the apnea test on continuous positive airway pressure, and used higher positive end expiratory pressures (PEEP) over 6 h. This was compared to standard ventilatory management with tidal volumes in the range of 10–12 cc/kg. Low tidal volume and high PEEP resulted in a significant increase in donor lung eligibility and procurement [1]. The major limitations of this study; however, included that it remains unclear which particular intervention in their strategy has the greatest impact and the implication for retrieval of other organs other than lungs. If we

were to extrapolate from studies of ventilator associated lung injury and its potential to worsen end organ function, one could postulate that this strategy would have the potential to improve all organs (Fig. 5.2).

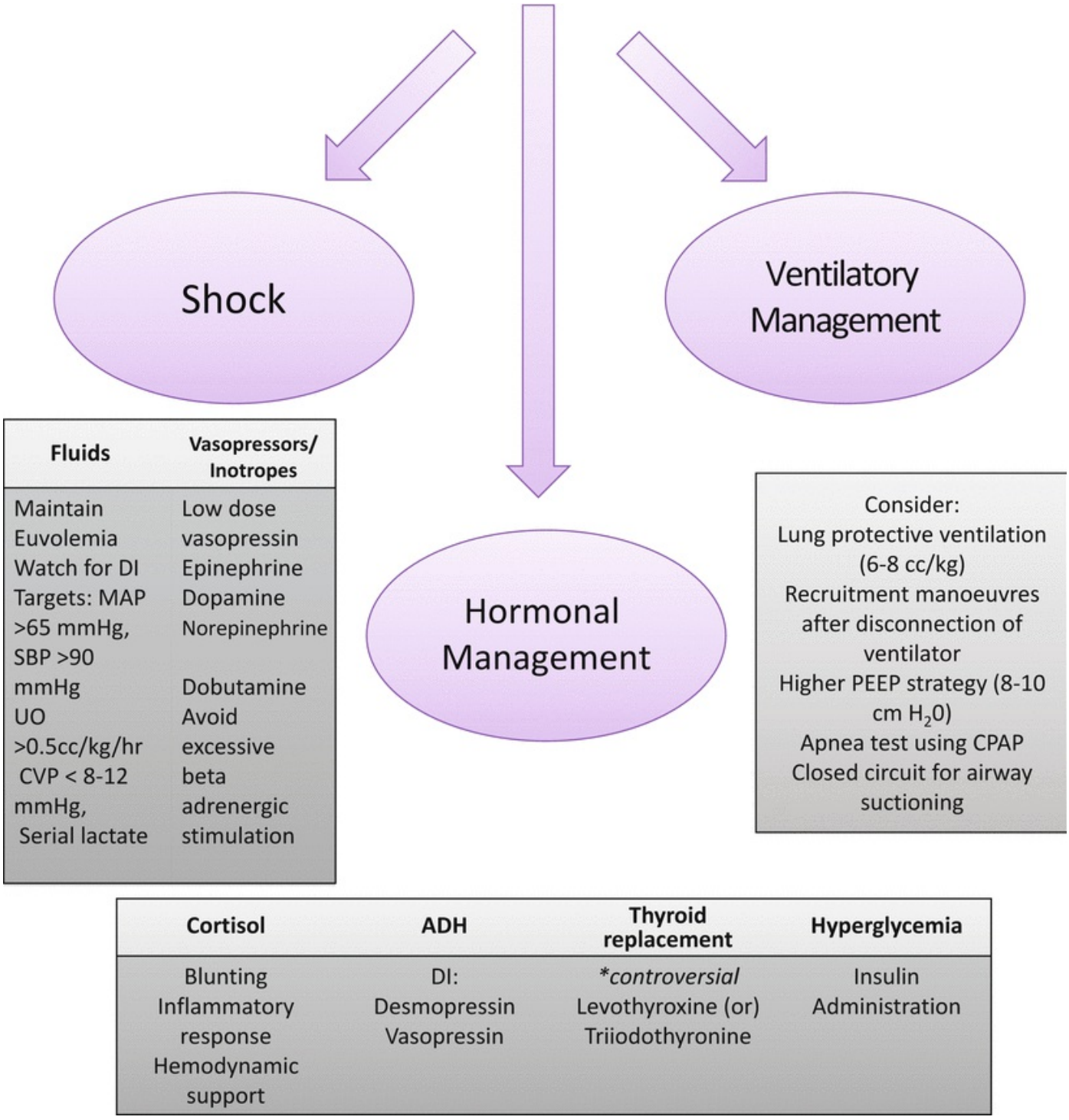

Fig. 5.2 Donor management

Organ-Specific Considerations

Lungs

Unfortunately , lungs are the most fragile organs in the multiorgan donor and most susceptible to the hostile environment of the brain dead donor. Less than 10 % of lungs are procured for transplantation. Therefore, meticulous attention to prevent iatrogenic lung injury is crucial to increase lung procurement. Fluid administration and atelectasis are two crucial reversible factors that have the potential to impair lung function. Previous studies have demonstrated that maintaining a more restrictive fluid balance, whether it be by titrating fluids to a more conservative central venous pressure measurement or extravascular lung water threshold, improve the number of organs that are eligible [43, 54].

One observational study found that preload responsive organ donors (i.e., PPV > 13 %) were less likely to donate lungs for transplantation compared to preload unresponsive donors [10]. This study suggests that inadequate resuscitation may result in loss of lung for donation and thus a balance has to be maintained between conservative fluid balance and optimal resuscitation. Maintaining a central venous pressure less than 7 mmHg increased the number of lungs eligible for transplant but the lower threshold did not have any impact on kidney donation or graft function suggesting that traditional thresholds for central venous pressure quoted in older guidelines could potentially be a modifiable target based upon the organs of interest [55].

Animal studies demonstrated enhanced clearance of pulmonary edema after treatment with beta agonists [56]. This exciting finding prompted a recent randomized controlled trial assessing its use in 500 potential organ donors. Unfortunately, the results did not translate to any clinically significant change in donor oxygenation [57].

Franklin and colleagues evaluated the benefit of introducing donor management protocols to critical care units and created end points to target during resuscitation. This study demonstrated a favorable impact of donor management protocols increasing the number of organs retrieved per donor with the thoracic organs having the greatest expansion in numbers retrieved [58].

Possibly the most exciting area that has contributed to the expansion of the donor pool for lung transplant is the creation and use of normothermic ex-vivo lung perfusion (EVLP) post organ retrieval. EVLP attempts to simulate the in-vivo environment of the organ donor by continuing to provide ventilation and perfusion. After the first clinical experience with its use in Toronto for evaluation of marginal lungs from brain-dead or donation after cardiac death donors, 4–6 h of EVLP converted the lungs, that would have otherwise been ineligible to eligible for transplant with no increase in the rates of primary graft dysfunction, duration or mechanical ventilation or mortality [59].

Heart

The most delicate area of management for potential donor hearts surrounds the use of

beta agonist therapy. Excessive use leads to the down regulation of beta receptors, potentially compromising cardiac contractility after transplant [46]. Approximately 15 % of brain dead donors progress to cardiac arrest [60] as hemodynamic support with traditional measures were not sufficient. Extracorporeal life support has been evaluated for the multiorgan donor and in a small retrospective review of its impact, it not only provided support to facilitate donation of hearts, kidneys, and livers, in three heart transplant recipients whose donors were supported with extracorporeal life support, all recipients had an uneventful recovery after 1 year of follow up [61]. Given the potential for development of an acute cardiomyopathy after brain death declaration and the reversibility of this process, serial echocardiograms may be needed to reevaluate function if originally found to be impaired. Evaluation must occur following resuscitation and the role for serial echocardiography has yet to be determined [26].

Liver

From a hemodynamic perspective, a more liberal fluid management strategy has been found to benefit graft function following liver transplant. Careful titration of PEEP is also essential in order to avoid over-PEEP, an increase in west zone 1, decreasing venous return and resulting in hepatic venous congestion [43, 54, 62].

High serum sodium concentrations in the donor (>155 mq) have been associated with poor graft function [63]. High intraosmotic cell concentrations develop as a consequence and when exposed to a normonatremic environment in the organ recipient, a sudden influx of free water into the cells have the potential to lead to cell edema, lysis, and organ dysfunction. Most organizations recommend targeting a serum sodium of <150 mq [26].

Kidney

In addition to maintaining adequate intravascular fluid status [43, 54], the kidneys are especially susceptible to extra-renal processes including ventilator associated lung injury, excessive use of vasopressors resulting in tissue hypoperfusion, low cardiac contractility impairing renal perfusion, contrast dye necessary for angiography, hyperchloremia from excessive saline resuscitation and pre-brain death nephrotoxic agents (mannitol, antimicrobials). These factors can increase the risk of delayed graft function.

No consensus on the optimal combination of catecholamines has been established but prior research demonstrates that low-dose vasopressors can enhance renal perfusion and graft function; however, when used in excess, in the absence of sufficient intravascular volume repletion, renal hypoperfusion may result [24, 64, 65].

See Table 5.1 for organ-specific considerations.

Donation After Cardiac Death

Donation after cardiac death (DCD) is a method by which patients who do not fulfill brain death criteria can donate organs. Four categories for DCD have been established (Table 5.2). In North America, Maastrich categories 3 and 4 are practiced. During DCD, after a decision is made for withdrawal of life sustaining therapy, the family is approached for the possibility of organ donation if that was consistent with the desires of the patient. Organ procurement occurs after withdrawal of life-sustaining therapy and a necessary time period of cardiac arrest observed by a clinician not part of the transplant team. Different organ groups have different thresholds of time to death during which they choose to proceed with or forgo organ recovery.

Table 5.2 Donation after cardiac death

Maastrich category 1	Dead on arrival	Cardiac arrest and decision not to resuscitate, palliation, declaration of death, consent for donation, extracorporeal life support initiation, assessment for candidacy of donation
Mastrich category 2	Unsuccessful resuscitation	Cardiac arrest and decision not to resuscitate, palliation, declaration of death, consent for donation, extracorporeal life support initiation, assessment for candidacy of donation
Maastrich category 3	Awaiting cardiac arrest	Decision made to withdraw life support, consent obtained from family, assessment for candidacy of organ donation, palliation and elective withdrawal of therapy, declaration of death, assessment of time to death
Maastrich category 4	Cardiac arrest in brain dead donor	Decision made to withdraw life support, consent obtained from family, assessment for candidacy of organ donation, palliation and elective withdrawal of therapy, declaration of death, assessment of time to death

The major difference between donation after brain death and donation after cardiac death is the potential for a more prolonged warm ischemic time following withdrawal of life support. Typically the “optimal” time to death for various organs includes 30 min for liver, 1 h for kidney, and 1 h for lungs. In the age of ex vivo therapeutics, a more prolonged warm ischemic time is tolerated (2 h of warm ischemia in the setting of DCD for lung transplant [59]. DCD has proved to be a critical source of organs in many jurisdictions with outcomes being comparable to that of donation from brain dead donors and currently accounts for 20 % of donor organs [66].

Of utmost importance during the DCD process is the end of life treatment of the patient. Providing adequate analgesia for symptom management and alleviation of suffering during the withdrawal process precedes any organ procurement interventions, which occur following determination of death. At some centers, the process of withdrawal occurs in the ICU with the initiation of indicated sedation and hypoventilation. At other centers, the withdrawal process in its entirety occurs in the operating room.

Conclusion

Meticulous attention to the hemodynamic and hormonal changes that occur as a result of brain death with goal directed intensivist-lead management can have a profound impact on organ eligibility and retrieval rates. While more high-quality research is needed in donor management support, extrapolation, and application of best practice from current landmark critical care trials will likely enhance organ recovery and preserve allograft function.

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6. Anesthetic Management of Donor Organ Retrieval in a Multiorgan Donor

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Introduction

As the need for organs for transplantation continues to increase, supply frequently remains a limiting factor. It was estimated that in 2002, 6679 patients died on organ waiting lists in the United States. This number has continued to grow as the number of indications for organ transplantation has expanded. As the gap between organ demand and organ supply widens, government agencies and regulatory groups, such as the United Network of Organ Sharing (UNOS), continue to explore methods to increase rates of organ donation [1]. Careful patient preparation and anesthetic care during organ retrieval is essential to improve organ viability and graft survival. However, care of multiorgan donors can be challenging given the hemodynamic instability associated with brain death and the specific needs of individual procurement teams [2]. This chapter will describe the unique characteristics of multiorgan donors as patients, the preparation for and process of organ procurement, and the specifics of perioperative

management of multiorgan donors.

Multiorgan Donors

The brain-dead, heart-beating organ donor is often considered the ideal multiorgan donor. Such donors are able to provide a variety of organs and tissues and these organs demonstrate improved viability over non-heart beating donors, more commonly known as donation after cardiac death (DCD) donors . Additionally, cost per organ is reduced significantly for brain-dead, heart-beating donors, when compared to living donors [3]. Prior to the creation of brain death criteria and laws allowing the procurement of organs from brain-dead, heart-beating donors, DCD donors were the most common multiorgan donors. DCD donors represent a large pool of potential donors; however, questions exist regarding the viability of organs retrieved from such donors given the increased warm ischemia time. It has been argued that organs from DCD donors are also less tolerant to cold preservation [4]. Given that the use of DCD donors has the potential to greatly expand the donor pool, some groups and hospital systems are continuing to perform DCD and research ways to improve graft viability in this population of donors [5].

Brain-Dead, Heart-Beating Donors

In 1980, the Uniform Determination of Death Act was enacted and helped to define and differentiate between brain death and cardiopulmonary death. Since this time, the majority of multiorgan donors are brain-dead, heart-beating donors. The benefit of organ retrieval in such patients derives from continuous perfusion of critical organs, thus limiting warm ischemic times. The shortened warm ischemia time has resulted in increased rates of transplantation of organs that are particularly susceptible to prolonged warm ischemia, including heart, lungs, liver, and pancreas [5].

The most common causes of brain death in adults are subarachnoid hemorrhage and traumatic brain injury [6]. In 1968, a Harvard Medical School committee [7] became one of the first groups to closely examine the topic of brain death and irreversible coma. This committee helped to more clearly define brain death, differentiated brain death from severe brain injury, and provided basic guidelines for clinical determination of brain death. Guidelines set forth by this committee form the basis of the neurologic examination used today to determine brain death, including lack of movement to painful stimuli, loss of brainstem reflexes, and apnea. After clinical assessment is consistent with brain death, confirmatory tests may be used at the discretion of the physician, but such tests are not mandatory in the United States. Confirmatory tests may include electroencephalogram, cerebral angiography, transcranial doppler, and cerebral scintigraphy [6].

Care of brain-dead patients is complicated by the multitude of physiologic changes that occur after brain death. Immediately following herniation and ischemia of the medulla, unopposed sympathetic discharges result in release of endogenous catecholamines, vasoconstriction, tachycardia, hypertension, arrhythmias, myocardial ischemia, and decreased perfusion to other vital organs. By the time most patients present for organ retrieval this sympathetic storm has subsided and the clinical picture is that of vasodilation, hypotension, hypothermia, and endocrine deficiency. This period is also associated with release of inflammatory mediators, including interleukins, interferons, and tumor necrosis factor [2].

Endocrine abnormalities are common in brain-dead donors. Such abnormalities are often due to pituitary infarction and can result in hemodynamic instability with subsequent negative impacts on graft viability [2]. Many studies have focused on how best to manage the clinical effects of hormonal aberrations and myocardial depression. Recommendations and commonly used medications in brain-dead donors will be discussed further in the "Perioperative Management" section below.

Overall, brain-dead, heart-beating donors afford improved organ viability through continued perfusion of vital organs during the process of procurement. It is of great importance for the anesthesiologist caring for these donors to carefully manage the endocrine dysfunction and hemodynamic instability that follows the diagnosis of brain-death.

DCD Donors

Recently, there has been renewed interest in the use of DCD donors in the United States in order to expand the pool of potential organ donors. DCD donors generally fit into one of two categories; (1) life support withdrawn and organs retrieved with the patient in stable condition (controlled DCD) and (2) unexpected cardiopulmonary arrest and failure to resuscitate (uncontrolled DCD) [4]. Overall, results are mixed as to the viability of organs harvested from DCD donors.

The University of Wisconsin is unique in that this organization has continued to regularly use DCD donors and has documented success with transplantation of kidneys, lungs, liver, and pancreas from such donors. The University of Wisconsin has estimated that DCD donors represent about 10–15 % of all donors in their hospital system [5]. In 2003 the University of Wisconsin Hospital and Clinics Organ Procurement Organization [5] published an evaluation tool that was shown to help determine the suitability of potential DCD donors. Factors used in this evaluation tool identified patient characteristics that are associated with decreased time to expiration after extubation, which impacts a patient's suitability as a DCD donor. Patients were referred to the study team for evaluation when "imminent death" was expected. Characteristics among these subjects that were found to be most associated with decreased time to expiration after

extubation were age greater than 51 years, need for multiple vasopressors, lack of spontaneous respirations after 10 min, oxygen saturation less than 79 %, and presence of an endotracheal tube rather than a tracheostomy [5].

Foley et al. [8] compared outcomes in patients receiving liver grafts from DCD donors and brain-dead donors at the University of Wisconsin. Results demonstrated that graft survival was reduced in the DCD group at both 1 and 3 years. The recipients of liver transplants from DCD donors experienced higher rates of biliary stricture, hepatic artery stenosis, hepatic abscess formation, and biloma formation. Poor outcomes, such as biliary stricture, were more likely to be seen in grafts from DCD donors greater than 40 years old [8].

A similar comparison from the author's institution by De Vera et al. [9] in 2009 also demonstrated reduced graft survival in liver transplants from DCD donors compared with brain-dead donors at 1, 5, and 10 years. This study found that biliary complications were more common in the livers from DCD donors and worse outcomes were found when warm ischemic time was greater than 20 min, cold ischemic time was greater than 8 h, and donor age was greater than 60 years.

In a retrospective analysis by Locke et al. [10] it was found that kidney grafts from DCD donors demonstrated 20 % increased incidence of delayed graft function (DGF) when compared with grafts from brain-dead donors. However, this increased incidence of DGF did not translate into decreased overall graft survival in this analysis. The authors postulate that the lack of difference in long term survival between groups was due to improved tolerance to DGF by the DCD kidneys when compared with grafts from brain-dead donors. It was found that among all kidneys that went on to develop DGF the DCD kidneys had 23–52 % decrease in actual graft loss when compared to kidneys retrieved from brain-dead donors. The group also found that the best outcomes were found in DCD kidneys from donors less than 50 years old or with cold ischemic time less than 12 h [10].

In summary, most available studies indicate that DCD donors can help expand the donor pool and may serve as viable donors when carefully selected.

The Process of Organ Retrieval

Understanding the basic policies and procedures surrounding the procurement of organs will help the anesthesiologist to better care for multiorgan donors. We will primarily discuss these procedures as they relate to brain-dead, heart-beating donors.

Organ Retrieval in Brain-Dead, Heart-Beating Donors

Prior to the declaration of brain-death, a potential donor is identified and evaluated for exclusion criteria. Such exclusion criteria vary between institutions and may include age

greater than 65 years, sepsis, some communicable diseases not treatable with antibiotics, and certain malignancies [11]. Declaration of brain-death is then performed and consent obtained by a physician not directly involved with the process of organ procurement. At this point the patient is transferred to the operating room for organ retrieval.

The anesthesia team assumes care of the brain-dead multiorgan donor from the time of transport from the intensive care unit until aortic cross-clamp. Due to characteristics of both the procedure and the patients, there is potential for considerable blood loss and hemodynamic instability. The anesthesiologist should be prepared for abrupt changes in blood pressure, dysrhythmias, and even possible cardiopulmonary arrest; thus, emergency drugs, invasive monitoring, and the ability to follow blood gases and other laboratory tests should be readily available in the perioperative period [11].

On arrival to the operating room, the patient is placed supine on the operating table and a midline incision is made from suprasternal notch to pubis, followed by sternal opening. Organs retrieved may include liver, heart, lungs, kidneys, bowel, and pancreas. Additionally, nonperfusable tissues can be retrieved including eyes, skin, dura, bones, and heart valves [11].

In the non-heart and lung donor, surgeons first dissect the aorta and inferior vena cava to allow for placement of a flush line in cases of unexpected cardiac arrest. After the chest and abdomen are opened, the liver is mobilized and the inferior mesenteric vein is cannulated to flush the liver [12]. If the pancreas is to be donated it is mobilized after the liver. After the liver, pancreas, bowel, and kidneys are dissected the supraceliac aorta below the diaphragm is prepared for placement of the cross-clamp. Heparin at a dose of 300 units/kg is administered followed by cross clamping of the aorta. Prior to aortic cross-clamping phentolamine, an alpha-adrenergic antagonist , is often also administered given its ability to cause potent vasodilation thus increasing blood flow to donor organs. At this point, the organs are perfused with cold preservative solution and the ventilator can be disconnected. After organ procurement, tissues from the spleen and lymph nodes are used for tissue typing. Clamping of the supraceliac aorta corresponds to the beginning of cold ischemia time and the anesthesia end time [12, 13].

Today, a commonly used alternative technique is the rapid flush technique. This involves an en bloc resection after aortic cross clamping and flushing of preservative solution through the distal aorta. Dissection of the individual donor organs then occurs at the recipient transplant center just prior to transplantation [13].

In the case of heart and lung donors, these organs are removed first. The pericardium is opened and the heart is examined for function. During dissection of the trachea and lungs, pressure on the great vessels and lungs themselves can result in significant hemodynamic instability and difficulty in ventilation. The great vessels are dissected and, following 300 units/kg of heparin, a cardioplegia catheter is inserted in

the ascending aorta. The distal aorta is ligated and an aortic perfusion cannula is placed. The aorta is cross clamped proximal to the innominate artery and at the diaphragm, and cardioplegia solution, lung preservative flush solution, and cold preservative solution for the abdominal organs are infused. The inferior vena cava at the diaphragm is opened to allow for outflow of preservative solution. The superior vena cava and trachea are cut, the heart and lungs are removed, and the remaining organs are then procured [12].

Organ Retrieval in DCD Donors

A physician not involved in the transplant team accompanies the patient to the OR and life sustaining therapies are discontinued. After cardiopulmonary death occurs, the body is cooled with a preservative solution infused through a cannula placed in the aorta. At this point, the abdomen is opened, packed with ice, and the organs quickly removed. If an anesthesiologist is involved, his or her role ends at the time of cardiac death. Anticoagulants and vasodilators are often used in DCD donors, but the timing of their administration in these patients varies between institutions [13].

Perioperative Management

Maintaining hemodynamic stability is the primary goal in caring for brain-dead, heart beating multiorgan donors in the perioperative period. The basic hemodynamic goals should include maintaining cardiac output and perfusion pressure (without excessive use of inotropes), euvolemia, normal acid–base status, and hormonal homeostasis. After brain death, an inflammatory milieu ensues, which has an effect on many organ systems, and, in the long term, may impact organ viability. Many specific treatment strategies have been investigated for use during the process of organ procurement in the multiorgan donor. These treatment strategies will be addressed individually below.

Maintaining Hemodynamic Stability

It is estimated that hemodynamic instability results in the loss of approximately 25 % of potential organ donors, even with aggressive treatment [14]. Hypotension frequently ensues after brain death and can impact eventual graft viability. In the brain-dead donor, hypotension may be secondary to vasodilation, hypovolemia, or cardiac dysfunction and its cause must be elucidated in order to initial appropriate management. After brain death, widespread vasodilation results from the loss of sympathetic outflow from the central nervous system. Hypovolemia is very common in brain-dead multiorgan donors, resulting from neurogenic shock leading to venous pooling, presence of diabetes insipidus, and the use of mannitol and diuretics for elevated intracranial pressure. For these reasons, the most common cause of decreased cardiac output and organ hypoperfusion is hypovolemia [15, 16].

Myocardial dysfunction is also commonly observed in patients following brain death. Studies have estimated that 42 % of potential organ donors have some degree of systolic dysfunction [16]. This is caused most frequently by depletion of catecholamines and changes in myocardial energy storage [17]. Treating myocardial dysfunction and maintaining adequate myocardial perfusion is critical for all patients, but particularly potential cardiac donors. It has been estimated that up to 44 % of potential cardiac donors are not used, most commonly because of decreased systolic function [16].

Given the potential for hemodynamic instability, brain-dead multiorgan donors should be monitored closely in both the intensive care unit and operating room throughout the period prior to aortic cross clamping. Invasive blood pressure and electrocardiogram should be closely followed given the potential for cardiopulmonary arrest, wide swings in blood pressure, and arrhythmias. Atrial and ventricular arrhythmias as well as heart block are not uncommon in such patients given the effects of increased intracranial pressure, myocardial dysfunction, electrolyte disturbances, and loss of vagal innervation. Monitoring fluid balance in such patients is critical, given the potential for hypovolemia and the negative effects of over-hydration, including liver congestion, pulmonary edema, and cardiac failure [12]. Urine output can serve as an excellent indicator of fluid status and organ perfusion in multiorgan donors, with the goal of maintaining urine output greater than 0.5 ml/kg/h; however it must be considered that the frequent presence of diabetes insipidus in brain-dead donors can complicate the use of this parameter [15]. Proposed mechanisms for monitoring intravascular volume status and organ perfusion in multiorgan donors include central venous pressure (CVP) monitoring, echocardiography, noninvasive devices to measure cardiac output, and pulmonary artery catheters [16].

Studies have demonstrated that pulmonary artery catheters and echocardiography are particularly useful for potential cardiac donors. A consensus conference held in 2001 [18] to address management of cardiac donors and improvement in organ viability, recommended the use of pulmonary artery catheters in patients with an ejection fraction of less than 45 % and set forth specific hemodynamic parameters. The hemodynamic goals that were established include, a mean arterial pressure of greater than 60 mmHg, CVP 4–12 mmHg, pulmonary capillary wedge pressure 8–12 mmHg, and cardiac index of greater than 2.4 l/min/m. It is recommended that organ recovery should proceed when these goals are met without excessive inotropic requirements, including dopamine or dobutamine less than 10 μg/kg/min [18]. The United Network for Organ Sharing (UNOS) has incorporated these parameters in their current Critical Pathway for the Organ Donor (Fig. 6.1).

Patient name: _____

Critical Pathway for the Organ Donor

ID number: _____

Collaborative Practice	Phase I Referral	Phase II Declaration of Brain Death and Consent	Phase III Donor Evaluation	Phase IV Donor Management	Phase V Recovery Phase
The following professionals may be involved to enhance the donation process. *Check all that apply.* ❍ Physician ❍ Critical care RN ❍ Organ Procurement Organization (OPO) ❍ OPO coordinator (OPC) ❍ MedicalExaminer (ME)/ Coroner ❍ Respiratory ❍ Laboratory ❍ Pharmacy ❍ Radiology ❍ Anesthesiology ❍ OR/Surgery staff ❍ Clergy ❍ Social worker	❍ Notify physician regarding OPO referral ❍ Contact OPO ref: Potential donor with severe brain insult ❍ OPC on site and begins evaluation Time _____ Date _____ ❍ Ht_____ Wt _____ as documented ❍ ABO as documented _____ ❍ Notify house supervisor/ charge nurse of presence of OPC on unit	❍ Brain death documented Time _____ Date _____ ❍ Pt accepted as potential donor ❍ MD notifies family of death ❍ Plan family approach with OPC ❍ Offer support services to family (clergy, etc) ❍ OPC/Hospital staff talks to family about donation ❍ Family accepts donation ❍ OPC obtains signed consent & medical/social history Time _____ Date _____ ❍ ME/Coroner notified ❍ ME/Coroner releases body for donation ❍ ***Family/ME/Coroner denies donation—stop pathway—initiate post-mortem protocol—support family.***	❍ Obtain pre/post transfusion blood for serology testing (HIV, hepatitis, VDRL, CMV) ❍ Obtain lymph nodes and/or blood for tissue typing ❍ Notify OR & anesthesiology of pending donation ❍ Notify house supervisor of pending donation ❍ Chest & abdominal circumference ❍ Lung measurements per CXR by OPC ❍ ***Cardiology consult as requested by OPC (see reverse side)*** ❍ ***Donor organs unsuitable for transplant—stop pathway—initiate post-mortem protocol—support family.***	❍ OPC writes new orders ❍ Organ placement ❍ OPC sets tentative OR time ❍ Insert arterial line/ 2 large-bore IVs ❍ Possibly insert CVP/Pulmonary Artery Catheter ❍ See reverse side	❍ Checklist for OR ❍ Supplies given to OR ❍ Prepare patient for transport to OR ❍ IVs ❍ Pumps ❍ O_2 ❍ Ambu ❍ Peep valve ❍ Transport to OR Date _____ Time _____ ❍ OR nurse ❍ reviews consent form ❍ reviews brain death documentation ❍ checks patient's ID band
Labs/Diagnostics		❍ Review previous lab results ❍ Review previous hemodynamics	❍ Blood chemistry ❍ CBC + diff ❍ UA ❍ C & S ❍ PT, PTT ❍ ABO ❍ A Subtype ❍ Liver function tests ❍ Blood culture X 2 / 15 minutes to 1 hour apart ❍ Sputum Gram stain & C & S ❍ Type & Cross Match _____# units PRBCs ❍ CXR ❍ ABGs ❍ EKG ❍ Echo ❍ Consider cardiac cath ❍ Consider bronchoscopy	❍ Determine need for additional lab testing ❍ CXR after line placement (if done) ❍ Serum electrolytes ❍ H & H after PRBC Rx ❍ PT, PTT ❍ BUN, serum creatinine after correcting fluid deficit ❍ Notify OPC for ___ PT >14___ PTT < 28 ___ Urine output ___ < 1 mL/Kg/hr ___ > 3 mL/Kg/hr ___ Hct < 30 / Hgb >10 ___ Na >150 mEq/L	❍ Labs drawn in OR as per surgeon or OPC request ❍ Communicate with pathology: Bx liver and/ or kidneys as indicated
Respiratory	❍ Pt on ventilator ❍ Suction q 2 hr ❍ Reposition q 2 hr →	❍ Prep for apnea testing: set FiO_2 @ 100% and anticipate need to decrease rate if PCO_2 < 45 mm Hg	❍ Maximize ventilator settings to achieve SaO_2 98 - 99% ❍ PEEP = 5cm O_2 challenge for lung placement FiO_2 @ 100%, PEEP @ 5 X 10 min ❍ ABGs as ordered ❍ VS q 1° →	❍ Notify OPC for ____ BP < 90 systolic ____ HR < 70 or > 120 ____ CVP < 4 or > 11 ____ PaO_2 < 90 or ____ SaO_2 < 95%	❍ Portable O_2 @ 100% FiO_2 for transport to OR ❍ Ambu bag and PEEP valve ❍ Move to OR →
Treatments/ Ongoing Care		❍ Use warming/cooling blanket to maintain temperature at 36.5° C - 37.5 °C ❍ NG to low intermittent suction →	❍ Check NG placement & output →		❍ Set OR temp as directed by OPC ❍ Post-mortem care at conclusion of case
Medications			❍ Medication as requested by OPC →	❍ Fluid resuscitation—consider crystolloids, colloids, blood products ❍ DC meds except pressors & antibiotics ❍ Broad-spectrum antibiotic if not previously ordered → ❍ Vasopressor support to maintain BP > 90 mm Hg systolic ❍ Electrolyte imbalance: consider K, Ca, PO_4, Mg replacement ❍ Hyperglycemia: consider insulin drip → ❍ Oliguria: consider diuretics ❍ Diabetes insipidus: consider antidiuretics ❍ Paralytic as indicated for spinal reflexes	❍ DC antidiuretics ❍ Diuretics as needed ❍ 350 U heparin/kg or as directed by surgeon →
Optimal Outcomes	The potential donor is identified & a referral is made to the OPO.	The family is offered the option of donation & their decision is supported.	The donor is evaluated & found to be a suitable candidate for donation.	Optimal organ function is maintained.	All potentially suitable, consented organs are recovered for transplant.

Shaded areas indicate Organ Procurement Coordinator (OPC) Activities.

This Critical Pathway was developed under contract with the U.S. Department of Health and Human Services, Health Resources and Services Administration, Division of Transplantation.

Cardio-Thoracic Donor Management

1. **Early echocardiogram for all donors —** Insert pulmonary artery catheter (PAC) to monitor patient management (placement of the PAC is particularly relevant in patients with an EF < 45% or on high dose inotropes.)
   - ❍ use aggressive donor resuscitation as outlined below

2. **Electrolytes**
   - ❍ Maintain Na < 150 meq/dl
   - ❍ Maintain K+ > 4.0
   - ❍ Correct acidosis with Na Bicarbonate and mild to moderate hyperventilation (pCO_2 30-35 mm Hg)

3. **Ventilation — Maintain tidal volume 10-15 ml/kg**
   - ❍ keep peak airway pressures < 30 mm Hg
   - ❍ maintain a mild respiratory alkalosis (pCO_2 30-35 mm Hg)

4. **Recommend use of hormonal resuscitation as part of a comprehensive donor management protocal — Key elements**
   - ❍ Tri-iodothyronine (T3): 4 mcg bolus; 3 mcg/hr continuous infusion
   - ❍ Arginine Vasopressin: 1 unit bolus: 0.5 - 4.0 unit/hour drip (titrate SVR 800-1200 using a PA catheter)
   - ❍ Methylprednisolone: 15 mg/kg bolus (Repeat q 24° PRN)
   - ❍ Insulin: drip at a minimum rate of 1 unit/hour (titrate blood glucose to 120-180 mg/dl)
   - ❍ Ventilator: (See above)
   - ❍ Volume Resuscitation: Use of colloid and avoidance of anemia are important in preventing pulmonary edema
     - ❍ albumin if PT and PTT are normal
     - ❍ fresh frozen plasma if PT and PTT abnormal (value ≥ 1.5 X control)
     - ❍ packed red blood cells to maintain a PCWP of 8-12 mm Hg and Hgb > 10.0 mg/dl

5. **When patient is stabilized/optimized** repeat echocardiogram. (An unstable donor has not met 2 or more of the following criteria.)
   - ❍ Mean Arterial Pressure ≥ 60
   - ❍ CVP ≤ 12 mm Hg
   - ❍ PCWP ≤ 12 mm Hg
   - ❍ SVR 800-1200 dyne/sec/cm^5
   - ❍ Cardiac Index ≥ 2.5 l/min/M^2
   - ❍ Left Ventricular Stroke Work Index > 15
   - ❍ dopamine dosage < 10 mcg/kg/min

HIV = human immunodeficiency virus; VDRL = Venereal Disease Research Laboratory; CMV = cytomegalovirus; CVP = central venous pressure; CXR = chest x-ray; CBC = complete blood count; UA = urinalysis; C & S = culture and sensitivity; PT = prothrombin time; PTT = partial thromboplastin time; RBCs = packed red blood cells; ABGs = arterial blood gases; H & H = hemoglobin and hematocrit; BUN = blood urea nitrogen; Rx = prescription; Bx = biopsy; FiO_2 = fraction of inspired oxygen; PCO_2 = partial pressure of carbon dioxide; NG = nasogastric tube; EKG = electrocardiogram; SaO_2 = arterial oxygen saturation; PEEP = positive end-expiratory pressure; VS = vital signs; BP = blood pressure; HR = heart rate; PaO_2 = partial arterial oxygen pressure; DC = discontinue.

Fig. 6.1 Critical pathway for the organ donor (Reprinted with permission from the United Network for Organ Sharing, Richmond, VA, 2013)

Treatment of hemodynamic instability in brain-dead multiorgan donors can be complicated by many factors unique to this patient population. In the setting of brain death, bradycardia is resistant to atropine thus beta-agonists such as epinephrine or isoproterenol should be readily available [11]. Use of vasopressors and inotropes in multiorgan donors can affect organ viability, and this patient population requires particularly careful titration of these agents. Following brain death, there is loss of catecholamine stores. Use of exogenous catecholamines can be beneficial in maintaining perfusion pressure and inotropy while helping to avoid overuse of fluids in resuscitation which can result in volume overload and negative impacts on graft function. However, high-dose dopamine and norepinephrine use has been associated with poor graft outcomes in many studies [16]. The negative effects of exogenous catecholamines in multiorgan donors is related to increases in myocardial oxygen demand, further catecholamine depletion of the myocardium, and decreased blood flow to the kidneys and liver [12].

Treating Endocrine Dysfunction

Hormonal abnormalities are common after brain-death, with diabetes insipidus being one of the most commonly encountered endocrine aberrations [15]. Hormone replacement, including the use of thyroid hormone, corticosteroids, arginine vasopressin, and/or insulin, has been shown to have beneficial effects on hemodynamic stability of the donor and organ viability [18–20]. Studies investigating the use of combined hormone therapy, with use of thyroid hormone replacement, corticosteroids, and vasopressin together, have demonstrated improvements in graft function when compared to the use of individual hormones alone [17].

Arginine Vasopressin

Following brain death, dysfunction of the pituitary and hypothalamus frequently occurs, resulting in lack of secretion of antidiuretic hormone (ADH) and neurogenic diabetes insipidus (DI) [12, 17]. If not aggressively treated, the subsequent high urine output can cause severe hypovolemia, hyperosmolality, and electrolyte disturbances, including hypernatremia, hypokalemia, hypermagnesemia, and hypocalcemia. Generally, a hypotonic solution is used with the goal of replacing urine output and baseline maintenance fluid requirements. Electrolytes should be monitored regularly, at least every 4–6 h, with goals of serum sodium less than 155 mEq/l and serum potassium greater than 3.5 mEq/l [12].

Arginine vasopressin (AVP) is commonly used in cases of severe DI in brain-dead

patients, and studies have demonstrated improved hemodynamics and reduced inotropic requirements when such patients are treated with AVP [21]. Pennefather et al. [21] compared hemodynamic parameters in brain-dead multiorgan donors treated with low dose AVP infusion (dose of 300 mU/kg/min) versus saline infusion. This study determined that the use of AVP was associated with reduced dopamine requirements and improved blood pressure without worsening of hemodynamic parameters or graft function. Pennefather et al. [21] concluded that use of a vasoconstrictor, such as AVP, in brain-dead patients is beneficial given the loss of vasomotor tone often found in such patients and that, frequently, inotropic agents are inappropriately used in this setting. It is recommended that AVP be given as a low dose infusion in order to avoid the potential for end organ damage with high dose vasoconstrictor use.

Desmopressin , a synthetic vasopressin analogue commonly used to treat DI, has an antidiuretic-to-pressor ratio of 2000 to 4000:1 compared with a ratio of 1:1 seen with AVP. Studies comparing treatment of multiorgan donors with desmopressin versus AVP have demonstrated that both are equally effective in treating DI symptoms, such as high urine output, and resulted in equivalent kidney graft outcomes. Thus, both desmopressin and AVP are effective in treating DI in the brain-dead patient; however desmopressin is less effective in elevating system blood pressure in such patients given its profile as a weak vasopressor when compared to AVP [17].

Thyroid Hormone Replacement

Use of triiodothyronine (T3) and thyroxine (T4) replacement in brain-dead patients has been found to be associated with improvement of metabolic acidosis and hemodynamic instability in brain-dead patients while lowering requirements for both bicarbonate and inotropic agents [15]. It has been postulated that brain death results in decreased levels of T4 and T3, hormones necessary for storage of energy in the myocardium, ultimately resulting in hemodynamic instability [14, 17].

Replacement of thyroid hormone does, however, remain controversial in this patient population. Goarin et al. [22] postulated that T3 is low in brain-dead patients and that this euthyroid sick syndrome must be a component of myocardial dysfunction seen in this patient population. However, when comparing patients given a placebo versus T3, no difference was found in hemodynamic parameters between groups or in echocardiography interpretation. Other studies have demonstrated similar results and found little correlation between thyroid hormone levels and degree of hemodynamic instability.

In contrast, other studies have demonstrated hemodynamic improvement in patients treated with thyroid hormone. In one study by Salim et al. [14], hemodynamically unstable brain-dead patients showed a statistically significant decrease in vasopressor requirements after treatment with T4. Such studies indicate that use of thyroid hormone

replacement improves energy metabolism in the myocardium thus reducing acidosis and improving cardiac function.

Given that T4 is a prohormone which is converted to biologically active T3, T3 is generally considered first line for thyroid hormone replacement in this patient population [17]. Given the continued controversies regarding the efficacy of thyroid hormone replacement in brain-dead multiorgan donors, there remains much variability between institutions in its use for this indication and further research is indicated.

Corticosteroids

At the time of brain death, a multitude of proinflammatory cytokines are released, resulting in hemodynamic instability. It has been postulated that corticosteorid use attenuates the release of these proinflammatory mediators, benefitting both the donor throughout the organ procurement process and the recipient after subsequent organ transplantation. Additionally, the stress response associated with brain death can result in adrenal insufficiency, providing another proposed mechanism for benefit of corticosteroids in brain-dead patients [23].

Controversy exists regarding the degree of adrenal suppression found in brain-dead multiorgan donors. Dimopoulou et al. [24] found that adrenal cortisol secretion was impaired after stimulation in brain-dead patients; however, other studies have demonstrated normal adrenal function in brain-dead patients during the period surrounding organ procurement. Several studies have failed to demonstrate an abrupt decline in cortisol levels, indicating that perioperative steroid replacement may not be advantageous in brain-dead multiorgan donors 16].

Although some studies question the need for corticosteroids in all organ donors, many institutions and transplantation programs include corticosteroids in the perioperative care of multiorgan donors. Currently, UNOS recommends a bolus dose of methylprednisolone in brain-dead multiorgan donors in preparation for organ procurement and has included this in the Critical Pathway for cardio-thoracic donors (see Fig. 6.1).

Insulin

Hyperglycemia is a common manifestation of brain death, and many studies have looked to determine if the cause is pancreatic dysfunction secondary to brain death. Overall, evidence shows that endocrine pancreatic function remains effective in most patients after brain death and that hyperglycemia is, most likely, secondary to peripheral insulin resistance [2, 25]. Exogenous catecholamine administration and physiologic stress place brain-dead patients at particular risk for development of insulin resistance [17]. Regardless of the cause, treatment of hyperglycemia is necessary in brain-dead patients as hyperglycemia has been shown to result in osmotic diuresis, electrolyte

abnormalities, and worsening of graft function. Lung and heart grafts appear to be particularly susceptible to the negative effects of hyperglycemia [2, 18].

Anesthetic Agents During Organ Procurement

After brain death spinal reflexes remain intact, and thus spontaneous movement is possible in brain-dead patients. During organ procurement it is recommended that neuromuscular blocking agents be given in order to prevent movement and provide optimal surgical conditions [2, 12]. It is commonly recommended that brain-dead donors do not require anesthesia during organ procurement. However, the fact that brain-dead multiorgan donors demonstrate increased release of catecholamines in response to painful stimuli during organ procurement has prompted several studies to examine the role of opioids in such patients. A study by Fitzgerald et al. [26] found that a dose of 7 μg/kg of fentanyl did not suppress this catecholamine discharge or attenuate the hemodynamic response to surgical stimulation when compared to placebo during organ procurement in brain-dead donors.

Like opioids, volatile anesthetics have been hypothesized to attenuate the sympathetic response to surgical stimulation. However, few studies have closely examined this hypothesis. Some transplant teams do advocate the use of volatile anesthetics in brain-dead multiorgan donors, instead for their potential ability to reduce ischemia-reperfusion injury in donor organs [27].

Treating Coagulopathy

Preventing anemia in organ donors is key to maintaining adequate cellular oxygenation and improving graft viability. It is recommended that patients be transfused prior to and during organ procurement to maintain a hemoglobin greater than 10 g (g)/dl and hematocrit greater than 30 %, international normalized ratio (INR) less than 2, and platelet count greater than 50,000 μl^{-1} [2, 11]. Brain-dead patients are at particular risk for anemia and coagulopathies given the potential for blood loss due to associated injuries and the hypothermia that ensues after the onset of brain death. The presence of necrotic brain tissue also results in the release of tissue fibrinolytic agents and plasminogen activators, which cause further bleeding potential. Treatment with packed red blood cells, platelets, and coagulation factors is recommended to treat coagulopathy and anemia. Given the potential for thrombosis in donor organs, however, antifibrinolytics are not recommended for use in multiorgan donors [12].

Ventilation Strategies

Careful management of ventilation and oxygenation is important for all multiorgan donors , but is of particular necessity when lung donation is expected. As a result of

many factors, it is estimated that lungs are only procured from approximately 16 % of donors [16]. During the period surrounding trauma and brain death, many factors can damage lungs, including aspiration, contusion, pneumonia, and mechanical ventilation. Pulmonary edema is also common after the onset of brain death. The sympathetic storm immediately following brain death results in intense alpha adrenergic stimulation leading to increases in afterload, ventricular dysfunction, and eventual pulmonary edema. Increased release of cytokines also changes pulmonary capillary permeability, resulting in pulmonary edema [16].

Mechanisms to protect lungs and improve oxygenation in brain-dead multiorgan donors include ventilator recruitment maneuvers to prevent atelectasis, reducing the risk of barotrauma, decreasing potential for aspiration, and restricting fluids [12, 16]. Fractional inspiration of oxygen should be maintained at approximately 40 % in heart and lung donors to minimize oxygen toxicity. Ventilatory parameters should be adjusted to maintain a partial pressure of carbon dioxide around 35–45 mmHg and partial pressure of oxygen around 74–150 mmHg. Brain death is associated with lower rates of oxygen consumption and carbon dioxide production, thus ventilation parameters should be reduced to prevent respiratory alkalosis and left-ward shift of the oxyhemoglobin dissociation curve, and arterial blood gases should be monitored regularly [12].

Temperature Regulation

Brain death results in progressive hypothermia due to the loss of hypothalamic temperature regulation and the inability to compensate for heat loss [12, 15]. Thus, brain-dead multiorgan donors must be actively warmed with warming blankets and fluid warming devices. According to the UNOS Critical Pathway, temperature should be maintained between 36.5 and 37.5 °C (see Fig. 6.1). Hypothermia in multiorgan donors increases the risk of coagulopathies, dysrhythmias, and tissue ischemia due to a leftward shift of the oxyhemoglobin dissociation curve, particularly when core temperature drops below 32 °C [12].

Conclusion

Given the unique characteristics of multiorgan donors, anesthetic care of this patient population can be challenging. The onset of brain death results in homeostatic dysfunction and hemodynamic instability. Improving organ viability through close monitoring and careful management by the anesthesia team is increasingly important as the gap between organ demand and supply continues to widen.

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Part II
Lung Transplantation

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7. Preoperative Evaluation and Preparation for Lung Transplantation

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Introduction

The first human lung transplant was performed in 1963 by Dr. James Hardy, with the recipient surviving 18 days before ultimately dying from renal failure and malnutrition [1]. In subsequent decades, many lung transplant procedures were performed with outcomes limited by perioperative complications such as bronchial anastomosis dehiscence and allograft rejection. With the advent of cyclosporine in 1980 and improved surgical techniques, lung transplant outcomes improved significantly with the first successful long-term single lung and double transplantation performed in 1983 and 1986 [2, 3]. Currently, lung transplantation is an acceptable treatment for an increasing number of patients with end-stage lung disease, as over 43,000 lung transplantation procedures have been performed worldwide over the last three decades [4].

Indications for Lung Transplantation

Lung transplantation was initially limited to patients with interstitial lung disease and pulmonary arterial hypertension and patients with cystic fibrosis were excluded due to concern for infectious risks. The indications for lung transplantation have broadened over time to include diseases of the pulmonary parenchyma, airways, and vasculature. Chronic obstructive pulmonary disease (COPD) has been the leading indication for lung transplantation since 1995, accounting for over one-third of all procedures worldwide [4]. In the past decade, the percentage of recipients with COPD has steadily declined while the percentage of recipients with interstitial lung disease (ILD) has risen to almost 30 % of all lung transplants. Cystic fibrosis (CF), despite being a contraindication to lung transplantation in the early 1980s, now accounts for almost 17 % of all lung transplants. Pulmonary arterial hypertension, although previously was considered a dominant indication, now only accounts for 3 % of all lung transplants. This decline most likely reflects the improvement in medical care of patients with pulmonary arterial hypertension over the past few decades. Other less common indications include non-CF bronchiectasis, COPD secondary to α-1 antitrypsin deficiency, and sarcoidosis. One indication that has become more prominent in the last decade is re-transplantation, which accounts for 2.6 % of all lung transplants [4]. The most common reason for re-transplantation is bronchiolitis obliterans syndrome (BOS) , a progressive airflow obstruction in the absence of other etiologies [5].

Candidate Selection

The median survival of lung transplant recipients during the last decade has been 5.6 years [4]. This shortened survival compared to survival from other solid organ transplants, combined with the scarcity of organs, has directed the adoption of contraindications to lung transplantation by the lung transplant community. The presence of significant extra-pulmonary organ dysfunction precludes isolated lung transplantation, however acceptable outcomes have been achieved with dual organ transplantation such as combined heart and lung transplantation or liver and lung transplantation [4, 6]. Another absolute contraindication is recent malignancy, except for non-melanomatous skin cancer. Solid organ transplant recipients are at increased risk for the development and progression of malignancies secondary to required immunosuppressive therapy, although some immunosuppressants used in lung transplantation appear to have anti-neoplastic effects [7]. Documented noncompliance with medical therapy, absence of a consistent and reliable social support network, and severe and poorly controlled psychiatric illness are also considered to be absolute contraindications to lung transplantation. Ongoing or recent cigarette use, illicit drug abuse, and alcohol abuse are associated with depression, poor social support, and noncompliance; these are also considered to be strong contraindications to lung transplantation [8]. Lastly, uncontrolled or untreatable pulmonary or extra-pulmonary infection prior to lung

transplantation also results in increased perioperative mortality and often patients who are actively listed for lung transplantation are placed inactive until such infections are controlled.

Age over 65 years was once considered to be an absolute contraindication for lung transplantation, however more recent studies suggest comparable short term outcomes to younger recipients [9] . From 2006 until present, approximately 10 % of all lung transplants were performed in patients older than 65 years with 3 % of recipients being 75 years or older at the time of lung transplantation [4]. Coronary artery disease can complicate the recipients listed for lung transplantation. Based on the published clinical reports, the incidence of CAD was estimated to be 11 % [10]. The value of routine coronary angiography before lung transplantation has been questioned. As elderly patients with end stage lung disease are no longer excluded from having transplantation, the decision to evaluate for CAD has to be made based on the patient's risk factors. No difference was seen in immediate postoperative and long-term outcomes in patients with or without coronary artery disease in a recently published study [11]. Patients with significant CAD can be treated by preoperative percutaneous coronary intervention or in some patients by open revascularization at the time of transplantation. Both strategies produced equivalent effects on survival and perioperative mortality [12].

Both malnutrition and obesity are associated with increased mortality after lung transplantation [13]. Most lung transplant centers consider a body mass index (BMI) less than 18 kg/m^2 or greater than 30 kg/m^2 to be a relative contraindication for transplantation, although acceptable outcomes in patients beyond these BMI limits have been achieved [14]. Mechanical ventilation prior to lung transplantation has been associated with a 1.5 times increased risk of mortality in the first year after lung transplantation [4]. More recent data suggests that despite increased intensive care unit length of stay, patients requiring mechanical ventilation have similar survival; as a result more patients are bridged to lung transplantation with mechanical ventilation [15]. Previous thoracic surgery and prior pleurodesis may lead to increased perioperative risk of complications such as bleeding and may stand as a relative contraindication to lung transplantation depending upon the experience of the transplant surgeon [16].

A number of pretransplant infections have significant implications for lung transplant candidacy. Chronic viral infections such as HIV and hepatitis C have historically been considered absolute contraindications to lung transplantation. More recent evidence suggests that lung transplantation can be successfully performed in infected recipients with special attention toward immunosuppression and other pharmacologic therapies [17, 18]. Chronic infection or colonization with fungus or other microorganisms should also be considered when evaluating a potential recipient. Patients with a positive respiratory culture for aspergillus are at increased risk of tracheobronchitis and anastomotic complications after lung transplantation, which can

influence survival [19]. Non-tuberculosis mycobacterial infections occur in approximately 9 % of patients and can result in significant morbidity and permanent graft dysfunction [20, 21]. Thus, attempts must be made at eradicating these pathogens prior to lung transplantation to avoid complications. Multidrug-resistant gram negative bacteria can also be a source of significant complications post lung transplant and can also influence overall survival [22]. Burkholderia cepacia complex, specifically genomovar III (B cenocepacia), is associated with worse survival during the first six postoperative months in those patients infected prior to lung transplantation [23]. However, other subtypes of Burkholderia cepacia have similar posttransplant survival compared to the general cystic fibrosis population [24]. As a result, most lung transplant centers consider prior infection with Burkholderia cepacia complex a contraindication to lung transplantation.

Disease-Specific Guidelines for Candidate Selection and Listing

Listing for lung transplantation should be considered at a time when survival from advanced lung disease is considered to be less than survival after lung transplantation. To date, there are no prospective, randomized, well-powered studies that outline the timing of referral and listing for lung transplantation. Current recommendations from the International Society of Heart and Lung Transplantation are based upon small studies and expert opinion consensus (Table 7.1). Early referral to a lung transplant center, prior to the anticipated need for listing, is highly encouraged to initiate patient and family education and to identify and correct potential barriers to lung transplantation (e.g. obesity, substance abuse, psychosocial support).

Table 7.1 Disease-specific criteria for listing for lung transplantation

Chronic obstructive pulmonary disease BODE index of at least 7 or at least 1 of the following: • FEV1 < 20 % predicted and either DLCO < 20 % predicted or homogenous distribution of emphysema • History of recurrent exacerbations with associated hypercapnia (pCO_2 > 50 mmHg) despite aggressive medical management • Pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy
Idiopathic pulmonary fibrosis Histologic or radiographic evidence of UIP and any of the following: • A 10 % or greater decrement in FVC during 6 months of follow-up • A decrease in pulse oximetry <88 % during a 6-minute walk test • Honeycombing on high-resolution CT of the chest • A DLCO <39 % predicted
Cystic fibrosis

• FEV_1 < 30 % predicted or rapidly declining lung function • Pulmonary hypertension • Increasing oxygen requirements • Baseline hypercapnia (pCO_2 > 50 mmHg)
Pulmonary hypertension • Persistent NYHA class III or IV symptoms on maximal medical therapy • Low or declining 6-min walk • Failing therapy with intravenous epoprostenol or equivalent • Cardiac index <2 L/min/m^2 • Right atrial pressure >15 mmHg

Adapted from Orens et al. [46]

Preoperative Evaluation

To determine the appropriateness for listing for lung transplantation, several studies should be performed during the evaluation process. Complete pulmonary function testing, including measurement of FEV_1, FVC, lung volumes, and bronchodilator challenge when appropriate, allows the medical team to gauge the severity and trajectory of lung function. A 6-min walk test assesses exertional hypoxia and functional status of a potential candidate. Radiographic imaging of the chest with chest x-ray and CT scan is necessary to measure the size of the chest cavity and to exclude any underlying malignancy or invasive pulmonary disease. A ventilation and perfusion scan provides information about segmental pulmonary blood flow and helps determine which lung to transplant in the case of single lung transplantation. As preoperative assessment, an electrocardiogram and left heart catheterization is performed in individuals over 45 years of age. An echocardiogram and right heart catheterization can be performed to assess for cardiac contractility and underlying pulmonary hypertension respectively, which can affect the priority on the transplant waiting list. A barium swallow, pH probe, and esophageal manometry help gauge the presence and severity of gastroesophageal reflux and risk of microaspiration, which may be clinically significant in patients with known esophageal dysfunction such as scleroderma. Age-appropriate health maintenance exams for malignancy screening such as a colonoscopy, PAP smear, and mammogram along with bone densitometry to assess for osteoporosis and fracture risk are also required to exclude these comorbidities.

Hematologic and biochemical laboratory assessment through blood sampling is essential to assess for end-organ disease. A sputum culture is necessary to assess for fungal or bacterial colonization of the tracheobronchial tree and to assess for indolent invasive pulmonary disease. Serologies to assess for cytomegalovirus, Epstein-Barr virus, hepatitis B and C virus, toxoplasmosis, varicella, and herpes simplex virus

exposure are utilized to determine antimicrobial prophylaxis and risk stratify recipients after lung transplant. Additional immunologic testing includes HLA typing, blood group typing, and HLA antibody assessment to ensure an adequate donor and to avoid immediate complications such as hyperacute rejection.

Multidisciplinary Approach to Evaluation

Due to the inherent complexity of evaluating a chronically ill patient for an extraordinary intervention—transplantation—transplant programs almost uniformly consist of a number of health care providers who have complementary areas of expertise. Involvement of the many team members begins with the detailed evaluation process that typically extends over several days. In the initial years of lung transplantation, evaluations were uniformly conducted in the inpatient setting; however, for well over a decade now, the testing and consultations are accomplished in the outpatient arena. In addition to the testing outlined above, patients and a family member undergo individual evaluations by the team members listed in Table 7.2. These consultations provide an opportunity for the team members to assess the medical, surgical, psychosocial, and financial issues that impact a patient's suitability for lung transplant listing. In addition, they provide an opportunity for the team members to educate the patient and family, particularly with respect to the risks and benefits of transplant for the specific patient, and the rigors of post transplant care. Lastly, the multiple meetings and consultations provide opportunities to make an informed decision regarding whether transplant is consistent with life goals and whether the patient wishes to endure the complex surgery, commit to the demanding medical regimen and attend routine follow-up appointments essential for long term survival after lung transplantation.

Table 7.2 Transplant team members

Transplant pulmonologist
Transplant surgeon
Transplant infectious disease physician
Transplant cardiologist
Transplant nurse coordinator
Transplant pharmacist
Social worker
Nutritionist/dietician
Financial coordinator
Behavioral health specialist/psychiatrist
Pulmonary rehabilitation specialist/physical therapist

Speech pathologist
Primary care physician

At the conclusion of the evaluation process, most transplant programs have a candidate selection committee meeting to make team recommendations and decisions on transplant candidacy. At the meeting, each team member who interacted with the patient is provided an opportunity for input, specifically expressing concerns that impact the patient's candidacy. After discussion, one or more recommendations are made to the patient and referring provider, including a decision to list for transplant, decline for transplant, or defer listing for one more reasons. When patients are referred prior to becoming critically ill on high flow oxygen, there are often remediable issues that can be addressed to alleviate concerns and convert an unacceptable candidate for transplant into an eligible patient. Prime examples of such issues are obesity or malnutrition, deconditioning, and completion of vaccinations. More complex and nebulous are issues related to significant comorbidities, including coronary artery or other vascular disease, psychiatric issues related to depression and/or anxiety, and degree of psychosocial and financial support to ensure medication compliance and optimal post transplant care.

Lung Allocation Score

Prior to May 2005, lungs were allocated to recipients based upon waiting time on the transplant list. This practice resulted in early listing for noncritical lung dysfunction, large wait lists, frequent deactivation and activation of lung transplant candidates, and extremely long wait times for transplantation. Patients often waited well over 2 years for lung transplantation, which led to high mortality rates for patients with more rapidly progressive pulmonary disease such as idiopathic pulmonary fibrosis. In May 2005, the policy for lung allocation was changed by the Organ Procurement and Transplantation Network (OPTN) to a system that allocates lungs based upon a lung allocation score (LAS) , which reflects medical urgency rather than waiting time [25]. The LAS reflects an adjusted scale from 0 to 100 that represents a weighted combination of a potential recipient's predicted survival during the following year on the wait list and predicted survival during the first year following a transplant. The LAS considers the net benefit of the transplant to the candidate as well as clinical urgency; it is calculated using pre-transplant clinical diagnostic data that is predictive of both pre- and post transplant outcomes (Table 7.3). In the years following implementation of the LAS, the wait times for lung transplantation decreased and the LAS for recipients increased, reflective of the clinical urgency for lung transplantation in recipients with advanced respiratory failure [26].

Table 7.3 Factors involved in the lung allocation score calculation

Factors predicting wait list survival	Factors predicting transplant survival
Forced vital capacity	Forced vital capacity (B, D)
Pulmonary arterial diastolic pressure (A, C, D)	Pulmonary capillary wedge pressure (D)
Oxygen requirement at rest (A, C, D)	Mechanical ventilation
Age	Age
Body mass index	Creatinine
Diabetes mellitus, insulin-dependent	Functional status
Functional status	Diagnosis
6-min walk distance	
Mechanical ventilation	
Diagnosis (A, C, D)	
pCO_2	

Diagnosis group: A—COPD/emphysema; B—pulmonary hypertension, congenital heart disease; C—cystic fibrosis, bronchiectasis; D—interstitial lung disease/IPF
Adapted from Orens and Garrity [47]

Type of Lung Transplant

Until 1989, the most common type of lung transplantation in the United States was combined heart lung transplantation; currently double lung transplantation has become the most common type of transplant. Single lung transplantation may extend the limited supply of donor organs to more patients, but provides less lung function as a buffer for complications and is also associated with worse long-term survival [4]. Elderly patients may benefit more from single lung transplantation due to the lower perioperative risk [27]. However, the lower survival associated with single lung transplantation may be more associated with age-related morbidity and mortality rather than type of transplant procedure. The underlying lung disease is also an important factor in determining which type of transplant procedure to perform. Bilateral lung transplantation is the procedure of choice in patients with suppurative lung diseases such as cystic fibrosis, due to the risk of crossover infection from the native lung to the transplanted allograft. Bilateral lung transplantation is more common in patients with COPD, which may be due to the increased risk of hyperinflation of the native lung resulting in compression of the transplanted allograft in single lung recipients and improved survival after the onset of chronic allograft failure in double lung recipients [28, 29]. Currently the majority of single lung transplant procedures are performed in patients with IPF. Single lung transplantation appears to have a short term survival benefit whereas double lung transplantation confers a long term survival benefit in recipients with IPF [30]. Combined heart lung transplantation was originally the

procedure of choice in patients with pulmonary hypertension. Now patients with pulmonary hypertension generally receive double lung transplantation due to the plasticity of the right ventricle, which recovers shortly after lung transplantation. Heart lung transplantation is generally reserved for patients with concomitant lung and heart disease, which cannot be treated by lung transplantation alone, such as congenital heart disease with Eisenmenger syndrome.

Virtual Crossmatch

Patients who have circulating antibodies that recognize human leukocyte antigens (HLA) on the donor organ are at increased risk of developing hyperacute rejection and graft failure shortly after lung transplantation. Even low levels of antibodies reactive to donor lung antigens may lead to upregulation of immune cell pathways resulting in rejection; thus more sensitive antibody tests are critical to reduce the risk of antibody-mediated damage after lung transplantation. HLA antibody testing provides an accurate assessment of a potential transplant recipient's sensitization status and identification of the HLA antigens targeted by those antibodies. The tests to identify HLA antibodies are based upon reactions of antibodies to panels of lymphocytes (complement-dependent lymphocytotoxicity) and to purified HLA antigens couples to microspheres (Luminex, flow cytometry). Historically, prospective serologic crossmatches using serum from the recipient and lymphocytes from the donor were utilized to predict alloimmune reactivity; these were often time-consuming and limited lung donors from geographically distant locations. Crossmatch results can now be predicted prior to lung transplantation when the patient's antibody specificities are identified using recombinant single HLA antigen bead testing and potential donor HLA type is known. The Luminex single HLA antigen bead assays report antibodies in terms of titer (dilutional positivity) and strength (mean fluorescent intensity), which may not correlate with a positive prospective crossmatch or have clinical relevance. More sensitive assays, such as C1q reactivity that is associated with complement fixation of the antibody, are more sensitive at predicting a positive prospective crossmatch and risk of antibody-associated allograft dysfunction [31].

Induction Strategies at the Time of Lung Transplantation

One main strategy of induction agents is to suppress the potentially robust T cell immune response to the allograft in the immediate postoperative period after lung transplantation. Virtually all lung transplant programs use high dose methylprednisolone for immunosuppression prior to implantation of the donor organ. Currently available induction agents are adjuncts to steroids and deplete existing T cells and/or interrupt T cell activation and proliferation. These induction strategies can be classified into two

groups: Monoclonal and polyclonal agents. Despite these theoretical benefits, the use of induction agents in lung transplantation remains controversial, with only 53 % of lung transplant programs using induction therapies [4]. The decision for using induction therapy and which type must be made on a patient-centered approach based upon comorbidities to balance the effects of immunosuppression on both risk of infection and rejection.

The most common monoclonal induction agent utilized in lung transplantation is basiliximab. This monoclonal antibody binds to the alpha-subunit of the interleukin-2 receptor on T cells, thus inhibiting their activation and proliferation, but not depleting existing T cells. Basiliximab in typically administered intraoperatively and again on the fourth postoperative day [32]. Overall, it is well tolerated with few reports of cytokine release syndrome after administration. Due to its immunosuppressive effects and tolerability, basiliximab is used in approximately 37 % of patients [4].

The second type of monoclonal induction agent used in lung transplantation is alemtuzumab . This monoclonal antibody binds to the CD52 antigen present on most T cells and some B cells, leading to lymphocyte depletion via a complement-mediated and direct cellular cytotoxic pathway [33]. Induction with alemtuzumab has been associated with a greater freedom from the development of both acute and chronic rejection in lung transplant recipients [34]. To reduce the risk of a cytokine storm syndrome, acetaminophen, solumedrol, and diphenhydramine are typically administered prior to the infusion of alemtuzumab. Alemtuzumab has been associated with more profound lymphopenia and pancytopenia compared to other induction agents, and antimicrobial prophylaxis with valganciclovir and voriconazole or itraconazole is typically administered for up to six months after lung transplantation to reduce the risk of opportunistic infections [35, 36].

Anti-thymocyte/lymphocyte globulin (ATG) is a polyclonal antibody preparation that nonspecifically binds to antigens on the surface of T cells, resulting in lymphocyte depletion. Binding of these antibodies to numerous T cell surface receptors may also result in anergy and immune tolerance [37]. Currently, ATG is used as an induction strategy in approximately 11 % of lung transplant patients. ATG is typically dosed on day one after lung transplantation and then daily for up to 3–5 days after the initial dose. There are few reports of serum sickness and anaphylaxis with the administration of ATG, and thus acetaminophen, diphenhydramine, and steroids are used as premedications.

Ventilatory and Hemodynamic Support

Cardiopulmonary bypass (CPB) has been the standard method for those patients who require hemodynamic support during lung transplantation. In general, candidates who have pulmonary hypertension with a mean pulmonary artery pressure greater than 30

mmHg or have a transpulmonary artery pressure greater than 20 mmHg require some type of hemodynamic support during lung transplantation. More recently, extracorporeal membrane oxygenation (ECMO) has been used for hemodynamic support due to a lower risk of perioperative problems including bleeding complications [38]. Historically, pretransplant ECMO has been considered a contraindication for lung transplantation because of increased perioperative morbidity and overall mortality compared to conventional support. More recently, ECMO has been utilized as a bridge to lung transplantation with comparable post-lung transplantation short and mid-term outcomes as well as low mortality [39–41]. Most patients who require ECMO support pretransplant require concurrent mechanical ventilation, which can result in ventilator-associated pneumonia and lung injury, multisystem organ failure, and ultimately increased mortality in the setting of lung transplantation [42]. To decrease the risk that mechanical ventilation may add, some transplant centers are exploring "awake ECMO" in which nonintubated patients are supported with ECMO as a bridge to transplantation [43, 44]. ECMO support in patients who are awake and not intubated represents a promising bridging strategy, which should be further evaluated to determine its role in patients with end-stage lung disease awaiting lung transplantation. In general, patients are considered candidates for ECMO as a bridge to lung transplantation who are <65 years old and previously robust, and who have an acute to subacute decompensation in their respiratory status. Another strategy used in patients with high urgency hypercapnic respiratory failure is interventional lung assist technology, which removes carbon dioxide and decreases respiratory acidosis by an extracorporeal membrane device such as the Novalung. In one report of 12 patients, who were bridged to transplantation using Novalung interventional assist therapy, 80 % were alive at 1 year after transplantation. The duration of lung assist varied from 4 to 32 days [45].

Summary

In conclusion, preoperative evaluation and preparation of lung transplant recipients require a team based multidisciplinary approach with transplant pulmonologists providing the action plan. With this approach, lung transplant recipients are well prepared before the surgery; this improves the opportunities and potentially the outcome of patients with end-stage lung disease. Management of acutely ill lung candidates is evolving with newer approaches such as "awake" ECMO and interventional lung assist devices holding promise.

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8. Bilateral Sequential Lung Transplantation: What the Anesthesiologist Needs to Know About the Surgical Approach

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Introduction

Lung transplantation provides a characteristic venue for multidisciplinary collaboration between different medical specialties in the provision of complex clinical care. In fewer instances, however, is such collaboration more crucial than in the operating room (OR). The teamwork between cardiothoracic surgery and anesthesiology teams is the cornerstone of patient safety and optimal transplant outcomes. In order to best expound on these, it is beneficial to look at the transplantation process in three distinct phases: preoperative, intraoperative, and postoperative care. Attention paid to these individual phases, with the occasional use of thoughtful checklists, best allows the anesthesiologist and surgeon to assess and manage the recipient and positively influence the clinical trajectory.

Preoperative

Preoperative management of end-stage lung disease is largely under the auspices of the pulmonologists caring for the individual patients. The anesthesiologist's introduction to the recipient typically occurs after the selection process has been completed. Although there may be minimal decision making at this introductory juncture, an understanding of the patient's preoperative status is crucial in predicting the conduct of the operation. Extensive clinical documentation is often readily available, in keeping with the severity and complexity of the patient's illness and the high resource intensity of lung transplantation. At our medical center, it is now standard for listed patients to be evaluated in the anesthesia preoperative clinic to allow early identification of individual needs. The recipients are typically ASA Class IV, but, admittedly, may each have arrived at this level of acuity via different paths and additionally, may have deteriorated clinically since the time of initial listing. One must seek to appreciate any changes occurring after the previously documented clinical assessment and to understand the underlying etiology of the lung disease. Suppurative disease processes such as Cystic Fibrosis and Kartagener's Syndrome , for example, have different, preoperative antimicrobial considerations, pathophysiological implications, and potential cardiopulmonary bypass requirements than those for Interstitial Pulmonary Fibrosis (IPF) or Chronic Obstructive Pulmonary Disease (COPD).

It is incumbent upon the anesthesia team to be well versed with the extent of the patient's disease, comorbidities, supplemental oxygen requirements, lifetime tobacco exposure, potential for difficult airway, drug allergies, and medical history as a whole. Reviewing the pulmonary function tests (PFTs) allows an understanding of the severity of the patient's pattern of disease and provides insight into possible intraoperative issues that may arise. The preoperative studies used to evaluate cardiopulmonary function may also be used to predict operative strategy. Right heart catheterization, for instance, may identify severe pulmonary hypertension that may alert the team as to the need for intraoperative extracorporeal support. These may also allow anticipation as to which vasoactive infusions may be required, what potential pitfalls may emerge during induction and ultimately, what intraoperative plan would be safest.

Preoperatively, the anesthesiologist should carefully evaluate the patient's airway and decide upon a strategy to be used for double lumen endotracheal tube placement in these patients, all of who, by definition, have marginal respiratory status and poorly tolerate any airway mishap. Different sizes of laryngoscopes, a fiberoptic pediatric bronchoscope, and an endotracheal tube exchanger should be available. There should also be ready availability of other adjuncts such as the bougie, laryngeal mask airway, and video laryngoscope particularly if there is any concern for a challenging airway. At some institutions, the surgical fiberoptic bronchoscope is used in lieu of the pediatric bronchoscope. In addition to the appropriately sized and sided double lumen

endotracheal tube, a single-lumen endotracheal tube should also be available for placement in the event there is any difficulty passing the double lumen endotracheal tube. Bronchial blockers are used as a less preferred option.

It is advisable to have more than a single size of each endotracheal tube, given patient variability. A clamp will be required for single lung ventilation if a double lumen endotracheal tube is to be used. Other important adjuncts include the transesophageal echocardiography (TEE) probe; large bore intravenous (IV) access lines, a pulmonary arterial (PA) catheter, nitric oxide (NO), epoprostenol sodium (flolan), defibrillator pads, and cardiopulmonary bypass, among others.

A review of the clinical notes and documented studies, coupled with a discussion with the surgeon about the patient and intraoperative plan allows for a valuable combined team approach. The authors strongly advocate for a preoperative "huddle" with the entire team to review these critical aspects in these challenging cases. An understanding of split function lung tests helps to accurately predict which side the surgeon is likely to start with—usually the more diseased side, with the least perfusion. These discussions allow for the opportunity to troubleshoot potential challenges ahead of time and also to establish the positioning of the patient, the side the IV lines may best be placed, size and weight considerations of the donor, clinical issues that would be of most concern and importantly, how each of these may be safely mitigated.

If the patient has severe pulmonary hypertension, it is prudent to have NO available in the OR before induction of anesthesia so that it can be initiated immediately after endotracheal intubation as needed. The positioning of the intravenous (IV) lines depends on whether or not bypass will be required. In view of the high acuity of the patients we cater to, we frequently utilize cardiopulmonary bypass for double lung transplantation. Thus, a discussion should occur as to whether the anesthesiologists should access the left internal jugular or femoral veins for the placement of accessory lines to allow the surgeons access to the right internal jugular and femoral veins for percutaneous cardiopulmonary support. The groins are exposed and prepped into the operative field. The post-induction TEE is useful in highlighting other structural cardiac abnormalities and that may or may not have worsened since the last preoperative echocardiographic evaluation. The TEE is used throughout the case and is of significant diagnostic utility for both structure and function. A checklist of the drugs (immunosuppressants, antibiotics, etc.) allows early acquisition from the pharmacy and prevents delays. Blood products should be immediately available in the room as the margin of error in these cases is narrow.

Intraoperative

Once in the OR, the anesthesiology care now contributes to the overall ischemic time and so there is a need for expediency, in view of the potential for delay and resultant

graft dysfunction. Proper marking of the operative side in single lung transplantation, ABO blood group verification, and serologic verification should be performed in the preoperative holding area. After transferring the patient into the OR, a surgical time-out should be promptly performed to allow the procedure to begin placement of standard ASA monitors, invasive arterial line and defibrillator pads. Antibiotics and immunosuppression are given as determined by allergies, colonization, antibiograms, and cytomegalovirus (CMV) status. We typically use Alemtuzumab (Campath) except in the context of malignancy or CMV mismatch, where we opt instead for Basiliximab (Simulect) [1]. These drugs are administered at the surgeon's request immediately after induction of anesthesia. The surgical team and perfusion should be present for induction as patients can potentially decompensate during this time. Once intubation has been performed, access lines should be inserted and a PA catheter is passed into the proximal PA under TEE guidance. The surgical team will undoubtedly be standing by to begin the procedure as soon as the double-lumen intubation, IV access lines, TEE probe, and foley have been placed. The anesthesiologist is encouraged to report the findings and pathology seen on TEE and the surgeons to expound further on their operative plan. Right ventricular dysfunction, a patent foramen ovale, tricuspid regurgitation, and aortic atheromatous disease can each influence surgical decision-making and should be discussed with the surgical team. Intravenous fluid administration should be kept to a minimum throughout the case. Flexible bronchoscopy is used liberally by both the surgeon and anesthesiologist to evaluate the airway for additional pathology and correct endotracheal tube positioning.

In our institution, we typically place patients in the supine position with their arms in a padded brace strapped above their heads (Fig. 8.1). This affords us the exposure necessary by both "clamshell" (bilateral anterolateral thoracosternotomy—Fig. 8.2) and "minimally invasive" approaches. (sternum-sparing anterolateral thoracotomy incision —Fig. 8.3) [2]. This latter incision allows bilateral lung procedures to be performed without dividing the sternum and may possess theoretical differences in postoperative analgesia requirements and resumption of physical activities. The position of the arms, however, may be cumbersome to the anesthesiology team and affect the "typical access" to the airway and peripheral IV lines (Fig. 8.4). Moreover, a radial arterial line may cease to function in this position necessitating the preoperative placement of a femoral arterial line. For single lung transplantation, we have used two approaches depending on the patient anatomy. Our preferred approach is the same position as for a bilateral sequential transplantation and the operation is performed via an anterolateral thoracotomy (Fig. 8.5). This approach affords easy groin access should cardiopulmonary support be required. Like others, we less commonly use the lateral decubitus position and a posterolateral thoracotomy incision for single lung transplantation.

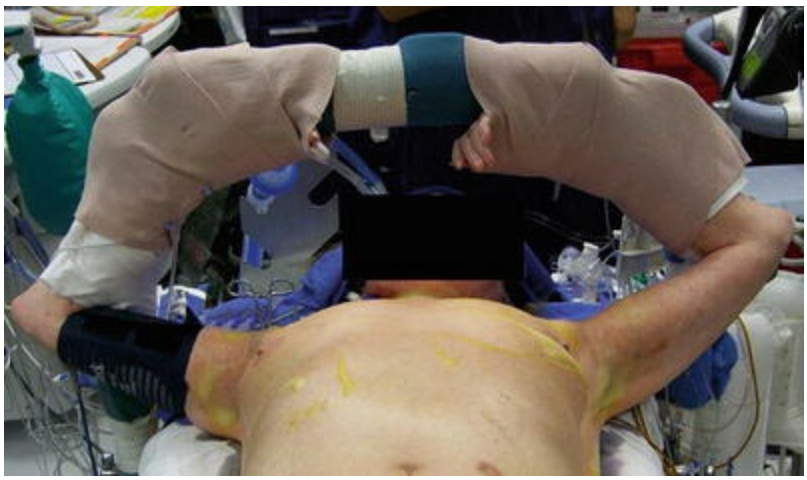


Fig. 8.1 Standard patient positioning for bilateral sequential lung transplantation at our center

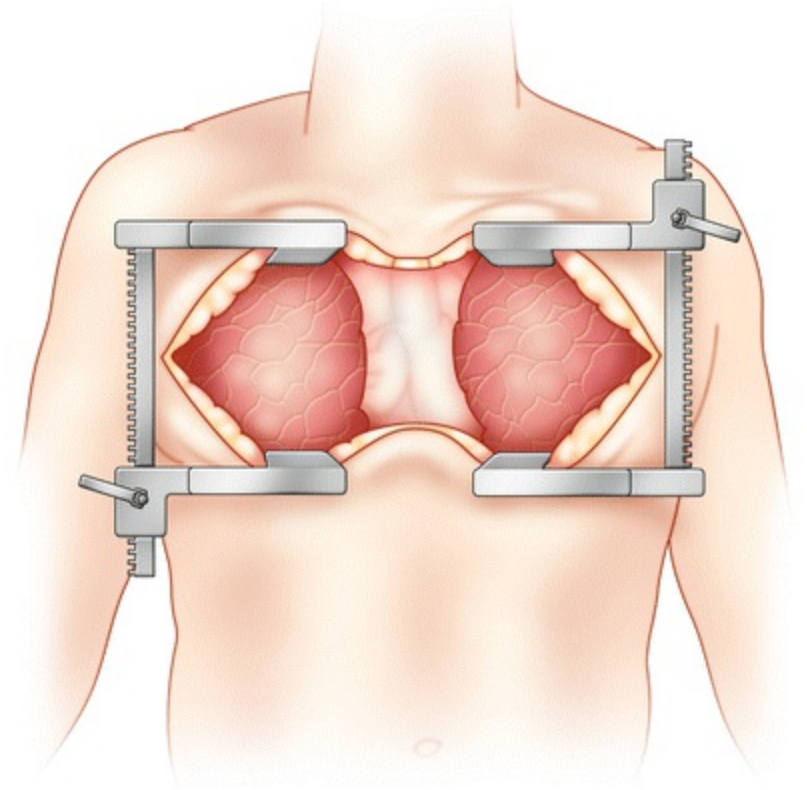


Fig. 8.2 Clamshell incision for bilateral lung transplantation

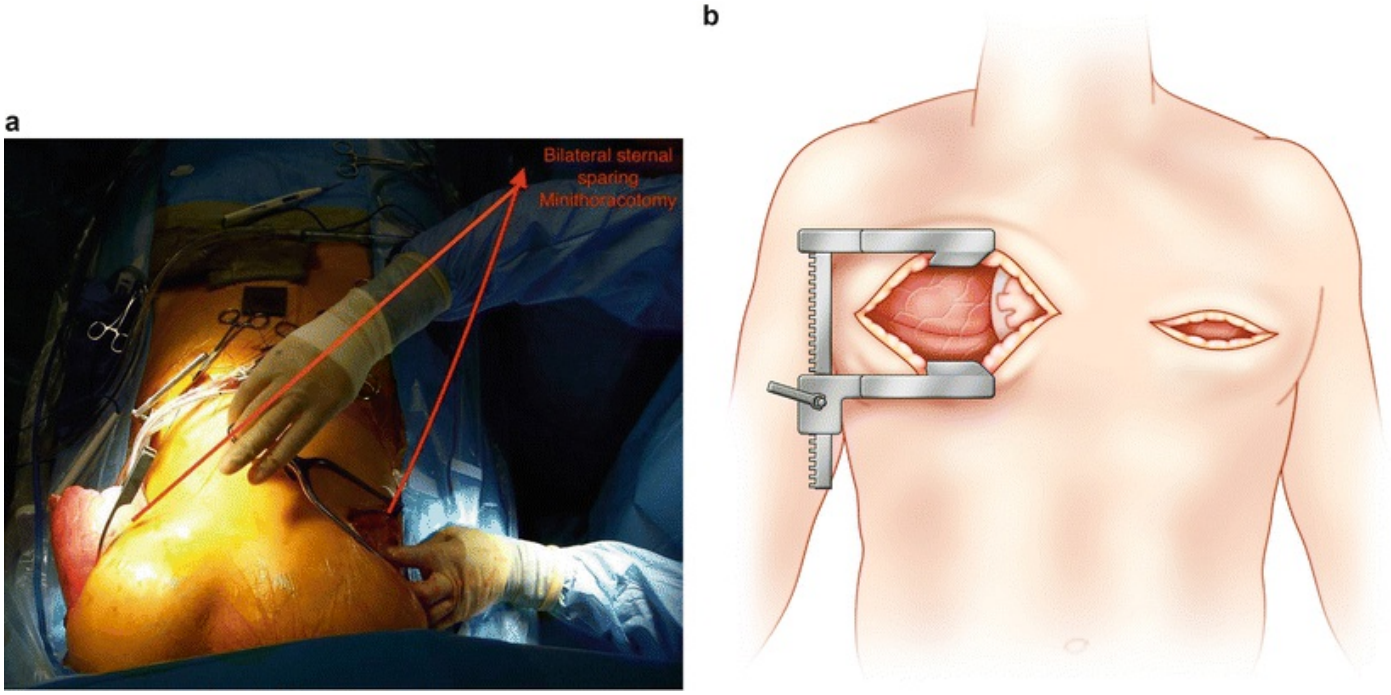


Fig. 8.3 Bilateral anterolateral thoracotomy incisions for double lung transplantation. (**a**) Anesthesia view of surgical field. (**b**) Anatomic view of surgical field

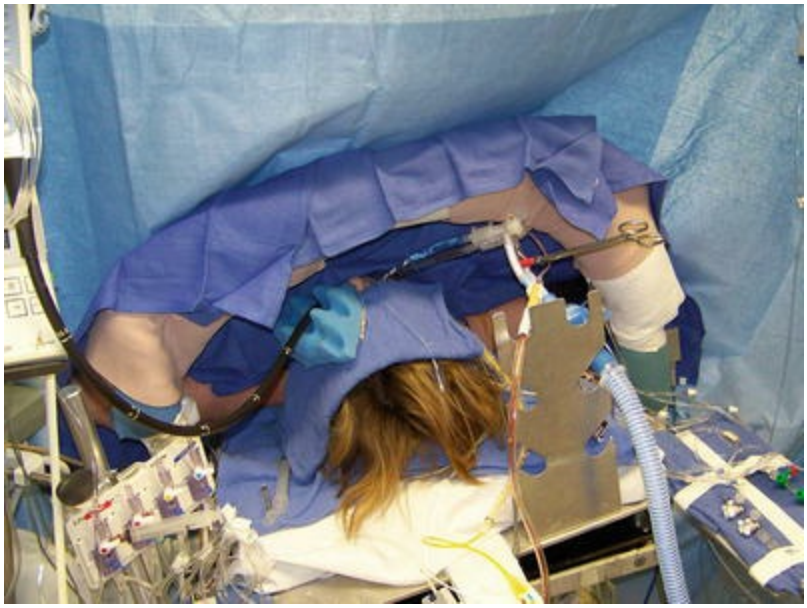


Fig. 8.4 Access to the endotracheal tube and central access for anesthesia care team can be limited by patient positioning. Upper limb arterial and venous accesses are not reliable during this position

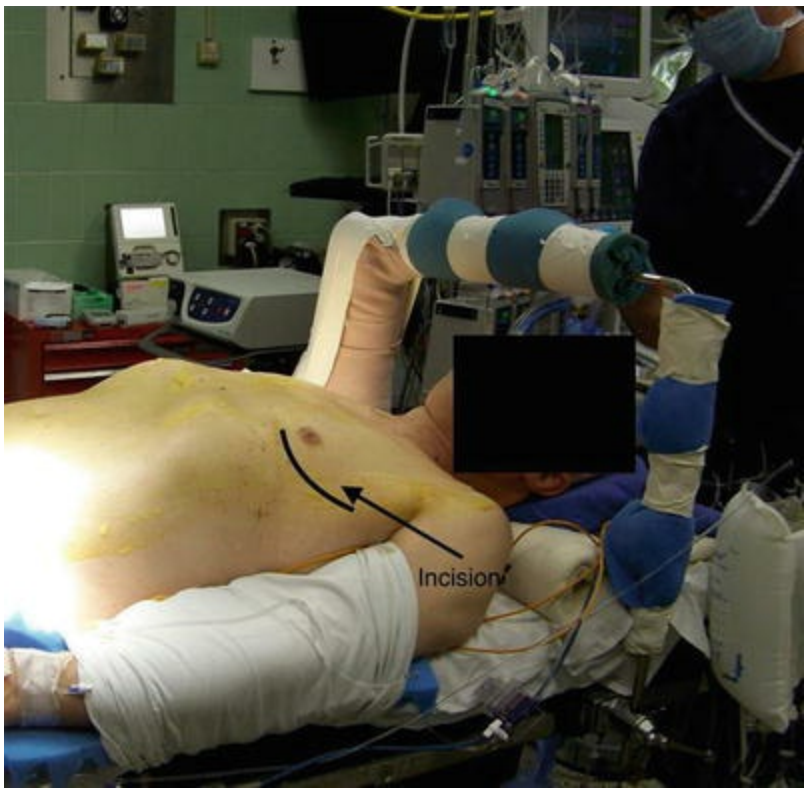


Fig. 8.5 Positioning and incision for single lung transplantation (*left*)

Once the incision has been made with the knife at the level of the skin, the procedure involves dissection using electrocautery through the soft tissue, muscle division, and entry into the thorax. This is typically done simultaneously with an operator on each side. For the typical transplant with obstructive disease, we enter via the fifth interspace. For restrictive disease, we enter the 4th interspace. Almost immediately there will be a need to deflate one lung to facilitate the dissection. The ability to do this expediently is of great utility. The bronchial balloon may inadvertently herniate out of the left mainstem bronchus and the anesthesiologist is called upon to quickly make the diagnosis in the context of a lung that will no longer deflate. The ability to use the fiberoptic bronchoscope and reposition the tube when necessary (often underneath the sterile drapes) is expected (Fig. 8.6). There is an increased risk of parenchymal injury when lungs cannot be deflated particularly in the context of dense adhesions. These, in combination, may spark a fire, which can have serious, often lethal consequences. To further minimize risk of fire, we flood carbon dioxide into the operative field throughout the case. Further, when the airway is open, we reduce fraction of inspired oxygen (FiO_2) to room air levels. Unstable arrhythmias may be frequently encountered requiring cardioversion via external or internal means. Careful attention to the patient's body temperature throughout the case is also prudent and warming via standard means should be ongoing throughout the procedure.

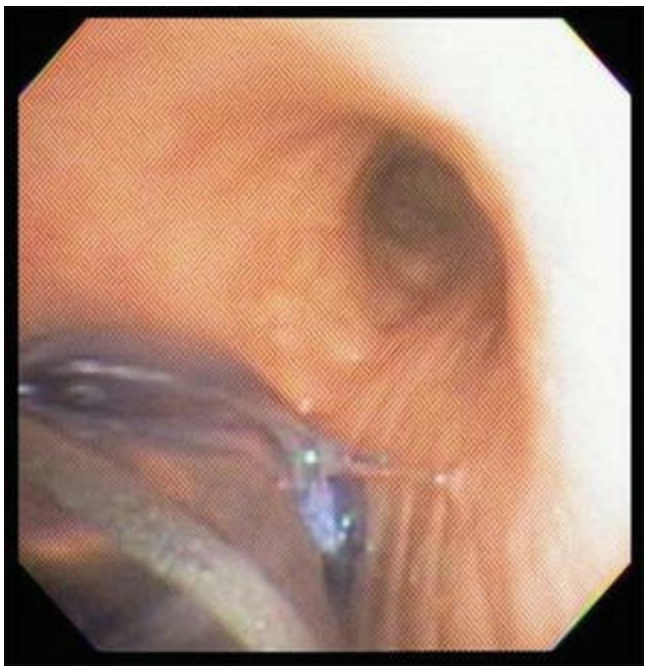


Fig. 8.6 Endobronchial cuff herniation during surgical manipulation

Once the hilar structures have been exposed, the airway and vascular structures (pulmonary artery, superior pulmonary vein, and inferior pulmonary vein), on each lung are sequentially isolated and prepared for stapling. Once the structures have been isolated, the surgeon may decide to use cardiopulmonary bypass depending on the stability or pathophysiology of the patient. This is tested by snaring the PA using a tourniquet and monitoring the vitals for 5–10 min thereafter (Fig. 8.7). The tip of the PA catheter should be pulled into the proximal PA prior to snaring or clamping. The team monitors for escalating PA pressures and an increase to greater than two-thirds of systemic pressure is an approximate indicator that cardiopulmonary support is required. Right ventricular function should be monitored by TEE during this time also. Once the decision to go "on pump" has been made, the standard options include central (ascending aorta to right atrium) or peripheral cannulation (femoral vessels).

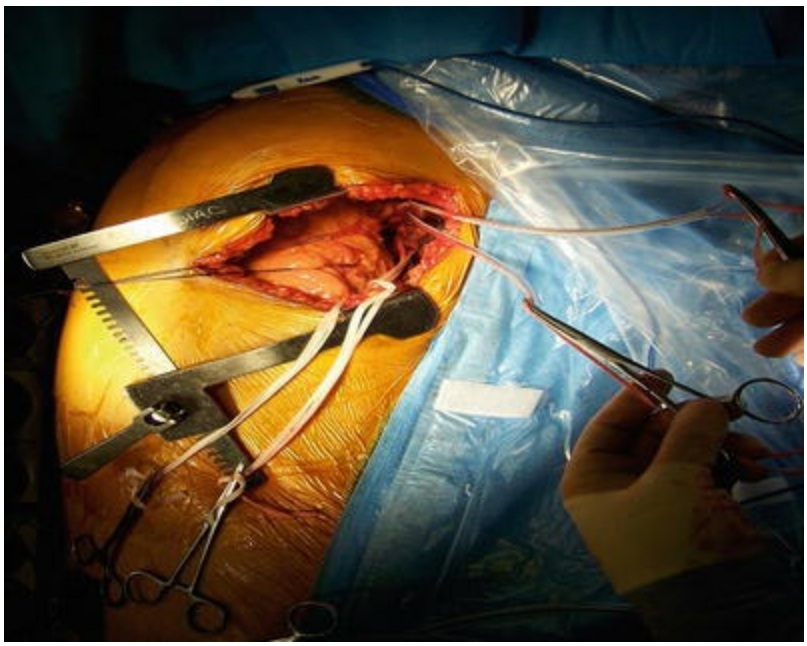


Fig. 8.7 Snaring of pulmonary vessels for decision making whether to use cardiopulmonary support for lung transplantation procedure

The use of cardiopulmonary support adds the perfusionist to the operative equation. The three clinical teams now collaborate with each other with the perfusionist directing the rate of perfusion and the extent of anticoagulation with serial activated clotting times (ACTs) . The anesthesiologist administers the initial heparin dose, but thereafter the perfusionist may administer the heparin directly into the circuit. The perfusion team also guides volume status and optimizes hematocrit and the electrolyte milieu, replacing fluid volume as necessary using both blood products and cell-saver, depending on the amount of blood loss and the set-up of the circuit. On full bypass, typically about 4–5 l/min, the anesthesiology team may be requested to withhold ventilation entirely, deflating both lungs for an extended duration so as to facilitate dissection and implantation. Despite the delegation of perfusion to the perfusionist, the use of bypass still dictates vigilant monitoring by the anesthesiology team. Drugs administered, mixed venous gas patterns, cerebral oximetry, oxygen saturation, hemoglobin, extent of paralysis, number of twitches, mean arterial pressures, and PA pressures still require close monitoring. The surgical team benefits from the use of bypass as it allows for a decompressed field in which to perform the recipient pneumonectomy and the transplantation. The team should be prepared for any significant blood loss during the vascular dissection.

Recently, our group has used central or peripheral extracorporeal membrane oxygenation (ECMO) as a means of cardiopulmonary support [3]. This has been quite successful to date with reduced bleeding complications; however, the nuances of using ECMO must be familiar to all members of the team as there is no way to give volume back to the patient and the circuit must remain free of entrained air. Newer perfusion circuits allow one to switch from ECMO to full cardiopulmonary bypass without having

to exchange the circuit. Indeed this remains an active area of investigation for the future.

During the pneumonectomy, each PA and PV is divided using multiple firings of the reticulating endoscopic (EndoGIA) stapler. The bronchus is the last structure to be divided and this is done free-hand using a scalpel. At this particular juncture, communication between the surgery and anesthesia teams is crucial because once the airway is divided, the surgical field is exposed to oxygen and inhalational gases. During this portion of the case the surgery team may request that the endobronchial tube be withdrawn to avoid severing it with the blade. The FiO_2 should be decreased to 30 % (or less) and suction applied to the ipsilateral side of the double lumen tube so as to minimize the entrainment of high flow oxygen with ongoing use of electrocautery due to the risk of sparking a fire. Once the pneumonectomy has been performed, the specimen is carried off the field and sent to pathology for permanent fixation and sectioning. Once cautery is completed, the FiO_2 can then be increased once more, if the patient is not on bypass or ECMO.

After the donor lungs are delivered to the OR, a brief back-table preparation is performed to prepare the lungs for sequential implantation (Fig. 8.8). The sequence begins with the most posterior anatomical structure, the bronchial anastomosis (Fig. 8.9). This is performed using a continuous 3–0 polypropylene suture. The anastomosis is reinforced with two figure of eight 3–0 polypropylene stitches because of the running suture line (Fig. 8.10). At the completion of this, the anesthesiologist is called upon to place a bronchoscope in the airway and inspect the endoluminal integrity of the anastomosis. After the bronchial anastomosis, we typically tack an edge of the intervening donor pericardium between the bronchus and PA. The PA is fashioned next (Fig. 8.11). Before sewing the PA, however, a “cold shot” is infused by the perfusionist into the PA using a handheld cannula. This comprises 500–800 cc of cold blood with glutamate, aspartate, lidocaine, adenosine, nitroglycerin, verapamil, deferoxamine, ascorbic acid, dextrose, and insulin. This flows antegrade from the PA and exits through the PV. The “cellsaver” is used to suction and recirculate it as necessary. The PA is clamped (after ensuring the PA catheter is not caught in the jaws) with a Satinsky (or Derra) clamp and staple line removed sharply. The donor and recipient PA are then fashioned to appropriate length and anastomosed in an end-to-end fashion using a single running 5–0 polypropylene suture (Fig. 8.11). The PVs are then clamped with a Satinsky clamp and the donor and recipient pulmonary vein cuffs are anastomosed in an end-to-end fashion using a single running 4–0 polypropylene suture (Fig. 8.12). Upon nearing the completion of the left atrial anastomoses, the anesthesiologist administers 250 mg IV solumedrol. Neither anastomosis is knotted down immediately so as to allow flushing and deairing. Prior to reperfusion, we use a cardioplegia needle to administer 500–800 cc antegrade of “hot shot” into the PA. We ensure there is adequate drainage from the pulmonary vein suture line. This comprises terminal warm blood with the same additives as the “cold shot”, after which the allograft is reperfused. The lung is

reperfused by releasing the Satinsky clamp on the PV thereby slowly allowing for de-airing via the left atrial suture line. The suture line is secured. Careful attention to de-airing is prudent as air on the left side at this point could be devastating. TEE during this time may help guide decisions in this regard. The PA clamp is then removed slowly over the course of 5–10 min and this suture line is secured. The vascular suture lines are checked for bleeding and the need for repair stitches. The "Shumway" tap is performed with the suction tip on each suture line to ensure that no low pressure points of bleeding are hidden from view. The lung is then gently re-expanded and this may be promoted by using a gentle Valsalva to overcome the atelectatic de-recruitment that occurs during the procedure but should be careful to avoid barotrauma.

Fig. 8.8 Lung back table preparation

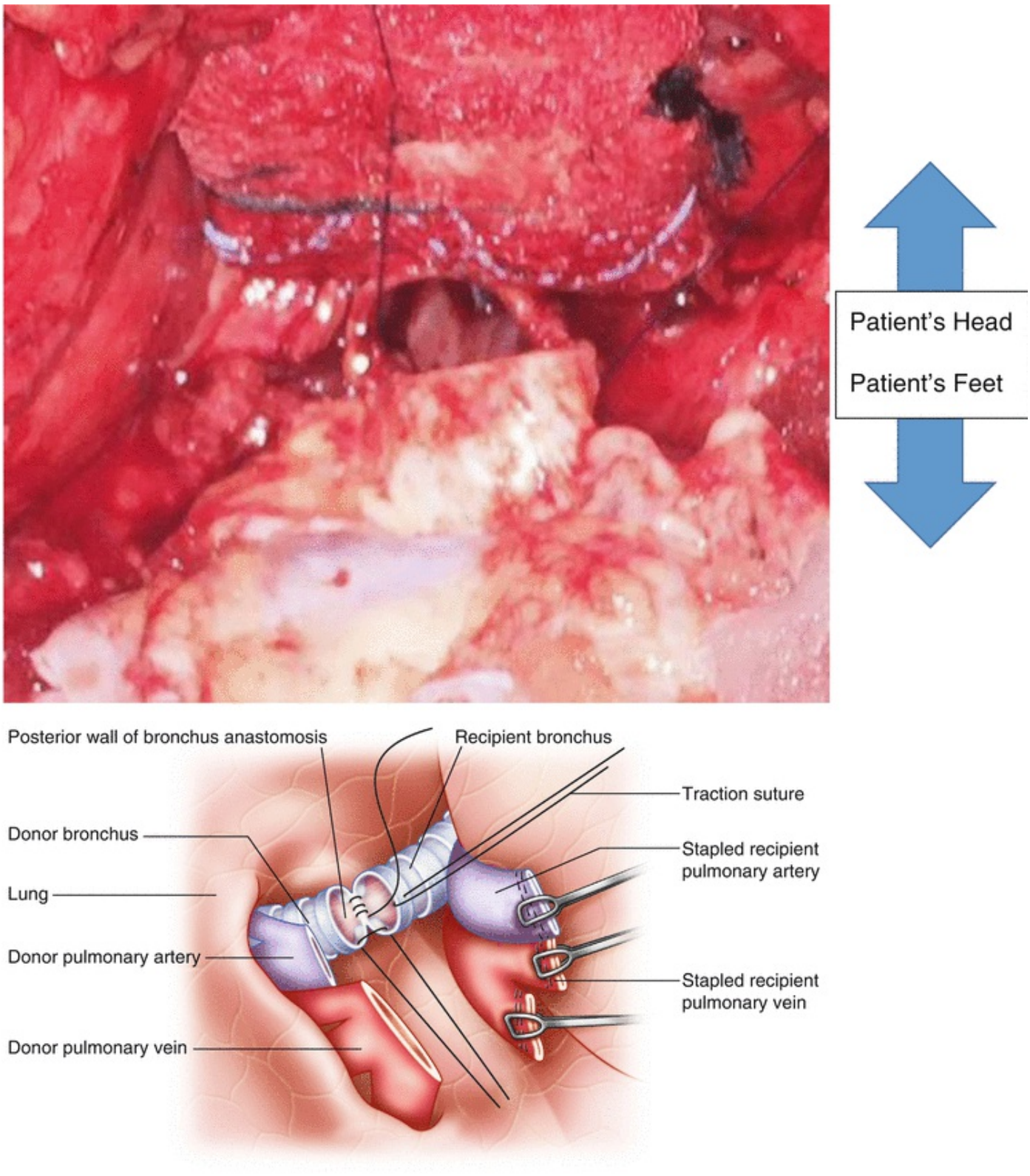


Fig. 8.9 Illustration of the anastomoses in a right-sided implantation of lung for lung transplantation

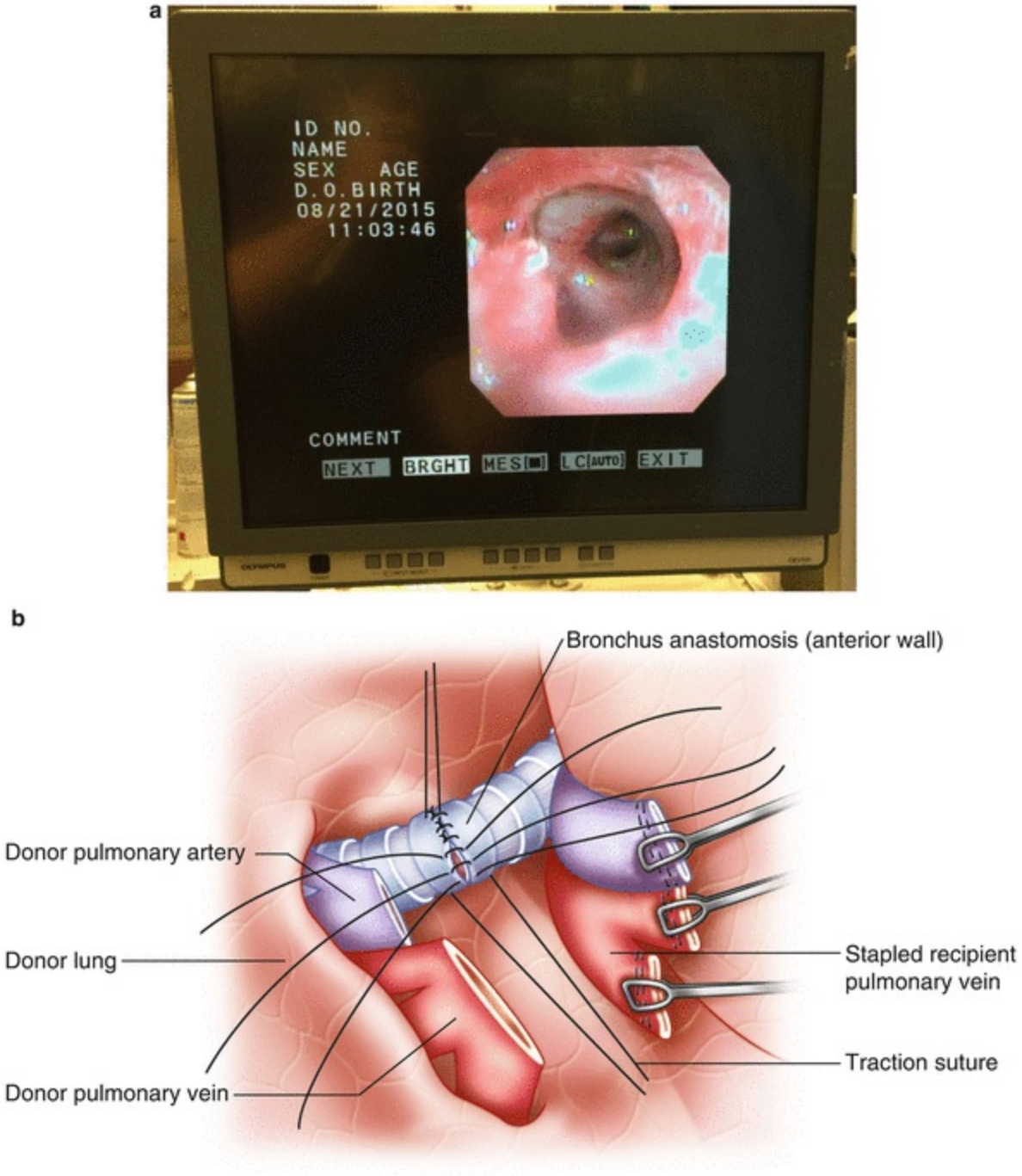
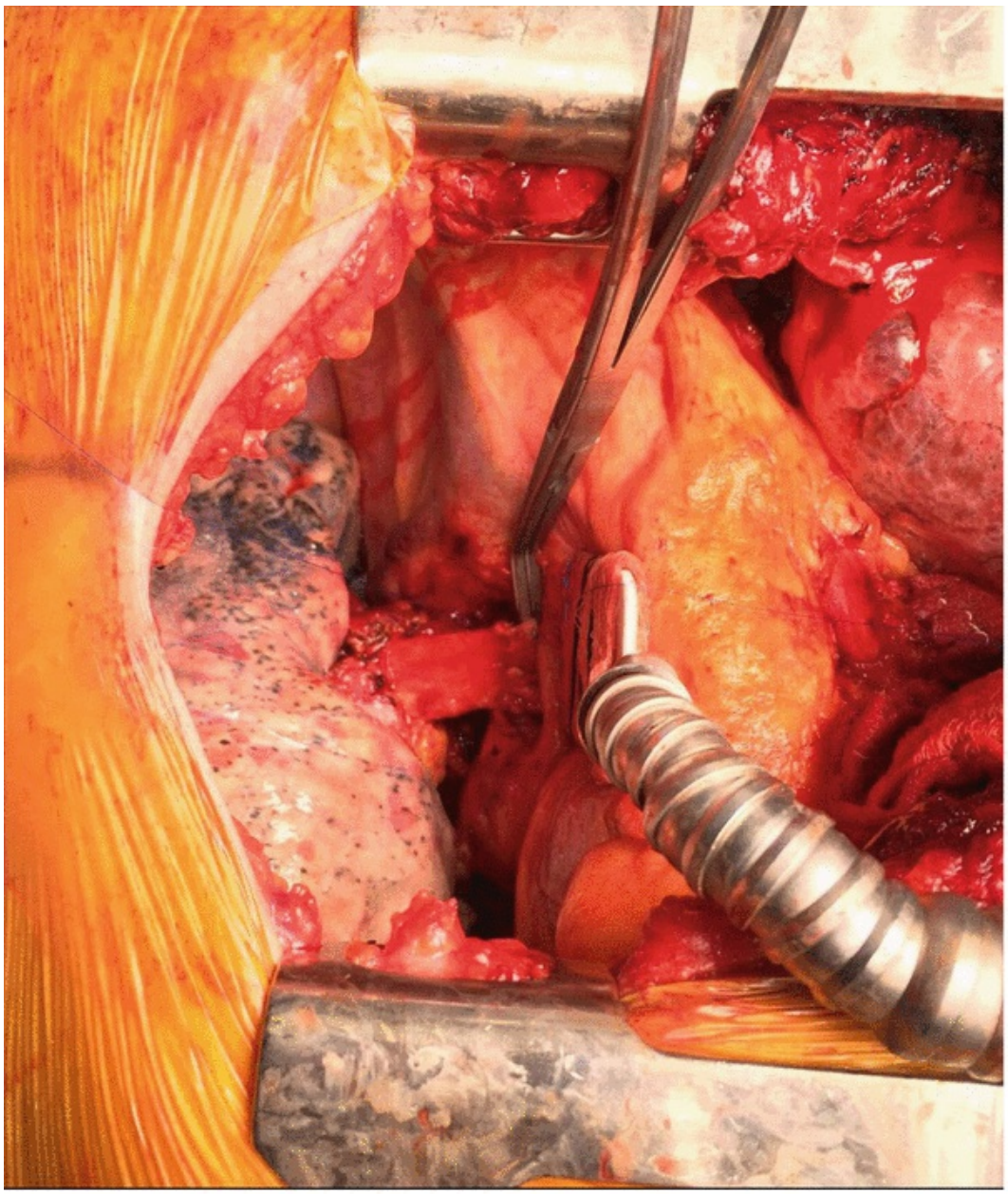
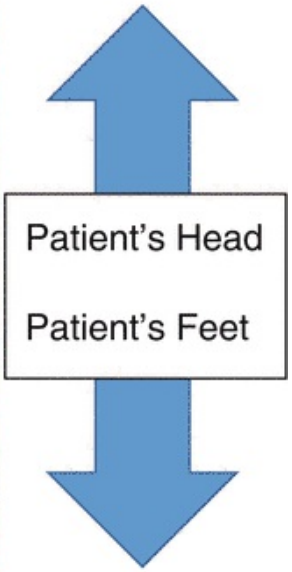


Fig. 8.10 Bronchoscopic appearance of bronchial anastomosis




Patient's Head
Patient's Feet

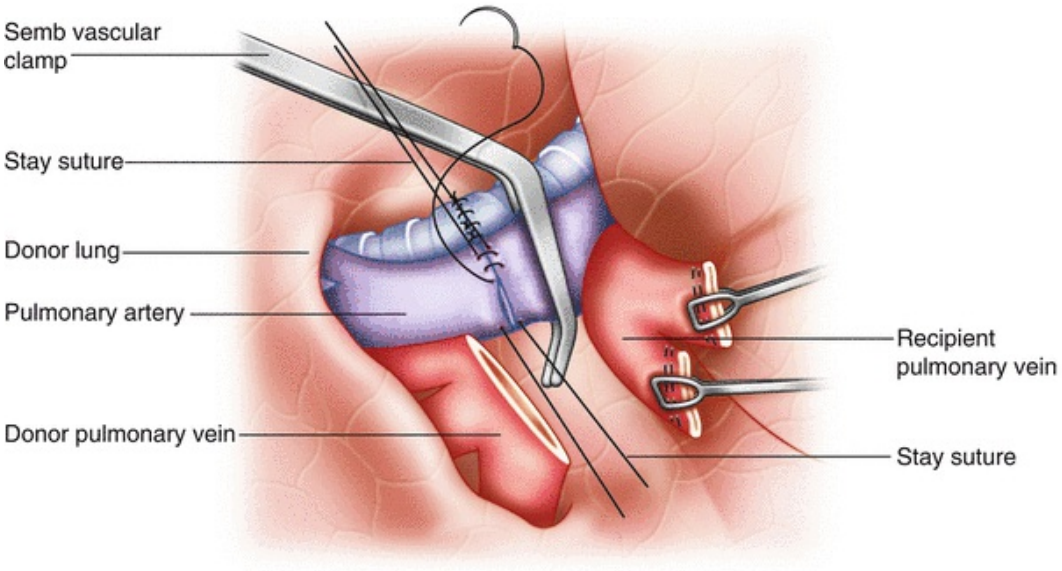
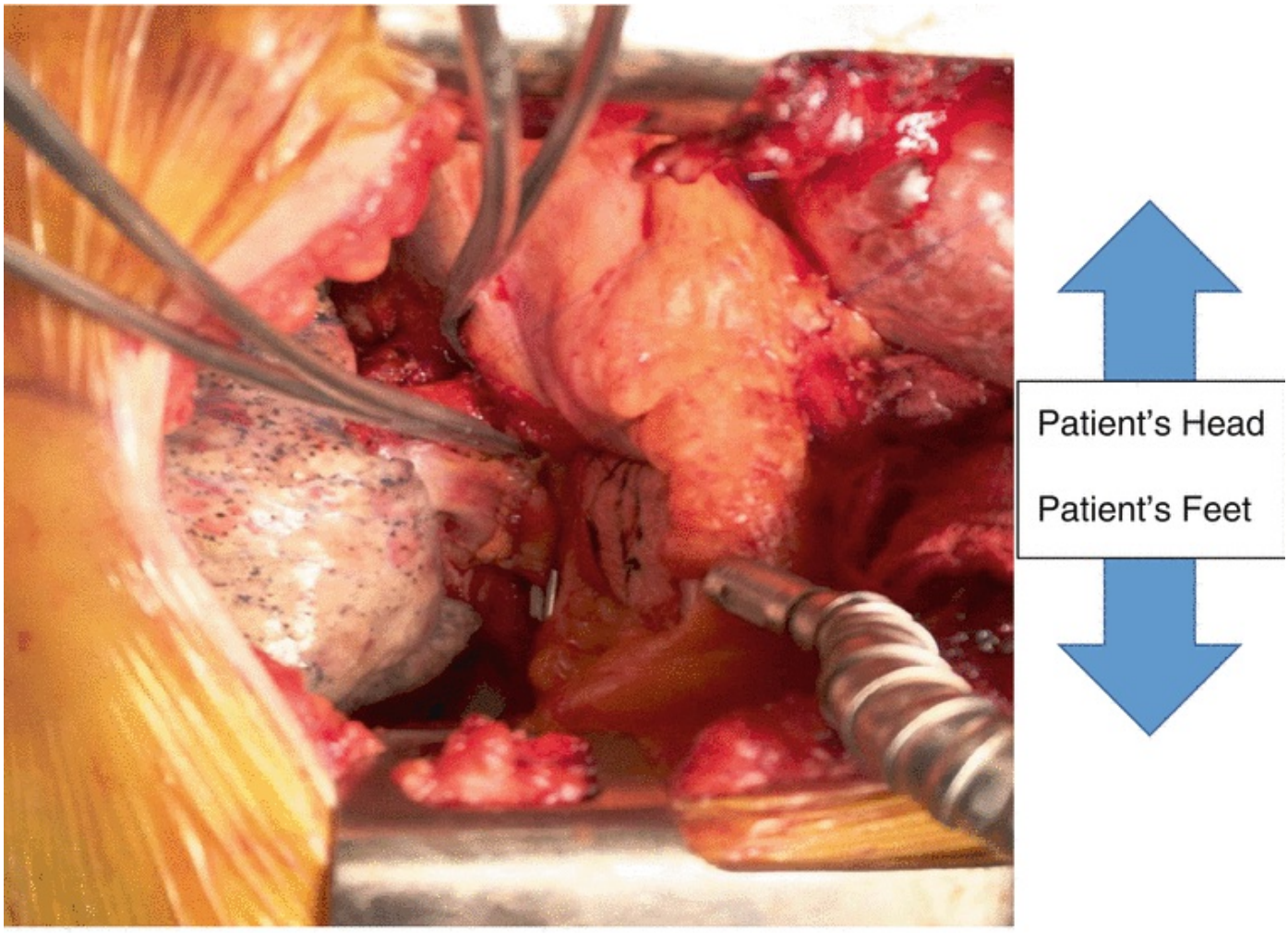

Semb vascular clamp
Stay suture
Donor lung
Pulmonary artery
Donor pulmonary vein
Recipient pulmonary vein
Stay suture

Fig. 8.11 Pulmonary artery anastomosis in an end-to-end fashion using a single running 5–0 polypropylene suture



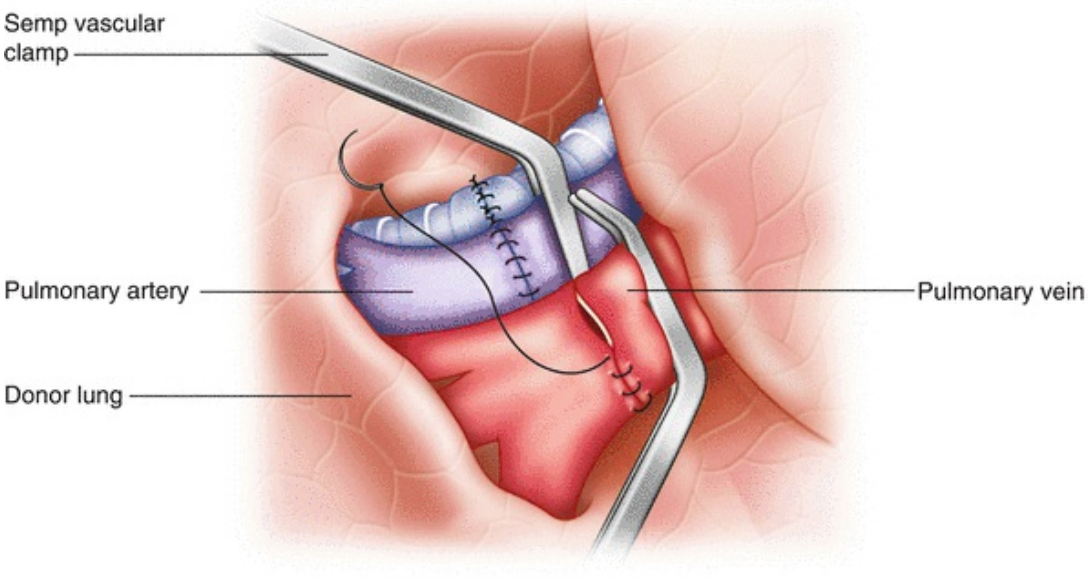


Fig. 8.12 Pulmonary vein cuffs anastomosed in an end-to-end fashion using a single running 4–0 polypropylene

suture

Protective ventilator management is necessary using tidal volumes of 6 ml/kg of the donor body weight and high positive end expiratory pressure (PEEP) with peak and mean airway pressures less than 30 cm H_2O. The bronchial anastomosis is checked for leaks under saline immersion to 25–30 mmHg pressure with a gentle Valsalva maneuver. After allowing the new lung to recover for 10–15 min, the opposite lung is then sequentially isolated. The pneumonectomy and implantation of the opposite lung follows similar steps as for the first lung. It is not uncommon to need cardiopulmonary support at this point if not being used already as the new lung may not be optimally functional from the very outset. Further, there may be hemodynamic compromise particularly with the dissection on the left side, which is often deeper and more challenging. Following completion of the second lung, each lung is carefully inspected for parenchymal injury and the hilum inspected for bleeding.

Adjuncts such as NO and flolan may be used when PA pressures have been elevated, but are weaned off rapidly in the first 12 h postoperatively to allow for extubation. There is often a surgeon's preference for NO while in the OR, likely due to greater familiarity with this inhalational drug rather than a true evidence-driven difference in outcomes. Once the second lung has been implanted (and re-expanded in similar fashion) the patient may be weaned off cardiopulmonary support. We typically use conservative FiO_2 levels of 40 % or less in the immediate postoperative phase to avoid the theoretical risk of free radical-induced oxygen toxicity, though the latter practice is institution dependent. The left atrial anastomoses may be inspected by TEE for patency and velocity. Weaning involves a series of coordinated steps starting with the resumption of mechanical ventilation while still on "full flow," and proceeding with the administration of weight-based protamine to reverse the effects of anticoagulation and the infusion of vasopressors and inotropes to allow successful separation. Once off bypass and protamine has been given, an ACT is checked to ensure return to baseline. Arterial blood gases are followed serially for oxygenation and ventilatory status. A complete blood count, coagulation screen, and thromboelastogram may also be used to guide component-specific replacement. Following closure, the anesthesiology team withdraws the TEE probe and switches the double to a single lumen to facilitate transfer to the intensive care unit (ICU) and postoperative mechanical ventilation thereafter. The surgeon typically performs a final bronchoscopy while in the OR to clear secretions from the airway, which are almost invariably present.

On occasion, the chest may be left open temporarily due to over-sizing the allograft, bleeding, or hemodynamic instability during attempted closure. If this is the case, only the skin is closed using a temporary closure dressing. Management of this type of patient and the algorithm employed to achieve closure of the chest is discussed in detail in a previous report [4].

Postoperative

The patient is then transferred from the OR to the ICU. The anesthesiologist maintains a diligent record of the intraoperative events and tally of blood products administered. This record is central to the hand-over that occurs in the ICU between the operative and perioperative teams. A combined de-briefing of the case between anesthesia, perfusion, and the surgical team is encouraged so as to highlight any problems during the case so as to continually reevaluate and improve performance. In the ICU, the patient is resuscitated. Perfusion is optimized for end organs as the lungs recover. We typically ventilate the patient at a PEEP of 10 for 24 h and then begin the process of weaning towards extubation. Hemodynamic support is weaned and laboratory parameters normalized over this period of time.

Cardiac index, mixed venous oxygen saturation, blood lactate levels, and urine output are among the most important parameters to follow in this setting. Chest tube output is monitored for the presence of bleeding complications. The patient typically undergoes bronchoscopy prior to extubation to clear secretions. The typical patient is extubated within 24–48 h. Postoperative maintenance immunosuppression comprises triple drug regimen including tacrolimus, mycophenolate mofetil, and steroids. Valgancylcovir and voriconazole are used for antimicrobial prophylaxis against cytomegalovirus and fungus respectively. Once making satisfactory progress, the recipient is transferred to the regular ward for ongoing recovery and one may anticipate a 14 day hospital stay for an uncomplicated bilateral sequential lung transplant patient (7–10 days for a single lung).

Pain control is critical in the postoperative setting to avoid respiratory complications. Our preference is nurse-administered narcotics while intubated in the ICU. We prefer hydromorphone to others because it is cleared in patients with renal dysfunction. Once the patient is extubated, we transition to a hydromorphone patient controlled analgesia pump. When the patient is tolerating PO and on a positive trajectory towards discharge, we then transition to oral pain medications. Recently, we have had excellent success with the use of paravertebral blocks and epidurals as useful adjuncts that may be placed postoperatively. We prefer paravertebral catheters when able and our anesthesiologists will place these on postoperative day #1 in the ICU under ultrasound guidance [5, 6].

Conclusions

Lung transplantation remains a viable life-saving therapy for those patients afflicted with end stage pulmonary disease. An understanding of the process from the preoperative evaluation to the postoperative setting is critical to the effective care coordination of patients. An enhanced understanding of the critical collaborative

teamwork that must take place in the OR between all involved will lead to improved outcomes for patients in the perioperative setting. It is our hope that this chapter will provide useful detail from the surgical perspective and serve to enhance the dialogue between disciplines in an effort to improve the care delivered to these patients. This collaboration will be increasingly important as we evaluate and transplant older recipients, more complex cases, and with the introduction of newer technologies such as ex vivo perfusion. Indeed, this team approach will be critical to providing the best possible outcomes in an era where donors are still at a premium as many recipients await their chance at receiving the gift of life through lung transplantation.

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9. Anesthetic Management for Lung Transplantation

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Introduction

Lung transplantation (LTx) has emerged as an accepted therapy to extend survival [1] and improve health-related quality of life [2] in selected patients with end-stage parenchymal lung or pulmonary vascular disease.

LTx includes lobar, single lung, double lung, and heart–lung en bloc transplant procedures. The procedure selected depends on recipient factors, donor organ factors, and institutional biases. Double LTx has surpassed single LTx as the most common type of operation performed overall, with higher actuarial survival observed after double compared to single LTx [3] (Fig. 9.1). Double LTx is now most commonly performed without cardiopulmonary bypass (CPB) using a bilateral sequential technique , rather than the older method of en bloc double LTx on CPB . Heart–lung transplant is performed infrequently in certain patients with severe concomitant cardiac and pulmonary impairment.

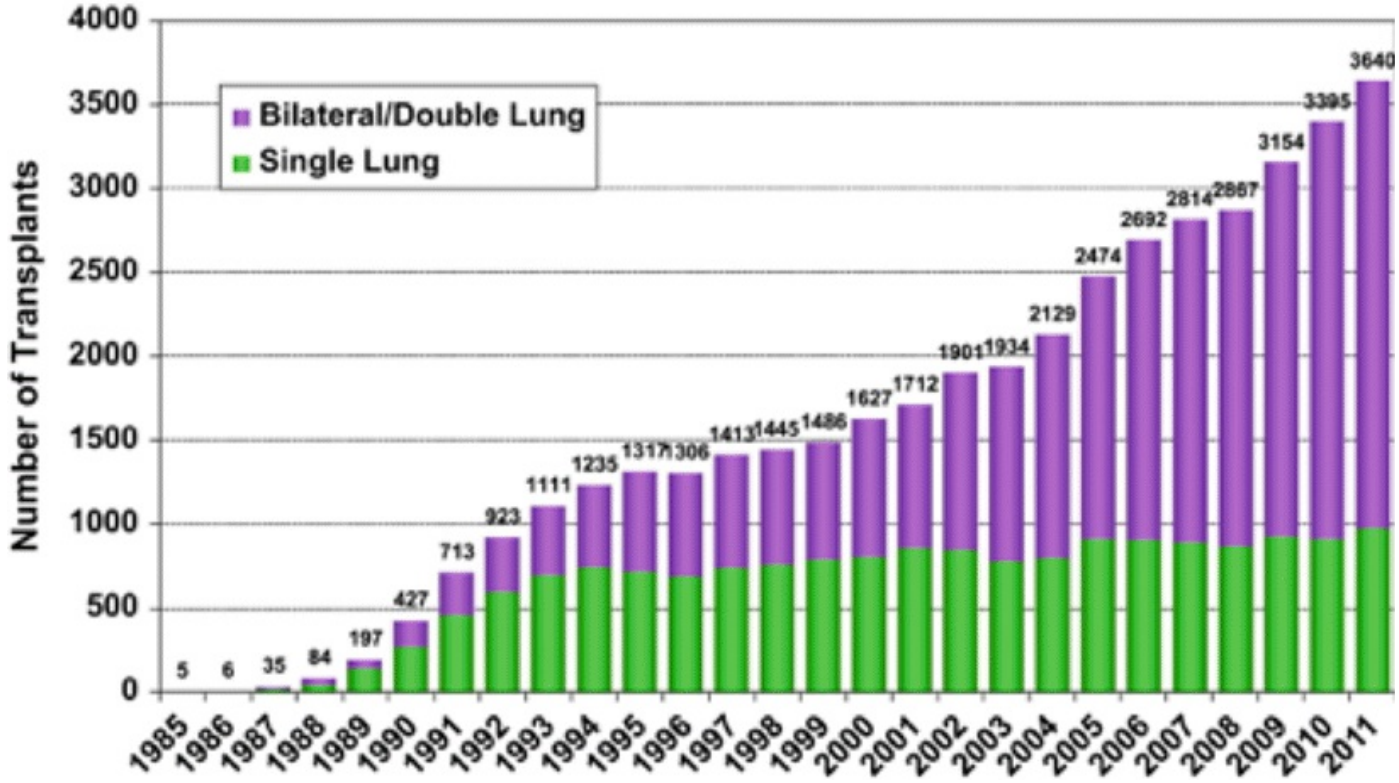

Fig. 9.1 Number of reported adult lung transplants by year and procedure type reported to the International Society for Heart and Lung Transplantation Registry (Data from Wong et al. [3])

Preoperative Evaluation

LTx surgery tends to be performed on an emergency basis providing the anesthesiologist limited time in which to conduct an expedited but thorough preoperative evaluation. Potential lung transplant recipients undergo a comprehensive multidisciplinary pretransplant evaluation, the results of which must be immediately available to the anesthesia team. Key investigations that impact intraoperative management are reviewed in Table 9.1.

Table 9.1 Relevance of key preoperative investigations to anesthesia management

Investigation	Relevant information
Spirometry and lung volumes	Type and severity of lung disease influences ventilator management
Ventilation perfusion scan	Indicates which lung will better tolerate one-lung ventilation. Worst lung will be the one to be transplanted first
Computed chest tomogram and/or plain radiograph	Anatomic factors possibly affecting double-lumen tube placement and dissection of mediastinum for pneumonectomy
Echocardiogram	Left and right ventricular size, wall thickness, and systolic function; valvular disease; estimated pulmonary artery pressure; presence of intracardiac shunts
Cardiac catheterization	Hemodynamics/right-sided pressures extent of coronary artery disease

Since a significant time interval may have elapsed since completion of the pretransplant evaluation, the anesthesiologist must ascertain if any changes in health status have occurred in the interim (e.g. worsening functional status, increased oxygen requirements, signs/symptoms of decompensated right heart failure). Recipients should be questioned regarding potential contraindications to transesophageal echocardiography. The patient's fasting status should be determined, with consideration given to premedication for gastric aspiration prophylaxis . A discussion about postoperative analgesia, blood transfusion, and postoperative mechanical ventilation should also take place at this time. The availability of blood products should be confirmed with blood bank personnel. The anesthesiologist should ensure that critical preoperative medications such as pulmonary vasodilators, bronchodilators, and antibiotics are continued without interruption.

Appropriate perioperative antimicrobial prophylaxis should be initiated based on available microbiology data and local antimicrobial resistance patterns. The anesthesiologist is also typically responsible for initiation of the immunosuppressive regimen, which commonly includes methylprednisolone and an induction agent such as alemtuzumab (anti-CD52, Campath) or basiliximab (anti-CD25, Simulect). Alemtuzumab is commonly associated with infusion reactions (fever, chills, hypotension, urticaria, dyspnea) and therefore requires premedication with acetaminophen 500–1000 mg, famotidine 20 mg (anti-H_2) and diphenhydramine 50 mg (anti-H_1) 30 min prior.

Once the surgical team confirms the suitability of the donor lung(s) for transplant, the recipient is taken to operating theater. Limited premedication (midazolam 1–2 mg) may be considered according to the patient's level of anxiety and respiratory compromise, but only under continuous monitoring for decompensation.

Vascular Access and Monitors

Reliable, large-bore intravenous access is required as is the availability of a rapid infusion device. Typically, invasive arterial pressure monitoring is established prior to induction of general anesthesia allowing continuous monitoring of systemic arterial pressure and blood gases. Femoral artery pressure correlates best with central aortic pressure and avoids issues of poor radial artery line reliability associated with arm positioning on over-arm boards during lengthy surgical procedures. Arterial catheterization at a second site allows for redundancy and permits uninterrupted arterial pressure monitoring during frequent sampling of blood gas samples.

Central venous and pulmonary artery (PA) catheters may be placed before or after induction of anesthesia depending on availability of suitable peripheral venous access and the patient's ability to assume a recumbent position. PA catheters that allow

continuous measurement of cardiac output, RV loading conditions and mixed venous oxygen saturation (SvO_2) are preferable to allow rapid assessment of intraoperative changes in cardiac output and oxygen delivery. Although significant tricuspid regurgitation (TR) confounds cardiac output measurement by such catheters, SvO_2 measurements remain valuable provided the results are calibrated periodically against laboratory measurements of mixed venous blood gas and hemoglobin values.

Near infrared reflectance spectroscopy monitoring has proven very useful in monitoring the adequacy of cerebral oxygenation during both ECMO and CPB, as well as detecting lower limb ischemic complications related to femoral cannulation [3].

Awareness monitoring is probably routinely indicated during LTx on the basis of widespread use of muscle relaxants and the frequent occurrence hemodynamic depression necessitating reductions in end-tidal anesthetic gas concentrations to below 0.7 MAC.

Induction

Due to the lack of evidence of the superiority of any particular induction regimen, the choice is mainly influenced by individual and institutional preferences. The overall aim is to avoid factors which increase PVR (hypoxia, hypercarbia, acidosis, light anesthesia) and thereby prevent the occurrence of pulmonary hypertensive crisis resulting in decompensated RV failure and circulatory collapse. Avoidance of systemic hypotension and subsequent right ventricular (RV) hypoperfusion is of paramount importance. A common choice of induction medications is low dose fentanyl combined with etomidate. Adequate depth of anesthesia is necessary to avoid an abrupt sympathetically mediated increase in pulmonary vascular resistance (PVR) in response to laryngoscopy and tracheal intubation. At the same time, excessive anesthetic depth and its attendant hemodynamic depression is also to be avoided. For these reasons, rapid sequence induction may be undesirable and a brief period of gentle mask ventilation with cricoid pressure may be necessary to avoid rapid oxyhemoglobin desaturation while titrating anesthetics and achieving muscle relaxation.

Vasopressor and inotropic infusions should be ready for immediate infusion on primed and programmed infusion pumps; epinephrine infusion may be started preemptively to support the circulation during induction of anesthesia in patients with RV dysfunction. Patients judged to be at excessive risk of cardiovascular collapse upon induction of general anesthesia and positive pressure ventilation (e.g. patients with severe pulmonary hypertension and evidence of right ventricular (RV) dysfunction) may have femoral vessels accessed under local anesthesia in order to facilitate rapid cannulation should rescue with extracorporeal support become necessary. Depending on the surgical plan, preemptive cannulation and/or institution of extracorporeal membrane

oxygenation (ECMO) may even be considered prior to induction of anesthesia [4]. For all patients, we ensure that both the cardiothoracic surgeon and perfusionist are available with a primed cardiopulmonary bypass unit on standby should urgent institution of extracorporeal support become necessary.

Airway Management

A double lumen endobronchial tube (DLT) provides the most expedient means of lung isolation, particularly for bilateral sequential lung transplants during which a bronchial blocker would need to be repositioned multiple times. A left DLT is preferred due to the comparatively short length of the right main bronchus that necessitates withdrawal of a right DLT during bronchial anastomosis. DLTs also provide means of enabling postoperative independent lung ventilation, occasionally necessary following single lung transplant for patients with emphysema.

Intubation with a single lumen tracheal endotracheal tube may be initially preferable in two circumstances: (1) to more quickly and easily secure the airway when intubation is difficult, and (2) to facilitate toilet bronchoscopy and obtain bronchial washing for microbiological cultures in patients with cystic fibrosis and other forms of bronchiectasis.

Positioning

Single LTx can be performed either through a posterolateral thoracotomy in the lateral position (with access to the femoral vessels), or, via anterolateral thoracotomy in the supine position with a wedge placed under the operative side for better access. Double lung transplant is performed in the supine position, which increases shunt fraction during one-lung ventilation relative to the lateral position. One of three approaches can be used for double LTx: (1) bilateral transverse thoracosternotomy ("clamshell") incision, (2) bilateral anterolateral thoracotomies sparing the sternum, or (3) median sternotomy, depending on patient factors and institutional preference.

Arms are often abducted or elevated and secured to an over-arm board which improves surgical exposure, but impedes access to and can limit the usefulness of upper extremity venous and arterial catheters. Care should be taken during arm positioning to avoid excessive stretching of the brachial plexus and peripheral nerve compression.

Prior to skin prep and sterile draping, placement of multifunction external defibrillator pads is advisable to provide rapid means of cardioversion should unstable arrhythmias arise.

Transesophageal Echocardiography

Transesophageal echocardiography (TEE) is used extensively during lung transplant surgery for diagnostic and monitoring purposes. Intraoperative TEE during LTx is supported by ASA practice guidelines as "the nature of the planned surgery or the patient's known or suspected cardiovascular pathology might result in severe hemodynamic, pulmonary, or neurologic compromise" or in situations of unexplained persistent hypotension or hypoxia [5]. The authors routinely use TEE intraoperatively during LTx unless contraindicated and place the TEE probe immediately after tracheal intubation to begin treatments directed at optimization of right ventricular performance and loading conditions.

In patients with severe pulmonary hypertension being evaluated for lung transplantation who had already had transthoracic echocardiograms, Gorcsan et al found that TEE provided new findings that significantly altered surgical decision making in 25 % of patients [6].

The initial intraoperative TEE examination focuses on the assessment of right and left ventricular function, identification of intracardiac shunts (Fig. 9.2a–c), and baseline assessment of the pulmonary arteries and veins. Echocardiographic assessment of the right ventricle and tricuspid regurgitation (TR) is summarized in Tables 9.2 and 9.3. A dilated RV with an under-filled left ventricle (LV) suggests RV dysfunction (Fig. 9.3a, b).

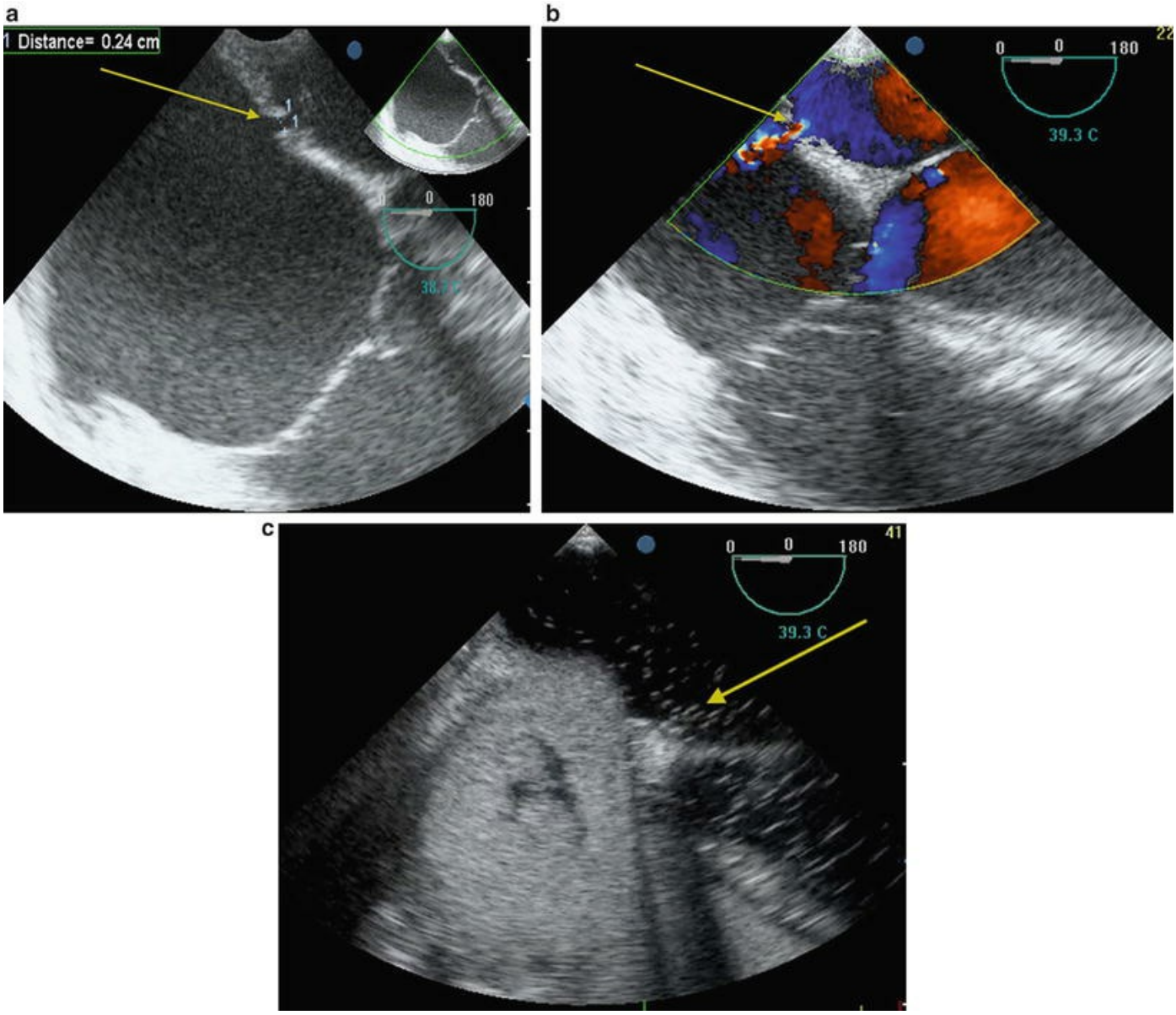

Fig. 9.2 Echocardiographic demonstration of intracardiac shunt in a patient undergoing double lung transplantation . (**a**) Two-dimensional echocardiography showing atrial septal defect (*arrow*). (**b**) Color Doppler showing flow through atrial septal defect (*arrow*). (**c**) Positive bubble study with air in the left side cardiac chambers (*arrow*)

Table 9.2 Echocardiographic assessment of the right heart

Parameter	Criteria
Right ventricular enlargement	RV size >2/3 LV size RV minor axis: >42 mm at the base >35 mm at the mid-level RV longitudinal axis >86 mm
Right ventricular systolic dysfunction:	RIMP: >0.40 by PW >0.55 by TDI

	TAPSE < 16 mm 2-D FAC < 35 % S′ < 10 cm/s
Tricuspid regurgitation jet max velocity	RV systolic pressure can be used to estimate PA systolic pressure if no PAC available
RV hypertrophy	Free wall thickness >5 mm
Leftward displacement of VS	RV *pressure* overload Entire cardiac cycle, but mostly in end-systole RV *volume* overload Mid- to late diastole

Data from Rudski et al. [66]
RV right ventricle, *LV* left ventricle, *RIMP* RV Index of myocardial performance, *TAPSE* tricuspid annular plane systolic excursion, *2-D FAC* 2-dimensional fractional area change, *SPAP* systolic pulmonary artery pressure, *PA* pulmonary artery, *PAC* pulmonary artery catheter, *VS* ventricular septum

Table 9.3 Echocardiographic criteria for *SEVERE* tricuspid regurgitation

Tricuspid valve: Abnormal/flail leaflet/poor coaptation
RV/RA/IVC usually dilated if chronic TR RV, at end-diastole: 2/3 LV size RV minor axis: >42 mm at the base, >35 mm at the mid-level RV longitudinal axis >86 mm RA, at end-diastole: Diameter or minor axis >44 mm Length or major axis >55 mm IVC > 21 mm
Jet area in central/non-eccentric jets on CFD: >10 cm^2
Vena contracta width >0.7 cm
PISA radius >0.9 cm Using baseline shift with the Nyquist limit at 28 cm/s
Jet signal density and contour on CW: Dense, triangular with early peaking
Hepatic vein systolic flow reversal

Data from Zoghbi et al. [67]
TR tricuspid regurgitation, *RV* right ventricle, *RA* right atrium, *IVC* inferior vena cava, *CFD* color flow Doppler, *PISA* proximal isovelocity surface area, *CW* continuous wave Doppler

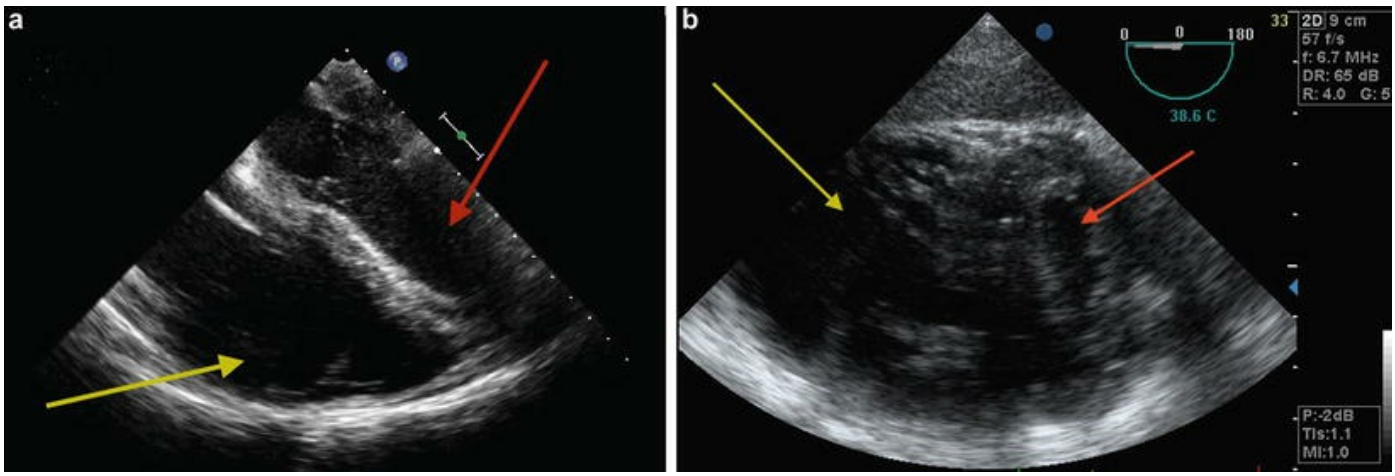

Fig. 9.3 TEE showing dilated RV with underfilled LV suggestive of RV dysfunction. (**a**) Midesophageal four chamber view. (**b**) Transgastric short-axis view; note flattening of the interventricular septum. *Red arrow* indicates LV and *yellow arrow* indicates RV

Patent foramen ovale (PFO) is a common finding that may result in intracardiac shunting and hypoxemia (Fig. 9.4). However, no definitive evidence is available to advise whether concomitant surgical closure is indicated at the time of lung transplant [7].

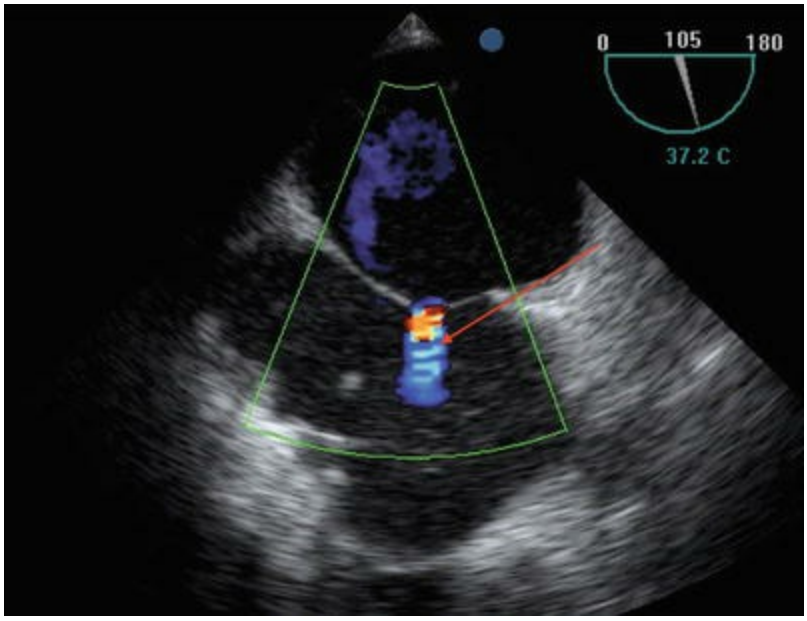

Fig. 9.4 Midesophageal bicaval view showing patent foramen ovale (*arrow*)

Similarly, no consensus exists on the surgical management of TR at the time of lung transplant. Frequently, no intervention is performed on the tricuspid valve, yet TR severity decreases in the post-transplant period due to a decrease in pulmonary vascular resistance (Fig. 9.5a, b) [7].

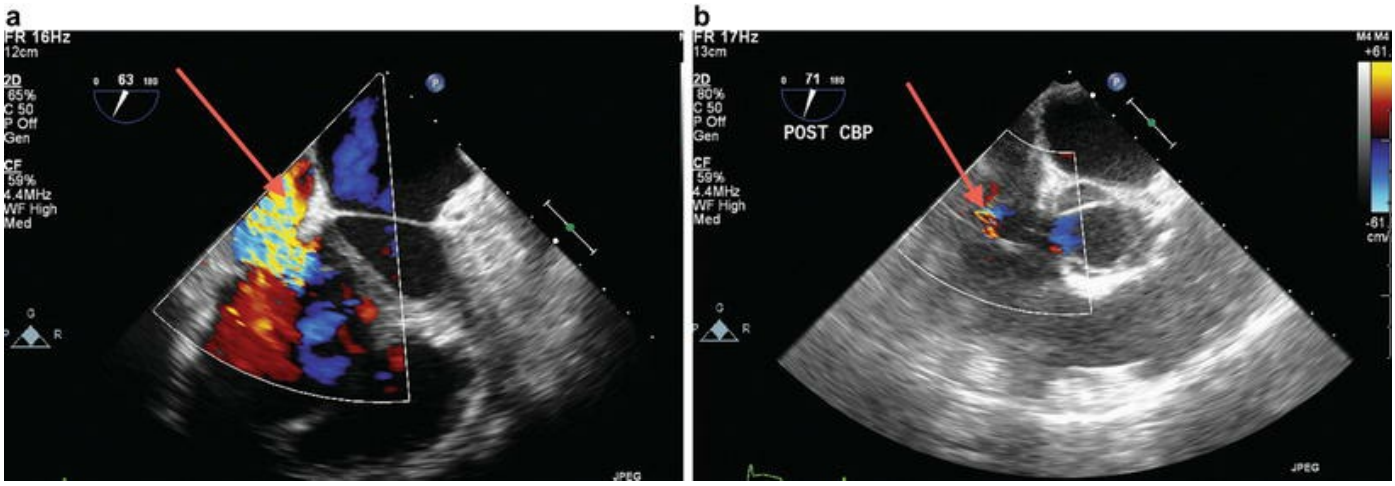

Fig. 9.5 Severe tricuspid regurgitation (TR) in a patient with end-stage lung disease and severe pulmonary hypertension. Severe prebypass TR (**a**) became mild (**b**) after new lung implantation with decreased pulmonary vascular resistance

All four pulmonary veins (PVs) should be identified by two-dimensional (2D) and color flow Doppler and the normal biphasic systolic-diastolic spectral Doppler flow pattern should be confirmed. Anatomic variation in PV drainage is common with the typical arrangement occurring in 60 % of the population, a right trifurcation pattern in 20 %, a right common pattern in 8 %, and a left trifurcation pattern in 8 % [8]. Scanning for aortic atheroma (Fig. 9.6) is also important, should the patient require cannulation for extracorporeal support.

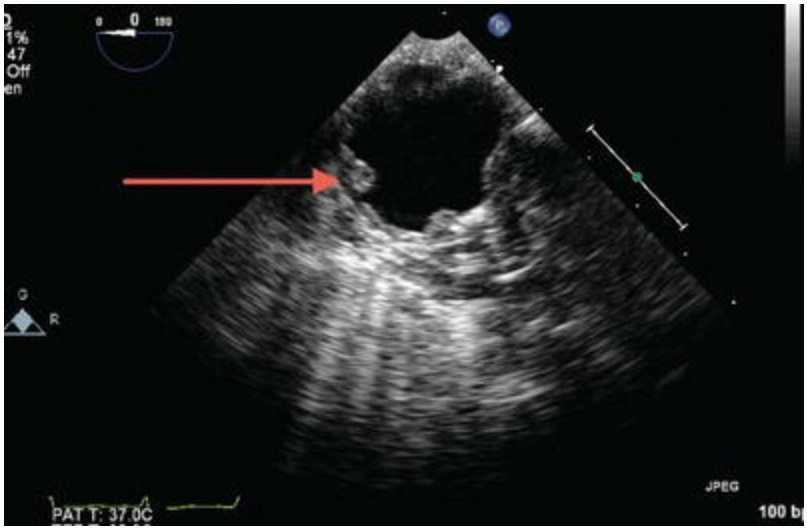

Fig. 9.6 Severe atheromatous disease of the aorta

TEE is also useful in cases of difficult PA catheter placement and to avoid too distal placement in the right or left PA that could increase risk of PA rupture or allow the catheter to become ensnared or damaged during pneumonectomy (Fig. 9.7).

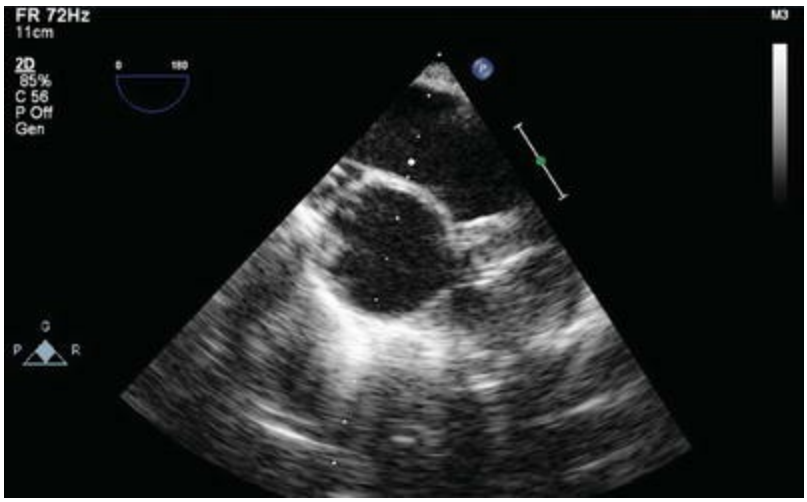

Fig. 9.7 Pulmonary artery catheter tip position (*arrow*) confirmed in the main pulmonary artery by TEE

Pneumonectomy: Anesthesia Considerations

The pneumonectomy phase requires attentive anesthetic management, particularly in cases of LTx performed off-pump. As discussed previously, in bilateral sequential LTx the lung with the least perfusion on the V/Q scan is transplanted first. One lung ventilation (OLV) is initiated of the contralateral lung allowing deflation of the operative lung and the hilar dissection is performed. If extensive adhesions are encountered (e.g. due to previous thoracic surgery, pleural disease, or bronchiectasis) the dissection may be lengthy and associated with significant bleeding or lung injury. Hypertrophy of the bronchial circulation seen in many LTx recipients may also predispose to hemorrhage. Close communication with the surgeon is necessary as surgical manipulation of mediastinal structures results in hemodynamic fluctuations. Surgical exposure of the left hilum is often more difficult because of the heart requiring more retraction and compression [9]; when manipulations cause significant hypotension the surgeon should be alerted so that he/she may modify technique or intermittently cease manipulation allowing hemodynamics to stabilize. Fluids, blood products, inotropes, pulmonary vasodilators, and vasopressors should be administered as indicated to maintain cardiac output and blood pressure, allowing surgical progress to continue.

Intraoperative hypoxemia can significantly impede surgical progress. Refractory hypoxemia during OLV can be ameliorated by PA occlusion, which reduces shunt fraction through the nonventilated lung. Test occlusion of the PA is first performed under close monitoring for hemodynamic deterioration, changes in PA pressures, and signs of RV dilation or hypokinesis on TEE. If test occlusion is tolerated the procedure can often proceed safely without the need for extracorporeal support. If there is a significant rise in PA pressure but no deterioration in RV function, pharmacologic treatment with

inhaled pulmonary vasodilators (nitric oxide (NO) or prostacyclin) may be administered to reduce PVR and off-pump transplantation may be attempted without extracorporeal support [10–12]. In contrast, if occlusion causes RV dilatation and dysfunction, the decision is made to support the circulation with ECMO or CPB. Next, the PA and veins are ligated and divided. Following this, the main bronchus is stapled and divided. Subsequently, the native lung is explanted and the hilar structures are prepared for allograft implantation.

During pneumonectomy and particularly incision of the bronchus, the anesthesiologist and should pay close attention to the heightened risk of airway fires with the use of electrocautery (Fig. 9.8a, b) [13]. Three components are necessary for a fire to occur: (1) fuel (e.g dry laparotomy sponge, polyvinylchloride endotracheal tube (ETT), or alcohol-based skin antiseptics), (2) an oxidizer enriched environment (oxygen or nitrous oxide) and (3) an ignition source (electrosurgical cautery or laser). Precautions should be taken to avoid chest cavity and airway fire, as this can result in significant mortality and morbidity (Table 9.4). In the event of a fire, oxygen should be immediately discontinued, saline instilled into the chest, and, if involved, the ETT should be removed and replaced. Bronchoscopic examination of the airway is required at this time to evaluate the extent of injury.

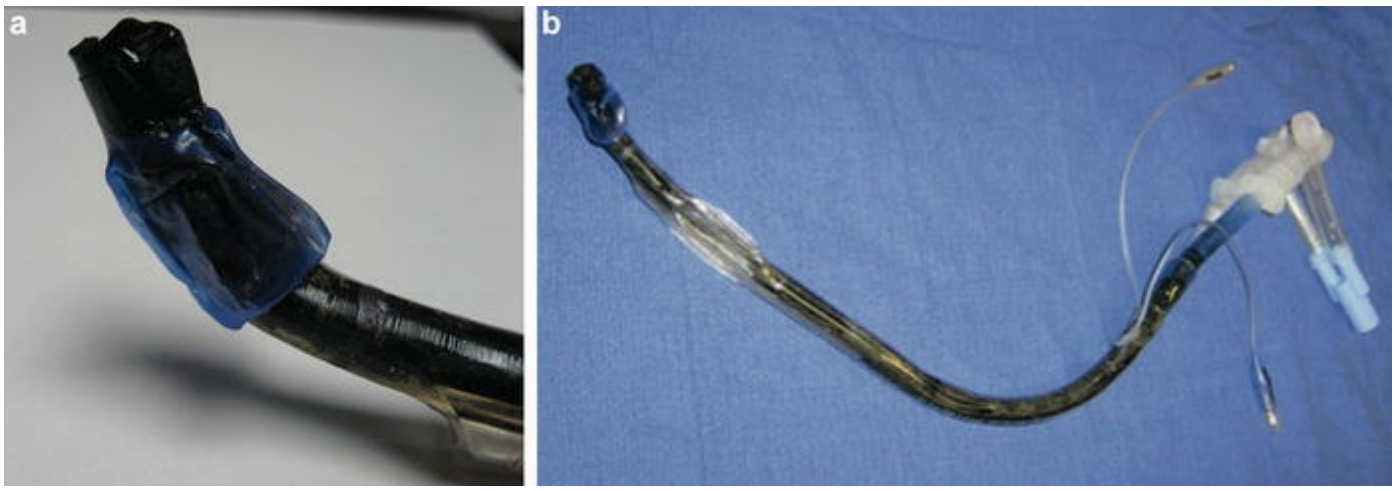

Fig. 9.8 (**a**, **b**) Airway fire during lung transplantation leading to complete destruction and charring of the double lumen endotracheal tube

Table 9.4 Prevention of surgical fires during lung transplantation

Preparation
• Lung transplant surgery represents a high-risk situation; all team members should be vigilant to avoid the use of an ignition source (electrocautery) in proximity to an oxidizer (oxygen) and fuel source (endotracheal tube, drapes, sponges)
• All personnel in theater should have predetermined and rehearsed actions to follow in the event of an airway fire according to institutional protocol, which should preferably be displayed in the operating theater
Prevention

- The surgeon should be advised against using electrocautery to enter the airways
- Delivered oxygen concentration should be reduced to the minimum required to avoid hypoxia. During off pump double-lung transplantation, the ipsilateral pulmonary artery may need to be snared down to improve arterial oxygen saturation by eliminating the intrapulmonary shunt through the nonventilated lung
- Wait a few minutes after reducing the oxygen concentration before approving the use of an ignition source
- Ensure that there is no air leak from around the ETT cuff into the operative field
- Continuous suction may be applied to the nonventilated lung prior to dividing the bronchus in order to scavenge excess oxygen
- The operating field may be flooded with carbon dioxide to minimize the oxidizer concentration if use of electrocautery is necessary to achieve hemostasis
- Avoid dry sponges when cauterizing near the airway

Extracorporeal Support

Extracorporeal cardiopulmonary support (including CPB or extracorporeal membrane oxygenation (ECMO)) may be necessary in the perioperative period. Preoperative ECMO support with a veno-venous (VV) or veno-arterial (VA) configuration is used increasingly as a bridge-to-transplant [13].

Intraoperative extracorporeal support may become necessary at several points during LTx: (1) for a concomitant cardiac surgical procedure (such as closure of atrial septal defect or coronary artery bypass grafting), (2) continuation of preexisting ECMO or conversion to another modality, (3) electively in patients with severe pulmonary hypertension, (4) due to refractory hypoxemia or acidosis during OLV for pneumonectomy, (5) hemodynamic instability, usually following anesthetic induction or related to RV failure at the time of PA occlusion, and (6) to support oxygenation after lung implantation when graft function is poor. If CPB is used to facilitate LTx, the heart is kept warm and beating unless cardioplegia is required for a cardiac repair.

Intraoperative support during LTx has historically been provided with CPB but in recent years VA ECMO has emerged as the method of choice in some centers including the University of Pittsburgh. Observational studies report improved outcomes using intraoperatitve ECMO relative to matched patients who received CPB [14, 15]. Compared to CPB, ECMO uses a smaller circuit with reduced priming volume and lacks both a venous reservoir and cardiotomy suction resulting in no air-blood contact, reduced heparin requirements, less hemodilution, and less severe activation of the systemic inflammatory response. ECMO also has the added versatility of preoperative application as a bridge-to-transplant or postoperative bridge-to-recovery in patients with severe primary graft dysfunction.

Cannulation sites for VA ECMO may be peripheral (femoral, internal jugular, or axillary vein to femoral or axillary artery) or central (right atrium to aorta). TEE is useful for confirming guidewire placement during cannulation and for confirming appropriate cannula position for both ECMO and CPB modalities. A detailed

description of perfusion management for LTx is described in elsewhere in this text.

During ECMO support, anesthesia management is directed at maintaining adequate intravascular volume as no venous reservoir is present, and monitoring for LV overdistension and continuing inotropic therapies to ensure LV ejection across the aortic valve and decrease risk of thrombus formation. TEE is helpful in troubleshooting low ECMO flows and can quickly differentiate between hypovolemia and poor venous drainage from cannula malposition, both of which are common during LTx. Note also that VA ECMO should prompt conversion to total IV anesthesia due to limited pulmonary blood flow and uptake of inhalation anesthetics.

Hemodynamic Support and Fluid Therapy

Hemodynamic instability during LTx is multifactorial and can be related to fluid deficits, blood loss, RV dysfunction, cardiac manipulation, and vasoplegia. Anesthesiologists must use clinical judgment to appropriately intervene during the surgical procedure, considering data obtained from observation of the surgical field, real-time monitors (e.g. mean arterial pressure, SaO_2, central venous pressure, PA pressure, SvO_2) and laboratory tests (e.g. pH, hemoglobin (Hb), PaO_2, lactate, base excess) to inform decisions. Until further research in this patient population defines specific target parameters, goal-directed hemodynamic therapy with fluids, blood products, and inotropic and/or vasoactive medications should seek to optimize cardiac output, filling pressures, SvO_2, and arterial blood gas values.

Commonly-used vasopressors include norepinephrine and vasopressin. Vasopressin may be preferable in patients with pulmonary hypertension because it does not constrict the pulmonary vasculature (in contrast to norepinephrine and other phenylephrine) and may in fact reduce PVR via endothelial release of NO [16]. Milrinone and epinephrine are the primary inotropes used in the authors' practice, often in combination. Milrinone has the advantage of reducing PVR and RV afterload but at the cost of a high incidence of systemic hypotension, particularly when a loading dose is given. Vasopressin again may have advantages in the setting of milrinone-related hypotension because of a more selective action on systemic vessels and more favorable effect on the PVR/SVR ratio [17].

Hemodynamic swings are especially challenging in LTx performed off-pump without the support of ECMO or CPB. In these circumstances, SvO_2 is a good monitor of the overall adequacy of systemic oxygen delivery, with persistent low SvO_2 (below 65 %) indicating the possible need to convert to an on-pump approach. Left-sided implantation can be more hemodynamically challenging than right-sided surgery. Partial clamping of the left atrium (LA) during anastomosis of the atrial cuff frequently causes hypotension, which is best treated by adjustment of the clamp rather than overzealous

fluid administration.

Fluid management is complicated by the lack of a validated intraoperative monitor of optimized fluid status and the susceptibility of the newly reimplanted allograft to the development of pulmonary edema due to increased vascular permeability [18] and lack of lymphatic drainage. Multiple observational studies have correlated liberal fluid administration with acute lung injury (ALI) after pneumonectomy [19] and pulmonary resection for cancer [20, 21]. Based on the above small series, some recommend restricting intraoperative fluid to 2000 mL or less [22]. Both colloids and crystalloids have been implicated in the genesis of ALI. In a retrospective analysis of LTx patients, increased intraoperative fluid infusion correlated with poorer oxygenation and reduced extubation rates [23].

Intraoperative red cell transfusion is aimed optimizing oxygen delivery to the tissues and therefore should be based on objective evidence of oxygen debt such as SvO2, arterial base deficit or lactate rather than hemoglobin triggers, although transfusion is generally indicated below a hemoglobin concentration of about 8 g/dL in the intraoperative setting. Massive transfusion may be required if there is extensive bleeding due to adhesive disease or surgical injury to the PA and the potential for severe coagulopathy exists. Patients with preoperative or intraoperative anticoagulation requirements because of extracorporeal support may also be at risk for increased bleeding. More evidence is needed to define the predictors of transfusion and transfusion-related outcomes in the LTx patient population. Cell salvage should be utilized as part of a blood conservation strategy unless a contraindication exists.

Mechanical Ventilation

Induction of anesthesia, muscle paralysis, positive pressure ventilation, and supine position can all induce changes in functional residual capacity and negatively impact gas exchange. Ventilation strategies for the diseased lungs preimplantation may vary compared to post-implantation ventilation of the graft lungs. For example, principles of high PEEP, low tidal volume lung-protective ventilation may not be feasible during one lung ventilation in patients with end-stage lung disease undergoing double lung transplant since the primary goal in this setting is to maintain adequate oxygenation and avoid severe respiratory acidosis until graft implantation, at which time ventilator settings can be adjusted. The following is a description of general ventilation strategies useful in the two major groups of LTx recipients, those with chronic obstructive lung disease and those with restrictive lung diseases such as pulmonary fibrosis.

Chronic obstructive pulmonary disease (COPD) including alpha-1 antitrypsin deficiency is the most common indication for adult LTx. Due to expiratory airflow obstruction there is gas trapping which can be progressive during positive pressure ventilation leading to dynamic hyperinflation and intrinsic positive end-expiratory

pressure (PEEP) , also known as auto-PEEP . Some degree of auto-PEEP is common during one lung ventilation, even in the absence of significant COPD [24, 25], and, if excessive, can lead to decreased cardiac preload, hypotension, and even cardiac arrest. The pressure- and flow-versus time displays on modern anesthesia ventilators can be used to readily identify auto-PEEP, showing nonzero end-expiratory flow and pressure. This entity should be considered in any LTx patient with hemodynamic deterioration as the treatment is unique (disconnect the circuit for a period of seconds until airway pressure decreases to zero) and failure to treat this problem will impede any other attempts at resuscitation.

With respect to optimizing ventilator settings for COPD patients, application of extrinsic PEEP is unlikely to improve oxygenation if significant intrinsic PEEP is present [26]. Ventilator settings are aimed at maximizing expiratory time by adjusting inspiratory flow, I:E ratio, and using lower rates (8–12 breaths per minute). Hypercapnia may be tolerated. Suggested clinical goals are minute ventilation (MV) <8 L/min, plateau airway pressures <30 mmHg [27]; higher *peak* airway pressures are acceptable as they are mostly dissipated within larger airways and do not reflect alveolar pressures.

Interstitial and fibrotic lung diseases such as idiopathic pulmonary fibrosis are characterized by destruction of lung architecture with increased lung stiffness (decreased lung compliance) and impaired gas exchange. Patients with end-stage IPF can be extremely difficult to ventilate and oxygenate and few evidence based recommendations can be made regarding optimal ventilator management [28]. Because of inhomogeneity of the lung parenchyma, conventional tidal volumes (8–10 mL/kg) are thought to cause overdistension of normal lung units and therefore ventilation with lower tidal (4–6 mL/kg ideal body weight) is reasonable with higher respiratory rates to maintain minute ventilation. On occasion, the ventilator integrated into the anesthesia gas machine proves inadequate and an intensive care unit (ICU) ventilator is required. High levels of PEEP may also overinflate intact lung units and do no improve oxygenation. High PEEP (>10 cm H_2O) in this patient population was independently associated with higher mortality [29].

Permissive Hypercapnia

The concept of permissive hypercapnia arose in the context of lung protective ventilation for acute lung injury and the adult respiratory distress syndrome, which commonly results in some degree of hypercapnia in order to avoid the deleterious effects of stretch. Subsequent investigations have raised the question whether hypercapnia may in fact confer a protective effect in the pathogenesis of lung injury [30].

While not necessarily intentional, some degree of hypercapnia is invariably

encountered during LTx and occasionally reaches extreme levels ($PaCO_2 > 100$), which may be well tolerated by the patient (if not the anesthesiologist) until severe levels of acidosis occur. Below a pH of about 7.2 evidence of myocardial depression is observable by echocardiography which can then be reversed by administration of tromethamine (THAM), a buffer that does not increase pCO_2 [31]. As a side note, it would not be appropriate to administer bicarbonate in the setting of isolated respiratory acidosis as the CO_2 created cannot be eliminated.

One related area of uncertainty relates to whether a relatively abrupt normalization of $PaCO_2$ levels that may be seen following ventilation of the new lungs during LTx could cause dangerous decreases in cerebral blood flow. The authors have observed decreases in cerebral oxygen saturations in several patients this setting, suggesting clinically significant cerebral vasoconstriction, but there has been no observable adverse impact on postoperative neurological status. This clinical observation certainly needs further investigation.

Anesthetic Maintenance

Inhalation anesthetics and IV narcotics provide maintenance of anesthesia and analgesia, respectively. A high-dose narcotic technique is no longer practiced at our institution. Small intermittent boluses of IV fentanyl (100–200 μg/h) are most commonly used for intraoperative analgesia. During OLV, inhibition of hypoxic pulmonary vasoconstriction by newer volatile agents at ≤1 MAC does not significantly affect oxygenation, except perhaps in the most marginal patients [32, 33]. Ischemic preconditioning is often cited as an advantage of volatile agents.

Nitrous oxide (N_2O) is avoided during LTx due to several undesirable properties: (1) Like O_2, N_2O is an oxidizer and should not be used during airway surgery with heightened risk of fires. (2) N_2O has been shown to have pulmonary vasoconstrictive properties in patients with elevated PVR [34]. (3) N_2O expands the volume of air emboli and both venous and arterial air emboli are possible during LTx.

As noted above, Patients receiving circulatory support with VA ECMO may not have sufficient pulmonary blood flow to ensure adequate uptake and distribution of inhalation anesthetics, increasing risk of intraoperative awareness. An infusion of intravenous anesthetic such as propofol is useful in this scenario to maintain hypnosis and, if titrated based on an awareness monitor such as bispectral index, hypotension can be minimized. If LTx is performed on full CPB, an inhalation anesthetic can be delivered through a vaporizer attached the CPB circuit.

Temperature Management

While often difficult to maintain, normothermia is the goal as significant hypothermia is associated with coagulopathy and platelet dysfunction, atrial and ventricular dysrhythmias, and increased pulmonary vascular resistance. Toward this goal, use of a fluid warmer is necessary. Due to the wide surgical field there is limited access to place forced air blankets over the patient except above the ether screen covering the head and arms and from mid-thigh down, making underbody warming blankets useful.

Graft Implantation and Reperfusion

For a detailed discussion of bilateral sequential LTx surgical technique at the University of Pittsburgh, see the excellent description published recently by our surgical colleagues [35]. Briefly, the allograft is kept cool with crushed sterile ice or a cooling jacket to minimize warm ischemic time during back table preparation and when it is placed into the recipient pleural cavity.

Implantation proceeds sequentially, commencing with anastomosis of the most posterior structure, the bronchus. The bronchial anastomosis is immediately inspected by fiberoptic bronchoscopy , which can be performed by the anesthesiologist while the surgeon views real-time images on a video display. The graft is flushed with pulmoplegia solution delivered into the open PA and flowing out the PVs to remove any air or vasoactive substances. This is followed by the PA anastomosis which remains untied and the PA remains clamped. Lastly the left atrial anastomosis is fashioned where a small cuff of donor left atrium incorporating both PV orifices is sutured to the recipient left atrium. Methylprednisolone 250-500 mg is administered as the left atrial anastomosis is near completion. The left atrial suture line is also left untied allowing for further flushing and de-airing with warm blood “hotshot” pulmoplegia, thereby reperfusing the allograft. The PV clamp is then partially opened to de-air and TEE is monitored for evidence of left-sided air (Fig. 9.9).

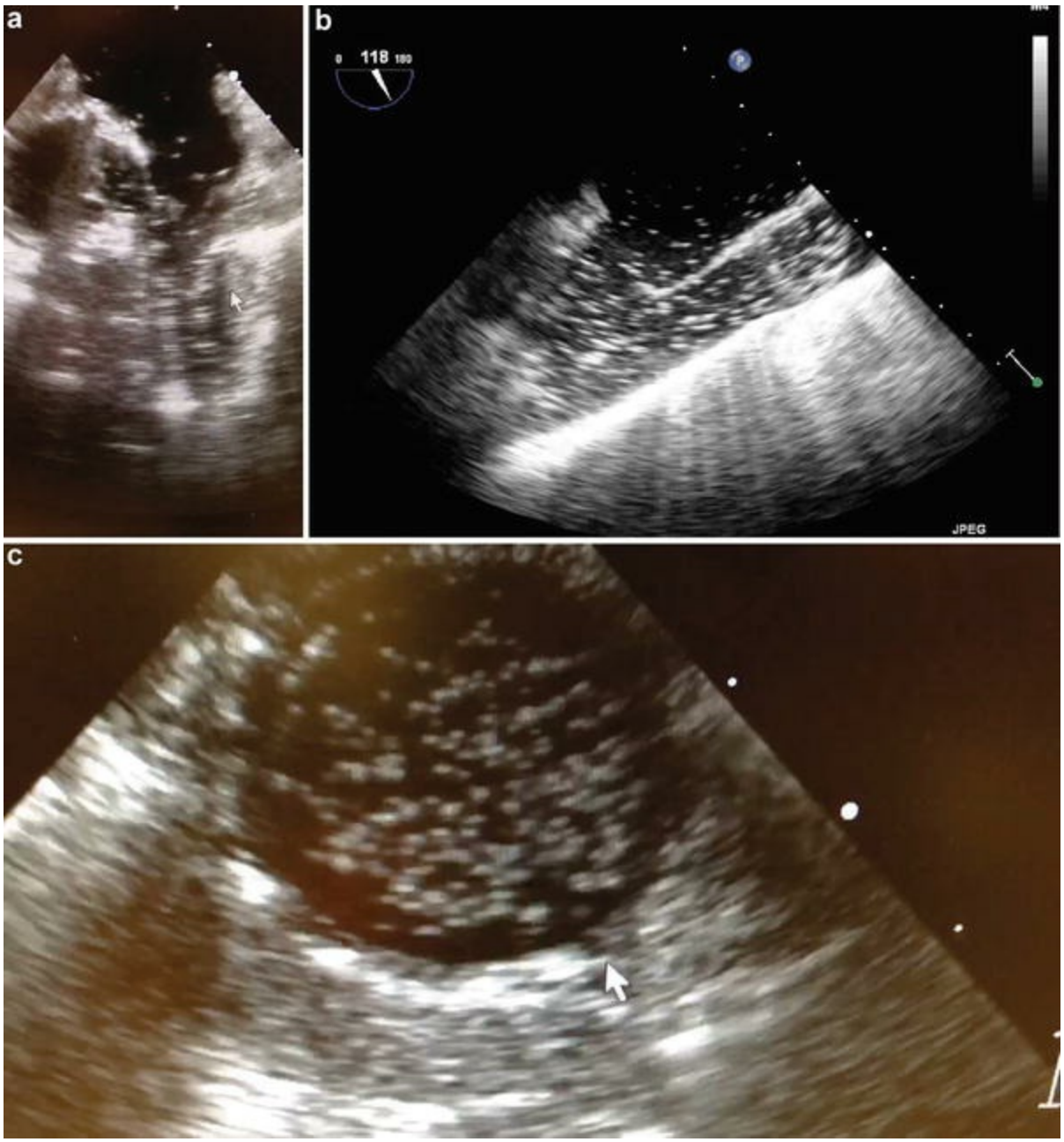

Fig. 9.9 Air embolism during lung transplantation diagnosed by TEE. (**a**) Air in the left atrium and left ventricle. (**b**) Air in the left ventricle and ascending aorta. (**c**) Air in the descending aorta

Le Guen et al. described a case of cerebral air embolism during LTx due to inadequate deairing which was diagnosed by the finding of intracardiac air on TEE and accompanied by a fall in bispectral index; the patient recovered after hyperbaric oxygen therapy [36]. ECMO circuits and cannulation sites can also be a source for air entrainment during LTx.

Reperfusion proceeds gradually as the PA is unclamped over a period of 5–15 min to prevent graft hyperperfusion and the PA suture line is tied down. Reperfusion may be associated with systemic hypotension due to circulation of vasoactive substances,

requiring anticipation and preemptive adjustment of hemodynamic support.

Ventilation of the allograft is initiated with minimal FiO_2 (<30 %) due to evidence that reactive oxygen species are involved in pathogenesis of reperfusion injury [37]. Gentle recruitment maneuvers are combined with moderate PEEP (8–10 cm H_2O) to overcome alveolar de-recruitment. Tidal volumes (V_T) of 6 mL/kg (based on donor ideal body weight) are used and plateau pressures are limited to <30 cm H_2O based on accumulating evidence that lung protective ventilation reduces mortality in the adult respiratory distress syndrome [38, 39] and that traditional tidal volume ventilation (>6–8 mL/kg) is injurious to patients who are at risk of developing ALI, even when used for relatively short periods of time during surgery [40]. LTx recipients are certainly at risk of ALI given the insult of ischemia-reperfusion and that OLV in and of itself has been identified as a risk factor for ALI [20, 41]. Furthermore, a trial randomizing potential lung donors to lower tidal volumes (6–8 mL/kg) versus traditional tidal volumes (10–15 mL/kg) improved the suitability of lungs for donation [42].

The next step in sequential bilateral off-pump LTx requires OLV of the newly implanted allograft during second lung pneumonectomy. This creates a shunt; hypoxemia will persist until the PA of the second lung is snared. Even if the first lung was implantated without extracorporeal support, patients may require it at this time depending upon allograft function, technical factors, bleeding, hemodynamic stability. The sequence of second LTx is then repeated in identical fashion.

In bilateral sequential LTx performed on CPB or VA ECMO, ventilation and perfusion of the allograft continue during implantation of the second allograft. Maintaining some pulsatility in the PA waveform is recommended and can be achieved by partially clamping the venous line. Patients are then weaned off of extracorporeal support after ventilation and perfusion to the second lung is established. Arterial blood gas is checked before protamine administration. Blood products are given as indicated by clinical bleeding and point of care coagulation tests. PEEP and FiO_2 can be increased to maintain PaO_2 > 70 mmHg and SpO_2 > 90 %. Postoperative VV or VA ECMO support may be required in patients with significant graft dysfunction, with the ECMO configuration determined by whether there is an isolated problem with gas exchange (VV) or need for circulatory support (VA).

Postprocedure TEE

Evaluation of anastomotic sites during LTx is a class IIb indication for intraoperative echocardiography according to American College of Cardiology/American Heart Association/Amercian Society of Echocardiography guidelines [43].

The right PA anastomosis can easily be evaluated by TEE, whereas visualization of the left PA anastomosis is variable. Although no commonly accepted echocardiographic

criteria exist for PA anastomotic stenosis, the diagnosis is suspected if the luminal diameter is less than 75 % compared to the proximal portion of the artery or if turbulent color flow is present [7]. The diagnosis may be confirmed by invasive measurements demonstrating a pressure gradient across the anastomosis [44].

Pulmonary venous obstruction is a common and serious complication after LTx [45–47], for which effective treatment exists if diagnosed in a timely fashion. PV obstruction may occur due to thrombosis, anastomotic stenosis, or kinking of the PVs. 2D examination should exclude thrombus and/or narrowing of PV diameter (normal PV diameter >0.5 cm). Color flow Doppler should show laminar PV flow, without significant turbulence or flow acceleration. Normal pulse wave Doppler velocities are <60 cm/s with hemodynamically significant stenosis suggested by velocities >100 cm/s or peak gradients >10–12 mmHg [7] (Fig. 9.10). Doppler measurements are affected by multiple factors including cardiac output and left atrial pressure; therefore elevated velocities are expected during bilateral sequential LTx until after implantation of the second lung. Furthermore, obstruction may be present without elevated velocities in low output states in which case continuous PV flow may be seen with velocity failing to return to zero [48]. As with the left PA, imaging of the left inferior PV may be difficult with TEE and epicardial or surface ultrasound may be a useful adjunct [49].

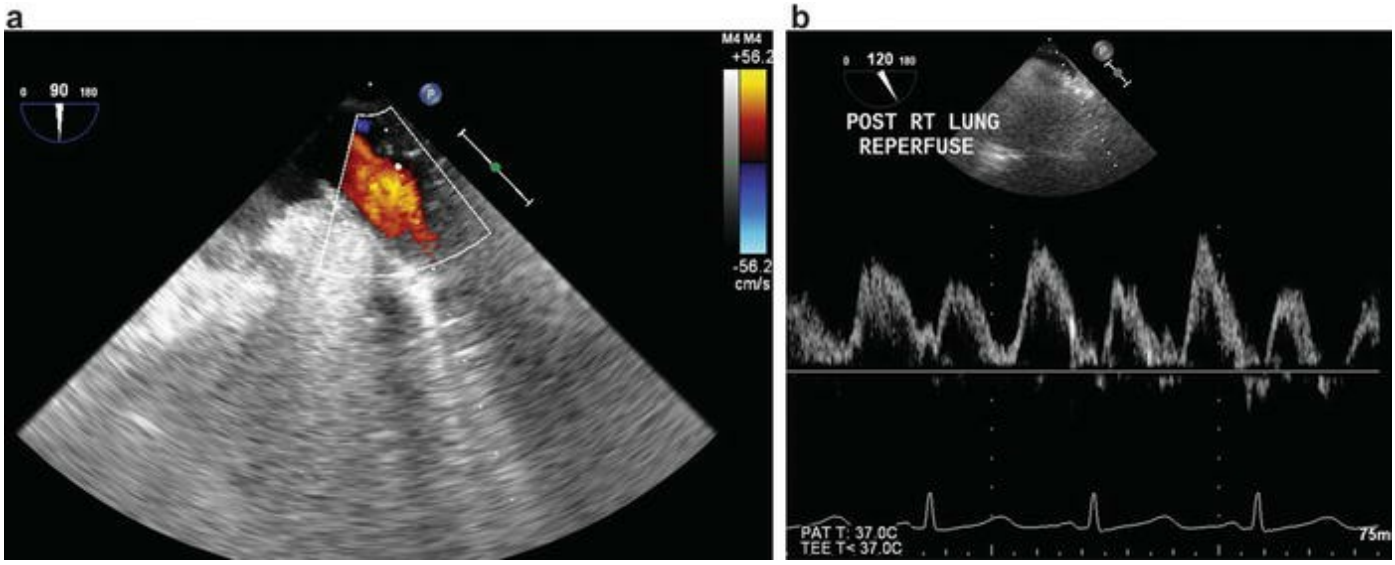

Fig. 9.10 Post lung transplantation evaluation of pulmonary venous anastomosis by color flow (**a**) and spectral Doppler (**b**)

Biventricular size and function, severity of tricuspid regurgitation, presence or absence of interatrial shunting, and integrity of the aorta should all be evaluated and documented as part of the comprehensive post-procedure exam.

Closure and Transport

Three chest tubes are placed in each pleural cavity, as well as a pericardial drain if the pericardium was opened. Hemostasis is assured. The thoracotomy incision may be closed primarily or left open if there is significant PGD, size mismatch or coagulopathic bleeding. If a DLT is in place, it is changed to a single lumen ETT. Significant airway edema may complicate the ETT exchange, and should be evaluated for by careful. Direct or video- laryngoscopic examination prior to removal of the DLT. The use of an airway exchange catheter should be considered to facilitate reintubation and to provide a means for emergency oxygenation should intubation failure occur. Flexible bronchoscopy is performed and a nasoenteral feeding tube is inserted under fiberoptic surveillance to avoid misplacement of the feeding tube into the airway. The patient is transported with intravenous sedation as tolerated to the ICU with continuous monitoring, ventilatory support. If used during the procedure, inhaled NO is continued during transport as sudden withdrawal of NO risks catastrophic rebound pulmonary hypertension [50]). If the patient remains on ECMO support at completion of surgery, the patient is accompanied by a perfusionist. Emergency airway equipment and drugs should be readily available, as critical events can occur during transport and transition of patient care.

Special Conditions

Cystic Fibrosis

It is important to recognize that cystic fibrosis (CF) is a multi-system disease and a multi-disciplinary approach involving pulmonologists, infectious disease specialists, endocrinologists, gastroenterologists, hepatologists, nutrition specialists, intensivists, and respiratory therapists is essential for optimal perioperative outcomes. Understanding systemic involvement is important to provide optimal intraoperative care [51] (Table 9.5). Bronchiectasis due to CF and other causes of impaired ciliary clearance is associated with secretions that are thick, inspissated, and difficult to manage, particularly with a 3.5 mm fiberoptic bronchoscope. Initial single lumen intubation is useful to allow thorough bronchoscopic lavage of secretions using a standard adult size bronchoscope. Chronic airway infection is common and may involve multidrug-resistant organisms necessitating specific antimicrobial coverage in consultation with infectious disease and pulmonary medicine specialists. During LTx surgery, after explantation of the native lung, the open bronchus is irrigated with povidone-iodine/sterile saline solution instilled through the DLT (Table 9.6) and pulsatile antibiotic irrigation is applied to the pleural cavity in the surgical field.

Table 9.5 Cystic Fibrosis systemic involvement

Pulmonary	Nasal polyps and sinusitis Impaired mucociliary clearance, viscous secretions, mucous plugging, and atelectasis Respiratory tract colonization and infections, often with antimicrobial resistance (*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Hemophilus influenza*, *Stenotrophomonas maltophilia*, Gram negative organisms, *Burkholderia cepacia*, *Aspergillus fumigatus*) Obstructive disease with apical blebs and spontaneous pneumothorax Chronic hypoxia, pulmonary hypertension, and cor pulmonale
Pancreas	Exocrine involvement requiring enzyme supplements Endocrine involvement with diabetes mellitus requiring insulin perioperatively
Liver	Cirrhosis, abnormal liver function tests impairing metabolism of drugs Hypoalbuminemia altering pharmacokinetics of drugs, coagulation problems Gall stones, cholecystitis
Gastrointestinal tract	Distal intestinal obstruction syndrome (DIOS)—avoid dehydration, minimize opioids which impair GI motility, continue nutritional support and fat soluble vitamin supplementation (A, D, E, K) perioperatively
Bone disease	Low mineral density—careful during patient movement and positioning

Table 9.6 Procedure for pulmonary lavage during lung transplantation for suppurative pulmonary disease

Scope This document applies to all lung transplant procedures performed for suppurative lung diseases at the University of Pittsburgh Health System. It does not apply to lung transplantation performed for any other indication Procedure 1. Preprocedural lavage: (a) Patient is to be intubated with a single lumen endotracheal tube (SLETT) for purposes of lavage. Suction all the secretions before starting lavage. Lavage shall be performed by the anesthesiologist with warm saline using a bulb syringe to instill and suction fluid from the SLETT. Care should be taken to ensure that the patient does not endure excessive SpO2 decreases. Care should be taken to suction any remaining fluid from the lungs using an airway suction catheter (b) When no purulent material is evident in the returned solution, lavage can be terminated and the patient is then reintubated with an appropriately sized double lumen endotracheal tube (DLETT) 2. Preimplantation lavage: (a) Following division of the bronchus and at the appropriate time as indicated by the surgeon, the recipient trachea and bronchus is irrigated with a 1:1 warm saline and betadine solution (b) Confirmation must be obtained of the correct lumen of the DLETT to be lavaged; closed-loop communication with the surgeon is essential to avoid the solution from being instilled into the wrong side (c) Confirm the correct position of DLETT and bronchial cuff inflation before starting lavage (d) This is to occur with the airway open prior to the anastamosis of the bronchus with the donor lung. Fluid is to be instilled with a clean bulb syringe. The fluid will be suctioned by the surgeon in the surgical field. Care must be taken to coordinate this procedure with the surgeon so as to avoid unnecessary contamination of the field

Connective Tissue Diseases and Other Uncommon Disorders

Systemic sclerosis or scleroderma is an autoimmune disorder characterized by

increased production and accumulation of collagen in various tissues including the skin, blood vessels, mucous membranes, lungs, heart, and kidneys. Ventilator management is similar to other restrictive lung diseases. Anesthesia considerations related to other organ system involvement are detailed in reference [52] and summarized in Table 9.7. It is prudent to avoid radial artery cannulation in patients with Raynaud's phenomenon. Difficult intubation, especially with DLT, should be anticipated due to small mouth opening and fibrosis in the neck limiting extension and positioning. Esophageal pathology like thickening, ulceration, and dilatation are not uncommon and may predispose to pulmonary aspiration. History of dysphagia and regurgitation should alert the anesthesiologist to review preoperative gastro-esophageal endoscopy findings before TEE insertion. If TEE risk is deemed acceptable, consideration may be given to use of a pediatric transducer and minimizing Manipulation of the TEE probe within the esophagus. In addition to RV dysfunction related to pulmonary hypertension, diastolic dysfunction may also complicate hemodynamic management.

Table 9.7 Scleroderma —systemic manifestations and anesthetic implications

Scleroderma manifestations	Anesthetic considerations
Raynaud's phenomenon	Avoid excessive peripheral vasoconstriction Avoid hypothermia Attention with high dose vasopressors Avoid radial arterial line placement Brachial vs. femoral arterial line
Dermal thickening Calcifications Contractures	Difficult peripheral IV placement Nerve entrapment neuropathies Attention to positioning and padding
Skin tightening, microstomia, limited neck extension	Difficult intubation
Telangiectasias	Oral and/or nasal bleeding
Esophageal dilatation, decreased lower esophageal sphincter tone	Risk of aspiration
Intestinal malabsorption	Decreased vitamin K dependent factors Risk of coagulopathy
Renal disease	Hypertension Requires higher MAP for autoregulation Decreased renal clearance of drugs Scleroderma renal crisis Oliguric ARF, microangiopathic hemolytic anemia, thrombocytopenia, pulmonary edema, HA, blurred vision, hypertensive encephalopathy, generalized seizures
Immunosuppression	Adrenal insufficiency May requires perioperative stress dose glucocorticioid coverage
Pulmonary hypertension	Avoid further increase in PVR

	Risk of RV failure
Myocardial infarction	Systolic dysfunction
Pericardial effusion	Risk of tamponade physiology depending on chronicity and volume of fluid
Myocardial fibrosis Myocarditis Pericarditis	Conduction defects Need to continue home antiarrhythmics Pacemaker/defibrillator in situ Intraoperative arrhythmias requiring cardioversion/defibrillation Coronary vasospasm Ventricular hypertrophy Increased myocardial oxygen demand Diastolic dysfunction Dependence on SR/atrial contribution to CO Dependence on slow heart HR Risk of pulmonary edema

IV intravenous, *MAP* mean arterial pressure, *ARF* acute renal failure, *HA* headache, *PVR* pulmonary vascular resistance, *RV* right ventricle, *SR* sinus rhythm, *CO* cardiac output, *HR* heart rate

Sarcoidosis, systemic lupus erythematosus, rheumatoid arthritis, polymyositis, lymphangioleiomyomatosis, and interstitial pneumonitis are other systemic conditions associated with end-stage lung disease. Detailed description of these diseases and their manifestations are not within the scope of this textbook. Anesthesiologists should be aware of the systemic manifestations of these respective diseases and take appropriate precautions when managing such patients for LTx.

Pain Management

Thoracic epidural analgesia (TEA) is employed at many centers as the foundation of a multimodal strategy to control pain, optimize pulmonary function, and facilitate extubation after LTx. Proponents cite superior analgesia with reduced opioid requirements and several small observational studies in the LTx population suggest that TEA as part of an early extubation strategy is feasible [53–56]. We do not place epidural catheters preoperatively due to several concerns. With respect to timing, advance placement may expose the patient to all the risk with no benefit if surgery is canceled, and the timing of LTx often requires the patient be anesthetized and prepared for surgery expeditiously as soon as donor lungs are visualized. If a “bloody tap” occurs, surgery cannot be postponed. Furthermore, we are unable to predict which patients will require heparinization for ECMO or CPB, or which patients will develop significant coagulopathy. Evaluation for signs and symptoms of epidural hematoma is problematic in patients who are anesthetized or sedated postoperatively. For these

reasons, we prefer to place epidural catheters, if needed, after surgery around the time of extubation. Many patients are comfortable and have sufficient respiratory function to be extubated using only opioid and nonopioid analgesics. Continuous thoracic paravertebral analgesia, used successfully in non-LTx thoracic surgery [57], may present an alternative to TEA with the possible advantage of less hypotension but may expose patients to higher risk of systemic local anesthetic toxicity when bilateral catheters are required; further research is required in the LTx population.

Primary Graft Dysfunction

Primary graft dysfunction (PGD) (synonymous with lung ischemia-reperfusion injury) encompasses a spectrum of ALI occurring in the first 72 h post-LTx characterized by severe hypoxemia and radiographic evidence of diffuse alveolar infiltrates [58]. PGD is a common complication affecting 10–57 % of patients, depending on the definition used, and independently predicts both short and long term mortality with possible links to the development of bronchiolitis obliterans syndrome [59]. PGD shares clinical and histopathologic features with other forms of ALI. At the severe end of the spectrum, International Society for Heart & Lung Transplantation grade 3 PGD shares a clinical definition with ARDS [60]. PGD is characterized by increased pulmonary vascular permeability leading to noncardiogenic pulmonary edema, reduced lung compliance, and increased airway pressures.

Management of PGD is supportive and follows protective ventilation principles used in ARDS. Excess fluid administration must be avoided in the setting of increased pulmonary vascular permeability, but adequate perfusion to end-organs and bronchial anastomoses must be maintained [61]. iNO has attracted interest in the treatment of PGD and may reduce PA pressures and improve oxygenation in the setting of established PGD [62, 63]. However, no randomized trials have demonstrated any outcome benefit. Trials examining iNO started at the time of reperfusion have found no benefit in the prevention of PGD [64, 65]. In severe cases, VV ECMO may be required; at our center we advocate early VV ECMO when patients are clinically deteriorating and require $FiO_2 >$ 70 % to prevent further ventilator induced lung injury.

Conclusion

Perioperative management of patients undergoing LTx is complex and requires close coordination between anesthesiologists, surgeons, perfusionists, and critical care physicians. Thorough preoperative evaluation, careful anesthesia induction, intensive intraoperative monitoring, meticulous titration of anesthetic and vasoactive medications, and clear communication with the surgical and postoperative care team are essential for optimal outcomes. LTx can frequently be performed without extracorporeal support; the

decision to implement extracorporeal support is based on clinical judgment and consideration of preoperative information and intraoperative stability. Intraoperative TEE plays an important role in hemodynamic management and detecting and early detection and management of complications. PGD is a common source of morbidity and mortality and requires optimal supportive care by the intraoperative and postoperative teams. Postoperative pain management with epidural block may facilitate recovery after lung Tx.

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10. Postoperative Critical Care of Lung Transplant Patients

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Introduction

Lung transplantation is the modality of choice for treatment of end-stage lung disease. The use of lung transplantation has evolved considerably during the last 30 years since the performance of the first successful lung transplant at Toronto General Hospital [1]. There are several areas of progress that have promoted lung transplantation. This includes the development of potent immunosuppressant medications, advances in organ donor preservation, the introduction of new antimicrobial regimens, and the refinement in surgical techniques. More importantly, there is an increased understanding of the genetic and molecular mechanisms of immunity as well as an improved knowledge of the pathophysiology and complications underlying the lung transplant recipient, which

has resulted in the development of advanced perioperative care and optimization protocols.

According to the Thirtieth Adult Lung and Heart-Lung Transplant Report of the registry of the International Society for Heart and Lung Transplantation (ISHLT) published in 2013, the actual median survival for adults undergoing lung transplant is 5.6 years, with unadjusted survival rates of 88 % at 3 months, 79 % at 1 year, 64 % at 3 years, 53 % at 5 years and 31 % at 10 years [2]. Despite a notable improvement in short-, and mid-term survival, the long-term survival rates are less than ideal. Another significant issue is the limited availability of donor organs. The role of the multidisciplinary critical care team is to prevent complications and to provide prompt diagnosis and expedite treatment of early complications to minimize their impact in survival and long-term outcomes. Consequently, a comprehensive knowledge of the complications and critical issues relevant to lung transplant recipients is of particular importance for the contemporary intensive care professional. This chapter will focus on the immediate postoperative critical care issues from an organ system perspective, as well as complications that require care of the lung transplant patient in the intensive care unit (ICU).

Critical Care Issues in the Post-Lung Transplant Patient

The lung transplant recipient has progressive end-stage lung disease in maximal medical treatment with limited life expectancy. In most cases, transplant candidates have multiple organ systems compromised due to chronic effects of impaired lung function and gas exchange, as well as the effects of the primary disease process in other organ systems. Ideally, during the preoperative period such effects in organ function are identified and controlled and the overall status of the patient should be optimized. However, this patient population is highly susceptible to further organ function deterioration. As such, the combination of their overall fragile baseline status and the multiple intraoperative and postoperative physiologic alterations can result in significant multiorgan system dysfunction. The issues facing the critically ill lung transplant recipient during postoperative care in the ICU will be discussed in an organ system approach.

Neurologic Complications in Lung Transplant Recipients

Lung transplant recipients are exposed to chronic hypoxia due to end-stage lung disease. The presence of chronic hypoxia and hypercarbia with respiratory acidosis may contribute to cerebral hypoperfusion with neuronal damage, and to alteration in mechanisms of cerebral blood flow autoregulation and subsequent cerebral edema. This baseline injury represents a substrate, which added to significant perioperative events,

such as hemodynamic instability, hypoxia, hypercarbia, and thromboembolism, result in an increased risk for neurologic complications. In a recent study of a large cohort of lung transplant patients the incidence of early major neurologic complications was 9.2 %. The most common neurologic complications reported were stroke (41 %), severe metabolic encephalopathy (37 %), and severe hyperammonemia (6 %). The factors associated with increased risk of death from early major neurologic complications were advanced age, prolonged use of cardiopulmonary bypass (CPB), and severe primary graft dysfunction (PGD). The presence of neurologic complications after lung transplant carried a significant increase in morbidity and mortality, as well as worse survival at both short- and long-term [3].

The main source of stroke in this setting is thromboembolism. A well-recognized mechanism of cerebral embolism is thrombosis of the pulmonary vein anastomosis, which has been reported to occur in 15 % of patients. Unfortunately, this is not always diagnosed by intraoperative transesophageal echocardiography (TEE) [4–6]. Other important mechanisms include atrial fibrillation and other atrial arrhythmias, as well as the use of CPB and veno-arterial extracorporeal membrane oxygenation (VA ECMO) .

The occurrence of other complications including encephalopathy and delirium have been explained in part by the superimposed effects of embolic injury and perioperative inflammatory response exacerbating the baseline neuronal injury present as consequence of end-stage lung disease, making these patients more prone to manifest the effects of embolic neurologic injury. However, although delirium is a multifactorial event, it can also be caused specifically by neurotoxicity related with the use of medications such as corticosteroids and calcineurin inhibitors. In any case of an acute posttransplant confusional state, consideration should be given to switching from FK-506 to cyclosporine or from calcineurin inhibitors to other alternative immunosuppressants. A complete neurologic evaluation should include an assessment for cardioembolic source with TEE (i.e., pulmonary vein thrombus, intramural thrombosis, patent foramen ovale), and a carotid Doppler ultrasound. There should also be a complete metabolic encephalopathy evaluation. The suspicion of any new neurologic deficit in the immediate postoperative period should trigger an expedited evaluation to rule out acute ischemic or hemorrhagic cerebrovascular events. In general, a cerebral computed tomography (CT) scan is obtained immediately with a follow up at 24 or 48 h.

The occurrence of *posterior reversible encephalopathy syndrome* (PRES) in lung transplant recipients is associated to calcineurin inhibitor therapy and uncontrolled systemic hypertension. It constitutes a differential diagnosis for altered mental status accompanied with neurologic deficits. Management should focus on alternative immunosuppression therapy and blood pressure control. The definitive diagnosis requires brain magnetic resonance imaging (MRI) [7], however in many patients this is contraindicated due to presence of metallic surgical devices. In addition, safe transport and monitoring of patients in the MRI suite represents a logistic challenge for the ICU

team.

It is important to avoid secondary injury after neurologic events in particular stroke, in order to prevent extension of the primary damage, and improve functional outcome. In this regard, adequate hemodynamics (with optimization of cerebral perfusion pressure and oxygen delivery), normothermia, normoglycemia, pain control, and anxiety management are necessary for treatment of lung transplant patients with neurologic injury. Preventive measures, in particular meticulous surgical technique, especially intima-to-intima apposition with the left atrial cuff anastomoses can decrease left atrial thrombus formation. Intraoperative TEE should also assess for a *patent foramen ovale* that may allow for right-to-left intracardiac shunt with embolic phenomena to occur.

Hyperammonemia Syndrome

Hyperammonemia syndrome is a relatively uncommon complication that has been reported in 4.1 % of patients following lung transplantation. Patients with this complication have a high mortality rate (67 % reported) [8]. These patients present with rapidly progressing altered mental status and encephalopathy that can result in seizures, status epilepticus, coma, cerebral edema, and death. The clinical picture is associated with highly elevated ammonia levels with normal or minimally elevated liver function tests. The cause of this syndrome is unclear, however it is hypothesized that catabolic stressors (e.g., gastrointestinal bleeding, infections, seizures, renal insufficiency, etc.) cause a negative nitrogen balance that could trigger hyperammonemia. Other contributing factors are high protein intake via enteral or parenteral nutrition, acute kidney injury, and the presence of pulmonary hypertension [8]. The management is multimodal, focusing in decreasing the production of nitrogenous waste and increasing removal (including elimination of parenteral amino acids and maintaining a high caloric intake that blocks the catabolic state). Other important interventions are aggressive control of stress factors, institution of renal replacement therapy, enteral lactulose, neomycin, infusion of ammonia controlling agents (e.g., sodium benzoate, sodium phenylacetate, and arginine), and potentially avoiding corticosteroids and calcineurin inhibitors [9].

Postoperative Cardiovascular Complications in Lung Transplant Recipients

Lung transplantation represents a period of significant hemodynamic changes that add to the fragile cardiopulmonary physiology of the lung transplant recipient. The cardiovascular system provides compensatory mechanisms intended to minimize the consequences of chronic hypoxia and hypercarbia. The intraoperative period is characterized by profound alterations in hemodynamics, with blood loss, fluid shifts,

hypotension, and acute changes in perfusion pressure, arrhythmias, vasodilatation, acute right and left ventricular dysfunction, and acute changes in pulmonary vascular resistance. The interaction of acute perioperative changes with a cardiovascular system chronically challenged predisposes the patient to acute intra- and postoperative hemodynamic deterioration. Among the multiple potential causes of hemodynamic instability in the immediate postoperative period in the ICU are the following; hypovolemia, perioperative arrhythmias, postoperative vasodilatory shock, right ventricle (RV) dysfunction, Cor pulmonale physiology, cardiac tamponade, left ventricle (LV) dysfunction, and increased intra-thoracic pressure.

Hypovolemia

Hypovolemia is a common occurrence after lung transplantation. Hypovolemia can be caused by blood loss, significant fluid shifts, interstitial fluid accumulation, and aggressive use of diuretics. The effects of hypovolemia are exacerbated by the use of epidural analgesia (with its additional sympathectomy), and the negative effects of positive pressure ventilation on venous return. There is also the potential for significant fluid losses in the pleural spaces.

Atrial Fibrillation

Cardiac arrhythmias, specifically *atrial fibrillation* (AF), are common after lung transplantation. The reported incidence of early postoperative AF varies between 16 and 39 % of lung transplant patients [10–13]. Factors independently associated with increased risk of AF after lung transplant are age, bilateral lung transplantation, and presence of AF prior to transplant [13]. Other identified risk factors include coronary artery disease, enlarged right atrium, and increased number of postoperative vasopressors [11]. Among the implicated etiologic mechanisms are inflammation, edema, ischemia-reperfusion injury, increased sympathetic output, hemodynamic alterations, and mechanical distortion of the atria. Importantly, ICU and hospital length of stay are increased in lung transplant recipients with AF, increasing health care cost and morbidity. There are conflicting reports about AF as an independent risk factor for increased overall mortality [11, 13–15]. However, the presence of AF is clearly associated with increased in-hospital mortality [11, 13]. From a morbidity point of view, it is important to implement aggressive treatment for AF due to the high risk of thromboembolism and stroke with poor outcomes. In particular, up to ~50 % of lung transplant patients with AF receive amiodarone and 28 % require cardioversion [13]. The use of beta-blockers and calcium channel blockers could be poorly tolerated due to RV dysfunction and hemodynamic instability.

Right Ventricular (RV) Dysfunction

RV failure or dysfunction represents a common and significant problem after lung transplantation. In particular, the lung transplant patient is exposed to chronic pulmonary hypertension (PHT) and can develop progressive RV dysfunction. Importantly, there is a direct association between decreased preoperative RV function and poor postoperative outcomes. Moreover, the presence of preoperative RV dysfunction is complicated by acute intraoperative changes in pulmonary vascular resistance (PVR) due to hypoxemia, hypercarbia, single lung ventilation, acute increase in airway pressure and surgical manipulation of the pulmonary vasculature. Such interactions highly increase the risk of perioperative acute RV failure. Other potential contributors are the presence of *patent foramen ovale* with right-to-left interatrial shunt causing hypoxemia, and also ventilator dysynchrony. It is also known that increased PVR and PHT occur after lung transplantation [15].

The management of acute postoperative RV dysfunction/failure requires decreasing RV afterload by controlling the causes of increased PVR and supporting the RV contractile function. Therapeutic management with administration of vasodilatory agents (i.e., nitroprusside, nitroglycerin, prostaglandin, and prostacyclin) is limited by systemic hypotension and potential increase in intrapulmonary shunting [16]. The use of more selective pulmonary vasodilators in particular inhaled nitric oxide (iNO) is advocated in lung transplant patients in order to decrease elevated PVR, improving RV performance and helping to stabilize pulmonary functions [17, 18]. The use of beta-adrenergic agonists is warranted with consideration of the possible increase in predisposition to cardiac arrhythmias in particular atrial fibrillation. Agents such as milrinone and dobutamine can be useful for management of RV dysfunction with increased PVR. The potential for systemic hypotension and accumulation in the presence of renal dysfunction are limitations for the use of milrinone.

Left Ventricular (LV) Dysfunction

Patients with end-stage lung disease generally have an incidence of LV dysfunction of only 6 %. When PHT is present the incidence of LV dysfunction increases to 19.6 %. Pulmonary hypertension causes RV pressure overload with leftward interventricular septum shifting that impairs LV filling [17]. It is postulated that chronically impaired LV filling can lead to loss of LV contractile function. After lung transplantation, the acute decrease in PVR leads to improvement in RV afterload and performance. Therefore, the interventricular septum displaces to the right and LV diastolic filling is acutely improved as a result of both, improved pulmonary flow and RV function. In a chronically under filled LV, the decreased ability to acutely handle end-diastolic volume can result in acute LV failure. Moreover, this altered physiology is even less tolerated in a ventricle with impaired contractile function [18]. In this situation, acute pulmonary

edema can present. Other causes of acute pulmonary edema (such as reperfusion injury) and LV deterioration (e.g., myocardial ischemia) need to be evaluated with cardiac catheterization and echocardiography. It is important to detect this situation and to establish expedite management with cathecolamines (for improvement in contractility) and intra-aortic ballon counterpulsation (IABP) for afterload reduction. The prophylactic perioperative use of IABP in patients at risk is an alternative [18].

Cardiac Tamponade

During lung transplantation the pericardium is incised to allow vascular anastomosis of the pulmonary venous drainage. After such incision, usually the pericardium maintains communication with the pleural cavity. Therefore, tension accumulation of fluid is rare [19]. However, there could be one-way fluid accumulation in the pericardium causing progressive cardiac tamponade physiology. This is typically seen as a focal area of hemopericardium inhibiting RV filling or outflow. Other potential mechanisms of tamponade physiology are increase in intrathoracic pressure, oversized allografts, high PEEP and positive pressure ventilation in the setting of edematous and poorly compliant lung(s). The increase in intrathoracic pressure can cause impairment in venous return and extrinsic compression of the right-sided cardiac cavities decreasing LV preload, ultimately leading to cardiogenic shock due to cardiac tamponade [20]. This phenomenon can present also in case of donor graft and recipient chest cavity mismatch. Pneumopericardium formation secondary to pulmonary air leak, bronchial anastomosis dehiscence or fistula, barotrauma and infection can also cause cardiac tamponade [21], although this is exceedingly rare with appropriate placement of chest tubes.

The diagnosis of cardiac tamponade is made by the presence of persistently increased central venous pressure (CVP), reduction in systemic arterial and pulmonary arterial pressures, and respiratory variations in the arterial and pulmonary waveforms (*pulsus paradoxus*). TEE examination will confirm compression of the right-sided heart cavities and LV end-diastolic volume decrease, as well as cyclic variation in pulmonary and hepatic vein flow upon Doppler evaluation [20] (Fig. 10.1a, b). The management can include surgical drainage of accumulated fluid if necessary, decreasing intrathoracic pressure by decreasing positive airway pressure or even extubation when possible. Pneumoreduction of the allografts may be indicated in instances of donor allograft-recipient chest cavity mismatch. In some instances, the use of ECMO may be necessary in order to provide hemodynamic stability and decrease intrathoracic pressures relieving the tamponade [21], although the timely and accurate diagnosis and subsequent drainage of pericardium remains the treatment of choice.

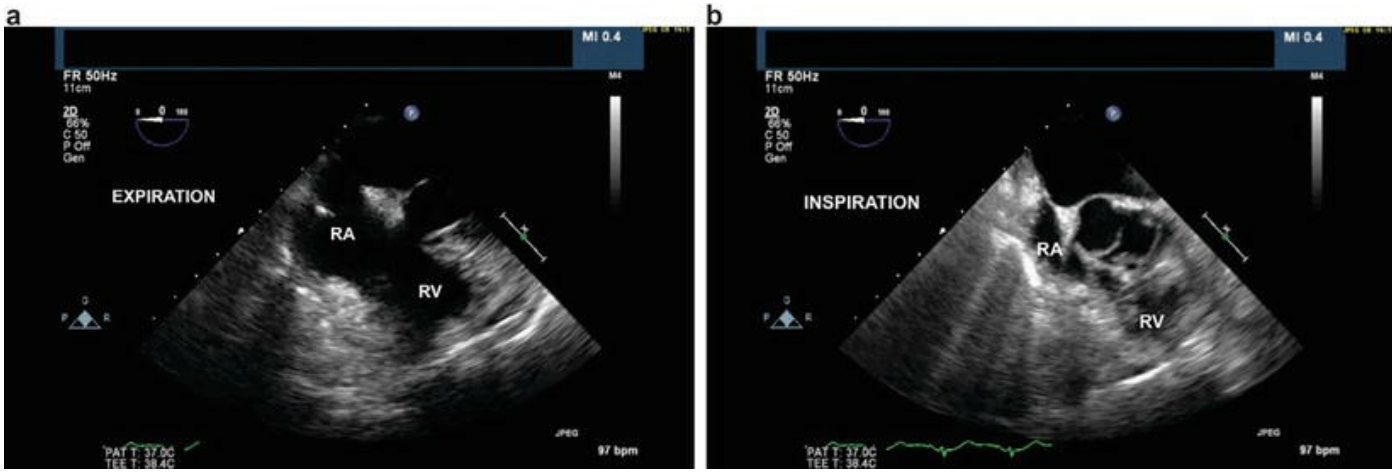

Fig. 10.1 (**a**) Cardiac tamponade in lung transplant recipient with oversized allografts (during *expiratory phase* of the ventilatory cycle). Transesophageal echocardiogram (TEE) image obtained at mid-esophageal level depicting the right atrium (RA) and right ventricle (RV) cavities. The image demonstrates the RA and RV normally open during diastole. This patient was intubated and mechanically ventilated. TEE was performed in order to evaluate the possible etiology of hemodynamic instability in the immediate postoperative period after bilateral lung transplantation. (**b**) Cardiac tamponade in lung transplant recipient with oversized allografts (during *inspiratory phase* of the ventilatory cycle). Transesophageal echocardiogram (TEE) image obtained at mid-esophageal level depicting the right atrium (RA) and right ventricle (RV) cavities. The image demonstrates the RA and RV are completely collapsed by extrinsic compression during diastole. TEE examination confirmed diagnosis of cardiac tamponade caused by increased intrathoracic pressure in the setting of positive pressure ventilation and oversized allografts

Acute Postoperative Respiratory Care of the Lung Transplant Patient

The goals for postoperative respiratory management are to provide adequate gas exchange that will meet the metabolic needs of the patient while limiting ongoing perioperative lung injury and minimizing ventilator-associated complications. Optimal respiratory management in the immediate postoperative period can also decrease the possibilities of both, acute and long-term complications. The mainstay interventions are the use of protective ventilatory strategies, early extubation, optimization of respiratory mechanics, and obtaining the best pain control possible.

In the immediate postoperative period, frequent assessment of gas exchange by arterial blood gas measurement is essential to determine stable lung function, to safely decrease inspired oxygen concentration (minimizing oxygen toxicity) and to help detect early life-threatening complications (e.g., hyperacute rejection, primary graft dysfunction, etc.). Additionally, periodic determination of mixed venous oxygen saturation allows evaluation of global balance between oxygen delivery and consumption; the use of a continuous oximetry pulmonary artery catheter is an effective alternative. Other indirect indicators of global perfusion can help to assess the adequacy of oxygen delivery (e.g., pH, base deficit, bicarbonate level, lactic acid determination).

Optimizing the global balance between oxygen delivery and consumption requires an adequate cardiac index with appropriate hemoglobin content. In this patient population it can be challenging to achieve a normal cardiac output due to the combination of postoperative acute right and/or left ventricular dysfunction, perioperative vasodilatory shock, and hypovolemia. The benefit of improved oxygen carrying capacity should be balanced against the risks of red blood cells transfusion. It is unlikely that data extrapolated from other clinical areas, regarding transfusion thresholds are adequate or appropriate in this patient population. However, red blood cells transfusions following lung transplantation have been associated with worse survival and increased infections [22]; and judicious transfusion practices are likely warranted in these patients.

The use of protective ventilatory strategies aims to prevent or reduce the incidence of acute lung injury (ALI) . Such interventions include a combination of ventilator modes and procedures that intend to decrease inflammation and diffuse alveolar damage characteristic of ALI [23]. In this environment, protective ventilatory strategies can limit volu- and barotrauma, minimize pulmonary endothelial damage, and the so-called bio-trauma secondary to cytokine release, all factors associated with occurrence of ALI [24]. The use of protective ventilatory strategies have been extrapolated, from the evidence available for use of low tidal volume in ARDS patients, into the integral intraoperative management of pulmonary resection and perioperative management of thoracic surgical patients as standardized practice [25]. Those techniques include combination of the use of low-tidal volume (6–8 ml/Kg, ideal body weight in two lung ventilation), low peak inspiratory pressure (<20 cm H_2O above PEEP level), low plateau airway pressure (<30 cm H_2O), moderate PEEP (8–10 cm H_2O), preferable use of pressure-controlled ventilation, and intermittent recruitment maneuvers [23]. The available evidence supporting the use of lung protective strategies (compared to traditional approaches) due to lower risk of mortality, earlier extubation, lower risk of respiratory failure, decrease evidence of ALI, improved ventilation-perfusion matching, suggest that their use in lung transplantation could be beneficial [26, 27]. Additionally, minimizing inhaled fraction of oxygen (FiO2) is believed to decrease the production of oxygen free radicals and subsequent PGD. It is important to balance the effects of recruitment maneuvers in preventing atelectasis and improving oxygenation with the potential barotrauma and hemodynamic instability in lung transplant patients. There is little clinical impetus to perform frequent recruitment maneuvers provided oxygenation and ventilation remain adequate.

A ventilation weaning protocol should be implemented as soon as patient hemodynamic status is improved and gas exchange is stable. Importantly, the inspired fraction of oxygen (FiO_2) should be weaned as soon as possible in order to minimize oxygen toxicity. The goal of early extubation is paramount in order to avoid complications such as hospital-acquired pneumonia. The single most important

intervention to accomplish early extubation is optimization of respiratory mechanics by achieving adequate pain control. The early institution of continuous thoracic epidural analgesia is safe and effective, and provides evidence of earlier extubation, better pain relief and decreased rates of re-intubation and postoperative respiratory complications, when compared with systemic intravenous analgesia [28]. The use of thoracic epidural analgesia is part of a multifaceted approach that includes minimization of long-acting sedation medications, avoidance of systemic opioids, avoidance of postoperative neuromuscular blockade and early recovery of neuromuscular function in anticipation of early extubation.

At our institution, in order to avoid issues with intraoperative anticoagulation, epidural analgesia is instituted postoperatively, when there is clear evidence of resolution of coagulopathy. We use a combination of low concentration bupivacaine and low dose hydromorphone, which provides synergistic neuroaxial effect and have minimal systemic absorption. It is important to wait until postoperative shock and hemodynamic instability have resolved before starting epidural analgesia. In our experience, it is safe to initiate at a low infusion rate institute when inotropic and vasopressor medications are being weaned.

Optimization of respiratory mechanics and early extubation can be achieved by a multidisciplinary strategy based on thoracic epidural analgesia for acute post-thoracotomy pain control that allows several additional interventions. Such interventions include, aggressive chest physiotherapy with periodic bronchodilators and postural drainage, early mobilization out of bed and ambulation, and most importantly complemented by an intensive exercise and physical therapy plan even if the patient is still intubated. Early tracheostomy in patients with suspected prolonged intubation will facilitate management of pulmonary secretions, increase early mobilization, and optimize patient comfort [9]. Early and liberal use of bronchoscopy is of vital importance not only to detect significant early complications and to assess the status of bronchial anastomosis, but also to maximize clearance of secretions increasing the possibilities of successful extubation.

Acute Respiratory Failure After Lung Transplantation

Acute respiratory failure is the most common complication following lung transplantation. It is also responsible for a 45 % mortality rate in patients who develop it. Similarly, it is a source of significant morbidity. In the acute postoperative period, PGD, acute rejection, and surgical technical complications are the most common causes of acute respiratory failure. After 3 months, the most prevalent causes are infections, acute rejection, and obliterative bronchiolitis [29]. The most important noninfectious entities responsible for the occurrence of acute respiratory failure in the immediate postoperative period will be reviewed in the following section.

Primary Graft Dysfunction/Severe Reperfusion Injury

The term "Primary Graft Dysfunction" (PGD) describes an entity that has received different names in the past (e.g. reperfusion injury, reperfusion edema, re-implantation response, re-implantation edema, primary graft failure, and early graft dysfunction) [30]. This complication occurs in up to 25 % of lung transplant recipients and represents the main cause of early mortality and morbidity [2]. In addition, this condition has other poor outcome consequences, including increased ICU and hospital length of stay, increased duration of mechanical ventilation and decreased exercise capacity [31]. PGD is a form of early ALI that leads to acute lung allograft failure. One of the leading mechanisms responsible for this form of ALI is the development of ischemia–reperfusion injury. The clinical syndrome consists of development of acute diffuse alveolar infiltrates consistent with pulmonary edema of noncardiogenic origin and secondary severe hypoxemia.

The ISHLT Working Group on PGD provided a standardized definition in their 2005 consensus statement. The definition includes the presence of "diffuse allograft alveolar infiltrates" by radiography within 72 h of reperfusion and hypoxemia based on partial pressure of oxygen (PaO_2) to FiO_2 ratio (PaO_2/FiO_2) (Table 10.1). The working group recommends inclusion of the timing of lung dysfunction (T_0—within 6 h of lung perfusion, T_{24}, T_{48}, and T_{72}—24, 48, 72 h after first blood gas) [30]. They also recommend mentioning certain subgroups in the description while defining PGD; pulmonary venous occlusion, left ventricular dysfunction, hyper-acute rejection, and infectious process. Importantly, patients who develop grade 3 PGD have increased long-term mortality, as well as increased incidence of chronic allograft rejection (or *Bronchiolitis Obliterans syndrome*) and decreased maximum allograft function [22, 32] The clinical risk factors identified for PGD are: transplantation of an organ with donor history of smoking, elevated FiO_2 during allograft reperfusion, preoperative sarcoidosis or pulmonary arterial hypertension, use of CPB, single lung transplant, large-volume blood product transfusion, elevated postoperative pulmonary arterial pressures, and overweight or obese recipient body habitus [22]. Other previously associated factors included prolonged ischemic time, donor lung contusion or aspiration, and the use of high-potassium preservation solutions [33, 34]. The mechanisms involved are multiple but they involve a common path to endothelial and epithelial lung damage, which includes release of cytokines, cell damage by neutrophils and lymphocytes activation, complement activation, upregulation of multiple inflammatory cascade mediators, oxidative stress and reduction in endogenous NO production. The final result is increased cell death and apoptosis [35–37].

Table 10.1 Recommendations for grading of primary graft dysfunction severity

Grade	PaO_2/FiO_2	Radiographic infiltrates consistent with pulmonary edema

0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

From Christie et al. [30]; with permission

The above mentioned observations have led to the development of several strategies in order to prevent or reduce the incidence and severity of PGD with particular emphasis in modifiable clinical risk factors observed in a large prospective study (e.g., FiO_2 on reperfusion, avoiding the use of CPB, and pretransplant recipient weight loss) [22]. Otherwise, suggested preventive interventions include standardizing enhanced procurement and preservation of donor lung techniques, controlled intraoperative reperfusion pressures, and leukocyte depletion of transfused blood products. Interestingly, there are reports about the use of NO added to the flush solution at time of harvest, as well as early use of iNO to attenuate the incidence and severity of PGD [38–40]. Inhaled NO is effective in reducing pulmonary arterial pressure, improving ventilation-perfusion matching and optimizing PaO_2/FiO_2 ratio, and has potential anti-inflammatory properties [9, 29, 40]. The use of this and other approaches deserve further investigation in order to address if they improve outcomes. However, neither iNO nor other pharmacologic interventions when formally studied have been shown to be clearly effective in preventing PGD following lung transplantation [41–43].

The mainstay of critical care management and treatment of patients with PGD is a multisystem approach that minimizes further injury by using low pressure protective ventilatory strategies, and by controlling existing pulmonary edema and minimizing further pulmonary edema formation. The use of veno-venous ECMO in cases of severe PGD intends to avoid the use of injurious mechanical ventilator settings, therefore avoiding additional pulmonary insult [44]. Otherwise, treatment and prevention of pulmonary edema requires the use of intravenous diuretics and a fluid management strategy that avoid pulmonary vascular congestion. In a recent study, a central venous pressure (CVP) > 7mmHg was associated with prolonged mechanical ventilation and also with a tendency to increased ICU and in-hospital mortality [45]. Nonetheless, it is important to highlight that is necessary to assume an strategy with careful hemodynamic monitoring and management relying in the use of inotropes, pulmonary vasodilators, and vasopressors; while minimizing intravascular volume resuscitation and maintaining hemodynamic stability and adequate global perfusion and oxygen delivery. Typically a pulmonary artery catheter is required to provide pertinent hemodynamic measurements and help guide resuscitative efforts.

Acute Rejection

The occurrence of hyperacute/humorally-mediated rejection is uncommon in the literature, but is more likely in patients with high levels of preformed anti-Human Leukocytes Antibodies (HLA) (i.e. panel reactive antibody (PRA)) [9]. The clinical syndromes of acute rejection , infection, and PGD can be difficult to differentiate. Patients with acute rejection present with inflammatory response-like syndrome (including low-grade fever) and dyspnea, along with hypoxemia and perihilar infiltrates. In many cases, patients receive empiric therapy for rejection after infectious etiologies are ruled out. In this regard, acute rejection findings are nonspecific and the diagnosis is made retrospectively. The gold standard for diagnosis of acute rejection is the pathologic evaluation of serial transbronchial biopsies. However, the use of transbronchial biopsies can underestimate the incidence of acute rejection when compared with open surgical biopsy [46]. The risk of open surgical biopsy must be weighed against the diagnostic yield in selected cases. Acute rejection is a common complication presenting in the first year following lung transplantation, with about 40–60 % of recipients having at least one episode of acute rejection during the first year [2]. This complication is characterized by airway-centered inflammation in the pathologic form of lymphocytic bronchitis / bronchiolitis. There is a clear association between the frequency and severity of acute rejection episodes and later development of chronic allograft dysfunction characterized by *bronchiolitis obliterans* . The treatment of acute rejection aims to address the acute episode and to decrease the possibilities of further events. The main therapy is the use of methylprednisolone 10–15 mg/kg for 3–5 days, followed by an oral steroid taper for 2–3 weeks, depending on the maintenance steroid dose. There is some controversy as to the need to treat clinically undetectable grade 1 acute rejection episodes that may be diagnosed by surveillance bronchoscopy. Much emphasis in the prevention of acute rejection is made on the use of induction protocols based on interleukin-2 receptor blockers (e.g. basiliximab) or antibody depletion with antithymocyte globulin.

Dynamic Lung Hyperinflation

This complication occurs in patients who have received single lung transplantation for emphysematous diseases. In the postoperative period, there is preferential gas flow to the highly compliant, diseased, native lung with its progressive over distension and potential mediastinal shift with hemodynamic instability in severe cases. The pathophysiology of this entity is caused by the difference of compliance between the donor allograft and the remaining lung, which causes differential gas flow with positive pressure ventilation. That process is aggravated by the occurrence of PGD in the allograft. In such cases, the donor lung becomes less complaint, causing further native lung over distension. As a result, the PVR in the native lung increases and causes

increased shunting of blood to the dysfunctional lung allograft with subsequent worsening of ventilation-perfusion mismatch. Management of this situation requires use of ventilator strategies that avoid air trapping, including decreasing tidal volume, lower respiratory rates, low PEEP, and long expiratory times; or converting the patient to a spontaneous ventilatory mode whenever possible. The patient should also receive aggressive bronchodilator therapy and lateral decubitus ventilation with the transplanted side up in order to maximize gas flow to the allograft. This approach can cause a mild degree of hypoxemia and hypercarbia with respiratory acidosis that are usually transient and well tolerated. In cases of hemodynamic instability or severe hypoxemia and hypercarbia, the patient can be managed with independent / differential mechanical ventilation, after other causes of instability and hyperinflation, such as tension pneumothorax and allograft mucous plugging are ruled out. This later approach requires placement of a double lumen endotracheal tube and use of separate mechanical ventilators with settings appropriate for each lung. Limitations for the use of this technique are the specialized management required for endotracheal tube placement, and the challenge that represents maintenance of proper position. Dynamic hyperinflation improves when the compliance of the transplanted lung increases, usually after 24–72 h. Although there is not enough evidence of improved outcomes to support the routine use of this technique, there are reports of successful management in several patients [47, 48].

Noninfectious Airway Complications

There are multiple possible airway complications after lung transplantation including, bronchial anastomotic dehiscence, bronchial stenosis, obstructive granulomas, bronchomalacia, and bronchial fistula formation [49]. The incidence of central airway complications after lung transplantation ranges from 9 to 33 % with an associated mortality of 2–4 %. Importantly, among all airway complications, 9–13 % will require intervention [50]. The recognized risk factors for airway complications in lung transplantation are: ischemia of donor bronchi, surgical technique used, length of donor bronchi, presence of donor or recipient colonization or infection, donor/recipient bronchial size discrepancy, postoperative infection, postoperative mechanical ventilation, and use of immunosuppression [51, 52]. The improvement in surgical techniques as well as in donor and recipient management has greatly reduced the incidence of these complications. The most common airway complication is bronchial stenosis. This complication most commonly occurs between 2 and 9 months after transplantation. Such stenosis occurs after significant necrosis, dehiscence, and infections, particularly with *Aspergillus* species [50, 53, 54]. Another important complication is bronchial anastomosis dehiscence, which usually occurs within the first 5 weeks after transplantation, as a result of mucosal necrosis. This complication,

thought quite uncommon is associated with high mortality and morbidity [55]. Although most airway complications are not fatal, they impose a high rate of morbidity and can require complex and multidisciplinary management that include interventional bronchoscopic airway treatment and airway stent placements. Ultimately, bronchomalacia and bronchial strictures can be the long-term result of anastomotic dehiscence and infections [49].

Acute Kidney Injury After Lung Transplantation

Acute kidney injury (AKI) is a common complication after lung transplantation. Data from the recent 2013 ISHLT registry report showed that 23.3 % of lung transplant patients developed AKI within 1 year, and 55.4 % within 5 years. More importantly, according to the registry, patients have a high incidence of severe renal dysfunction given the fact that 24 % of patients develop creatinine >2.5 mg/dl, dialysis or transplant requirement within 5 years after lung transplantation. In a similar fashion, 41 % of patients will experience any of the same complications within 10 years. More specifically, the need for chronic dialysis is 1.7 % within 1 year and increases to 3.2 % within 5 years [2]. In contrast, two recent studies of early AKI demonstrated a higher incidence of AKI by using RIFLE criteria (39 and 54 %, within 72 h and 30 days after lung transplantation, respectively). Both studies also concluded that AKI is more common after bilateral lung transplantation. Another factor associated with the development of AKI after lung transplant is high volume blood transfusion. Those findings suggest the influence of surgical and perioperative factors, as well as procedural complexity in the occurrence of AKI after lung transplantation [56]. This is in opposition to the traditional belief that the dominant etiology for AKI in transplant patients is nephrotoxicity from immunosuppressant medications, in particular cyclosporine and tacrolimus [56, 57].

It is also noteworthy that hypovolemia and vasopressors have not been identified as risk factors in contemporary studies [56]. The most important implication of AKI after lung transplant is its association with poor outcomes, including increased duration of mechanical ventilation and hospital length of stay [56]. Long-term, the main determinants of the progression of renal dysfunction remain pretransplant renal function and the severity of AKI in the early period after transplantation. Therefore, minimal GFR requirements (40–50 ml/min) should be established during the evaluation phase [58, 59]. Likewise, renal function after transplant requires close monitoring because the more severe the AKI after lung transplant, the more rapid the progression of renal dysfunction [60]. Other risk factors associated with long-term renal impairment are the presence of diastolic hypertension, and the use of cyclosporine instead of tacrolimus. Additional mechanisms implicated in the development of chronic kidney disease are the use of nephrotoxic medications other than calcineurin inhibitors, such as amphotericin

and aminoglycosides. Identification of patients at risk allows for early detection of any degree of AKI, avoidance of secondary injury, adjustment of immunosuppression medication (e.g., lower doses, substitution therapy), and aggressive treatments of hypertension and diabetes, particularly with optimal blood glucose control.

Hematologic Complications After Lung Transplantation

Thrombotic Thrombocytopenic Purpura (TTP)/Hemolytic–Uremic Syndrome (HUS)

Both HUS and TTP are uncommon but potentially fatal causes of acute renal failure that occur as complications after solid organ transplantation. These syndromes are characterized by thrombotic microangiopathy due to platelet activation and microthrombi formation with consequent thrombocytopenia, hemolysis, and renal failure. Their occurrence is associated with the use of calcineurin inhibitors by poorly understood mechanisms. These syndromes occur early after lung transplantation, most commonly within 3 months. The mainstay of treatment is plasma exchange therapy , which can be combined with antiplatelet agent and glucocorticoids [61].

Heparin-Induced Thrombocytopenia/Thrombosis (HIT/T)

Thrombocytopenia remains a very common finding following lung transplantation. It is routinely a self-limiting state that reverts over the first few days after surgery. However, it can occasionally require platelet transfusion and can be associated with bleeding complications. Mechanical circulatory support, such as ECMO for PGD, commonly causes thrombocytopenia. Likewise, antimicrobial medications such as gancyclovir and voriconazole often lead to platelet consumption. *Heparin-Induced Thrombocytopenia* (HIT) occurs in up to 10–15 % of lung transplant recipients [62], as noted by presence of PF-4 antibodies or positive *serotonin release assay*. This can occasionally lead to a thrombotic phenotype (HITT) causing ubiquitous complications including deep venous thrombosis, pulmonary emboli, strokes, and ischemia. Treatment of this serious condition requires anticoagulation with pharmacologic agents alternatives to heparin, such as bivalirudin or argatroban, in order to minimize diffuse thrombotic events.

Venous Thromboembolic Disease, Including DVT and PE (VTE)

VTE occurs in up to a third of lung transplant recipients and can lead to symptomatic limb swelling, central venous occlusion, and pulmonary embolism. In addition to the usual risk factors of major surgery and immobilization, the placement of indwelling

central lines during surgery, as well as long-term IV access such as with peripherally inserted central catheters (PICC) , can lead to lower or upper extremity DVTs . Sequential compression devices are routinely used on the lower extremities with uncertain benefits. However, early extubation, adequate pain control, and rapid mobilization are likely the best defenses against venous thrombus formation. The role of routine DVT prophylaxis with subcutaneous unfractionated or low molecular weight heparin (LMWH) is not firmly established in these patients. The bilateral thoracotomy incisions and extensive dissection of the hilar structures provide ample soft tissue for postoperative hemorrhage to occur and posttransplant decreases in GFR due to AKI may decrease LMWH clearance and increase the risk of bleeding. Although additional research is needed in this area, implementing routine DVT prophylaxis in our patients did not alter the rate of perioperative VTE complications, but was associated with an increase in bleeding complications [63].

Gastrointestinal Complications After Lung Transplantation

Gastrointestinal (GI) complications after lung transplantation are common. Approximately, 51 % of patients develop GI complications early in the postoperative course. In particular, most complications (73 %) occur within the first month. However, the majority of GI complications require conservative therapy only [64, 65]. Reported GI complications include, esophagitis, pancreatitis, gastric atony, adynamic colonic ileus, gastroesophageal reflux, peptic ulcer disease, gastritis, GI bleeding, *Cytomegalovirus* (CMV) colitis, CMV hepatitis, diverticulitis, cholecystitis, and *Clostridium difficile* diarrhea/colitis [9]. Major GI complications requiring surgical intervention occur in 18 % of patients, and have a high mortality (68 %). Such surgical complications are difficult to diagnose due to many masking/confounding factors, such as immunosuppression. Importantly, delayed diagnosis is associated with high mortality. The most common acute abdominal surgical complications are bowel perforation, appendicitis, cholecystitis, colitis, and pneumatosis intestinalis [66]. Interestingly, a benign and asymptomatic pneumotosis phenomenon can present and generally requires temporary bowel rest and close monitoring, but rarely requires surgical intervention. Another common GI complaint before and after lung transplantation is gastroesophageal reflux disease (GERD) . Uncorrected GERD has been correlated with accelerated chronic allograft failure and BOS [67]. Likewise, actively identifying patients with oropharyngeal dysphagia and implementing protective strategies from aspiration can improve long-term outcomes [68].

Perioperative Infectious Concerns

Prevention remains the key in regards to infectious complications following lung

transplantation. Each recipient's perioperative antibiotic regimen is partially determined by that patient's pretransplant microbiologic data. Also, it is important the integration of information from the donor's culture results. These can include sputum and bronchial lavage samples from the donor hospital, as well as samples sent intraoperatively by the implantation team from the donor airways. The infection prophylaxis protocols used by the Duke Lung Transplant Program are outlined in Table 10.2.

Table 10.2 Duke University infection prophylaxis

Infection prophylaxis
Bacterial
Standard regimen
Ceftazidime: 2 g IV preop on induction per anesthesia, then 1 g IV q8 h for 7–10 day or until invasive lines are out. (Adjust doses for renal insufficiency)
Vancomycin: 1 g IV preoperatively on induction per anesthesia, then 1 g IV q12 h for 7–10 days or until invasive lines and chest tubes are out. (Adjust doses for renal insufficiency)
The standard regimen should be amended as indicated (by consultation with the transplant pulmonologist and surgeon and infectious disease consultant) to include:
• *Coverage for any other known preoperative pathogens in the recipient. This is particularly indicated for recipients with cystic fibrosis, bronchiectasis, and other septic lung diseases*
• *Coverage for any additional organisms identified from donor cultures*
NOTE
Foreign objects, such as breast implants, Hickman catheters, PIC lines, and port-a-caths will be removed at the time of the transplant operation. Gastrostomy tubes will generally be left in place. Patients will be informed of this policy prior to surgery
Pneumocystic jeroveci
Septra SS 1 po daily starting 1 week postoperatively, continuing indefinitely
If sulfa allergy: Dapsone 50 mg po QD *or* Aerosolized pentamidine 300 mg q month continuing indefinitely
Fungal
• Nystatin suspension 5 cc swish and swallow qid for oral candida prophylaxis. Continue for 6 months
• Inhaled amphotericin B liposomal complex (Abelcet) 100 mg daily for 4 days, then 50 mg weekly while hospitalized immediately posttransplant
CMV prophylaxis after transplant
D−/R−:
• Standard protocol: Acyclovir (Zovirax) 200 mg TID OR Valacyclovir (Valtrex) 500 mg BID × 3 months (no renal dosing needed unless creatinine clearance <10)
• Check EBV status → if recipient has negative EBV serologies, *MUST* confirm donor EBV status
– IF donor is EBV+, Recipient EBV− AND both are CMV negative, then valganciclovir 450 mg qd for 1 year. If patient cannot afford valganciclovir, consult with transplant ID. Consider EBV PCR monitoring after prophylaxis ends
• Give only leukocyte-reduced blood products

D+/R+ and D−/R+:
• Standard protocol: Ganciclovir induction dose when in hospital then valganciclovir for 1 year
• If patient cannot afford valganciclovir:
– Ganciclovir maintenance dose for 3 months
– Intense monitoring protocol below to start just before ganciclovir ends
D+/R−:
• Standard protocol: Ganciclovir induction dosing while in hospital, then valganciclovir indefinitely
• If patient cannot afford valganciclovir:
– Ganciclovir maintenance dose for 6 months
– Intense monitoring protocol below to start AFTER ganciclovir ends

Perioperative Immunosuppression

While the optimal immunosuppressant regimen is not known, most programs use a triple drug regimen using a calcineurin inhibitor (Cyclosporin or Tacrolimus), an anti-proliferative agent (Azathioprine or Mycophenolate Mofetil), and corticosteroids. Induction therapy using either an anti-CD25 agent (Basiliximab or Daclizumab), or an immune cell depleting strategy such as polyclonal anti-T cell agents (Thymoglobulin, ATGAM), or most recently anti-CD52 (Alentuzumab) are used in approximately 50 % of lung transplant recipients. While acute rejection occurs commonly after lung transplant with 40–60 % of patients having at least one episode of rejection in the first 6 months, it is an uncommon cause of early mortality. Mortality early after lung transplant is most commonly secondary to primary allograft dysfunction, infection, and GI complications.

Highly sensitized patients present a particular challenge, with pretransplant presence of Class II HLA antibodies being associated with diminished long-term survival [69]. We systematically use intravenous immunoglobulin preparation (IVIG) in highly sensitized patients. Historically, a desensitization protocol had been utilized that included Rituximab and plasmapheresis; however, that did not demonstrate efficacy in our experience and is not routinely performed now [70].

Very rarely, a patient may receive an allograft from a donor with a positive virtual crossmatch based on the presence of preformed HLA antibodies specific to the donor. Similarly, a retrospective positive crossmatch may be observed, perhaps from non-HLA antibodies. In these instances, we do continue to treat these patients with a protocol that includes Rituximab, plasmapheresis, and IVIG perioperatively. Our program's routine immunosuppression protocol is noted in Table 10.3.

Table 10.3 Duke University immunosuppression protocol

Duke University Medical Center
Lung Transplant Protocol

Immunosuppression and Clinical Management		
Preoperative		
FK506: *1 mg sublingual on admission. If patient is receiving voriconazole, posaconazole, or fluconazole postoperatively give 0.5 mg sublingual*		
Azathioprine: 2 mg/kg IV on induction of anesthesia		
If Cellcept is used 1 g IV on induction of anesthesia		
Intraoperative		
Solu-Medrol		
500 mg IV prior to reperfusion of each transplant lung if bilateral		
500 mg IV prior to reperfusion of single transplanted lung		
Basiliximab (Simulect): *20 mg IV following induction of anesthesia*		
Postoperative		
FK506: 1 mg given sublingually every 12 h. *For patients who will receive voriconazole, posaconazole, or fluconazole postoperatively, reduce dose to 0.5 mg sublingual q12 h*		
Adjust to achieve a trough level of 10–15 ng/ml. Switch to p.o. when GI motility is restored. *If creatinine >1.5, target FK506 level 8–12		
Azathioprine: 2 mg/kg IV or po qd to maintain WBC > 3000		
If Cellcept is used 1 g IV every 12 h		
Steroids: Solu-Medrol 125 mg IV q12 h × 48 h, then prednisone 20 mg po qd		
Basiliximab (Simulect): *20 mg on p.o.d. #4*		
Maintenance		
FK 506: q12 h dosing adjusted to maintain trough FK 506 levels	Months 0–6	10–15 ng/ml FK506
	>6 months	8–12 ng/ml FK 506
Lower level may be required if patient develops significant renal insufficiency		
Azathioprine: 2 mg/kg/day po adjusted to maintain WBC > 3000		
Prednisone	Months 0–3	20 mg/day
	Months 4–6	15 mg/day
	7–9 months	10 mg/day
	>9 months	5 mg/day

Future Directions

Lung transplantation is established as the treatment of choice for end-stage pulmonary disease. Refinement in surgical techniques and perioperative care allowed improved survival and quality of life for a highly complex patient population. There are challenges imposed by the limited availability of donor organs. In this area, there will continue to be advancements in the expansion of the donor organ pool by utilizing allografts from older donors and nonbeating heart donation. There are also innovative allocation and prioritization criteria that intent to improve utilization of the existing pool

and expediting intervention in the sickest patients.

Of particular importance, is the promising development of techniques that allow use of marginal organs such as *ex-vivo lung perfusion*, as well as improved procurement and preservation techniques. Such approaches would promote pre-implantation lung repair, as a new frontier for lung transplantation.

The increase in donor's age, comorbidities, and overall complexity is of high relevance for individual clinicians and for the health community in general. Such issues are the result of an aging population and liberalization of the eligibility criteria for lung transplantation recipients. The critical care multidisciplinary team must be prepared for this evolving challenge.

Another area of significant growth is the implementation of perioperative optimization protocols and the more widespread use of life support techniques such as ECMO that are given an opportunity to patients that otherwise would have minimal chance of survival.

There is active research elucidating the mechanisms and potential preventive measures and therapeutic interventions for BOS being one of the most feared complications in lung transplantation.

Summary

Lung transplantation recipients in the immediate postoperative period represent some of the most significant challenges for the critical care multidisciplinary team. This is a highly complex population requiring that the critical care professional develops an elevated level of knowledge and understanding of their unique clinical issues. Advancements in critical care will continue to contribute to the success of contemporary lung transplantation.

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Part III
Heart Transplantation

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11. Heart Transplant Patient Selection and Preparation

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Introduction

Heart failure (HF) is a progressive disease affecting over six million Americans and by 2030 that number is expected to increase by over 25 %. End-stage HF is associated with a poor quality of life and contributes to almost 60,000 deaths annually in the United States [1]. Cardiac transplantation remains the gold standard for treatment of eligible patients with end-stage HF. With advances in immunosuppression, current 1 year survival post-cardiac transplant approaches 90 %, with almost 50 % of patients surviving greater than 11 years [2]. Unfortunately, limited donor availability makes this treatment available to only a small fraction of the patients who need it. The number of heart transplants done in the United States has remained stable for the past two decades at approximately 2200 cases per year.

With this critical organ shortage, risk stratification and patient selection for transplant remains vital to ensuring the best use of the limited resource. Additionally,

the increasing number of end-stage HF patients and rising proportion of extremely ill patients listed for heart transplantation (HTX), obliges the evaluation for mechanical circulatory support (MCS) as a bridge to transplantation an important part of the HTX evaluation.

When a patient is referred for HTX, the initial evaluation involves several stages. First, the severity of the HF state must be assessed to determine if the patient is appropriate for transplant consideration. Any potential reversible causes of HF, such as ischemia, valvular disease, arrhythmias, or alcohol use, should be identified and treated. The current medical therapy should be evaluated and optimized with uptitration of beta-blockers, vasodilators, and diuretics. Biventricular pacing should be considered if clinically indicated. If possible, a few months of optimal medical therapy should be attempted to assess for clinical response. If no reversible causes are identified and medical therapy is optimized, but severe HF symptoms persist, then the transplant evaluation should begin. Screening for cardiac transplantation involves an extensive evaluation to rule out contraindications, assess perioperative risk, and estimate the chance for meaningful long-term survival. Treatment options for patients referred for evaluation while in cardiogenic shock and/or inotrope dependent are typically limited to HTX, MCS, or palliative care and an abbreviated evaluation may need to be done.

Indications for Cardiac Transplantation

Indications for HTX includes one or more of the following conditions [3]:

1. Cardiogenic shock requiring either continuous intravenous inotropic support or circulatory support with an intra-aortic balloon counter pulsation device or mechanical circulatory support.

2. Persistent New York Heart Association (NYHA) functional class 4 HF symptoms refractory to maximal medical therapy (left ventricular ejection fraction < 20 % ; peak VO2 < 12 ml/kg/min).

3. Intractable or severe angina symptoms in patients with coronary artery disease not amenable to percutaneous or surgical revascularization or severe transplant coronary artery disease.

4. Intractable life-threatening arrhythmias unresponsive to medical therapy, catheter ablation, surgery, and/or implantable cardioverter-defibrillator.

5. Congenital heart disease with NYHA functional class 3–4 HF not amenable to palliative or corrective surgery. Patients with complex intra-cardiac abnormalities and significant pulmonary vascular obstructive disease may require heart-lung transplantation.

Ischemic or non-ischemic cardiomyopathy represented the major pathologies of patients receiving heart transplantation between 2006 and June 2012 (Table 11.1). Patients with infiltrative disorders such as amyloidosis are only considered for transplantation in some centers. From the 2013 ISHLT report (Transplants between 1982 and June 2011) one year survival is highest in patients with ischemic or non-ischemic cardiomyopathy than other etiologies. Long-term survival conditional to first year survival is highest for congenital heart disease. Re-transplantation is associated with worse prognosis than other etiological groups [4]. The 2013 American College of Cardiology/American Heart Association heart failure recommendations on HTX indications are described in Table 11.2 [5].

Table 11.1 Etiologies in Heart Transplantation Recipients between 2006–June 2012

Non-ischemic Cardiomyopathy	54 %
Ischemic Cardiomyopathy	37 %
Congenital Anomalies	2.9 %
Valvular Cardiomyopathy	2.8 %
Re-transplantation	2.5 %
Other causes	0.9 %

Data from Lund et al. [4]

Table 11.2 ACC/AHA guidelines indications for cardiac transplant

ACC/AHA guidelines indications for cardiac transplant
Absolute indications in appropriate patients:
• For hemodynamic compromise due to heart failure
– Refractory cardiogenic shock
– Documented dependence on intravenous inotropic support to maintain adequate organ perfusion
– Peak than 10 ml/kg/min with achievement of anaerobic metabolism
• Severe symptoms of ischemia that consistently limit routine activity and are not amenable to coronary artery bypass surgery or percutaneous coronary intervention
• Recurrent symptomatic ventricular arrhythmias refractory to all therapeutic modalities
Relative indications: • Peak VO2of 11–14 ml/kg/min (or 55 % of predicted) and major limitation of the patient's daily activities • Recurrent unstable ischemia not amenable to other intervention

• Recurrent instability of fluid balance/renal function not due to patient noncompliance with medical regimen
Insufficient indications:
• Low left ventricular ejection fraction
• History of functional class II or III symptoms of heart failure
• Peak VO2 greater than 15 ml/kg/min (or greater than 55 % of predicted) without other indications

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Cardiopulmonary Reserve Evaluation

Finding the optimal time to transplant a patient when they are sick enough to justify the morbidity and mortality associated with this major procedure, but not so severely ill that their perioperative mortality is prohibitive, remains a significant challenge. Unfortunately, there are a limited number of tools to risk stratify transplant candidates.

Cardiopulmonary reserves of ambulatory patients are assessed by measuring peak oxygen utilization (aerobic capacity) and altered ventilatory response (ventilatory efficiency). Generally, the peak VO2 (VO2 max) provides an objective assessment of functional capacity in patients with advanced heart failure and is one of the best predictors of when to list a patient for cardiac transplantation [6]. Peak VO2 was initially evaluated as a prognostic tool for determining when to list a patient for cardiac transplant prior to the widespread use of beta-blockers. However, several studies have demonstrated the continued usefulness of peak VO2 with beta-blocker use [7, 8]. Peak VO2 less than 14 ml/kg/min has traditionally been a cut point for cardiac transplantation, but with improved medical and device therapy for advanced heart failure peak VO2 less than 10–12 ml/kg/min appears to be a better threshold [9].

Ventilatory response as assessed by slope of minute ventilation to carbon dioxide production (V_E/VCO_2) [10, 11] or breathing pattern (exercise oscillatory breathing EOB) [12] can improve the predictability of exercise testing and their utility in determining the transplantation candidacy [13]. Assessing ventilatory efficiency is particularly helpful in patients who cannot reach adequate effort on exercise since the performance at submaximal effort can define the slope.

Though the above parameters guide the selection of heart transplant candidates, particularly by third-party payers, no single test or value should be used alone to determine transplant candidacy. Rather, a patient's entire clinical, social, and support situations should be evaluated.

If candidacy cannot be determined un-equivocally by clinical and objective laboratory assessment, survival assessment models are used to define the high risk patient. Several risk models have been developed to guide the selection of cardiac transplant patients including the Heart Failure Survival Score (HFSS) and Seattle Heart Failure Model (SHFM) . Heart Failure Survival Score (HFSS) is one of the widely

used predictive models [14] developed in 1990s by Aaronson et al. Multivariate proportional survival models were created using 80 clinical characteristics of the derivation cohort (n = 286) and validated in a group of 199 subjects. The score is calculated by the seven most significant prognostic factors: presence or absence of coronary artery disease, resting heart rate, left ventricular ejection fraction, mean arterial blood pressure, presence or absence of an intraventricular conduction delay on ECG, serum sodium, and peak VO2 [14]. The HFSS then stratifies patients into low, medium, or high risk with validated 1 year survival rates in these strata of 89, 72, and 60 %. Patients, who are identified as medium or high risk of adverse outcome, can be considered for Heart transplantation. Even though many advances in heart failure treatment have been made since 1997, HFSS retains the discriminatory power between risk groups [13].

The SHFM is a 21-variable risk model prospectively validated in almost 10,000 heart failure patients [15]. The model provides an accurate estimate of 1-, 2-, and 3-year survival and allows the operator to add in an estimated effect of different interventions on a patient's prognosis. Overall, SHFM tends to under-estimate and HFSS tends to over-estimate the risk of death [3].

Contraindications to Cardiac Transplantation

Careful investigation is needed to identify patients with coexisting systemic diseases that are not likely to improve or could be worsened by transplantation. Contraindications to transplantation are continually evolving and vary somewhat from center to center. The major hemodynamic factor excluding patients from cardiac transplantation is irreversible pulmonary hypertension (pulmonary vascular resistance >6 Wood Units (WU), Normal PVR <1.5 WU). Fortunately, pulmonary hypertension in many patients with HF is due to neuro-humoral vasoconstriction without irreversible structural changes in the pulmonary vasculature, such as calcification or intimal or medial hyperplasia. Patients with irreversible pulmonary hypertension have an increased risk of postoperative right ventricular failure because the normal donor right ventricle is acutely subjected to a marked increase in afterload. Right heart catheterization is performed in all candidates during the transplant evaluation to identify patients with elevated pulmonary pressures. A vasodilator challenge should be administered when the pulmonary artery systolic pressure is greater than 50 mmHg and either the transpulmonary gradient is greater than 15 mmHg or the pulmonary vascular resistance is greater than 3 WU. Protocol to test the pulmonary vascular responsiveness varies between institutions. Sodium nitroprusside, dobutamine, milrinone, prostaglandin E_1, prostacyclin, phosphodiesterase type 3 inhibitors, and inhaled nitric oxide are some of the agents used to reduce PVR and test for reversibility of elevated PVR [16–20]. In patients with positive response to vasodilator challenge, a continuous infusion of

milrinone, dobutamine, or prostaglandin E_1 for several weeks has been used in some patients as a bridge to transplantation [21, 22]. Mechanical circulatory support has also been shown to be effective in decompressing the failing ventricle and decrease the pulmonary pressures.

When an acute vasodilator challenge is unsuccessful, hospitalization with 24–48 h of hemodynamic monitoring and treatment with diuretics, inotropes, and pulmonary vasodilators is done. If the pulmonary hypertension can be reduced with a vasodilator challenge, candidacy may be considered. Serial right heart catheterizations should be performed in patients with borderline pulmonary pressures or response to vasodilator challenge to determine their ongoing acceptability for cardiac transplantation. Patients with irreversible pulmonary hypertension are occasionally considered for combined-heart lung transplantation in select centers.

Active malignancy from origins other than the skin is another absolute contraindication to cardiac transplantation. Malignancy may be worsened by the immunosuppression that is given to prevent transplant rejection. Even without a preexisting cancer, the incidence of malignancy is increased follow transplantation [23]. Patients with a history of prior malignancy where there has been adequate time to determine whether the malignancy has been cured may be considered for transplantation. The required duration of tumor free interval varies depending on the type of prior malignancy. An ISHLT transplant registry study by Oliveira et al indicates that transplantation can be safely performed in selective patients with history of malignancy and chemotherapy-induced cardiomyopathy with results non-inferior to transplant after non-ischemic cardiomyopathy [24]. Therefore, oncology consultation is an important prerequisite prior to listing these patients. Finally, patients with any other systemic illness with a life expectancy less than 2 years despite cardiac transplantation should not be considered.

Relative Contraindications to Cardiac Transplantation

With few absolute contraindications to cardiac transplantation, a thorough and careful risk assessment of comorbidities that may negatively affect outcomes is essential to ensure optimal allocation of this scarce resource. Consequently, the transplant evaluation focuses on screening for and identifying potential relative contraindications and comorbidities that may increase perioperative and/or long-term risk. We will outline the major comorbidities and how they are assessed as part of the transplant evaluation (Table 11.3).

Table 11.3 Recommended schedule for heart transplant evaluation

Test	Repeat				
	Baseline	3	6	9	12 months (and

		months	months	months	yearly)
Complete H and P	×				
Follow-up assessment		×	×	×	×
Weight/BMI	×	×	×	×	×
Immunocompatibility					
ABO	×				
Repeat ABO	×				
HLA tissue typing	Only at transplant				
PRA and flow cytometry	×				
• >10 %	Every 1–2 months				
• VAD	Every 1–2 months				
• Transfusion	2 weeks after transfusion and then 9 months × 6 months				
Assessment of heart failure severity					
Cardiopulmonary exercise test with RER	×				×
Echocardiogram	×				×
Right heart catheter (vasodilator challenge as indicated)	×		×		×
ECG	×				×
Evaluation of multiorgan function					
Routine lab work (BMP, CBC, LFT)	×	×	×	×	×
PT/INR More frequent per protocol if on VAD or coumadin	×	×	×	×	×
Urinalysis	×	×	×	×	×
GFR (MDRD quadratic equation)	×	×	×	×	×
Unlimed urine sample for protein excretion	×	×	×	×	×
PFT with Arterial blood gasses	×				
CXR (PA and lateral)	×				×
Abdominal ultrasound	×				
Carotid Doppler (if indicated or >50 years)	×				
ABI (if indicated or >50 years)	×				
DEXA scan (if indicated or >50 years)	×				
Dental examination	×				×
Ophthalmologic examination (if diabetic)	×				×
Infectious serology and vaccination					
Hep B surface Ag	×				
Hep B surface Ab	×				
Hep B core Ab	×				
Hep C Ab	×				
HIV	×				

RPR	×				
HSV lgG	×				
CMV lgG	×				
Toxoplasmosis lgG	×				
EBV lgG	×				
Varicella lgG	×				
PPD	×				
Flu shot (q 1 year)	×				
Pneumovax (q 5 years)	×				
Hep B immunizations: 1_2_3_	×				
Hep B surface Ab (immunity)	6 weeks after third immunization				
Preventive and malignancy					
Stool for occult blood × 3	×				×
Colonoscopy (if indicated or >50 years)	×				
Mammography (if indicated or >40 years)	×				×
Gyn/Pap (if indicated ≥18 years sexually active)	×				×
PSA and digital rectal exam (men >50 years)	×				×
General consultations					
Social work	×				
Psychiatry	×				
Financial	×				
Neuro/psych (if applicable)	×				

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Age

Among the relative contraindications to cardiac transplantation, age has historically been the most controversial factor. Previously, older patients had been excluded from consideration for transplantation. However, advances in posttransplant care have led to improved survival in older groups that is comparable with younger transplant patients [25–27]. Currently, 70 years old is considered the general upper age limit. However, consideration of carefully selected patients over age 70 is acceptable [28]. For these patients, use of an alternate donor program (typically organs from older donors) is often considered. According to ISHLT report the median recipient age increased to 56 years by 1996 and has remained fairly constant since then. The proportion of transplanted patients in the age group 60–69 years has increased from 14 to 24 % between the eras of 1982–1995 and 2006–2012 [4]. Even though the incidence of systemic illnesses and infection tend to increase with age, older individuals have increased immunotolerance

towards the graft.

Obesity

Pretransplant body mass index (BMI) greater than 30 kg/m^2 has been associated with a shorter time to high grade rejection, increased annual high-grade rejection frequency, and increased 5-year mortality when compared to normal weight recipients [29]. Moreover, obese patients have a greater risk of perioperative complications including poor wound healing, increased risk of infection, lower extremity thrombosis, and pulmonary complications [26, 30]. In general, most centers will consider patients with a BMI up to 35 kg/m^2 for transplantation. For patients who are severely obese, weight loss is mandatory before listing for cardiac transplantation. In patients who are unable to achieve adequate weight loss with diet and exercise alone, strategies using mechanical circulatory support to stabilize the heart failure syndrome followed by gastric bypass prior to transplantation have been utilized.

Renal Insufficiency

Renal insufficiency is common among patients with severe heart failure. In many patients, renal function will improve with improved cardiac output posttransplant but this improvement is often limited. However, numerous operative and posttransplant factors (prolonged cardiopulmonary bypass, tacrolimus therapy, etc.) may also worsen renal function. Renal function should be evaluated in all patients being considered for transplantation using an estimated glomerular filtration rate (eGFR) or creatinine clearance. No uniform criteria for renal function exist, but a majority of centers in the United States have indicated that a serum creatinine greater than 3 mg/dl is an absolute contraindication to transplant [31]. Evidence of renal dysfunction should prompt further investigation including renal ultrasound, estimation of proteinuria, and evaluation for renal arterial disease to exclude intrinsic and/or possible reversible causes. In patients with significant renal dysfunction, consideration should be given to combined heart/kidney transplantation.

Diabetes

Patients with diabetes mellitus may be considered for HTX depending upon the extent of associated diabetic complications. Diabetes with evidence of significant end-organ damage and/or significant renal dysfunction is a relative contraindication to transplantation [28]. However, carefully selected diabetic patients on insulin or drug therapy can undergo HTX with similar morbidity and mortality as non-diabetics [32]. Analysis of UNOS database by Russo et al. concluded that uncomplicated diabetes does not put recipient at survival disadvantage. But this comparable survival was not seen in

patients with diabetes mellitus complicated by renal insufficiency (SCr > 2.5 mg/dl), morbid obesity, peripheral vascular disease, or past history of stroke [33]. It is important to understand a patient's diabetic status because corticosteroids used as part of the postoperative immunosuppression regimen can worsen glucose control or unmask underlying disease. Renal effects of calcineurin inhibitor are comparable between uncomplicated diabetics and non-diabetics over time [34]. Diabetes mellitus is screened for during the transplant evaluation with a fasting serum glucose and HgbA1C, if clinically indicated. Endocrinology assessment is recommended for diabetic patients being considered for transplantation to optimize control of blood sugar. Uncontrolled diabetes despite optimal education and medical management is considered a relative contraindication for transplantation.

Peripheral Vascular Disease

Peripheral vascular disease may be considered as a relative contraindication to transplantation if it is extensive enough to be thought to increase surgical risk or limit posttransplant rehabilitation. Clinically severe symptomatic cerebrovascular disease not amenable to revascularization is considered a contraindication to transplantation [28]. Peripheral arterial Dopplers of the upper and lower extremities, carotid arterial Dopplers, and ankle-brachial index (ABI) are used for screening during the transplant evaluation.

Lung Disease

Advanced obstructive or restrictive lung disease is associated with a higher risk of postoperative lung complications, including infections associated with immunosuppressive therapy. Pulmonary function tests, chest x-ray, and CT scans of the chest are used to evaluate for lung disease. A force one-second expiratory volume (FEV1) of less than 1.0 l, a forced vital capacity of less than 50 % of predicted, or a forced expiratory volume-to-vital capacity ratio of less than 1.0 are generally accepted exclusion criteria.

Tobacco Use

The harmful effects of tobacco exposure in the general population are well known. Cardiac allografts are particularly susceptible to the deleterious effects of tobacco with an increased risk of coronary allograft vasculopathy, malignancy, and decreased posttransplant survival [35]. A detailed tobacco use history is obtained as part of the transplant evaluation. Patients should ideally be abstinent from tobacco use for 6 months prior to transplant. In patients considered to be high risk, this may be evaluated and monitored with urinary measurements of nicotine and cotinine at regular intervals to

ensure continued compliance to smoking cessation. Despite adherence to imposed tobacco cessation for 6 months to 1 year before surgery, approximately one in four heart transplant recipients return to tobacco abuse after transplantation [36, 37].

Substance Abuse

Active drug or alcohol abuse should be considered an absolute contraindication to transplantation [28]. In patients with a recent history of substance abuse, a structured rehabilitation program may be required prior to consideration for transplantation. Since substance abuse, in particular alcohol, is known to lead to cardiomyopathy, complete cessation from alcohol and drug use is critical in patients in patients with a known alcohol- or substance abuse-induced cardiomyopathy.

Evaluation for drug and alcohol abuse begins with a detailed patient history. Periodic alcohol and drug screens may be used as part of the transplant evaluation to ensure compliance to abstinence. Additionally, many transplant centers use written behavior contracts to outline specific expectations about patient's modifying their high-risk behaviors and clearly state what is expected prior to consideration for transplantation. The risk of recidivism following cardiac transplant is unknown. A small study in the liver transplant population demonstrated an 11 % alcohol relapse rate at 1 year and 30 % at 2 years; abstinence for greater than 6 months before transplantation significantly lowered the rate of relapse [38].

Psychosocial Evaluation

Medication noncompliance is a risk factor for acute graft rejection, transplant vasculopathy, and mortality [39]. Therefore, a complete psychosocial assessment that focuses on identifying social and behavioral factors that could cause difficulty with transplantation is a critical part of the transplant evaluation. This should include an assessment of the patient's ability to give informed consent and comply with posttransplant drug therapy, lifestyle changes, and regular follow-up. Additionally, the patient's family and other support systems, including their willingness to commit to long-term support, must be assessed.

Like the medical criteria, psychosocial evaluations are utilized to identify the patients who will most likely benefit from and maintain the scarce resource of donor organs. Unfortunately, there are limited data on the reliability and validity of psychosocial criteria to predict outcomes after transplantation. It remains challenging to ensure that psychosocial assessments that may affect posttransplant outcomes are not confused with personal opinions by the transplant selection committee on a candidate's social worth. Recently developed tools that objectively attempt to predict the transplant psychosocial outcome are promising, but have yet to become widely adopted [40].

Immunocompatability Testing

Immunocompatability testing should include ABO blood group typing. United Network for Organ Sharing (UNOS—a private organization that is under contract to the federal government to manage the United States' organ transplant system) requires ABO testing on two separate occasions and a second person to verify the correct blood type as it is entered into the active UNOS wait list . Panel-reactive antibody (PRA) testing is done to screen for humoral sensitization. Sensitization may be caused by pregnancy, blood transfusion, prior transplant or other allograft, or placement of a ventricular assist device. Blood transfusions should be avoided while awaiting transplantation to avoid humoral sensitization. If a blood transfusion is required, PRA testing should be done 2 weeks after transfusion and then monthly for 6 months.

Serologies and Vaccinations

Infectious serologies should be obtained during the initial transplant evaluation to identify infections such as Hepatitis B, Hepatitis C, Tuberculosis, and HIV that may influence candidacy for transplant. Heart transplantation in patients with chronic viral infections remains a subject of debate and practices vary between transplant centers. Individuals with chronic hepatitis B or hepatitis C who undergo heart transplantation have an increased frequency of liver disease, but survival is not reduced [41, 42]. Evaluation of these patients usually involves assessing for levels of viremia and consideration of a liver biopsy to determine if cirrhosis is present.

With the advent of highly active antiretroviral therapy (HAART) , HIV infection may not be sufficient reason to refuse transplantation. Good posttransplant outcomes have been demonstrated in a small series of highly selected HIV positive patients with low or undetectable viral loads and without recent significant infections [43]. These findings require further confirmation and consideration of HIV positive patients for transplantation varies between transplant centers. Immunizations prior to transplantation against influenza, pneumococcus, and Hepatitis A and B virus are recommended by many centers.

Age-Appropriate Screening

Additional selected screening should be done as would otherwise be recommended based on age, gender, and underlying risk factors. All patients should be screened for occult gastrointestinal bleeding and patients over 50 years of age should also undergo colonoscopy. Women over age 40 should have a yearly mammogram and clinical breast exam. Sexually active women or those over 18 years of age should have annual Papanicolaou (Pap) tests. Men should undergo annual prostate cancer screening. Routine labs, including basic metabolic panel, complete blood count, liver function

tests, INR, and urinalysis, should be done at baseline and as a part of periodic follow-up exams. Other evaluations, including dental exam and dual-energy x-ray absorptiometry (DEXA), should be considered if they would be otherwise indicated.

Ongoing Evaluation

Continued evaluation of the patient's heart failure stability and evolution of any comorbidities should occur while the patient remains on the wait list . Right heart catheterizations should be done at least every 6 months to evaluate filling and pulmonary pressures and cardiac output. This should be considered more frequently in patients with borderline pulmonary vascular resistance or if there is a significant change in clinical status that would require more aggressive hemodynamic support and consequently raise a patient's listing status. Pulmonary function testing and chest x-ray should be routinely obtained to monitor for lung and thoracic abnormalities. Serum chemistries should also be periodically monitored to evaluate renal function. Finally, age appropriate preventive screening should be kept up to date.

Final Decision Making in Organ Allocation

After the transplant evaluation has been completed, a multidisciplinary transplant team will consider the patient's severity of illness, medical comorbidities, support system, and financial situation to assess the suitability for transplantation. If it is determined that the patient is a candidate, they will be added to the wait list to receive a new organ. In order to ensure equitable distribution of donor hearts, UNOS has created an organ allocation system [44].

Allocation of thoracic organs in the United States is made according to the recipient's priority on the United Network for Organ Sharing (UNOS) waiting list (Table 11.4) and geographic distance from the donor. Priority on the waiting list is determined by a recipient's assigned code and time accrued within a status code. Patients with the highest medical urgency and the lowest expected short-term survival are generally assigned a higher status code

Table 11.4 UNOS priority status for heart transplant

UNOS priority status for heart transplant
Status 1A • Reside in the transplant listing center and at least one of the following:
– On mechanical ventilation
– On intra-aortic balloon pump, total artificial heart, or extracorporeal membrane oxygenator
– Hemodynamic monitoring with single high-dose intravenous inotrope or multiple intravenous inotropes (e.g., dobutamine >7.5 μg/kg/min plus milrinone 0.5 μg/kg/min)

• For 30 days after implantation with a left and/or right ventricular assist device for acute decompensation (need not be admitted to the listing center)
• LVAD with a device-related complication (such as thromboembolism, device infection, mechanical failure, or life-threatening ventricular arrhythmias)
Status 1B:
• Infusion of intravenous inotropes
• Supported by an implanted chronic (left and/or right) mechanical assist device
Status 2:
• All candidates who do not meet 1A or 1B requirements
Status 7:
• Temporarily unsuitable to receive a thoracic organ transplant. During the inactive period there is no gain or loss of accrued time

Once a donor is identified, appropriate allocation of the organ depends on the following:

1. ABO blood group compatibility.

2. Approximate size match—In general, the donor should be ±20 % of the potential recipient's body weight; for recipients with elevated PVR, the donor should be at least the same weight, if not greater.

3. Distance from the procurement site.

4. Degree of urgency—depending on the listing category of the patient.

5. Degree of allo-sensitization—With highly sensitized recipient, many centers consider the transplantation after negative prospective cross-match.

6. In situations where there are a number of potential recipients with identical characteristics, priority should be given to the patient who has been waiting the longest.

Survival benefit of transplantation may not be attained in status two patients' secondary to advances in heart failure therapy [45, 46]. This has resulted in the increasing trend of transplanting higher acuity patients, which highlights the importance of perioperative care in these challenging groups of patients.

Summary

Appropriate risk stratification of patients with end-stage heart failure is critical for transplant patient selection and allocation of scarce donor organs. The selection of cardiac transplant candidates is a multidisciplinary process that continues to evolve. The ultimate decision about whether to place a patient on the heart transplant waiting list is made by a multidisciplinary team and is based on a combination of the patient's heart failure severity, comorbidities that may increase the perioperative and long-term risk, social support system, and clinical judgment.

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12. Surgical Techniques of Heart Transplantation and Heart–Lung Transplantation

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Keywords Heart transplantation – Heart–Lung transplantation – Transplantation – Surgery – Technique – Operative – Cardiomyopathy – Heart failure – Donor

Abbreviations

CPB Cardiopulmonary bypass
IVC Inferior vena cava
LA Left atrium
LSPV Left superior pulmonary vein
LVAD Left ventricular assist device
MCS Mechanical circulatory support
PA Pulmonary artery
RA Right atrium
RSPV Right superior pulmonary vein
SVC Superior vena cava
TEE Transesophageal echocardiogram
UW University of Wisconsin

VAD Ventricular assist device

Introduction

> The Wright brothers' first flight was shorter than a Boeing 747's wing span. We've just begun with heart transplants.
>
> Dr. C. Walton Lillehei

Heart transplantation is an exhilarating endeavor, and outcomes have improved markedly over recent decades. A number of trends have become evident. First, the number of heart transplants has plateaued to a rate of approximately 2400 per year in the U.S. Second, an increasing proportion of transplanted patients are listed as status I at the time of transplantation. The percentage of patients who were status I at the time of transplant increased from 73 to 95 % during the last decade. In effect, status 2 patients are only rarely receiving a heart these days. Third, the percentage of patients who have been bridged to transplantation with mechanical circulatory support (MCS) has increased over the past decade from 23 to 41 %, and it is expected that this percentage will continue to increase if the present allocation system remains intact. These acuity and profile changes imply that we are operating on a sicker category of patients with more complex implantation surgeries [1].

Heart–Lung transplantation is a rarely performed operation. In the United States, there are fewer than 30 performed annually, with Stanford University and the University of Pittsburgh performing the bulk of these, and other centers performing the procedure sporadically [2]. Currently, this operation is reserved predominantly for patients with both end-stage cardiac and pulmonary disease. Moreover, with the growth of lung transplantation, many patients who were previously listed for heart–lung transplantation are now undergoing isolated lung transplantation along with reparative surgery for the heart.

In this chapter, I summarize the operations for heart transplantation and heart–lung transplantation. Isolated lung transplantation is discussed elsewhere in this text. Figure 12.1 outlines the rationale and sequence of the chapter's sections. For each of the headings of heart transplantation and heart–lung transplantation, the donor and recipient operations are separately described. Finally, ramifying scenarios of these procedures lead to the separate sections of this publication, as follows and as shown in the figure:

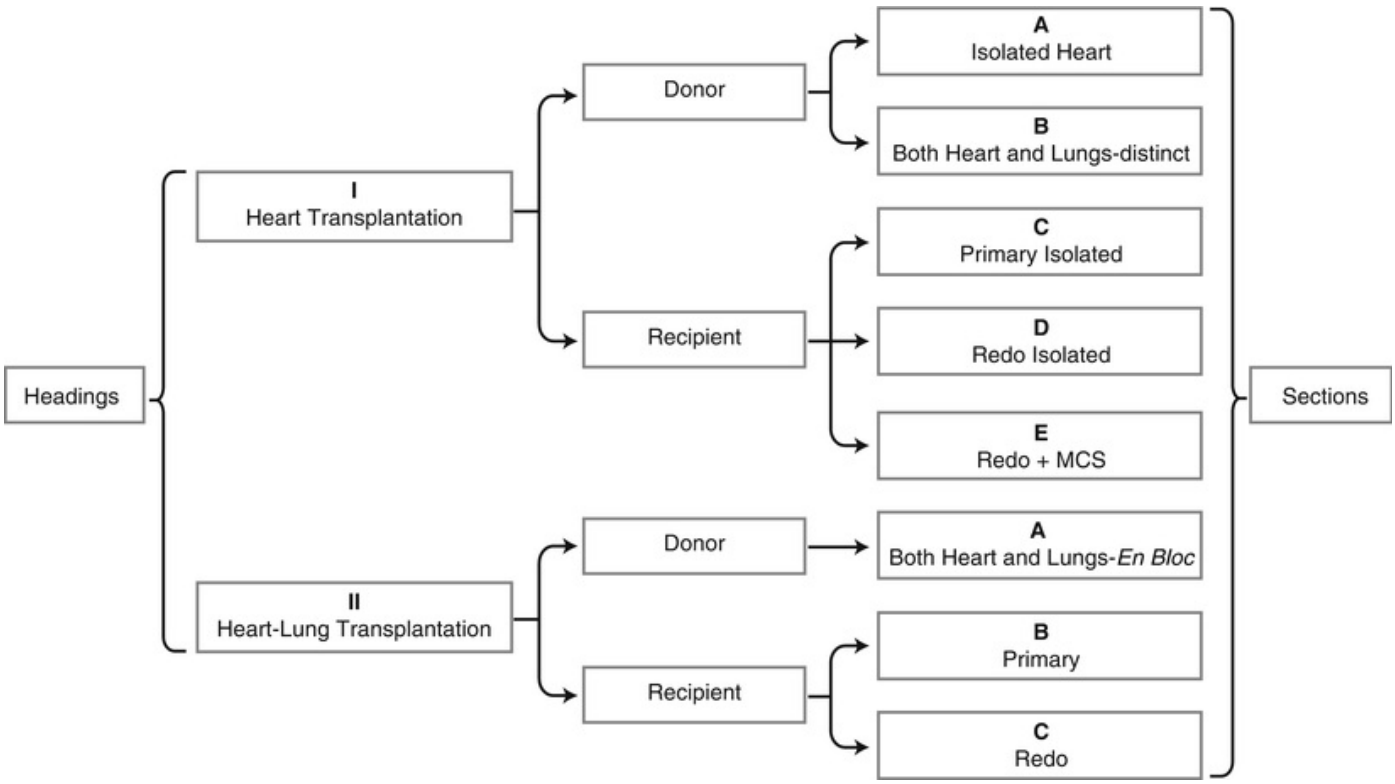


Fig. 12.1 Rationale and sequence of chapter. The headings, subheadings, and sections are displayed in columns from *left* to *right*

I. Heart Transplantation

   A. Isolated heart donor harvest for heart transplantation.

   B. Combined Donor Harvest of the Heart and Lungs for Distinct Recipients

   C. Heart Implantation Technique: Primary Operation

   D. Heart Implantation Technique: Reoperative Surgery

   E. Heart Implantation Technique: Bridged Patients

II. Heart–Lung Transplantation

   A. Combined Heart and Lung Harvest for Heart–Lung Transplants

B. Combined Heart and Lung Implantation: Primary Operation

C. Combined Heart and Lung Implantation: Reoperative Surgery or Surgery in a Potentially Hostile Pleural Space

For each of these procedures, safeguards and pitfalls are enumerated. Anesthesia management, preoperative care, and postoperative care are discussed in other chapters in this textbook, and so will not be addressed here in any depth. The reader is referred to these chapters for further information. The reader is also referred to Donald McRae's riveting account of the race to perform the world's first heart transplantation for further historical context [3].

Heart Transplantation

The donor operations are herein described for an isolated heart harvest and a combined heart and lung harvest for separate recipients; a description of the en-bloc harvest of the heart and lungs for a single recipient will be discussed in Sect. "Combined Heart and Lung Harvest for Heart–Lung Transplants". The cardiac recipient operation is discussed under this heading for three separate scenarios: primary implantation, reoperative implantation, and implantation in patients bridged with a left ventricular assist device (LVAD) .

Historically, the cardiac implantation techniques have been classified by the type of atrial connections constructed: classical biatrial implantation, bicaval implantation, and total heart implantation (see Fig. 12.2). The last procedure [4], where almost all the recipient atrial tissue is excised, is infrequently used because of the additional ischemic time required without a demonstrable benefit. Therefore, it has been largely abandoned and will not be discussed further here. The reader is referred elsewhere for the technical details of this operation [4].

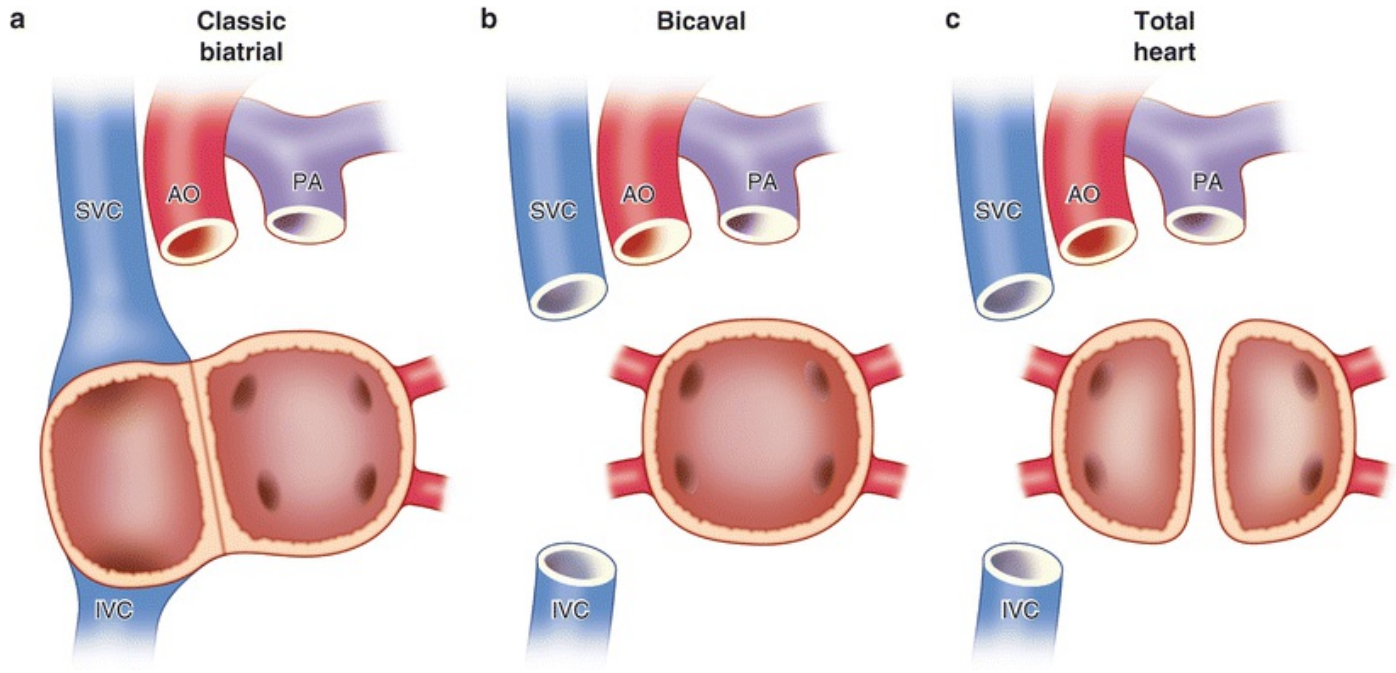


Fig. 12.2 The three different types of orthotopic heart implantation based on atrial connections. (**a**) Classical biatrial implantation. (**b**) Bicaval implantation. (**c**) Total heart implantation

The relative timing of the donor and recipient operations is planned so as to minimize ischemia time, defined as the interval from donor cross-clamp application to recipient cross-clamp removal. The best outcomes are achieved with ischemia times under 4–6 h, although longer times are acceptable depending on the clinical scenario. Figure 12.3 illustrates the complexity of coordinating the donor and recipient procedures. A summary of the sequential steps for the donor and recipient tracks, as well as the communication requirements, are depicted. A general rule of thumb we adopt is, "When in doubt, make the phone call." I suppose in the modern era we can modify that rule of thumb to the following: "When in doubt, send the text." Precise timing is paramount and miscommunications will be to the detriment of the recipient.

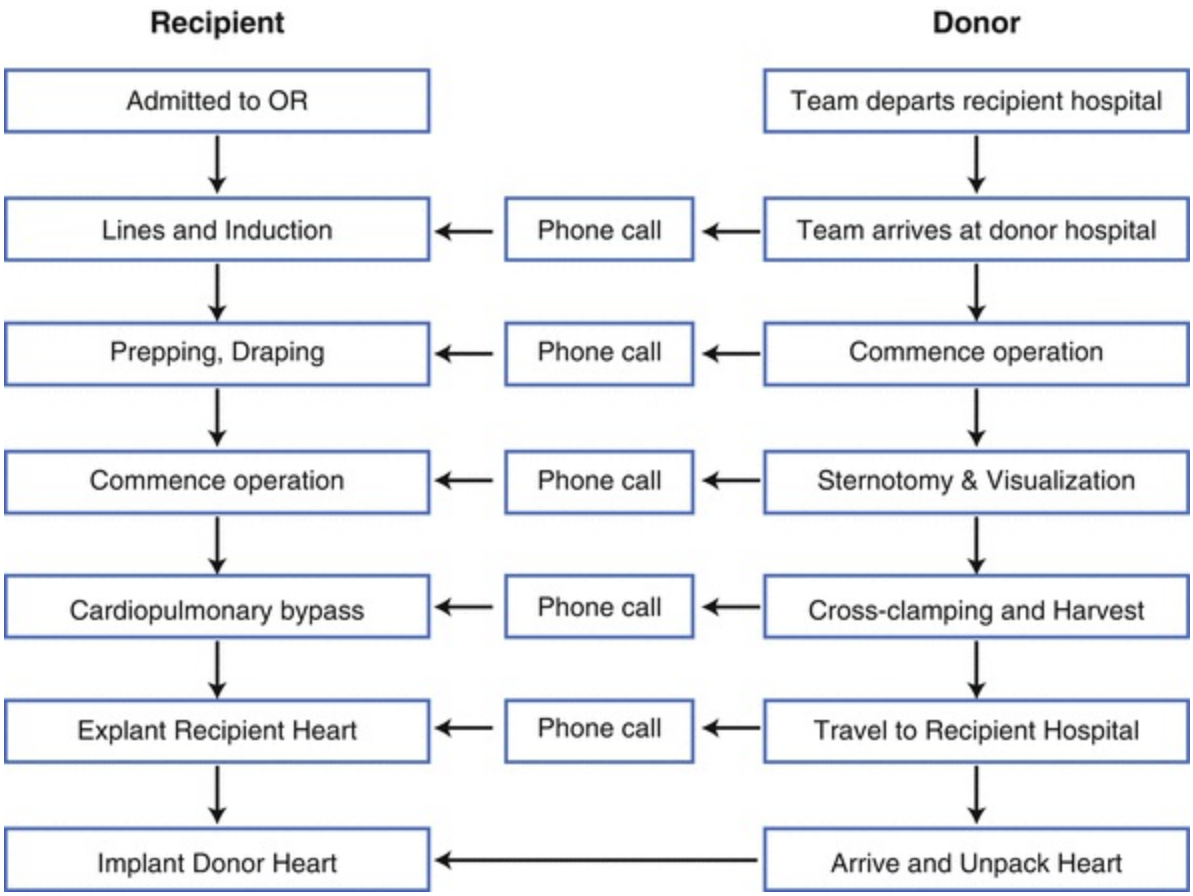


Fig. 12.3 Coordination of the recipient (*left*) and donor (*right*) operations. *Vertical arrows* indicate progression of the recipient and donor tracks, *short horizontal arrows* indicate communication opportunities between the tracks, and a *longer horizontal arrow* indicates the fusion of the donor and recipient tracks

Ideally, the donor heart should arrive in the recipient operating room just as the recipient team is ready to go on cardiopulmonary bypass (CPB) . It is therefore critical to plan the timing as meticulously as possible. This is usually undertaken by working back in time from the planned timing of the actual heart implantation to the initial events on the donor and recipient tracks so as to create a timetable template, as illustrated in Fig. 12.3. The most important *recipient* characteristics that play a role in the timing include whether the recipient is hospitalized or at home, requires a cross-match, is on oral anticoagulation therapy, has had prior cardiac surgery, and/or is on mechanical circulatory support (MCS) . The traditional cross-match is usually the component that requires the most time, since tissue must travel from the donor hospital to the recipient hospital prior to a final decision regarding whether to accept the organ. Some centers have started adopting virtual cross-matching of HLA antibodies, but this is not universal at present for thoracic organ transplantation [5, 6]. The most important *donor* characteristics that play a role in the timing include the travel time between the donor and recipient hospitals and whether other donor organs are being procured. The actual scheduling of the donor operation is usually at the discretion of the donor hospital, so

this will often dictate the actual timetable of the donor and recipient tracks. Unfortunately, because of the regularly scheduled operations at often busy donor hospitals, the donor harvest may be relegated to the nighttime hours.

The decision regarding whether to accept a specific remote donor based on projected ischemia time is rarely made in isolation. Other important factors influencing the acceptable ischemic time for a particular donor include the donor cardiac function, the degree of donor inotropic support, the recipient's hemodynamic stability, and the likelihood that the recipient will get another heart offer in a reasonable time period. For example, a longer donor ischemic time may be acceptable for the unstable recipient if the donor heart function is excellent and the donor is on minimal inotropic support. There are thus few hard-and-fast rules, and decisions needs to be individualized.

Isolated Donor Harvest for Heart Transplantation

The Operation

Prior to departing for the donor hospital, the donor team reviews all the relevant data. In addition to all the background data on the donor, it is critical to confirm on multiple occasions the ABO compatibility of the donor and recipient. At the very least, ABO compatibility needs to be confirmed and documented at the following mileposts:

- Upon initial donor online screen
- During the initial phone conversation between the donor surgeon and the organ procurement organization on-site coordinator
- At the time of arrival at the donor operating room, and
- At the time the donor heart arrives in the recipient operating room.

An incompatible match is disastrous for the recipient, and therefore the foregoing "belt-and-suspenders" approach is essential.

During the travel to the donor hospital, ongoing communication occurs between the donor and recipient teams, as outlined in Fig. 12.3. This communication continually and repeatedly occurs during the entire process to ensure that timing gets resynchronized in an iterative fashion, since seldom is the initial timetable accurate. The goal, again, is to have the donor heart arrive at the time the recipient team is ready to go on CPB. Occasionally, hemodynamic instability in the recipient mandates going on CPB while the donor team is *en route*, but this is fortunately a rarity.

Upon arrival at the donor hospital, the donor team again reviews the data, confirms ABO compatibility, and directly visualizes the most recent echocardiogram and coronary angiogram, if available. If the heart is deemed acceptable at this point by the donor team, confirmation is communicated to the recipient team. In addition, revised times are agreed upon by the donor/recipient teams (see Fig. 12.3).

Given that many donor cardiectomies are performed at hospitals unfamiliar to the operating surgeon, it is critical for the cardiac surgeon to communicate with the anesthesia team regarding relevant parameters and mileposts during the harvest—e.g., where to maintain the mean arterial pressure and central venous pressure, what kind of volume to administer, what inotropic or pressor agents to use if necessary, when the central venous line should be withdrawn, and when disconnection from the ventilator is appropriate.

Typically, the donor harvest proceeds in two stages. First, the initial sternotomy, evaluation, and preparatory dissection are performed. Second, once the other organ harvest teams are ready, the heart is arrested, explanted, and prepared for transport.

Commencing the first stage, a time-out is performed and the donor is prepped and draped. The back table that will be used for preparing the heart for transport is set up with basins, three sterile bags, and a suitable container (I use a wall-suction container available in most units). The individual donor teams make their respective incisions (usually a continuous sternotomy and laparotomy incision). Once the sternotomy is performed, a retractor is inserted. If available, a retractor with sternal spikes is used, since it is common for nonspiked retractors to slide down towards the abdomen during the harvest. The spikes press into the marrow and keep the retractor from sliding along the long axis of the sternum. Hemostasis of the bone marrow with bone wax is helpful. Bleeding should be under tight control, since the operation may take several hours until cross-clamping occurs. Substantial blood and volume loss can occur during this interval if one is not meticulous.

The pericardium is opened, and stay sutures are placed circumferentially. Observation and palpation of the heart is then undertaken. Observation focuses primarily on cardiac function and the presence of scars or contusions. Each of the cardiac chambers and great vessels is palpated for thrills. In the modern era, it is rare for surprises to occur that were not apparent on the preoperative echocardiogram. If, however, any abnormality is noted, a TEE should be considered intraoperatively and results communicated to the implanting team. Next, the coronaries are palpated to confirm the absence of significant plaque or calcifications, especially if the patient has not had a left heart catheterization prior to the operation. Once the heart has thus been visualized and palpated, the recipient team is again contacted to let them know if the heart is acceptable.

It is important to remark that there is a tradeoff in the amount of dissection performed at the initial stage of the donor harvest. Generally speaking, once the initial cardiac dissection is complete, it takes at least an hour and sometimes more before the other teams are ready for cross-clamp application. Therefore, one needs to be cautious about causing any hemodynamic instability—either from myocardial dysfunction or inadvertent injury—during the initial dissection phase that would prompt premature cross-clamping.

Accordingly, the initial dissection is limited to relatively safe maneuvers, and will depend on the experience of the operating surgeon. The aorta and pulmonary artery (PA) are separated and freed up from their pericardial attachments. The aorta should be freed up to the arch. The superior vena cava (SVC) and inferior vena cava (IVC) are dissected away from their respective pericardial attachments, and care should be taken not to injury the azygous vein as it enters the SVC posteriorly. Clearing cardiac structures from the pericardium and from each other while the heart is full will facilitate the explantation when the heart is empty, since it is harder to find dissection planes when the heart is flaccid. Two silk ties are placed around the SVC above the azygous vein entry site. An additional tie is placed around the azygous vein if this can be done with ease. Umbilical tapes are passed around the aorta and the IVC. At this juncture, the donor heart team needs to pause for the abdominal organ teams to complete their preparatory dissection to be ready for cross-clamping. An estimate of the time remaining from the abdominal team is obtained, and this information is relayed to the recipient team, with adjustments made to the timetable.

Prior to leaving the operating table at the end of the first stage, the surgeon ensures that he has selected his cross clamp and has communicated his suture and other disposable needs for the second stage to the scrub nurse or technician.

Figure 12.4 shows the sequence of events for the second stage of an isolated heart harvest.

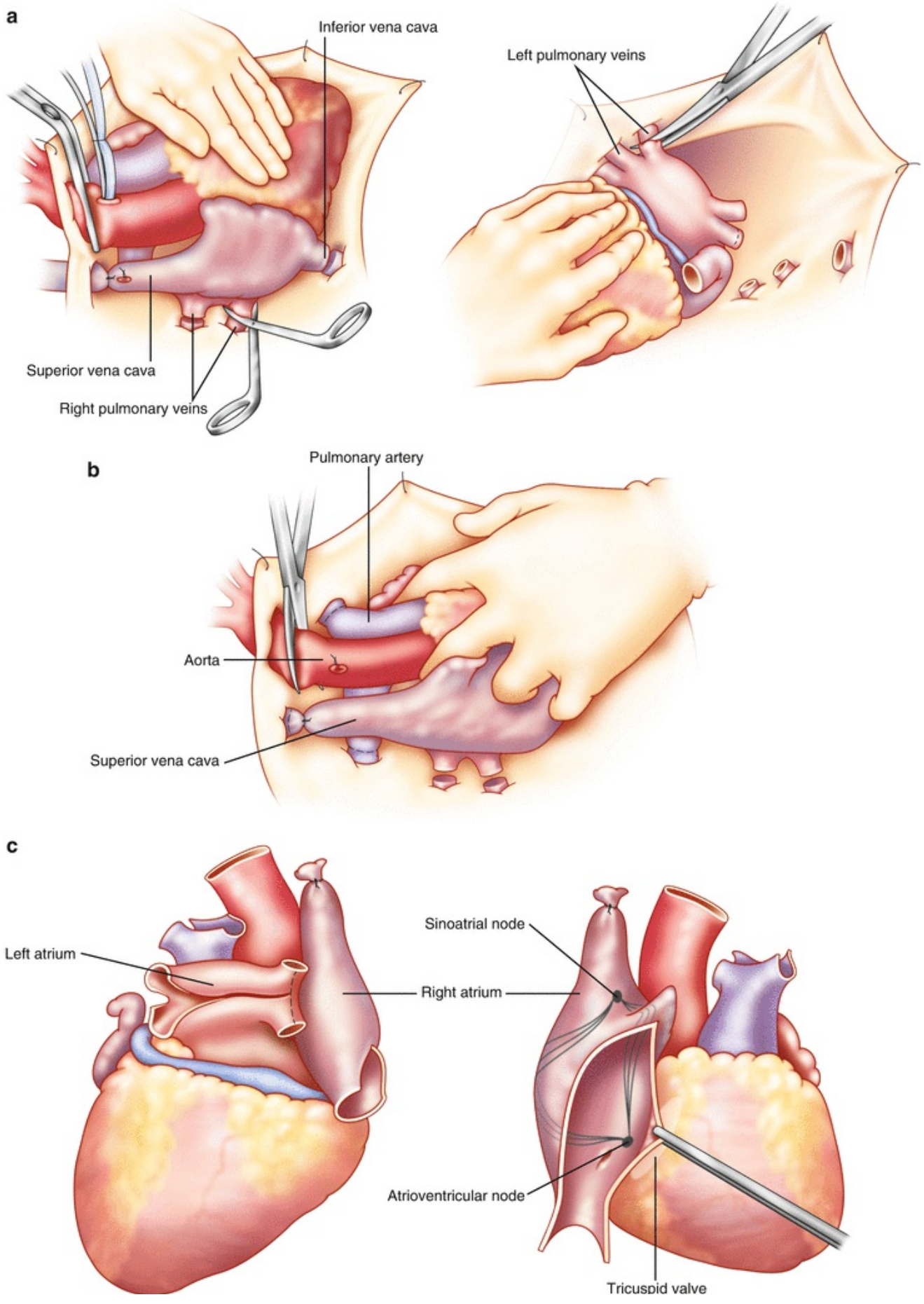

a
Inferior vena cava
Left pulmonary veins
Superior vena cava
Right pulmonary veins
b
Pulmonary artery
Aorta
Superior vena cava
c
Left atrium
Right atrium
Sinoatrial node
Atrioventricular node
Tricuspid valve

Fig. 12.4 Steps in the performance of the cardiac harvest . (**a**) The heart has been arrested and the cardioplegia administered. The SVC has been ligated, an incision made in the IVC, and the right sided pulmonary veins are divided at the pericardial reflection. With the heart retracted cephalad and to the right by the surgeon's left hand, the left-sided pulmonary veins are divided. (**b**) With the surgeon's left hand retracting the heart towards the patient's feet, the branch pulmonary arteries are divided at the pericardial reflection and the aorta divided just proximal to the cross clamp. (**c**) At the back table, the back wall of the left atrium is opened, as is the pulmonary artery. In addition, for planned right atrial anastomosis, an incision is created from the orifice of the IVC towards the right atrial appendage, avoiding the sinus node

The second stage is launched once the abdominal team is near-ready for cross-clamping. A dose of 30,000 units of heparin is administered by the anesthesia team. Three minutes are allowed to pass to allow recirculation of the heparin. During this time, the cardioplegia bag (1–2 L) and line are prepared. The line is deaired and clamped at the field. A purse-string suture is placed in the mid-ascending aorta, and the cardioplegia cannula is inserted within the purse string. The purse string is snared down, the cannula is deaired and then attached to the previously deaired cardioplegia line. A pressure line may be attached if desired, but palpation of the aorta during cardioplegia administration usually suffices. The cardioplegia line should be kept clamped at the field to prevent inadvertent premature administration of cardioplegia prior to crossclamping.

An incision is made in the right edge of the pericardium at the level of the diaphragm down to abut the lateral aspect of the IVC. This incision will allow egress of blood return from the IVC and coronary sinus down into the right pleura, preventing rewarming of the heart. This maneuver is not performed if the right lung is being harvested.

Once the abdominal team is ready for cross-clamping, the cardiac surgeon asks the anesthesiologist to withdraw any central lines traversing the SVC. Two suction cannulae are prepared and placed in the mediastinum. These will be managed by the first assistant. The goal will be to clear the field of blood to (1) enable visualization of the heart and (2) prevent rewarming of the heart. Accordingly, one suction will be placed with its tip by the IVC, and the second, by the left inferior pulmonary vein (PV)—i.e., the sites where the initial venting incisions will be placed. The SVC is then ligated once, leaving the other ties to be secured after cardioplegia delivery. The location of the IVC hemisection site sometimes needs to be negotiated with the liver team; however, one must ensure that the coronary sinus is not injured by cutting too high. The coronary sinus can be protected by the surgeon's placing his left hand with his index and middle fingers straddling the cavoatrial junction and then gently retracting cephalad. Once this hemisection is complete, a second hemisection is performed of the left inferior PV. Now, both the right and left ventricles are vented. Once the heart is decompressed after several beats, a cross clamp is applied to the ascending aorta distal to the cardioplegia line, and the cardioplegia is administered by the perfusion team. The aortic root should

be palpated to confirm that the root is adequately distended. Again, a pressure transducer can be used if so desired. Further details regarding myocardial preservation are discussed in the next section (*vide infra*).

At cross-clamping, another phone call should be made to the implant center to resynchronize the time schedules (see Fig. 12.2).

As cardioplegia is being administered, ice slush is repeatedly placed on all surfaces of the heart, and blood and cardioplegia effluent is evacuated from the pericardial space. As stated above, one suction cannula is placed at the IVC incision, and the other at the left inferior PV incision. Besides making sure all the effluent is displaced from the heart, the surgeon must also pay close attention to the heart to ensure that it is not getting distended. The right heart may get distended if the IVC incision is too small; the left heart may get distended if aortic insufficiency is induced by the pressurized root or the left inferior PV incision is too small. Once the cardioplegia is completed, the cardioplegia purse-string and cannula are removed.

It is important to develop a standard sequence for excising the heart, since there are a variety of possible permutations. Since the heart is ischemic at this point it is imperative that the heart be kept as cool as possible and excised efficiently. My protocol is as follows: The assistant manages the suction cannulae, since blood will continue to pool in the field as the heart is being excised. The assistant is also responsible for adding slush to the heart intermittently to maintain preservation. It is generally a good rule of thumb to habitually excise as much of the aorta and SVC as possible, particularly if the recipient has congenital heart disease or the recipient operation is reoperative.

The first maneuver is to tie the remaining ties on the SVC and azygous vein. Once this is complete, the SVC is divided between its two ties, and the azygous vein is divided at its connection to the SVC. The tie on the SVC remnant in the patient is placed to minimize further blood return to the pericardial space. (It is helpful here if the SVC had already been dissected completely during the initial stage of the harvest.) Next, the surgeon places a slush-packed lap pad in his left hand, and gently lifts the acute margin of the heart towards the patient's left shoulder. He will then retract the heart progressively cephalad as the IVC and then the PVs are transected (Fig. 12.4a). In isolated heart harvests—where the lungs are not being harvested—the PV transections should be placed at the pericardial edge, to maximize the length attached to the left atrium. Once all the PVs are divided, the heart is released. The surgeon places his left index and middle finger splayed around the aortic and pulmonic roots and gently retracts the heart towards the patient's feet (Fig. 12.4b). The branch pulmonary arteries are now divided at the pericardial reflection. Next, the aorta is transected just distal to the innominate artery at the arch. Finally, the surgeon wraps his left hand around the base of the heart and great vessels and exerts slight upwards retraction towards the ceiling. The remaining attachments to the pericardium and mediastinum are now severed. Please see

Fig. 12.4a–c.

For the reader's convenience, Table 12.1 lists the basic differences in cannulation, preservation requirements, venting requirements, and incisions of the heart transplantation and heart–lung transplantation recipient operations.

Table 12.1 Heart vs. heart and lung procurement

Step	Isolated heart	Both heart and lung
Cannulation	Aorta alone	Both aorta and PA
Preservation	Heart alone	Both heart and lungs
Venting	RA	RA and LA
Left atrial incisions	PVs at pericardium	LA between sulcus and PVs
PA incisions	Branch PAs at pericardium	Main PA at bifurcation

Heart Preservation, Preparation, and Transportation

As stated previously, 1–2 L of cardioplegia is administered to the heart prior to excision. If any concerns are raised about the adequacy of the preservation—e.g., a moderately hypertrophied heart, delay in arresting the heart, or induced aortic insufficiency, then a second liter may be given at the discretion of the operating surgeon. There are several cardioplegia solutions available; I have the most familiarity with the University of Wisconsin (UW) solution (Belzer). Most centers, like our own, use an intracellular solution for the heart—i.e., one with a relatively high potassium concentration to induce a diastolic arrest of the heart. The components of UW solution are listed in Table 12.2.

Table 12.2 Contents of University of Wisconsin solution

Component	Concentration
Sodium	35 mM
Potassium	125 mM
Magnesium	5 mM
Sulfate	5 mM
Phosphate	25 mM
Bicarbonate	100 mM
Raffinose	30 mM
Glutathione	3 mM
Adenosine	5 mM
Allopurinal	1 mM
Hydroxyethyl starch	50 g/L
Dexamethasone	16 mg/L
Insulin	40 U/L

Penicillin	200,000 U/L

The role of myocardial preservation solutions is to preserve the microvascular, cellular, and functional integrity of the heart. The main protective components of the cardioplegia solution are (1) hypothermia, (2) potassium to arrest the heart, (3) impermeants to prevention cellular swelling (e.g., lactobionate and raffinose), (4) magnesium to prevent calcium accumulation in the sarcoplasmic reticulum, and (5) free radical scavengers to prevent free radical injury. Experimental and clinical use of the UW solution, which is an intracellular (high potassium) solution that includes the above ingredients, have provided sufficient evidence to support the expectation of excellent myocardial preservation for at least 6 h of ischemic time [7].

Once the cardioplegia is completed and the heart excised, the heart is transposed to the back table that previously had been set up. The surgeon places the heart on a lap pad in a basin filled with iced saline, and the heart is then examined in the order of the normal pathway for blood flow: The RA, the tricuspid valve, the pulmonic valve, the LA, the mitral valve, and the aortic valve.

To facilitate the exam and the later implantation, the following steps are taken in the field. The atrial septum is investigated through the IVC. If a biatrial anastomosis is planned (*vide infra*), then the RA may be opened from the IVC orifice towards the RAA, veering anterior to the sulcus terminalis to avoid injury to the tail of the SA node. The TV can then be examined as well for its morphology. The coronary sinus is visualized as it enters into the RA to ensure there has been no injury to this structure during the IVC transection (see Fig. 12.4c).

The left atrium adjacent to the PA is separated from PA by severing the attachments connecting the two. The PA is then opened with an incision connecting the branch PAs, and the pulmonary valve is inspected. The LA incision is opened by bridging the orifices of the pulmonary veins. Further trimming of the aorta, LA, and PA is left for later at the time of the implant. The AV and MV are examined for their morphologies as well. As mentioned previously, there are not likely to be any surprises relating to the cardiac valves.

Upon examination of the interatrial septum, if a patent foramen ovale (PFO) is present, it is helpful to close this during the donor operation with 5.0 prolene; this should be tied on the RA side. All PFOs , no matter how small, need to be addressed, since the frequent occurrence of postoperative right ventricular dysfunction may lead to considerable hypoxemia from right-to-left shunting otherwise. The heart is then placed in a sterile bag with cold UW solution. The untied bag is then placed in a rigid container (e.g., a wall suction container) containing slush. The first bag is then de-aired and tied, and the container is filled to the rim with slush. The container is closed and then sequentially wrapped in two additional sterile bags contained ice. Each bag should be tied. The heart, along with its enveloping bags and container, are placed in an ice cooler

and transported back to the implant center.

Communication between the teams continues at appropriate times during the transportation to continually resynchronize the timing (see Fig. 12.2).

In recent years, several centers have participated in trials of warm perfusion circuits to maintain blood flow to the coronary circulation after explantation and during the transportation process. The PROCEED II trial evaluated the TransMedics® Organ Care System Heart technology, and a marketing application has been submitted to the FDA. At this point it is too early to predict what role continuous warm perfusion will play in the future of donor heart preservation [8]. The possibility of resuscitating and reevaluating warm perfused hearts that had been considered marginal has generated enthusiasm among those in the field.

Combined Donor Harvest of the Heart and Lungs for Distinct Recipients

Modifications to the above steps are required if the lung is being harvested simultaneously for a different recipient(s). The focus in this section will be on how lung procurement for separate recipients impacts the cardiac procurement. For further details, please see Chap. 8. Prior to prepping and draping, a bronchoscopy is performed to evaluate the tracheobronchial tree and obtain a specimen for gram stain and culture. Upon entry into the chest, the pleura are opened first and the lungs examined. The heart is evaluated and prepared as previously described.

During the second stage, both the aorta and the PA are cannulated for the delivery of preservative solution to the heart and lungs, respectively. There are a number of alternatives for pneumoplegia solution that lie outside the scope of the present discussion. When the abdominal team is ready for cross-clamping, 500 μg of prostaglandin E is injected into the PA for pulmonary vasodilatation. Once hypotension occurs (confirming systemic circulation of the prostaglandin E), the SVC is tied as before, and the IVC is hemisected. Instead of incising the left SPV, however, the LA appendage is grasped and amputated to vent the left side. This maneuver preserves the integrity of the left pulmonary veins for the lung team. The cross-clamp is then applied on the aorta, and both the cardioplegia and pneumoplegia are infused. The pneumoplegia infusion usually takes considerably longer than the cardioplegia infusion. Slush is applied to both the heart and the lungs, along with cold solution.

Once both the cardioplegia and pneumoplegia are completed, the aortic and pulmonary artery cannulae and purse-strings are removed. The remaining SVC and azygous ties are secured, the SVC is transected between the SVC ties, and the IVC incision is completed. The heart is elevated cephalad as before, but instead of cutting the PVs, the left atrium is incised with an 11 blade mid-distance between the coronary sinus and the left-sided pulmonary veins. Please refer to Fig. 12.5. The incision is

continued with scissors in a counterclockwise direction, leaving the pulmonary veins with the patient. Care is taken to provide an adequate venous cuff for the lung team, while at the same time ensuring that there is an adequate rim of LA tissue for the heart implantation. Generally speaking, only about a 1 cm cuff is needed on the cardiac specimen. On the right side, Waterston's groove in the interatrial septum is developed (see Fig. 12.5c), and an incision placed on the right side within the groove. The inside of the LA is then visualized, and the incisions are joined so as to leave a cuff of left atrium posteriorly for the lung team to divide later. Lastly, the main PA is divided just proximal to the bifurcation, and the heart is transferred to the back table for further preparation as previously described (see Fig. 12.6b).

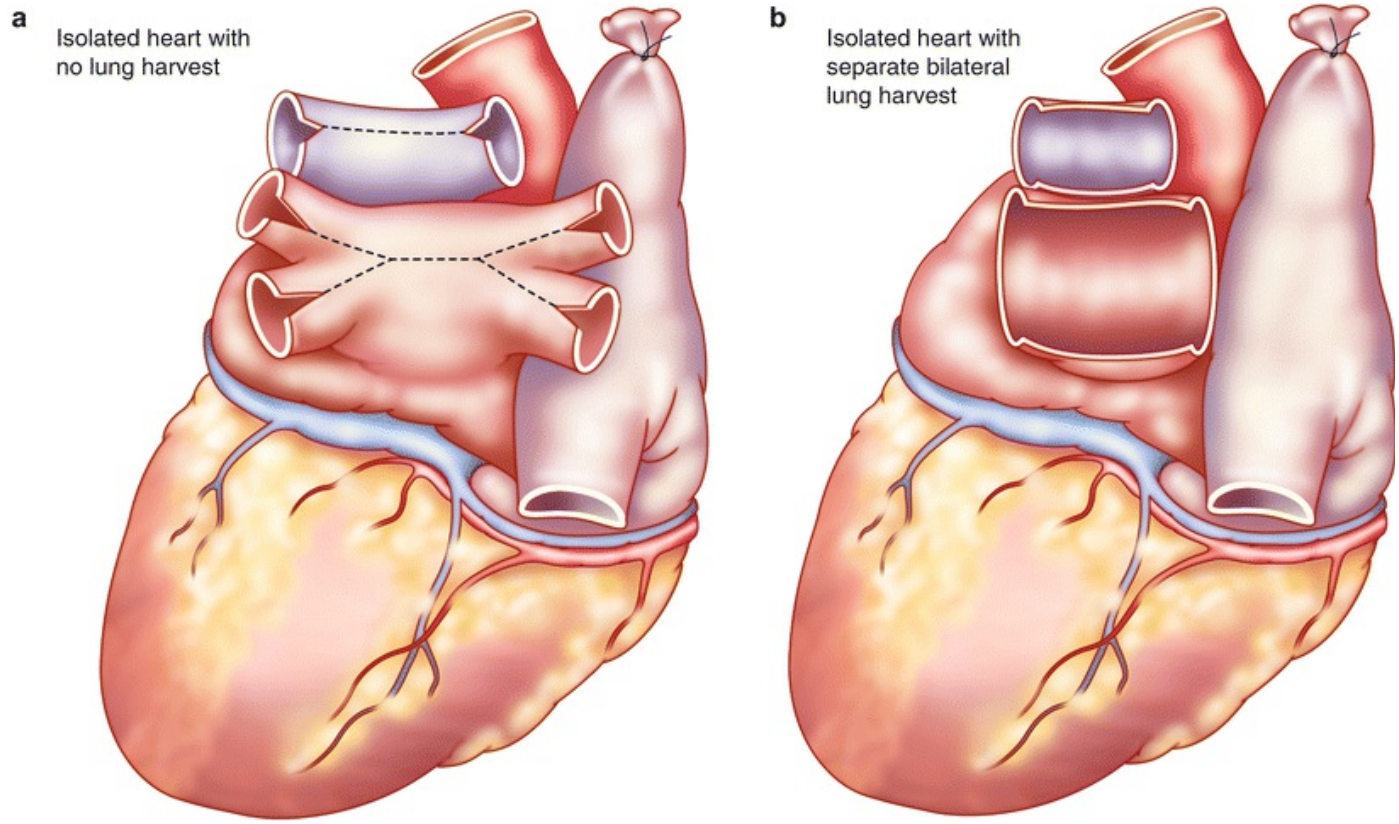


Fig. 12.5 The contrast in the left atrial and pulmonary artery incisions when an isolated heart harvest is performed (a) and when the heart is harvested simultaneously with the lungs (b)

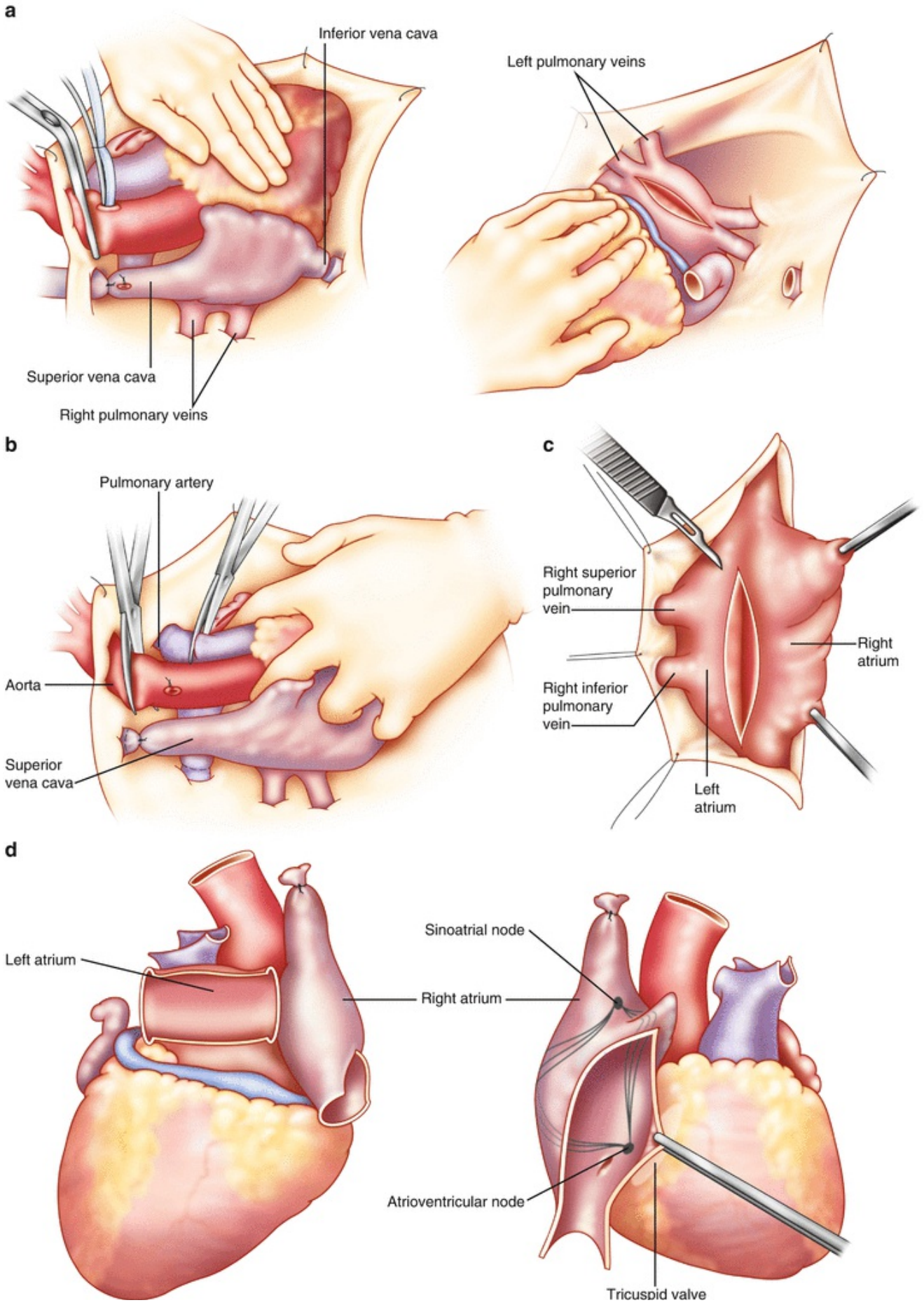

a
Inferior vena cava
Superior vena cava
Right pulmonary veins
Left pulmonary veins
b
Pulmonary artery
Aorta
Superior
vena cava
c
Right superior
pulmonary
vein
Right inferior
pulmonary
vein
Right
atrium
Left
atrium
d
Left atrium
Right atrium
Sinoatrial node
Atrioventricular node
Tricuspid valve

Fig. 12.6 Steps in the performance of the cardiac harvest when the lungs are simultaneously harvested. (a) The heart has been arrested after infusion of the cardioplegia. The SVC has been ligated. Notice that the IVC is divided, but the pulmonary veins are left intact. (b) With the surgeon's left hand retracting the heart towards the patient's feet, the central pulmonary artery is divided just proximal to the bifurcation, and the aorta divided just proximal to the cross clamp. (c) Waterston's interatrial groove is developed with a blade so as to optimize the amount of the left atrial cuff. (d) The final appearance of the excised heart and the incision from the IVC to the right atrial appendage

Heart Implantation Technique: Primary Operation

Before the Donor Heart Arrives

At the appropriate coordinated time, the recipient undergoes induction of general anesthesia and intubation (see Fig. 12.3). Lines are placed, if they have not been inserted before. If the patient has a defibrillator, it is inactivated prior to any incisions, and the internal pacemaker placed on internal mode if the patient is pacer-dependent or inactivated if the patient is not pacer-dependent. Defibrillator pads are placed on the patient's torso, particularly in reoperative cases. The chest, abdomen, and lower extremities are prepped and draped in the usual sterile fashion.

Conventional sternotomy is performed, and the pericardium is suspended. Purse-strings are placed on the distal ascending aorta or arch, high on the SVC, and on the IVC at the cavoatrial junction.

Once the donor heart is approximately 5 min out from arrival, the patient is heparinized and cannulated. Caval tapes are placed around the SVC and IVC. A carbon dioxide line is attached at the uppermost part of the skin incision. This will insufflate carbon dioxide onto the operative field so as to minimize undissolved air entry into the cardiovascular system.

After the Donor Heart Arrives

Once the donor heart has arrived in the OR, cardiopulmonary bypass (CPB) is instituted with systemic cooling to 28 °C. The donor team then unwraps the donor heart under sterile conditions and the heart is then carefully transferred to a back table with ice slush in a basin. Any dissection that has not been completed at the donor hospital back table is now completed. The PA is separated completely from the LA and from the aorta. Excess lymphatic tissue is trimmed. A PFO is closed if this was not done before.

A decision is reached regarding implantation technique. The three available options are as follows: (1) Classic biatrial, (2) Bicaval, and (3) Total heart implantation (see Fig. 12.2). As mentioned previously, despite initial enthusiasm, very few centers currently perform total heart implantation because of the additional time and complexity associated with the two pulmonary vein anastomoses.

Most centers use either the biatrial approach or the bicaval approach , with a trend in recent years towards the latter. The advantage of the *biatrial* approach is that it can

be performed faster, since there are only four large anastomoses. Although the *bicaval* approach takes a bit longer due to its five anastomoses—i.e., SVC to SVC and IVC to IVC instead of just RA to RA—it appears to be associated with a lower incidence of sinus node dysfunction perioperatively, lower requirement for a permanent pacemaker, and improved tricuspid valve function [9]. For both of these approaches, the only difference consists in the way the recipient and donors' RAs are connected. All the remaining anastomoses are the same. My general approach is to plan on a bicaval implantation, unless the mediastinum is unusually deep, the adhesions are particularly dense in the areas around the right atrium, or the ischemia time is a major concern.

Once the implant technique has been selected, the recipient cardiectomy is performed, as shown in Fig. 12.7. Prior to snaring the SVC and IVC, the swan-ganz catheter is withdrawn by the anesthesia team. The SVC and IVC are snared. The aorta is cross-clamped. The aorta and PA are transected just above the valve commissures. The RA is entered at the RA appendage, and the incision is carried out inferiorly towards the IVC, stopping about 2 cm short of the cavoatrial junction and veering towards the AV groove anteriorly. When in doubt, the surgeon should leave more tissue on the recipient side, since it can always be trimmed later. The RA incision is then carried out superiorly to the junction with dome of the LA, entering the latter chamber. If the patient has any pacing leads traversing the SVC, these are placed on some tension and cut as high as possible. (The remainder of the leads and the pacemaker generator will be removed after the heart implantation is complete and heparin has been reversed through a left infraclavicular incision.) The LA incision is now extended inferiorly across the fossa ovalis and through the coronary sinus. The incision adjacent to the IVC is now joined with this medial incision to complete the RA transection. With visualization of the pulmonary veins from within the initial LA incision, the incision is extended superolaterally towards the LA appendage (excising it) and then down towards the mitral annulus, staying well anterior to the entry of the PVs. The inferoseptal incision is now joined across the lower LA posteriorly to meet the other LA incision. The cardiectomy is now complete, and the recipient heart is removed. Hemostasis is obtained of the posterior mediastinum (see Fig. 12.7).

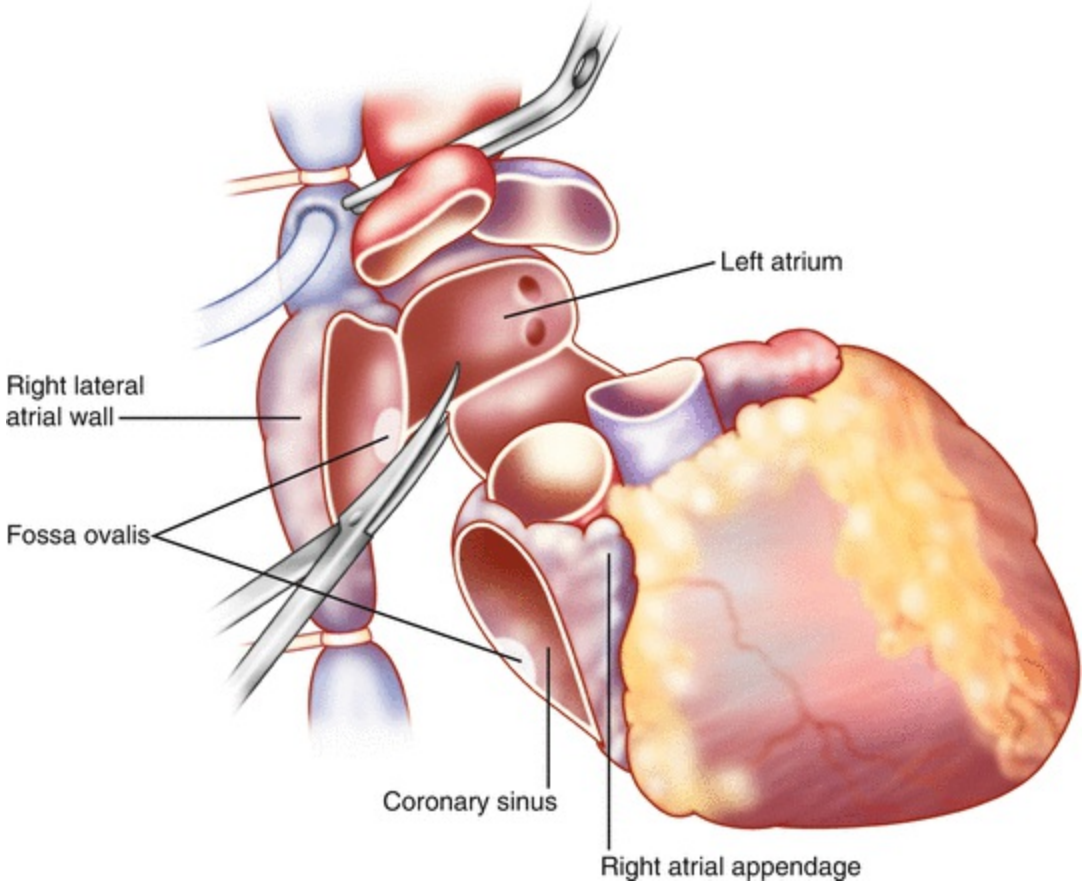


Fig. 12.7 Recipient cardiectomy : The recipient cardiectomy is performed after cross-clamping by transecting the aorta and the pulmonary artery at the level of the valves and transecting the atria as described in the text. Shown here is the heart as the explantation is near completion

If a biatrial anastomosis will be performed, the atrial incisions are trimmed and rounded (see Fig. 12.8a). If a bicaval anastomosis is performed, a portion of the posterior wall may be left in situ or excised (see Fig. 12.8b). The advantage of the former is that the posterior wall remnant will prevent retraction of the SVC and IVC, which will facilitate these anastomoses.

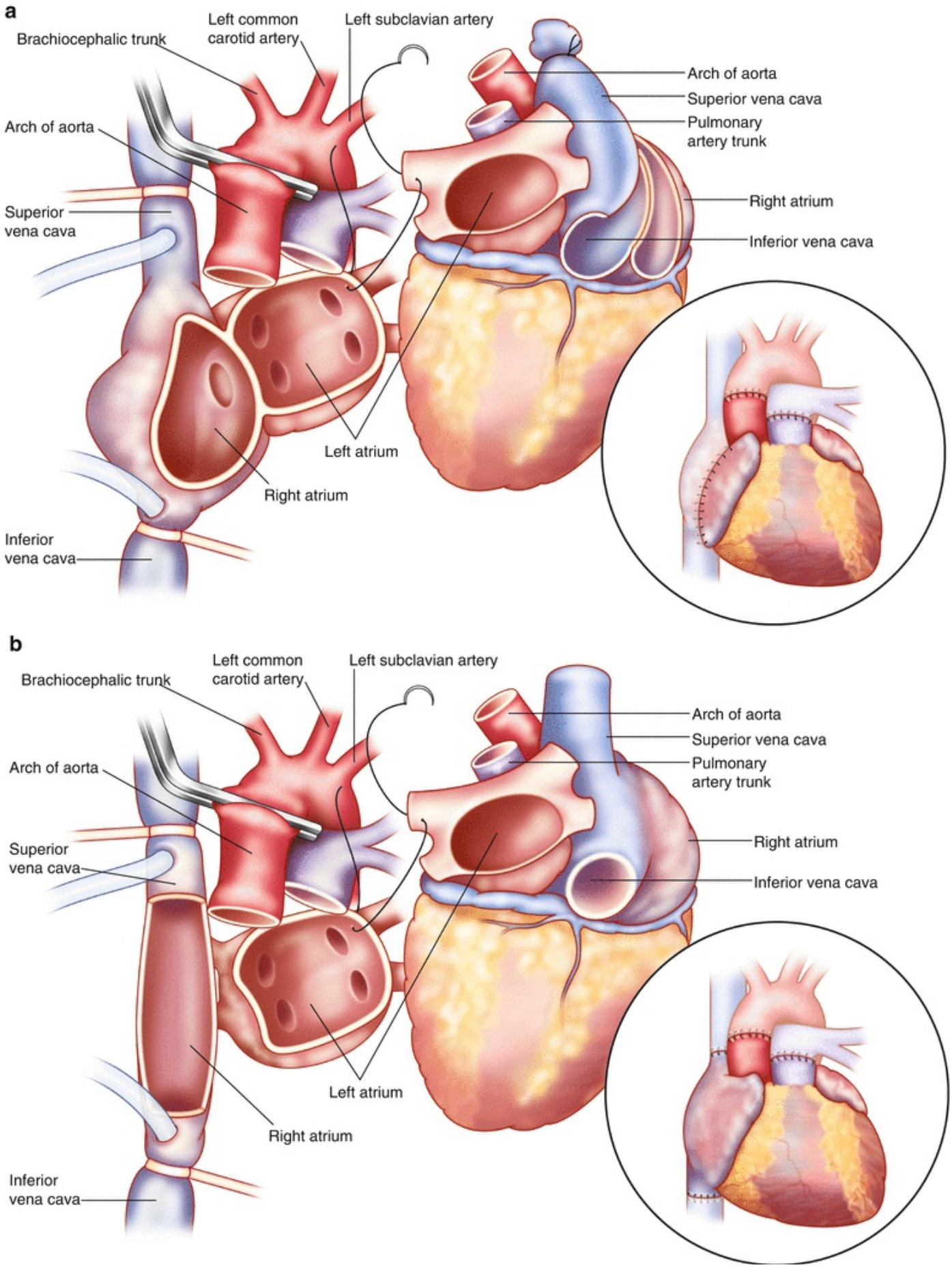

a
Brachiocephalic trunk
Left common carotid artery
Left subclavian artery
Arch of aorta
Superior vena cava
Pulmonary artery trunk
Right atrium
Inferior vena cava
Left atrium
Right atrium
Inferior vena cava
b
Brachiocephalic trunk
Left common carotid artery
Left subclavian artery
Arch of aorta
Superior vena cava
Pulmonary artery trunk
Right atrium
Inferior vena cava
Left atrium
Right atrium
Inferior vena cava

Fig. 12.8 Different techniques of implantation. (**a**) The heart implantation being performed using a biatrial approach . The *inset* shows the completed implantation. (**b**) The heart implantation being performed using a bicaval approach . The *inset* shows the completed implantation

Prior to commencing the left atrial anastomosis, an insulation pad is placed on the posterior pericardium to include the left phrenic nerve area. Ice slush will be placed posterior and anterior to the heart after each anastomosis is complete.

Just prior to the implantation, a purse-string suture is placed on the recipient's right superior pulmonary vein (RSPV), and a vent cannula is inserted here. This is attached to an ice-cold saline infusion line to be initiated once the LA anastomosis is completed. This will serve to topically cool the left-sided endocardium during the implantation. This infusion line will be converted to a vent line just prior to the performance of the aortic anastomosis to allow deairing of the heart and to prevent distention.

The usual order for the performance of the anastomoses in the biatrial approach is as follows: LA, RA, PA, and then Aorta. Some prefer to reverse the order of the PA and aortic anastomoses so as to allow earlier reperfusion of the heart while the PA anastomosis is performed. I find it much easier to sew the PA first. It will generally mean an extra 5–10 min of ischemia time, but the tradeoff is worth the ease of exposure of the PA with the aorta out of the way. It is helpful prior to starting the atrial anastomoses to tack the recipient aorta and PA to the superior mediastinum with a pop-off silk suture through the adventitia of the vessels. This will retract the great vessels out of the way for the atrial anastomoses.

The atrial anastomoses are performed with a 54-in. 3.0 polypropylene suture on a large needle (see Fig. 12.9a). The LA anastomosis is usually begun in the region of the LAA attachment on both the donor and recipient hearts. However, the appendages are removed from both to minimize the risk of thrombosis postoperatively. The first few sutures are placed at a distance with the heart resting on an iced lap pad over the left hemisternum. After three suture bites are taken on both the donor and recipient LAs, the heart is parachuted into position. The suture is tightened as the LA tissue edges are everted. It is better to keep the tissue everted, since—if the edges are inverted—a thrombogenic ridge may otherwise be created inside the LA. In addition, if the internal suture line is quite prominent, it may take on the appearance of a *cor triatriatum* on TEE. The surgeon first sews clockwise to complete the posterior (i.e., lateral and inferior portions of the) suture line, and then takes the other end of the suture to sew the anterior layer in counterclockwise fashion (see Fig. 12.9b). Prior to completing the anterior suture line, the RSPV catheter is positioned with its tip in the LV. The left side of the heart is then filled with cold saline from a large syringe, and the LA suture is tied. Ice-cold saline irrigation is started via the catheter at a rate of 50 cc/min to topically cool the LV internally. Usually, 2 L of the iced saline will be infused during the course of the operation.

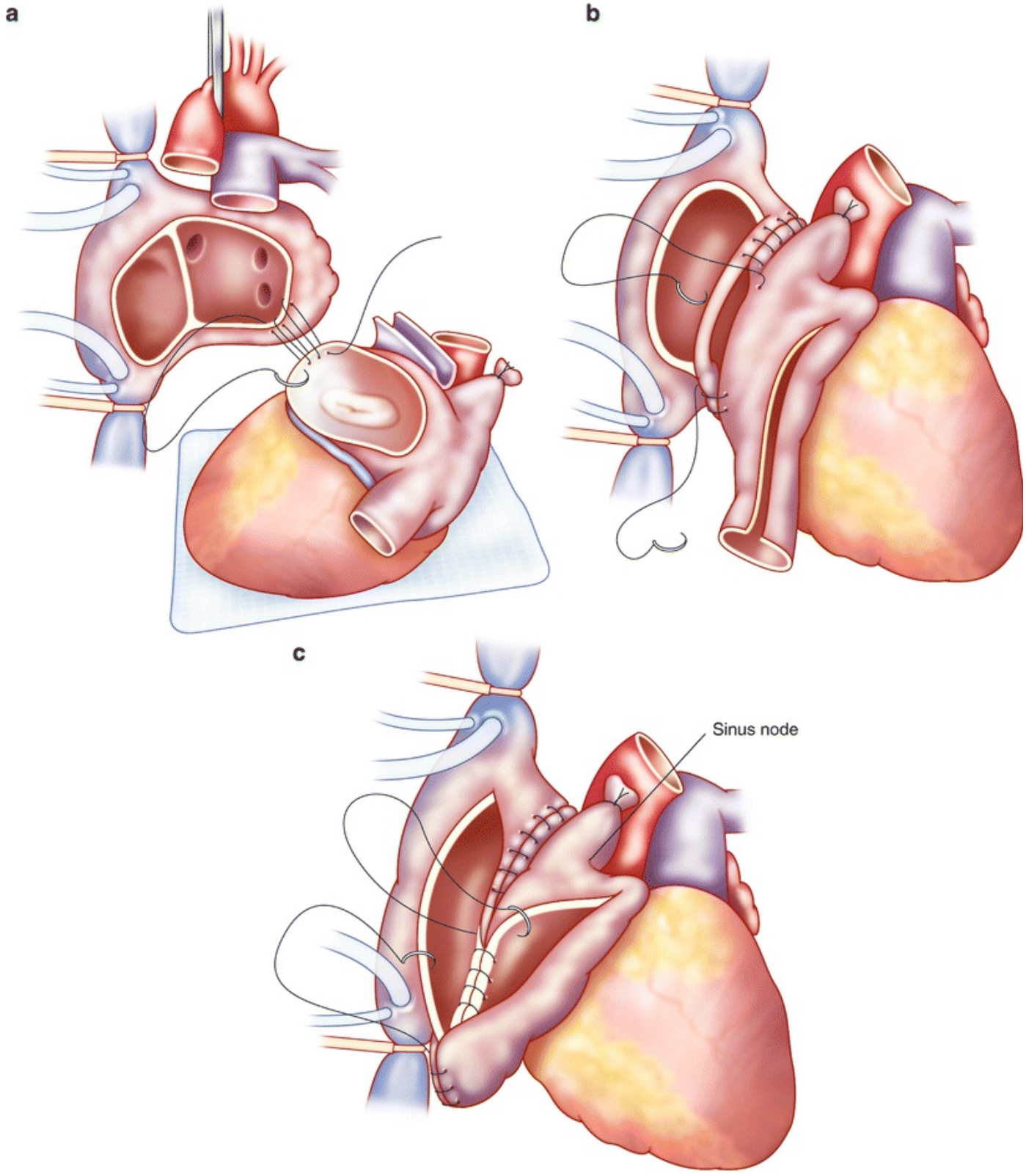


Fig. 12.9 The initial stages of heart implantation using a biatrial approach . (**a**) The left atrial anastomosis being initiated. (**b**) The left atrial anastomosis being completed. (**c**) The right atrial anastomosis being performed

If a *biatrial* anastomosis is performed on the right side, the donor heart is opened from the IVC towards the RA appendage, approximating the length for the required

suture line (see Fig. 12.9b). It is important to spiral this incision well medial of the *sulcus terminalis*, since one limb of the subordinate sinus node tissue lies here and some of the preferential atrial pathways towards the AV node lie more posteriorly. The donor SVC is then oversewn in two layers with 5.0 prolene, keeping a distance from the SA node. The suture line is begun at the midportion of the interatrial septum, and the initial suture is brought down inferiorly along the septum towards the IVC. The bites along the septum will incorporate the prior LA suture line along the interatrial septum. The other end of the suture is then carried anteriorly and counterclockwise towards the IVC (see Fig. 12.9c). Care should be taken not to grasp the tissue in the vicinity of the donor sinus node. The best way to accomplish this is to maintain visualization of the SVC at all times while suturing the anterior layer superiorly.

If a *bicaval* anastomosis is performed on the right side, the donor IVC is left intact. Following completion of the LA anastomosis, the IVC connection is made (see Fig. 12.10). There should be an ample recipient cuff available, since the donor IVC is generally somewhat short because of the length compromise made with the liver donor team. If the Eustachian valve tissue is generous, I excise it so as not to interfere with the proper performance of the anastomosis. The anastomosis is completed with running 4.0 polypropylene suture, starting at the end of the IVC opposite the surgeon. The posterior wall is completed first, being mindful not to injure or incorporate the coronary sinus. This is followed by the anterior wall. Tissue should be everted during the suturing so that an obstructing ridge does not form within the cavoatrial junction. Once the IVC anastomosis is completed, the SVC anastomosis is performed in a similar fashion with running 5.0 prolene (see Fig. 12.10). Once must be careful not to injury the adjacent sinus node while suturing. Small bites are taken of the SVC on both the donor and recipient, since SVC obstruction can occur if the bites are too generous. The SVC anastomosis is the one most likely to be narrowed during the performance of the bicaval approach .

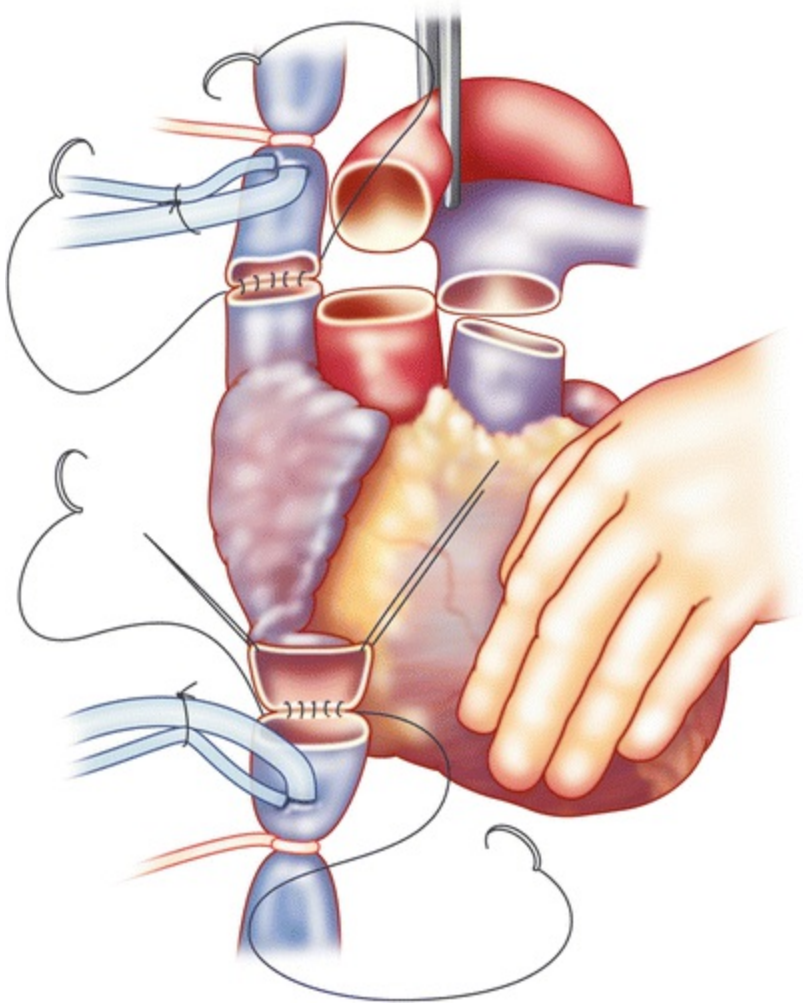


Fig. 12.10 The initial stages of heart implantation using a bicaval approach

The great vessel anastomoses are performed next (see Fig. 12.11). The adage, "The donor PA can never be too short, and the donor aorta can never be too long," is followed. Excessive donor PA can lead to kinking of the anastomosis and outflow obstruction, particularly if the heart is relatively oversized. This would be disastrous if it is not avoided, since the right ventricular outflow obstruction will likely lead to right ventricular failure. It is rare that the PA can be made so short as to be under tension. Hence, I keep the PA quite short, about 1 cm beyond the tops of the commissures of the pulmonic valve. Contrarily, the aortic length is generally left quite generous, since the extra length is usually well tolerated, the aorta usually does not kink, and the additional length allows easy visualization of the posterior aortic suture line after weaning from CPB to inspect for bleeding.

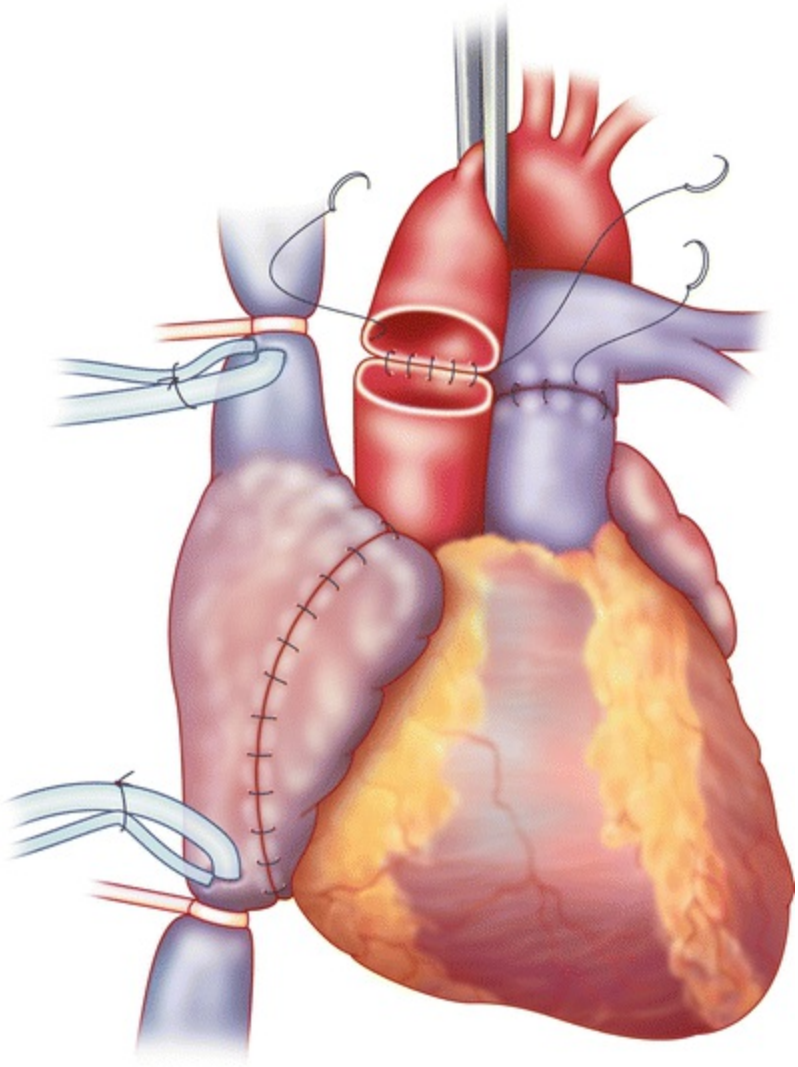


Fig. 12.11 The final stages of implantation. The PA and aortic anastomoses are shown being performed. The PA suture is left untied to allow deairing of the right side of the heart and to maintain decompression of the right heart

The PA's need to be lined up properly prior to performing the anastomosis. The PA anastomosis is performed with running 4.0 polypropylene. It is started at the end opposite the surgeon. The posterior suture line is performed first, followed by the anterior suture line. I have a low threshold for using an autogenous pericardial strip to bolster either the PA or aortic suture line, particularly when the recipient great vessel tissue appears friable or diseased. Once the PA suture line is complete, it is not tied. Instead, it is placed on a snare and left loose (see Fig. 12.11). This maneuver will allow venting of the RV during the initial weaning of CPB, allowing an extra layer of protection against RV distension. (Once the patient has been off CPB for about 15 min and there have been no RV issues, the suture can then be tied.)

Prior to performing the aortic anastomosis, the LV infusion line is converted to a vent and rewarming is begun. The aortic anastomosis is then completed in the same fashion as for the PA anastomosis (see Fig. 12.11). Following completion of the suture

line, an aortic root vent is then placed distal to the anastomosis to facilitate de-airing once the cross clamp is removed. If the prior cannulation site is available on the donor aorta, that site can be used for the vent. A dose of 1 g of solumedrol is administered intravenously just prior to cross-clamp removal. Rewarming is completed, and appropriate inotropes and pressors are started. The suture lines are inspected to ensure hemostasis. All heart transplant recipients receive both atrial and ventricular temporary pacing wires. Typically, I place patients in AAI mode at a rate of 110 through the early postoperative period to optimize cardiac output. Inhaled nitric oxide or an alternative inhaled pulmonary vasodilator is kept at the ready should RV function be compromised or pulmonary hypertension be encountered during the weaning process. I have a low threshold for starting the inhaled pulmonary vasodilators if I anticipate any right-sided issues. The patient is then weaned from CPB gingerly, with careful attention to RV function. The Swan-Ganz catheter is refloated. TEE evaluation assesses cardiac and valvular function, as well as the adequacy of de-airing. More than any other cardiac operation, weaning from bypass should be gradual and focused on RV function. The remainder of the operation is carried out as per conventional cardiac surgery. Once the chest is closed, the pacemaker components are removed via an incision over the pacemaker pocket.

Heart Implantation Technique: Reoperative Surgery

In any reoperative cardiac case, it is advisable to obtain a chest CT preoperatively to assess the mediastinal structures and the proximity of the heart to the undersurface of the sternum. Moreover, patients who have had prior bypass surgery, a left heart catheterization is useful to ensure safe sternal reentry. Because of the importance of timing, one tries to avoid any situation that might prompt premature initiation of CPB.

I have a low threshold for remote cannulation in reoperative patients undergoing heart transplantation. I will usually perform right axillary artery cannulation as well as percutaneous femoral vein cannulation with a cannula that extends to the RA unless I am confident that the reentry will be uncomplicated (see Fig. 12.12). The axillary artery dissection is performed first. At the appropriate time, 5000 units of heparin is administered, and the axillary cannulation completed. I usually directly cannulate with either an 18 or 20 French arterial cannula, but will use an 8 mm graft if the vessel is difficult to access or is small. The cannula and arterial line are then de-aired, and the connection is completed. The axillary cannula and tubing are secured with 0 silk pop-off sutures at multiple locations along the chest wall.

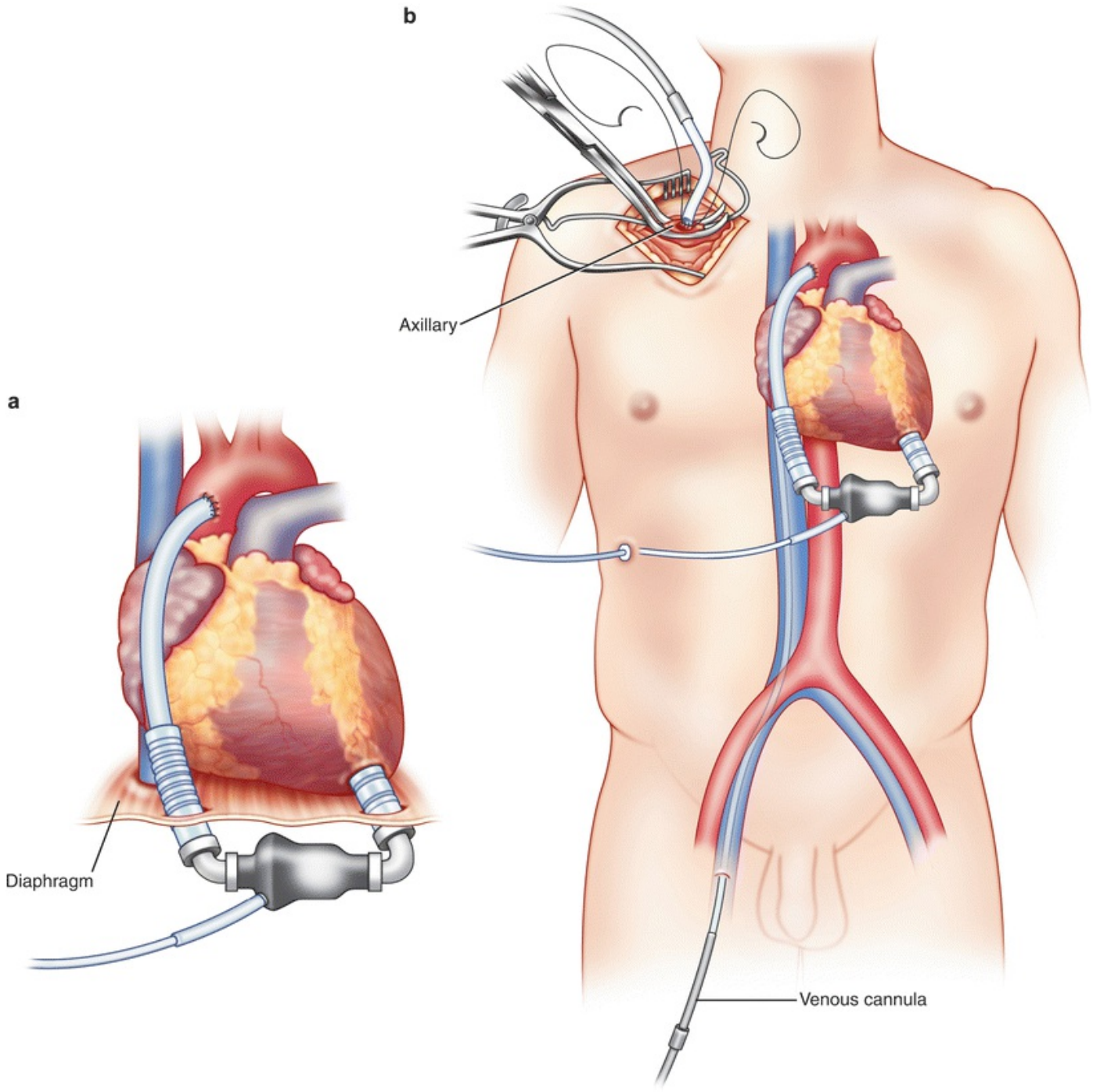


Fig. 12.12 The setup for reoperative cardiac surger y and/or prior LVAD in place. (**a**) A depiction of the relevant anatomy of the LVAD with respect to the heart. (**b**) Remote access with right axillary artery cannulation and femoral venous cannulation for redo operations

A "Y" is placed in the venous circuit to allow the addition of an SVC cannula once the chest has been entered. Percutaneous cannulation of the femoral vein is performed via Seldinger technique with serial dilatation and the use of an appropriately size cannula for the size of the patient. The tip of the cannula is positioned in the right atrium under TEE guidance. (The cannula is withdrawn into the IVC once the SVC cannula is

in position.) One limb of the Y is then connected to this cannula, and the cannula is secured at multiple locations in the groin and thigh. Both venous limbs are clamped until CPB is started.

CPB is usually not instituted until the donor heart arrives. The exception will be if the patient develops hemodynamic instability during the reentry. The tradeoff for early institution of CPB is a longer bypass time.

Sternal reentry is then accomplished. My approach is to reenter via the prior chest incision, use electrocautery down to the sternum, and then remove all the sternal wires. If the right ventricle or aorta appears adherent to the undersurface of the sternum, the wires can be cut and left in place to protect the heart while the oscillating saw is used to cut the sternum. While both the assistant and surgeon elevate each hemisternum with a rake retractor under the rib cage, the oscillating saw is used to cut both the superficial and deep layers of the sternum. Once the sternum has been divided, topical hemostatic agents are applied to the marrow surface. Table-mounted Rultract® Skyhook retractors are then used to elevate each hemisternum as the dissection is completed. Once the sternum is cleared bilaterally, a sternal retractor is placed within the chest. Dissection proceeds commencing at the inferior diaphragmatic surface of the heart and proceeds counterclockwise to free up the RA, the IVC, the SVC, and the aorta. A purse string is now placed high on the SVC, and a second cannula is added and connected to the other venous limb of the CPB circuit. In addition, the previously placed femoral cannula is withdrawn under TEE guidance so that its tip lies just below the cavoatrial junction.

The remainder of the surgery now proceeds as for a primary heart implantation. Once the donor heart arrives, CPB is instituted, and the aorta is cross-clamped. Once the recipient heart is excised, care must be taken to obtain good hemostasis within the pericardium. Patent bypass grafts remaining on the aorta are oversewn. Alternatively, if the graft takeoffs are low on the aorta, these can be removed with the aortic specimen. A patent LIMA graft is also oversewn.

Heart Implantation Technique: Bridged Patients

At present, approximately 40 % of all patients who undergo heart transplantation have an LVAD in place [1]. The presence of the LVAD complicates the operation considerably when compared to a patient undergoing transplantation without a device. Preoperatively, the patients are given intravenous vitamin K as early as practicable to reverse the warfarin effect. Unfractionated heparin is started to protect the patient should the transplant be delayed so that the LVAD does not thrombose prematurely. FFP is also made available for the operating room, in addition to other blood products.

The steps below apply to patients who have a *Heartmate II* ® in place (see Fig. 12.12). Minor adjustments will need to be made for other LVADs.

The operative setup is generally similar to that for other reoperative surgeries, as

described above, with the following exceptions. Although it is a challenge to sterilize the driveline, one can do a reasonable job by prepping the patient with an assistant holding the driveline and controller up in the air lateral to the patient's body. The driveline can then be prepped vigorously and wrapped in a sterile towel that is secured with an ioban (iodine-impregnated) drape. The wrapped driveline is then rested on the patient's abdomen with the remainder of the driveline crossing to the controller off the operative field. The controller is connected to the system monitor and power module.

Once prepping and draping is complete, the same preparatory steps are taken for the reoperative sternotomy as described in Sect. "Heart Implantation Technique: Reoperative Surgery." I routinely cannulate the right axillary artery and right femoral vein for patients who are bridged to transplantation. Once the sternal reentry is completed and the chest retractor is in position, there will usually be a synthetic membrane such as Gore-Tex® protecting the heart and VAD components (see Fig. 12.13a). Some centers have started using a CorMatrix ECM® patch to decrease the adhesions surrounding the heart, but at this point there is insufficient data to recommend its use. If there is a Gore-Tex® membrane, it is excised to its junction with the pericardial edges. It usually lifts off the underlying epicardium fairly easily. If the diaphragmatic surface of the heart is accessible, dissection is begun here as before. Sometimes the access is poor if the pump body overlies the junction between the heart and the diaphragm (see Fig. 12.13b). In that situation, dissection is commenced along the right surface of the heart, with care to identify and preserve the outflow graft that usually is positioned along the right atrium. The graft is encircled with an umbilical tape, which is then used to retract the graft to facilitate further dissection along the SVC and aorta. The SVC is exposed and cannulated, and the cannula is connected to the Y in the venous circuit. The remainder of the cardiac dissection is completed. Umbilical snares are placed around the SVC and IVC. The left side of the heart is then dissected from the surrounding mediastinal tissue. Initially, the heart and LVAD inflow cannula are maintained in continuity and dissected out as a unit. Ideally, the outflow graft is low enough on the aorta that it can be excised. If not, it can remain in situ and be oversewn.

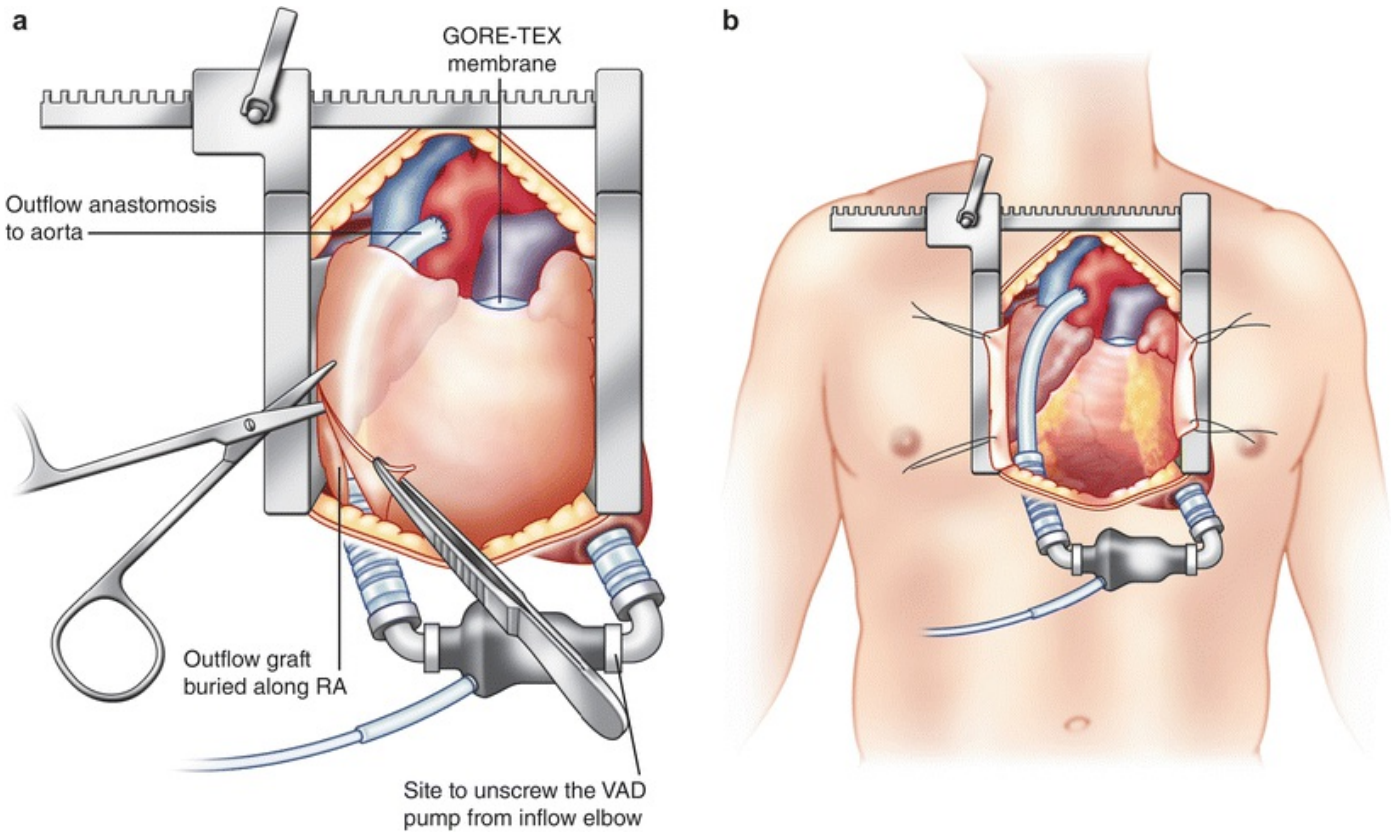


Fig. 12.13 The recipient operation in a patient with a prior LVAD in place. (**a**) After sternotomy, the Gore-Tex® sheet is dissected from the heart. (**b**) The relevant anatomy once the heart and LVAD are dissected out

Once the heart arrives and as CPB is initiated, the LVAD is turned off and the outflow graft is clamped. A cross clamp is applied to the aorta beyond the graft, and the heart and LVAD are dissected away from the mediastinum and abdominal wall. Once the heart and LVAD are mobilized, the LVAD can be unscrewed at its inflow elbow (see Fig. 12.13b). A sump is then placed within the inflow elbow to vent the LV. The graft is transected adjacent to the aorta and proximal to the clamp. If insufficient aorta remains to remove the graft, the graft is clamped and transected, and will be oversewn later. The proximal end of the graft is then disconnected from the body of the LVAD pump, and the graft is removed from the field. The heart, together with the attached inflow cannula, is now explanted. From here, the explantation proceeds much as described in Sect. “Heart Implantation Technique: Reoperative Surgery.” Once the cardiectomy is complete, the heart along with the inflow cannula are removed from the field. The body of the LVAD and the driveline are left in place until after the implantation. The VAD is covered with antibiotic-soaked lap pads.

The remainder of the implantation proceeds as previously discussed, either with a bicaval or biatrial anatomosis. Once the patient is weaned from CPB, the heparin is reversed, and the patient decannulated. The LVAD and the driveline are now completely mobilized. The driveline is transected, and a gloved tip is placed over each end of the

driveline and tied in place to minimize contamination. (The inside of the driveline is not sterile.) The LVAD body and attached driveline portion are removed from the surgical field. The remaining driveline is then dissected from the surrounding tissues with electrocautery to its exit at the skin. The driveline is typically well enmeshed in the patient's abdominal wall. Near the conclusion of the operation, the driveline wound is left open and packed with a wet-to-dry dressing.

Heart/Lung Transplantation

The heart–lung transplantation was first performed successfully by Dr. Bruce Reitz at Stanford Hospital in 1981 [10], but has always been a rarely performed operation. Annually in the United States, fewer than 30 heart–lung transplants have been performed over each of the last 4 years [1]. Cumulatively, the Stanford and University of Pittsburgh programs have been the busiest [11, 12].

Unlike isolated heart transplantation when the lungs are harvested as well, the cardiac connections to the lung are not severed but instead are procured and implanted *en bloc*. The only vascular connections that are transected in the donor and the recipient are the aorta and the right atrial connections.

Importantly, because of the greater technical complexity of the heart–lung transplantation, there is no place for "marginal" donors or marginal recipients for these operations. And, except in very unusual circumstances, reoperative surgery for a heart–lung transplantation should seldom be performed due to the often prohibitive bleeding that can be encountered.

Combined Heart and Lung Harvest for Heart–Lung Transplants

The Operation

A bronchoscopy is performed in the operating room to evaluate the tracheobronchial tree and collect an aspirate for gram stain and culture. For details on lung protective strategies and other specifics of the lung harvest, the reader is referred to the chapter on Lung Transplantation. Prepping and draping are the same as that described for the heart harvest. Once the chest is entered via a median sternotomy, both pleural spaces are opened and the lungs examined by both inspection and palpation. Atelectatic areas can be managed by local recruitment efforts. The inferior pulmonary ligaments are divided bilaterally with electrocautery. If the lungs pass muster, attention is next directed to the mediastinum.

The pericardium is opened and the heart is evaluated and prepared as previously described. Once the cardiac dissection is complete, the posterior pericardium between the aorta and the SVC is longitudinally divided, and dissection is carried down to the trachea several centimeters above the carina. An umbilical tape is passed around the

trachea, with great care taken not to injure the membranous portion posteriorly (see Fig. 12.14a). Dissection distally on the trachea is minimized so as to preserve tracheal collaterals. Ventilation continues throughout the harvest until the trachea is transected near the end of the harvest. The pericardium is excised anteriorly from phrenic to phrenic to facilitate later removal (see Fig. 12.14b).

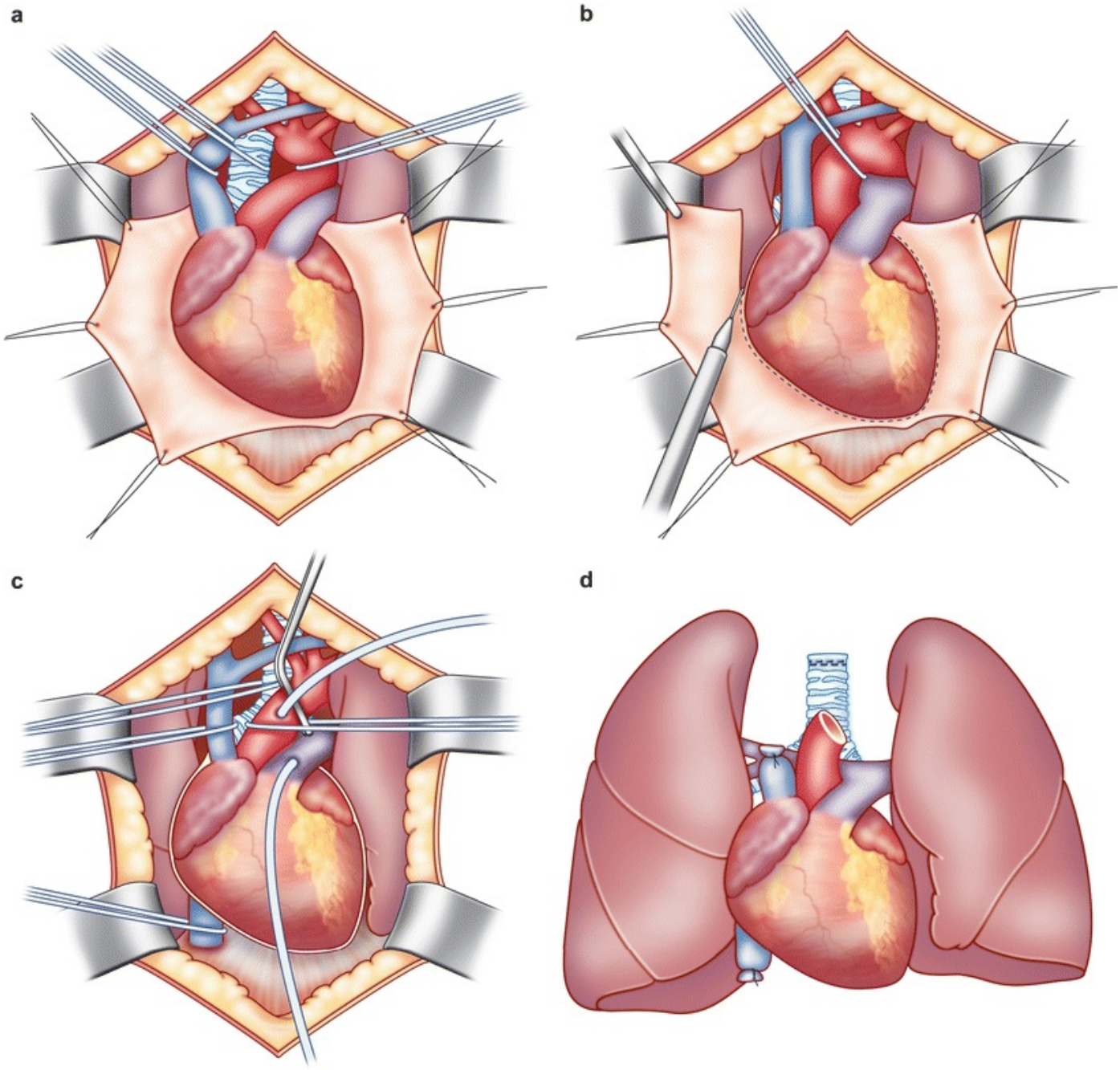


Fig. 12.14 The donor operation for heart–lung transplantation : (**a**) After the pericardium has been opened and the cardiac evaluation is complete, the trachea is dissected out between the aorta and the SVC. (**b**) The pericardium is excised from phrenic nerve to phrenic nerve. (**c**) The aorta and PA are each cannulated for the infusion of cardioplegia and pneumoplegia , respectively. (**d**) The heart and lung block as it is being removed from the donor

Once the abdominal donor teams are ready, preparations are made for harvesting the heart and lungs. Heparin, 30,000 units, is administered and allowed to recirculate for 3 min. Purse-strings are placed on both the aorta and the PA, and cardioplegia and pneumoplegia cannulae are inserted, respectively (see Fig. 12.14c). The preservation solution bags are hung and the lines de-aired. It is my practice to use UW® solution for the heart and Perfadex® for the lungs, but other preservative solutions are acceptable. Once all the harvest teams are ready for cross-clamping, the 500 μg of the pulmonary vasodilator prostaglandin E_1 is injected directly into the PA and hypotension is allowed to ensue to confirm adequate circulation of the prostaglandin prior to proceeding with the right-sided inflow interruption. Just as for the heart and lung harvest described in Sect. "Combined Donor Harvest of the Heart and Lungs for Distinct Recipients," the SVC is tied, the IVC is hemisected, and the LAA is amputated. Once again, the first assistant's main roles are dual: to keep the operative field clear with the use of two suction cannulae and to keep the thoracic organs cold with slush. The heart is allowed to beat until empty, and the aortic cross-clamp is applied. Both cardioplegia and pneumoplegia are initiated. A total of 1–2 L of cardioplegia is given as previously described, and 6 L of pneumoplegia is given. Care must be taken to ensure that both the right and left ventricles remain empty, and that the effluent from the IVC and the LAA remains free-flowing. Carefully inserting a pool sucker into the opened LAA is sometimes helpful. Slush is applied to both the heart and lungs. Continued ventilation of the lungs is carried out with half-normal tidal volumes. Both the heart and the lungs need to be kept cool with slush throughout the harvest. The lung is examined to ensure that there is blanching of the parenchyma by the pneumoplegia . One of the best ways to ensure that the preservative gets well distributed is to compress one of the branch PAs at the bifurcation so that flow preferentially goes to the underperfused contralateral lung for a period of time.

Once the cardioplegia and pneumoplegia are completed, the heart and lungs are explanted *en bloc* as follows: The SVC and azygous ties are completed, and the SVC, IVC, and aorta are transected. If not completed before, the inferior pulmonary ligaments on both sides are cut to the level of the inferior pulmonary veins. The posterior pericardium is transected just above and parallel to the diaphragm to allow access to the pre-esophageal plane. With clamps on the posterior pericardial edge, retraction is exerted up towards the ceiling and cephalad as the dissection plane is developed up to the carina. One would like to remain as close to the esophagus as possible so that inadvertent entry into the membranous trachea is avoided. Any posterior hilar attachments are dissected away from surrounding tissue with electrocautery. Attention is redirected to the trachea in the upper mediastinum, and a TA-55 stapler (Unites States Surgical, Norwalk, CT) is positioned at the highest point that is easily accessible. Again, one must be careful behind the trachea not to enter the membranous portion posteriorly when going around with the stapler. The endotracheal tube is mobilized

proximally so that the tip is above the intended transection site. The lungs are filled to approximately half the normal tidal volume and held. This strategy prevents overdistension of the lungs during transport, particularly if nonpressurized air travel is anticipated. The trachea is then stapled and transected. With gentle skyward retraction of the distal tracheal stump, the remaining attachments of the heart–lung block to the mediastinum are divided with electrocautery, taking the adherent lymphatic and vascularized tissue in continuity with the tracheobronchial tree (see Fig. 12.14d).

The *en bloc* heart and lungs are brought to the back table, and the heart is prepared as previously described for the RA, the interatrial septum, and the aorta. Either bicaval or an atrial anastomosis is feasible for the right side. Access to the PA, LA, and mitral valve is not available in combined heart–lung transplantation, and retrograde flush of the lungs cannot be accomplished without enlarging the opening in the LA appendage, if that is so desired. The heart and lung block is preserved and bagged in a fashion similar to that described for the heart preparation above.

Heart and Lung Preservation, Preparation, and Transportation

The heart is protected as previously described. The lungs can be protected by a variety of solutions, depending on the experience of the transplantation team. The lung perfusate should be administered by gravity, and equitable perfusion to each lung assured by gentle manipulation or compression of the branch pulmonary arteries. Perfusion is ensured when the pulmonary parenchyma blanches homogeneously and diffusely. The reader is referred to the chapter on Lung Transplantation for further details about lung preservation.

Combined Heart and Lung Implantation: Primary Operation

As is the case for isolated thoracic organ transplantation, extensive communication occurs between the donor and recipient teams in order to optimize timing. In this scenario, survival of the recipient is dependent on two vital organs that have experienced ischemia functioning well after the surgery, so—as expected—outcomes after combined heart–lung transplantation are inferior to that with either organ transplanted alone.

After prepping and draping the recipient, the chest is entered through a median sternotomy. If the operation is a reoperative case or adhesions are expected, considerable extra time needs to be allowed for the dissection in the recipient—especially if the pleural spaces have been violated in the past. If dense adhesions in the pleural spaces are anticipated, consideration should be given to performing a clamshell incision [13]. This approach allows better exposure to the pleural cavities so that

troublesome bleeding can be more easily addressed. Nonetheless, if the adhesions in the pleural space are so dense that the operation puts the patient at risk of exsanguination after the implantation, consideration should be given here to foregoing the operation and closing the patient. Please see additional details regarding reoperative heart–lung transplantation in Sect. "Combined Heart and Lung Implantation: Reoperative Surgery or Surgery in a Potentially Hostile Pleural Space." As for other thoracic transplants, a carbon dioxide line is secured to the field.

The pericardium is opened but not excised at this juncture to allow easy dissection and cannulation. Cardiac preparations proceed much as per the prior discussions. Umbilical tapes are passed behind the aorta, SVC, and IVC. When the timing is appropriate, heparin is administered and allowed to recirculate, purse-strings are placed in the aorta, SVC, and IVC, and these vessels are cannulated. Most of the dissection occurs after the initiation of CPB. Once on CPB, the aorta is cross clamped and the snares around the SVC and IVC are tightened. The donor cardiectomy is performed first as per the prior discussion, and the removal of RA tissue is tailored to the implantation technique (bicaval vs. right atrial anastomoses). The heart is explanted. The pericardium is now removed anteriorly, along with the overlying thymic tissue, ending about 2 cm anterior to the phrenic nerve on either side. Throughout the remainder of the operation, meticulous attention needs to be paid towards preserving the phrenic nerve function bilaterally. There will be much manipulation of the adjacent pericardium, so one needs to be cautious in the way the area is handled. Transecting the nerves are easily avoided, but traction or thermal injury is not if one is not cautious.

The inferior pulmonary ligaments are then divided, and dissection is continued to separate the visceral pleura from the hilar vessels. The hilar vessels are mobilized from all surrounding tissue, including the pericardium. A generous slit in the pericardium is fashioned that will later serve to admit each donor lung from the mediastinum to the pleural spaces (see Fig. 12.15). The pericardium is incised just anterior to the hilum, keeping a liberal distance from the phrenic nerve. This slit is developed circumferentially around the pulmonary hilum. The simplest method to remove each lung is to staple separately across the branch PA and PVs at the hilum. The bronchi are dissected to the junction with the trachea, with attention paid to not dissecting up the trachea in order to maximally preserve the blood supply to the trachea. Both bronchi are then divided with a TA 30 stapler just distal to their origins. The lungs are now completely mobilized and removed. The remnants of the PAs and PVs can be removed or left in situ. If removed, a generous segment of the LPA is left attached to the ligamentum arteriosum so as to protect the recurrent laryngeal nerve. The mediastinum and pleural spaces are now carefully evaluated for any evidence of bleeding, since there will be limited access to these areas once the heart and lungs are in place. This is a critical step in the operation and cannot be overemphasized. Argon laser can be a useful adjunct here for profuse bleeding, and sutures and clips should be used liberally.

Consider this step in the operation the critical point-of no-return *vis-à-vis* control of bleeding in the posterior mediastinum and pleura.

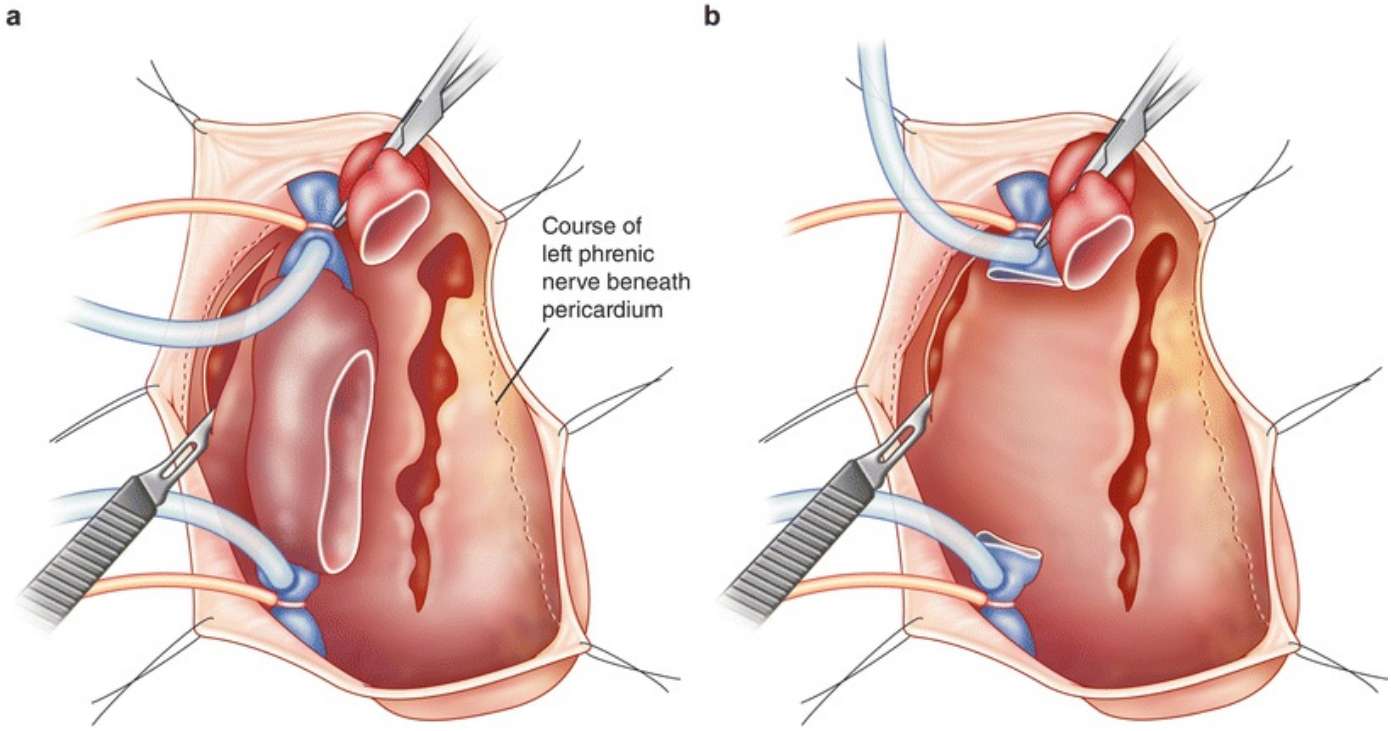


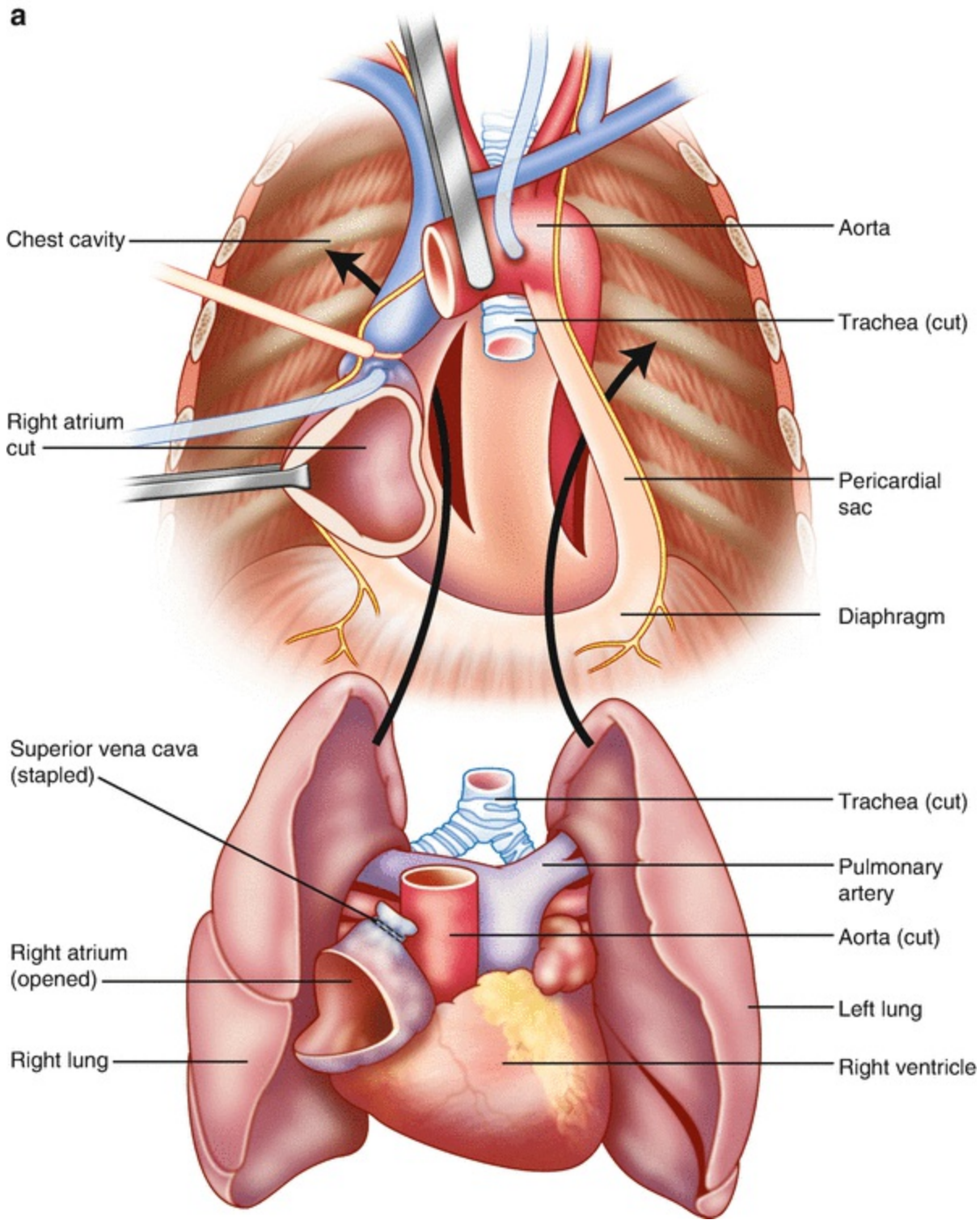
Fig. 12.15 Bilateral incisions in the posterolateral pericardium to remove the native heart and lungs and allow the donor hila to traverse from mediastinum to pleural spaces. (**a**) Appearance of mediastinum for a planned biatrial approach . (**b**) Appearance of mediastinum for a planned bicaval approach

Special attention must be paid to the five nerves that can be injured during this operation: both phrenics, both vagi, and the left recurrent laryngeal nerve. As previously mentioned, the phrenic nerves can injured when strips are being created bilaterally and when the lungs are insinuated behind them during the implantation. The left is more susceptible because of its closer proximity to the hilum [14]. The vagi can be injured posterior to the lung hila if not carefully dissected away during the explantation. Finally, the left recurrent laryngeal nerve must be protected by leaving a cuff of left PA attached to the aorta so the space is not violated.

The implantation then proceeds as follows: The heart and lung block is prepared on the back table prior to implantation. Any dissection that was not completed at the donor hospital is now addressed. The aorta is freed up from the PA, and the SVC and IVC are prepared as previously described. The hole created in the LA appendage is closed with 4.0 prolene.

The recipient trachea is now divided one ring space above the carina, and the peritracheal tissue preserved. Err on the side of leaving a generous tongue of membranous trachea posteriorly, since it tends to retract and one does not want any tension on the suture line here.

An insulation pad is placed in the posterior pericardial space. The heart and lungs are transferred to the mediastinum, and slush is applied repeatedly to the heart and lungs. Topical hypothermia is extremely important here because of the additional time that a heart–lung block takes to be implanted. Each lung is then insinuated in the space behind each respective phrenic nerve so as to traverse from the mediastinum into the pleura (see Fig. 12.16a). If profuse bleeding from the pleural spaces was encountered during the dissection of the recipient, consideration can be given to placing the lung hila anterior to the phrenic nerve, as described by Copeland's group [15] (see Fig. 12.16b). This maneuver will allow greater access to the posterior mediastinum and pleura if bleeding is troublesome after the implantation, since medial rotation of the lung will not be constrained by the phrenic strip. In addition, because less dissection in the vicinity of the phrenic nerve is involved, it is less likely to be injured. Regardless, the right lung must pass behind the RA if a biatrial cardiac anastomosis is planned. If a bicaval anastomosis is intended, then the RA can be removed, which will facilitate the lie of the right lung as it crosses from the pericardial to pleural space on the right.


a
Chest cavity
Aorta
Trachea (cut)
Right atrium
cut
Pericardial
sac
Diaphragm
Superior vena cava
(stapled)
Trachea (cut)
Pulmonary
artery
Aorta (cut)
Right atrium
(opened)
Left lung
Right lung
Right ventricle

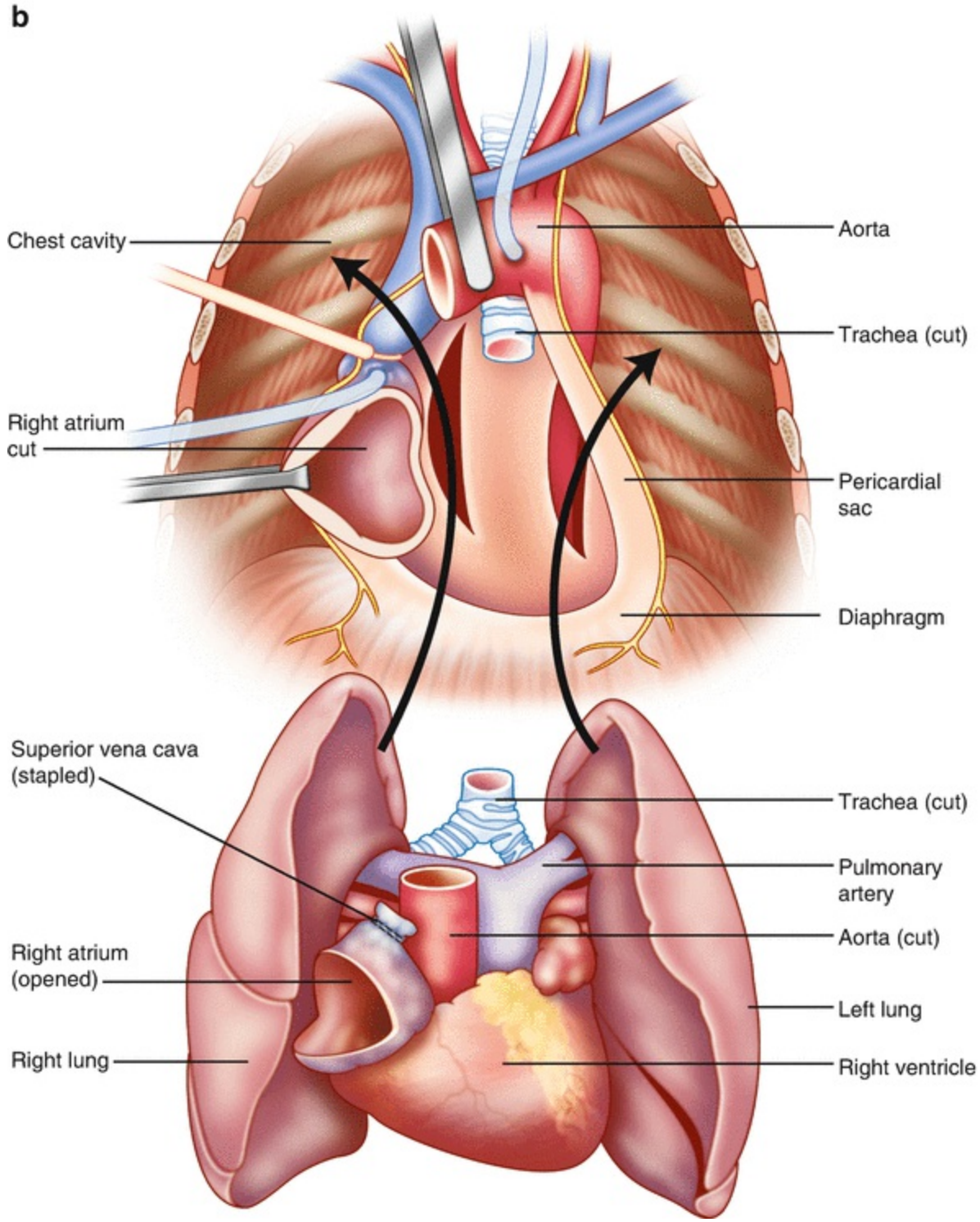


Fig. 12.16 Options for coursing the hila for implantation. (a) Hila can traverse the previously fashioned slits in the posterolateral pericardium (see *arrows*). (**b**) Hila can traverse anterior to the phrenic nerves (see *arrows*)

The distal trachea and bronchi remnants are dissected and removed after transecting the trachea one cartilage ring just above the carina. It is critical not to disrupt the tissues surrounding the native trachea proximally so as to preserve the vascular supply arising from above. The tracheal anastomosis is performed with running 4.0 prolene, being

cautious to have a snug but not strangulating suture line. It is helpful to interrupt the suture line at the corners on each side where the membranous and cartilaginous trachea meet to avoid a purse-string effect. The suture line is started at the junction of the cartilaginous portion of the trachea with the membranous portion on the left side of the patient. The suture line is continued along the membranous trachea posteriorly until reaching the junction on the right side. A new suture is placed adjacent to the prior one on the side opposite the surgeon, and the surgeon then brings the suture to himself along the cartilaginous trachea, incorporating one ring above and one ring below in the suture line. With the suture line snug but not so tight as to render the tissues ischemic, the sutures are tied. Although I do not wrap the trachea in mediastinal tissue, some authors advocate doing so.

The cardiac connections are performed as previously described for the isolated heart harvest. For the RA-RA connection, the sequence is RA followed by aorta (see Fig. 12.17). For the bicaval connection, the sequence is IVC, SVC, and then aorta. One can consider performing the aortic anastomosis before the SVC to allow earlier reperfusion, but I find the small amount of time saved is outweighed by the hindrance of blood return from the coronary sinus interfering with the surgical field. A suture repair of the PA cannulation site is performed if it has not been resected, and the aorta is cannulated with a vent, as previously described. In addition, aortic and RSPV vents are placed to assist with the de-airing. With the vents turned on and the patient in Trendelenburg position, the aortic cross-clamp is removed and the heart–lung block reperfused. Leukocyte depletion of the arterial CPB line may be a useful adjunct here.

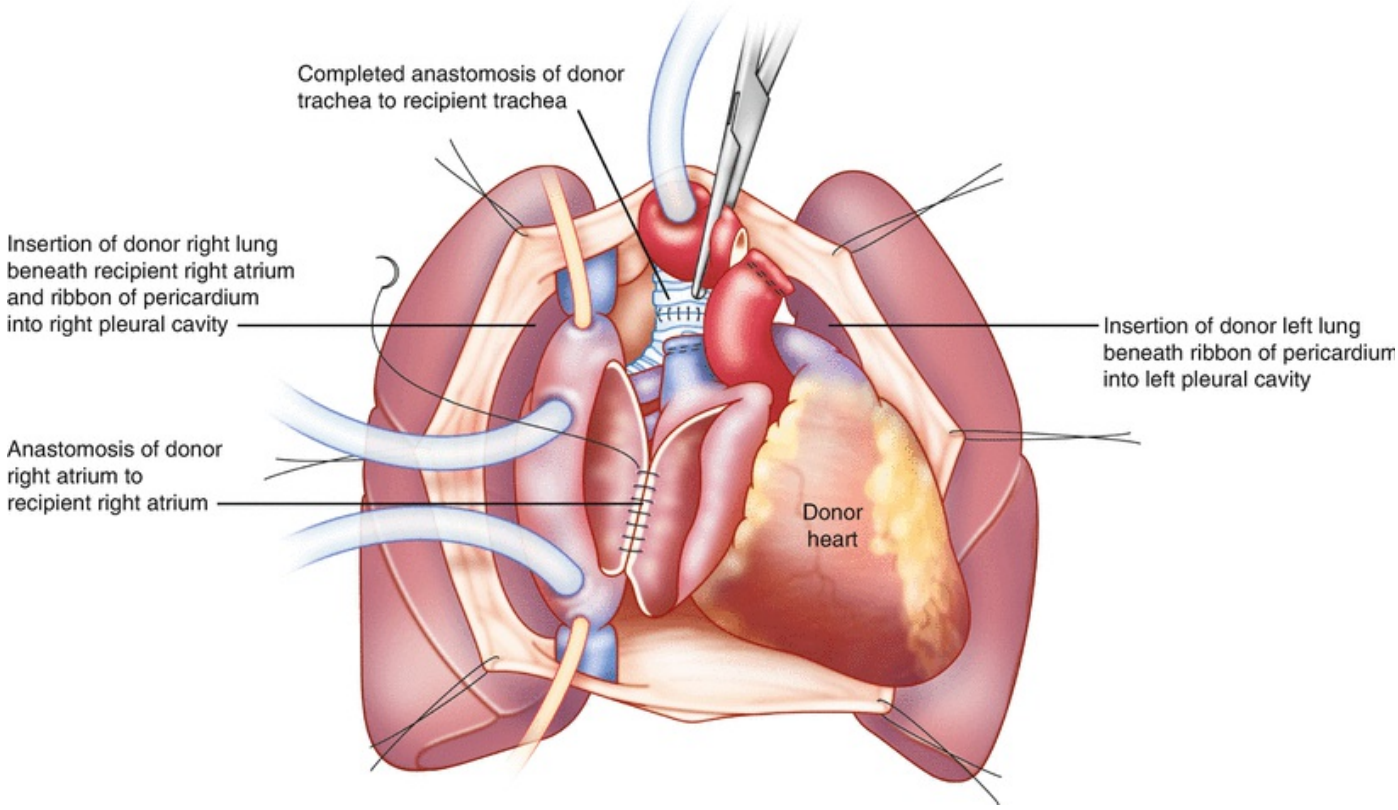


Fig. 12.17 The heart–lung transplant operation near completion. The tracheal anastomosis is shown, and the right atrial anastomosis is being performed. The aortic anastomosis will be performed last

A prolonged period of resuscitation, for at least 30 min, should be carried out prior to considering weaning from cardiopulmonary bypass. The tracheal anastomosis is tested by inflating the lungs with the tracheal anastomosis submerged in saline. Once CPB is weaned, some time may need to be spent obtaining hemostasis, particularly for patients in whom the pleural spaces contained dense adhesions.

Combined Heart and Lung Implantation: Reoperative Surgery or Surgery in Potentially Hostile Pleural Space

Of all the reoperative surgeries, redo combined heart–lung transplantation can be the most daunting [14]. If the pleural space is relatively pristine, but the pericardial space has been violated, consideration should be given to cannulating the patient before chest entry as previously described. However, if the pleural space has been violated or predicted to be hostile for reentry, then the better part of valor would be to dissect out the axillary artery and place a wire in the femoral vein. This will allow easy access to CPB in the case of an emergency without the need to administer heparin before opening the chest. Once the chest is entered, if the pleural spaces are truly obliterated, careful consideration should be given towards abandoning the procedure because the risk of bleeding perioperatively will be prohibitive.

For the aforementioned reasons, one should have a relatively high threshold for reoperative surgery in the setting of heart–lung transplantation [16]. Although these are now performed much more commonly than before, it can still be a precarious endeavor.

Summary

The surgical techniques necessary to harvest and implant the heart and lungs for either heart transplantation or combined heart–lung transplantation have been described, with safeguards and pitfalls enumerated during the course of their depictions. It is hard to believe that the first heart transplant was performed by Dr. Christiaan Barnard almost 50 years ago. Although some modifications to the procedures have been applied over the years, significant changes to the technical aspects are not expected in the future. Major developments that may alter the future of heart transplantation and heart–lung transplantation may be the continuing progression of mechanical circulatory support and the ever-present possibility of xenotransplantation becoming feasible with continued developments in immune suppression. Nonetheless, we have come a long way since the early days of Dr. Barnard's pioneering surgery, when patients were confronted with a decision that seem to place them between Scylla and Charybdis. In Dr. Barnard's own words:

> For a dying man it is not a difficult decision [to agree to become the world's first heart transplant] … because he knows he is at the end. If a lion chases you to the bank of a river filled with crocodiles, you will leap into the water convinced you have a chance to swim to the other side. But you would not accept such odds if there were no lion.
>
> Christiaan Barnard

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13. Anesthetic Management of Cardiac Transplantation

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Introduction

Cardiac transplantation has become an established modality of treatment for many patients with end-stage heart failure with severely impaired functional capacity. These patients have a poor quality of life and/or an estimated life expectancy of less than 18 months with medical therapy. Understanding the pathophysiology of heart failure (HF) , the medical and surgical treatment of these patients and perioperative management remains essential to optimize the outcome from this lifesaving procedure. According to the 2013 American Heart Association (AHA) update on HF, there are an estimated 5.1 million patients with HF in the USA and about 23 million worldwide [1]. Many of these patients develop intractable progressive HF that does not respond to conventional medical and surgical therapy. Up to 40 % of these patients die within 1 year of first hospitalization [2]. Cardiac transplantation can both improve survival and quality of life in selected patients with severe HF . Unfortunately, the number of heart transplantations performed is limited by available donor organs and has reached a plateau at around 2000 per annum in the USA. Some of these patients require assistance with mechanical

circulatory support (MCS) while waiting for transplantation. Improved treatment of HF and MCS has led to a decline in death while on a waiting list resulting in increasing strain on available resources.

According to the International Society for Heart and Lung Transplantation (ISHLT) Report (2013) which captures 66 % of all the worldwide heart transplants, the unadjusted 1-year survival for patients who received transplants from 2006 through June 2011 was 84 %, and the estimated 5-year survival conditional on 1-year survival was 85 % [3]. Although barriers to long-term survival remain, careful patient selection and advances in the perioperative management lead to improved outcomes of heart transplant recipients, most notably over the last decade. This overall reduction in mortality is predominantly related to the survival improvement in the first post-transplant year [4]. After the first year, 50 % of the patients survive up to 13 years. The underlying etiology of HF appears to impact survival rates, where patients with coronary artery disease (CAD) and cardiomyopathy typically possess the highest 1-year survival, and long-term survival is highest in patients with congenital heart disease. Unfortunately, patients undergoing redo heart transplantation (HT) continue to have diminished survival rates as opposed to other groups with primary HT.

History of Heart Transplantation

Christian Bernard performed the first human heart transplant in 1967 in Capetown, South Africa, after successful animal experiments by the Stanford Group [5, 6]. The Stanford Group led by Shumway performed the first successful heart transplant in the USA and accomplished the first successful case series [7]. This initial success in HT was limited, and many transplant centers discontinued their heart transplant programs in the early 1970s secondary to immune mediated graft failure and surgical inexperience. Introduction of cyclosporine and monoclonal antibodies into the immunosuppression regimen, and surveillance for rejection with endomyocardial biopsy, has led to the improved management of graft failure with such a demonstrable improvement in survival rate that HT reemerged as a widely accepted therapy for end-stage heart disease. By the 1990s, many tertiary care and academic centers had established programs for HT [8], and currently, over 5000 heart transplants are estimated to be performed worldwide, a level that is limited by donor availability.

Evaluation and Listing of Patients for Heart Transplantation

Improved clinical outcomes from HT have led to a consensus in expert agreement, recommending HT evaluation for selected patients with severe HF, debilitating refractory angina, or ventricular arrhythmia that cannot be controlled despite drug, device, or alternative surgical therapy [9–12]. It is well recognized that it is important

to balance the risk of HT with the risk of dying if not transplanted [13]. This is especially true in the current era of improved surgical and nonsurgical HF therapy, decreasing waiting list mortality, and shortage of donor organs. Therefore, several clinical risk assessment models [14–16] and parameters indicative of physiological reserve have been proposed to prognosticate these patients, differentiating high risk HF patients who will benefit from HT, from relatively low risk patients in whom HT can be safely deferred. Interagency Registry for Mechanical Assist Devices (INTERMACS) classification for advanced HF is increasingly being adopted in many institutes to define the severity of patient decompensation and assist in decision-making. The transplant centers today practice dynamic listing with interval reassessment of heart failure severity, to determine the appropriate urgency level for the given candidate, and to maintain fairness in the list. It is the severity of the disease process, not the duration on the waiting list that essentially determines the candidacy for transplant. Preoperative evaluation and preparation of heart transplant recipients are described in detail in another chapter.

Pathophysiology of End-Stage Heart Failure

End stage heart failure is the final clinical syndrome resulting from functional and structural myocardial failure after the initiating insult. The initial event leads to several neurohormonal adaptations resulting in the clinical picture of HF. This chronic low output state is characterized by increased renal salt and water retention due to increased renin and aldosterone production, impaired visceral, splanchnic and renal perfusion and increased catecholamine levels, which in time produce significant downregulation of beta receptors and diminished myocardial catecholamine reserves [17]. The cardiac output can no longer meet the minimum metabolic demands of the body when the compensatory mechanisms become maladaptive to result in the end stage disease with progressive deterioration in the end organ function. Medical treatment has progressed considerably in last two decades, with primary focus being on preventive measures and neurohormonal antagonism. In spite of the advances, heart failure is known to progress relentlessly and outcome remains dismal worldwide. Depending on the stage of HF (Table 13.1), a patient will be on various pharmacological or non-pharmacological treatments. Understanding these therapies and their perioperative implications is essential for the anesthesiologist taking care of the HF patient. If there are no contraindications, Stage D HF patients with functional limitation are considered for HT.

Table 13.1 American College of Cardiology/American Heart Association classification of advanced heart failure

Stage	Description
Stage A	At high risk for HF, but without evidence of structural heart disease
Stage B	Evidence of structural heart disease, but without signs or symptoms of HF

Stage C	Clinical signs or symptoms of HF—current or past
Stage D	Refractory HF requiring specialized interventions

Adapted from Yancy et al. [1]

Pharmacologic Therapy and Implications

Ambulatory HF patients listed for heart transplant will be on neurohormonal antagonists and diuretics with or without inotropes. Neurohormonal blockers such as β blockers, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), and aldosterone antagonists help in controlling the adaptive neurohormonal changes of HF with slowing down the progression of the disease. These medications are known to reverse the adverse remodeling and prevent left ventricular hypertrophy. They can also have a salient hemodynamic effect such as decreasing the afterload with improving myocardial performance. With anesthetic induction, some of these patients can have profound hypotension and may require high-dose vasopressors to maintain acceptable perfusion pressure. Even though there is lack of evidence in this subset of patients, one of the hypotheses is angiotensin being one of the important pressors maintaining blood pressure under conditions of anesthesia-mediated sympatholysis. These medications can result in hypotension by interfering with that pathway.

Diuretics are introduced into the treatment regime to treat fluid retention secondary to decreasing organ perfusion. They act at different sites on the renal tubule preventing sodium reabsorption resulting in diuresis (Table 13.2). Diuretics can cause significant electrolyte imbalance especially when associated with intravascular volume changes. Vasodilators are recommended to treat HF symptoms despite optimal medical treatment especially in the African American heart failure population and also as an adjunct in patients who cannot tolerate some neurohormonal antagonists. Hydralazine and nitrates are the common vasodilators used in current practice.

Table 13.2 Common diuretics used in advanced heart failure

Class of diuretics	Medications commonly used	Site of action
Loop diuretics	Furosemide, bumetanide, torsemide	Acts at distal ascending loop of Henle
Thiazide diuretics	Hydrochlorthiazide, metolazone	Distal convoluted segments
Potassium sparing diuretics	Spironolactone, triamterene, eplerenone	Antagonizes aldosterone effect on cortical collecting tubules

Digoxin is a positive inotropic agent used in the treatment of symptomatic advanced HF resistant to other pharmacological therapy. It has a narrow therapeutic index and plasma levels that need to be monitored to prevent toxicity. Associated renal insufficiency and electrolyte abnormalities, which are common in this subset of patients,

can further decrease the therapeutic window. Common features of toxicity are gastrointestinal disturbances (nausea, vomiting), neurological symptoms (confusion, yellow vision), and arrhythmias (conduction abnormalities and reentrant arrhythmias).

HF syndrome continues to progress relentlessly with decompensation of failure state and is a leading reason for hospital admission of elderly patients [18]. Readmission rates for acute decompensated heart disease remains the highest among all medical admissions to the hospital. Acute decompensation is often due to progression of underlying cardiomyopathic pathology with overwhelmed compensatory processes or can be de nova from acute myocardial injury (endocarditis, myocarditis, myocardial infarction). After treating precipitating cause (Table 13.3), treatment is directed towards improving cardiac performance by altering loading conditions and enhancing contractility or mechanical support, if necessary. These patients can be classified into different clinical profiles depending on the presenting signs and symptoms (Fig. 13.1). This profiling is derived from the initial Forrester Classification [19] of HF in patients presenting with acute myocardial infarction, and has shown to have prognostic implications with cold and wet patients having a 6-month mortality of up to 40 % [20].

Table 13.3 Common precipitants for acute exacerbation of chronic heart failure

1.	Noncompliance with heart failure treatment
2.	Arrhythmias
3.	Anemia
4.	Systemic infection

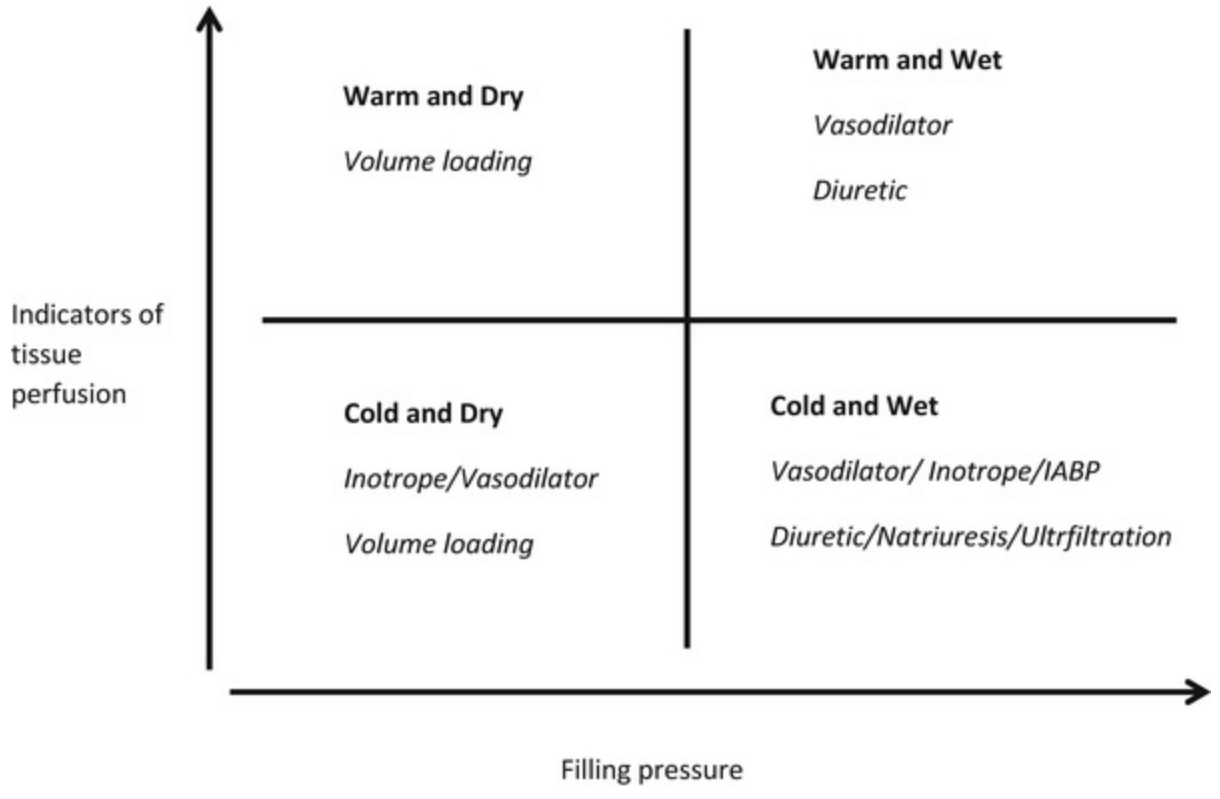

Fig. 13.1 Clinical profiles of decompensated heart failure and treatment options

These patients with significant perioperative implications (Table 13.4) are treated in monitored settings, quite often in intensive care units (ICU) for early detection of clinical deterioration and to titrate the treatment options to clinical effect. Supplemental oxygen is administered to maintain adequate peripheral oxygen saturation and, if necessary, noninvasive ventilation is used to decrease work of breathing. Caution needs to be exercised when altering the intrathoracic pressure in patients with right HF. Positive pressure ventilation and tracheal intubation is necessary if the patient is in respiratory distress or unable to protect the airway secondary to neurological deterioration.

Table 13.4 Preoperative implications of acute decompensated heart failure

1.	Pulmonary edema and respiratory support
2.	High-dose diuretics and renal function
3.	Electrolyte imbalance
4.	Inotropic support and adequacy of systemic perfusion
5.	IABP in situ and position
6.	End organ function and altered pharmacokinetics

Invasive monitoring is only indicated if the HF state is worsening with evidence of deteriorating organ functions in spite of adequate diuresis and afterload reduction. A pulmonary artery catheter (PAC) is used to guide the inotropic support by measuring the filling pressures and mixed venous saturation. In the failing heart, ventricles are operating on flat portion of Frank Starling relationship; increase in preload can have no incremental rise in cardiac output. Many of these patients are volume-overloaded upon admission and require parenteral high-dose diuretics. In resistant cases ultrafiltration is necessary to achieve desirable effect on preload. If the blood pressure is normal, afterload reducers are continued and intravenous vasodilators are introduced to achieve immediate reduction in afterload to improve cardiac output.

Common vasodilators used are sodium nitroprusside and Nitroglycerine (Table 13.5). Sodium nitroprusside is easily titrable and lacks tachyphylaxis, but has concerns for accumulation of toxic metabolites with organ dysfunction and higher total dose. Nitroglycerine can induce arterial vasodilation at higher doses and its use is limited by the development of tolerance within 24 h. Nesiritide, a recombinant product of human B-type natriuretic peptide is a potent vasodilator along with natriuretic properties that can decrease the filling pressures and improve congestive symptoms in decompensated HF. Given the associated cost without any demonstrable clinical benefits over other vasodilators, its use is limited in the current management of HF [21]. Vasodilators can

result in significant hypotension in the setting of low intravascular volume and anesthetic induction. Given the fact that HF state can worsen with discontinuation of afterload reducers, and the intravenous vasodilators used have short effective plasma half-life, these medications are continued until anesthetic induction.

Table 13.5 Dosing of intravenous vasodilators in decompensated heart failure

Nitroglycerine	Start at 5–25 μg/min Titrate up to 200 μg/min	Hypotension, tolerance
Sodium nitroprusside	Start at 0.2–0.4 μg/kg/min Titrate up to 5 μg/kg/min	Hypotension, cyanate toxicity
Nesiritide	Bolus 2 μg/kg Infusion 0.015–0.03 μg/kg/min	Hypotension

If the congestive state does not improve or the low output state continues to worsen with adequate diuresis and afterload reduction, inotropic support (Table 13.6) is considered. There should be evidence of organ hypo perfusion and low measured cardiac output before administering inotropic agents [22, 23]. Inotropic agent should be viewed as an intermediary bridge to transfer the critically ill patient to more definitive treatment options. They need to be discontinued as early as possible as the clinical condition is stabilized, as evidence points towards increase in short- and long-term mortality with their use [24]. Invasive blood pressure and filling pressure monitoring are essential for optimal titration of the vasodilators and inotropic medications to desirable effects avoiding hemodynamic side-effects. Epinephrine is reserved for cardiac arrest or impending hemodynamic collapse and is not recommended for the treatment of HF. Levosimendan being a calcium sensitizer and K_{ATP} inhibitor has a theoretical benefit over adrenergic agonist by not downregulating the adrenergic receptors. Conclusive clinical evidence is lacking even though a recent meta-analysis from 45 randomized clinical trials suggests a mortality benefit of using levosimendan in cardiac surgery patients [25]. Levosimendan is not yet approved by the Federal Drug Administration (FDA) for the treatment of HF. Vasopressors (nor-epinephrine) are only indicated in a resistant heart failure state when inotropic support and fluid challenge fail to increase the systolic blood pressure above 90 mmHg and improve the organ perfusion.

Table 13.6 Common inotropes used in treating acute decompensation of heart failure

Dobutamine	2–20 μg/kg/min	Dose-dependent adrenergic agonist
Milrinone	Optional bolus[a]—50 μg/kg over 20 min Infusion—0.25–0.75 μg/kg/min	Type 3 phosphodiesterase inhibitors
Levosimendan	Optional bolus[a]—12 μg/kg over 10 min	Calcium sensitizer Binds to Troponin-C

	Infusion—0.05–0.2 μg/kg/min	

[a]Bolus is not recommended if systolic blood pressure is less than 100 mmHg

Preoperative Mechanical Circulatory Support

In resistant cases of acute exacerbation of chronic HF, an intra-aortic balloon pump (IABP) is inserted to effectively reduce the afterload and augment the diastolic pressure, improving the coronary perfusion. It is used to avoid impending hemodynamic collapse and subsequently bridge the patient to advanced therapies. On very rare occasions heart transplantation is considered in HF patients on extracorporeal circulatory support (Table 13.7). With recent developments in MCS, patients who are clinically deteriorating while waiting for a suitable donor organ can be safely transitioned to a left ventricular assist device (LVAD). Improved circulation should not only improve the physiological condition, but also enhance end-organ function. The number of patients with assist devices used as bridge to transplantation is on the rise and as per the 2013 ISHLT report, 37 % of the patients receiving HT had LVAD [1]. Patients with assist devices have diverse anesthetic considerations (Table 13.8) and may need invasive monitoring prior to induction. Sternal reentry plan should be discussed with the surgical service, especially if the outflow graft is close to the sternum. These patients are at increased risk of intraoperative bleeding secondary to dissection of dense mediastinal adhesions and preoperative anticoagulation. Coagulation profile is obtained on arrival and warfarin induced anticoagulation can be safely reversed with either fresh frozen plasma (FFP, 10–15 mL/kg) or pro-thrombin complex concentrates (PCC) . Vitamin K 10 mg is routinely administered intravenously once the decision is made to reverse the anticoagulation. FFP is associated with transfusion related risks and volume overload in these tenuous patients. PCC can reverse vitamin K antagonist anticoagulation rapidly and reliably [26, 27]. Dosing of PCC depends on presenting International Normalized Ratio (INR), and in spite of variability in dose response, INR can be reduced to 1.5 or below with a total dose of 10–30 units/kg. Appropriate response can be expected in 15 min and redosing can be considered if the INR is higher than 1.5. Right heart failure is a well-known complication after LVAD implantation; albeit lower incidence has been reported with newer generation pumps, it has significant implications [28, 29]. A failing right heart is sensitive to changes in loading conditions and these changes should be minimized prior to cardiopulmonary bypass. Controlled device-related infection is an important indication for transplantation and appropriate antibiotics should be continued perioperatively.

Table 13.7 Pretransplant mechanical circulatory support in recipients between 2006 and June 2011

Left ventricular assist device (LVAD)	27.3 %
Right ventricular assist device (RVAD)	3.8 %
Total artificial heart (TAH)	0.9 %
Intra aortic balloon pump (IABP)	6.2 %
Extracorporeal membrane oxygenation (ECMO)	1 %

Adapted from Stehlik et al. [4]

Table 13.8 Considerations in LVAD patient with perioperative implications

1.	Assure proper device functioning
2.	Anticoagulation status
3.	Acquired Von Willebrand disorder
4.	Appropriate intravascular volume prior to anesthetic induction
5.	Right heart function and positive pressure ventilation
6.	Associated infection and continue antimicrobials

Cardiac Implantable Electronic Devices (CIED)

Significant numbers of advanced heart failure patients have cardiac resynchronization therapy (CRT) with or without cardioverter defibrillator (ICD). CRT reduces the morbidity and mortality in selected individuals (Left ventricular ejection fraction [LVEF] ≤35 % and QRS duration >120 ms) by optimizing the interventricular and intraventricular conduction [30–32]. ICD is often employed for both primary and secondary prevention in heart failure individuals [33]. Evidence for clinical utility of ICDs for primary prevention is more robust for HF from ischemic etiology than non-ischemic etiology [33, 34]. These Cardiac implantable electronic devices (CIED) need to be interrogated prior to surgery. ICD therapy function should be turned off and transcutaneous defibrillator pads be applied. All rate responsive functions and any enhancements on CIED are discontinued. Monopolar cautery during surgery should be employed in brief bursts to prevent inhibition of a pacemaker. The device should not be in the current pathway between the cautery applicator and return pad. If electromagnetic interference is resulting in hemodynamic compromise and patient is pacemaker dependent, CIED can be programmed to asynchronous mode. Placing central lines in these patients can be challenging at times with indwelling wires and sclerosis of the veins.

Right Heart Function and Preoperative Pulmonary Hemodynamics

Morphologically adult right ventricle (RV) with a wall thickness of less than 5 mm is designed to pump blood into low pressure pulmonary circulation and is relatively sensitive to afterload changes. It will adapt to chronic increase in pulmonary arterial hypertension (PHT) with increase in wall thickness and decrease in wall stress. But acute increase in pulmonary arterial pressure (PAP) is poorly tolerated by the RV [35] especially when exposed to ischemia reperfusion as in transplantation. Chen et al. [36] designed an experimental animal model to study the performance of the RV in a transplanted heart in the setting of pharmacologically induced chronic PHT . They found that RV could maintain the blood flow at increased energy expenditure and decreased efficiency. Brain death is also demonstrated to decrease the RV functional reserve against acute increase in afterload [37, 38]. It is not clear whether this detrimental effect can be improved or reversed by changes in donor management.

Pulmonary circulation in end stage HF is exposed to long-standing increased left atrial pressure resulting in passive venous congestion and secondary changes in pulmonary vasculature. This results in secondary PHT from both anatomical remodeling of the pulmonary vascular tree and endothelial dysfunction [39]. There is a gradual progression of PHT as the HF state worsens and increased PAP can be reactive to a variable degree. From early experience in 46 recipients, Kirklin et al. [40] identified the pulmonary vascular resistance (PVR) and pulmonary vascular resistance index (PVRI) as important predictors of early and late outcomes after HT. They found that the effect of PVR on risk of death was incremental with increasing PVR. Stanford experience [41] from 301 transplants between 1980 and 1988 identified that preoperative PVR of more than 2.5 Woods units (WU) increased the mortality rate within 90 days by more than twofold (17.9 % vs. 6.9 %). In their series, transpulmonary gradient (TPG) of 15 mmHg differentiated high-risk recipients for early postoperative mortality (90 days) from low risk recipients. They checked the responsiveness of pulmonary vasculature to sodium nitroprusside in patients with pulmonary artery systolic pressures (PASP) more than 40 mmHg. Patients who were responsive to nitroprusside as defined by decrease in PVR to less than 2.5 WU without inducing systemic hypotension (systolic arterial pressure less than 85 mmHg) were identified to have five to six times lower mortality than high risk group (6 % vs. 33.3 %). Murali et al. [42] retrospectively analyzed their HT cohort between 1980 and 1991 to identify preoperative TPG more than 15 mmHg (not PVR), recipient age, female sex, era of transplantation as the independent predictors of early post-transplant mortality. They postulated that TPG being a flow independent variable may be more predictive of outcomes after HT. The risk of RV failure will increase if the PASP exceeds 60 mmHg along with other aforementioned variables. Efforts should be directed towards decreasing the PAP by unloading the failing left ventricle (LV) in these patients. Failure of optimal medical therapy including inotropic support should be demonstrated by serial right heart catheterization before considering MCS such as IABP or LVAD [43]. Over

the years, even though listing criteria has been proposed by the ISHLT, it is difficult to define a cut-off value for PAP above which HT is absolutely contraindicated. This can be because of improved understanding and treatment of RV physiology and failure.

Transpulmonary Gradient (TPG) = Mean pulmonary artery pressure (MPAP) – Pulmonary capillary wedge pressure (PCWP)

PVR in WU = TPG mmHg/Cardiac output (liters/min).

Vasodilator challenge after optimization of HF therapy, to define the reactiveness of the pulmonary vasculature, can help in identifying patients who are at high risk of complications after HT. If the PHTN is nonreactive or fixed, it may portend a worse prognosis after HT [41]. If PVR can be reduced to <2.5 WU without systemic hypotension, post-HT outcomes are comparable to patients without PHT [41, 44]. In contemporary practice, common vasodilators used in the vasodilator challenge are nitric oxide, prostaglandin, sodium nitroprusside, and sildenafil. The protocol and hemodynamic end points for clinical decision-making vary from one institution to another. Advances in assist device technology and patient management have resulted in long-term outcome of patients with assist devices rivaling the transplant results. This opens up another avenue for patients with fixed PHT to receive transplant if there is demonstrable decrement in PAP after MCS.

Anesthetic Management

HT almost always is performed as an emergency procedure as it depends on the availability of a donor organ. Though these patients undergo a thorough evaluation and preparation there is usually a time interval between the evaluation and the actual surgery. Therefore, careful preoperative exam is essential to manage these patients and full stomach precautions are employed if the fasting status is not desirable. These patients can have varied level of hemodynamic stability depending on the level of heart failure severity. Ambulatory patients will be on multiple medications to alter the loading conditions and inotropy favorably to alleviate the congestive state. Patients in higher INTERMACS levels may be on inotropic infusions and may also be on mechanical assist devices like IABP or extracorporeal membrane oxygenation (ECMO) . Historically LVAD recipients receive 30 days elective period of status 1A after the initial peri-implantation period. This practice has been questioned recently as the technology and clinical outcome of these patients has improved substantially over the years introducing disparity in severity of status 1A patients [45].

Close communication between the transplant coordinator, the team harvesting the donor heart and the team preparing the recipient remains vital to minimize the ischemic time of the donor organ. The recipient should be on cardiopulmonary bypass (CPB) , with the recipient heart dissected when the donor heart arrives; however, induction of the recipient and incision should not take place until the harvesting team is in the

operating room and has the opportunity to actually examine the donor heart to be certain it is suitable.

Anesthetic Induction

It is now well appreciated that the failing heart is preload dependent and afterload sensitive, and these patients do not tolerate even the most trivial perturbations in these and other parameters such as heart rate, rhythm and contractility that the anesthesiologist is well versed in manipulating. There is no evidence that any particular anesthetic agent is preferable in HF patients. It is important to recognize the physiological changes these agents induce and identify these changes with sensitive monitoring. Invasive monitoring such as arterial line and PAC are placed pre-induction to facilitate making right interventional decisions during hemodynamic deterioration. If the invasive monitoring is placed preoperatively to optimize the HF status, consideration should be given to change the invasive lines prior to sternotomy, to decrease the possibility of line-acquired blood stream infection in immunosuppressed patients. The anesthesiologist and the surgical team should be ready to escalate the circulatory support in the event of hemodynamic compromise with anesthetic induction. Spontaneous inhalational induction offers an advantage of minimizing rapid decrease in preload, which is not tolerated well in HF patients, especially those with RV dysfunction. In emergency situations, and if patient is at risk of pulmonary aspiration, rapid sequence induction is performed. With the diminished cardiopulmonary reserves in end stage HF, efforts should be directed towards preserving these compensatory mechanisms. Sympatholysis with high-dose opioids is avoided unless somebody is tolerant to opioids. Post intubation ventilator parameters are adjusted to prevent hypercarbia and optimize oxygenation in order to minimize the effect on pulmonary vascular resistance. In patients on preoperative inotropes, it is important to continue these infusions during the induction phase of the anesthesia. It may also be necessary to start an infusion of vasopressors, typically norepinephrine to offset the effects of the general anesthesia and all the induction medications.

HT is beneficial in selected cases of muscular dystrophy [46] and these patients may be at increased risk for malignant hyperthermia. Careful preoperative evaluation should be done, and consideration should be given for non-trigger techniques in such patients [47].

Immunosuppression in the Perioperative Period

The goal of optimal immunosuppression is to maintain native host immune reactivity suppression in order to prevent rejection of the graft and balance the risk of side-effects, including increased risk of opportunistic infection from over-immunosuppression (Table 13.9). This can be achieved by closely monitoring for adverse effects and measuring

blood levels of immunosuppressive drugs. Corticosteroids (CS) are weaned if tolerated and it is observed that the use of CS declines but the use of proliferation signal inhibitors (PSI) doubles between 1 and 5 years after HT [1]. With the available evidence, it is not possible to advocate a preferred combination of drugs for immunosuppression following heart transplantation. The selection is essentially driven by the side effect profile in the given patient and organ function. Higher incidence of acute rejection in the early postoperative period has led to the practice of inducing intense immunosuppression during the early perioperative period (Table 13.10). According to 2013 ISHLT report, this practice of empirical induction therapy has decreased in 2012, with overall 47 % during the first 6 months of 2012 [3]. Induction of immunosuppression is usually achieved by monoclonal or polyclonal antibodies. Decision to utilize induction therapy, essentially depends on institutional practice as there is no conclusive evidence demonstrating their utility (Table 13.11) [48]. They have been associated with adverse effects such as infection, prolonged leukopenia, and risk of malignancy [49]. Prior to induction therapy with antibodies, patients are routinely premedicated with corticosteroids, antihistamines, and antipyretics.

Table 13.9 Applied pharmacology of common immunosuppressants during perioperative course of heart transplantation

Class	Medications	Mechanism of action	Adverse effects
Corticosteroids (CS)	Methylprednisone Prednisone	Alter gene transcriptional regulation with suppressed inflammatory and immune response of WBCs	Psychiatric effects, poor wound healing, hypertension, adrenal suppression
Calcineurin inhibitors (CNI)	Cyclosporine Tacrolimus	Inhibits transcription of cytokines (IL-2) involved in immune response	Hypertension, renal insufficiency, neurologic toxicity, dyslipidemia, hyperglycemia
Antimetabolites	Azathioprine Mycophenolate mofetil	Interferes with cell cycle regulation	Myelosuppression, nausea/vomiting, diarrhea
Proliferation signal inhibitors (PSI)	Sirolimus (FDA approved for OHT)	Inhibits a kinase (TOR) controlling the proliferation of lymphocytes	Renal dysfunction, impaired wound healing, diarrhea, myelosuppression

IL interleukin, *TOR* target of rapamycin

Table 13.10 Immunosuppression induction agents prior to heart transplantation

Monoclonal Antibodies—28 % of heart transplants	
CD25 antagonists (IL-2 receptor on T lymphocytes)	Basiliximab (Simulect) Daclizumab
CD52 binding (T and B lymphocytes)	Alemtuzumab
Polyclonal Antibodies—11 % of heart transplants	

Rabbit anti-thymocyte globulin (RATG)
Horse anti-thymocyte globulin (HATG)

Data from Roger et al. [2]

Table 13.11 Proposed indications of induction therapy

1.	Decreased risk of acute rejection in allosensitized recipients
2.	Rapid induction of immunosuppression during rejection
3.	Delay the initiation of CNIs in patients with renal insufficiency
4.	Permit delay in introduction of CNIs
5.	Facilitate regimens with low-dose steroids
6.	Provides flexibility for corticosteroid weaning

Perioperative Implications of Allosensitization

Allosensitization is defined as development of antibodies to human leukocytic antigen (HLA) molecules secondary to a sensitizing event. These antibodies were initially recognized to be responsible for poor renal allograft function and rejection in 1969 [50]. HF patients are often exposed to these during their disease course. Common sensitizing events are identified in the Table 13.12. It is important to recognize that even leukocyte reduced red blood cell (RBC) transfusion can result in sensitization and red cells also present major histocompatibility complex (MHC) class 1 antigens on their cell membrane, albeit in lower concentrations than lymphocytes [51]. Allosensitization is important because of its relevance in adverse outcomes after organ transplantation. Patients with immunological sensitization as measured by panel reactive antibodies (PRA) tend to have a worse outcome after HT than those without sensitization [52, 53]. It is routine in current practice to check serial PRAs on potential recipients to identify development of sensitization. Antibodies tend to disappear after the initial triggering event without further exposure. Antibodies formed after transfusions disappear in 5–11 months after the trigger. Multiple triggering events can induce broader sensitization as measured by sensitive cytotoxic methods [54]. The broader sensitization will decrease the available donor pool, resulting in longer waiting period for HT.

Table 13.12 Risk factors for allosensitization

1.	Blood and blood product transfusion
2.	Previous allografts
3.	Pregnancy
4.	Prior cardiac surgery with allografts
5.	Cardiac assist devices

6. Hematological malignancies

MCS especially LVAD are increasingly used more to treat end stage HF patients on transplant waiting list [3]. It is well known now that these devices can induce immune sensitization independently. In spite of modern rotary pumps not having bioprosthetic material in their design, there is evidence of allosensitization albeit to a lower degree than older pulsatile pumps [55]. Risk of sensitization appears to be higher in the first 3 months after implantation [56]. Pre-sensitized patients may be at risk of broader sensitization after implantation of pulsatile flow devices. Retrospective analysis of patients transplanted on assist device from United Network for Organ Sharing (UNOS) database between 2004 and 2009 revealed a longer waiting time for those with PRA > 10 % (205 days [interquartile range, 81–344] vs. 124 days [interquartile range, 51–270]) [57]. Notably, alloimmunization after assist devices has not been shown to result in poor survival or translate into higher rejection rates after HT [55, 57, 58]. This brings up the question of functional relevance of these antibodies after device implantation. Advances in immunological testing and clinical experience with these devices should shed some light on this question.

This immunological sensitization is identified by screening the recipients for anti-HLA antibodies directed at set of panel antigens of random donors (e.g., PRA). The threshold to define significant sensitization is still debatable and varies from PRA level of 10–25 % [53, 59]. The UNOS online calculator can be used to define the calculated PRA (cPRA), which signifies the percentage of the general donor pool against what recipient demonstrates antibodies. Once allosensitization is identified by PRA level, specificity of these antibodies are further improved by identifying antibodies against specific human HLA molecules. Modern solid-phase assays can identify antibodies against both classes of MHC antigens and their binding strengths. This will enable the transplant team to confirm donor specific antibodies (DSA) when there is an offer, by matching against antigens identified by donor tissue typing. This process is termed virtual cross-matching (VxM) and is widely used in confirming the immunological compatibility of donor organs [60]. Stehlik and colleagues studied the utility of VxM in HT by comparing it with prospective cross match, and in their series of 14 patients VxM had a negative predictive value of 92 % and positive predictive value of 79 % [61]. It helps in defining the functional relevance of the identified antibodies and accepting donors without the need for a prospective cross match [62]. This should help in accepting organs from a wider geographical zone [63]. Retrospective cross-matching is performed in all sensitized recipients to guide the management of immunosuppression. Aggressive immunosuppression with close surveillance for rejection may be required in those with positive retrospective cross-match results.

Some recipients are very highly sensitized, and preoperative management of these patients is challenging considering balancing the risk of graft failure versus death on the

waiting list. Therapeutic immunomodulatory strategies to alleviate this immunological disadvantageous state by desensitization techniques using plasmapheresis, IV Immunoglobulin (IVIG), monoclonal antibodies, or proteasome inhibitors have been advocated by certain transplant centers [64, 65]. It has yet to be proven that these strategies have predictable success. Moreover, the effectiveness of these strategies is negatively affected by serious complications like infections and morbidity associated with these medications. According to the survey conducted across multiple transplant centers, 8 % of the transplant patients underwent desensitization therapy prior to HT [66]. There is lack of evidence to support desensitization therapy in this fragile group of patients over watchful avoidance of mismatch donors using modern immunological methods.

Intraoperative Transesophageal Echocardiography (TEE)

TEE is an essential intraoperative monitor, and history should be sought to rule out any contraindications before insertion of the esophageal probe. Intraoperative TEE is ideally suited to identify acute complications during cardiac transplantation and titrate the hemodynamic support to the cardiac function especially in the post-implantation stage [67, 68] (Table 13.13).

Table 13.13 Utility of TEE during orthotopic heart transplantation

Preoperative period
1. Ventricular function
2. Rule out intracavitary thrombus
3. Significant aortic atherosclerotic disease
4. Assist in placement of cannulae for CPB
Post-CPB
1. Ventricular and valvular function
2. De-airing of the graft
3. Rule out intracardiac shunt
4. Anastomotic complications
5. Assist in placement of cannulae for mechanical circulatory support
6. Confirm IABP position
7. Rule out aortic dissection post decannulation

Conduct of Cardiopulmonary Bypass and Surgical Techniques

With more than 99,000 adult HT performed worldwide, surgical technique of implantation has been refined, and there is gradual adoption of the bicaval technique to

implant the graft [69]. Original Lower and Shumway technique involves bilateral atrial anastomosis, with retention of some native atrium [70]. In the early 1990s, the bicaval technique was described in two different clinical series, with complete excision of native atrium and direct anastomosis of superior and inferior vena cava [71, 72]. Preserving normal atrial anatomy and function was the objective of this technique. Potential advantages of bicaval technique includes decrease in:

1. Atrial dysfunction

2. Sinus nodal dysfunction

3. Valvular insufficiency

4. Thrombus formation

Longer surgical time can be a disadvantage with bicaval technique with a possibility of prolonging graft ischemic time. Although many single center studies have described decreased complications (atrial arrhythmias, tricuspid regurgitation, nodal dysfunction) immediate post transplantation with bicaval technique [73–76], evidence for long-term survival benefit is not clear [77]. A retrospective UNOS data analysis of 11,931 primary HT between 1999 and 2005 found no difference in survival between matched groups with bi-atrial vs. bicaval techniques [78]. Nonetheless, the bicaval technique was associated with lower permanent pacemaker (PPM) implantation and shorter hospital length of stay. Another multivariate analysis of UNOS database [79], over 10 years (1997–2007) demonstrated small but significant survival advantage of the bicaval technique and improved PPM free period. Authors attributed this discrepancy to the longer period of analysis, the increase in bicaval technique, and difference in statistical methods.

Anticoagulation for cardiopulmonary bypass (CPB) is achieved by unfractionated heparin 350–450 units/kg, unless contraindicated, to achieve an activated clotting time (ACT) above 480 prior to proceeding on CPB. Despite, the lack of correlation between ACT and heparin levels, ACT remains a reliable and safe monitoring technique in managing heparin-based anticoagulation for CPB. Certain physiological changes (hemodilution, hypothermia) and pathological conditions (conditions with release of inflammatory mediators, protein S resistant states) can make ACT monitoring less reliable. If these clinical circumstances are suspected, monitoring methods using Heparin Dose Response (HDR) can be used to maintain certain plasma concentration of heparin.

If the patient is diagnosed with heparin induced thrombocytopenia (HIT) and the

anti-PF4 antibody titers were elevated within 100 days, anticoagulation is typically achieved by direct a thrombin inhibitor such as bivalirudin (Table 13.14). Risk of bleeding increases with bivalirudin as the anticoagulation is not reversible. This is especially true in patients with renal insufficiency. Heparin can be used for CPB only in somebody with remote history of HIT, as the anti PF4 antibodies decrease to clinically insignificant levels in 3 months of non-exposure. It is important for all the personnel involved in patient care to understand that this patient with remote history cannot be reexposed to heparin after CPB and all precautions should be taken to prevent reexposure (Table 13.15).

Table 13.14 Recommended bivalirudin dosing and management plan for cardiac surgery on cardiopulmonary bypass

	Dose prior to CPB	**Dose during CPB**	**Dose after CPB**
PATIENT	1.0 mg/kg IV bolus followed by 2.5 mg/kg/h IV infusion ACT >4 times the baseline	• 2.5 mg/kg/h IV infusion • Stop infusion 15 min prior to anticipated CPB discontinuation • If not possible to separate from CPB and decannulate in 20 min rebolus 0.5 mg/kg and restart infusion at 2.5 mg/kg/h	None
Flush solutions	0.1 mg/mL bivalirudin	Same as dose prior to CPB	Same as dose prior to CPB
CBP pump	50 mg priming dose (suitable for all priming volumes)		50 mg priming dose f/b 50 mg/h
Graft storage	*BLOOD BASED* • 1:12 CPD or ACD to blood *CRYSTALLOID BASED* • 0.1 mg/mL bivalirudin in crystalloid solution	Same as dose prior to CPB	None
Cell saver	1:12 CPD or ACD to blood	Same as dose prior to CPB	None
Cardioplegia	*CRYSTALLOID* • No anticoagulant needed *BLOOD* • Sourced directly from CPB circuit without reservoir	Same as dose prior to CPB	N/A
• Stagnant blood in the CPB venous reservoir may begin to clot: if more than 1 L blood exists in the reservoir, it is recommended to store the excess blood in CPD or ACD bags at a ratio of 1:12 (CPD or ACD:blood volume) • Due to a low remaining blood volume in the circuit resulting in high concentrations of bivalirudin, it should be processed in the cell saver prior to reinfusion to the patient			

Table 13.15 Precautions to prevent intraoperative heparin reexposure in documented and/or suspected HIT patients

1. Discontinue both fractionated and unfractionated heparin
2. Transducer flush solutions should be free of heparin
3. Invasive lines should be non-heparin coated
4. CPB circuits are non-heparin coated
5. Heparin should not be used in any form on the surgical prep table
6. Citrate Phosphate Dextrose-A or Acid Citrate Dextrose solution to be used in cell saver for anticoagulation

Standard arterial and bicaval cannulation techniques are used in primary HT. In redo sternotomy with assist device, it is not uncommon to open the sternum under CPB with femoral venous and arterial cannulations especially if the outflow cannula is in proximity to the sternum. Serum electrolyte concentrations should be closely monitored on pump as hemodilution can further exaggerate the derangements (hyponatremia, hyperkalemia) present from HF and its treatment. Modified ultrafiltration on CPB is often employed to decrease body water that has expanded in patients with HF. This strategy is particularly helpful when right ventricle is at risk of failing and cannot accommodate the excessive intravascular volume without dilation.

Once examined in the back table, a graft is implanted (left atrium, great vessels followed by IVC and then SVC) while cold cardioplegia and topical cooling is providing ischemic protection. Left atrial vent is introduced to prevent distension and rewarming. Usually SVC anastomosis is done under partial CPB with reperfusion of the graft.

Hemostasis and Transfusions

Significant proportions of heart transplant recipients are at increased risk for post CPB bleeding because of preoperative risk factors and CPB related hemostatic derangements (Table 13.16) [80–82]. Antifibrinolytics such as tranexamic acid (TA) and epsilon aminocaproic acid (EACA) are useful to decrease the perioperative bleeding in these patients. The Butterworth [83] modification of dosing regime is helpful for maintaining stable predictable plasma EACA concentrations in cardiac surgeries on CPB. EACA bolus dose of 50 mg/kg is administered over 20 min before initiation of CPB followed by the infusion (25 mg/kg/h), which is continued until the skin closure. TA is ten times as potent as EACA , and variable dosing regimens have been described [84]. Postoperative seizures have been reported with the use of very high doses of TA [85]. Clinical superiority and cost-effectiveness of TA over EACA are not established.

Table 13.16 Risk factors for post CPB bleeding

Preoperative risk factors

1. Preexisting coagulopathy
2. Preoperative antiplatelet medications and anticoagulants
3. Renal dysfunction
4. Preexisting right heart failure with hepatic congestion and hepatic dysfunction
5. Redo sternotomy
6. Preoperative mechanical circulatory support
Risk factors related to CPB
1. Hemodilution
2. Hypothermia
3. Thrombin generation with activation of inflammatory cascade and platelets
4. Platelet consumption and thrombocytopenia
5. Fibrinolysis

Significant coagulopathy deemed not due to inadequate surgical hemostasis may require blood product transfusion for rapid control of nonsurgical bleeding and maintaining oxygen-carrying capacity of blood. Absolute or stringent triggers for transfusion cannot be definitively defined but rather transfusion considerations require an integrated approach of reviewing the patient's current hematocrit, volume status, coagulopathy state (i.e., bleeding deemed not due to inadequate surgical hemostasis), evidence of ongoing organ ischemia, preexisting end-organ disease, cardiac output, and mixed venous oxygen saturation. Requirement of blood products can be determined by coagulation studies and point-of-care testing such as thromoboelastogram (TEG) and rotational thromboelastometry (ROTEM).

Coagulation parameters should be normalized and normothermia should be maintained throughout the perioperative course. All fluids except platelet concentrates and cryoprecipitates should be administered through heated circuit, and rapid infuser system should be readily available to achieve the same. Desmopressin (0.3–0.4 μg/kg) can be considered in patients with preexisting hepatic and renal dysfunction. Activated recombinant factor 7 is used as a last resort to contain life threatening bleeding in view of high risk of thrombotic complications [86]. The use of PCC to correct preoperative coagulopathy is described in the previous section. PCC can correct coagulopathy with less volume infusion compared to FFP, which is beneficial in HT recipients to avoid RV overload and graft failure.

Weaning from CPB

Discontinuation of extracorporeal circulation should be gradual with continuous assessment of the new graft to varying loading conditions by both hemodynamic (TEE) and visual assessment. Most of the centers practice reperfusion of the graft with mean

systemic pressures between 50 and 70 mmHg for variable period prior to weaning from CPB. Low-dose inotropic infusion is started on removal of aortic cross clamp and titrated according to the graft function. All physiologic variables influencing PVR are maintained so as to prevent afterload mismatch of the load sensitive RV. Intravascular volume should be expanded under the guidance of TEE and filling pressures. Volume overload results in chamber dilation and ventricular dysfunction. In the event of inadequate graft function, patient should be promptly returned to extracorporeal circulation. Further attempts to wean should follow reperfusion and escalation of pharmacological support as indicated. Sinus rhythm is the most common rhythm after reperfusion, usually at a rate more than 100 beats/min with complete parasympathetic denervation. Sinus node dysfunction or conduction abnormalities are less common with bicaval technique.

Perioperative Graft Failure

Early graft dysfunction is one of the leading identified causes of mortality in the first 3 years after heart transplantation [3] and will clinically manifest within 24 h of graft perfusion. It is associated with decreased early and late survival [87] signifying the importance of prompt diagnosis and treatment of graft dysfunction. Graft failure can be due to primary organ dysfunction or secondary to inability of the new organ to function in the testing host environment. The report from the ISHLT consensus conference on PGD has laid down definitions and clinical parameters to facilitate better management of this morbid complication [88].

Primary Graft Dysfunction (PGD)

Incidence and Diagnosis

The incidence of PGD related deaths has not changed since 1994 and was responsible for 36 % of all deaths in the first month following orthotopic heart transplantation (OHT) in the decade of 2002 till 2012 as per 2013 ISHLT official report. Russo et al. [89], in their study of de-identified UNOS data from 1999 till 2007 found the incidence of primary graft failure as 2.5 % in 16,716 transplants. Primary graft failure was defined as death or retransplantation within 90 days. Therefore, the reported incidences tend to be underestimated considering the hard end point requisite in the definition. Primary graft failure accounted for 23.4 % of total deaths within 90 days in the same cohort. At present there is no universally accepted definition of PGD and the preconditions required for the diagnosis varies between different institutions and the era of transplantation, resulting in the observed variability of the diagnosis between different transplant centers. Depending on the criteria used in defining the PGD and donor–recipient characteristics, the incidence of PGD varies between 2.5 and 26 %

[90–93].

Etiology and Pathophysiology of PGD

PGD is often the result of one or multiple risk factors (Table 13.17) and can result in univentricular or biventricular dysfunction of varying severity. It is important to identify and treat secondary precipitating factors before diagnosing PGD. RADIAL score is the only predictive score for PGD described and validated in the current clinical practice [94] (Table 13.18). This was derived by a single center experience of OHT between 1984 and 2006 in Spain. Authors identified the independent risk factors for PGD by multivariable analysis and have built a predictive model with validation in a cohort of patients between 2006 and 2010. RADIAL score was applied to the contemporary cohort by the same group of investigators and have demonstrated the predictive ability of the score [95].

Table 13.17 Risk factors for primary graft dysfunction

Donor factors	Recipient factors	Procedural factors
– Cardiac dysfunction with high inotropic support	– Prior mechanical circulatory support	– Hypothermia
– Coronary artery disease	– Age	– Ischemic time
– Age	– Mechanical ventilation	– Reperfusion injury
– Concomitant lung retrieval	– Etiology of heart failure	– Size mismatch
– PGD of other organs from the same donor		

Table 13.18 RADIAL risk score —prediction of primary graft dysfunction

*R*ight atrial pressure ≥ 10 mmHg
*A*ge (recipient) ≥ 60 year
*D*iabetes mellitus
*I*notrope dependence
*A*ge (donor) ≥ 30 year
*L*ength of ischemic time ≥ 240 min

Risk Factors

In order to preserve an adequate graft function as it adapts to the new host environment, it is recommended to limit cold ischemic time to below 5 h with the standard preservation method. During this obligatory ischemic period, metabolic demand of the organ is decreased by hypothermia, and preservative solutions aid in containing the ischemic insult while providing substrate for the critical energy needs. Ischemic time of more than 5 h can be considered acceptable only if other contributing factors for graft dysfunction such as donor age, high inotropic support and significant ventricular dysfunction are absent. In their retrospective analysis of 33,640 heart transplants

between 1987 and 2004, Russo et al. [96] concluded that ischemic tolerance defined by post-transplant survival is affected by donor age measured in terciles 0–19 years, 20–33 years, and more than 33 years. There was a trend towards increased incidence of death across time intervals when donor organs from two older terciles were subjected to more than 3.5 h of ischemia, indicating the relationship between donor ischemic time and age.

Hemodynamic and neurohormonal disturbances following brain death are postulated to contribute for donor organ dysfunction. Catecholamine storm following brain death can lead to myofibrillar degeneration resulting in poor graft function with inadequate cardiac output. Brain death also leads to immunological activation of the organs with increased expression of MHC class 1 and 2 molecules. Mediators for this upregulation are not identified yet.

The graft should be visualized for any contusions and visible CAD. Preload optimization is guided by hemodynamics and invasive monitoring, which is important as the goals of volume resuscitation between different harvesting teams differ. Donor management is an important part of any transplant process and about 60 % of available hearts and lungs from cadaveric donor are lost due to poor donor organ features [97]. Inadequate donor management has been cited for up to 1/4th of donor organ loss [98]. Recommendations for efficient organ management published in 2001 from the conference on "Maximizing Use of Organs Recovered from the Cadaver Donor" at Crystal City, VA [97] have been adopted into the United network for organ sharing pathway. It provides a systematic approach to hemodynamic monitoring along with indications for vasopressor therapy and neurohormonal replacement.

Hypothermia and Preservation

Hypothermia decreases the metabolic demand and prolongs the tolerable ischemic period. Hypothermia can induce adverse ultrastructural changes that can lead to compromised graft function. Hazards of static hypothermic preservation [98–100] include the following.

1. Intracellular acidosis from anaerobic metabolism—Anaerobic glycolysis leads to accumulation of lactic acid.

2. Increase in intracellular calcium—Acidosis can lead activation of sodium–hydrogen exchanger (Na+-H+) with rise in intracellular sodium. This will subsequently result in Na–Ca antiporter activation with increase in intracellular calcium.

3. Cellular edema—Intracellular sodium and chloride concentration increases with the suppression of NA+-K+ ATPase by hypothermia and water will follow the ionic gradient.

The degree of this injury is variable and primarily time dependent. Preservative solutions are designed to prevent or decrease the effect of these changes in order to maintain the structural integrity and functional capacity. Preservative solutions achieve electromechanical arrest of the donor heart by altering the transmembrane potassium gradient. Preservative solutions can be divided into intracellular or extracellular solutions depending on which environment is reflected by their ionic composition. Extracellular solutions have sodium concentrations more than 70 mEq/L and intracellular being lower than 70 mEq/L [98] (Table 13.19). Donor heart can be effectively preserved up to 4–6 h, beyond which the harmful effects of cold ischemic arrest with both types of solutions might be clinically significant [101]. Addition of colloids and changing the osmotic pressure of the solutions can decrease interstitial edema and extravasation of cellular elements. There are few reports of lowered adjusted 1-month mortality with intracellular preservation solutions [102, 103]. However, there is not enough evidence to recommend one over another for clinical practice at present [104].

Table 13.19 Commonly used preservative solutions

Intracellular solution	Extracellular solution
UW-standard	Celsior
Collins	St. Thomas
Euro-Collins	Krebs
Bretschneider	UW-modified
Collins-Sachs	Stanford
Roe	Plegisol

UW University of Wisconsin

Advances in organ preservation should not only improve the allograft function, but also prolong safe ischemic period with better organ utilization. Animal studies [105] have shown improved functional recovery after continuous perfusion of the preservative solutions. Garbade et al. [106] compared conventional practice of hypothermic cardioplegic arrest to controlled normothermic perfusion of the porcine hearts without cardioplegic arrest. Controlled normothermic perfusion group demonstrated preserved ultrastructural properties and better functional recovery than conventional practice up to 12 h of perfusion. Preliminary human studies are suggestive of decreased ischemic

insult and better functional preservation with continuous perfusion [104, 107]. PROCEED 2 (Prospective Multicenter Safety and Effectiveness Evaluation of the Organ Care System Device for Cardiac Use) is a multicenter trial to study the effect of ex vivo sanguineous warm perfusion of the allograft with an organ care system on 30-day clinical outcome and graft function. Preliminary results showed noninferiority to standard care preservation method in HT [108]. Apart from the need for continuous monitoring, there is considerable cost and personnel required with using this system today.

Taking cue from hibernating phenotype model, Dobson and colleagues are working on cardioplegia technique maintaining the polarized state of the resting membrane [109]. They have demonstrated in rodent model that solution containing adenosine and lidocaine in Krebs–Henseleit buffer offered better myocardial preservation compared to standard cardioplegia solutions [110–112]. In their experiments resting membrane potential remained near −85 mmHg during arrest period with better myocardial recovery on reperfusion. They have postulated downregulating of myocardial and endothelial metabolic needs along with maintenance of intracellular ionic milieu in the polarized or hyperpolarized state to be responsible for this protection against ischemia and reperfusion.

Reperfusion

Reperfusion after ischemia can result in numerous deleterious changes both at intracellular and extracellular levels resulting in paradoxical decrease in function as observed in the operative room immediately after the release of aortic cross clamp (Fig. 13.2) [113]. Patho-mechanistic network processes are described [114] resulting in multiple complex injury pathways following abrupt reperfusion of tissue following anoxic insult. Opening of nonspecific pore on the mitochondrial membrane called Mitochondrial permeability transition pore (MPTP) secondary to cellular stress has been demonstrated to result in activation of both necrotic and apoptotic pathways and is a field of ongoing research to define therapeutic targets [115, 116]. Myocardial and endothelial dysfunction amplifies the processes by cellular activation and release of inflammatory mediators. Cellular calcium handling is further compromised resulting in sustained elevated intracellular calcium concentration resulting in contracture due to loss of actin–myosin breakdown. Reperfusion induced diffuse microvascular injury with significant contractile dysfunction is well recognized after acute coronary syndrome and is often referred as a “no reflow” phenomenon [117]. Uncontrolled reperfusion after ischemic insult resulting in extreme form of myocardial dysfunction (Stone heart) was initially reported by Cooley et al. [118]. Exposure of anoxia primed endothelium to oxygenated reperfusate leads to generation of harmful oxygen free radicals with resultant oxidative stress. The clinical manifestations vary depending on the degree of ischemic insult on the substrate and subsequent perfusion highlights the importance of

preservation and reperfusion for the perioperative physician [119].

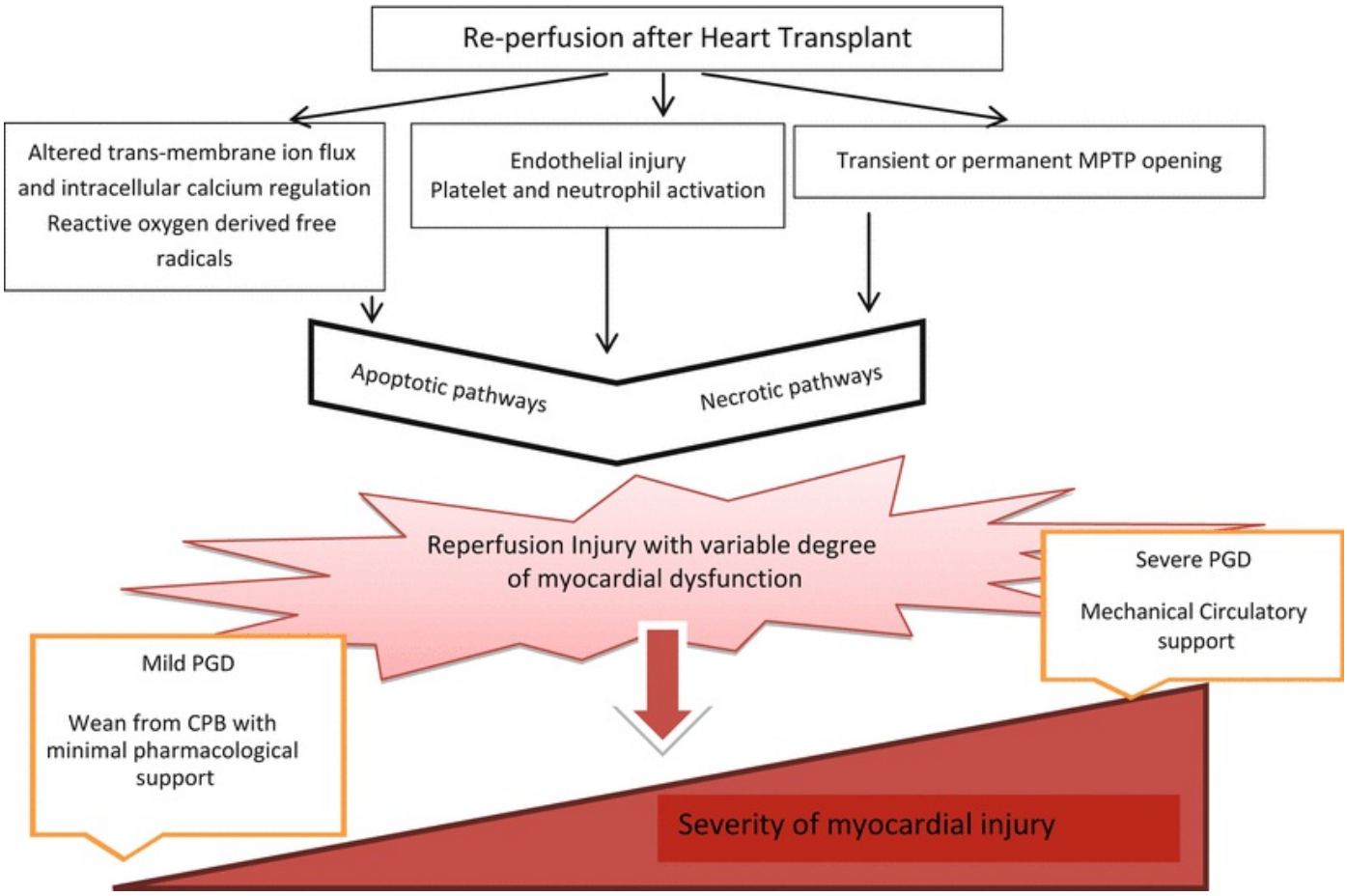

Fig. 13.2 Patho-mechanism of Reperfusion injury after heart transplantation

It is obvious that any single intervention is unlikely to protect against functional impairment mediated by multiple mechanisms. Various combinations of methods to address the identified mechanisms of ischemic injury during the transportation and implantation stage have been tried so far without definite success in preventing IR injury.

Controlling the reperfusion in order to improve graft function has drawn attention from the transplant community after the pioneering work of Buckberg et al. [120] in porcine model. Apart from pharmacological intervention to limit the injury, there is growing interest in modifying the reperfusion to prevent the injury. Controlling the physiological variables of interest such as reperfusion pressure and oxygen content of the reperfusate is hypothesized to decrease the endothelial dysfunction and subsequent oxidative stress [121, 122].

Mesenchymal stromal cells based cell therapies have been described to have immunomodulatory effects and demonstrated to reduce the effects of IR injury in various nonhuman organs by influencing both innate and adaptive immune processes [123].

MicroRNAs, having regulatory effects on cell differentiation, degeneration and immunomodulatory through specific negative effects on gene expression are areas of active interest to decrease the IR injury in organ transplantation [124].

Diagnosis and Treatment of PGD

PGD is diagnosed when the transplanted heart cannot generate required cardiac output without significant pharmacological support in the early posttransplant period. Acute rejection, surgical causes such as tamponade or defective anastomosis, pulmonary hypertension, and vasoplegia can lead to secondary graft dysfunction and needs to be ruled out prior to the diagnosis. Attention to adequacy of de-airing prior to weaning from cardiopulmonary bypass is important. Systematic approach is essential for prompt diagnosis to facilitate titrated treatment (Tables 13.20 and 13.21).

Table 13.20 Clinical, hemodynamic, and imaging parameters in the diagnosis of PGD

Hemodynamic
Low cardiac index (CI) with high filling pressures (Right atrial pressure >15 mmHg, PCWP > 20 mmHg and CI < 2 L/min/m^2)
Systemic hypotension
Imaging
Echocardiography—LVEF < 40 %, RV dilation with systolic dysfunction
Chest X Ray—Pulmonary edema
Clinical
Decreased cardiac output
Decreased urine output, rising lactate and decreased mixed venous oxygen saturation
High inotropic support to maintain systemic perfusion

Table 13.21 Tricuspid regurgitation post orthotopic heart transplantation

Early causes
1. Pulmonary hypertension
2. Surgical—biatrial technique
3. Right ventricular dilation
4. Organ size mismatch
Late causes
1. Graft rejection
2. Tricuspid valve damage secondary to endomyocardial biopsy

In isolated primary RV failure, PAP remains low with increased right atrial pressures. Prompt treatment of PHT is warranted if the right ventricle is failing

secondary to afterload mismatch. Inhalational pulmonary vasodilators such as inhaled nitric oxide and epoprostenol do not significantly affect systemic blood pressure unlike intravenous drugs (milrinone, sodium nitroprusside). However, they require special equipment and specific ventilator modifications for delivery. Patients should be closely monitored during weaning of inhaled nitric oxide, which should be done gradually to avoid rebound PHT.

Mechanical Circulatory Support (MCS) and Retransplantation in Graft Failure

Early experience in graft dysfunction after heart transplantation demonstrated that the dysfunction can be of variable severity and potentially reversible. Therefore, timely and adequate support of the circulation is advocated in life threatening graft failure [125]. Patients with PGD, who have survived 30 days post transplantation, tend to have similar survival as those without PGD [125]. In a single center retrospective study, Mihaljevic et al. reported PGD was treated by mechanical circulatory support (MCS) [an incidence of 3.7 %] in 1417 heart transplants performed between 1990 and 2010 [126]. Excellent long-term survival comparable to overall survival of the cohort was observed in patients who were successfully weaned.

Type of the device used for MCS depends on the operator and institutional preference. IABP is less invasive than extracorporeal devices and is tried first to decrease the afterload to facilitate ventricular performance. Veno-arterial ECMO has become the common and reliable modality of temporary mechanical support because adequate support can be achieved with relative ease and expeditiously [126, 127]. If the vasculature is amenable, peripheral ECMO is used to facilitate chest closure and weaning can be done in ICU [128]. Limb ischemia is an important concern in peripheral cannulation and adequacy of distal perfusion should be closely monitored. Presence of significant atheromatous disease is a relative contraindication for retrograde femoral perfusion. Many centers routinely use axillary artery cannulation, which offers antegrade perfusion instead of using the femoral artery. During ECMO support, exposure of blood to nonendothelial surface leads to activation of inflammatory processes, platelets, and coagulation cascade. In order to counter this pro-thrombotic activity, anticoagulation is initiated once mediastinal and chest tube output is minimal, after consulting surgical service. Heparin is the most common anticoagulant used unless contraindicated with an infusion titrated to maintain activated thromboplastin time of 45–65 s. The fibrinolytic system is activated by the upregulation of the coagulation process, leading to fibrinolysis after prolonged extracorporeal support, which puts the patient at risk of DIC and bleeding. D-Dimers are measured daily in order to detect hyper-fibrinolysis.

Once MCS is instituted, ECMO flows are maintained for 48 h with intermittent graft

ejection before attempting to wean. Functional recovery of the graft is evaluated by serial turn down hemodynamic and echocardiographic assessment with graduated decrease in the mechanical support.

Secondary Graft Failure

A transplanted heart can fail secondary to unfavorable pathophysiological conditions during the perioperative period (Fig. 13.3). These conditions should be ruled out before making a diagnosis of PGD.

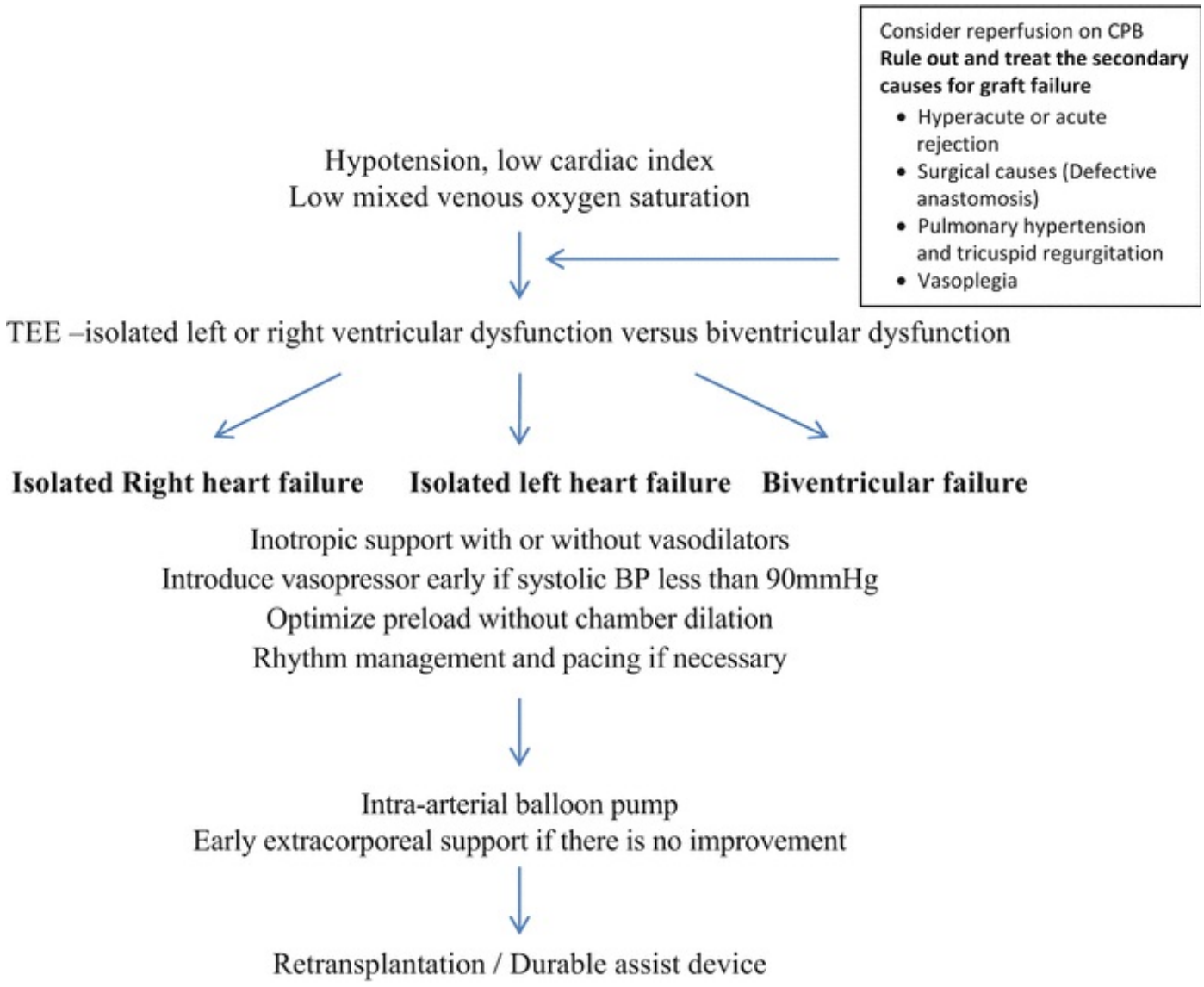

Fig. 13.3 Systematic approach to diagnosis and management of primary graft dysfunction

Vasoplegia is defined as a vasodilatory state resulting in resistant hypotension, metabolic acidosis and low systemic vascular resistance. In a cohort of 311 patients, Patarroyo et al. reported 11 % incidence of vasoplegia after OHT and identified high

body mass index, long CPB time, redo sternotomy, mechanical circulatory support, preoperative aspirin use and thyroid disease as possible risk factors for the development of vasoplegia [129]. Vasoplegia in the setting of PHT is a challenging clinical situation. Vasopressors used to treat vasodilation can have variable effect on pulmonary vasculature and can subsequently lead to or exacerbate RV failure. MCS is indicated if resistant vasoplegia is associated with severe graft dysfunction because the possibility of immediate recovery of graft function is remote in this situation.

Tricuspid regurgitation (TR) early after HT is relatively common [130] and numerous risk factors are described for the development of significant TR (Table 13.21). Recipients with more than mild TR immediately after HT are reported to have decreased long-term survival [131]. Even though tricuspid annuloplasty has been advocated by some authors [132], its utility should be individualized depending on the identifiable etiology, hemodynamic deterioration from TR and potential reversibility of functional TR . Measures such as avoiding volume overload of failing RV and treatment of PHT should be instituted perioperatively to decrease the severity of TR. TEE plays a vital role in making this decision by identifying significant TR and change in RV geometry secondary to failure. Late development of TR can be prevented by limiting the number of endomyocardial biopsies (EMB) and developing effective noninvasive methods to identify rejection episodes.

Hyperacute rejection is an antibody mediated severe immunological response observed immediate reperfusion of a donor organ in recipients with high titers of donor specific antibodies. This process was first described in rapid graft destruction after xenotransplantation [133]. Even though an arbitrary period of first 24 h of reperfusion has been used to diagnose hyperacute rejection, caution should be exercised especially when induction therapy is used delaying the response into the perioperative period [134]. Large titers of preformed antibodies can fix the complement on binding to endothelial antigens of the graft and result in inflammatory changes with diffuse thrombosis and tissue necrosis. Hyperacute rejection is associated with high mortality and fortunately rare in the modern era of transplantation. Current practice of transplantation relies on identifying allosensitized recipients and preventing hyperacute rejection by accepting donors with a negative prospective cross match, or those with defined acceptable antigens.

Acute rejection can be either an antibody or cellular mediated immunological reaction against the graft during the postoperative course. Acute cellular rejection (ACR) is more common than antibody mediated rejection (AMR) and is differentiated by histopathological appearance. Clinical presentation of rejection is vague and ill-defined with variable hemodynamic compromise. Furthermore early rejection in many patients is asymptomatic resulting in difficult clinical decision-making. Risk of rejection is highest in the first 6 months and, therefore, surveillance EMBs are performed more frequently during this period. Rejection should be ruled out if primary graft dysfunction

shows no signs of resolution on supportive treatment for 2–3 days and also unexplained hemodynamic compromise during the early postoperative course should raise the suspicion of rejection. Multidisciplinary team coordination is essential in patients with severe hemodynamic compromise to arrive at a diagnosis and make necessary changes in the immunosuppressive regimen while managing life sustaining therapies. MCS is instituted in severe life-threatening rejection, and a decision on durable assist device is made if the antirejection treatment does not improve the graft function. Retransplantation in these situations carries very high mortality risk and is not considered as an option.

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14. Postoperative Care of Heart Transplant Patients

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Early Postoperative Care of Heart Transplant Patients

In 2010, the International Society for Heart and Lung Transplantation (ISHLT) published evidence-based guidelines regarding the postoperative care of heart transplant recipients [1]. Whilst comprehensive, most recommendations within the guidelines are necessarily based on expert consensus rather than large randomised controlled trials, and significant variability still exists between centres in routine protocols and postoperative management.

Routine Care

Early postoperative care of heart transplant recipients occurs in the intensive care unit (ICU), enabling continuous and invasive monitoring, stabilisation of organ function, optimisation of graft support, and timely identification and management of complications.

On arrival to the ICU from the operating theatre, a structured handover from the

operating theatre team to the intensive care team takes place. This includes details of recipient history and co-morbidities, relevant donor and organ history, intraoperative course, and duration of donor organ ischemia, along with current inotrope and immunosuppressive therapy. Ideally, patients are assigned to a single-bedded room; however, this is not always practicable and is not essential. Strict aseptic techniques and hygiene by staff and visitors, however, are essential at all times. Patients typically arrive sedated, mechanically ventilated, with multiple invasive lines and monitors, temporary epicardial pacing, and multiple drug infusions in situ. Following structured handover, monitoring is transferred from the patient's transport monitors to the ICU monitors.

Monitoring

Routine monitoring includes electrocardiography (ECG), invasive arterial blood pressure, and monitoring of right atrial pressure (RAP) or central venous pressure (CVP), with intermittent or continuous monitoring of left atrial pressure (LAP) or pulmonary capillary wedge pressure (PCWP), cardiac output (CO), and cardiac index (CI). Continuous monitoring of arterial oxygen saturation using pulse oximetry is also routine, with intermittent arterial blood gas (ABG) analysis confirming arterial oxygen saturations. Urine output is measured continuously via urinary catheter. A 12-lead ECG and chest X-ray (CXR) are performed on arrival in the ICU—enabling confirmation of heart rate and rhythm, and correct positioning of the endotracheal tube, chest drains, and invasive monitoring lines. Conduction abnormalities are common after heart transplantation—with one study reporting an abnormal initial ECG in 73 % of patients post-heart transplantation [2]. The ECG may also display two p waves—one from the new graft and the other from residual native atrial tissue. This is a normal finding in orthotopic heart transplantation using the atrial anastomosis technique.

Transesophageal echocardiography (TEE) is recommended for assessment of hemodynamic instability, and allows rapid diagnosis of common postoperative problems such as hypovolemia, vasoplegia, left or right ventricular dysfunction, or cardiac tamponade. TEE is also useful in assessing response to subsequent therapy. It is important to note that moderate sized pericardial collections may be present without cardiac tamponade, due to the relatively small size of the new donor heart in comparison with the large pericardial sac in most recipients—which allows relatively little cardiac compression for a moderate to large volume of blood. However, the transplanted heart tolerates compression poorly, so clinical tamponade can occur quickly once enough blood has pooled in the pericardium to cause constriction. Table 14.1 summarises the TEE findings in each of the common causes of early postoperative hemodynamic instability.

Table 14.1 TEE findings in causes of early postoperative hemodynamic instability

Cause	End diastolic area	End systolic area	Contractility	Other findings
Hypovolaemia	↓↓	↓	Normal	
Vasoplegia	Normal	↓↓	Normal	
LV dysfunction	Normal or ↑	↑	↓↓	If severe, spontaneous echo contrast in LV cavity
RV dysfunction	Normal or ↑	↑	↓↓	Tricuspid regurgitation Abnormal septal motion
Tamponade	↓	↓↓	Normal or hyperdynamic	Pericardial collection Distended vena cavae Pseudohypertrophy RV diastolic collapse Right atrial (RA) or left atrial (LA) systolic collapse Restrictive transmitral and pulmonary venous patterns on pulsed wave (PW) Doppler Respiratory variation in transmitral flow velocities (>25 %)

Laboratory Investigations

Routine laboratory investigations performed on arrival in the ICU include ABG, mixed venous oxygen saturation (SvO_2), full blood count (FBC), serum electrolytes, creatinine and liver function tests, and coagulation studies including activated partial thromboplastin time (aPTT), prothrombin time (PT), fibrinogen, platelet count, activated clotting time (ACT), and thromboelastography (TEG). Troponin levels are initially measured on the first postoperative day. The frequency of ongoing monitoring of these parameters varies, but occurs at least every 6 h for ABG and SvO_2, and daily for other parameters in stable patients; with more frequent measurement in patients with organ dysfunction or bleeding. Immunosuppressant drugs, such as cyclosporine and tacrolimus, have levels measured daily, and drug doses adjusted accordingly.

Hemodynamic Management

Optimal hemodynamic parameters include a mean arterial blood pressure (MAP) ≥65 mmHg, a CVP ≤12 mmHg, and PCWP or LAP ≤12–14 mmHg, CI ≥2.5 L/min/m^2, with an SvO_2 of ≥65 %. However, in the early postoperative period, increased atrial pressures (CVP 12–15 mmHg and PCWP 14–18 mmHg) may be necessary due to graft dysfunction [3].

Vasoactive drugs are usually required to achieve and maintain optimal hemodynamics in the early postoperative period (Table 14.2). Ideally, continuous infusions of agents with chronotropic and inotropic effects are used to maintain CI, (e.g.,

epinephrine, dobutamine, dopamine, isoproterenol, and milrinone) whilst agents with vasoconstrictor effects (e.g., norepinephrine, epinephrine, phenylephrine, and vasopressin) are used to maintain target MAP. The lowest effective dose is recommended [1]. Agents with pulmonary vasodilator effects (e.g., milrinone, sodium nitroprusside, nitroglycerine, prostacyclin, prostaglandin E1, sildenafil, and inhaled nitric oxide) are useful in the management of right ventricular (RV) dysfunction and pulmonary hypertension [4–6]; however, intravenous agents are often associated with systemic hypotension. Inhaled nitric oxide has been consistently demonstrated to lower pulmonary vascular resistance (PVR), pulmonary artery pressure, and transpulmonary gradient, and increase CO following cardiac transplant, without significant systemic hypotension [4, 7]. Vasopressin and methylene blue are both effective in the treatment of catecholamine resistant vasoplegia following cardiopulmonary bypass (CPB) [8, 9]. Vasopressin in low dose (0.03–0.1 U/min) does not significantly reduce inotropy or CO, but may significantly increase systemic vascular resistance (i.e., MAP). Vasopressin may be particularly useful in patients with pulmonary hypertension and RV dysfunction as, unlike other vasopressors, it causes selective pulmonary vasodilatation at low doses [10].

Table 14.2 Properties of vasoactive drugs used following heart transplantation

Drug	Peripheral vasoconstriction	Peripheral vasodilatation	Chronotropic effect	Inotropic effect	Arrhythmia effect
Epinephrine	+++	+	++	++++	+++
Dobutamine	–	++	++	+++	+
Dopamine	++	+	++	+++	++
Isoproterenol	–	+++	++++	++++	++++
Milrinone	–	++	+	+++	++
Norepinephrine	++++	–	+	+++	+
Vasopressin	++++	–	–	–	–

Importantly, each vasoactive drug has different potential side effects, and no agent has been demonstrated alone to improve mortality after heart transplantation—thus, vasoactive therapy is usually adjusted to hemodynamic parameters and altered if unacceptable side effects, such as arrhythmias or metabolic disturbance, occur. Weaning of vasoactive supports usually occurs over a period of 3–5 days, even in stable patients, and is dictated by hemodynamic parameters, and end-organ function.

Patients are externally paced via temporary epicardial wires, at 90–110 beats/min. Moderate tachycardia is beneficial because graft ischemia and subsequent reperfusion cause significant diastolic dysfunction in the immediate postoperative period, with limited ability of the graft to increase stroke volume in response to increased preload. Thus, chronotropy is essential to maintain adequate cardiac output. It is preferential to

use atrial pacing if atrioventricular (AV) conduction is normal, but in the presence of AV conduction abnormalities, sequential pacing is used.

In the event of severe graft dysfunction, which is refractory to high inotrope and vasopressor support, the use of an intra-aortic balloon pump (IABP) or mechanical circulatory support (MCS) may be considered. The ISHLT guidelines recommend escalating support from pharmacotherapy, to IABP, to MCS [1]. The indications for, and use of MCS are discussed in Chap. 18.

Fluid therapy to maintain target CVP 5–12 mmHg ensures adequate cardiac filling and output, but avoids over distension of the left ventricle (LV) or RV. Blood and blood components therapy are commonly required to maintain target hemoglobin (usually >80 g/L) and normalise coagulation parameters. The ISHLT guidelines recommend blood and blood components are leucocyte-depleted, and cytomegalovirus (CMV)-negative if both donor and recipient are CMV negative [1]. Blood products must be appropriately matched, and in the case of non-ABO compatible transplant patients, blood and blood products must be compatible for both donor and recipient. Other fluids used may include albumin solutions (e.g., 4 % albumin) as colloid replacement, or crystalloid solutions (e.g., Plasmalyte®). Evidence indicates the use of synthetic starch colloid solutions is associated with increased renal injury and possibly increased mortality, and thus these solutions are avoided [11, 12]. Perioperative use of sodium chloride 0.9 % has been implicated in renal, gastrointestinal, and metabolic dysfunction [13–15], and thus, a balanced electrolyte solution is the most appropriate crystalloid solution.

Respiratory Management

Mechanical ventilation allows control of arterial oxygen and carbon dioxide levels, with target normal PaO_2 (>80 mmHg) and low-normal $PaCO_2$ (35–40 mmHg) levels avoiding increases in PVR. Commonly used ventilation modes are pressure control or volume control. Regardless of which mode is used, lung-protective strategies are recommended. Lung-protective strategies include:

1. Low tidal volume ventilation (4–8 mL/kg predicted body weight)

2. Use of positive end-expiratory pressure (PEEP) (usually 5–10 cmH_2O)

3. Plateau airway pressures ≤30 cmH_2O

4. Intermittent recruitment manoeuvres

Recruitment manoeuvres reduce ventilation-perfusion mismatch, helping to minimise

increases in PVR by optimising gas exchange, but also by optimising lung mechanics. The use of lung-protective ventilation may reduce ventilator-associated lung injury (VALI), and reduce morbidity and mortality in postoperative and critically ill patients [16, 17]. It is important to note that high levels of PEEP may raise intrathoracic pressure significantly, and increase PVR, and RV afterload. PEEP levels should be carefully adjusted to avoid deleterious effects on CO.

Once patients are stable and receiving low levels of inotrope and ventilator support, with no excess bleeding, weaning and progress to extubation can occur. A small number of patients will not be able to routinely progress and wean, due to ongoing hemodynamic, respiratory, metabolic, or neurologic dysfunction. In those receiving ongoing mechanical ventilation, ventilator-associated pneumonia (VAP) is a major morbidity risk. VAP prevention strategies include: [18]

1. Regular surveillance for VAP (CXR, microbiology samples of sputum and airway secretions)

2. Strict adherence to hand hygiene protocols

3. Nursing patient in a semi-recumbent position (30–45°)

4. Regular antiseptic (e.g., chlorhexidine) mouthwashes

5. In-line or subglottic suctioning of endotracheal tube

6. Maintain endotracheal cuff pressure >20 cmH_2O

7. Avoidance of proton-pump inhibitor drugs in patients not at high risk of ulceration or gastritis

8. Daily review of sedation ± sedation reduction or breaks

9. Asepsis in respiratory equipment and cares

For patients requiring prolonged mechanical ventilation and weaning, percutaneous tracheostomy is usually performed.

Renal and Metabolic Management

In cardiac surgery, acute kidney injury (AKI) occurs in approximately 20–30 % of patients [19, 20], with 1–2 % of patients requiring renal replacement therapy (RRT) [21]. AKI following heart transplantation is less well studied and reported, with reported rates between 5 and 30 % [22–24], and RRT in 5–15 % of patients [22, 24, 25]. Risk factors for post-heart transplant AKI include previous cardiac surgery, length of ischemic time, blood transfusion, and degree of troponin release [22]. AKI is independently associated with increased mortality [22, 25, 26].

Strategies to prevent AKI include:

1. Intraoperative avoidance of anaemia and blood transfusion (e.g., cell salvage, meticulous surgical technique, consideration of small CPB circuits)

2. Careful postoperative monitoring of urine output and creatinine

3. Optimisation of hemodynamic and respiratory parameters—with particular attention to volume status and perfusion pressures

4. Avoidance of nephrotoxins

5. Immunosuppression adjustment in the presence of preoperative renal dysfunction, early oliguria, or creatinine increase (e.g., delayed initiation of calcineurin inhibitors).

Several drugs have been studied as preventative agents for AKI, including dopamine, frusemide, nesiritide (B-type natriuretic peptide), fenoldopam, diltiazem, *N*-acetylcysteine, atrial natriuretic peptide, and corticosteroids. Fenoldopam, atrial natriuretic peptide, and nesiritide may have some efficacy; however, studies are small and no large randomised controlled trials exist to support their use currently [27].

It is common for heart transplant patients to have intravascular fluid overload following transplantation, due to fluid administration, effects of corticosteroids and the stress response to surgery, and renal dysfunction. Increased intravascular fluid can cause worsened RV dysfunction and tricuspid regurgitation (TR). Loop diuretics are used to initiate diuresis and improve fluid balance, as bolus or infusion, and may be combined with thiazide diuretics or aldosterone antagonists. For patients with early oliguria, anuria, or other indications (e.g., hyperkalaemia, acidemia), RRT may be necessary, and should be initiated early to avoid worsening RV dysfunction.

Abnormalities of serum electrolytes, especially sodium, potassium, and magnesium, are common, with hypokalaemia, hyponatraemia, and hypomagnesaemia due to diuretic therapy, fluid therapy, or nutritional deficit, and hyperkalaemia due to renal dysfunction.

Hypocalcaemia can occur with large volume blood product transfusion. It is important to monitor serum electrolytes regularly and supplement as necessary. The optimal serum potassium level in the immediate postoperative period is usually high-normal (e.g., 4.5–5.0 mmol/L).

Infection Control

Heart transplant patients are at increased risk of nosocomial and opportunistic infections, due to the combination of major surgery, invasive lines and monitors, immunosuppression, and, often, preoperative debilitation. Patients are ideally nursed in a single room, with strict hand hygiene maintained by healthcare workers and visitors. Maintaining asepsis during procedures and access of invasive lines is mandatory. Early removal of tubes, lines, drains, and catheters minimises the risk of infection. Blood glucose levels should be controlled to within normal limits. Prophylactic antibiotics are commenced prior to transplant, with selection based on prevalent skin flora (especially *Staphylococcus* species) and sensitivities [1]. Cephalosporins are most frequently used as prophylaxis. In patients with chronically infected pacemakers or ventricular assist devices in situ, or if bacterial infection was present in the donor, antibiotic therapy is based on microbiologic culture and sensitivities. Anti-viral prophylaxis (against CMV) is recommended, with therapy (CMV immunoglobulin, ganciclovir) based on both donor and recipient CMV status [28, 29]. Oral anti-fungal prophylaxis (nystatin drops or clotrimazole lozenges) is commenced following extubation. Anti-protozoal (*Pneumocystis jirovecii* and *Toxoplasma gondii*) prophylaxis is also commenced in the early postoperative period. Most commonly, trimethoprim/sulfamethoxazole is used. Infection control is further discussed in Chap. 4.

Immunosuppression

Immunosuppression usually consists of triple therapy with:

1. A calcineurin inhibitor (CNI) (e.g., tacrolimus, cyclosporin)

2. A corticosteroid (e.g., methylprednisolone, prednisone)

3. And an antiproliferative agent (e.g., azathioprine, mycophenolate mofetil, sirolimus, everolimus)

CNI-based therapy remains the cornerstone in adult heart transplant immunosuppression protocols. Tacrolimus is now the preferred CNI used worldwide—used in 81 % of heart transplants in 2012 [30]. Whilst corticosteroids are used in the majority of recipients, corticosteroid weaning or avoidance may be accomplished in

patients with significant side effects and without recent rejection episodes [31]. Antiproliferative agents reduce the onset and progression of cardiac allograft vasculopathy (CAV), and are therefore recommended [1, 32].

Induction therapy with interleukin-2 receptor (IL-2R) antagonists, antithymocyte globulin, polyclonal or monoclonal antibody preparations may be used in patients at high risk of rejection or renal dysfunction, and can be used to delay or avoid the use of a CNI or corticosteroid [33]. The ISHLT Thirtieth Official Adult Heart Transplant Report notes that induction therapy use is decreasing, with a 47 % overall use in the first 6 months of 2012 [30].

Long-term immunosuppression is associated with side effects including infection, renal dysfunction, and malignancy. These are further discussed later in this chapter.

Statins are associated with reduced rejection, malignancy, and mortality, and are recommended to commence 1–2 weeks after transplantation, regardless of cholesterol levels [1, 34, 35]. Low statin doses are initially used, due to the potential for interactions with CNIs and subsequent toxicity.

Nutrition

Optimisation of nutrition is important, as patients are often debilitated prior to transplant, and in a catabolic state post-transplant. Usual targets for caloric intake are 25–30 kcal/kg/day, with enteral nutrition via nasogastric tube commenced early in the postoperative period. If enteral nutrition is not possible, parenteral nutrition is commenced. Essential vitamins and minerals are also administered. Hyperglycaemia is common following heart transplant, due to the surgical stress response and administration of corticosteroids. Insulin is administered by infusion to normalise blood glucose levels.

Early Complications

In the early postoperative period, the most important complications are bleeding and coagulopathy, primary graft failure and hyperacute rejection, tricuspid regurgitation, infection, and arrhythmias.

Bleeding and Coagulopathy

Bleeding is common immediately following heart transplantation. Contributing factors include preoperative anticoagulation with warfarin, CPB effects on the coagulation system, hypothermia during surgery, pre-existing hepatic dysfunction due to RV failure, and previous cardiac surgery or presence of a ventricular assist device. Patients with continuous flow ventricular assist devices have a high incidence (nearing 100 % after 1 month) of acquired von Willebrand disease [36], and increased bleeding associated

with this. Preoperatively, warfarin anticoagulation is reversed with low dose vitamin K, and a combination of fresh frozen plasma (FFP) and factor concentrates, targeting a PT <1.5 [1]. Coagulation studies are performed on arrival in intensive care, and include aPTT, PT, fibrinogen, platelet count, ACT, and thromboelastography (TEG). Coagulopathy is corrected with targeted blood product transfusion (e.g., FFP, platelets, cryoprecipitate) as indicated by coagulation results—aiming for near-normal coagulation parameters. Recombinant factor VIIa may be considered in persistent excessive bleeding, but has not been well studied in heart transplantation. Residual heparin effect is corrected with protamine. Tranexamic acid may be used if excess fibrinolysis is present. Hypothermia can be contributory to coagulopathy, and care should be taken to restore normothermia. Coagulation testing is repeated following transfusion of blood products, or in the presence of ongoing bleeding.

Cardiac tamponade may present after excess bleeding, typically with progressive hypotension, rising CVP, and low CO. Tachycardia may not be present, partially due to denervation of the donor graft. The incidences of excess bleeding and cardiac tamponade are not well reported, but in one study of 88 heart transplant patients, 31 (35 %) developed pericardial collections in the immediate postoperative period, and 3 (3.4 %) developed tamponade requiring intervention [37].

Primary Graft Failure

Primary graft failure (PGF) is the leading cause of early mortality after heart transplant, accounting for 36 % of deaths during the first 30 days post-transplant in the years 2002–2012 in the ISHLT Registry [30]. PGF presents as severe ventricular dysfunction (usually predominantly RV dysfunction, however predominant LV dysfunction or biventricular failure also occur) in the immediate post-bypass period. Aetiology of PGF is multifactorial. The graft has often suffered insult due to prolonged ischemic time, limited myocardial protection, and manipulation during transport and surgery. Further insult occurs due to reperfusion injury. The graft is removed from a donor with normal PVR, and often transplanted to a recipient with chronically elevated PVR. Additionally, acute elevations in PVR are common during surgery and anaesthesia due to raised intrathoracic pressure with mechanical ventilation, atelectasis, ventilation-perfusion mismatch, acidemia, or hypoxemia. The systemic inflammatory response of the recipient is likely to contribute further insult to the graft. The process of brain death is also likely to contribute—it is well recognised that brain death causes impaired myocardial contractility [38]. Last, size mismatch between donor and recipient may result in acute increases in workload for the donor graft. Ventricular dysfunction is therefore promoted by many factors, and RV dysfunction is particularly common due to the relative inability for the RV to compensate for increases in afterload, and due to the preload dependence of the RV. Risk factors for PGF are summarised in Table 14.3.

Table 14.3 Risk factors for primary graft failure

Donor factors	Surgical factors	Recipient factors
Age	Ischemic time	Age
Ventricular dysfunction on echo	Donor to recipient weight mismatch	Preoperative inotrope support
High-dose inotrope support	Female donor to male recipient	Preoperative mechanical ventilation
Cause of brain death	Concomitant lung retrieval	Preoperative mechanical support
		Pulmonary hypertension
		Obesity
		Diabetes mellitus

Adapted from Iyer et al. [38]

Signs of acute RV failure are hypotension with rising CVP, and falling PAP. RV failure can be difficult to distinguish from other causes of hemodynamic instability (e.g., tamponade), therefore TEE use to diagnose and assess response to therapy is recommended. LV failure similarly presents as hypotension or low cardiac output, with normal or elevated LA pressures.

Management of PGF is challenging—despite maximal supportive therapies, the mortality rate for PGF remains substantial (close to 20 % in a 2011 retrospective single centre study of patients requiring MCS post-transplant) [39]. Management is with inotropes and pulmonary vasodilators, as discussed earlier, and measures to minimise PVR. Levosimendan has also been used in this setting, with reported success [40]. If medical therapy is inadequate, MCS is recommended. MCS in this setting is further discussed in Chap. 18.

Hyperacute rejection is an uncommon cause of early, severe primary graft dysfunction, and is an antibody-mediated immune response against the allograft. Antibody production initially occurs in the recipient due to prior exposure to alloantigens—most commonly HLA or ABO antigens—termed allosensitisation. Risk factors for allosensitisation are previous blood transfusion, mechanical circulatory support, previous pregnancy, and previous transplant. Repeat antigen exposure occurs with cardiac transplantation and triggers the immune response, typified by a severe inflammatory reaction in the myocardium, with complement, macrophage, and immunoglobulin deposition in capillaries and endothelial swelling. Clinical symptoms and signs are of primary graft failure. Diagnosis is made by clinical presentation supported with intraoperative endomyocardial biopsy. Treatment is both supportive—including mechanical support, if indicated—and specific, with high dose corticosteroids, plasmapheresis, intravenous immunoglobulin (IVIG), or cytolytic immunosuppressive therapy [1]. Retransplantation may be considered but is associated with high mortality. Therapy should be commenced without delay.

Coronary artery disease with ischemia may also cause PGF, and where ECG or TEE

findings suggest ischemia, early assessment with coronary angiography is appropriate. Consideration of percutaneous or surgical revascularisation is appropriate in the presence of graft coronary artery disease.

Tricuspid Regurgitation

TR occurs in up to 84 % of patients after heart transplant, and is significant in its association with increased morbidity and mortality [41]. TR may be functional or anatomical. Functional TR is due to dilatation or distortion of the RV and tricuspid annulus, resulting in poor leaflet coaptation and a central TR jet; whilst anatomic TR is due to pathology of the leaflets or chordae, such as rupture or flail (e.g., due to trauma during endomyocardial biopsies) and often produces an eccentric jet of TR. Management of functional TR includes inotropic support, treatment of RV dysfunction and measures to lower PVR, along with diuretic therapy to optimise intravascular volume. If significant TR (worse than mild) is present intraoperatively, consideration of surgical management with a tricuspid annuloplasty may be warranted [1, 42]. Anatomical TR may also require surgical intervention if significant.

Arrhythmias

Arrhythmias are common following heart transplantation, occurring in approximately 50–70 % of recipients [2, 43]. The most common arrhythmias are junctional bradycardia, sinus bradycardia, atrial flutter, atrial fibrillation, and other supraventricular tachycardias. Ventricular arrhythmias are uncommon. Multiple factors contribute to the development of arrhythmias.

The surgical procedure causes cardiac denervation, cardiac ischemia, and tissue trauma (particularly atrial), all of which affect the conduction system, and in particular, the sinoatrial (SA) node. Two different surgical techniques for heart transplant are possible—the atrial anastomosis method, or the bicaval anastomosis method. The atrial method anastomoses native left and right atrial remnant cuffs to graft atria (with consequent enlargement of both atria). The bicaval method anastomoses native vena cavae to graft vena cavae, and anastomoses graft left atrium to a smaller native remnant cuff of left atrial tissue, containing the pulmonary vein insertions. The bicaval method therefore offers better preservation of graft anatomy. The bicaval method is associated with a reduced incidence of postoperative atrial arrhythmias, and also a reduced incidence of left atrial and systemic thrombosis [44, 45].

Autonomic denervation of the heart results in loss of parasympathetic innervation to the SA node, causing increased SA node automaticity, an increased resting heart rate (usually 90–110 beats/min), and an inability to rapidly adjust heart rate. Loss of sympathetic innervation to the SA node diminishes responsiveness to stress and exercise, resulting in a decreased maximal heart rate. Over time, partial sympathetic re-

innervation occurs, which may further contribute to arrhythmias by causing regional alterations in coronary blood flow and subsequent ischemia.

Acute rejection or cardiac allograft vasculopathy (CAV) causing graft failure, with reduced compliance, chamber enlargement, and patchy diffuse disturbance of the myocardium may cause tachy- or brady-arrhythmias [46]. In a study of 729 patients following heart transplantation, the presence of atrial fibrillation after the immediate postoperative period was consistently associated with rejection or CAV [47]. In another study of 85 patients, late atrial fibrillation was associated with rejection and increased mortality [43]. Clinical symptoms or signs consistent with rejection or graft failure, or onset of atrial fibrillation after 2 weeks post-transplantation, or any persistent tachyarrhythmia is an indication to screen for rejection and CAV and consider increased immunosuppression [1, 47]. Less common causes of arrhythmia include systemic sepsis, trauma due to endomyocardial biopsies, or drug effect [46].

Tachyarrhythmias are managed with antiarrhythmic pharmacotherapy (aiming for rate control) and electrical cardioversion, and if drug resistant or persistent, may be managed with catheter ablation. It is important to note that due to cardiac denervation, several drugs have reduced efficacy in arrhythmia control following heart transplant—including atropine and digoxin, whilst amiodarone may display exaggerated effects. Bradyarrhythmias (most commonly junctional bradycardia) usually resolve over time, and are managed with chronotropic pharmacotherapy and temporary epicardial pacing, however if persistent (>3 weeks post-transplant) or late onset, a permanent pacemaker insertion may be required (4–17 % of patients) [1, 46].

Infection

Early infections are most commonly bacterial, with a high incidence of gram-negative organisms in nosocomial sepsis (e.g., *Pseudomonas* spp.), with common sites including lung, wound, and bloodstream. Careful surveillance with regular specimen culture and clinical review is crucial in the early identification of infection. As a consequence of critical illness, immunosupression, and presence of other therapies (e.g., renal replacement therapy), usual signs of infection (e.g., fever, leucocytosis) may be absent. Viral and fungal (*Aspergillus*) infections usually occur after several weeks to months.

Gastrointestinal Complications

Gastrointestinal (GI) side effects due to immunosuppression are relatively common and include nausea, vomiting, and diarrhoea. These symptoms may, however, portend more serious complications such as CMV infection, systemic sepsis, or uncommon GI complications such as bleeding, pancreatitis, cholecystitis, or mesenteric ischemia. GI complications are often difficult to detect and diagnose, and a high index of suspicion is required, with early investigation of non-specific symptoms and signs, to identify

significant pathology.

Long-Term Care of Heart Transplant Patients

Routine Recovery

Multidisciplinary Care and Rehabilitation

A multidisciplinary approach is recommended to enable all aspects of the heart transplant recipient's care to be optimised, with regular scheduled meetings of the heart transplant team enabling planning at all stages—prior to listing for transplant, through transplantation, and postoperatively through long term. The multidisciplinary team includes cardiac transplant physicians, cardiac surgeons, critical care specialists, pharmacists, dieticians, social workers, and psychiatry specialists [1]. Daily multidisciplinary team rounds may reduce hospital length of stay, and reduce subsequent readmission rates [48].

Functional Status

Heart transplantation results in substantial improvements in functional status and quality of life for patients, as well as survival. ISHLT Registry data shows that at 3 years after transplant, nearly 90 % of survivors have functional status capable of normal activity [30].

Complications

Acute Rejection

Acute rejection refers to the normal immune response of the recipient to the donor heart, recognised as non-self. Acute rejection is usually cell-mediated, largely by T lymphocytes, but may also occur due to antibody-mediated responses, similar to hyperacute rejection [49]. Acute rejection is difficult to detect and diagnose, and may occur without clinical symptoms and signs, or present with non-specific fever, weight gain, or malaise. Acute rejection, however, may cause abnormal ECG findings, arrhythmias, hypotension, or cardiac failure [3]. The severity of rejection does not reliably correlate with clinical presentation. Acute rejection accounts for 11 % of deaths in years 1–3 following heart transplant [30]. Risk factors for acute rejection include grafts from female and younger donors.

Surveillance for rejection is performed with periodic endomyocardial biopsy during the first 6–12 months post-transplant. Biopsies are recommended weekly during biopsies 1–5, fortnightly for biopsies 6–8, every 3 weeks for biopsies 9–10, monthly for biopsies 11–13, and every 6 weeks following until 1 year post-transplant [1].

Intermediate-term surveillance (e.g., 2–5 years post-transplant) is recommended for recipients at increased risk of late rejection [1]. Two non-invasive techniques are recommended for monitoring of acute rejection, in specific recipients. Gene expression profiling used in low risk patients may exclude acute rejection, whilst intramyocardial ECGs in centres with experience in ventricular evoked potentials (VERs) monitoring may also be used for rejection surveillance [1].

Several other non-invasive screening techniques have been investigated, including monitoring of b-type natriuretic peptide (BNP), troponin I or T, or C-reactive protein (CRP) levels, systemic inflammatory marker level monitoring, magnetic resonance imaging (MRI), and echocardiography, and ECG parameter monitoring. Currently none of these techniques are highly specific and sensitive, and are therefore not recommended for routine acute rejection surveillance [1].

Treatment of severe acute rejection is with high-dose corticosteroid therapy (e.g., methylprednisolone or prednisone), antibiotic prophylaxis, and supportive care as indicated. Cytolytic immunosuppressive therapy may be used in patients with hemodynamic instability [1]. Repeat endomyocardial biopsy is recommended following completion of anti-rejection therapy [1]. Serial assessment of cardiac function with echocardiography is appropriate, and used to assess response to anti-rejection therapy. If rejection is mild and asymptomatic, monitoring alone may be appropriate [49].

Cardiac Allograft Vasculopathy

CAV is an accelerated fibroproliferative process involving the coronary arteries of cardiac allografts. Depending on how it is diagnosed, CAV occurs in approximately 30 % of heart transplant recipients by 5 years and 50 % by 10 years [50]. CAV is one of the leading causes of death beyond the first year following transplantation and remains so indefinitely for the life of the recipient [51, 52].

CAV is predominantly an immune mediated process involving T lymphocytes resulting in chronic vascular inflammation and endothelial dysfunction. There is proliferation of smooth muscle cells, accumulation of lipid-laden foam cells, and vascular fibrosis [50, 53]. In contrast to atherosclerotic coronary artery disease, which is typically focal and eccentric, CAV tends to cause diffuse, circumferential intimal thickening. However, CAV can co-exist with atherosclerotic coronary artery disease making a clear distinction between the two conditions difficult. Risk factors for CAV include the number of HLA-DR mismatches, older donor age, male donor, donor co-morbidities (hypertension, diabetes), and younger recipient age [52].

CAV is difficult to diagnose clinically due to absent or atypical features of myocardial ischemia secondary to allograft denervation. In one study, of 22 transplant recipients having 25 myocardial infarctions, only five episodes of chest or arm pain occurred and only seven infarcts were associated with typical Q-waves on the ECG.

However, ten infarctions were associated with heart failure or cardiogenic shock, and seven patients died during the acute phase of infarction. Frequent manifestations of CAV include allograft dysfunction (heart failure), silent infarction, new late-onset cardiac arrhythmias, and sudden death. Thus, early diagnosis of CAV by surveillance testing is important. Useful methods of diagnosing CAV are dobutamine stress echocardiography, stress radionuclide myocardial perfusion imaging, coronary angiography, and intravascular ultrasound (IVUS) [50]. Of these tests, IVUS is the most sensitive [50], but is not available in all centres. The IHSLT recommend annual or biannual coronary angiography, with or without IVUS, to assess the development of CAV [1].

Recommended preventative strategies include strict control of coronary artery disease risk factors (hypertension, dyslipidemia, glucose control, smoking cessation, obesity), and statin therapy in all patients, irrespective of lipid levels [1]. Once diagnosed, alterations to the immunosupression regimen can slow or possibly reverse the progression of CAV [54, 55], in particular substitution of a proliferation signal inhibitor drug such as everolimus or sirolimus in place of MMF or azathioprine [1]. For discrete flow limiting lesions, percutaneous coronary intervention utilising drug eluting stents is appropriate [1].

Chronic Kidney Disease

Chronic kidney disease (CKD) is common following heart transplant and is a strong predictor of adverse outcome. ISHLT registry data indicate that severe CKD (creatinine >2.5 mg/dL [>220 μmol/L], dialysis, or kidney transplant) occurred in 18 % of patients 5 years post-transplant during the period 2001–2008, which is less than the 27 % incidence reported for the period 1994–2000 [52]. This finding suggests that, while it remains a serious postoperative problem, CKD may be decreasing over time.

The aetiology of CKD is typically multifactorial and includes preoperative renal dysfunction, perioperative AKI, systemic atherosclerosis, and, most importantly, drug-induced nephropathy [56]. In particular, renal dysfunction is an important side effect of the CNIs (cyclosporine and tacrolimus), which are considered essential post-transplant immunosuppressive drugs. While the proliferation signal inhibitor drugs (everolimus or sirolimus) are not themselves nephrotoxic, they do potentiate the nephrotoxic effects of CNIs when used with standard doses of CNIs [56].

Interventions to slow the progression of CKD include reducing the exposure of CNIs to the lowest level compatible with effective immunosupression, strict glucose control, and effective treatment of hypertension with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) [1].

Hypertension, Diabetes, and Dyslipidemia

Hypertension , impaired glucose tolerance, and dyslipidemia are all common in heart

transplant recipients. ISHLT registry data indicate incidences at 5 years post-transplant of 90 % for hypertension, 39 % for diabetes, and 91 % for dyslipidemia [52]. These conditions may be pre-existing or be caused or exacerbated by immunosuppressive drugs. For instance, impaired glucose tolerance is associated with corticosteroids, MMF, and sirolimus. Dyslipidemia is associated with MMF, sirolimus, everolimus, and CNIs. Hypertension occurs with corticosteroids and CNIs.

As these conditions exacerbate CAV and CKD, strict pharmacologic control of blood pressure, glucose, and lipids is essential. While there are no transplant-specific recommendations for treating these conditions, as noted above, statins are appropriate for all patients and ACEIs or ARBs are effective for both treating hypertension and slowing the development of CKD.

Malignancy

As with other solid organ transplants, the risk of malignancy is increased in heart transplant recipients as a consequence of long-term immunosupression. Malignancy is rare in the first year following transplantation but relatively common thereafter, being responsible for approximately 20–25 % of all deaths on an ongoing basis [52]. Skin cancers are the most frequent form of malignancy, constituting 50 % of post-transplant cancers [57]. The cumulative incidence of skin cancer following heart transplantation is approximately 10 % at 5 years and 20 % at 10 years [52]. Most skin cancers are curable with appropriate surveillance and treatment. The next most common malignancies are lymphoma and lung cancer, each comprising approximately 10 % of post-transplant cancers [57]. Other cancers include prostate, liver, bladder, colon, and stomach, each constituting between 2 and 5 % of malignancies.

Risk factors for malignancy include previous transplant, an episode of treated rejection prior to first discharge, increased recipient age, and longer allograft ischemic time [52]. The incidence of post-transplant malignancy appears to be falling, with the rate 5 years post-transplant having reduced by 5 % between 2001 and 2010 [52]. Possible reasons for this lower incidence are reduced use of OKT3 for induction immunosupression, and increased use of antiviral prophylaxis with ganciclovir, which in addition to protecting against CMV infection may also help prevent virally mediated cancers such as lymphoma (associated with Epstein-Barr virus) and squamous cell cancers (associated with human papillomavirus) [57].

Close surveillance for skin cancer is appropriate; however, screening for breast, colon, and prostate cancer should be according to standard guidelines [1].

Bone Disease

Osteoporosis is a side effect of long-term corticosteroid therapy. Heart transplant recipients should receive calcium and vitamin D supplements prior to and following

transplantation. Bisphosphonates are recommended in addition to calcium and vitamin D to further reduce bone resorption. Regular muscle strengthening and weight bearing exercises should commence as soon as possible in the postoperative period, to preserve bone density and reduce the incidence of both falls and fractures [1].

Reproductive Health

Pregnancy is not precluded by heart transplantation; however, prior to pregnancy, consideration of current graft function, immunosuppression, and the risk of acute rejection and infection, is recommended [1]. During pregnancy, corticosteroids and CNIs should be continued, with closer monitoring of blood levels of CNIs, as the normal physiological changes of pregnancy can alter CNI pharmacokinetics [1]. MMF should be discontinued during pregnancy, as it has been associated with first trimester pregnancy loss and congenital malformations. Due to alterations in immunosupression therapy and the changes of pregnancy, frequent surveillance for rejection is recommended [1].

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Part IV
Special Considerations for Thoracic Transplantation

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15. Perioperative Management of Pulmonary Hypertension

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Keywords Pulmonary hypertension – Heart transplant – Lung transplant – Perioperative care – Anesthesia – Epidural block

Introduction

Pulmonary hypertension (PH) is a common ailment in heart transplant (HTX) and lung transplant (LTX) candidates. Appropriate perioperative management of elevated pulmonary artery pressure (PAP) is of paramount importance for a favorable outcome after thoracic organ transplantation. Multidisciplinary care involving PH experts, cardiologists, cardiac surgeons, anesthesiologists, and intensivists is crucial; anesthesiologists in particular should take a central role in this significant task [1–3]. This chapter reviews the classifications of PH, the physiology of right heart and lung interaction, therapeutic approaches designed for surgical patients with PH, and perioperative management of these critically ill patients presenting for HTX and LTX. Different classes of PH patients demonstrate variable and at times opposing responses to pharmacological interventions; therefore, it is essential to emphasize that perioperative management of PH patients should be tailored and carried out with consideration for the specific underlying pathophysiology of increased pulmonary vascular resistance (PVR) in each surgical candidate.

Definition of Pulmonary Hypertension

The pulmonary arterial bed is a low pressure, high flow system with a low resistance, measured as 40–120 dyn s/cm^5 or 0.9–1.4 Wood units (WU). PVR is a calculated parameter.

$$\text{PVR} = \frac{\text{Mean Pulmonary Arterial Pressure (MPAP)} - \text{Pulmonary Capillary Wedge Pressure (PCWP)}}{\text{Cardiac Output}}$$

PH is defined as a persistent increase in MPAP ≥ 25 mmHg, measured by right heart catheterization (RHC) at rest, coupled with PCWP ≤ 15 mmHg and PVR >240 dyn s/cm^5 or interchangeably >3 WU [4–8]. PH patients with left-sided heart disease and who frequently present with PCWP > 15 mmHg are the exception [9]. Classification of PH severity (mild, moderate, and severe) based on the three parameters of PVR, MPAP, and transpulmonary gradient [TPG = MPAP − PCWP] is shown in Table 15.1. In a large cohort study by Vakil et al. on data from the United Network for Organ Sharing (UNOS) database, PVR and TPG were well-correlated (r = 0.85) but the correlation of MPAP with PVR and TPG was only modest. More importantly, PVR and TPG were shown to provide more accurate information than MPAP on the degree of vascular resistance [4]. RHC is considered the gold standard in the diagnosis of PH [5, 6]. In addition to pulmonary artery systolic pressure (PASP), RHC provides information regarding left atrial pressure, PCWP, left ventricular end diastolic pressure, TPG, and PVR.

Table 15.1 Classification of pulmonary hypertension severity based on different definitions

Definition	None	Mild	Moderate	Severe
Pulmonary vascular resistance (Wood units)	<2.5	2.5–3.4	3.5–4.9	≥5.0
Transpulmonary gradient (mmHg)	<13	13–16	17–19	≥20
Mean pulmonary artery pressure (mmHg)	<25	25–34	35–44	≥45

Transthoracic echocardiography (TTE) has been validated as an important tool for screening and follow-up studies in conjunction with RHC for the assessment of PH patients [7]. It is important to note that TTE cannot be used interchangeably with RHC, the gold standard for definite PH diagnosis [5]. Right ventricular systolic pressure (RVSP) is measured by Doppler echocardiography using peak velocity of tricuspid regurgitation (TR) jet (Fig. 15.1). A simplified Bernoulli equation is utilized in the calculation of RVSP from TR velocity jet.

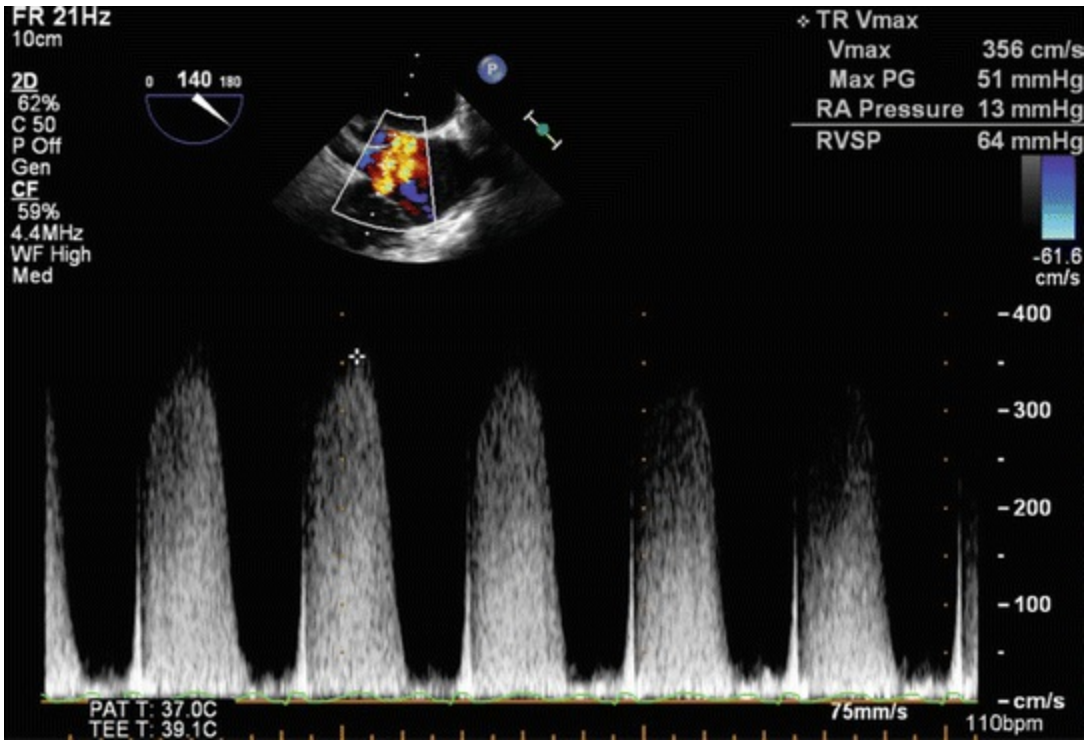

Fig. 15.1 Measurement of right ventricular (RV) systolic pressure from tricuspid regurgitation (TR) jet

$$\mathrm{RVSP} = 4V^2 + \mathrm{RAP}$$

V = Peak velocity of regurgitant jet across tricuspid valve

RAP = Right atrial pressure

The caveat is that the accuracy of echocardiographic estimation of RVSP is operator-dependent and limited by feasibility of obtaining reproducible TR jet velocities. In the absence of pulmonic valve stenosis and RV outflow obstruction, PASP is assumed to equate with RVSP. Additionally, TTE is a proven useful noninvasive guide in the evaluation of ventricular size and function, valvular abnormalities, and intra-cardiac shunts.

RAP and right ventricular end diastolic pressure can be quantified during RHC or noninvasively using echocardiography through measurement of inferior vena cava (IVC) diameter or IVC collapse index [8].

Pathophysiology and Classification of Pulmonary Hypertension

Chronic hypoxemia, inflammatory and vascular mediators, and increased shear forces secondary to pathological increases in cardiac output or venous back-pressure can result in impairment of endothelial nitric oxide (NO) synthase and cyclooxygenase activity. Decreased availability of endothelial-derived NO and prostacyclin (PGI_2) and

increased production of thromboxane A_2, endothelin-1 (ET-1), angiotensin-2, and superoxide radicals result in pulmonary vasoconstriction, vascular smooth muscle proliferation, and platelet aggregation. Endothelial damage along with platelet aggregation leads to in situ thrombosis, which ultimately culminates in the formation of plexiform lesions, irreversibly obliterating pulmonary arterioles [9–15].

Patients included in groups 1, 3, 4, and 5 in the World Health Organization (WHO) classification of PH, although of different etiologies, are all characterized by endothelial dysfunction in the pulmonary vasculature (Table 15.2). What ensues is vascular remodeling and histopathological abnormalities, which include intimal and adventitial proliferation, smooth muscle hypertrophy, fibrosis, and plexiform and thrombotic lesions in distal pulmonary arteries [16, 17]. The increase in PVR and elevation in PAP without an increase in PCWP is pathognomonic for patients in groups 1, 3, 4, and 5. Group 2 patients in the WHO PH classification (PH secondary to pulmonary venous hypertension) constitute the majority of PH patients. In post-capillary PH (class 2 WHO), prolonged, untreated elevation of left ventricular end diastolic pressure can result in passive backpressure in the pulmonary veins, which ultimately leads to raised PAP. Vasoconstriction ensues with time, culminating in vascular remodeling of pulmonary arterioles. In contrast to groups 1, 3, 4, and 5, group 2 PH patients may not demonstrate pathophysiologic changes evident in groups 1, 3, 4, and 5. Also, RHC reports for group 2 patients would indicate PCWP values greater than 15 mmHg. Obviously, there is a spectrum of clinical presentations in group 2 patients, evident by PVR in ranging from <240 to >240 dyn s/cm^5. This phenomenon correlates with degree of reversibility of PH. High output states constitute another important class of PH patients as PAP = Left atrial pressure + (Cardiac output × PVR)/80. Conversely, in the clinical setting of increased cardiac output caused by inotropes or increased blood volume, PVR will decrease via enrollment of open vessels in the pulmonary circulation [18]. Because of disparate underlying pathophysiology, medical management and perioperative care for group 2 patients fundamentally differ from those designed for group 1, 3, 4, and 5 patients.

Table 15.2 World Health Organization (WHO) updated clinical classification of pulmonary hypertension [8]

1.1. Idiopathic PAH
1.2. Heritable
1.2.1. BMPR2
1.2.2. ALK1, endoglin, SMAD9, CAV1, KCNK3
1.2.3. Unknown
1.3. Drug- and toxin-induced
1.4. Associated with
1.4.1. Connective tissue diseases

1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. Schistosomiasis
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1″. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension due to left heart disease
2.1. Left ventricular systolic dysfunction
2.2. Left ventricular diastolic dysfunction
2.3. Valvular disease
2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due to lung disease and/or hypoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitudes
3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1. Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3. Metabolic disorders: glycogen storage disease, Gaucher's disease, thyroid disorders
5.4. Others: tumor, obstruction, fibrosing mediastinitis, chronic renal failure

Pulmonary Hypertension and Outcome Studies in Cardiac and Noncardiac Surgery

A paucity of appropriately controlled studies involving surgical patients with PH, varied definitions of PH in case reports and case series, reliance on different methodologies (RHC versus echocardiography studies) for evaluation of PH, and inclusion of patients with varied underlying pathophysiology in these studies have hindered the publication of firm recommendations by clinicians and scientists [19].

While some differences in outcomes have been reported in the literature, PH clearly represents an important risk factor for perioperative morbidity and mortality. Most of these studies of PH patients presenting for noncardiac surgery point to an increased rate of postoperative respiratory failure, delayed tracheal extubation, hemodynamic

instability, arrhythmia, heart failure, sepsis, renal insufficiency, and longer intensive care unit (ICU) stay [1, 20–23]. Retrospective outcome studies on noncardiac surgery, although not useful guides for predicting outcomes after HTX and LTX, point to the importance of developing appropriate perioperative management strategies in this complex surgical population. In reviewing the literature on PH patients undergoing cardiac surgery, existing data points to increased morbidity and mortality. Deterioration of preexisting right ventricle (RV) failure has been identified as the leading cause of morbidity and death in this group of patients [24–28]. A relatively large cohort study published in 1999 included 2149 patients undergoing coronary bypass grafting. This study identified PH as an independent predictor of mortality (odds ratio 2.1, $P = 0.029$) [25].

Pulmonary Hypertension and Thoracic Organ Transplantation

RV function is the main focus in patients with preexisting PH undergoing HTX and LTX. In general, RV failure in ICU patients prognosticates higher morbidity and mortality. Low systemic blood pressure, hyponatremia, and increased levels of plasma brain natriuretic peptide, C-reactive protein, and serum creatinine are some negative prognostic factors for acute right heart failure in PH patients [29, 30]. Myocardial ischemia, endothelial dysfunction induced by endotoxemia, and pro-inflammatory cytokines such as tumor necrosis factor α have been implicated in the pathogenesis of RV dysfunction [31–33]. Studies investigating therapeutic approaches to isolated RV failure are scarce and mostly non-randomized. Of note, Haddad et al. reviewed the literature on RV failure in detail [34, 35].

Pulmonary Hypertension and Outcomes After Heart Transplantation

Although clinicians and scientists agree that preexisting PH prior to HTX portends an increased rate of morbidity and mortality, results of outcome studies are far from consistent and at times conflicting [36–46]. Tenderich et al. retrospectively assessed the long-term survival of 400 consecutive PH patients presenting for orthotopic HTX (OHTX). Enrolled patients were followed over 3.5 years. The authors concluded that post-cardiac transplantation 30-day mortality and cumulative 1- and 5-year survival rates were not adversely affected in PH patients (PVR ≥ 5 WU, TPG > 15 mmHg) compared to the control group [47].

Chang et al. conducted a single center cohort study on 172 HTX recipients (41.3 % of which were defined as having PH). Enrolled patients were followed for up to 15.1 years. The study concluded that mild to moderate preoperative PH was associated with the development of early but not late posttransplantation PH. Although

posttransplantation PH was not found to be consistently associated with increased mortality, a potentially worse prognosis was suggested. However, the other conclusion derived from this study indicated that greater than 50 % of first year mortality was attributable to cellular rejection rather than graft failure due to PH [28].

Klotz et al. conducted a prospective study of 217 OHTX recipients (168 patients with normal pulmonary pressure and 49 patients with reversible PH) over 10 years. All PH patients had successful reduction of PVR to ≤2.5 WU and TPG to ≤12 with use of PGI_2 or PGE_1 prior to HTX. In their study, HTX recipients with reversible PH were found to have significantly higher posttransplantation PAP compared to recipients without PH. These patients were also found to have significantly higher incidences of right heart failure [48].

To evaluate the impact of pretransplant PH, Vakil et al. conducted a large, multicenter cohort study utilizing data derived from 26,649 HTX recipients between 1987 and 2012 (UNOS database). The results demonstrated that the presence of pretransplant PH was a modest but significant predictor of early but not long-term posttransplant mortality. The study also concluded that the increase in adverse events seen in posttransplant patients with preexisting PH occurs, regardless of severity of the disease assessed by PVR, TPG, and MPAP. Additionally, the study demonstrated that institution of mechanical circulatory support as a bridge to transplantation diminishes the incidence and severity of pretransplant PH [4].

Management of Pulmonary Hypertension Before OHTX

Transplant centers have adopted variable cutoff values for PVR and TPG for placing PH patients presenting with end-stage heart failure on transplant lists, and the strategy involved in the process appears to be extremely fluid. According to guidelines issued by the International Society of Heart And Lung Transplantation, the presence of severe pretransplant hypertension, defined as PVR > 5 WU or TPG > 16 mmHg, is associated with early graft dysfunction, increased 30-day mortality, and is considered a relative contraindication for HTX [42, 49]. That being said, no absolute cutoff values for PAP, TPG, or PVR to declare a candidate unsuitable for OHTX have been reported in the literature [45, 50, 51].

RHC in conjunction with pulmonary vasodilator response testing is considered an integrated part of preoperative assessment for OHTX and lung transplant (LTX) candidates. Evidently, less than 10 % of PH patients are considered responsive to acute pulmonary vasodilator testing conducted during RHC. The use of pulmonary vasodilators in “nonresponders” is not recommended clinically and perioperatively [52]. It is noteworthy that the phenomenon of vasoreactivity has not been defined quantitatively and transplant centers have proposed different values as reactive. Acute vasodilator response tests are considered by some experts to be positive when there is a

20 % decline in PVR in response to administration of a pulmonary vasodilator without a reduction of cardiac output [53, 54].

Left ventricular assist device (LVAD) implantation has been used to decrease PVR prior to HTX. Implantation is performed only if raised PVR in an OHTX candidate demonstrates a positive response to continuous infusion of milrinone along with up-titration of pulmonary vasodilator therapy, documented by serial RHC. A number of HTX candidates with severe class 2 WHO PH have benefited from prior implantation of pulsatile or axial-flow ventricular assist devices, leading to successful OHTX with reduced incidence of right heart failure and desirable postoperative PVR [55]. Conversely, RV ischemia and dysfunction is a frequently encountered problem after LVAD implantation. This phenomenon is manifested following separation from cardiopulmonary bypass (CPB) and may require placement of a right ventricular assist device (RVAD) [56, 57]. It has been postulated that the high dP/dT ratio of pulsatile RVAD potentially leads to detrimental injuries of the pulmonary microcirculation, causing a further increase in PVR and elevation of PAP. But theoretically, continuous flow micro-pump modeled RVAD can potentially improve systemic hemodynamics without negatively impacting PVR [58].

Lung and Heart–Lung Transplantation for Pulmonary Hypertension Patients

Currently, the majority of PH patients presenting for LTX undergo double LTX [59]. Single LTX patients have been observed to experience a more complicated postoperative course than their peers receiving double LTX. This is due to ventilation-perfusion mismatch inherent to single LTX surgery [60]. Fewer postoperative deaths [61] and a better survival trend [59] have been noted in double LTX versus single LTX recipients with PH.

PVR declines to normal ranges within 24 h post transplantation (single and double lung), but it takes several weeks for RV dysfunction to resolve. RV hypo-contractility, despite normal PVR, is an important factor contributing to hemodynamic instability and mortality in the immediate postoperative period [62]. Heart–lung transplantation is advocated by some transplant centers for end stage lung disease patients presenting with severe RV dysfunction. However, heart–lung transplantation has not been proven to be superior to double LTX in PH patients, except in patients with Eisenmenger's syndrome with ventricular septal defect [63]. Additionally, heart–lung grafts are scarce and heart–lung transplantation surgery is a technically complex procedure with longer CPB time. Moreover, postoperative heart–lung recipients may experience cardiac allograft dysfunction, complicating an already difficult postoperative course.

RV systolic function is a product of preload, contractility, afterload, and ventricular

interdependence. Ventricular interdependence is a physiological phenomenon that explains how size, shape, and mechanical properties of one ventricle directly impact the other ventricle. Systolic ventricular interdependence is mostly brought about via function of the interventricular septum, whereas for diastolic ventricular interdependence, the pericardium also plays a crucial role. Ventricular interdependence plays a significant role in the pathophysiology of acute RV failure [64]. Ventricular interdependence in RV failure is demonstrated by decreased LV cavity size and impaired LV filling (Fig. 15.2). Post LTX, following resolution of impedance to RV output, LV size and function will eventually normalize. But in the immediate postoperative period, LV diastolic dysfunction will continue to hamper cardiac output and potentially cause donor allograft pulmonary venous engorgement, which in turn may result in pulmonary edema, complicating the postoperative course.

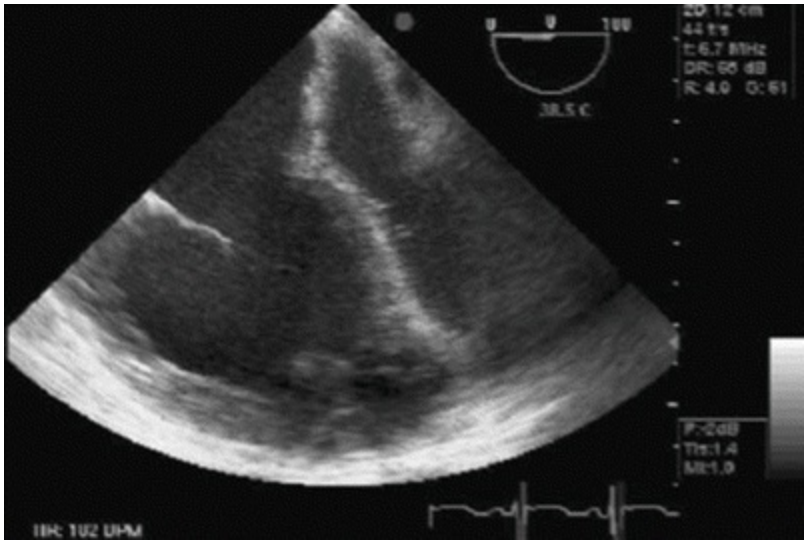

Fig. 15.2 Dilated RV, underfilled left ventricle (LV) and shift of interventricular and interatrial septum to the left indicating acute pulmonary hypertensive crisis in a patient undergoing pulmonary transplantation

Anesthetic Considerations

LTX candidates with PH are considered critically ill and require special anesthesia management plans for their perioperative safety (Table 15.3) [65]. Once the suitability of a donor-recipient pair is concluded, to reduce allograft ischemic time, placement of invasive monitoring and induction of anesthesia should be carried out within a reasonable time frame. The involvement of skilled anesthesiologists specializing in invasive hemodynamic monitoring and airway instrumentation with comprehensive knowledge of the pathophysiology of PH is crucial for the care PH patients undergoing HTX and LTX.

Table 15.3 Safety precautions to avoid pulmonary hypertensive crisis and circulatory collapse during induction of

anesthesia

• Continue preoperative pulmonary vasodilators and inotropes (milrinone, prostaglandins)
• Judicious use of anxiolytics as premedication
• Position patient in head-up position for comfort with breathing
• Arterial line placement before induction and continuous blood pressure monitoring during induction
• Consider central venous catheter and Swan–Ganz catheter placement before induction as appropriate
• Surgeon and perfusion team members in the operating room during induction
• Consider preinduction groin exposure and ECMO cannulation in severe compromised patients with suprasystemic pulmonary hypertension
• Continue pulmonary vasodilators and milrinone through induction and consider starting epinephrine before induction of anesthesia
• Preoxygenation and hyperventilation after paralysis to avoid hypoxemia and hypercarbia
• Maintain systemic blood pressure and avoid hypotension (avoid propofol)
• Smooth and rapid intubation by experienced team member, with single lumen tube if necessary to avoid hypoxemia/hypercarbia
• Avoid Trendelenberg position for central line placement (venous pressures are high so this position usually with no advantage)
• TEE probe placement immediately after intubation to evaluate right heart and optimize hemodynamics (preload, afterload, and contractility)
• Nitric oxide available in the operating room and started immediately after intubation

Preoperative Considerations

PH-specific medications should be continued preoperatively, since withdrawal can precipitate a rebound and hence PH crisis. Extreme care also needs to be taken to avoid exacerbation of PH secondary to sympathetic stimulation caused by anxiety and pain. Anxiolytics and sedatives (benzodiazepines and narcotics) administered during placement of thoracic epidural catheter and invasive monitoring devices, if used judicially, have minimal impact on systemic vascular resistance (SVR) and PVR.

Another dilemma the transplant team faces is transportation of transplant candidates on high ventilatory support to the operating room. Transport ventilators and bi-level positive airway pressure devices are often inadequate to provide necessary support. These patients may not withstand hypoxia- and hypercarbia-induced elevation of PVR and are prone to develop circulatory failure due to acute RV decompensation. Commonly, patients with severe RV failure and near systemic PH may require establishment of extracorporeal membrane oxygenation (ECMO) in the ICU prior to transport to the operating room or before induction of anesthesia in the operating room.

Induction of Anesthesia

Perturbation of hemodynamics during induction should be mitigated by all means

possible. Avoidance of PH crisis and systemic hypotension are the two major goals for anesthesia management in PH patients. PAP is maintained preferably within the 15 % range of preoperative values to avoid acute RV decompensation [66]. Insertion of a pulmonary artery catheter (PAC) before induction of anesthesia to monitor PAP and cardiac index (CI) can be useful. Central venous access inserted before induction also ensures reliable delivery of inotropes and vasopressors if needed. However, insertion of PAC and central access in a patient who cannot lie supine because of their compromised cardiorespiratory status can be challenging. Administration of sedation during the procedure can further exaggerate hypoventilation.

Most anesthetic agents administered in induction doses potentially have the ability to depress cardiac contractility and SVR precipitously. Patients with fixed PH are prone to circulatory collapse in the face of abrupt sympatholysis associated with induction of anesthesia [67, 68]. Maintenance of systemic blood pressure and SVR plays a major role in the prevention and management of RV dysfunction. Stages of right heart failure in patients with pulmonary hypertension are explained in Fig. 15.3. Slow progression of PVR in long-standing PH would allow the RV to adapt and hypertrophy; therefore, PH patients theoretically better tolerate abrupt increases in PVR. As RV hypertrophies and RV systolic pressure approaches aortic root systolic pressure, RV perfusion during systole is decreased or completely ceased. Therefore, higher systemic pressure will be required to maintain adequate RV perfusion. As PH progresses and the RV fails, the rise of RV end diastolic pressure further compromises RV perfusion, which is limited to diastole. Increased oxygen consumption from any stress results in RV ischemia and failure [69]. Therefore, systemic hypotension needs to be preempted and treated by all means possible during induction and maintenance [31, 70]. In order to prevent circulatory failure and emergency institution of CPB following induction of anesthesia, establishment of ECMO prior to induction of anesthesia has been advocated by some authors [71].

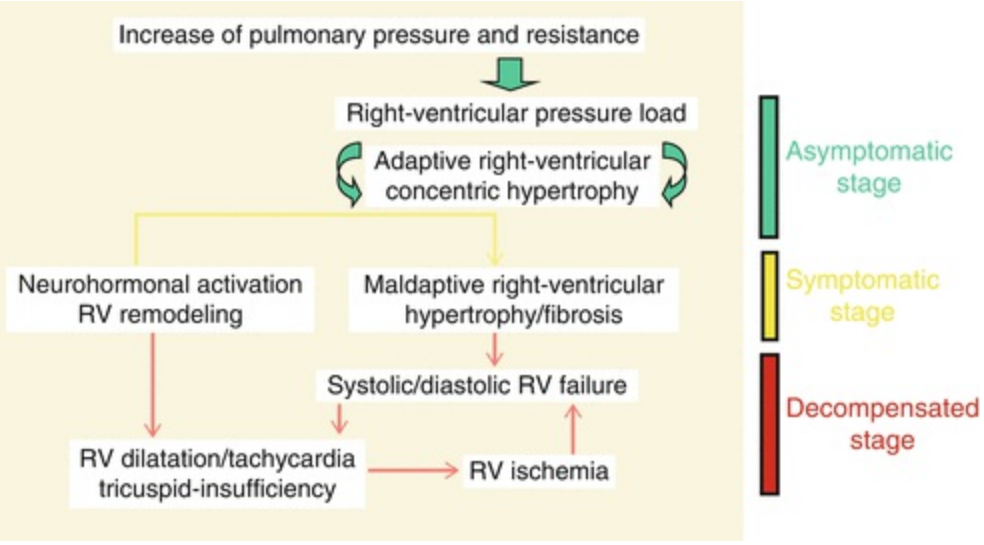

Fig. 15.3 Pathophysiology of RV dysfunction in pulmonary hypertension (Adapted from Gille et al. [173].)

Airway Management

Patients presenting for organ transplantation may not be fasting due to the time constraints attributable to the logistics of transplantation. If a transplant candidate is judged to have a full stomach due to inadequate preoperative fasting or decreased gastric emptying secondary to gastroparesis, following adequate preoxygenation with 100 % O_2, modified rapid-sequence induction (ventilation with cricoid pressure) is carried out. Otherwise, effective mask ventilation to avoid hypoxia and hypercarbia prior to instrumentation for intubation is required. Smooth induction and tracheal intubation while avoiding hypoxia and hypercarbia is not only desired but also essential. Also, with initiation of positive pressure ventilation, intrathoracic pressure should be monitored closely to prevent an unwanted increase in plateau pressure. Airway instrumentation following induction of anesthesia and awake fiber-optic intubation in patients deemed to be difficult intubation cases must be carried out by the most skilled anesthesiologist present to prevent undue sympathetic stimulation, hypoxia, and hypercarbia. Dexmedetomidine is an appropriate agent to facilitate awake fiber-optic intubation. As an agent that can provide sedation and analgesia without untoward depression of spontaneous respiration, dexmedetomidine has been successfully used to allay undue anxiety and alleviate pain.

Anesthesia Drugs and Pulmonary Hypertension

Etomidate has been recommended as the induction agent of choice for PH patients presenting for OHTX and LHTX [72]. Etomidate allows stable induction of anesthesia due to its minimal impact on SVR and myocardial contractility [73, 74]. The other commonly used induction agent propofol is not considered an appropriate choice for PH patients [73]. Propofol , when used in induction doses, can cause RV hypoperfusion secondary to a precipitous drop of SVR. Thiopental reduces SVR and RV contractility without impacting PVR [75], making it unsuitable for induction of anesthesia in PH patients. Although ketamine has been found to increase PVR in adults [76], it does not appear to increase PVR when used in conjunction with pulmonary vasodilators [18]. Morray et al. studied the hemodynamic effects of ketamine in children with congenital heart disease undergoing cardiac catheterization and concluded that ketamine neither altered the patients' clinical status nor impacted the information obtained by cardiac catheterization [77]. Williams et al. indicated that ketamine could be used as an induction agent in PH children undergoing congenital heart defect repair. Ketamine was demonstrated to not increase PVR in PH children undergoing sevoflurane anesthesia and spontaneous ventilation [78].

As part of a balanced anesthetic technique, narcotics and inhalational agents (≤1

MAC), if used with diligence, do not significantly affect hemodynamics. Fentanyl and sufentanil were also found to minimally impact PVR [79]. Inhalational anesthetic agents (isoflurane, desflurane) inhibit hypoxic pulmonary vasoconstriction and hence can further exacerbate hypoxemia. They also cause a dose-dependent decrease in SVR and myocardial contractility and impair RV-pulmonary artery coupling, which can be detrimental in the face of RV dysfunction [80, 81].

Intraoperative Monitoring

In addition to standard American Society of Anesthesiologists monitors (electrocardiography, pulse oximetry, temperature, exhaled end tidal carbon dioxide), indwelling arterial catheter (radial and femoral), PAC, and transesophageal echocardiography (TEE) are required monitoring devices during LTX and HTX surgeries (Fig. 15.4). In addition to direct measurements of PAP and PCWP, PAC is capable of measuring and calculating PVR, RV stroke work index, CI, ejection fraction, and mixed venous oxygenation (SvO_2) [82, 83].

Fig. 15.4 Typical standards of monitoring in patients undergoing lung transplantation [EKG, invasive BP (Femoral-*Purple*, Radial-*Red*), pulmonary arterial pressure (*yellow*), central venous pressure (*blue*), pulse oximetry, capnography, temperature, and cerebral (*red arrow*)/leg (*yellow arrow*) near infrared spectroscopic oximetry (*arrows*)]

Alternatively, continuous cardiac output (CCO)/mixed venous oxygen saturation (SvO_2) monitoring PACs can be used instead of regular PACs to provide clinicians with

instantaneous information, facilitating pharmacological, fluid, and ventilatory interventions in a timely fashion. SvO_2, being an indicator of oxygen-carrying capacity, is also a useful guide in guiding the transfusion of red blood cells (Fig. 15.5). Transfusion of blood products, if not warranted for tissue perfusion or coagulation, has been proven to increase morbidity without additional benefit. Specifically, in the cardiac surgery setting, RBC transfusion has been associated with infection, ischemia, and early and late mortality [84]. That being said, although an optimal hemoglobin concentration in heart failure has not yet been established, both systolic and diastolic heart failure patients with anemia have been found to have higher mortality rates [85].

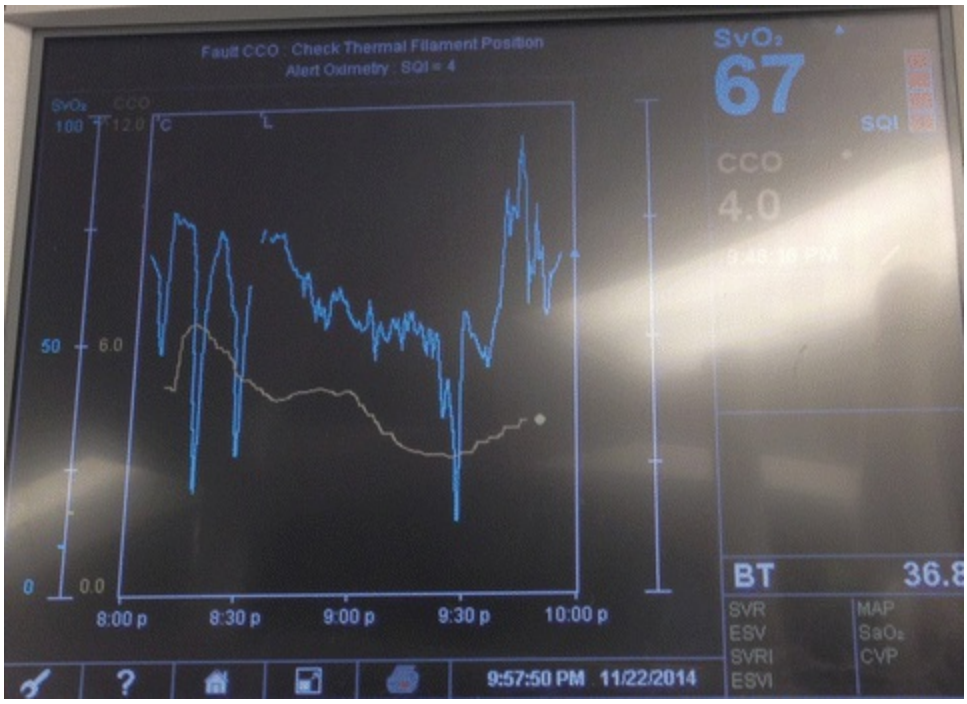

Fig. 15.5 The use of oximetric-continuous cardiac output Swan-Ganz catheters display useful information (Continuous cardiac output (CCO) and mixed venous oxygen saturation (SVO_2) in patients undergoing lung transplantation

Cardiac output measured using the PAC thermodilution method is deemed to be inaccurate in the face of significant TR, anatomical shunts, and tachyarrhythmia [83]. Therefore, in patients with significant TR and anatomical shunts, TEE will provide a more accurate estimation of cardiac output than PAC. Although PAC has not been found to impact outcome [86], especially when used in conjunction with TEE , PAC is a useful tool to assess the efficacy of treatment strategies. It also facilitates the titration of vasoactive agents to desirable end points.

Unlike TEE , PAC can also be continued for hemodynamic evaluation and management postoperatively in the ICU after transplantation. Any persistent rise in PAP or central venous pressure (CVP) associated with a fall in CI postoperatively should be

investigated by TEE for specific diagnosis (pericardial tamponade, RV dysfunction).

Maintenance of Hemodynamics, Ventilation, and Fluid Management

Patients undergoing HTX and LTX experience dramatic fluid shifts and changes in hemodynamics and ventilation during surgery. Avoiding all aggravating factors possible and attenuating the effects of stress, pain, sympathetic stimulation, and inflammation induced by surgery are essential to avoid PH crisis. PH crisis is defined as the acute onset RV failure secondary to abrupt increase of PVR (Table 15.4) [2, 87, 88]. Atrial fibrillation or third-degree atrioventricular block with its resultant increased filling pressure and decreased cardiac output are poorly tolerated in patients with acute RV dysfunction [89]. These rhythm abnormalities are a common occurrence in patients with baseline gaseous and metabolic abnormalities and can also be precipitated by the manipulation of the heart. Therefore, loss of sinus rhythm in the setting of acute RV dysfunction must be treated aggressively using synchronized cardioversion or pacing as needed.

Table 15.4 Factors that adversely affect pulmonary vascular tone and hypertension

Inadequate depth of anesthesia
Inadequate pain management
Administration of vasoactive medications
Excessive fluid administration
Lung volumes (excessive PEEP, inadequate ventilation with atelectasis)
Increased airway pressure
Hypoxemia
Hypercarbia and respiratory acidosis
Metabolic acidosis (inadequate tissue oxygen delivery from multiple causes; hypovolemia, vasopressors, hypoxemia, hypotension, cardiac manipulations, reduced cardiac output)
Cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia)
Hypothermia

Since there is an immense potential for fluid shifts in HTX and LTX surgeries, RV preload should be monitored closely and intravenous boluses and infusions must be administered judiciously to prevent acute RV distention. A failing, hypertrophied RV will neither tolerate hypervolemia nor hypovolemia; therefore, goal-oriented fluid therapy in transplantation is of pivotal importance. Each case needs a carefully tailored fluid administration strategy, best dictated by real-time TEE findings. In addition to RV distention, increasing severity of TR and leftward interventricular septal shift should give important clues to anesthesiologists regarding fluid status. Another important TEE-

derived indicator, tricuspid annular plane systolic excursion (TAPSE) , is an important diagnostic tool in the setting of acute RV dysfunction [90–92]. TAPSE , which is quantified using M-mode echocardiography in four-chamber view or transgastric view, reflects longitudinal systolic excursion of tricuspid annulus towards apex and is used for quantitative assessment of RV systolic function (Fig. 15.6) [93]. Also, rise of RA pressure in the presence of patent foramen ovale would exacerbate hypoxemia, further deteriorating an already precarious situation.

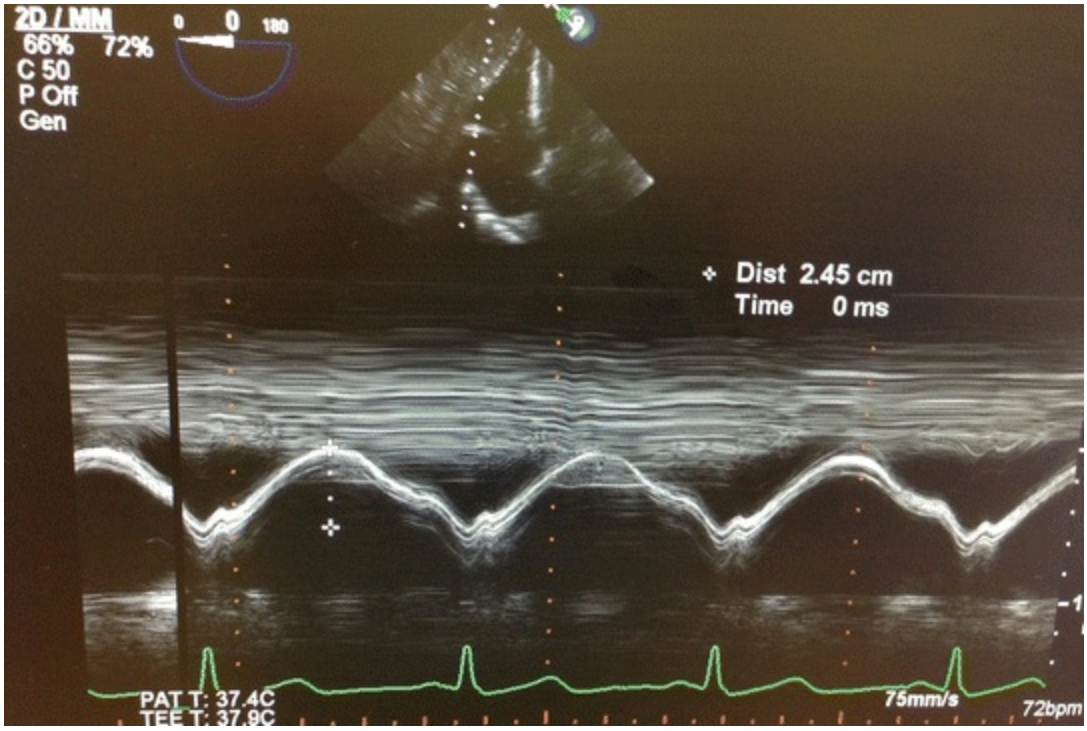

Fig. 15.6 Tricuspid annular plane systolic excursion (TAPSE) measured by M-mode transesophageal echocardiography transgastric view is used to evaluate RV function. TAPSE 24.5 mm indicates good RV function. TAPSE less than 10 mm indicates severe RV dysfunction

In the immediate postoperative period when real-time TEE assessment of RV contractility and filling status is no longer available, intraoperative, PAC information, which corresponds to TEE findings indicative of adequate RV filling, can potentially serve as a good guide for fluid therapy. The ultimate goal is to provide adequate RV preload without causing undue distention and/or interventricular septal shift. Another strategy that could be employed in the ICU setting is administration of 250 ml boluses of fluid while following CVP, PCWP, and systemic arterial pressures simultaneously. A rise in CVP that correlates with an increase in PCWP and mean arterial pressure is a sign that things are moving in right direction. Conversely, if a rise in CVP doses not correspond with positive changes in PCWP, further fluid administration should be halted. Intuitively, a simultaneous decrease in cardiac output and increase in systemic venous pressure manifested by a rise in CVP, which eventually leads to multiorgan

failure, should be prevented by all means possible. A failing RV is incapable of generating high pressures in the pulmonary arterial system. Therefore, it is important to note that declining PAP associated with a rise in CVP is an indicator of worsening RV function rather than decreased PVR. This can be confirmed by demonstration of a dilated hypocontractile RV on real-time echocardiography.

Optimal respiratory management for PH patients would include a strategy to ensure adequate oxygenation and ventilation without an undue increase in intrathoracic pressure [94, 95]. Induction of anesthesia and institution of mechanical ventilation, per se, cause an increase in intrathoracic pressure, resulting in decreased RV preload and cardiac output [66]. Once mechanical ventilation is established, a "U"-shaped relationship between lung volumes and PVR can be appreciated, with lung volumes close to functional residual capacity, providing the most favorable pulmonary and hemodynamic profile [18]. Intuitively, higher intrathoracic pressures brought about by higher tidal volume and high positive end expiratory pressures (PEEP) may adversely affect RV afterload, increase TR and RA pressures, and further deteriorate RV function. Also, higher PEEP values could cause compression of the pulmonary vasculature in well-ventilated areas of the lungs and divert blood to poorly ventilated areas, resulting in pulmonary shunting and hypoxemia. At times, balancing adequate oxygenation and ventilation along with avoidance of high airway pressure could be a tasking challenge in patients presenting with poor lung compliance, requiring sophisticated ICU ventilator and special ventilator strategies.

A ventilation strategy with a smaller tidal volume (6–8 ml/kg of ideal body weight) and higher respiratory rate (16–20) to target acceptable pH (between 7.25 and 7.4) is usually implemented [18, 66, 96]. Although hyperventilation with increasing respiratory rate can potentially decrease PVR by attenuating acidosis-induced pulmonary vasoconstriction, it should be implemented cautiously to avoid dynamic hyperinflation. Lung protective respiratory management strategies (utilizing low tidal volume 6–8 ml/kg and airway pressure <30 cmH_2O) are widely used in ICUs as an integrated part of postoperative care of patients with acute lung injury. Moreover, low tidal volume strategy has been proven to improve endothelial dysfunction via reduced cytokine production [97]. Following LTX, mechanical ventilation with a lung-protective strategy avoiding alveolar hyperinflation is recommended. Administration of optimal PEEP with lowest FiO_2 possible to prevent oxygen toxicity while ensuring SaO_2 > 90 % are important ventilatory considerations for preventing allograft dysfunction (Fig. 15.7). Appropriate postoperative ventilatory management plays a crucial role in protecting donor grafts in LTX patients and also in preventing undue increases in PVR in both HTX and LTX recipients.

Fig. 15.7 Lung protective ventilator settings after lung transplantation (Low FIO_2, low tidal volume, high respiratory rate, moderate PEEP, and airway pressure less than 30 mmHg)

Circulatory Support for Transplantation

While HTX is always performed using CPB, LTX can be conducted in some patients with PH without circulatory support. Preoperative oxygen requirement at rest (liters/min), increasing MPAP, dilated RV, severe tricuspid regurgitation, and severely depressed RV function were found to predict the need for CPB (unpublished observation). Avoidance of CPB reduced the days of postoperative ventilation and the need for tracheostomy in our PH patient cohort. Therefore, every effort is made to avoid CPB in patients with mild and moderate PH while severe PH patients will always require CPB for the procedure.

In bilateral sequential single LTX, further deterioration of oxygenation and ventilation during single lung ventilation may ensue, culminating in an acute rise of PVR, precipitating RV decompensation and circulatory collapse. This dreaded complication could be partly mitigated by dissecting the lung with inferior V-Q mismatch first. Additionally, inhaled pulmonary vasodilators and ino-vasotropic support may allow lung dissection without resorting to CPB. If ventilatory and pharmacological interventions are deemed futile, extracorporeal circulation (CPB or ECMO) will be necessary. ECMO can very well be extended to the postoperative period if allograft dysfunction results in intractable hypoxemia [68, 71, 98–100].

Clamping of the pulmonary artery is considered to be a perilous stage of LTX surgery requiring special preparation. During pulmonary artery clamping, acute rises in

PAP may result in near fatal RV dilatation, necessitating emergency establishment of CPB. That being said, it is abundantly evident that avoidance of CPB mitigates deleterious inflammatory effects such as coagulopathy and allograft dysfunction [101]. To avoid CPB, anesthesiologists need to preemptively implement ino-chronotropic, vasoconstrictor, and pulmonary vasodilatory support. Also, temporary clamping of the respective pulmonary artery prior to definite ligation would allow the surgeon and the anesthesiologist to evaluate the feasibility of transplantation without resorting to CPB, avoiding hazardous emergency cannulation and "crash bypass."

At times, surgical manipulations such as retraction required for exposure needed for left lung-atrial anastomoses could result in severe hemodynamic compromise, mandating institution of CPB. Institution of CPB in a timely fashion is advisable to avoid surgical complications secondary to emergency cannulation required for CPB.

Also, CPB may not be required for the second lung graft and hence terminated to decrease the duration of "on pump" time. Another critical stage in LTX surgery is the unclamping of pulmonary vessels. Profound systemic hypotension following completion of allograft anastomoses and unclamping of the pulmonary vasculature must be preempted and treated aggressively with up-titration of inotropes and vasoconstrictors. Additionally, fluid administration should be monitored closely to provide adequate RV preload while avoiding RV distention. One of the etiologies for posttransplantation pulmonary edema in donor graft is overzealous fluid therapy.

One of the most dreaded complications of LTX is primary graft dysfunction (PGD) , a form of ischemia–reperfusion injury manifested by pulmonary edema and severe hypoxemia and not attributable to pulmonary venous obstruction or left-sided heart failure [102]. Diagnosis of PH in the recipient is considered the most important risk factor for PGD. One can postulate that PH patients are more likely to present with severe RV failure, requiring CPB for completion of LTX, and PGD is a direct result of the systemic inflammatory response to CPB [101, 103].

It is crucial to implement all possible preemptions to ensure prevention of PGD. Assurance of donor arterial blood gas report of $PaO_2/FiO_2 > 300$, absence of contusion and infection in the donor allograft, and the donor's smoking status are important considerations in decreasing the risk of PGD [60, 103, 104]. Additionally, an allograft ischemic time of less than 4 h has been demonstrated to reduce the incidence of PGD. Also, allograft preservation with an extracellular solution has been found to be superior when compared to an intracellular solution in mitigating PGD [119]. When PGD is associated with severe refractory hypoxemia, institution of veno-veno ECMO is warranted [105, 106].

Epidural Block and Pulmonary Hypertension

Continuous thoracic epidural pain (CTE) management has been used as an integral part

of postoperative care in many LTX centers. This is to provide adequate analgesia without adversely impacting respiratory drive. Intraoperative use of CTE and its effect on pulmonary vasculature and right heart function have never been investigated in patients with PH undergoing transplantation. Animal studies provide some insight but it is difficult to extrapolate the results directly in humans. Homeometric autoregulation allows RV to tolerate acute increases in PVR and increase its stroke volume in response to pulmonary vasoconstriction (Frank Starling mechanism). There has been some concern that neuraxial blockade of the thoracic sympathetic fibers innervating the heart could potentially impair the right ventricular positive inotropic response to acute increases in PVR [107]. Additionally, it has been demonstrated that the negative ino-chronotropic effects of high thoracic epidural on an already compromised RV function can be detrimental [108]. Therefore, cautious titration of thoracic epidural analgesia is rigorously recommended [109–111].

Epidural anesthesia and analgesia have been successfully used in pregnant women for cesarean section in patients with PH [112–116]. The successful use of CTE for other noncardiac surgical procedures in patients with PH is limited to a few case reports [117, 118]. Reduction in PVR and PAP related to decreased preload, afterload, and decreased RV contractility have been reported [119]. However, a case report of intraoperative cardiac arrest after epidural bolus administration in a patient undergoing laparoscopic adrenalectomy has also been published [120]. Systemic hypotension induced by a sudden bolus of epidural anesthesia and its effect on RV perfusion may result in sudden cardiovascular collapse. While the effect of CTE-induced sympatholysis on SVR and mean arterial blood pressure is well known, the sympathetic innervation of the pulmonary vasculature and the effect of its blockade on PVR are highly debated [121, 122].

Therapeutic Approaches for Pulmonary Hypertension

In patients undergoing LTX and OHTX, any rise in CVP in the face of increased PVR suggests impending circulatory collapse secondary to severe RV failure. Basic strategies to decrease PVR such as administration of the highest fraction of O_2 possible, hyperventilation, correction of metabolic acidosis, and hypothermia must be employed promptly in the face of acute RV decompensation [123]. Assurance of adequate RV contractility with inotropic support and adequate RV perfusion by the maintenance of appropriate pressure gradient between the aorta and RV are essential. This will require vigilant use of inotropic and vasoconstrictor agents, which should be prepared as infusions and bolus medications and ready to go anytime during the procedure (Fig. 15.8). It is important to note that inotrope-induced hypercontractility in the setting of hypovolemia and hypertrophic RV can cause dynamic right ventricular outflow tract obstruction (RVOTO) and hence paradoxically decrease RV output [124]. RVOTO can

be readily diagnosed by TEE.

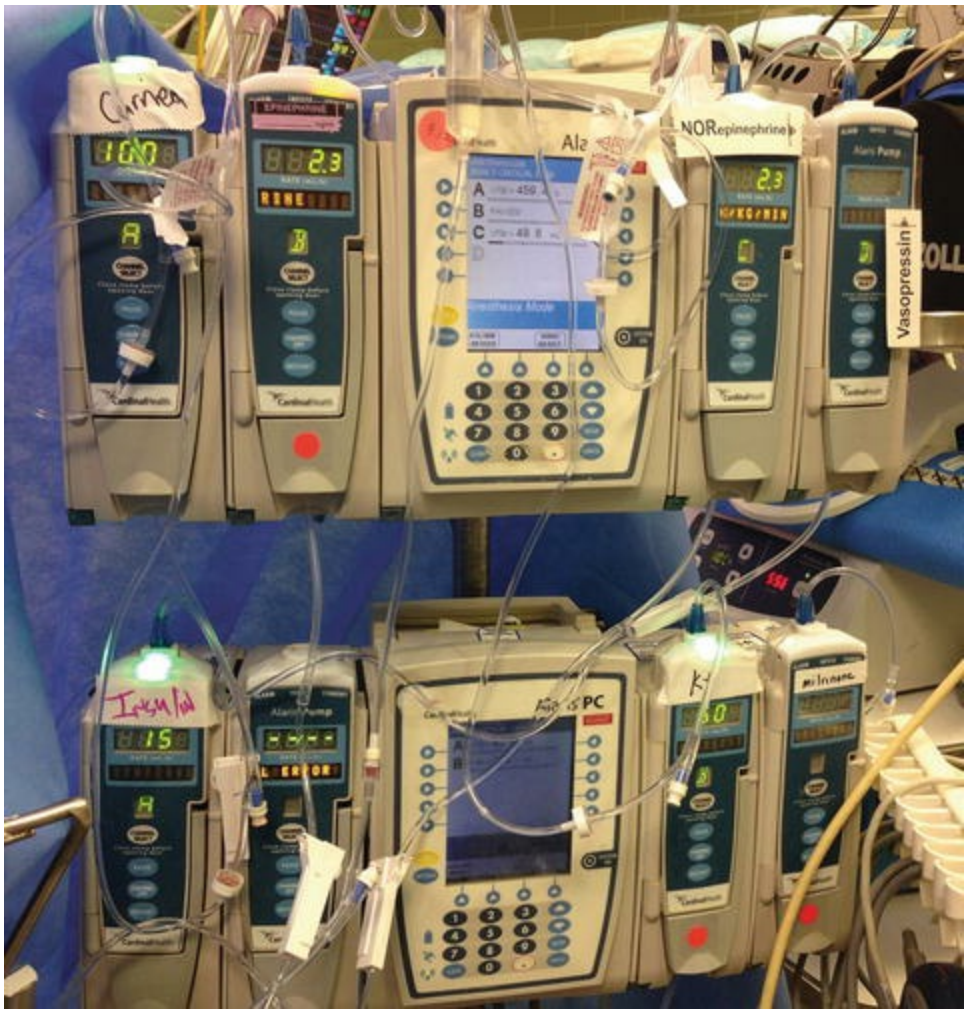

Fig. 15.8 Inotropic (epinephrine, milrinone) and vasoactive medications (vasopressin, norepinephrine) prepared and ready to go in a patient with severe pulmonary hypertension undergoing lung transplantation

Milrinone

Of all the inotropic agents, phosphodiesterase-3 inhibitors (milrinone, enoximone) are found to be more appropriate than epinephrine and dobutamine in the PH setting [125]. Phosphodiesterase-3 inhibitors exhibit a favorable profile in regard to PVR and SVR; hence, if used with diligence along with vasoconstrictors (norepinephrine, vasopressin [126]), RV perfusion pressure is maintained and RV contractility is optimized in the setting of acute RV failure. In their review of treatments for PH and right heart failure, Price et al. strongly recommended the use of phosphodiesterase-3 inhibitors but the use of low-dose dobutamine, levosimendan, norepinephrine, and vasopressin received only weak recommendation in their systematic review [127]. Therefore, milrinone (25–50 μg/kg/min, bolus, followed by 0.25–0.75 μg/kg/min, continuous infusion) is the inotrope of choice in the setting of RV failure. Nevertheless, the utility of milrinone may be

limited by its vasodilatory effect [128–131]; it has also been demonstrated that inhaled but not intravenous milrinone ameliorates endothelial dysfunction induced by CPB [132]. In a retrospective study, LaFlamme et al. [133] demonstrated the beneficial effects of combined milrinone and prostacyclin inhalation before CPB in 40 patients with PH undergoing cardiac surgery. Ultrasonic nebulization was used in their study and they showed reduced incidence of failed weaning from CPB and reduced need for vasoactive medications postoperatively. These findings are promising, but more research is required before integrating this practice into perioperative treatment of PH patients undergoing LTX and HTX. Low-dose dobutamine infusion (2–5 μg/kg/min) has also been found to improve RV contractility; conversely, higher doses of dobutamine (5–10 μg/kg/min) potentially induce tachycardia, resulting in subendocardial ischemia [12, 134].

Levosimendan

Another potentially useful inotrope in this context is levosimendan. Levosimendan is an inodilator agent that augments cardiac output, diminishes PVR, and improves regional perfusion and global oxygen delivery. Levosimendan exerts its pharmacological properties by sensitization of cardiac troponin C to the effects of intracellular calcium [135]. It also inhibits expression of adhesion molecules, potentially improving endothelial function [136]. Compared to dobutamine, levosimendan has been found to be more effective in restoring RV-pulmonary artery coupling due to its more specific pulmonary vasodilatory properties [137]. Also, the augmented myocardial contractility generated by levosimendan does not appear to be associated with increased myocardial O_2 consumption rate. But in clinical context, levosimendan's utility is limited by its propensity to cause an excessive drop in SVR [138]. The vasodilatory effect of levosimendan is proposed to be induced by activation of ATP-sensitive potassium channels in the mitochondria of smooth muscle cells [139] and inhibition of endothelin-1 receptors [140]

Vasopressors

In the setting of acute RV failure, maintenance of aortic root pressure is of paramount importance and infusion of low-dose norepinephrine or vasopressin in addition to inotropic support of RV is the mainstay of management of acute RV decompensation. Norepinephrine has been found to be especially beneficial in patients, who manifest hypotension and tachycardia while on dobutamine infusion [134]. It is important to note that only low-dose vasopressin and not norepinephrine has demonstrated the ability to decrease the PVR/SVR ratio in cardiac surgical patients [141]. Sparing the pulmonary vasculature with vasopressin can be explained by its actions on V_2 receptors in pulmonary vessels or by NO-mediated pulmonary vasodilatation.

Nesiritide

Another armament available for the management of RV decompensation is nesiritide, a recombinant brain natriuretic peptide. Nesiritide decreases PVR by increasing the availability of cGMP. An excessive drop in SVR associated with nesiritide use could be a prohibiting factor in vasodilatory shock associated with acute RV failure [142]. Another adverse effect associated with nesiritide is deterioration of renal function in patients with isolated RV failure and PH [143].

Sildenafil

Clinically, phosphodiesterase-5 inhibitors (slidenafil, tadalafil) have been used as part of a proposed treatment regimen for PH patients [144, 145]. Sildenafil exerts its vasodilatory effect by inhibiting cGMP breakdown and hence, increasing its availability. Sildenafil has been found to increase the response to NO and natriuretic peptides [146, 147]. Lepore et al. demonstrated that combined administration of sildenafil with NO creates an additive effect [148]. Perioperatively, oral slidenafil can be replaced by intravenous slidenafil to prevent acute rises in PAP [149]. Also, sildenafil has been successfully used to prevent rebound PH in patients on inhaled NO therapy [150, 151]. Sildenafil could be potentially useful in the perioperative setting as part of a posttransplantation management strategy [152] and also in other clinical scenarios culminating in acute RV failure [153].

Nitric Oxide

In the perioperative setting and critically ill patients, the maximum tolerated dose of intravenously administered pulmonary vasodilators is limited due to their ability to cause systemic hypotension. Also, systemically administered pulmonary vasodilators can potentially exacerbate hypoxemia by inhibiting hypoxic pulmonary vasoconstriction. To avoid untoward systemic hypotension caused by intravenously administered pulmonary vasodilators, inhaled agents have become the mainstay in the management of perioperative PH.

Administration of inhaled NO (iNO) (5–40 ppm) has been found to be especially effective in mitigating RV failure associated with increased PVR in the context of RV infarction and cardiogenic shock and also in the perioperative setting [154–156]. iNO exerts its pulmonary vasodilatory action through increased cGMP production. Absence of a systemic vasodilatory effect of iNO is due to its immediate inactivation by binding to hemoglobin [157].

In acute and chronic RV failure, combination therapy with iNO and dobutamine has proven to augment CO, improve oxygenation, and decrease PVR [158, 159].

Use of iNO for PH patients undergoing OHTX and LTX has been associated with

significantly lower mortality rates compared to its use in cardiac surgery or for hypoxemia in medical patients [160]. It is important to note that iNO can lead to pulmonary edema in stable severe heart failure. The redistribution of blood volume in previously vasoconstricted pulmonary circulation is postulated to result in pulmonary edema. Also, in left sided heart failure, in the absence of left sided afterload reduction, administration of iNO and other selective pulmonary vasodilators with resultant improved RV function and, consequently, improved LV preload, can cause pulmonary edema due to massive back pressure [157–159, 161, 162]. Therefore, in patients with decompensated left sided heart failure, administration of selective pulmonary vasodilators is not advisable.

Although iNO is a fairly effective pulmonary vasodilator, it is not completely innocuous and can be potentially toxic. iNO is capable of inducing methemoglobinemia and producing reactive nitrogen species. It is considerably expensive and requires complicated machinery for delivery and monitoring (Fig. 15.9). Additionally, abrupt interruption of iNO administration is associated with rebound PH [163]. Another contentious field for iNO use is the context of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Adhikari et al. demonstrated that with iNO use in the ALI and ARDS setting, methemoglobinemia and raised nitrogen dioxide were not found to be common or clinically important except when iNO is used at high doses for several days; more importantly, iNO was found to be associated with limited improvement in oxygenation [164].

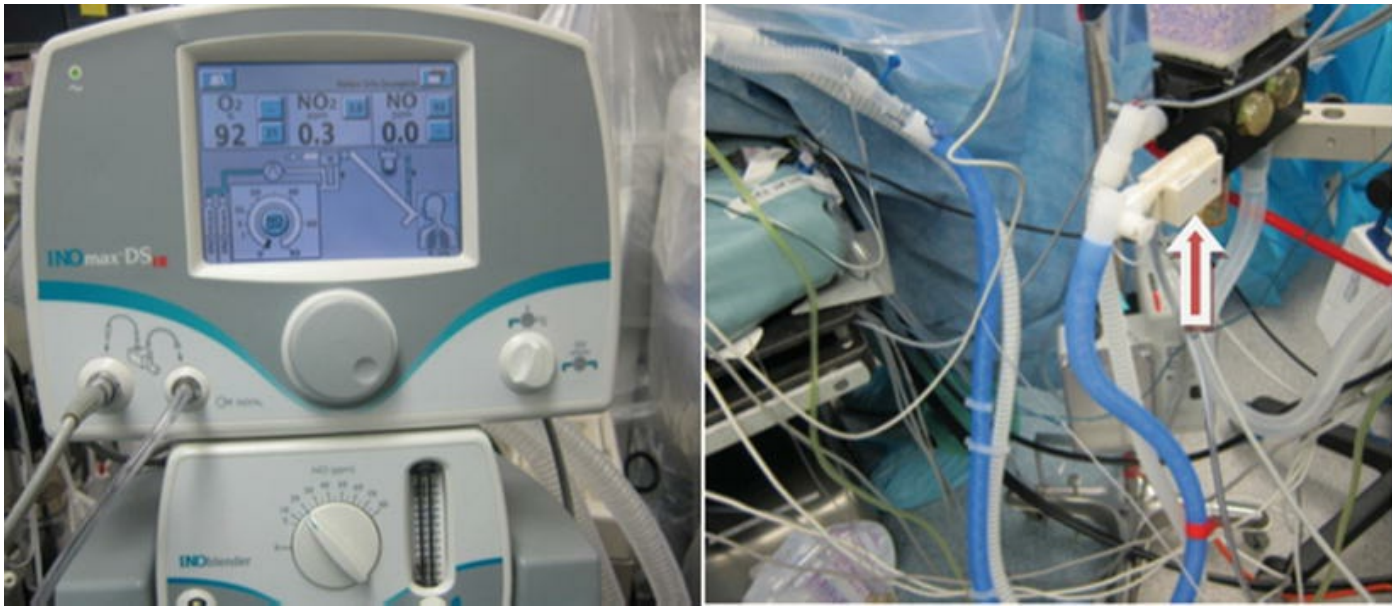

Fig. 15.9 Inhaled nitric oxide delivery system *Left*: Inhaled nitric oxide delivery system control panel. *Right*: Inhaled nitric oxide delivery circuit, the *arrow* indicates the inspiratory limb. (From Liu et al. [174]; with permission.)

Alternatively, prostacyclin and prostanoids may offer a less-expensive alternative

with no known significant toxic effects. Pharmacologically, NO-induced pulmonary vessel dilatation is achieved by cGMP formation in smooth muscle cells, whereas prostacyclin and prostanoids cause vasodilation by increased availability of cAMP. The major differences between NO and inhaled prostacyclin are listed. Prostanoids (epoprostenol, iloprost, treprostinil), are considered to be an integrated part of the treatment regimen for PH patients [165, 166]. Iloprost is available for oral, intravenous, and aerosol administration. Aerosolized prostacyclins (inhaled epoprostenol, iloprost, and treprostinil) have been used perioperatively to successfully manage elevated PVR. Inhaled iloprost (5–10 μg nebulized over 10 min) can be administered to spontaneously breathing patients preoperatively by ultrasonic nebulization (Fig. 15.10) or in the operating room through the anesthesia circuit (Fig. 15.11). Epoprostenol has a short half-life (2–3 min) compared to iloprost (20 min), thus mandating administration by continuous infusion (30–40 ng/kg/min) to the nebulizer attached to the breathing circuit (Fig. 15.12). Ultrasonic nebulizers are more effective than jet nebulizers in delivering the nebulized particles to the alveolus. In HTX and LTX patients, iNO and inhaled prostacyclin are both effective in decreasing PVR and CVP with improvement in CI and SVO_2 [167, 168]. Treprostinil, another inhaled prostanoid has a longer duration of action compared to other prostanoids but has been found to have a potency similar to iloprost [169, 170]. Treprostinil may have a potential application in the perioperative period. Additionally, simultaneous inhalation of milrinone and prostacyclin has been reported in the literature [171]

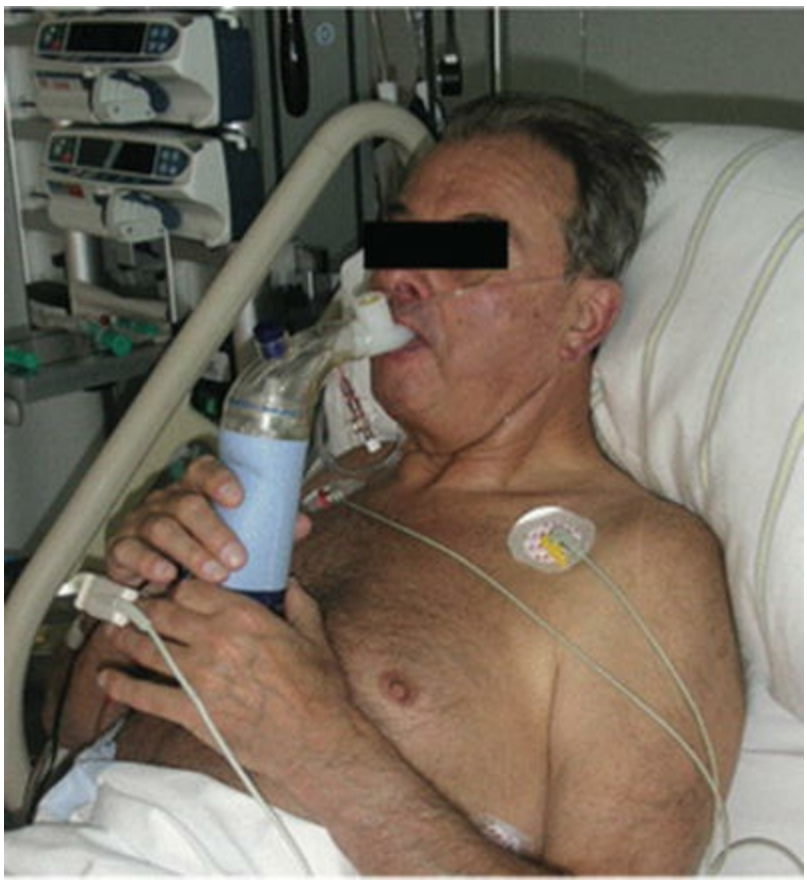

Fig. 15.10 Preoperative inhalation of iloprost through ultrasonic nebulization in spontaneously breathing patient (Reprinted from Gille et al. [173] under a Creative Commons Attribution license.)

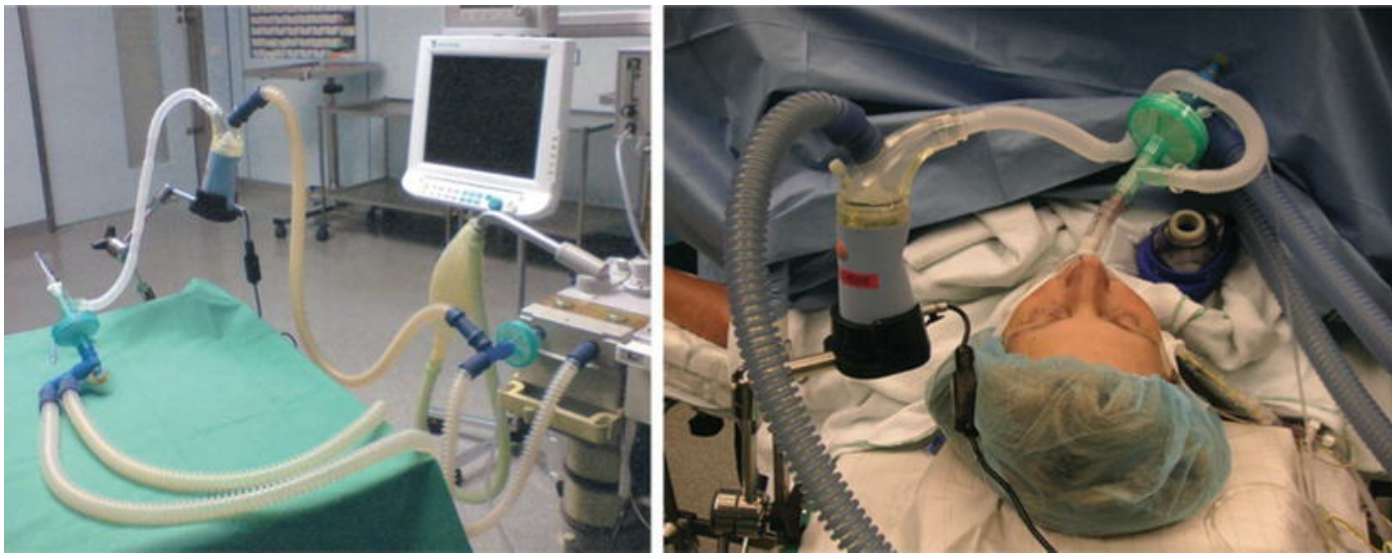

Fig. 15.11 Assembly instruction for the integration of an ultrasonic nebulizer (Multisonic) in the ventilatory circuit. Intraoperative selective pulmonary vasodilation with inhaled iloprost (Reprinted from Gille et al. [173] under a Creative Commons Attribution license.)

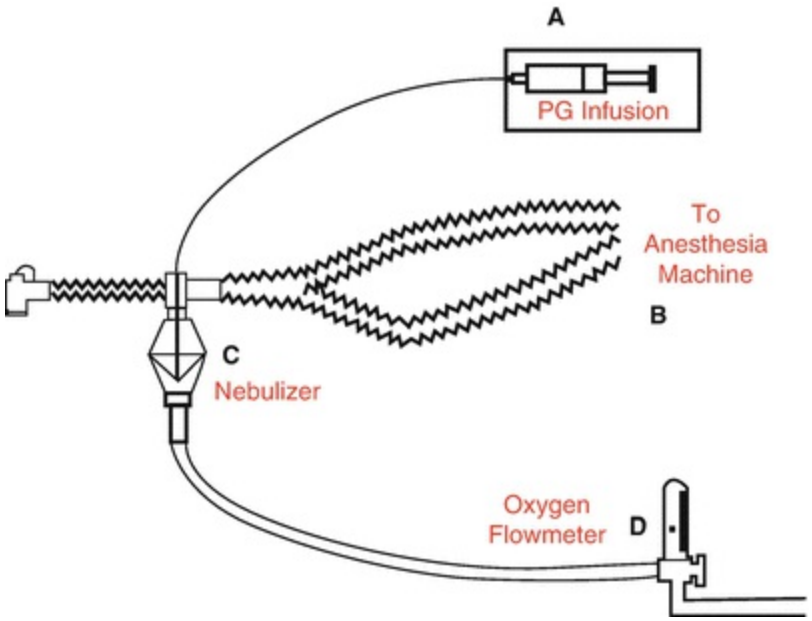

Fig. 15.12 Intraoperative nebulization of epoprostenol via continuous infusion

The perioperative application of another class of anti-PH medications, the endothelin receptor antagonists (bosentan, ambrisentan, and macitentan) [172] has yet to be investigated.

Summary

The perioperative management of PH patients undergoing HTX and LTX is a challenging undertaking. As more and more patients with near-systemic pulmonary pressures receive donor lungs and pulmonary pressure cutoff values for HTX candidates have become more and more fluid, perioperative physicians will be required to care for an increasing number of critically ill patients. Multidisciplinary care involving anesthesiologists, intensivists, PH experts, and cardiac surgeons is pivotal for a favorable outcome in this daunting task.

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16. Extracorporeal Life Support Following Thoracic Organ Transplantation

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Introduction

The term *extracorporeal life support* (ECLS) refers to devices used to support the heart and lungs, and includes extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VADs). These devices may be used as a bridge to transplantation or for cardiorespiratory support following transplantation. The primary focus of this chapter is the use of ECLS following thoracic transplantation.

Bridging to Transplantation

VADs are an effective treatment for advanced heart failure, either as a bridge to heart transplantation or as destination therapy [1]. VAD use as a bridge to heart transplantation is increasing. In 2011, 42 % of heart transplant recipients in the United States were transplanted from a VAD, compared to 27 % in 2001 [2]. In most

circumstances patients are transplanted from a long-term left ventricular assist device (LVAD) , such as HeartMate II (Thoratec, Pleasanton, CA) or HVAD (HeartWare, Miami Lakes, FL). These devices are all intracorporeal continuous flow pumps. Less commonly, a short-term VAD or ECMO is used for treating acute heart failure (e.g., for fulminant myocarditis, failure to wean from cardiopulmonary bypass) as a bridge-to-decision. Bridging in this circumstance may be to recovery, to a longer-term VAD, directly to heart transplantation, or withdrawal of intensive therapies (e.g., due to severe neurological injury). Short-term VADs used as bridge-to-decision are typically extracorporeal centrifugal pumps, as described below. In a series of 1467 unselected Medicare beneficiaries who received an emergency VAD following heart surgery, 56.2 % died in hospital, 33.6 % were discharged with a VAD, and 1.4 % underwent in-patient heart transplantation [3]. Thus, in most circumstances bridge-to-decision involves placement of a long-term VAD or withdrawal of intensive therapies.

In contrast to heart transplantation, ECLS as a bridge to lung transplantation is less well established. However, over the last 5-years there have been increasing reports of using ECMO for this purpose, with an emphasis on awake ambulant venovenous (VV) ECMO [4–7]. Part of the reason for the increased interest in ECMO as a bridge to lung transplantation is the poor survival figures for patients undergoing lung transplantation from mechanical ventilation. Data from the United Network for Organ Sharing indicate that from October 1987 to January 2008, of the 15,934 lung transplants performed, 586 patients were receiving mechanical ventilation. Unadjusted survival at 1 and 12-months was 83 % and 62 % respectively for mechanical ventilation versus 93 % and 79 % for nonventilated patients [8].

Outcome from ECMO bridging to lung transplantation is variable with survival rates of 60–90 % reported over the first 1–2 years [4–7], which is lower than in non-ECMO patients, but not dramatically so. Furthermore, in at least one report, a higher survival rate was observed in patients transplanted from awake ECMO compared to mechanical ventilation (80 % versus 50 % at 6-months) [4]. However, while the technique is effective, there is one important caveat. Median duration of ECMO support in these series was less than 3-weeks, and in one report only 3.5 days [6]. Thus, bridging to lung transplantation is only viable in large programs with short wait-times.

Extracorporeal Life Support Following Transplant

The principle indication for ECLS following heart or lung transplantation is primary graft dysfunction (PGD). Less commonly, ECLS is used for treating acute rejection or infection. PGD is the leading cause of death in the first 6-weeks after thoracic transplantation, with a mortality of approximately 5 % [2, 9]. However, the definition of PGD is complicated by the fact that some degree of graft dysfunction occurs in virtually all patients in the early postoperative period. For lung transplantation, the International

Society for Heart and Lung Transplantation (ISHLT) classifies PGD based on P_aO_2 and the presence of pulmonary infiltrates on the chest radiograph (Table 16.1) [10]. Using this definition, the incidence of the worst form of PGD (Grade 3) is 10–12 %, with an associated mortality of 40–65 % [11, 12]. A strict definition of PGD following heart transplantation is not in use. However, if the condition is defined as the need for high-dose inotropic therapy or ECLS an incidence of 20–25 % has been reported, with an associated mortality of 20–40 % [13–15].

Table 16.1 Grading of primary graft dysfunction following lung transplantation [10]

Grade	P_aO_2/F_iO_2 (mmHg)	Radiographic infiltrates consistent with pulmonary edema
0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

Lung Transplantation

The primary mode of ECLS following lung transplantation is VV ECMO. VV ECMO provides direct support of gas exchange, facilitates lung rest, and, indirectly supports cardiac function. While the direct consequence of PGD is impaired gas exchange and poor lung compliance, right ventricular (RV) dysfunction may be a significant contributor to the patient's cardiorespiratory state. Many patients undergoing lung transplantation have preexisting RV dysfunction due to chronically elevated pulmonary vascular resistance (PVR) . Hypoxia, hypercarbia, and acidemia arising as a consequence of PGD lead to further increases in PVR during the postoperative period. Elevated intrathoracic pressure, secondary to high peak inflation pressure (PIP) and high positive end-expiratory pressure (PEEP), increase RV afterload and contribute to RV dysfunction. Finally, cardiopulmonary bypass (CPB) , if utilized for surgery, greatly increases the sensitivity of the pulmonary circulation to the effects of hypercarbia [16, 17]. While VV ECMO provides no direct support of cardiac function, improved gas exchange and application of rest ventilator settings typically leads to improved RV function. VA ECMO only rarely required following lung transplantation, but is occasionally necessary for patients with severe RV dysfunction.

Indication for ECMO Following Lung Transplantation

PGD may present immediately following graft reperfusion or develop more slowly over the first few hours. One or both transplanted lungs may be involved. In the operating room, PGD typically presents acutely with the appearance of pulmonary edema fluid in the endotracheal tube following reperfusion of the graft. PGD that is bilateral may result

in an acute failure of gas exchange and the immediate need for ECLS. In the intensive care unit (ICU), PGD typically evolves more slowly over several hours with deteriorating gas exchange, worsening lung compliance, and alveolar shadowing on the chest radiograph.

Before diagnosing PGD it is essential to exclude pulmonary venous obstruction or obstruction within the airways. The pulmonary veins should be examined with transesophageal echocardiography (TEE) looking for signs of kinking or obstruction (Fig. 16.1). Pulmonary venous obstruction should be treated with immediate surgical revision. Obstruction within the airways can arise from mucus plugs or blood clots. Fiberoptic bronchoscopy should be performed, and any mucus plugs or blood clots removed under direct vision.

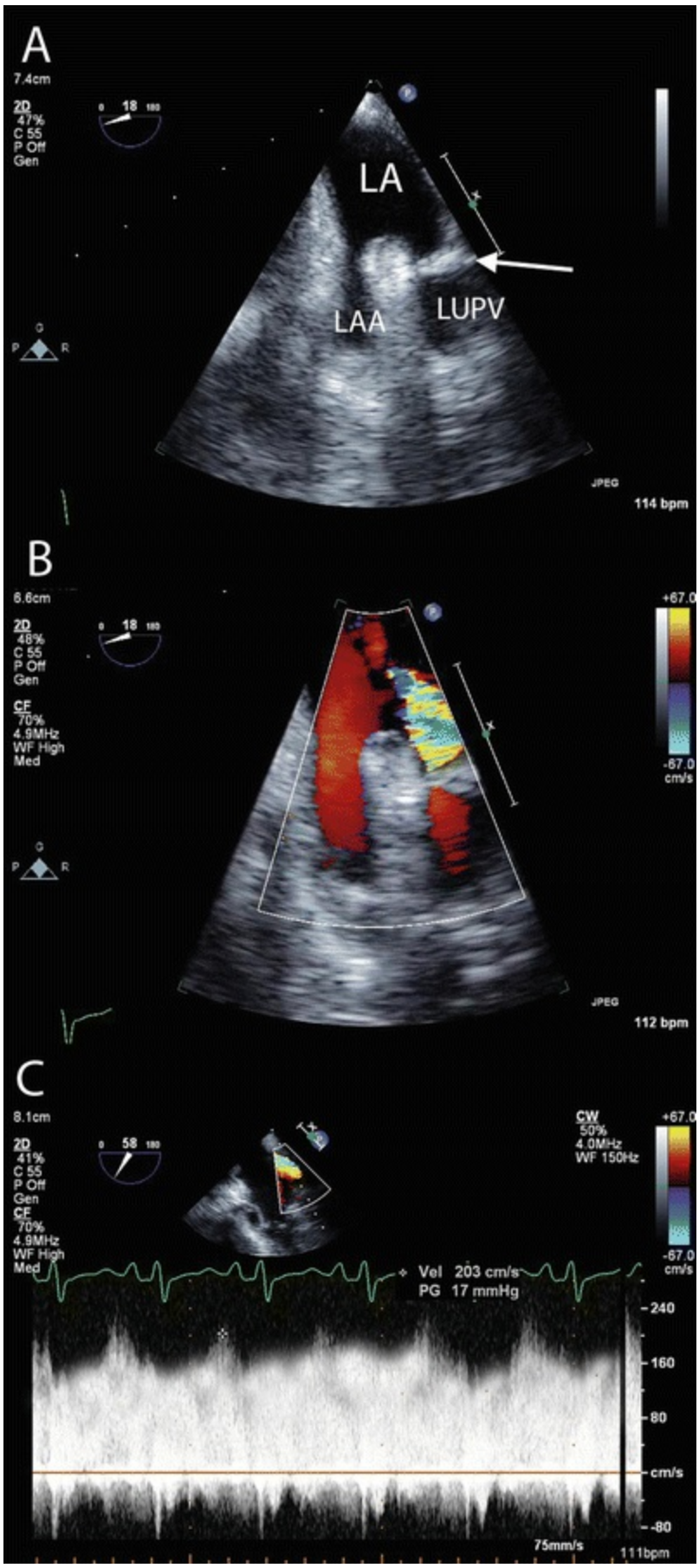
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Fig. 16.1 Pulmonary venous obstruction . (**a**) TEE imaging of the left upper pulmonary vein and left atrial appendage demonstrating obstruction (*arrow*) within the pulmonary vein. (**b**) Color Doppler imaging demonstrating turbulent flow at the site of obstruction. Flow in the pulmonary veins is normally laminar (similar to the flow in the adjacent atrial appendage). (**c**) Pulsed Wave Doppler imaging demonstrating increased velocity (203 cm/s) and loss of the normal phasic flow pattern within the pulmonary vein. The normal peak velocity of blood flow in the pulmonary veins is <1 m/s. *LA* left atrium, *LAA* left atrial appendage, *LUPV* left upper pulmonary vein

Conventional treatment of PGD involves lung-protective ventilation with increased PEEP (5–15 cm H_2O), inhaled pulmonary vasodilators (nitric oxide, prostacyclin), vasopressor and inotropic therapy to support RV function, fluid restriction, and correction of metabolic acidosis with renal replacement therapy. Lung protective ventilation involves limiting plateau airway pressure to 30 cm H_2O or less (or PIP ≤ 35 cm H_2O), using low tidal volume (VT) breaths (≤6 mL/kg), and accepting a degree of hypercarbia and respiratory acidemia. This approach improves survival in patients with acute respiratory distress syndrome (ARDS) [18]. While not of proven benefit, lung protective ventilation is also utilized following lung transplantation in the hope of minimizing PGD, and thereby potentially increasing survival and improving graft function over the longer-term. While permissive hypercarbia (P_aCO_2 50–70 mmHg, pH 7.1–7.2) is normally well tolerated in patients with ARDS, in lung transplant recipients this strategy may precipitate acute RV failure due to the adverse effect on PVR.

ECMO should be instituted if adequate gas exchange (P_aO_2/F_iO_2 > 80 mmHg, P_aCO_2 < 60–70 mmHg, pH > 7.2) cannot be maintained despite maximal lung protective ventilation (PIP 35 cm H_2O, PEEP 15 cm H_2O, respiratory rate [RR] 25/min, F_iO_2 > 0.6), or if the hemodynamic state is deteriorating (mean arterial pressure [MAP] < 60 mmHg, central venous pressure [CVP] > 15 mmHg, cardiac index [CI] < 2.0 L/min/m^2).

Technical Aspects of VV ECMO Following Lung Transplantation

Circuits and Cannulation for VV ECMO

Several cannula configurations may be used for VV ECMO (Fig. 16.2). Our preferred configuration is femeroatrial (Fig. 16.2a). For drainage, a long 25–29 French (Fr) multiport cannula is placed in the femoral vein and advanced so the tip lies in the inferior vena cava (IVC) just below the hepatic vein, 5–10 cm from the junction of the IVC and right atrium (RA) (Fig. 16.3). For return, a short 19 Fr cannula is introduced into the right internal jugular vein and advanced so the tip lies just proximal to the junction of the RA and superior vena cava (SVC). This arrangement typically allows a circuit flow in excess of 6 L/min. A commonly used alternative to femeroatrial cannulation is to use a purpose-designed double-lumen ECMO cannula (Avalon Elite Bi-Caval Dual Lumen Catheter, MAQUET, Rastatt, Germany) inserted into the right

internal jugular vein (Fig. 16.2c). The tip of the drainage lumen sits in the IVC at about the level of the hepatic vein, while the return lumen opens into the RA. For adults a 27 or 31 Fr cannula typically allows flows up to 5 L/min.

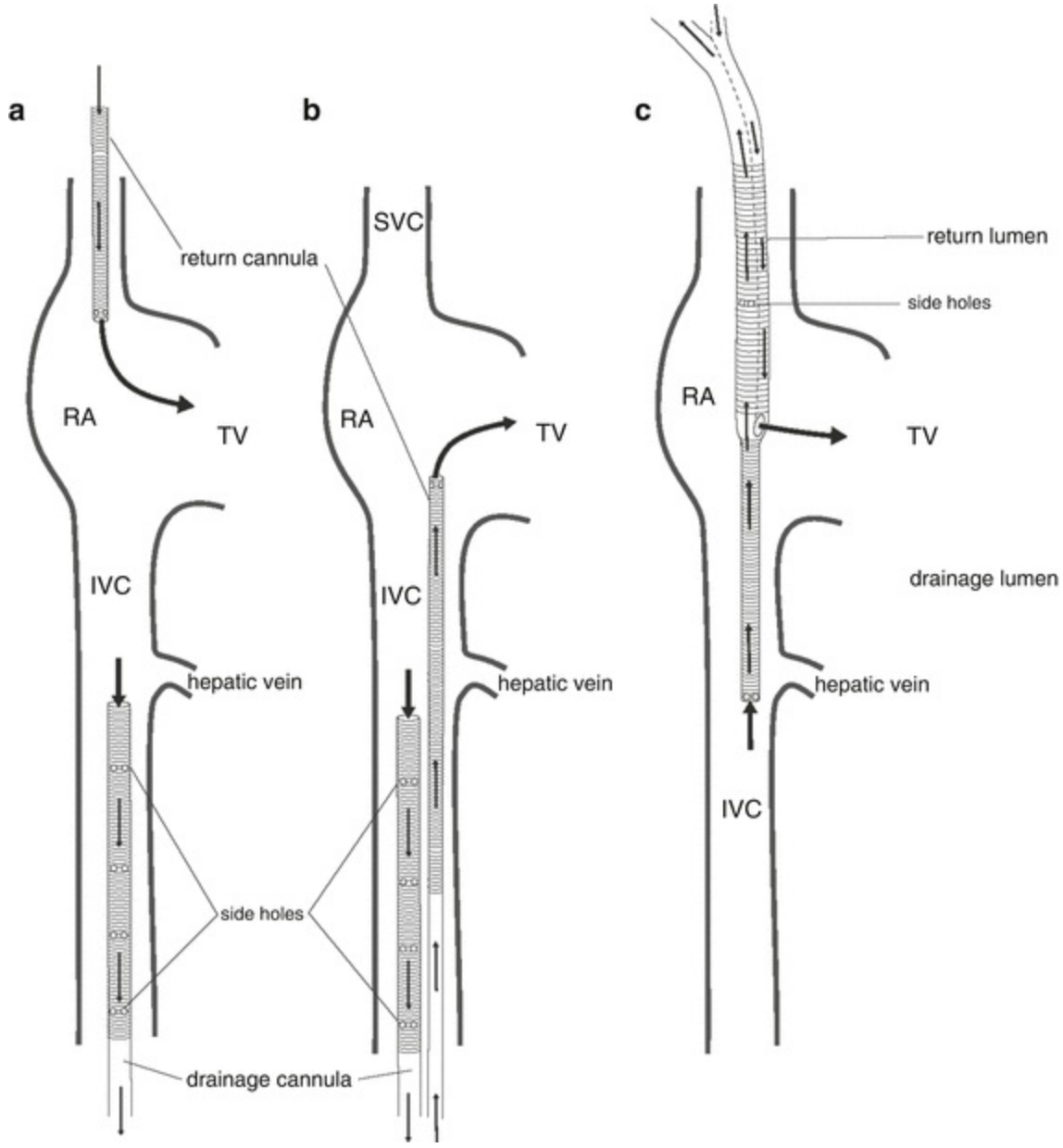

Fig. 16.2 Common cannula configurations for VV ECMO . (**a**) Femeroatrial cannulation. Drainage is via a large multiport cannula introduced into a femoral vein and advanced to the mid-inferior vena cava; return is via a short cannula introduced into the right internal jugular vein and advanced to the proximal superior vena cava. (**b**) Femerofemoral cannulation. Drainage is via a large multiport cannula introduced into a femoral vein and advanced to the mid-inferior vena cava; return is via a long cannula introduced into the contralateral femoral vein and advanced to the right atrium. (**c**) Double-lumen cannulation. Drainage and return are via a double-lumen cannula introduced into the right internal jugular vein. The cannula is advanced until the tip lies in the mid-inferior vena cava, just distal to the hepatic vein. Drainage is from the inferior and superior vena cavae. Return is to the right atrium. *RA* right atrium, *TV* tricuspid valve, *IVC* inferior vena cava. (From Sidebotham et al. [20]; with permission.)

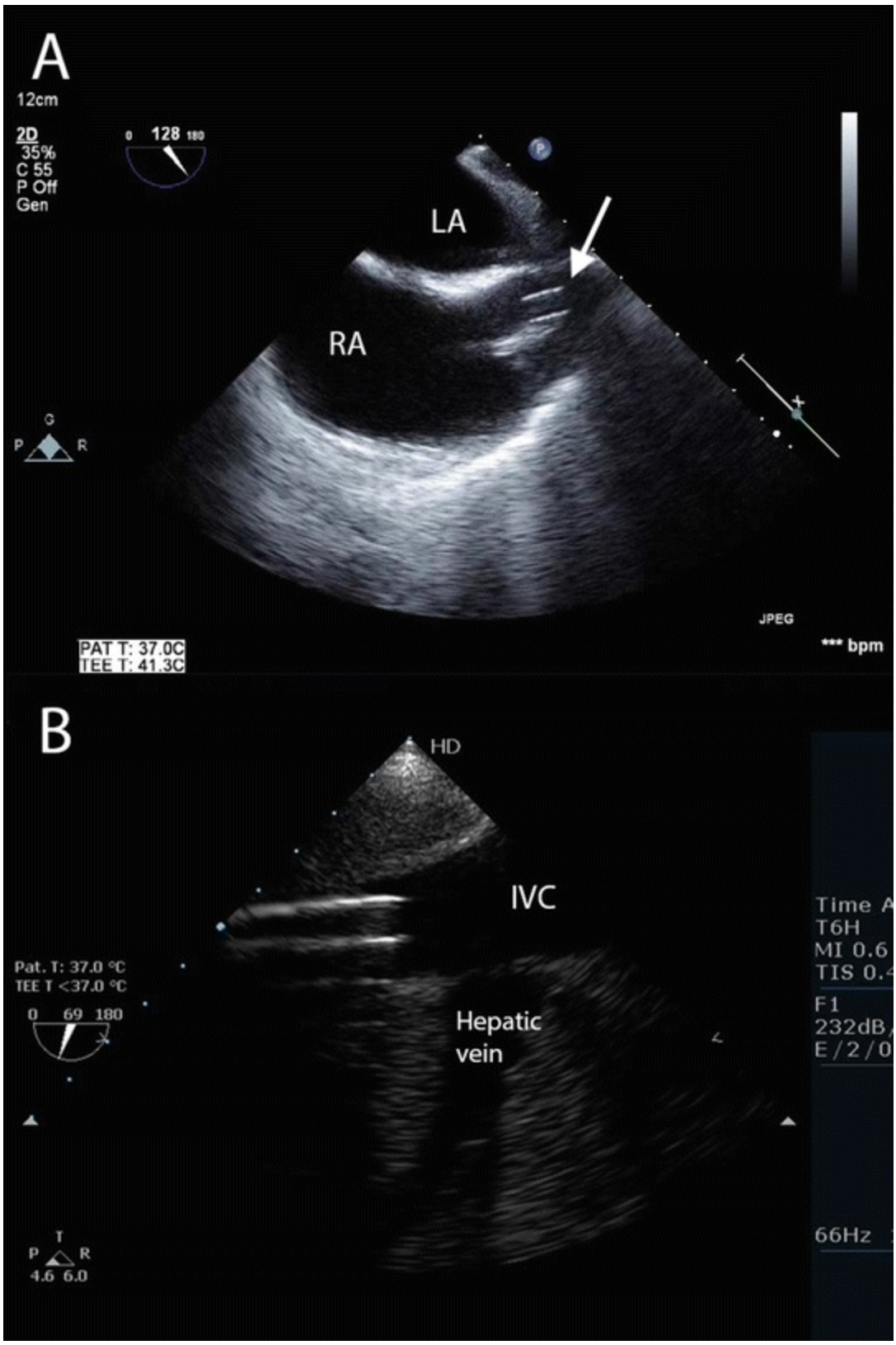

Fig. 16.3 Normal cannulae position for VV ECMO using femeroatrial arrangement (see Fig. 16.1a). (**a**) TEE imaging from the mid-esophageal bicaval view showing the tip of the return cannula (*arrow*) in the superior vena cava. (**b**) TEE imaging of the inferior vena cava and hepatic vein. The tip of the drainage cannula is seen in the inferior vena cava just distal to the origin of the hepatic vein. Compare to the arrangement for VA ECMO shown in Fig. 16.6. *LA* left atrium, *RA* right atrium, *IVC* inferior vena cava

EMCO cannulae may be inserted by a surgical cutdown or a Seldinger technique. A particular advantage of the Seldinger technique is avoidance of cannula-site bleeding that often occurs with surgical cutdown. Peripheral cannulation through the jugular and femoral veins is preferred to central cannulation through the wound, as this approach allows closure of the chest wound, minimizing surgical-site bleeding and reducing the risk of mediastinal infection. The position of guide wires and cannulae should be confirmed with TEE. Once ECMO has commenced, flow in the return cannula should be interrogated with color Doppler imaging to ensure it is directed through the tricuspid valve (see below) (Fig. 16.4).

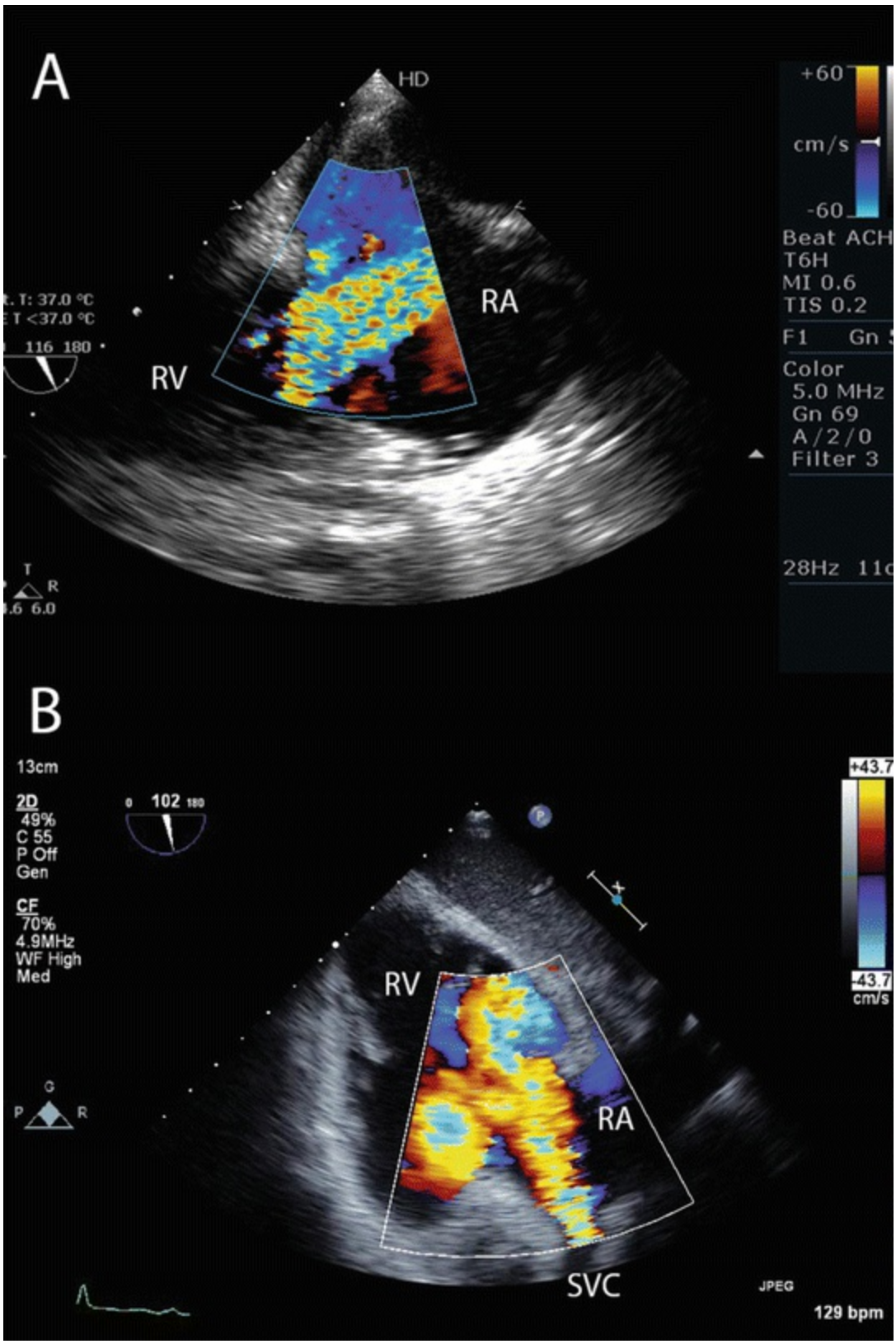

Fig. 16.4 Normal flow pattern of the return cannula during VV ECMO . (**a**) TEE imaging from a modified mid-esophageal bicaval view showing a high velocity jet passing from the right atrium, through the tricuspid valve, into the right ventricle. (**b**) TEE imaging from a transgastric view of the right ventricle. A high velocity jet can be seen originating from the superior vena cava, and passing into the right atrium and ventricle. In both images, the jet of oxygenated blood passes through the tricuspid valve. *RA* right atrium, *RV* right ventricle, *SVC* superior vena cava

Modern ECMO circuits are comprised of a polymethylpentene (PMP) oxygenator, a centrifugal pump, heparin coated tubing, a pump controller, a heater unit, a gas blender, and sampling ports (Fig. 16.5). Compared to older-style circuits comprising roller pumps and hollow fiber or silicone oxygenators, modern circuits are more durable, cause less damage to blood components, and provide more efficient gas exchange [19, 20].

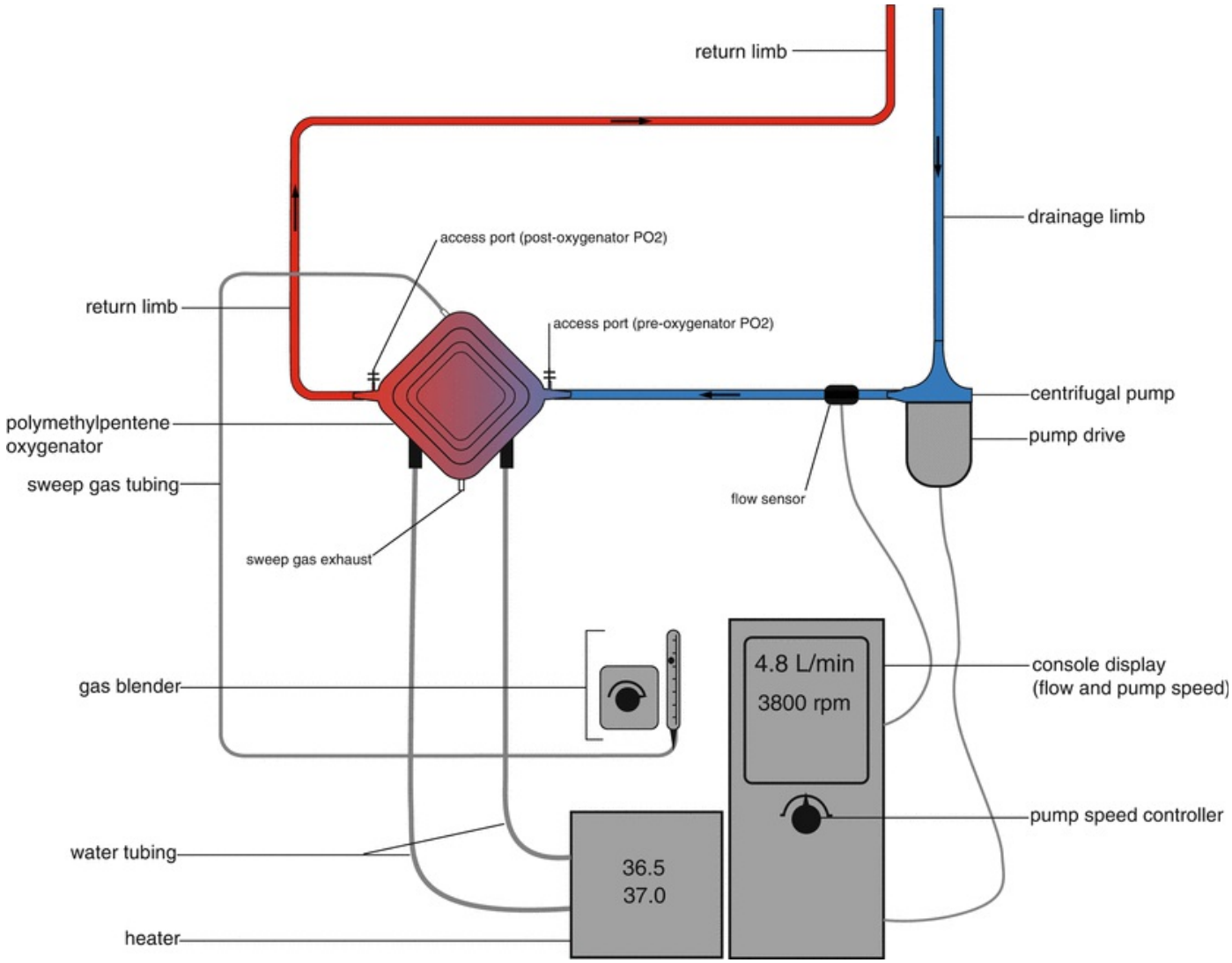

Fig. 16.5 Schematic of an ECMO circuit comprised of a polymethylpentene oxygenator, centrifugal pump, pump drive, pump controller, water heater, and gas blender. (Image modified from Sidebotham et al. [20]; with permission.)

Gas Exchange During VV ECMO

During VV ECMO, deoxygenated blood is drained from the IVC and oxygenated blood is returned to the RA. Ideally, all the blood from the return cannula passes through the tricuspid valve into the pulmonary circulation. Because oxygenated blood from the return cannula mixes with deoxygenated blood from the patient's systemic venous return,

it is not possible to achieve a normal S_aO_2 with VV ECMO. However, if ECMO circuit flow is at least 70 % of cardiac output, and the majority of the ECMO return blood passes into the pulmonary circulation, a S_aO_2 in the range 88–92 % can be achieved even if the lungs are not contributing to gas exchange [20].

The main determinant of S_aO_2 during VV ECMO is circuit flow. Low S_aO_2 (<88 %) despite adequate circuit flow (4–6 L/min.) may be caused by recirculation, abnormally high cardiac output (e.g., due to sepsis), or oxygenator failure. Recirculation occurs when oxygenated blood from the return cannula passes directly to the drainage cannula. Measuring the pre-oxygenator SO_2 in the circuit helps distinguish between recirculation and high cardiac output as the cause of hypoxemia. A high pre-oxygenator SO_2 (>75 %) suggests recirculation, whereas a low pre-oxygenator SO_2 (<60 %) suggests high cardiac output.

The severity of recirculation is influenced by intravascular volume, ECMO flow, and, most importantly, by the relative positions of the drainage and return cannulae. If recirculation is suspected, a TEE examination should be performed to assess the position and flow patterns of the ECMO cannula (Fig. 16.6). If recirculation is confirmed the cannulae positions should be adjusted under TEE guidance.

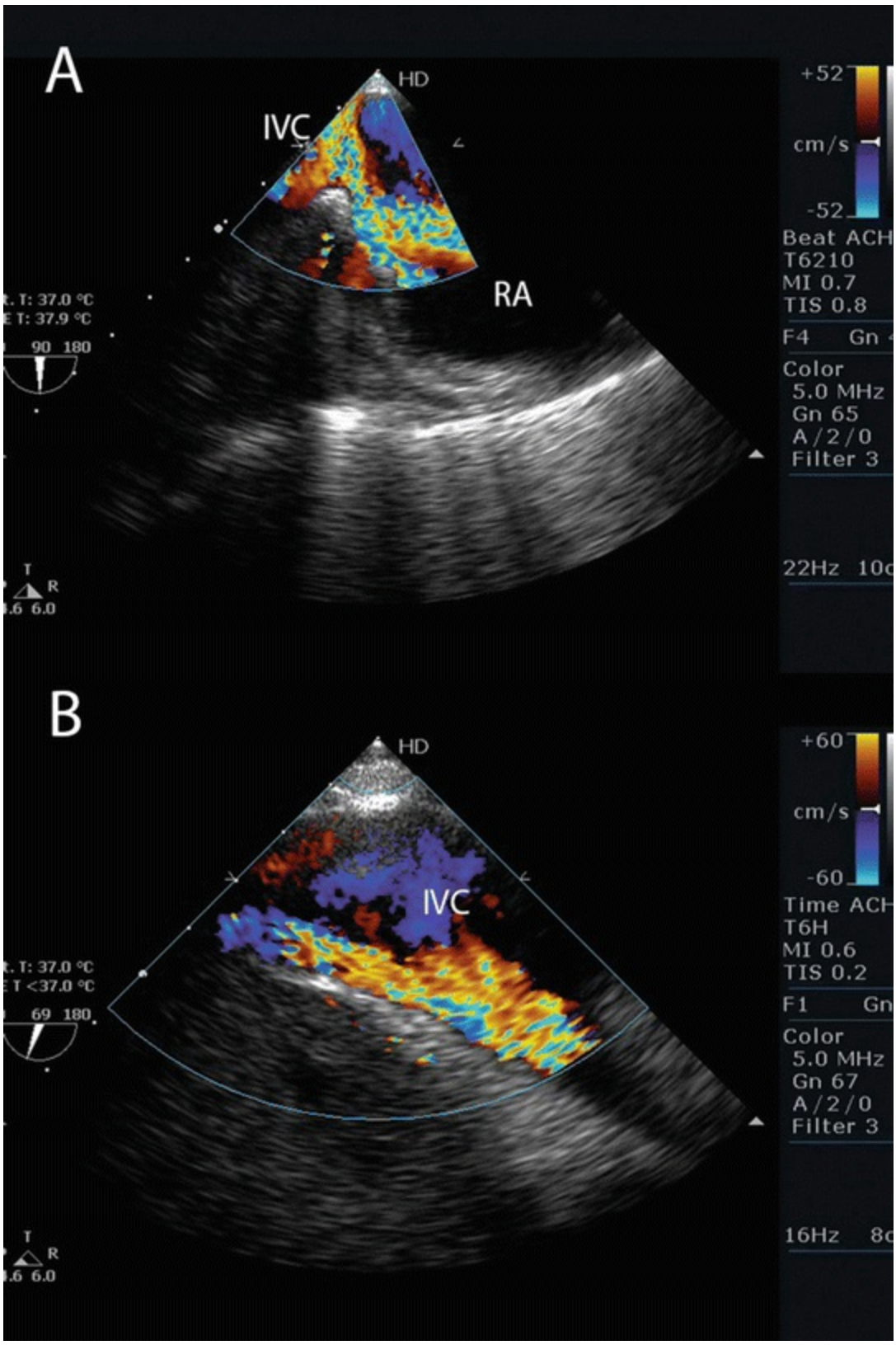

Fig. 16.6 Recirculation during VV ECMO . (**a**) TEE imaging from a modified bicaval view showing the jet of blood from the return cannula passing from the right atrium into the inferior vena cava. (**b**) TEE imaging in the same patient demonstrating flow in the inferior vena cava from the return cannula. In this patient, oxygenated blood in from the return cannula is likely to be entrained into the drainage cannula (not seen) leading to recirculation. *RA* right atrium, *IVC* inferior vena cava

P_aCO_2 is not influenced by circuit flow but by the balance between the sweep gas flow and the patient's metabolic state (i.e., CO_2 production). Normocarbia can usually be achieved with a sweep gas flow of 1–2 times the circuit blood flow.

Common problems and their potential solutions during ECMO support are listed in Table 16.2.

Table 16.2 Problems and solutions during extracorporeal membrane oxygenation

Problem	Possible causes	Diagnosis	Solution
Arterial hypoxemia (VV)	Low circuit flow Recirculation High cardiac output/increased metabolic rate Oxygenator failure	Check pre-oxygenator SO_2 Check post-oxygenator SO_2 TEE examination	Increase circuit flow Adjust cannulae position Replace oxygenator Active cooling
Arterial hypoxemia (VA)	Excessive ejection from LV in patient with pulmonary dysfunction Oxygenator failure	Compare SpO_2 in arm/leg Check post-oxygenator SO_2	See text for treatment of upper-body hypoxemia Replace oxygenator
Hypercarbia (VV, VA)	Inadequate sweep gas flow Increased metabolic rate Oxygenator failure	Check post-oxygenator P_aCO_2	Increase sweep gas Cool patient Replace oxygenator
Hypotension (VV)	Cardiac failure Vasoplegia	TEE examination	Inotrope or vasopressor Convert to VA ECMO
Hypotension (VA)	Vasoplegia Tamponade	TEE examination	Vasopressor Surgical exploration
Suction events (VA, VV)	Hypovolemia Malpositioned cannulae Tamponade (VA)	TEE examination	Give fluid Adjust cannulae Surgical exploration
Low pump flow /high pump speed (VA, VV)	Hypovolemia Obstruction in circuit (oxygenator/pump) Malpositioned cannulae Tamponade	Examine circuit for clots Check pressure drop across oxygenator TEE examination	Give fluid Replace circuit component Surgical exploration
Ventricular distension or intracardiac thrombus (VA)	Inadequate LV ejection Inadequate heparinization	Clinical signs of pulmonary edema TEE examination	Increase inotropes Increase circuit flow Create ASD
Heparin resistance (VA, VV)	Anti-thrombin III deficiency	High heparin dose requirements (>20 U/kg/h)	Give fresh plasma or recombinant antithrombin III
High plasma hemoglobin (VA, VV)	Thrombus in pump or oxygenator	Examine circuit Measure pressure drop across oxygenator	Replace circuit component

Adjuvant Therapy During ECMO Support [19–21]

Once EMCO has commenced the ventilator should be set to rest settings to minimize further ventilator-induced lung injury. Typical rest settings are a F_iO_2 0.4, PIP 20 cm H_2O, PEEP 10 cm H_2O, and a RR of 10/min.

Systemic anticoagulation with unfractionated heparin is routine during ECMO to prevent thrombus forming in the circuit. However, in the early postoperative period, when surgical-site bleeding is a concern, is may be appropriate to run the circuit heparin-free. ECMO can usually be managed heparin-free for several days without adverse consequences. Once postoperative bleeding has settled the patient should be fully heparinized. Traditionally heparin anticoagulation during ECMO has been monitored by measuring the activated partial thromboplastin time (APTT) . However, because APTT readings are highly variable between different laboratories and because APTT levels are influenced by factors other than heparin anticoagulation, many centers have moved to titrating heparin dose to the antifactor Xa level, aiming for a value of 0.3–0.7 U/mL [22]. Marked heparin resistance (heparin dose requirement >20 IU/kg/h) is suggestive of low antithrombin III (ATIII) levels. ATIII levels below 50 % of normal in the presence of high heparin requirements should be treated with fresh frozen plasma or recombinant ATIII. Bleeding is an ever-present risk while patients are anticoagulated for ECMO. If possible, invasive procedures (e.g., tracheostomy, intercostal drainage of simple pneumothoraces) should be deferred until ECMO has been discontinued.

To promote graft recovery a restrictive approach to fluid therapy and regular diuretic therapy is appropriate. Early institution of renal replacement therapy for control of metabolic acidosis and acute kidney injury is indicated. Strict attention to asepsis is essential as the combination of immunosupression, critical illness, and invasive cannulae all increase the risk of nosocomial infection. Two strategies of proven benefit that are particularly applicable to ECMO-supported patients are daily bathing with chlorhexidine-impregnated washcloths [23] and the use of chlorhexidine dressings for covering vascular (including ECMO) catheters [24]. Careful attention to hand hygiene, early institution of enteral nutrition, and daily circuit cultures are also important.

Weaning and Discontinuing ECMO

Signs of pulmonary recovery are indicted by reduced ECMO flow to maintain S_aO_2, an improving chest radiograph, and increased tidal ventilation. When the required circuit flows to maintain a S_aO_2 above 92 % has reduced to less than 3–4 L/min and tidal volume on rest ventilator settings have increased to more than 200 mL, a trial on standard ventilation (F_iO_2 0.4, PIP 25–30 cm H_2O, PEEP 5–10, RR 15 breaths/min.) off extracorporeal support is indicated. Leaving the circuit flow at 3–4 L/min but turning the sweep gas off keeps the circuit patent but provides a trial off ECMO support. If,

after 2–4 h, tidal volume and gas exchange are adequate (i.e., VT > 4–5 mL/kg, P_aO_2 > 80 mmHg, P_aCO_2 < 60 mmHg) ECMO may be discontinued and the patient decannulated. If an unmodified Seldinger technique has been used for insertion, the cannulae can be removed and manual pressure applied to the insertion site for 10–15 min. If the cannulae were inserted by a cut-down technique, surgical removal and repair of the veins is indicated.

Outcome from ECMO Following Lung Transplantation

Approximately 3–6 % of patients receive ECMO following lung transplantation [25–29]. Early survival is 50–80 % [25, 26, 30], which compares to more than 90 % for lung transplant recipients overall [9]. Longer term outcome is also worse in patients requiring ECMO. In one study, 3-year graft survival was 49 % in ECMO-supported compared to 74 % in non-ECMO-supported patients [25]. Follow up peak forced expiratory volume in 1 s was 58 % of predicted in the ECMO group compared to 88 % in the non-ECMO group.

However, several points are worth making regarding these outcomes. First, most of the reports include patients undergoing lung transplantation prior to the current era; i.e., before the widespread use of VV ECMO using modern circuits. Previously ECMO was used as a last resort in patients who were highly likely to die with conventional therapy. In many cases venoarterial (VA) ECMO was used, which is associated with worse outcome and more complications than VV ECMO following lung transplantation [27]. Second, the reduced survival associated with ECMO primarily relates to PGD [11, 12], rather than use of ECMO. It is likely, although not proven, that ECMO improves outcome from PGD by providing lung rest and avoiding exacerbating PGD. Finally, the above discussion relates to using ECMO for treating PGD. Acute respiratory failure that occurs beyond the first postoperative week is typically due to acute rejection or pneumonia. Outcome from ECMO in this group of patients is generally very poor, particularly when instituted for pneumonia/sepsis [28, 29, 31].

Heart Transplantation

Severe PGD following heart transplantation may present early, as failure to wean from CPB, or evolve over the first few hours in the ICU. One or both ventricles may be involved. Before diagnosing PGD it is necessary to rule out other causes of cardiorespiratory compromise, in particular cardiac tamponade. TEE is essential for assessing ventricular function and excluding cardiac tamponade and other cardiac abnormalities, such as severe valvular dysfunction or intracardiac thrombus.

The ISHLT have developed guidelines for the care of heart transplant recipients, which include recommendations for the perioperative use of vasoactive drugs and

ECLS [32]. ECLS should be initiated early for failure to wean from CPB or for signs of severe allograft dysfunction, as evidenced by the requirement for high-dose inotropic support with inadequate or deteriorating hemodynamics. Cardiac support should escalate from pharmacotherapy to IAPB to ECLS.

The ISHLT advocate using a VAD as the first line mode of ECLS following heart transplantation in adults [32]. While some authors have demonstrated similar outcomes with VAD compared to VA ECMO [33], others have found better results with VA ECMO, particularly for RV or biventricular dysfunction [34, 35]. Advantages of a VAD over VA ECMO include more complete unloading of the supported ventricle and, possibly, a reduced inflammatory response due to the smaller "foreign" surface area of a VAD. Advantages of VA ECMO include the ability to control gas exchange and the ability to provide biventricular support with a single circuit. While a VAD is appropriate for supporting a single failing ventricle, VA ECMO may be more appropriate for biventricular support and when there is concomitant respiratory insufficiency.

Three other considerations are important when deciding between a VAD and ECMO. First, with VA EMCO even mild aortic valve regurgitation can lead to catastrophic left ventricular (LV) distension [36]. For this reason, aortic regurgitation that is more than trivial can be considered a contraindication to VA ECMO. By contrast, mild (but not severe) aortic regurgitation is well tolerated with a LVAD. Second, in the absence of any LV ejection, VA ECMO is associated with significant LV distension due to the return of blood to the left heart from Thebesian veins, bronchial arteries, and any flow through the pulmonary circulation [19]. In the absence of LV ejection—as evidenced by a closed aortic valve on TEE examination—acute LV distension causes cardiac damage and acute pulmonary edema. Thus, if the LV is completely noncontractile, the improved unloading provided by a VAD is preferred. Finally, in the presence of a patent foramen ovale (PFO), an LVAD, which unloads the LV and therefore reduces left atrial (LA) pressure, can lead to marked right-to-left shunting and profound hypoxemia. A PFO must be excluded with TEE, or surgically closed if identified, prior to initiating LVAD support.

Indications for Extracorporeal Life Support Following Heart Transplantation

ECLS should be instituted if adequate hemodynamics (MAP > 60 mmHg, CVP < 15 mmHg, CI > 2.0 L/min/m^2, mixed venous oxygen saturation [S_VO_2] > 50 %) cannot be maintained despite high-dose inotropic support (e.g., epinephrine >0.2 μg/kg/min, or equivalent), epicardial pacing (HR ≥ 90/min). Additionally, ECLS should be considered if the hemodynamic state is deteriorating despite escalating inotropic support. Severe metabolic derangement (pH < 7.2, base deficit <−8, lactate >5 mmol/L)

should be treated with renal replacement therapy. If there is RV dysfunction or severe hypoxemia a selective pulmonary vasodilator, such as inhaled nitric oxide (10–20 parts per million) or nebulized iloprost (10–20 μg 4 hourly), should be administered prior to considering ECLS.

Ventricular Assist Devices

Extracorporeal Centrifugal Pumps

The most simple method of providing temporary VAD support following heart transplant is with an extracorporeal centrifugal pump. The most widely used system is the CentriMag (Thoratec Corporation, Pleasanton, CA) [37, 38], although other pumps such as the Rotaflow (MAQUET, Rastatt, Germany) or Bio-Medicus Bio-Pump (Medtronic Inc., Eden Prairie, MN) may be used. These devices can be implanted as an LVAD or right ventricular assist device (RVAD). For LVAD support cannulae are typically placed in the LA (via the right superior pulmonary vein) and ascending aorta; for RVAD support cannulae are placed in the RA and main pulmonary artery. Cannulae are surgically placed and exit via the sternotomy incision or brought out through adjacent subcutaneous tissues and skin, allowing the sternal wound to be partially closed. Patients are anticoagulated as for ECMO.

TEE guidance is essential to ensure free flow of blood into the atrial cannula, effective decompression of the supported ventricle, and adequate functioning of the nonsupported ventricle. Hypovolemia, excessive VAD flow, or inadequate functioning of the nonsupported ventricle leads to suction events and low circuit flows. Suction events are an abrupt loss of VAD flow necessitating decreasing pump speed to zero (to relieve suction on the drainage cannula), followed by slowly increasing pump speed to reestablish VAD flow. On TEE, suction events are seen as collapse of the supported ventricle. Initial treatment is to reduce VAD flows, administer intravenous fluids, and increase inotropic support to improve the function of the nonsupported ventricle. Persistent suction events may indicate the need to reposition the drainage cannula or to provide bi-ventricular support.

Percutaneous Ventricular Assist Devices

As an alternative to an extracorporeal centrifugal pump, a percutaneous VAD may be used. Two devices are currently available: TandemHeart (Cardiac Assist Inc. Pittsburgh, PA) and Impella (Abiomed, Danvers, MA). Systemic heparinization is used for both devices.

The TandemHeart is primarily designed for short-term LVAD support but may also be inserted as an RVAD. As an LVAD, a 21 Fr transseptal drainage cannula is inserted in the femoral vein and advanced into the right atrium (RA) and across the atrial septum

into the left atrium (LA). A 15 or 17 Fr return cannula is placed in the femoral artery, and flow is achieved via a small extracorporeal centrifugal pump. Flows up to 5 L/min are possible with the 15 Fr return cannula and up to 8 L/min with the 17 Fr return cannula. As an RVAD, drainage is from the RA and return is to the pulmonary artery. The TandemHeart may be inserted percutaneously in the catheter laboratory or surgically in the operating room.

The Impella system is used exclusively for LVAD support. The device is placed in the femoral artery and advanced through the aorta so the tip lies in the LV. A small intracorporeal axial pump is incorporated into the cannula. Blood is aspirated from the LV and returned proximally into the ascending aorta. The Impella 2.5 provides flows up to 2.5 L/min and may be placed via a Seldinger technique in the femoral artery. The Impella 5.0 provides flows up to 5.0 L/min and is inserted via a surgical cut down into the femoral or axillary arteries.

The TandemHeart and Impella pumps are primary used for treating nonsurgical cardiogenic shock; however, there is limited experience in heart transplant recipients. In one report, the TandemHeart device was used as an LVAD in a patient with acute rejection [39]. In another report, the combination of the Impella (as an LVAD) and the TandemHeart (as an RVAD) were used for biventricular support, also for acute rejection [40].

Venoarterial Extracorporeal Membrane Oxygenation

Many aspects of patient care during VA ECMO support are as described for VV ECMO above.

Central Versus Peripheral VA ECMO

Two forms of cannulation may be used for VA ECMO following heart transplantation: central and peripheral. With central cannulation the return cannula is placed in the ascending aorta and the drainage cannula is placed directly into the RA or vena cavae. Central cannulation may be used when VA ECMO is instituted in the operating room. The same cannulae as used for CPB can be connected into the ECMO circuit. With peripheral cannulation the return and drainage cannulae are inserted the femoral vessels. For return, a short 17–21 Fr cannula is placed in the femoral artery. For drainage, a 27–29 Fr multiport cannula is placed in the (contralateral) femoral vein and advanced so the tip lies in the RA (Fig. 16.7).

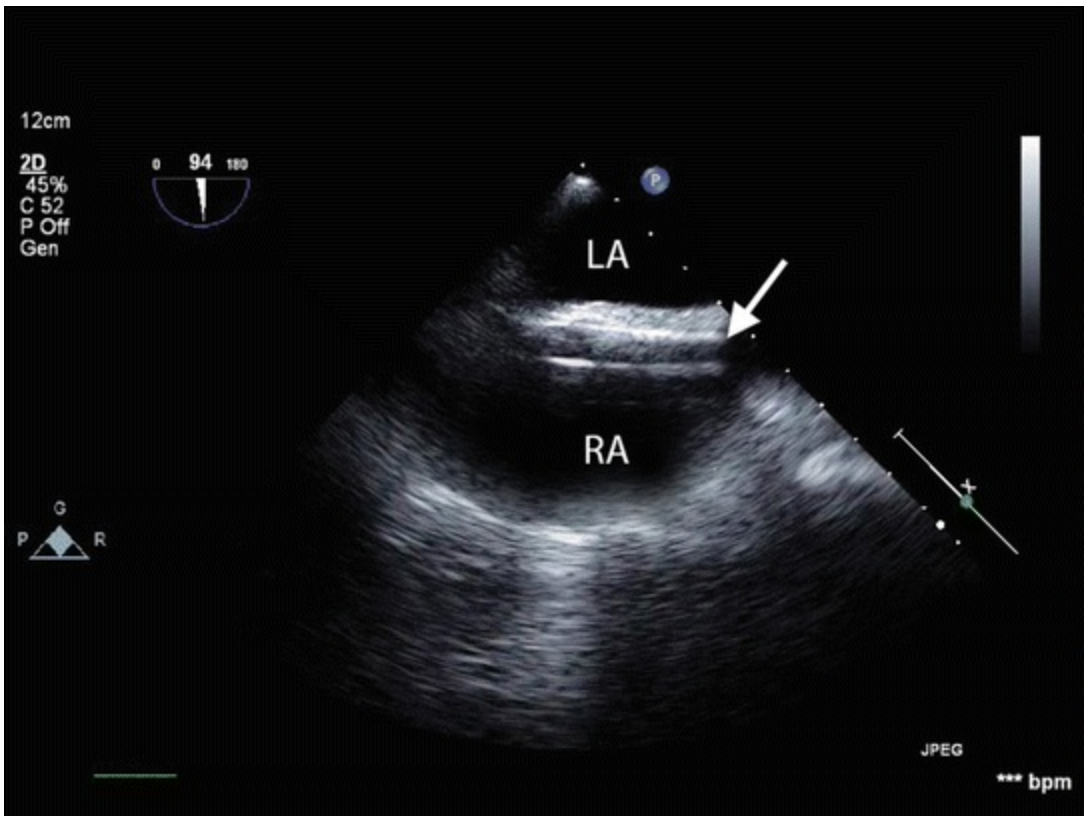

Fig. 16.7 Normal position of the drainage cannula during VA ECMO . TEE imaging from a mid-esophageal bicaval view. The drainage cannula has been advanced up the inferior vena cava (to the left of the sector scan) into the right atrium. The tip of the drainage cannula (*arrow*) can be seen in the superior right atrium close to the origin of the superior vena cava. Compare this to the position of the drainage cannula during VV ECMO shown in Fig. 16.3. *LA* left atrium, *RA* right atrium

While outcome from central and peripheral VA EMCO following heart transplant are similar [34], there are important differences between the two techniques. First, peripheral (arterial) cannulation can lead to upper body hypoxemia when there is significant LV ejection and severely impaired pulmonary function (Fig. 16.8). Since, cardiac function typically recovers before pulmonary function this problem is common when peripheral arterial cannulation is used for treating cardiorespiratory failure. The diagnosis is confirmed by identifying a higher S_PO_2 in the right upper limb than in the lower limbs. Upper body hypoxemia does not arise with central aortic cannulation (Fig. 16.8). For this reason, if VA ECMO is used for treating cardiorespiratory failure, central aortic cannulation should be performed. An additional problem with peripheral arterial cannulation is limb ischemia distal to the femoral arterial cannulation site. For this reason, placement of a distal femoral perfusion cannula is essential. Peripheral cannulation has the advantage of allowing the chest to be closed, which may help reduce postoperative bleeding and minimize the risk of mediastinal infection. Peripheral cannulation can be performed percutaneously using a Seldinger technique, and therefore can be undertaken in the ICU. Furthermore, patients can be potentially decannulated

without the need for a return to the operating room.

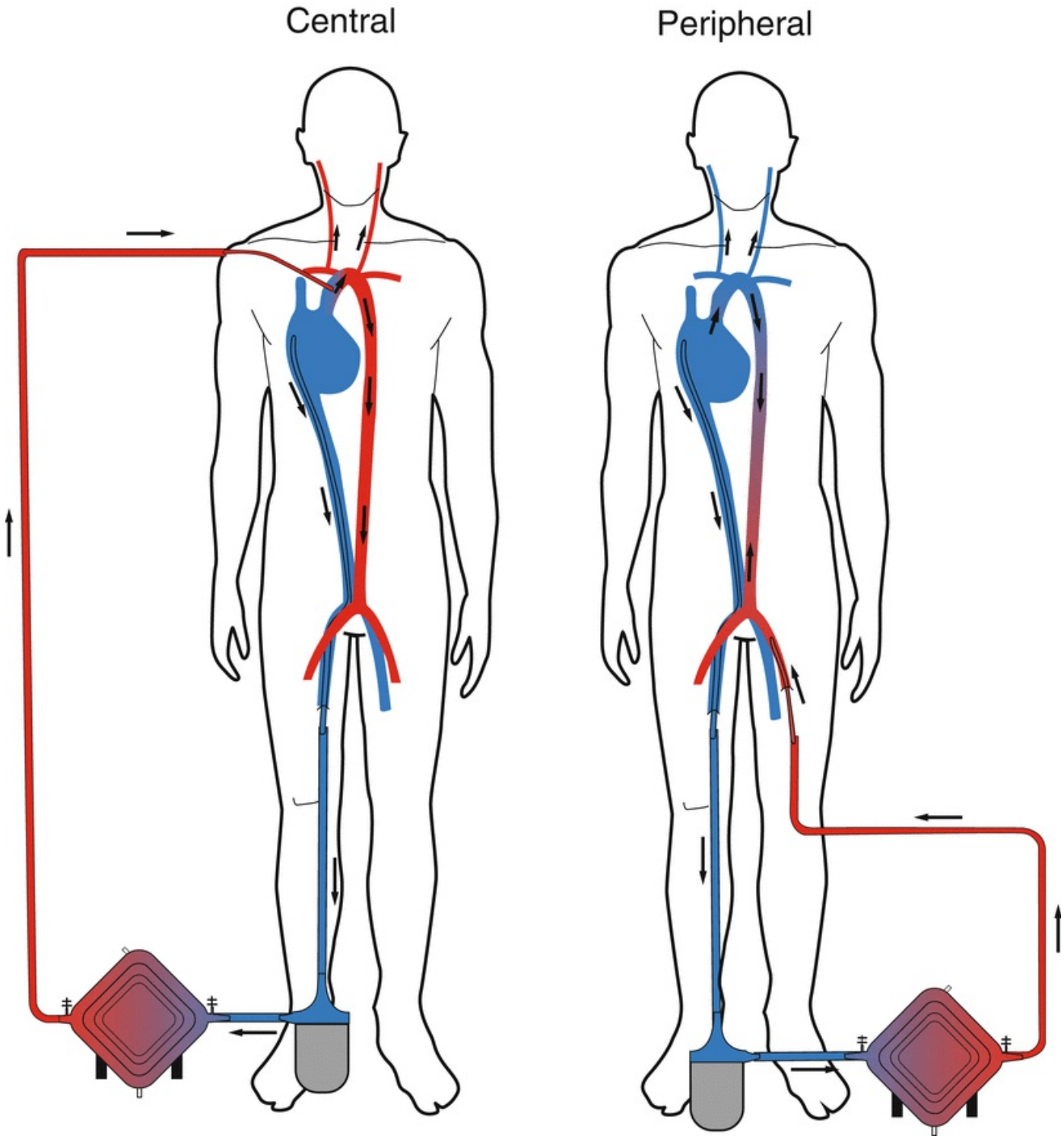

Fig. 16.8 Schematic showing the potential for upper body hypoxemia during peripheral VA ECMO in patients with impaired pulmonary function. In the *left-hand image* the return (arterial) cannula (oxygenated blood) is placed in the ascending aorta. The oxygen saturation of blood in the ascending aorta is dependent on the volume and oxygen saturation of blood ejected from the left ventricle and that from the ECMO circuit. If circuit flow is adequate, satisfactory arterial oxygen saturation can be achieved, even in the presence of severely impaired pulmonary function and good LV ejection. In the *right-hand image* the return cannula is placed peripherally in the femoral artery. In this

circumstance, if there is significant ejection from the left ventricle, the oxygen saturation of blood in the ascending aorta is mainly determined by pulmonary function. If pulmonary function is severely impaired the upper body (heart, brain, upper limbs) receives deoxygenated blood

Because pulmonary dysfunction, bleeding, and infection are common problems in ECMO-supported transplant patients, our preferred practice is to place the arterial cannula centrally in the ascending aorta and to place the drainage cannula peripherally in the IVC with the tip in the RA (Fig. 16.8). This technique still allows the chest to be partially closed (Fig. 16.9) but avoids the potential problem of upper body hypoxemia.

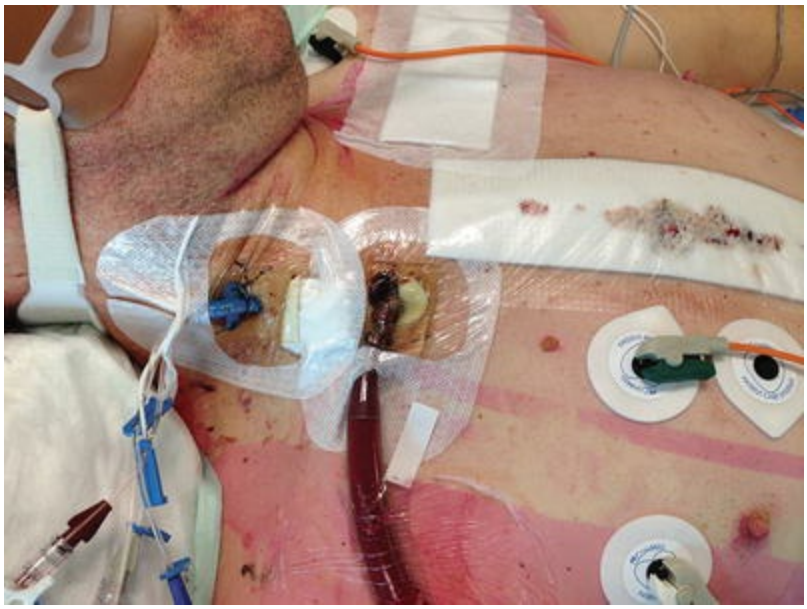

Fig. 16.9 Central arterial cannulation during VA ECMO following heart transplantation. The return (arterial) cannula (shown) is placed in the ascending aorta, exits the sternum via the sternal notch, and passes through the skin just lateral to the mid-line. The sternotomy incision has been closed but the sternum is unwired. Tunneling of the arterial cannula through the skin was performed following separation from cardiopulmonary bypass but before initiating ECMO. The drainage (venous) cannula (not shown) was placed peripherally in the femoral vein and advanced into the right atrium

Gas Exchange and Hemodynamics During VA ECMO

The same circuit is used for VA ECMO as for VV ECMO (Fig. 16.5). With VA ECMO, the relative outputs of the ECMO circuit and the LV determine the patient's S_aO_2. If there is no LV ejection, S_aO_2 is dependent on the oxygen saturation of blood in the ECMO return cannula, which is typically 100 %. Thus, with VA ECMO normal S_aO_2 (i.e., >97 %) can usually be achieved, and the F_iO_2 of the sweep gas need not be 1.0, but titrated to S_aO_2. If LV ejection is occurring and the lungs are working well, S_aO_2 will also be normal. However, as noted above, the presence of significant LV ejection and severely impaired lungs result in upper-body hypoxemia.

The balance between carbon dioxide production and sweep gas flow determines

P_aCO_2. Under most circumstances, normocarbia is achieved with a sweep gas flow of 1–2 times ECMO flow. During VA ECMO support the ventilator should be set to rest settings, as described for VV ECMO.

Assuming cardiac function is severely impaired, ECMO flows of 4–6 L are adequate for most adults. A pre-oxygenator SO_2 is a reasonable surrogate for S_VO_2, and ECMO flows should be titrated to maintain a value greater than 60 %. Hypotension (MAP < 60 mmHg) during VA ECMO support implies vasoplegia, and should be treated with a vasopressor such as norepinephrine. Hypertension (MAP > 90 mmHg) implies vasoconstriction, and should be treated with sedation, analgesia, and a vasodilator, such as sodium nitroprusside. Since centrifugal pumps are afterload dependent, arterial hypertension reduces pump flow for a given pump speed.

Problems and Troubleshooting

Common problems and their potential solutions during ECMO are listed in Table 16.2. Three problems encountered during VA ECMO support demand urgent attention: (1) severe LV distension, (2) cardiac tamponade, and (3) upper-body hypoxemia.

Severe LV distension is suggested by a nonpulsatile arterial waveform and the development of pulmonary edema clinically and radiographically. TEE examination should be performed to assess the severity of this problem. TEE features suggesting the need for urgent intervention are a severely distended noncontractile ventricle, absent opening of the aortic valve, severe mitral regurgitation, pronounced rightward bowing of the atrial septum, spontaneous echo contrast in the LV. LV distension may be ameliorated by increasing ECMO flow (to reduce pulmonary blood flow) and increasing inotropic support (to promote LV ejection). However, definitive treatment involves creating an atrial septal defect (ASD) to decompress the left heart and maintain intracardiac blood flow. An ASD can be created in the catheter laboratory using a balloon or blade catheter or, more commonly following heart transplantation, surgically in the operating room [41, 42].

Cardiac tamponade is an ever-present risk during ECMO support following thoracic surgery. Signs of tamponade include falling pump flow despite increasing pump speed, hypotension, rising CVP, and increased suction events. Suction events may indicate hypovolemia but can also signal cardiac tamponade. The diagnosis is confirmed with TEE. Urgent surgical decompression is indicated.

Both cardiac tamponade and acute LV distension can result in blood stasis within the heart, which is a potent risk factor for intracardiac thrombus formation, even in the presence of adequate anticoagulation. On TEE examination, the finding of spontaneous echo contrast within the chambers of the heart demands urgent intervention to promote intracardiac flow. These interventions include relief of cardiac tamponade, increasing inotropic support, and creating an ASD.

In the first instance, upper body hypoxemia should be treated with increasing ECMO flows to reduce blood flow through the lungs. Inotropic drugs should be discontinued to minimize LV ejection. In an emergency situation (e.g., $S_aO_2 < 80$ %) intravenous beta-blockade may be helpful. However, these interventions are likely to be temporary. Definitive treatment depends on the severity of the pulmonary injury and the extent of cardiac recovery, and includes: (1) weaning from ECMO support, (2) conversion to central VA ECMO, (3) conversion to VV ECMO, or (4) conversion to venoarteriovenous (VAV) ECMO. VAV ECMO involves placing a second return cannula in the right IJV, thereby delivering oxygenated blood to pulmonary artery. To avoid recirculation the drainage cannula must be withdrawn from the RA into the IVC, as described for VV ECMO.

Weaning VA ECMO

Unlike VV ECMO, turning off the sweep gas cannot be used as a trial off ECLS, as this maneuver creates a large right-to-left shunt of deoxygenated blood. Thus, VA ECMO is weaned by slowly reducing flows to 1–2 L/min under modest inotropic support (e.g., epinephrine 0.05 μg/kg/min.) using standard ventilator settings. Careful tracheal toilet should be performed before increasing ventilator settings. Weaning should be performed under TEE guidance, assessing the effect of reduced flows on ventricular function. ECMO flow should not be maintained at less than 2 L/min for sustained periods as blood clots may form in the circuit. If the patient is stable (MAP > 65 mmHg, CVP < 14 mmHg) on 1–2 L/min flow for 30 min circuit flow, plans for decannulation can be made. Unless peripheral cannulation has been used, decannulation should be performed in the operating room.

Incidence and Outcome from Extracorporeal Life Support Following Heart Transplantation

Approximately 10–25 % of patients require ECLS following heart transplantation [13, 34, 35, 43]. Early survival ranges from 40 to 75 % [13, 34, 35, 43, 44]. The need for ECLS is associated with worse outcome over the longer term. In one study, the need for ECMO following heart transplantation was associated with 1-year and 5-year survival rates of 39 % and 34 % respectively; similar figures for non-ECMO heart transplant recipients were 78 % and 71 % respectively [13]. However, as with lung transplantation, adverse outcome is likely to be related to the presence of PGD rather than the use of ECLS.

Duration of ECLS following heart transplantation is usually short, with most survivors being weaned in less than a week [35, 43]. In contrast to lung transplant, ECLS may also be used successfully for treating acute rejection in the early

postoperative period [39, 40].

Conclusions

Provision of ECLS may be lifesaving in patients with severe PGD following heart and lung transplantation. If indicated, ECLS should be instituted early to prevent further damage to the graft and minimize the risk of developing multiorgan failure. While the choice of ECLS is partly dependent on institutional experience and the nature and severity of the organ failure, some recommendations can be made. First, VV ECMO should be used as the primary mode of support following lung transplantation. Second, VA ECMO or a centrifugal VAD should be used following heart transplantation (we favor ECMO for biventricular or cardiorespiratory support). Finally, if there is significant pulmonary dysfunction, VA ECMO using a central arterial cannula should be used following heart transplantation.

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17. Perfusion Management for Thoracic Transplantation Surgery

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Introduction

Perfusionists play an important role in the perioperative management of thoracic transplantation surgery. In this chapter, we briefly discuss the history, equipment, indications, goals, and implications of different types of mechanical circulatory support, including full cardiopulmonary bypass (CPB) and veno-venous (VV) and veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) during lung and heart transplantation. We also explore some of the newer options for extracorporeal organ

preservation. Considerations, misadventures, and complications are highlighted throughout. Perfusion technology and operation are highly technical with a scope far beyond any single book chapter. This chapter is intended to provide the anesthesiologist with a broad overview of the use of extracorporeal life support in the setting of adult heart and lung transplantation as implemented at the University of Pittsburgh. Finally, implications and outcome studies related to the use of extracorporeal support in heart and lung transplant follow.

Indications for Mechanical Circulatory Support During Thoracic Organ Transplantation

The first successful operative use of CPB is credited to John Gibbon in May 1953 to facilitate atrial septal defect repair [1]. This landmark operation followed two decades of animal trials and his first fatal failure on a human the previous year. Initial systems have undergone significant improvements in safety, reliability, and biocompatibility over the last 60 years. While all heart and heart-lung transplantations require full CPB, many single- and double-lung transplants can be completed without the use of an extracorporeal circuit (ECC). Indications for ECC in lung transplantation (LTX) are influenced by patient factors, as well as the institution's and surgeon's preferences. While some institutions may prefer to perform all of their LTX with ECC, most others will choose their patients for intraoperative support based on elective preoperative factors or intraoperative hemodynamic and ventilator parameters. Mechanical support with VV or VA ECMO is initiated preoperatively in patients with significant life-threatening preoperative respiratory compromise (severe pulmonary hypertension, severe pulmonary fibrosis, and cystic fibrosis). LTX in such patients cannot be performed without ECC. Since VV ECMO will not offer enough hemodynamic support during pulmonary artery (PA) clamping and surgical manipulations, VV ECMO is converted to VA ECMO or full CPB for the procedure.

A variety of models have identified predictors of the need for intraoperative ECC in LTX, including double LTX, 6-min walk distance, right ventricle (RV) function, baseline oxygenation, presence of restrictive lung disease, desaturation with activity, and others [2]. Other studies find no reliable preoperative information useful as predictors in serial double LTX [3]. Patients with severe pulmonary hypertension, RV dysfunction, and severe tricuspid regurgitation are usually candidates for ECC support during transplantation or even before induction of anesthesia. Expected or unexpected difficult airway management in patients with extremely limited reserve may also necessitate ECC before the induction of anesthesia.

Otherwise, intraoperative cardiopulmonary behavior dictates the requirement for support in most patients. Increased PA pressures may necessitate bypass when unilateral

PA clamping would result in intolerable demands on the RV. Some patients undergoing LTX cannot tolerate single-lung ventilation in terms of either oxygenation or ventilation and require ECC. It is not uncommon for a newly reperfused single lung to have inadequate function to facilitate the second pneumonectomy and transplant without ECC.

In our institution, the decision to initiate ECC is based on a collaborative assessment between the surgeon, anesthesiologist, and perfusion team member. Our thoracic transplant anesthesia protocols call for access to the femoral artery and vein for nearly all LTX patients, even when off-pump or central support is planned. Peripheral bypass can be rapidly obtained by guide wire exchange in the event of catastrophe during any stage of the surgical procedure. For all thoracic transplant procedures, a perfusion team member with a primed ECC circuit is available at all times from induction until the patient is discharged from the operating room.

Perfusion Goals

The perfusion team's primary goal is to provide the substrates needed for cellular preservation (oxygen, electrolytes, glucose, etc.) and removal of metabolic by-products (lactate, CO_2, etc.) when the innate cardiopulmonary system cannot. CPB or VA ECMO also allows the surgeon improved access and visualization of the surgical field. Any of these techniques can be performed through central or peripheral cannulation.

Tissue perfusion is provided by flow through a large-bore cannula. The flow and pressure required for adequate perfusion depend primarily on tissue mass (body surface area [BSA]), temperature, metabolic factors, brain activity, and hemoglobin content. A cardiac index of 2–2.3 L/min/m^2 is considered adequate under normal conditions. In general, 1.7–2.5 L/min/m^2 of flow is standard practice; anything less than 2 L/min/m^2 is considered low flow. Metabolic needs are greatly reduced with hypothermia; anesthesia and paralysis and lower flows are tolerated under these conditions. Perfusion pressure is targeted to match the patient's baseline blood pressure ±20 % with increasing pump flows. This typically is a mean arterial pressure of 50–80 mmHg. This range is usually sufficient for the otherwise healthy transplant population, but may be altered for patients with uncontrolled hypertension, renal dysfunction, and known cardiac or vascular disease.

It is important to remember that circuit flow may be limited by cannula size, positioning, surgical manipulation, and volume status. In addition to pressure and flow targets, we monitor cerebral oxygenation using near-infrared spectroscopy (NIRS), serial arterial blood gases (pH, lactate levels), continuous in-line oximetry of arterial and mixed venous blood, and urine output. Patients with NIRS within 20 % of baseline, mixed venous saturation >60 %, or minimal metabolic acidosis who make adequate urine will likely receive adequate perfusion.

The Bypass Circuit

At a basic level, blood is drained via cannulas in the superior vena cava (SVC), inferior vena cava (IVC), and right atrium (RA) to the venous reservoir of the CPB machine; then, blood is pumped (with a roller or centrifugal pump head) through the oxygenator and pumped back into the patient's systemic circulation via the arterial cannula in the ascending aorta. ECMO circuit lacks venous reservoir and cannot compensate for sustained loss of venous return (Fig. 17.1).

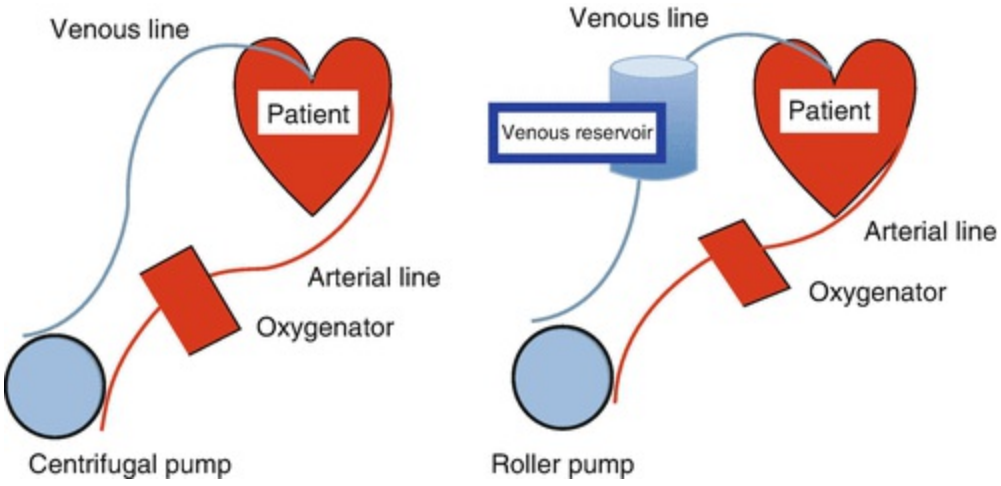

Fig. 17.1 Schematic representation of a cardiopulmonary bypass and ECMO circuit

At the start of surgery, it may be unclear which, if any, mechanical support (CPB versus ECMO) will be required. In the past, we would prepare both ECMO and CPB circuits separately in the operating room (Fig. 17.2a, b). Conversion from ECMO to full CPB may be required in the setting of poor venous return with inability to maintain adequate flows. This could result from blood loss, inadequate drainage from sequestration and cannula position, or kinking. The anesthesia team attempts to compensate for this by administration of volume via their vascular access, but this may not be sufficient or practical. Another reason for conversion to CPB is air entrainment into the ECMO system. During ECMO for LTX, any vascular injury or perforation in close proximity to the drainage cannula can cause air entrainment into the ECMO circuit and air embolism to the patient. Conversion of ECMO to CPB during such critical events can be desperate, clumsy, and potentially hazardous. We developed a hybrid bypass machine that allows a reservoir to be in parallel with, but excluded from, the ECMO circuit to allow conversion to full CPB with only the change of clamp position. This system can easily incorporate a reservoir for rapid fluid administration or removal of large air pockets without the need to change systems or cannula (Fig. 17.3).

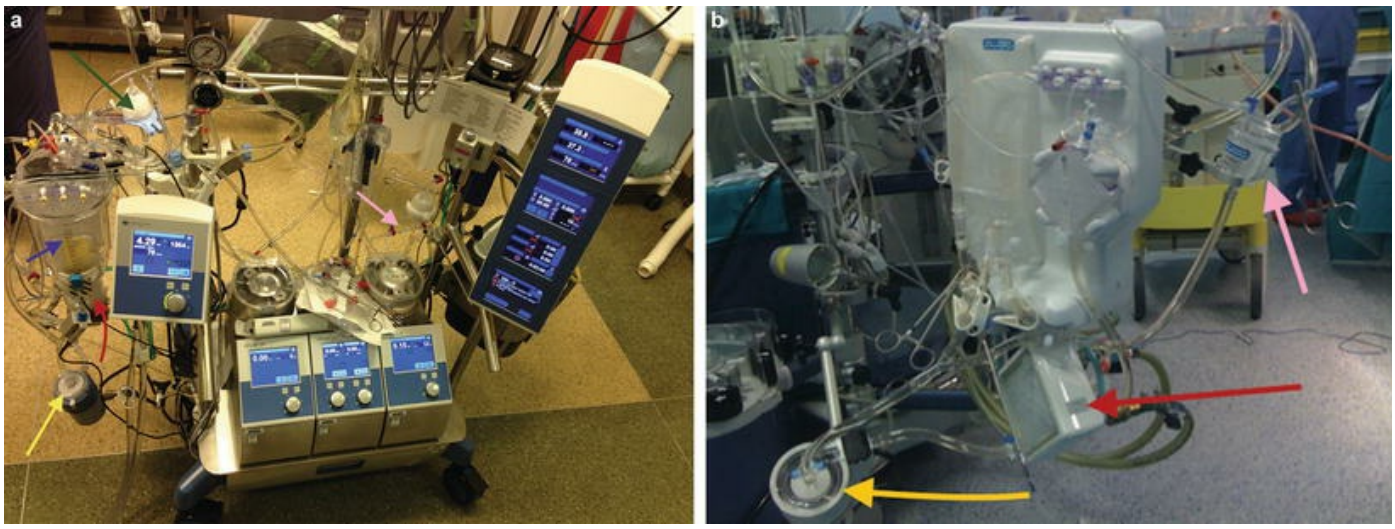

Fig. 17.2 (**a**) Cardiopulmonary bypass circuit . *Blue arrow*—venous reservoir, *yellow arrow*—centrifugal pump, *red arrow*—oxygenator-heat exchanger, *green arrow*—arterial line filter, *pink arrow*—pulmonoplegia delivery assembly. (**b**) ECMO circuit with oxygenator (*red arrow*) and pump (*yellow arrow*)

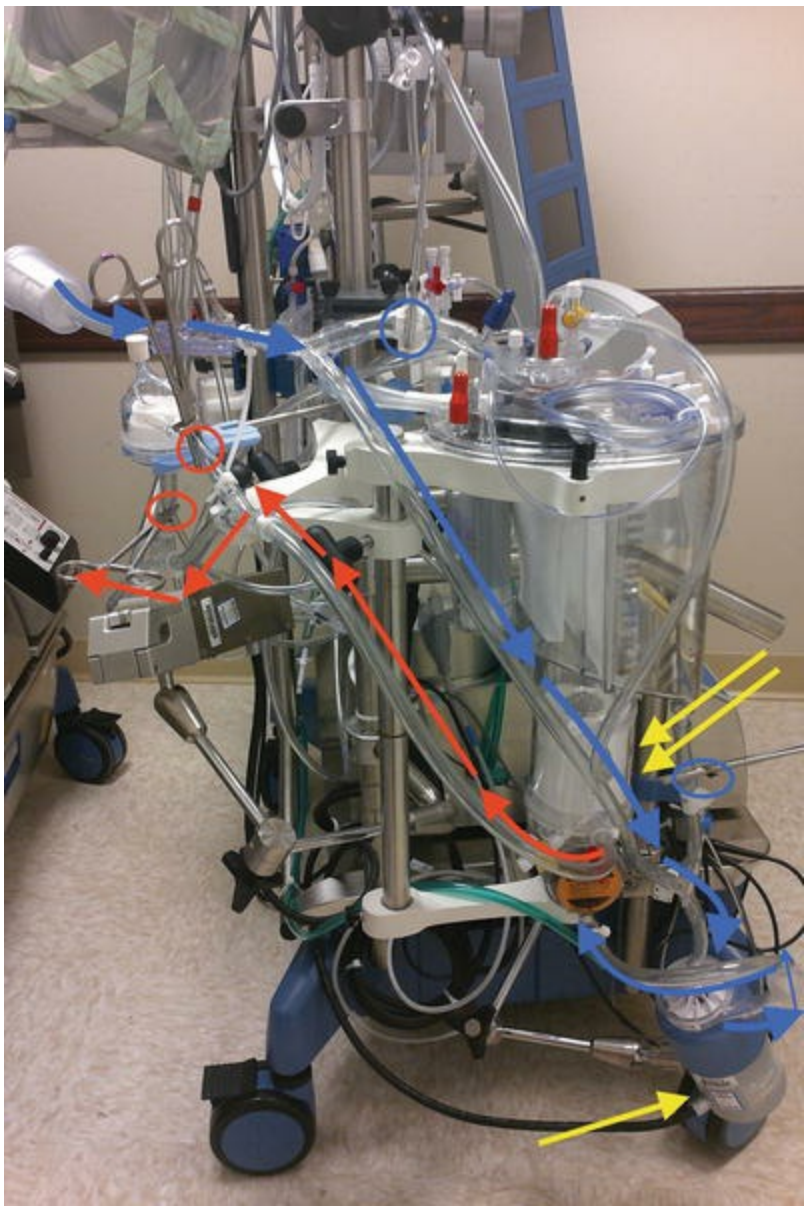

Fig. 17.3 Hybrid cardiopulmonary circuit . *Blue* and *red lines* indicate ECMO circuit bypassing venous reservoir (*blue circles* indicating clamps used to bypass venous reservoir) and arterial filter (*red circles* indicating clamps used to bypass arterial line filters). Blood flows from venous line, pumped by the centrifugal pump into the membrane oxygenator back into the patient in the ECMO circuit. Clamps shown in figure can be released to convert ECMO circuit to full CPB at any critical period during lung transplantation in this hybrid system. Clamps will be placed on ECMO circuit line before conversion

Cannulation

The cannulation site is variable during transplantation depending on the expected tolerance of anesthetic induction, space available in the chest cavity, peripheral vascular size, and expected difficulty with dissection and duration of expected post-procedure support. Cannulation can be central or peripheral (Fig. 17.4). Central cannulation allows for larger cannula placement and avoids peripheral vascular injury

during cut-down, percutaneous access, or dilation. Central cannulation is generally preferred for planned support, given the increased flow capability, but requires dissection and more preparation for direct access, which is not always possible. Central access may be further compromised in the setting of redo surgery when dissection is more difficult and anatomy is less clearly defined.

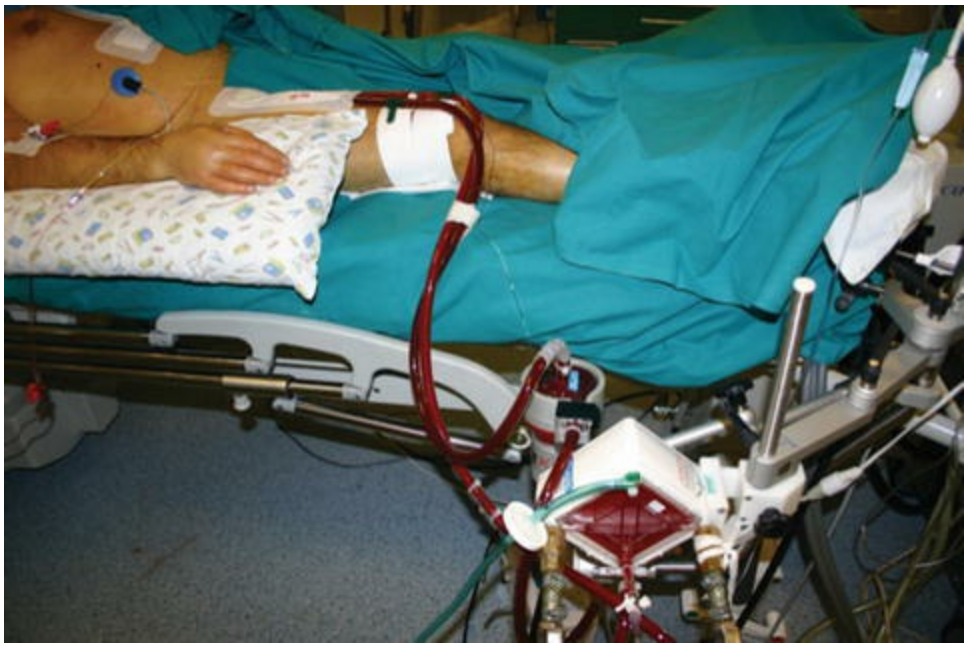

Fig. 17.4 Peripheral femoral venous to femoral arterial ECMO. (© 2013 Formica F, Paolini G. Published in [Formica F, Paolini G. Veno-arterial extracorporeal membrane oxygenation for refractory cardiogenic shock and cardiac arrest. In: Firstenberg MS, editor. Principles and Practice of Cardiothoracic Surgery. Rijeka: InTech; 2013. p. 273–292. DOI: 10.5772/54719] under CC BY 3.0 license)

Venous drainage cannulae are large and range from 10 to 40 French in size. Typically, an average-size patient is drained centrally using a single cannula with openings to receive blood from the IVC and RA (dual stage). Single-stage cannulas drain either the IVC or SVC. Three-stage cannulas have openings to drain the SVC, RA, and IVC through a single cannula.

Peripheral venous drainage of the SVC/RA junction is usually achieved via a long catheter inserted via the right femoral vein. If the patient already has an internal jugular venous cannula for VV ECMO, surgeons will connect the femoral and jugular access using a Y-piece for effective drainage. A peripheral venous cannula can be placed using cut-down or percutaneous methods. We prefer percutaneous access with a modified Seldinger technique of advancement of dilators and cannula over a wire (Fig. 17.5) because of reduced blood loss and infectious complications.

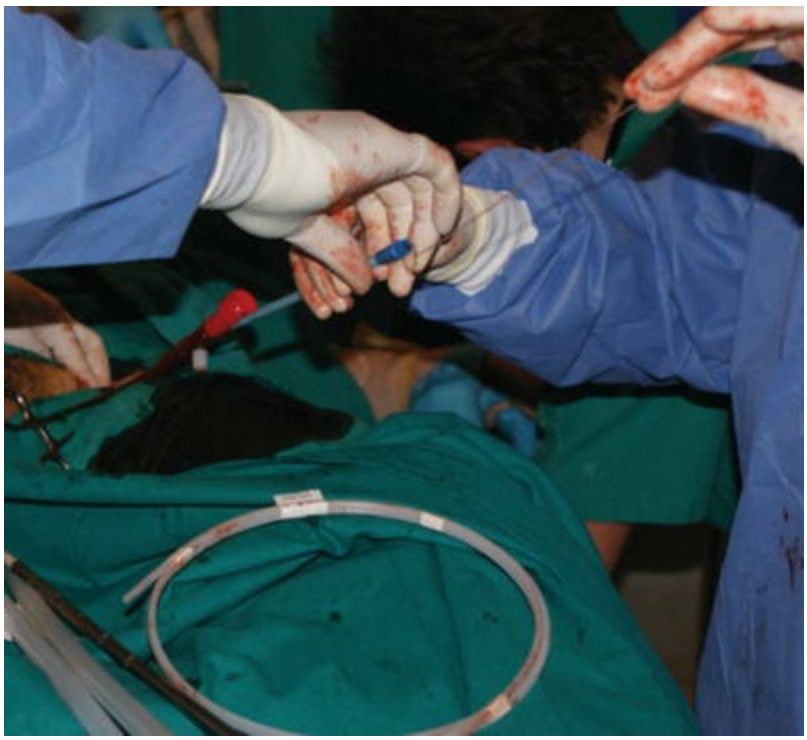

Fig. 17.5 Seldinger technique used for peripheral percutaneous arterial and venous cannulation for ECC. (© 2013 Formica F, Paolini G. Published in [Formica F, Paolini G. Veno-arterial extracorporeal membrane oxygenation for refractory cardiogenic shock and cardiac arrest. In: Firstenberg MS, editor. Principles and Practice of Cardiothoracic Surgery. Rijeka: InTech; 2013. p. 273–292. DOI: 10.5772/54719] under CC BY 3.0 license)

Venous drainage depends on catheter and tubing size, blood volume, height difference between the pump and patient, and the presence of vacuum-assisted drainage (on CPB). Obese patients with higher BSA and flow requirements do not also have concomitant peripheral vascular enlargement to facilitate insertion of bigger size cannula, and thus can be difficult to manage through peripheral cannulation.

Arterial access for CPB and ECMO can be obtained from any major artery, but is generally placed in the ascending aorta (central) or in the femoral artery (peripheral). A variety of cannula shapes and sizes exist. Ideally, flow is directed parallel to the aorta to avoid shear injury to the arterial wall. Cannulation can be direct or wire guided via the Seldinger technique (Fig. 17.5). Just as with venous cannulation, we prefer the percutaneous technique for femoral access. Arterial cannula shapes are variable to facilitate the desired direction of flow. Newer cannulae have thinner walls and multiple openings to improve flow characteristics and reduce vascular shear forces on the aorta. If flow is misdirected up a major arch vessel, hyperperfusion syndrome and a higher embolic burden to that vessel will be the end result. For this reason, we use transesophageal echocardiography (TEE) guidance to assure proper placement (Fig. 17.6a, b). With peripheral cannulation, it should be noted that aortic plaques may be more easily dislodged when aortic flow is reversed. Occlusion of arterial flow because of the catheter can cause distal limb ischemia. In our institution, we place a distal

perfusion cannula (5–8 F) that diverts flow to the affected limb (Fig. 17.7) if ischemia develops by physical exam or NIRS desaturation of a limb. Some institutions favor femoral or axillary arterial end-to-side anastomosis with a graft material before cannulating the graft. This is more invasive but precludes limb ischemia because the cannula is not obstructive.

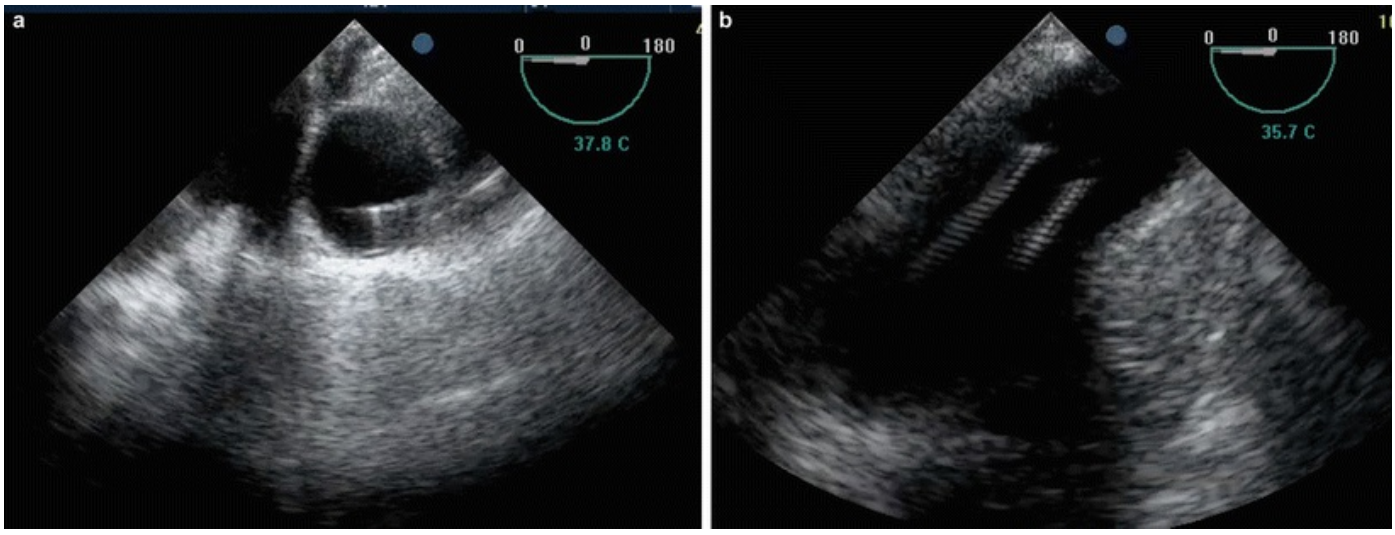

Fig. 17.6 (**a**) Wire confirmed in the descending thoracic aorta during femoral arterial cannulation (peripheral cannulation). (**b**) Central aortic cannulation confirmed by the position of the tip of the cannulae in the proximal arch of aorta

Fig. 17.7 Distal perfusion cannula to decrease limb ischemia during peripheral ECC. (© 2013 Formica F, Paolini G. Published in [Formica F, Paolini G. Veno-arterial extracorporeal membrane oxygenation for refractory cardiogenic shock and cardiac arrest. In: Firstenberg MS, editor. Principles and Practice of Cardiothoracic Surgery. Rijeka: InTech; 2013. p. 273–292. DOI: 10.5772/54719] under CC BY 3.0 license)

Cannula placement in the operating room is confirmed in real time using TEE. TEE-guided procedures add real-time identification of wires prior to vascular dilation and

allow accurate cannula positioning without the need for repeated manipulation. Dissection or other vascular injuries are dreaded complications of vascular access and can be monitored with TEE during and after cannulation.

Although pressure and flow are generated by the pump as described below, the resistance to venous drainage and to arterial flow is primarily determined by cannula and tubing diameter. The flow characteristics for each cannula are described in the manufacturer's documentation, but often underperform the listed benchmark values. The undersizing of cannula can significantly reduce the capability of ECC. Oversized cannulae can cause vascular injury or obstruction. When a cannula occupies much or all of a venous structure, blood flow peripherally will be compromised by venous back pressure. This can result in SVC syndrome or cerebral ischemia. With IVC obstruction, there can be hepatic, renal, bowel, or limb congestion.

Tubing

Clear polyvinyl chloride (PVC) tubing bonded with heparin and other advanced biocompatible coatings connect the components of the bypass circuit together. Enhanced biocompatible coatings reduce surface contact activation, and inflammatory response, and provide improved outcomes such as decreased time to extubation [4]. These tubes can be of any length and diameter, but most institutions use 3/8″ or 1/2″ diameter tubing for venous drainage during CPB and 3/8″ tubing for ECMO. The smaller 3/8″ tubing reduces priming volume and its dilution effect and has been shown to decrease transfusion and the inflammatory response [5, 6].

Use of smaller tubing can result in incomplete drainage of the surgical field and also necessitates the use of a vacuum to achieve sufficient venous drainage. Our microcircuit uses a 3/8″ venous line, a raised reservoir, vacuum-assisted venous drainage (VAVD), and an integrated arterial filter to reduce dilution of the patient. The ½″ pump uses a ½″ venous line with a reservoir placed below the patient's level to use gravitational forces to assist drainage. The venous line must be fluid filled or an airlock can occur.

During VAVD, negative pressure (maximum −40 mmHg) is applied to the venous reservoir to facilitate venous drainage. This allows initiation of CPB with a dry venous line to prevent further dilution. This form of augmented flow does not come without risks. VAVD can also result in air pulling out of the solution, causing the potential for gaseous microemboli in the patient if the negative pressure is too low. Safety devices on the vacuum regulator include a negativity safety vent that limits suction to −100 mmHg, as well as an excess positive pressure relief valve if the regulator gets over-pressurized. The pump also employs its own pressure relief valve. Air entrainment can create an airlock, stopping effective circulatory support. While an airlock can be remedied mechanically, air embolus can be devastating and has resulted in morbidity as well as frank brain death [7]. The use of assisted drainage also increases hemolysis [8].

Drainage in ECMO is not passive. ECMO is a closed circuit and blood is actively pulled into the system by the negative pressure generated by a centrifugal head (preload dependent).

Improper or loose connections between segments of tubing are a source of airlock and embolism and are therefore securely fastened with locking ties. Tubing may be misconnected at any point. This is more commonly done on the surgical field by misconnecting the venous cannula to the ECC-pressurized outflow and the aortic cannula to the venous drainage. Misconnections can be prevented on many levels. Clear plastic tubing is lined with color coding: blue, yellow, and red. In addition, there is usually a reduced diameter for arterial tubing since the venous outflow is facilitated by larger tubing. Pressure monitoring lines on the arterial circuit should confirm pulsatile pressure that correlates closely with the patient's arterial pressure prior to initiation of cardiopulmonary support. With initiation of ECC, the arterial pulse pressure should narrow and central venous and PA pressures should fall to zero.

Reservoir

The venous reservoir holds excess volume from the patient that was in the heart and lungs. Reservoirs are present only for true CPB and require intense anticoagulation since blood stagnates in this container. They are usually 3–4 L in capacity. This compartment provides a more consistent source of blood for the pump and eliminates the need for intravascular administration of volume while on bypass. Volume changes in the reservoir can be due to bleeding in the surgical field, surgical manipulations of the heart and major vessels, vascular tone (constriction or dilation), as well as urine output.

There are two types of reservoirs: soft and rigid. We use exclusively rigid reservoirs made of polycarbonate. The benefits of rigid reservoirs are twofold: more accurate volume measurement and automatic air venting. This helps with the estimation of the need for additional volume and estimation of the time before reservoir exhaustion. All CPB systems have level detectors that trigger an alarm and shut off the pump if the volume gets too low to prevent air entrainment into the arterial side of the pump. Rigid containers are automatically vented of air and allow mixing of cardiotomy drains, vents, and cannula drainage. The air-blood interface is a significant source of inflammatory response. A 47 μm screen filter is used to filter the returning venous blood. The screen filter also includes a polyurethane defoamer. The suction side of the reservoir has a depth filter to filter clot and any particulates that may enter the system from the vents and suction from the surgical field.

Soft reservoirs are basically a plastic bag that expands with venous return. As the bag collapses, volume measurements become inaccurate. Air entrained into these containers must be manually aspirated. Additionally, as the soft reservoir fills with fluid or air, it can create back pressure, reducing venous drainage. The benefit of a soft

reservoir is a smaller priming volume and less dilution.

Pump

There are two basic pump mechanisms: centrifugal impellers and roller pumps. At our institution, we use exclusively centrifugal impellers for both CPB and ECMO. These pumps generate forward flow through the oxygenators and filters and provide perfusion pressure.

Roller mechanisms are mechanically simple. A roller head in contact with the tubing partially compresses and rolls up the tubing some length before losing contact and another roller head a distance back repeats this action. This forces the blood ahead of the roller forward and creates a vacuum behind, drawing the venous return forward. Each pass of the roller creates a stroke volume and total flow is the product of this volume times the rotations per minute (RPMs). The rollers are set to be partially non-occlusive so as to reduce hemolysis. The amount of occlusion is set by the perfusionist. Formed elements are damaged by both under- and over-occlusion. Over-occlusion causes crush injury to the elements of blood. Under-occlusion results in a high-velocity backflow that causes shear injury to blood. This propulsion is afterload independent. Any partial occlusion, clamping, or kinking distal to the roller pump can cause the tubings to over-pressurize if the safety mechanisms are not activated. This over-pressurization can cause connectors to decouple, as well as cause cracks in the venous reservoir. Safety device alarms will make the perfusionist aware of a high pressure (usually 325–350 mmHg) and the pump will shut off if the pressure reaches a certain level (>375 mmHg). Safety systems will disable pumping when high pressures are sensed, but this reactionary mechanism may not prevent damage to components. On the other hand, an occluded venous return line may result in a cavitation phenomenon behind the roller. In this setting, without additional preload to fill the evacuated stroke volume, negative pressure is created and vaporizes soluble gases into bubbles, which can then be delivered to the patient.

The centrifugal pump head consists of a cone-shaped plastic housing that contains a magnetic impeller. The pump head is seated into the drive console that has magnetic bearings that spin, causing the impeller inside the cone housing to spin. This creates a vortex that pulls blood in by generating negative pressure at the inlet; then, the rotational force of the vortex pushes blood outward, creating positive pressure towards the outlet of the cone housing driving blood to the oxygenator and patient. If the pump becomes entrained with small amounts of air, bubbles will remain in the center of the vortex while denser elements move outward. Massive air intake will disrupt vortex formation and stop pump flow rather than forcing large volumes into the patient.

This centrifugal propulsion differs fundamentally in its reaction to loading conditions and in terms of cellular trauma. The centrifugal pumps are preload and

afterload dependent. The pump will not flow unless there is enough negative pressure to pull blood into the system. If the negative pressure is too low, cavitation of the cannula on the patient's vessels can occur. This can be due to cannula size and/or the volume status of the patient. If there is excessive negative pressure, the inflow line occludes and the pump lowers flows or stops flowing. Excessive negative pressure will also cause hemolysis. Afterload dependence can be seen when flow rate increases without a change in revolutions per minute (RPM), because of a decrease in the patient's systemic vascular resistance. Increased resistance to pump outflow causes flows to decrease without a change in RPM.

Both pump systems require electricity and most devices have built-in battery backup. Hand cranking of either mechanism is possible if battery reserves should fail during bypass. Modern equipment of either type is highly reliable.

Both roller and centrifugal pumps deliver essentially laminar, nonpulsatile flow. The argument that pulsatile flow (cyclic sheer stress) improves microvascular perfusion is yet unproven. Bench devices and ventricular assist technology will continue to investigate the benefits of pulsatile flow. Currently, the only way to provide this kind of flow intraoperatively is with the addition of balloon counter-pulsation.

Oxygenator/Heat Exchanger

Blood enters the heat exchanger before it enters the oxygenator. The heating and cooling of the patient change the solubility of gases; therefore, heat transfer occurs before oxygenation. Usually heat exchangers are made of stainless steel, aluminum, or polypropylenes, which all have good thermal conductivity. The heat exchanger has a water and a blood side. The blood side has surface agents to minimize blood activation and to maximize heating and cooling. The blood and water pathways flow in a countercurrent direction, which also reduces outgassing of solutions due to rapid changes in temperature. The temperature gradient should be kept at a maximum of 10° between the water temperature and the patient's blood temperature. Rapid cooling is much better tolerated than rapid rewarming, which can result in vaporization of dissolved gasses and increase the microembolic load.

Blood flows to the oxygenator before being returned to the patient. Historically, bubble oxygenation preceded the use of membrane oxygenators. These have been entirely replaced given the much higher risk of gas embolization that occurs when bubbles are added intentionally to the system. Membrane oxygenators are microporous hollow fiber membranes that have a semipermeable barrier, which separates fluid from the gas phase. The diffusive properties of the oxygenator membrane allow the transfer of O_2 and CO_2 between the phases by relying on differences in partial pressure of medical gases. Oxygenators work by blending compressed air and O_2 to maximize the driving

pressure difference for O_2 diffusion. The rate of fresh gas flow delivered is called the sweep rate and determines the amount of CO_2 removal.

After oxygenation and heating, blood is passed through a filter before being returned to the patient. Filters can be quickly changed if they become saturated with clot. It is important to monitor these filters, since they can be an early warning of ineffective anticoagulation.

Additional Safety Features

A number of other safety devices are installed on the ECC. These include pressure monitoring lines, bubble detection, reservoir exhaustion detection, emergency shutoff mechanisms, and a number of one-way valves to prevent flow reversal. These devices improve the margin of safety in operating these systems.

Much like in anesthesia care, despite all of the technology improvements and monitoring, it is inevitably the human that has the greatest impact on safe operation. The importance of communication and coordination of bypass operations cannot be understated. Checklists improve the reliability of assembly and operation of these complex machines. Transplantation is a team sport; good closed-loop communication, mutual respect, and vigilance are required by all players for optimal performance. All parties have a duty to report concerning or unusual findings or laboratory or monitoring values in real time.

In addition to those functions noted previously, ECCs have a variety of other built-in functions. There are ports for drug administration and blood gas sampling. A typical anesthesia vaporizer allows administration of volatile anesthetic when the lungs are bypassed. Small tubing lines allow recirculation to reduce stagnation and clotting. Additional devices called vents and pump suckers, which recover additional blood, may be incorporated.

“Pump Suckers”/Vents

Surgical dissection can cause significant blood loss depending on the degree of adhesions, coagulation status, and prior surgery. During CPB, blood recovered from the surgical field can be returned to the venous reservoir via pump suckers. LV distension during surgery can be caused by aortic insufficiency, Thebesian drainage, and bronchial drainage. Normally 1 % of cardiac output is directed towards the bronchial vessels. In the setting of advanced pulmonary disease (bronchiectasis), this may increase to as high as 9.3 % [9]. LV distention from these sources increases the oxygen demand of the myocardium. LV vents are used to decompress LV and vents return blood to the circuit. When ECMO is planned, the use of vents and pump suction is not possible. Blood from

the field can be recovered through cell salvage, albeit delayed. The advantage of CPB is such that return is immediate and also coagulation factors are not washed from the blood. This blood that has been extracted from the field does appear to have a higher inflammatory cytokine content, which can contribute to systemic inflammation and injury [10]. Aspiration of air, pericardial fat, and non-blood elements through vents and pump suckers may also cause hemolysis or microembolism and initiate the systemic inflammatory response [10].

Modified Ultrafiltration (MUF)/Hemoconcentration

Occasionally, patients present with or develop volume overload, especially in the setting of renal failure. By diverting a portion of the systemic outflow or returning venous blood to a specialized network of hollow fibers with micro-porous membranes, similar in concept to the CPB oxygenator, convective forces extrude plasma volume. These units can effectively remove volume without disrupting the balance of electrolytes or injury to the formed units of blood. They may also be used to minimize the effect of dilution associated with priming before separation from bypass.

Priming

The pump is primed with 1–1.5 L of isotonic fluid. Our institution uses a combination of Plasmalyte A®, heparin, and mannitol. This prime volume can also be used with blood if it is expected that the dilution will lead to unacceptable hemoglobin levels. Retrograde autologous priming (RAP) may be helpful with planned CPB. The primary goal of priming is to remove air bubbles from the circuit, which can be facilitated by gaseous CO_2 flush prior to liquid priming. Residual CO_2 bubbles are soluble and less harmful if embolized; these are cleared by the oxygenator sweeps during initial circulation testing. Fluid priming allows the pump function to be tested before it is connected to the patient. Following priming, flow is circulated and the circuit is pressurized to ensure ECC integrity. This allows testing of seals, one-way valves, and the mechanical drive system. After successful priming, the sterile portions of the tubing are handed off to the surgical field, where they are cut to length and eventually attached to the cannula.

Cardioplegia

Cardioplegia is delivered with the intent to arrest the heart. This reduces metabolic demands and improves the surgical field of view. Cardioplegia is not used for LTX unless a concomitant intracardiac procedure is performed (aortic valve replacement,

mitral valve repair). Antegrade cardioplegia is delivered to the aortic root proximal to the aortic clamp. This closes the aortic valve and pressurizes the root, forcing perfusion of the coronary arteries. Retrograde cardioplegia by way of a coronary sinus catheter placed through the RA is generally avoided during transplantation.

Organ Preservation

Organ procurement and transplantation come with obligatory periods of donor organ ischemia. Efforts to minimize organ damage start prior to procurement with good intensive care unit (ICU) care, minimizing insults and protective ventilation. Following donor death and organ procurement exists an obligatory period of warm ischemia. Traditionally, cold perfusate and packing in cold preservative and ice are used to preserve organs awaiting transplantation. Donor organ temperature is dropped to 4 °C with a 12-fold reduction in metabolism [11]. However, anaerobic metabolism persists with the need for additional protection measures to avoid tissue damage from free radicals, complement activation, leukocyte activation, endothelial injury, cytokine release, and calcium overload [12]. Various perfusion solutions are used along with hypothermia to provide additional organ protection. University of Wisconsin (UW) solution, an intracellular solution used for preservation of the heart, and Perfadex (PER), an extracellular solution, are used for lung protection at our institution (Table 17.1). UW solution has shown a slight survival advantage in heart transplantations, while PER has been shown to improve PaO_2/FIO_2 ratio and shorten the duration of ventilation for LTX patients [13].

Table 17.1 Preservation solutions during transport of organs for thoracic organ transplantation

	UW solution	PER solution
Intracellular/extracellular	Intracellular	Extracellular
Na^+ (mEq)	25	138
K^+ (mEq)	120	6
Impermeant/colloid	LactoB, raffinose, hydroxyethyl starch	Dextran
Buffer	Phosphate	Phosphate
Antioxidant	Allopurinol, glutathione	
Osmolarity (mOsmol/L)	330	292
Magnesium	5	0.8
Chloride (mEq)	20	142
Calcium	None	None
Glucose	None	5 mg

UW University of Wisconsin solution, *PER* Perfadex solution

Conventional cold preservation of organs depends on the decrease in cellular metabolism and decrease in need for nutrients. Topical cooling with ice can cause thermal injury. This ex vivo period is highly unphysiologic. In contrast, the recently utilized method of normothermic ex vivo perfusion keeps cell metabolism active and allows for reassessment of the organs before they are accepted for transplantation. Normothermic and physiologic preservation of organs is made possible for both lung and heart transplants with organ care systems (OCS). However, it is yet to be seen whether the use of these devices will provide better organ protection, extend the ischemic time, and increase the utilization of organs.

The OCS provides perfusion of the explanted heart with warm, oxygenated, nutrient-enriched donor blood. The heart is kept beating and is metabolically active (Fig. 17.8). Donor blood is perfused into the aorta to provide nutrients through the coronary arteries and the returned blood is collected through the PA. A heart solution is infused by standard intravenous pump into the donor blood to replenish the substrates. Venous lactate concentrations are measured to monitor the adequacy of perfusion. In a multi-center, open-label, and prospective study, Ardehali et al. showed that 30-day mortality after heart transplantation was comparable and non-inferior to standard cold preservation (PROCEED II clinical trial) [14]. OCS is promising, considering its ability to evaluate and potentially modify cardiac function before implantation into potential recipients. The role of these devices should also be evaluated with marginal donor hearts.

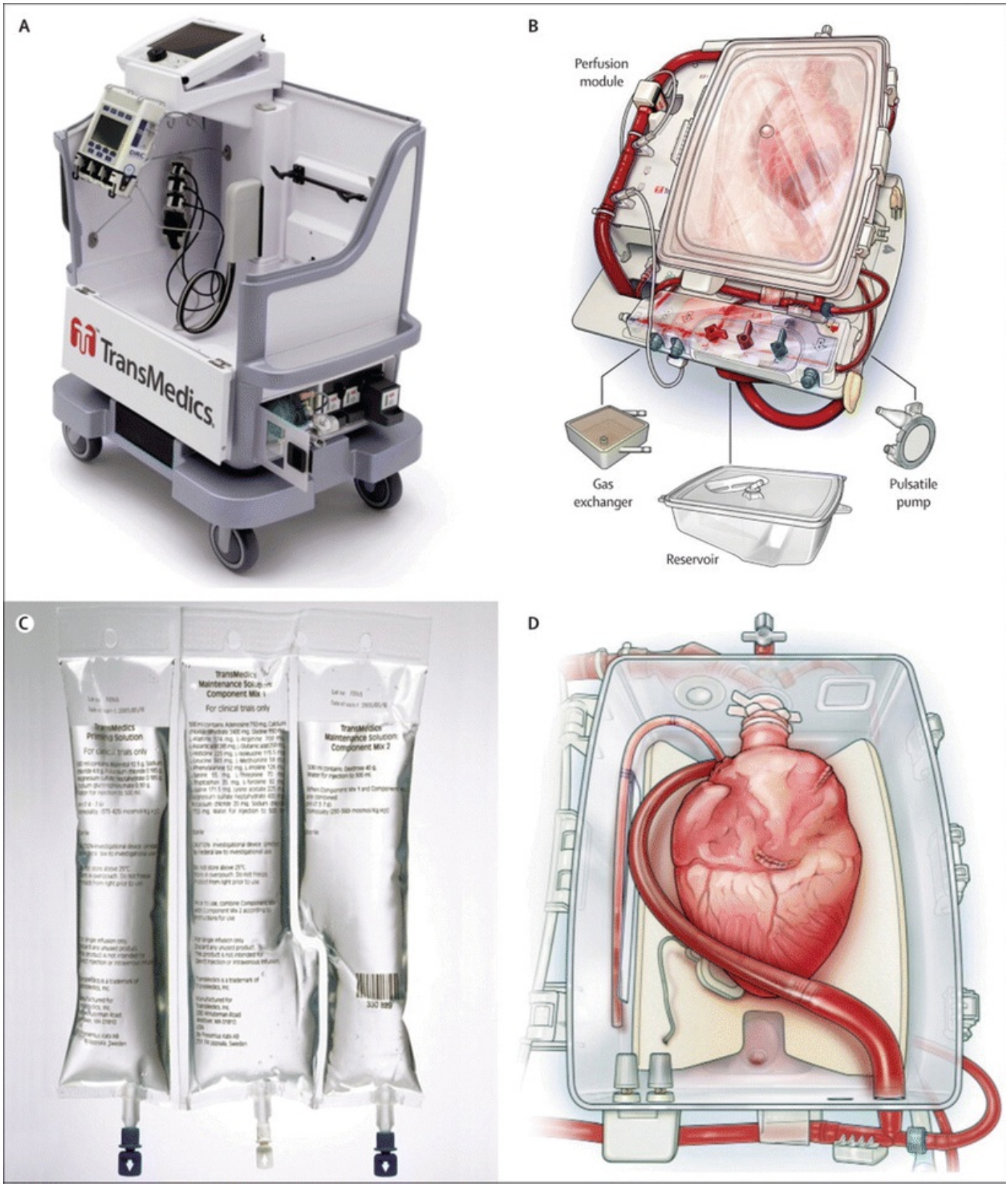

Fig. 17.8 The Organ care system for the heart: The organ care system is composed of a portable console with heart console (**a**), heart perfusion set (**b**), and heart solution set (**c**). The system is designed for ex vivo heart perfusion with warm, oxygenated, nutrient-enriched donor blood (**d**). The heart is beating and metabolically active. This figure has been reproduced by permission of Transmedics (Andover, MA) (from Ardehali et al. [14]; with permission)

For LTX, the effect of deflation, atelectrauma, and eventual re-expansion of donor lungs during cold static preservation are unlikely to be beneficial. Ex vivo systems have been used to support explanted lungs [15]. One such device, XVIVO, provides ventilation through the endotracheal tube inserted into the trachea to prevent atelectasis in the lungs (tidal volume 5–7 ml/kg, respiratory rate 7–20/min, PEEP 5 mmHg). The device also provides perfusion through a pump, membrane, heat exchanger, and leukocyte filter similar to a CPB machine (Figs. 17.9 and 17.10). Perfusion is done through the inflow cannula inserted into the PA, and PA pressure is kept between 15 and 20 mmHg. The perfusion solution used is normothermic (32°), acellular buffered extracellular solution (Steen solution) with optimum colloid oncotic pressure (dextran 40 and albumin added). At our center, XVIVO perfusion is started after the organ's arrival at the recipient's institution. Suitability of the perfused lung for transplantation is evaluated using PAO_2 (from LA)-to-FIO_2 ratio. A ratio of more than 400 after 4–6 h of XVIVO perfusion is considered the most important criteria for acceptance. Other parameters used for decision making include stable PA pressure, stable airway pressure, and pulmonary compliance.

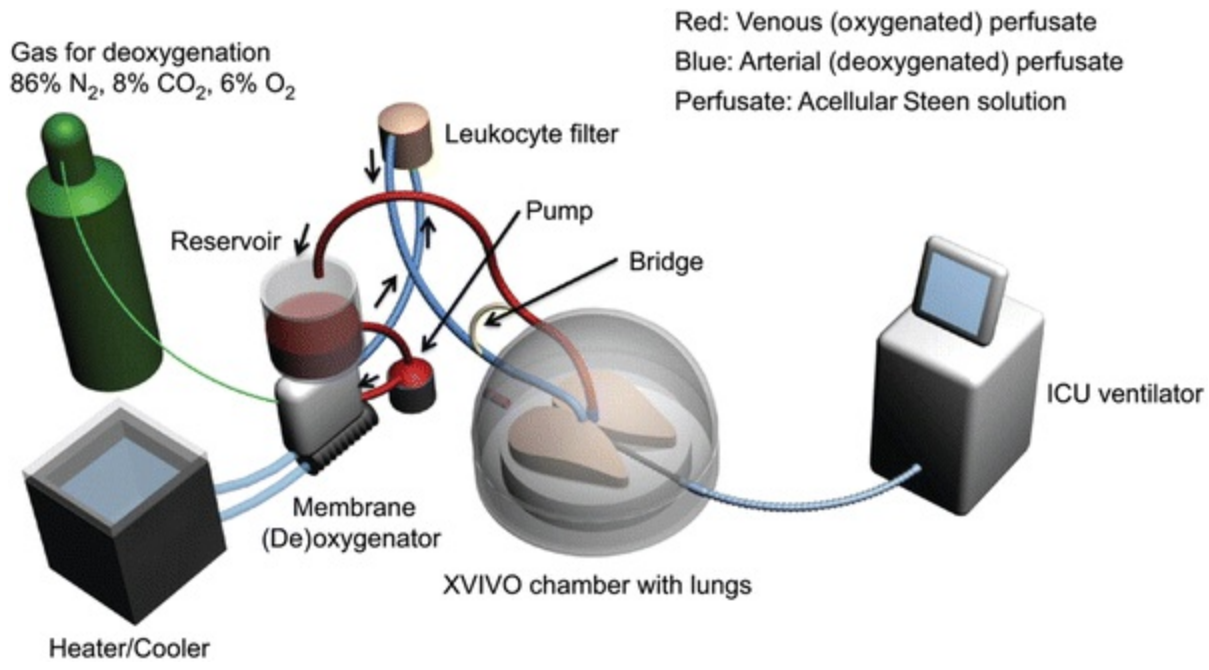

Fig. 17.9 Diagram of ex vivo lung perfusion circuit (from Yeung et al. [55]; with permission)

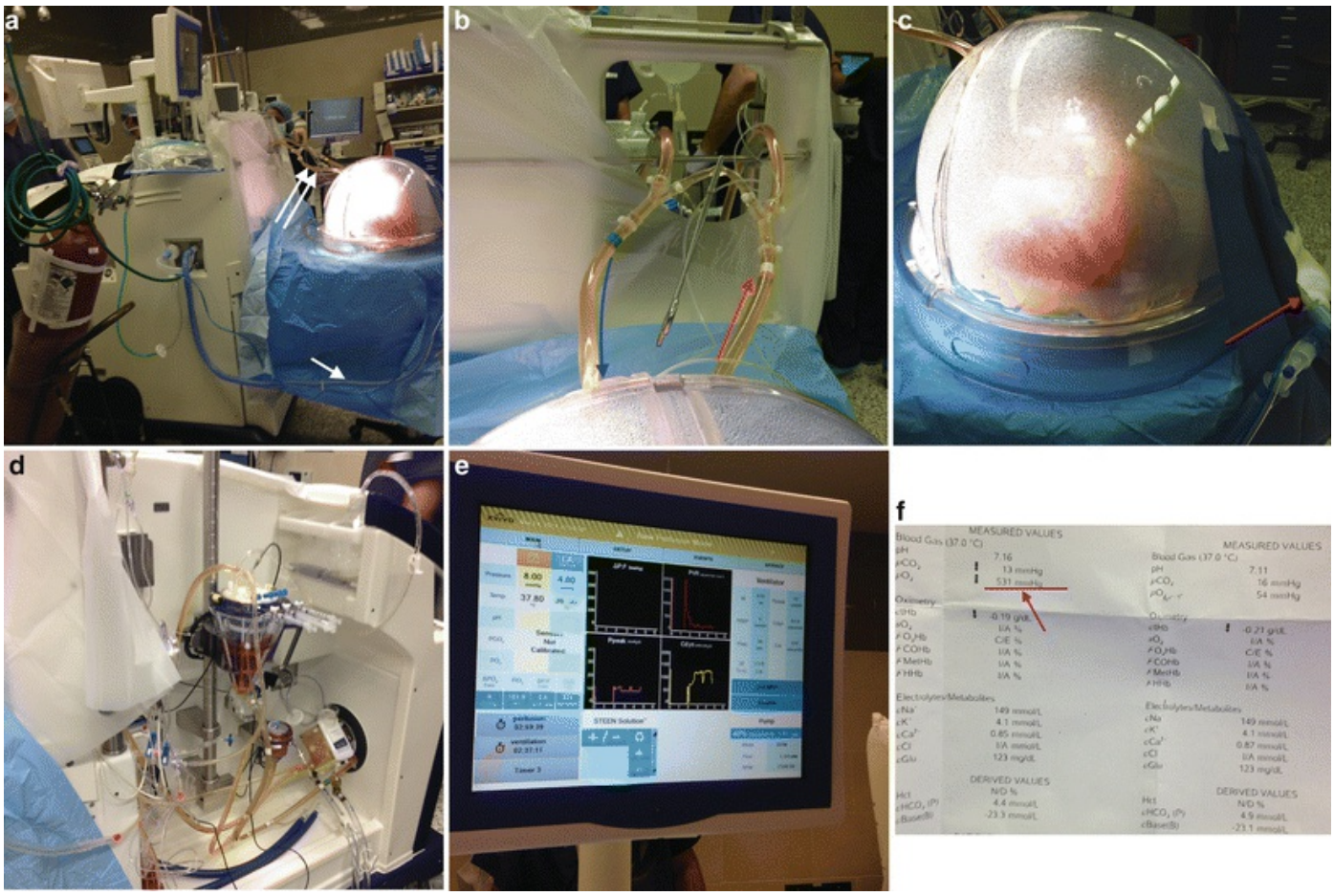

Fig. 17.10 Components of ex vivo lung perfusion circuit. (**a**) Ex vivo components, *single white arrow* is the ventilation circuit connected to the endotracheal tube and *double arrows* indicate perfusion line for STEEN solution; (**b**) perfusion circuit, *red arrow* indicates STEEN solution oxygenated exiting from left atrium and *blue arrow* is inflow of deoxygenated STEEN solution into pulmonary artery; (**c**) lungs are placed in this chamber for ventilation and perfusion; (**d**) side view of ex vivo lung perfusion system showing reservoir, pump, oxygenator, and arterial line filter; (**e**) EVLP monitor showing the ventilation-perfusion parameters and lung performance; (**f**) blood gas of the perfusion solution from left atrium and pulmonary artery. *Red arrow* indicates PaO2 values from left atrium with 100 % oxygen indicating suitability of lung for transplantation

There are three popular protocols for restoration of perfusion and ventilation to donor lungs: Toronto, Lund, and Transmedics [16]. These protocols describe how PA pressure and flow restoration, ventilation, and temperature should be managed. The goal is to minimize reperfusion injury and shear injury to blood vessels and prevent ventilator-induced injury. No comparative data on best practice exist. These protocols also differ as to the use of blood versus acellular perfusate. Cypel et al. from Toronto reported their experience with XVIVO lung perfusion on primary graft dysfunction (PGD) in 23 patients. Twenty lungs were found to be suitable after XVIVO perfusion and the incidence of PGD was 15 % using XVIVO perfusion for 4 h. This was comparable to a 30 % incidence of PGD with the standard cold preservation method (*n* = 112) [17].

Several marketed XVIVO lung-preservation devices are available nowadays. XPS™ (XVIVO Perfusion AB) is used at our institution. OCS (Organ Care System)™ Lung is another CE-marked portable device that can also be used during transport from donor to recipient hospital so that longer periods of cold ischemia are avoided. The goal is to keep the lungs in their natural physiologic state by ventilating and perfusing them with warm blood (Fig. 17.11). The INSPIRE randomized, multi-center clinical trial is currently evaluating OCS technology for warm physiologic lung preservation and comparing it with conventional cold preservation on PGD of the transplanted lungs. XVIVO technology can also be used to evaluate lungs from donors after cardiac death (DCD) and marginal donors. Several clinical trials are under way to evaluate the effect of reconditioning the lungs from extended criteria donors using XVIVO technology (NOVEL, EXPAND clinical trials) on graft and patient survival after transplantation.

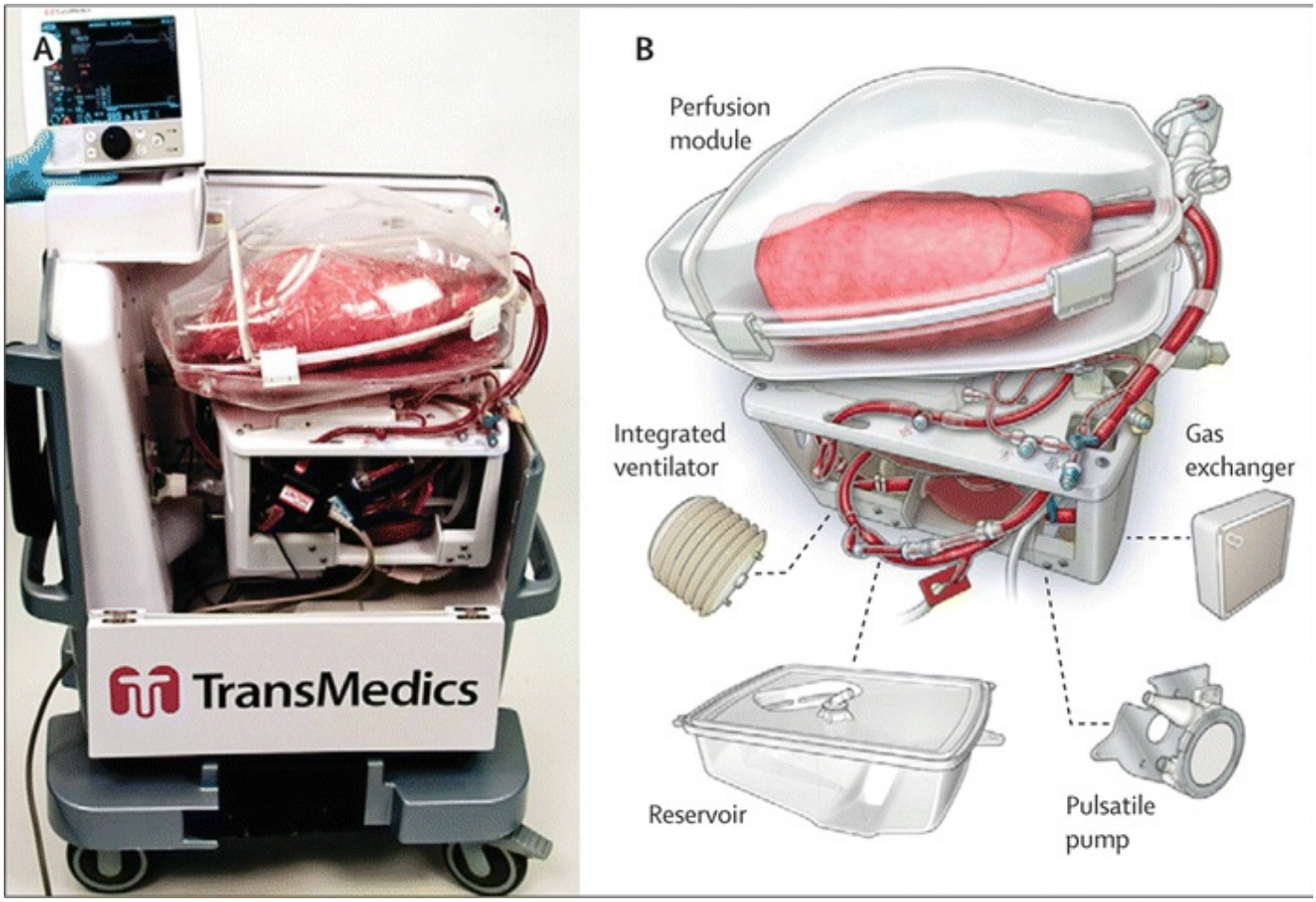

Fig. 17.11 Photograph of the portable organ care system lung (**a**) and schematic view of the perfusion module (**b**) The photograph shows the device (console with perfusion module in place and donor lung on circuit) with the cover removed and the handheld control and monitoring unit, which is connected to the device via Bluetooth. The disposable perfusion module integrates the low-resistance polymethylpentene membrane gas exchanger, a pulsatile pump, the fluid reservoir and tubing, an integrated ventilator, and an electric perfusate heater. Motors to drive the blood pump and ventilator are installed in the console (from Warnecke et al. [56]; with permission.)

Ex vivo lung perfusion (EVLP) has some exciting applications in addition to its role as a bridge to decision. XVIVO is also being tested for donor lung repair and immune graft modulation. The concept of reconditioning is a logical extension. These devices allow for the delivery of therapy. Beyond allowing for diagnostic/therapeutic bronchoscopy, the perfusate can be used to deliver other interventions. Hyperoncotic fluid is used to dehydrate edematous lungs. Prolonged perfusion allows dilution and removal of donor blood components and leukocytes. Antibiotics may be prophylactic or therapeutic. Reports of treating pulmonary emboli with urokinase prior to successful transplant also exist [18].

EVLP has been shown to decrease thermal injury and infectious organisms and has been shown to be successful with anti-inflammatory therapies in animal models [19, 20]. Immunocloaking is the concept that donor endothelium gene expression can be modified to reduce or potentially eliminate the host response to a new organ [21]. Despite these promising applications, the human data show some possible negative effects such as increased pulmonary vascular resistance and pulmonary edema, especially with longer duration of EVLP.

The organ-preservation process also extends to organ implantation. Protocols established by the University of Pittsburgh organ transplant and perfusion team are described in Table 17.2. Protocols vary between institutions and also between different surgeons within the same institution. Perfusion with cold preservative solution before implantation and reperfusion with warm solution are common practice.

Table 17.2 Intraoperative organ preservation solutions used during thoracic donor-organ transplantation

	Heart			**Lung**	
	Initial solution	**Maintenance**	**Hot shot**	**Initial**	**Hot shot**
Additive					
Pump blood (ml)	800	1000	1000		
Plasmalyte A (ml)	200			100–400	100–400
PRBCs if off ECC				1 U	1 U
Dextrose (gm)	5	2.5	5	5	5
Regular insulin (units)	20	10	20	20	20
Glutamate aspartate (ml)	20		20	20	20
Bicarbonate (mEq)	25	25	20	25	20
Lidocaine (mg)	100		100	100	100
Potassium chloride (mEq)	20		10		
Isolyte S (ml)	18	18	18	18	18
Adenosine (mg)	9		3	3	3
Ascorbic acid (mg)	250	250		250	
Nitroglycerine (mg)	1	1	1	2.5	2.5
Deferoxamine mesylate (mg)	125		125	125	125

Verapamil (mg)				2.5	2.5
Heparin (units)				1000	1000
Tham—E				Titrate to pH 7.4	Titrate to pH 7.4
Temperature (°C)	4	4	37	4	37
Hematocrit (%)	18–22	18–22	21–25	15–25	15–25
Volume given	~1000 ml	~500 ml	~500 ml	~500 ml/lung	~500 ml/lung

ECC extracorporeal circulatory support, *PRBC* packed red blood cells

Temperature Management

During bypass, temperature management falls largely in favor of the alpha-stat technique over pH stat for this population with mild hypothermia. We minimize recipient cooling with active warming during thoracic transplantation to avoid coagulation effects. Bladder and nasopharyngeal temperatures typically underestimate brain temperature, as measured by jugular venous measurements [22]. Hyperthermia of ischemic tissue increases metabolism and worsens neurologic outcome in the setting of injury [23–25].

Pump Versus No Pump for LTX

The question of whether or not the use of routine intraoperative mechanical support for LTX is advantageous has not been explored by proper randomized controlled clinical trials. In their best evidence paper, Nagendran et al. found 14 retrospective studies addressing this question [26]. Some studies noted a higher incidence of diffuse alveolar damage, worse gas exchange, greater chest infiltration score, and longer duration of mechanical ventilation, ICU stay, and hospital stay with the use of CPB [27–29]. A few studies also noted higher short-term and long-term mortality in patients who received mechanical support [27, 29, 30].

Several problems with the retrospective studies can be identified. Many studies do not differentiate between planned and unplanned use of CPB during transplantation [31]. While no significant differences existed between planned and unplanned CPB in some studies, others have shown that unplanned use of CPB can have a strong effect on mortality [32]. The need for emergent bypass is more likely a marker of unforeseen intraoperative events, a sicker patient population, or misadventure. It would be inappropriate to conclude that ECMO or CPB was the cause for mortality in these patients. Presumably, these emergent conversions would have had a 100 % mortality had they not crashed on bypass.

Similarly, pre- and postoperative ECMO use has been shown to correlate with mortality [33]. This could just represent a sicker patient population in whom

transplantation could not have been possible without the use of mechanical support. Similarly, CPB is often elected when additional procedures are required during LTX. Patients who would require atrial septal defect closure or other procedures are exposed to longer CPB time and have more complex operations that carry additional risk.

It is important to identify and control for the indication for transplantation, as the need for extracorporeal support during LTX varies with the indication for transplant and disease severity. When examined specifically in COPD patients, no differences were found for the duration of ventilation, ICU stay, and survival rates [34]. de Boer et al. found an improvement in 1-year survival of emphysema patients in CPB group [35]. In this study, they further demonstrated increased survival when HLA mismatch was taken into account, implying that the immunosuppressant effects of CPB could be beneficial. Others have documented the enhanced effect of steroids by CPB [36].

Other proposed benefits of using CPB are better technical access to the surgical field, hemodynamic stability, and controlled reperfusion [26]. In patients undergoing LTX without CPB, the implanted first lung is exposed to the patient's entire cardiac output after reperfusion. This may predispose them to hydrostatic edema and ischemia-reperfusion injury in the lung reperfused after a prolonged period of ischemia. CPB provides simultaneous controlled reperfusion of both lungs, which will protect the first implanted lung from being exposed to high reperfusion pressures. In this context, few surgeons prefer to implant the second lung under a short period of mechanical support, even though the first lung was implanted without support.

It is well documented that the coagulation and immune/inflammatory response are linked [37, 38]. Exposure of blood and plasma to extracorporeal systems leads to activation of both coagulation and the immune-mediated inflammatory response [39, 40]. It would be reasonable to expect some adverse effect from this relatively invasive form of support. While there is a physiologic basis for injury by exposure to artificial support systems, the clinically relevant extent is unclear. Abnormal inflammatory responses could represent the response to ischemic-reperfusion injury rather than the effect of CPB by itself. Severe acute lung injury or acute respiratory distress syndrome related to CPB after cardiac surgery is uncommon. Pulmonary gas exchange and oxygenation were similar after coronary bypass surgeries done with or without CPB.

Other considerations related to the use of CPB include the need for transfusion and neurologic dysfunction. CPB's effect on blood loss is less contested. Estimated blood loss and red cell transfusions are increased with the use of extracorporeal support. Fibrinolysis, platelet dysfunction, and dilution of coagulation factors all play a role in increasing bleeding after mechanical circulatory support. CPB also requires extensive heparinization. ECMO use may be associated with lower heparinization and transfusion requirements based on the available evidence (see the following section). Interestingly, the amount of blood transfused during LTX did not affect lung function (up to 6 months) or 1-year mortality in a recent study [41]. Among the blood products, platelet

transfusion was associated with higher in-hospital death and 1-year mortality [41, 42]. The effect of perioperative blood transfusion on short-term and long-term outcomes deserves further study.

CPB is associated with embolization of atheromatous plaques that can result in neurologic injury [43, 44]. In patients with severe lung disease, baseline hypercapnia is common; this is frequently exacerbated by lung-protective strategies. This permissive hypercapnia increases cerebral blood flow and therefore the risk of embolization to these sites at the time of cannulation and with the initiation of bypass. In addition to the risk of overt stroke, a growing body of evidence suggests more subtle neurocognitive dysfunction following cardiac surgery and LTX [45–47].

In conclusion, CPB is unavoidable in certain sick patients undergoing LTX and should be used when clinically indicated. In patients suitable for either approach (on-pump and off-pump), no definite advantage or disadvantage could be demonstrated by a high level of evidence based on one approach over another. Institutional experience, familiarity with one approach, patient factors, intraoperative hemodynamic conditions, and technical issues should dictate the selection of the approach.

ECMO Versus CPB for LTX

While arguments for [48] and against [49] the use of empiric CPB support for LTX remain a topic of debate, both the off-pump LTX approach and ECMO support have evolved. Retrospective studies have shown that intraoperative ECMO support was a safe and effective alternative to CPB [29]. CPB often leads to an inflammatory response, coagulopathy, and associated increased transfusions. This has caused some institutions to move away from CPB in favor of ECMO for routine intraoperative support.

A very-well-conducted retrospective case-control study by Machuca et al. [50] deserves special mention and further discussion. They reviewed data of their LTXs performed between 2007 and 2013. They excluded patients with pre-existing ECMO, those who needed emergent cannulation during transplantation, or those who required multiple procedures. They matched 33 cases who had ECMO for transplantation to a group of 66 CPB patients based on age, indication for transplant, and type of transplant (single vs. double LTX). Donor characteristics, ECC support duration, “pump time,” and warm ischemic time did not differ between the groups. They demonstrated that patients receiving transplantation with ECMO support had markedly improved outcomes. Duration of mechanical ventilation, length of ICU stay, and length of hospital stay were shorter in ECMO patients. Fewer ECMO patients required dialysis. Blood and blood product transfusions were lower in the ECMO group and there was a nonsignificant trend towards lower mortality (6 % in ECMO patients vs. 15 % in CPB patients). The study was retrospective in nature and the ECMO patients from the

database were more recent, which may just reflect an improvement in skill and experience.

Biscotti et al. [51] compared ECMO ($n = 47$) and CPB ($n = 55$) for LTX performed between 2008 and 2013. The CPB group required more intraoperative and postoperative transfusions (cell saver, fresh frozen plasma, platelets, and cryoprecipitate), higher reoperations, and higher rates of PGD at 24 and 72 h, postoperatively. No difference was seen in 30-day and 1-year mortality.

Bermudez et al. [52] also compared outcomes for LTX with ECMO support versus CPB support. They described similar demographic and operative profiles for both groups of patients. CPB patients had a higher incidence of reintubations, tracheostomy, and dialysis-requiring renal failure. No differences in perioperative red cell transfusions, PGD, or 30-day/6-month mortality were seen between ECMO and CPB patients. Ius et al. [53] identified re-transplantation [OR (95 % CI) 7 (1–43)] and transplantation with CPB support [OR (95 % CI) 4.9 (1.2–20)] as independent factors for in-hospital mortality by multivariable analysis. Their ECMO group had better survival at 3, 9, and 12 months compared to their CPB group.

Aigner et al. reported their experience with mechanical circulatory support; their survival rates were better for ECMO patients than for CPB patients [29]. Bittner et al. however reported increased transfusions, mortality, and infection rates in patients who received ECMO support compared to CPB support [54]. Small sample size, uncontrolled study design, and relative inexperience during initial days of ECMO use could have led to increased complications in their study.

It is always possible that the patients assigned to the CPB groups were sicker than those in the ECMO groups in the abovementioned studies, complicating the interpretation. A well-designed, multi-center, prospective, and randomized study will provide a definite answer, but may not be feasible and will be very expensive. At present, the trend is to perform more lung transplants with ECMO, based on available evidence from large-volume centers.

Conclusions

Extracorporeal circulation has advanced in 60 years from simple handcrafted systems to a level of technical sophistication that should be well understood by health care providers who interact with these technologies on a daily basis. This chapter is only an overview of the general principles for use of ECC in thoracic transplant population. Deeper knowledge acquisition and lengthy training are required to prepare perfusionists to manage patients undergoing surgery with ECC. Reliable and well-trained perfusionists allow medical teams to function safely during these operations using ECC. Understanding the design and pitfalls inherent for these machines improves the margin of safety for our patients. Incremental advances in technology have improved safety and

expanded the application of mechanical support outside of the operating room. The use of ECMO and EVLP technology continues to revolutionize the care of patients with failing heart or lungs. The optimal role of these newer technologies during the perioperative period of transplant patients is still being defined.

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18. Anesthesia for Noncardiac Surgery Following Thoracic Organ Transplantation

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Introduction

Annually, approximately 30,000 patients receive whole-organ transplants in the USA alone [1]. As the number of transplant procedures increases, survival continues to improve as well. According to the Organ Procurement and Transplantation Network, the 1- and 5-year survival rates following cardiac transplantation are currently 87 % and 73 %, respectively [1]. Advances in surgical technique, immunosuppression regimens, and anesthesia management have allowed for remarkable increases in survival following lung transplantation as well. The current 1- and 5-year survival rates are better than ever before, listed at 82 % and 46 %, respectively [1].

As survival following thoracic organ transplantation improves, anesthesiologists are progressively more likely to see transplant recipients presenting for noncardiac surgery. An estimated 9–34 % of patients following orthotopic heart transplant (OHTx) will present for general surgical conditions, either electively or emergently [2–5]. Consequently, anesthesiologists and surgeons need a basic knowledge of the physiologic changes that occur in the immediate postoperative period and ensuing years after thoracic organ transplantation. If time permits in the preoperative workup, discussing these patients with dedicated transplant teams is advantageous; however this is not

always possible. Because of this, general anesthesiologists must be prepared to manage transplant recipients [6].

The anesthesiologist managing the transplant recipient must always consider the physiologic changes associated with the transplanted organ over time, side effects of immunosuppression, potential for organ rejection, and infection-related risks [7]. The purpose of this chapter is to provide a comprehensive overview to guide the management of the thoracic transplant recipient presenting for noncardiac surgery.

Noncardiac Surgery Following Heart Transplantation

Introduction

Heart transplantation has conventionally been thought of as the best option for patients with end-stage heart disease. In 2013, over 2500 heart transplants were performed in the USA and this number rises annually [1]. Many patients have a drastic improvement in their quality of life following successful transplantation and oftentimes return to New York Heart Association class I functional capacity [7]. As mentioned previously, heart transplant recipients are also experiencing an improved survival and thus these patients are increasingly likely to present to the operating room for noncardiac surgery after transplantation. It is gravely imperative that the anesthesiologist understands the physiology of the transplanted organ as well as the common comorbidities following transplantation.

Physiology of the Transplanted Heart

Several differences exist between the native and the transplanted heart as outlined in Table 18.1. It has been well established that the surgical procedure required to procure a heart results in complete autonomic denervation of the donor organ. The transplanted organ does, however, maintain its intrinsic properties and autoregulatory functions and is solely responsible for the electromechanical activity after transplantation. Traditionally, the diseased heart is removed and an atrial cuff remains to allow for proper reimplantation of the donor organ. The atrium of the recipient retains intrinsic innervation, but electrical activity of the native atrium is unable to cross the suture line resulting in two distinct P waves on the electrocardiogram. Mechanisms that appear to be preserved in the transplanted, denervated heart include the following: a normal Frank-Starling pressure-volume relationship, intact alpha and beta-adrenoreceptors, and normal impulse formation and conduction [3].

Table 18.1 Differences between the native and transplanted heart

	Native heart	**OHTx recipient**
Innervation	Autonomic and sensory	Denervated initially—partial reinnervation time course. The exact time

	innervation intact	course is unclear at present
Resting heart rate	60–80 beats/min	90–110 beats/min
EKG findings	Normal	Commonly two P-waves
Arrhythmias	Not common	Very common
Response to stress	Intact reflex pathways	Loss of baroreceptor reflex, inability to increase heart rate with hypotension/hypovolemia

Transplanted hearts are known to have an elevated resting heart rate of approximately 90–110 beats/min [3, 7, 8]. This generally equates to a resting atrial rate that is 14–25 beats/min higher than the resting atrial rate for age- and sex-matched controls compared with non-transplanted hearts [9]. The elevation in heart rate in the transplant recipient is owed to the absence of vagal tone leaving the heart rate dependent upon the intrinsic rate of depolarization of the donor SA node [3].

Another significant difference between the transplanted heart and the normal heart is found in the response to physiologic stressors such as hypovolemia and hypotension. The normal heart has neural mechanisms in place that permit heart rate and cardiac output increases in response to stress, but the transplanted heart is denervated and lacks this ability [3, 8]. Early in the stress response, the heart rate and cardiac output of the transplanted heart are relatively fixed. The Frank-Starling mechanism of the transplanted heart does remain intact; consequently, increases in cardiac output are dependent upon increases in venous return leading to an increased LVEDV. For this reason, transplanted hearts are often referred to as “preload dependent” [3, 8]. Later into the course of the stress response, there is an increase in circulating catecholamines, but this process takes 5–6 min. Remembering that the transplanted heart has intact alpha and beta-adrenoreceptors, increasing circulating catecholamines yield an increase in chronotropy and inotropy [3].

Reinnervation of the transplanted heart continues to be a controversial topic. Recent studies show that between 33 and 41 % of patients exhibit a partially normalized response to exercise within the first year [10, 11]. This implies that partial reinnervation may occur very early in the post-transplant period. Reinnervation appears to be a continuous process that is very heterogeneous in nature [12]. Some patients will exhibit complete reinnervation with normalization of cardiac reflex pathways, but this does not typically occur until at least 15 years following transplantation [6, 12].

Cardiac denervation , not unexpectedly, alters the pharmacology of many drugs used in the perioperative period, which must be taken into account. It has been reported that the density of catecholamine receptors in the transplanted heart is unchanged compared to the native heart. Owing to this, direct-acting drugs such as epinephrine and norepinephrine will remain effective in increasing heart rate and contractility in OHTx recipients [7]. It was long hypothesized that drugs such as anticholinergics

(glycopyrrolate and atropine), muscle relaxants (pancuronium), and acetylcholinesterase inhibitors (neostigmine, edrophonium, pyridostigmine, and physostigmine) had zero impact on the denervated heart, but this topic should be approached with caution [13, 14]. It has been clearly shown that some component of sympathetic and parasympathetic innervation is established in most patients after heart transplantation leading to these patients having an unpredictable response to indirect-acting drugs [15]. In lieu of this fact, there are numerous reports of asystole following the administration of neostigmine for the reversal of neuromuscular blockade in transplant recipients [15–18]. Medication administration must be carefully thought out in this patient population and avoidance of neuromuscular blocking drugs may be best if at all possible.

Complications Following Heart Transplantation/Post-transplant Morbidities

Complications following heart transplantation can be separated into problems that arise in the immediate postoperative period and those that occur on a more long-term basis. Potentially catastrophic issues that develop shortly after surgery include right ventricular dysfunction, acute renal failure (ARF), and acute graft rejection. The years after transplant are also fraught with morbidities such as coronary vasculopathy, hypertension, chronic renal insufficiency, and malignancy. Anesthesiologists must be aware of these common disease processes to provide optimal patient care. Table 18.2 shows a detailed incidence of many of the post-transplant complications [19].

Table 18.2 Post-transplant morbidities : Incidence of common issues 10 years following heart transplantation

Disease process	Incidence at 10 years (%)
Renal insufficiency (Cr > 2.5 mg/dL)	14
Hypertension	97
Diabetes mellitus	39
Coronary artery vasculopathy[a]	52
Malignancy	34

[a]Anigographically proven
Reproduced from Taylor et al. [19], with permission

Right Ventricular Dysfunction

Pre-existing pulmonary hypertension confers an increased risk of acute right ventricular failure following cardiac transplantation. Given this concern, most transplant centers view elevated pulmonary vascular resistance as a contraindication to heart transplantation [20]. Right ventricular dysfunction may also be secondary to poor

preservation of the graft prior to transplantation [21]. Regardless of the etiology of right ventricular dysfunction, the management is similar to this issue occurring in the native heart. First, there should be rapid evaluation of oxygenation and ventilation. Secondly, pharmacotherapy may be extremely beneficial including drugs such as inhaled nitric oxide, inhaled and intravenous prostaglandin E1, milrinone, dobutamine, and epinephrine depending on the clinical scenario.

Acute Renal Failure

Oliguria and ARF after heart transplant surgery often develop as a result of cardiopulmonary bypass, low flow states, and cyclosporine induction therapy [21]. Prior to a 2010 study by Gude and colleagues, there was little incidence data on the topic of immediate post-transplantation renal insufficiency. This study retrospectively evaluated 585 heart transplant recipients and found a 25 % incidence of ARF. The primary risk factors associated with the development of ARF included *intravenous* cyclosporine administration, increased donor age, and increased recipient age. While patients who progressed to chronic renal insufficiency had an increase in mortality, it did not appear that the development of ARF in the immediate postoperative period is predictive of the subsequent need for dialysis or renal transplantation in this patient population [22].

Donor Graft Rejection

Prevention of graft rejection requires a delicate balance of the immunosuppression regimen with too much immunosuppression increasing infectious risks, but too little risking organ rejection [21]. Rejection episodes most commonly occur within the first 3 months following heart transplant surgery with a peak incidence near 6 weeks after transplantation [3]. According to the International Society for Heart and Lung Transplantation (ISHLT), the incidence of *treated* acute allograft rejection ranges from 21 to 30 % depending on the immunosuppression protocol followed [19]. It remains true that acute rejection is exceedingly unlikely after the first year but must be considered in any patient who is not taking their immunosuppressive regimen as indicated [6].

The gold standard of diagnosing a rejection episode hinges on the endomyocardial biopsy [21]. Common patient symptoms during an episode of rejection include arrhythmias, fever, fatigue, weight gain, peripheral edema, shortness of breath, and bradycardia [6]. A low level of suspicion must always remain to work up a potential rejection episode as this can prove to be a fatal event. Treatment of the acute rejection episode generally entails increasing the immnosuppression regimen for acute rejection, IV immunoglobulins and plasmapheresis for antibody-mediated rejection, and potentially temporary mechanical support depending on the severity of the presentation

[6].

Coronary Artery Vasculopathy

Coronary artery vasculopathy (CAV) is one of the leading causes of mortality following OHTx according to the ISHLT [23, 24]. CAV currently accounts for 10–14 % of deaths more than 1 year post-transplant [23]. Medical management and advances in immunosuppression have greatly improved survival after OHTx in recent years, but the CAV incidence remains unchanged. The current estimates for CAV among heart transplant recipients are 20 %, 30 %, and 45 % at 3, 5, and 8 years post-transplant, respectively [23].

It is likely that some coronary arterial disease is transplanted with the donor organ, but CAV frequently occurs in recipient organs that did not have any pre-existing coronary disease. Certain risk factors for the development of CAV have been clearly identified including recipient age, pre-existing ischemic heart disease, cyclosporine immunosuppression versus tacrolimus, and even use of a pre-transplant ventricular assist device for the treatment of heart failure [23]. Current treatment options used with an attempt to decrease morbidity and mortality from CAV include diltiazem and pravastatin or simvastatin. These have been shown to reduce, but not prevent, CAV development [25]. Aggressive ongoing research exists with an attempt to find a cure or more effective treatment for CAV. At this time, mTOR inhibitors are the most promising drugs to reduce CAV, but a survival benefit has not been shown to date and side effects can be troublesome [24].

Hypertension

Hypertension following OHTx is exceedingly common and typically due to cyclosporine therapy [3, 21, 26, 27]. Prior to the usage of cyclosporine as part of the immunosuppression regimen, hypertension after OHTx was only seen in approximately 20 % of patients [28]. More recently, the documented rate of post-transplant hypertension is greater than 90 % with one study citing a 97 % incidence at 10 years [19, 28, 29]. Patients at increased risk of developing early post-transplant hypertension include patients of advanced age and those with pre-existing hypertension. Pharmacotherapy is typically able to achieve sufficient blood pressure control and many patients can be controlled with single-drug therapy [30].

Chronic Renal Insufficiency

Common associations with chronic renal insufficiency in the OHTx recipient include the chronic low flow state associated with advanced heart failure leading to compromised renal arterial flow, cardiopulmonary bypass exposure, and the immunosuppression

regimen in the years following transplantation. Immunosuppression regimens are credited with marked improvements in survival following organ transplantation, but these drugs do not come without a cost. In particular, calcineurin inhibitors such as cyclosporine are well known for causing nephrotoxicity and renal failure [31–33]. Severe renal dysfunction, defined as a serum creatinine of greater than 2.5 mg/dl, is extremely common following heart transplant with numbers approaching 15 % by 10 years [19].

Recent studies have attempted to define the risk factors leading to severe renal dysfunction in the years following OHTx. Common risk factors include advanced age, recipient diabetes mellitus, and elevated preoperative serum creatinine [19, 34, 35]. Due to the known association of OHTx and renal failure, it is extremely important to avoid the co-administration of other nephrotoxic medications in this patient population.

Arrhythmias

Cardiac dysrhythmias are common in the cardiac transplanted recipient due to denervation, rejection, and increased endogenous catecholamine concentrations. The most common indication for permanent pacemaker (PPM) implantation after OHTx remains significant bradycardia that is typically secondary to sinus node dysfunction [3, 36, 37]. Recent studies show that the surgical technique is a strong predictor of the need for PPM with a biatrial technique significantly increasing the risk [37, 38]. In the past, it was believed that PPM was uncommon after OHTx, but more recent literature reveals that 10–20 % of patients will ultimately require pacemaker insertion [38, 39]. A topic that requires further investigation is the fact that there appears to be a decrease in long-term mortality in patients who have pacemakers placed in the perioperative period following transplantation [38].

Malignancy

It is well known that patients receiving solid organ transplants and immunosuppression are at a greater risk of malignancy than the general population. The most common types of cancers following OHTx are skin cancers with greater than 15 % of recipients ultimately being affected [19, 40, 41]. The largest database from the International Society for Heart and Lung Transplantation reports that by 10 years post-transplant only 66 % of patients will be free of any malignancy [19]. More serious diseases such as lymphoproliferative disease are not uncommon in this patient population with 1–2 % of patients impacted within the first 5 years after surgery [42].

Common Procedures After Orthotopic Heart Transplantation

It is well described that a substantial number of patients will present to the operating

room for general surgical conditions following OHTx [2, 5, 43]. The high rate of general surgery in this patient population is often attributed to the low flow state preoperatively, intraoperative cardiopulmonary bypass, and the use of immunosuppression in the postoperative period [2]. Diagnosing general surgical conditions in the heart transplant recipient can be challenging due to the fact that immunosuppressive drugs may mask the typical presenting symptoms and hasten the progression of disease.

The immediate post-transplant period represents the most likely time for an OHTx patient to require general surgery [2]. Surgeries in this time period are occasionally due to surgical complications, but may also include procedures such as exploratory laparotomy and bowel resections [44]. The requirement for general surgery within 30 days following OHTx confers a substantial increase in mortality partially owing to the fact that diagnosis is difficult in this period and immunsuppression makes recovery challenging [2, 44]. As you move further away from the time of transplant surgery, the most common general surgical conditions patient seek treatment for remain intra-abdominal pathology, such as cholecystectomy, hernia repair, and appendectomy [2, 5].

Preoperative Evaluation

The preoperative assessment of any transplant recipient must include a thorough assessment of graft function, infection, rejection, and the function of other organs that may be compromised as a result of chronic immunosuppressive therapy [7]. A dedicated transplant team closely monitors transplant recipients and it is prudent to discuss patient management with this team prior to performing elective noncardiac surgery. The transplant team is able to divulge important information regarding the immunosuppressive regimen, episodes of rejection, status of the transplanted organ, and complications that have arisen since the time of transplant. In the setting of more emergent surgery, the anesthesiologist must then rely on patient history and laboratory/other data that is available to best manage the OHTx recipient.

Necessary preoperative testing for the OHTx includes a current electrocardiogram, echocardiogram, and laboratory assessment [6]. It is best to be able to compare the current electrocardiogram with prior electrocardiograms to evaluate for any new findings. Preoperative echocardiography can be extremely helpful and yields a rapid way to evaluate ventricular function. Echocardiography may also shed light on any new valvulopathy since the time of transplant. In regard to laboratory evaluation, particular attention should be paid to markers of infection as well as renal indices given the high incidence of renal insufficiency following heart transplantation. The remainder of the preoperative examination should be no different between the OHTx recipient and any other patient.

Anesthesia Management and Considerations

Proper anesthesia management requires a detailed understanding of the physiology of the transplanted heart and the comorbidities associated with OHTx. After a comprehensive preoperative examination, standard premedication should be given as in non-transplant patients [7]. As in most cases, the type of anesthesia utilized is dictated by the surgical requirements. General, neuraxial, and regional anesthesia as well as monitored anesthesia care have all been safely used in this patient population [7]. A valid concern with the use of neuraxial anesthesia is that acutely decreasing preload may lead to severe hypotension in a patient who is "preload dependent." Intravascular volume administration prior to neuraxial block may help to augment the severity of hypotension, but some recommend avoiding neuraxial blocks in OHTx recipients due to the unpredictability of the hemodynamic response.

Intraoperative monitoring with standard ASA monitors may be all that is required for patients following OHTx [45]. If invasive monitors are planned in the setting of predicted large fluid shifts, one must weigh the risks of infection versus the benefits of invasive monitoring techniques. Strict care must be taken to ensure that complete aseptic technique is used with the insertion of invasive monitors due to the increased risk of infection in patients on immunosuppressive regimens [7, 46]. As opposed to a pulmonary artery catheter, transesophageal echocardiography may be a more helpful monitor to evaluate volume status and cardiac contractility with a decreased risk of infection [7].

Medication administration by the anesthesia provider must also be carefully considered. As mentioned previously, indirect-acting drugs such as anticholinergics may be of no benefit in increasing heart rate and contractility. The transplanted organ does maintain a normal density of intrinsic adrenergic receptors and direct-acting drugs such as epinephrine and norepinephrine are often the most useful in treating hypotension. Intravenous fluid boluses should also be considered early in the management of hypotension. The muscle relaxant used to maintain balanced anesthesia should be chosen with caution as well; *cis*-atracurium is often an excellent choice due to the fact that elimination is not affected by either renal or hepatic dysfunction. The choice of reversal of muscle relaxation must also be taken seriously because there are numerous reports of neostigmine-induced asystole following OHTx. Some providers avoid the use of neuromuscular blocking drugs entirely to avoid this described complication.

Noncardiac Surgery Following Lung Transplantation

Introduction

End-stage lung disease caused by obstructive, restrictive, and pulmonary vascular disease is often treated with either single- (SLTx) or double-lung transplantation

(DLTx). Lung transplantation (LTx) is becoming increasingly common to improve patient quality of life as well as extend survival. Graft survival and patient outcomes may be impacted by both immediate- and long-term complications that are well described following LTx surgery. Immediate concerns such as infection or graft rejection and long-term issues such as bronchiolitis obliterans, cancer, and systemic disease may all influence the final outcome [47].

As with most forms of organ transplantation, survival following LTx surgery continues to improve. The most recent statistics published by the Organ Procurement and Transplantation Network show the 1- and 5-year survival to be at 82 % and nearly 50 %, respectively [1]. Data published by the ISHLT shows that survival is influenced by both the type of disease requiring transplant and the type of transplant performed with patients receiving a DLTx living longer than SLTx recipients [48]. While survival advances, the number of organ transplanted is also on the rise with nearly 1800 LTx procedures occurring in the US annually [1]. With improved life expectancy and increasing numbers of transplanted organs, more patients following LTx are presenting to the operating than ever before for noncardiac surgery.

Physiology of the Transplanted Lung

Major physiologic changes occur in the transplanted lung secondary to the disruption of innervation, lymphatics, and bronchial circulation during lung procurement and insertion. The extent of physiologic change depends upon the type of transplant performed (single- vs. double-lung transplant), surgical technique, and the indication for transplantation. It is important for the anesthesiologist to be familiar with post-transplant physiology to optimally manage LTx recipients in the postoperative period and in the years following transplant.

Loss of the cough reflex distal to the site of the bronchial anastomosis is possibly the most devastating complication of denervation [49]. This occurs because the surgical procedure involves transection of the vagal nerve with resultant sensory and autonomic airway denervation distal to the site of airway anastomosis [50]. The current surgical technique attempts to preserve the carina at all cost in an attempt to maintain a normal reflex pathway in the proximal airway. The concern with losing the cough reflex comes from data indicating an increased risk of premature death as a result of infectious complications, a major cause of post-transplant morbidity and mortality [51]. While it was previously thought that loss of the cough reflex distal to the anastomosis was a permanent issue, newer literature suggests that this may not be true and that reflex pathways may be restored within 6–12 months following postoperatively [49, 50, 52].

Other physiologic consequences of denervation include impaired mucociliary transport and loss of baroreceptor input from the medulla to the lung [53–55]. Despite these changes, respiratory rate and rhythm appear to be unchanged following double-

lung transplantation [45]. It also appears that airway tone, which is mediated primarily by the parasympathetic nervous system (PNS), is not adversely affected. This is due to the fact that muscarinic receptors on transplanted lung/lungs remain intact and responsive to efferent signals sent by the PNS. The airway should remain responsive to the effects of beta-2 agonists such as albuterol [47].

Pulmonary blood flow following LTx depends on whether the patient receives an SLTx vs. DLTx procedure. DLTx recipient lungs have normal pulmonary blood flow, but SLTx patients have 60–70 % of the perfusion and ventilation going toward the transplanted lung [56]. Regardless of the type of transplant that is performed, it appears that hypoxic pulmonary vasoconstriction is preserved in LTx recipients [57]. One remaining concern in the LTx recipient is that these patients may be extremely sensitive to fluid shifts and fluid overload. Lymphatic interruption is a known side effect of the surgical procedure and small volume challenges may potentially cause pulmonary edema in LTx patients [58]. The lymphatic channels are eventually restored, but the timing and extent of reformation remain unclear [59, 60].

Complications Following Lung Transplantation/Post-transplant Morbidities

Recipients of transplanted lungs are at risk for numerous adverse events linked to the disease necessitating transplantation, the surgical procedure, and the immunosuppression regimens postoperatively. Major concerns in the immediate period following surgery include graft failure, bleeding, and infection. Moving further away from the time of transplantation, common morbidities seen are typically elicited or exacerbated by the immunosuppression regimen chosen and these are highlighted in Table 18.3. Two topics deserving further discussion in the patient following LTx are bronchiolitis obliterans and infection.

Table 18.3 Post-transplant morbidities : Incidence of common issues at 1 and 5 years following lung transplantation

Disease	Incidence at 1 year (%)	Incidence at 5 years (%)
Bronchiolitis obliterans	9.5	38.9
Hypertension	52.0	82.9
Creatinine <2.5 mg/dl	16.5	36.7
Dialysis dependent	1.7	3.2
Diabetes mellitus	25.5	40.5
Hyperlipidemia	25.0	57.9

Data from International Society of Heart and Lung Transplantation 2012 report. Reproduced from Christie et al. [48], with permission

Bronchiolitis Obliterans

Although short -term survival following LTx continues to improve, bronchiolitis obliterans (BO) remains a major threat to advances in long-term survival [61, 62]. The most recent report released from the ISHLT in 2012 describes the incidence of BO to be 48 % by 5 years and 76 % by 10 years post-transplant—see Fig. 18.1 for details. The diagnosis of BO confers a very high probability of mortality and survival following diagnosis is only 30–40 % at 5 years [63].

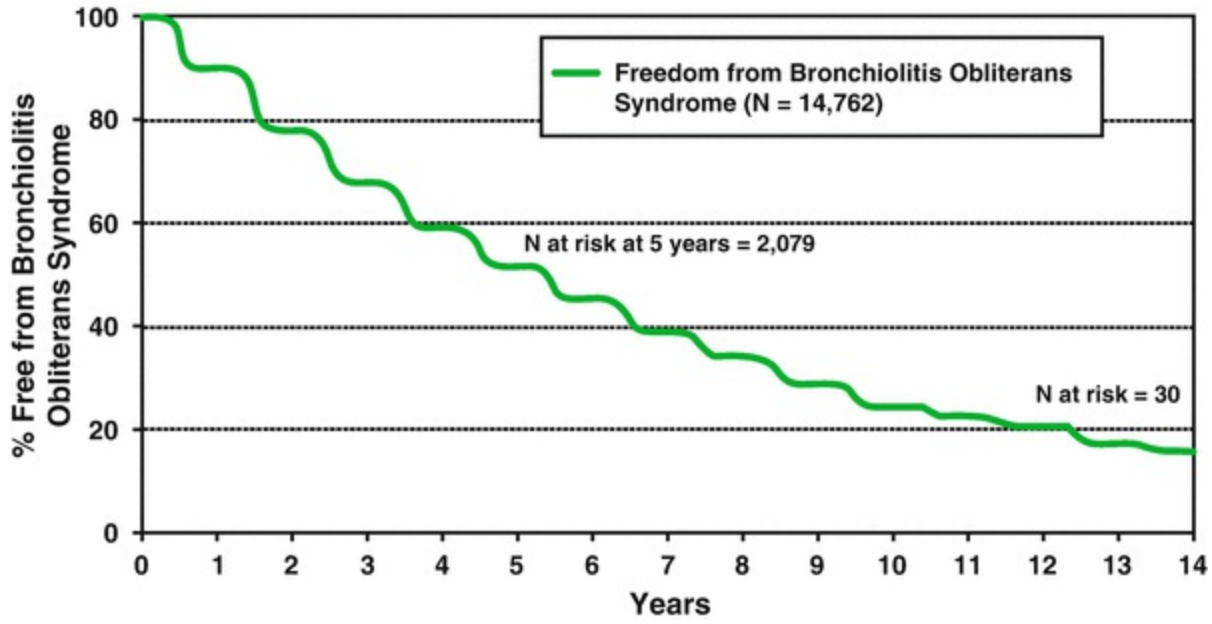

Fig. 18.1 Freedom from bronchiolitis obliterans syndrome in adult lung recipients for follow-up between April 1994 and June 2011, conditional on survival to 14 days (reproduced with permission from Christie et al. [48].)

Bronchiolitis obliterans was first described in 1984 at Stanford University in heart-lung transplant recipients who exhibited a progressive decline in forced expiratory volume in 1 s (FEV1) [64]. Despite advances in diagnosis and medical therapy, this disease continues to plague post-transplant recipients. The disease occurs most commonly between 1 and 4 years following transplantation and diagnosis before 6 months is extremely unlikely [65]. Early in the course of BO, clinical symptoms may be mild and nonspecific. As the disease progresses, productive cough is increasingly common and lower respiratory tract infections are frequent [61]. The vulnerability to lower respiratory tract infections is most likely due to bronchiectasis and the impairment of mucociliary function in patients with compromised immune systems [61]. The progression of disease is extremely heterogeneous, but most patients experience a rapid decline in pulmonary function eventually leading to respiratory failure and death.

Currently, the diagnosis of bronchiolitis obliterans syndrome requires a sustained decline in FEV1 for more than 3 weeks in the absence of other causes of pulmonary dysfunction [66]. The traditional detection of BO hinged upon surveillance

transbronchial biopsy (TBB) procedures and many centers continue to use this technique as the standard of care [67]. Recent literature shows that the detection of BO by TBB ranges from 15 to 45 % questioning the need for routine TBB in asymptomatic patients [68]. TBB may not be the best screening test for BO, especially after the first postoperative year, given that it requires an invasive, expensive procedure [61]. Other techniques that may aid in the diagnosis of BO include pulmonary function studies, chest radiographs, bronchoalveolar lavage, and exhaled nitric oxide levels. The sensitivity and specificity for each test vary greatly, but the objective is to provide an early diagnosis and initiate treatment in the early stages of disease. Treatment of suspected BO or acute rejection typically begins with an attempt to increase levels of immunosuppression. The first-line therapy used in most cases is additional steroid therapy and ensuring appropriate blood levels of other immune-suppressing medications [68]. As a last resort, retransplantation may ultimately be considered.

Infection

Rates of infections following LTx are substantially higher than infectious complications following other forms of transplant surgery [69]. The typical infections that complicate recovery and even long-term survival are bacterial infections involving the lower respiratory tract [70]. Factors that may increase the risk of pulmonary infection in this patient population include aggressive immunosuppression, blunted cough reflex, impaired mucociliary clearance, and even the passive transfer of organisms from the donor organ [70, 71]. The typical organisms that are seen in both early and late infections are gram-negative organisms, in particular *P. aeruginosa* [69, 72]. Other microorganisms that have commonly caused infections in the post-lung transplant patient include CMV, community-acquired viruses, and *Aspergillus* species [71]. Most centers use prophylactic antimicrobial regimens with an attempt to decrease infection and mortality following LTx, but the efficacy of such regimens remains in question [71].

Common Procedures After Lung Transplantation

Surgery is extremely common following lung transplantation with certain surgeries being more common in distinct post-transplant periods. These periods are typically divided into the immediate postoperative, surveillance, and general periods [47]. In the days following an LTx, patients are most likely to present to the operating room due to complications of the LTx surgery itself such as bleeding, cardiac tamponade, and wound or anastomosis dehiscence. The transplant anesthesia and surgical teams typically address surgery in this period. Common surveillance procedures following LTx include TBB and bronchoscopy and the frequency of these procedures is determined by the institution where the LTx occurred. Lastly, the general period refers to a period more distant from the time of surgery when patients present for elective and emergency

surgeries the same as the general population [47]. One type of surgery that deserves special mention is gastrointestinal surgery following LTx.

For unknown reasons, patients following LTx procedures seem to be at an increased risk for gastrointestinal complications and this is a major cause of morbidity in LTx recipients [73–76]. GI complications such as appendicitis, cholecystitis, peptic ulcer disease, and bowel obstruction may occur in as many as 50 % of patients postoperatively [73–76]. It appears that the most frequent condition requiring surgery after lung transplant may be cholecystitis eventually leading to cholecystectomy. Issues with bowel motility are the next most common gastrointestinal complication requiring surgery in most series [73–76]. Recipient risk factors such as cystic fibrosis and preoperative COPD may lend to the development of postoperative GI complications and a significant increase in post-transplant mortality [73].

Preoperative Evaluation

As mentioned previously, the preoperative assessment of transplant recipients is not significantly different from the routine used for the general population with a few exceptions. The anesthesiologist must pay particular attention to the function of the transplanted lung/lungs, complications resulting from immunosuppression, the presence of infection, and organ rejection [7, 47, 55]. As with any transplant recipient, it is extremely important to discuss perioperative care with the transplant team that routinely monitors the patient. The transplant team should be able to discuss the results of the most recent transbronchial biopsy and other indices of rejection as well as infectious complications that may require special antibiotic prophylaxis. Obviously, in the setting of emergency surgery this discussion may not be possible and history from the patient should clue the anesthesia provider into current graft function.

Other considerations to address in the preoperative evaluation of the LTx recipient include the pathology necessitating transplant, the status of the native lung if the patient received an SLTx, a comprehensive laboratory evaluation, and the current medication regimen. It is imperative that patients continue their home medications and immunosuppression regimen up until the time of surgery and provisions should be established for intravenous conversion of these medications if a prolonged NPO time is expected postoperatively. Lastly, the anesthesiologist must consider the requirements of the surgical procedure to adequately prepare the patient and family for the expected postoperative course. With these few provisions, the preoperative assessment is quite similar to that of non-transplant patients.

Anesthesia Management and Considerations

Optimal intraoperative management begins with a thorough preoperative assessment as outlined in the preceding section. Certain considerations must exist when caring for the

LTx recipient and it is the job of the anesthesiologist to predict which complications might arise as a result of pulmonary denervation, immunosuppression, differential ventilation, and the surgical procedure. Transplant recipients have successfully been managed with general, regional, and neuraxial anesthesia as well as monitored anesthesia care with little data to support one type of anesthesia over another [7]. The anesthesia plan and intraoperative monitoring strategy, as usual, are dictated by the proposed procedure and preoperative status of the patient. In the event that the anesthesia team decides to utilize invasive monitors, sterile technique is of utmost importance to minimize infectious risks [47]. Attention to detail in several other aspects of the anesthesia plan will likely provide for improved patient outcomes in the LTx recipient.

If general anesthesia with an endotracheal tube (ETT) is chosen, attention must be paid to airway management, infection, and intraoperative ventilation. As a result of chronic steroid therapy with resultant diabetes, patients following solid organ transplantation acquire morphologic features that increase the risk for unplanned difficult airway management [77]. A thorough airway examination should occur in all patients, but it is especially important in this patient population with known increased risk of difficult airway and gastric atony [73]. Proper placement of the ETT is vitally important to avoid possible airway trauma or damage to the bronchial anastomosis [47, 55, 78]. It is often recommended that a fiber-optic bronchoscope be used to assist with ETT placement in patients following LTx [47]. In terms of the route of intubation, orotracheal intubation is certainly preferred over nasal intubation to avoid possible contamination from local microorganisms [47]. Every attempt should be made to allow for early extubation to decrease the risk of respiratory tract infections following LTx [47].

Intraoperative ventilation in patients following DLTx does not differ markedly from the non-transplant patient, but special consideration must be given to patients after SLTx. After an SLTx, there may be a significant difference in the compliance of the native lung and the transplanted lung that is dictated by the pathology necessitating transplantation. For example, in patients with severe emphysema in the native lung, the majority of ventilation will be directed to the more compliant native lung. Remembering that 60–70 % of perfusion will be directed to the transplanted lung, positive pressure ventilation may lead to shunting and impaired oxygenation [56, 78]. In patients receiving an SLTx for restrictive lung disease, the transplanted lung should have significantly better compliance than the native lung and oxygenation/ventilation is unlikely to be compromised. Anesthesia providers should be aware that there are rare circumstances where the difference in compliance between the native and transplanted lung is severe enough to necessitate lung isolation and the use of two ventilators to avoid lung trauma and optimize oxygenation and ventilation [47, 79].

It is critical that the anesthesia provider manage fluid administration carefully in

LTx recipients. The primary concern with excessive fluid administration is pulmonary edema. It is known that interruption of the lymphatic system occurs with the procedure of lung transplantation [58]. Lymphatic channels will be restored over time, but the timing and completeness of restoration are unclear [59, 60]. If large volumes of crystalloid/colloid are deemed necessary, intraoperative ventilation with increased levels of PEEP may prevent interstitial pulmonary edema and allow for timely extubation [47].

Implications of Immunosuppression After Heart and Lung Transplantation

Advances in immunosuppression have afforded substantial increases in survival, but these drugs are well known to increase susceptibility to infections and have extensive side effect profiles as outlined in Table 18.4. Attempting to find the "right" amount of immunosuppression is the real challenge in patients following transplant procedures. Too much immunosuppression will weaken the immune system and may lead to life-threatening infections, but too little will increase the risk of rejection and graft dysfunction [55, 80]. In caring for the patient on chronic immunosuppression therapy, it is imperative that the anesthesiologist considers the systemic effects of immunosuppressive agents and understands the drug interactions that may occur in the intraoperative and postoperative periods.

Table 18.4 Side effects of commonly used immunosuppressant drugs following heart and lung transplantation

Drug	Side effect profile
Cyclosporine A	Nephrotoxicity Hypertension Tremor Headache Elevated triglycerides Increased risk of infection
Tacrolimus	Nephrotoxicity Hypertension Peripheral edema Tremor Headache/insomnia Glucose intolerance/diabetes mellitus
Azathioprine	Hepatotoxicity Leukopenia Increased risk of infection Malaise Nausea/vomiting

Corticosteroids	Weight gain Glucose intolerance/diabetes mellitus Hypertension Hyperlipidemia Adrenocortical unresponsiveness to stress Emotional instability
Mycophenolate mofetil (MMF)	Nephrotoxicity Elevated liver function tests Hypertension Peripheral edema Glucose intolerance Electrolyte abnormalities Leukopenia/anemia

Immunosuppression following transplantation is typically divided into three distinct phases. Firstly, the induction phase is when the immunosuppression regimen is started. This is a period of intense drug administration with hopes of preventing rejection episodes. The induction phase is followed by the maintenance phase. Maintaining immunosuppression for both heart and lung transplant patients generally involves a three-drug regimen with at least one part consisting of corticosteroids. In the maintenance phase, the hope is to provide sufficient immunosuppression to prevent rejection, but use low enough drug dosages to avoid side effects. The last phase is the acute rejection phase. The goal in this phase is to rapidly increase drug levels and diminish immune response to preserve the transplanted organ during periods of rejection. This is generally accomplished with large doses of corticosteroids [55].

Current immunosuppressive regimens in the OHTx recipient are variable among institutions, but the most common regimen seems to be a combination of tacrolimus, mycophenolate mofetil (MMF), and corticosteroids. Previously, cyclosporine was more likely to be used than tacrolimus, but cyclosporine is falling out of favor due to an increased incidence of renal dysfunction, hypertension, and hyperlipidemia [81]. LTx recipients also receive triple therapy for maintenance immunosuppression with the most common regimen being identical to that of heart transplant recipients. Several different regimens have been tested and used with varying degrees of success, but the important point is to note that all drugs used to suppress the immune system come with the cost of side effect profiles that must be weighed for the given transplant recipient.

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Part V
Kidney and Pancreas Transplantation

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19. Kidney Transplantation: Overview

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Introduction

Sixty years ago, end-stage renal disease (ESRD) was a uniformly fatal disease. With the advent of the first successful cases of transplantation (see Table 19.1) and the development of dialysis, end-stage renal disease was transformed into a serious but manageable chronic disease. Transplantation remains the most successful therapeutic option with superior patient survival and quality of life. Unfortunately, the majority of adults, some 75 %, are never referred for evaluation for transplantation largely because of advanced age and comorbidities. In addition, waiting times for those patients in good enough shape to get listed for a transplant are long, potentially 8–10 years, and more patients die waiting for a kidney than for liver, heart, and lung combined. This chapter serves as a brief overview of renal transplantation.

Table 19.1 History of kidney transplantation [1]

1902	Vienna Medical School Austria: Kidney transplantation in animals

	• Dr. Emerich Ullman: Autotransplant in a dog from normal position to vessels in the neck • Dr. Alfred von Decastello: Dog-to-dog kidney transplantation • Dr. Ullman: Dog-to-goat kidney transplantation
1906	Lyon, France: Xenograft transplantation • Mathieu Jaboulay: Two xenograft kidney transplants (pig and goat as donors, to human recipients) • Functioned for 1 h
1909	Lyon, France: Animal/human kidney transplant experiments • Dr. Ernst Unger: – Fox terrier to boxer: Kidney functioned for 14 days – Human stillborn child to baboon: No kidney function – Ape to human: No kidney function • Resulted in the recognition of a "biochemical barrier" that hindered successful transplantation
1933	Ukraine, Soviet Union: First human-human kidney transplantation • Dr. Yu Yu Voronoy: Human kidney blood group B to recipient blood group O: No kidney function • (By 1949) Six such transplants with no kidney function in any of the subjects
1940s	University of London: Early experiments on immunologic basis of organ transplantation and immunosuppression • Sir Peter Medawar
1946	Peter Bent Brigham Hospital, Boston • Drs Hufnagel, Hume, and Landsteiner: Human allograft kidney transplant to arm vessels under local anesthesia; brief period of function • Renewed interest in transplantation
Early 1950s	Increase in experimental and clinical kidney transplantation Recognition of the role of immunology and graft failure/rejection • Dr. Simonsen reported on the mechanism of kidney rejection • Dr. Dempster discovered that radiation delayed rejection • Dr. Hume observed that the blood group matching of graft and donor might be necessary Early attempts at immunosuppression • Total body irradiation and allograft bone marrow rescue – Difficult to manage – Graft vs. host disease frequent • High-dose steroids
1954	Boston: Transplant of a kidney from one twin to another twin, the first successful kidney transplant ever performed
Early 1960s	Introduction of azathioprine, 6-mercaptopurine, and methotrexate
Mid-1960s	Donor organ cooling accepted Low-dose steroids as effective as high-dose steroids
Late 1960s to 1970s	Development and improvement in HLA cross-matching
1980s to present	Ongoing improvements and advances • Cyclosporine, tacrolimus, mycophenolate mofetil, and other immunosuppressive agents • Improvement in techniques for organ procurement and preservation

Although dialysis is not a prerequisite for transplantation listing, the majority of patients undergoing kidney transplantation are on dialysis by the time they receive a kidney. Outcomes of kidney transplantation are negatively affected by prolonged periods on dialysis, and preemptive transplantation is associated with improved patient and graft survival [1, 2]. Patients can be listed once their estimated GFR is below 20 ml/min/1.73 m^2 and/or if they can identify a potential living donor. The pre-transplant evaluation process can take some time and can delay addition to the waitlist. As such, early referral is recommended in the setting of chronic kidney disease, especially in diabetics and those with rapid clinical progression to end-stage renal disease. An estimated GFR less than 30 ml/min/1.73 m^2 has been defined as the trigger for evaluation in some institutions [2]. A thorough pre-transplant evaluation is then undertaken to optimize the patient's condition prior to transplantation and maximize graft and patient survival as well as quality of life.

Recipient Evaluation

Candidates for renal transplantation are evaluated extensively to identify any medical or psychosocial factors that may result in an adverse outcome. Patients with ESRD often have associated comorbidities such as anemia and platelet dysfunction, bone and joint disease, gastritis, gastrointestinal bleeding, ileus, pulmonary edema, pleural effusions, hepatic disorders, and cardiovascular abnormalities. Of particular significance is the effect of ESRD on the cardiovascular system. Patients undergoing hemodialysis have a cardiovascular mortality rate 30 times that of non-uremic patients [1]. This increased risk is attributed to increased atherosclerosis, myocardial infarction, congestive heart failure, dysrhythmias, pericardial effusions, and cardiomyopathy. The presence of hypertension, hyperlipidemia, and diabetes is also common within this patient population. The purpose of the pre-transplant evaluation is to identify and treat coexisting medical problems that would increase a patient's morbidity and mortality after transplantation. It also identifies any psychosocial factors that may have a negative effect on outcomes. These factors include any financial difficulties, uncontrolled psychological issues, lack of social support, and history of medical noncompliance.

The evaluation process begins with a thorough history of the patient's renal disease. The etiology and pathology of ESRD can determine the risk of recurrence as well as define the associated comorbidities that will require further investigation. Other pertinent information includes dialysis status and dialysis access, urine production, any complications associated with dialysis access, thrombotic events, blood transfusions, and infections. Furthermore, it is important to determine if the patient has a history of prior transplantation, rejection episodes, allograft infections, or noncompliance. Knowing the outcome of a prior transplant may be predictive of the outcome of the subsequent transplant.

Recipient evaluation continues with an extensive review of the patient's medical history. This is to identify further any risk factors that would predict increased morbidity and mortality as well as any contraindications to transplantation. Of particular importance are cardiopulmonary symptoms, such as angina, history of myocardial infarction, pericarditis, pericardial effusion, valve disease, and congestive heart failure. Identification of these risk factors will determine the degree of workup necessary for cardiac clearance. Cardiac testing includes an electrocardiogram, echocardiogram, stress test, and possible coronary angiogram. A history of type I diabetes would also lead to the need for an aggressive cardiac workup, given the increased risk of silent coronary disease. Furthermore, the evaluation will also include an assessment of pulmonary, neurologic, psychologic, and urologic symptoms. This information will guide the need for additional testing such as pulmonary function testing, voiding cystourethrogram, carotid duplex, and neurovascular imaging. Screening for occult malignancy and inquiring about a history of malignancy are also part of the process. An infectious disease profile is obtained to determine exposure and risk factors for tuberculosis, HIV, and hepatitis B and C. Prior surgeries, medications, allergies, and social history are also pertinent. Overall, this process serves to identify any conditions that would require further investigation.

The physical exam highlights any clinical signs that may warrant further investigation. The vital signs may reveal such symptoms as uncontrolled hypertension or orthostatic hypotension. Carotid bruits may be a marker of significant carotid stenosis. Pulmonary and cardiac findings may identify underlying disease that may not have been fully evident in the patient's history. Abdominal exam may reveal scars of prior surgery or signs of an intra-abdominal process. Weak femoral and peripheral pulses may require additional workup to evaluate possible peripheral vascular disease. Finally, an assessment would screen for infections.

Extensive laboratory and imaging studies serve as screening tools to identify factors that will impact transplantation negatively. Not all procedures and tests are required for every patient. Rather, the need for a given study is guided by the patient's age, history, physical exam, and inherent risk factors. Patients with a significant medical history, positive review of systems, type I diabetes, or hypertensive renal disease should undergo a complete cardiac workup including a coronary angiogram. Finding significant coronary artery disease results in a cardiologist evaluation for revascularization by coronary angioplasty with stenting or coronary artery bypass grafting prior to transplantation.

Immunologic evaluation is performed to identify factors associated with a high risk for antibody-mediated hyperacute rejection. This involves ABO blood group antigen determination, HLA typing, percent panel reactive antibody level (PRA), and donor/recipient cross-matching. ABO blood group antigens are potential targets for the recipient's preformed cytotoxic anti-ABO antibodies. This may result in antibody-

mediated hyperacute rejection in ABO-incompatible donor-recipient groups. All transplant recipients and donors are HLA typed to determine the HLA class I and class II loci. Six major and multiple minor HLA antigens are identified, and the degree of incompatibility is determined by the number of antigens that are mismatched at each loci. Better outcomes have historically been noted with a zero antigen mismatch. The PRA is used to evaluate the recipient's sensitivity to HLA phenotypes in a given population. The recipient can become sensitized as a result of prior blood transfusions, transplants, or pregnancy. Cross-matching is used to determine if the recipient has any preformed anti-HLA antibodies specific to the prospective donor. The immunologic profile is also of particular importance with regard to organ allocation. The degree of mismatching can affect allocation of deceased donor kidneys. Organ allocation also takes into consideration individuals with a high (>95 %) PRA found to have a negative cross-match with a particular donor.

The evaluation process can be summarized by answering five basic questions:

1. What is the cause of renal failure?

2. Is a renal transplant indicated?

3. Are there any medical barriers to transplantation?

4. Are there any psychological or social barriers to transplantation?

5. Are there any immunologic barriers that would negatively affect transplantation?

This extensive evaluation process systematically answers these questions and identifies the patients who can be listed for kidney transplantation (see Table 19.2). It further identifies those with contraindications to transplant (see Table 19.3). The process also brings to attention those who would benefit from additional testing or intervention prior to a decision regarding transplantation.

Table 19.2 Pre-transplant evaluation [3]

1. History of renal disease
(a) Etiology
(b) Dialysis status
(c) Urine production
(d) Prior transplants and complications
(e) Review of systems
2. Past medical and surgical history

(a) History of blood transfusion
(b) Comorbid diseases
3. Physical examination
4. Gynecologic evaluation
(a) Pap smear
5. Mammography
6. Dental evaluation
7. Laboratory studies
(a) Complete blood count, chemistries, liver function tests, coagulation profile, parathyroid hormone level
(b) Malignancy screen: PSA
(c) Serologies: CMV, EBV, Varicella-Zoster, HIV, RPR, PPD, hepatitis B and C
(d) Urinalysis and urine culture
(e) Immunologic profile: Blood type, panel reactive antibody, HLA typing
8. Chest X-ray, abdominal ultrasound, CT scan of abdomen and pelvis (if indicated)
9. GI workup
(a) Upper endoscopy (if indicated)
(b) Colonoscopy (if indicated)
10. Cardiac workup
(a) EKG
(b) Echocardiogram
(c) Stress test (if indicated)
(d) Coronary angiogram (if indicated)
11. Vascular workup (if indicated)
(a) Lower extremities duplex
(b) Carotid duplex
(c) Cerebral imaging
12. Pulmonary workup (if indicated)
(a) Pulmonary function test
(b) Right-heart catheterization
13. Psychosocial evaluation

Table 19.3 Contraindications to kidney transplantation [3]

1. Reversible renal disease
2. Active infection
3. Chronic untreated infection
4. Active glomerulonephritis
5. Advanced/uncorrectable coronary or pulmonary disease
6. Life expectancy less than 1 year

7. Recent/untreated malignancy
8. Noncompliance
9. Active substance abuse
10. Uncontrolled psychiatric disorders
11. Lack of adequate social support

Living Donor Kidney Donation

A major limitation in kidney transplantation is deceased donor organ availability; some patients are fortunate enough to have a living donor. The major concern is the risk of subjecting a healthy patient to a nephrectomy. However, the morbidity associated with the procedure is less than 1 %, with a mortality 0.03 %. Donor life expectancy does not appear to be negatively affected and has been shown to be longer than that of the general population [3, 4].

The goal of the evaluation process for living donors is to establish that the potential donor is healthy enough to donate. As such, it is necessary to identify any underlying history that would suggest underlying renal dysfunction that would be negatively impacted by the loss of a kidney through donation (Tables 19.4, 19.5, and 19.6). Disease states such as hypertension and diabetes can affect renal function. A history of gestational diabetes is also of concern with a potential risk for type 2 diabetes later in life. In addition, the evaluation assesses a history of recurrent urinary tract infections, kidney stones, or prior renal trauma. A history of clotting disorders, deep vein thrombosis, heart disease, lung disease, or obesity serves as a possible indication of increased risk of donor morbidity and mortality.

Table 19.4 Evaluation of a potential living kidney donor [5]

1. Identification of potential living donor
2. History and physical examination
• Personal/family history of kidney disease
• Hypertension
• Diabetes/gestational diabetes
• Urinary tract infections
• Kidney stones
• History of DVTs or clotting disorders
• Heart/lung disease
• Cancer history
• Kidney injury history
• Use of NSAIDs
• Body-mass index/obesity

3. Immunologic evaluation
• ABO blood type
• HLA determination
• Cross-match
4. Psychosocial evaluation
5. Laboratory studies
• Complete blood count, chemistries, liver function panel, coagulation panel
6. Metabolic profile
• Fasting blood glucose
• Thyroid function test
• Uric acid level
• Fasting lipid profile
7. Urine studies
• Urinalysis, 24-h urine protein and creatinine, GFR
• ± Renal scan with differential renal function
8. Infectious profile
• Hepatitis A, B, and C serologies
• CMV/EBV serologies
• HIV/HTLV/RPR
• Urine culture
• PPD
9. Cancer screen
• Prostate-specific antigen (males >50 years)
• Pap smear (women)
• Mammogram (women >40 years, family history)
• Colonoscopy (age >50, family history)
10. Other
• Pregnancy test
• EKG
• ± Echocardiogram/stress test/coronary angiogram
11. Radiologic studies
• Chest X-ray/chest CT
• Renal ultrasound
• Renal CT scan with 3D angiography

Table 19.5 Absolute contraindications to living kidney donation [5]

1. Age <18 years
2. Hypertension (BP > 130/90)

• In donor age less than 50 years old
• Evidence of end-organ damage
• On two or more antihypertensive medications
3. Diabetes (diagnosis of diabetes)
4. Abnormal glucose tolerance test 2 h OGTT > 140
5. History of thrombosis or embolism
6. Psychiatric contraindications
7. Obesity: BMI > 35 kg/m^2
8. Coronary artery disease
9. Symptomatic valvular disease
10. Chronic lung disease with impairment of oxygenation or ventilation
11. Recent malignancy, or cancers with long times to recurrence
• Breast cancer
12. Urologic abnormalities of donor kidney
13. Creatinine clearance <80 ml/min/1.73 m^2, or projected GFR with removal of one kidney at 80 years old of <40 cc/min/1.73 m^2
14. Peripheral vascular disease
15. Proteinuria >300 mg/24 h
16. HIV infection (unless recipient is HIV positive)
17. Hepatitis C virus infection
18. Hepatitis B virus infection

Table 19.6 Relative exclusion criteria for living kidney donation [5]

1. Obesity (BMI 30–35)
2. Kidney stones
3. Distant history of cancer
4. Past history of psychiatric disorder

The nature of the physical exam is to identify signs of hypertension, evaluate for obesity, and determine any signs of cardiac, pulmonary, liver, or peripheral vascular disease. Additional importance is placed on the psychosocial evaluation, not only to ensure proper mental health and support but also to confirm that the motivation guiding donation is truly altruistic. The remainder of the evaluation process assesses ABO blood group to determine compatibility. Once compatibility is established, the remainder of the extensive evaluation can proceed. As outlined in Table 19.4, the process includes general laboratory blood work, immunologic studies, metabolic work up, as well as infection and cancer screening. The renal evaluation serves to evaluate not only function but also the anatomy. This will aid in the selection of the appropriate

organ for transplantation.

Donor nephrectomy is now more commonly performed laparoscopically. The most common causes of operative mortality are pulmonary embolism, bleeding, and infection. Most patients are discharged between postoperative days 1 and 3.

The donor nephrectomy results in an immediate decrease in renal function by approximately 50 %. This is followed by renal compensation occurring over the next 6 weeks, resulting in a new baseline renal function that is about 75–80 % of the pre-nephrectomy function. There is no documented long-term increase in the risk for renal dysfunction, hypertension, or cardiovascular disease [4, 5].

Deceased Donation

The process of deceased donation is inherently different from that of living donors. When a potential donor becomes available, the organ procurement organization quickly begins screening the donor for suitability (Tables 19.7 and 19.8). This evaluation begins with determining the etiology and duration of brain death, duration of cardiac arrest, and need for inotropic support. A history of pre-existing disease is important to assess the suitability of the organ for donation. A history of renal dysfunction, uncontrolled hypertension, or diabetes would require additional scrutiny before acceptance of that renal allograft. A history of high-risk behavior would be suggestive of an increased risk of transmissible infectious disease such as HIV or hepatitis B or C. A physical assessment is performed to evaluate hemodynamic stability, height, weight, body mass index, and any signs of intra-abdominal trauma that would suggest renal injury. Urine output and screening for hematuria is also a necessary aspect of this evaluation.

Table 19.7 Evaluation of the deceased donor [3]

1. Confirmation of brain death and appropriate documentation
2. History
• Etiology and duration of brain death
• History of cardiac arrest
• Pre-existing disease
• High-risk behavior
3. Physical exam
• Signs of physical trauma, prior surgeries, or infection
• Hemodynamic stability
• Pressor requirements
• Urine output
4. General lab work
• Complete blood count, complete serum chemistry, coagulation profile, urinalysis

5. Immunologic profile
• ABO blood type
• HLA typing
6. Infectious profile
• Blood cultures
• Urine culture
• Sputum culture
• Viral serology—CMV, EBV, hepatitis B and C
• HIV
• RPR
• Toxoplasma (for cardiac recipients)
7. Anatomic evaluation
• Intraoperative anatomic evaluation
• ± Kidney biopsy

Table 19.8 UNOS deceased donor kidney allocation system [3]

1. Blood type match
2. Zero antigen mismatched kidneys
3. Geographic sequence of allocation
(a) Local
(b) Regional
(c) National
4. Double-kidney allocation (at least two of the following conditions)
(a) Donor age >60 years
(b) Estimated creatinine clearance <65 ml/min
(c) Serum creatinine >2.5 mg/dl
(d) Adverse donor kidney histology
5. Expanded criteria donor kidney allocation
(a) Age >60 years
Or
(b) Age 50–60 years with two of the following:
• CVA as cause of death
• HTN
• Terminal creatinine >1.5 mg/dl
6. Point system allocation
Based on waiting time, quality of match, panel reactive antibody, pediatric recipient, prior donor, and medical urgency

Laboratory blood work includes ABO blood typing, HLA determination, complete

blood count, chemistries, coagulation profile, and urinalysis. Further, an infectious disease evaluation must be performed and includes viral serology, blood cultures, and sputum cultures. Blood is also obtained for cross-matching. Patients with a history of comorbidities affecting the kidney may require a biopsy which is obtained during organ procurement.

Deceased donor nephrectomy is performed with an en bloc technique through a midline abdominal incision; this generally takes place after recovery of the heart, lungs, liver, pancreas, and small intestine. The en bloc kidneys are then separated and their specific anatomy noted at the back table. This includes determining the size of the kidneys, length of the ureters, number of the arteries and veins, and any presence of anatomic defects. A renal biopsy is obtained at this time if indicated. The kidneys are then placed in a cold preservation solution, packaged sterilely, and transported to either the organ procurement organization or the transplant center accepting the kidney. In specific cases, the use of pulsatile perfusion has been utilized in an attempt to decrease the risk of delayed graft function. While kidney allografts have been observed to function after cold ischemia times as long as 48 h, the incidence of delayed graft function increases significantly with cold ischemia time greater than 24 h. Cold ischemia time should be minimized as much as possible [3, 6].

In addition to the above described, a new tool has been developed to assist in predicting the risk of graft failure. The Kidney Donor Risk Index (KDRI) , which is determined by a calculation using the characteristics of the deceased donor, is used to predict the probable risk of graft failure for a given donor compared to the median kidney donor from the prior year. The donor characteristics used to determine the KDRI include age, ethnicity, creatinine, history of hypertension, history of diabetes, cause of death, height, weight, donor type (DCD or DBD), and hepatitis C virus status. From the KDRI, the Kidney Donor Profile Index (KDPI) is derived and incorporated into the allocation criteria. It serves as a more useful tool than the ECD criteria since not all ECD are the same [7].

Kidney Transplantation Surgery

Once the transplant recipient has been selected, the patient is admitted and undergoes a re-evaluation prior to proceeding with transplantation. The emphasis is to identify any infectious disease or other medical conditions that would hinder going forward with the transplant. The patient is also evaluated for need for dialysis prior to surgery. Hyperkalemia greater than 5.5 mmol/L should be corrected.

Prior to the patient entering the operating room, the kidney must undergo a final inspection and back table preparation to confirm that there is no unreported damage that may affect the suitability of the kidney for transplantation. The renal artery and vein are carefully freed from retroperitoneal fat. Polar arteries are identified and reconstructed

to the main artery. Care is taken not to skeletonize the ureter, which may result in urethral ischemia.

This procedure requires general anesthesia, central venous access, and arterial line monitoring. Preoperative antibiotics are given routinely. After induction of anesthesia, a large Foley catheter is inserted into the urethra. Prior to incision, immunosuppression induction agents are initiated. Specific induction agents vary depending on center preference but always include corticosteroids and often an antibody induction agent.

The transplant site in the iliac fossa is accessed via a curvilinear incision extending from the midline suprapubic area to the level of the anterior superior iliac spine. The oblique muscles are divided, leaving the rectus muscle intact. Inferior epigastric vessels are identified and usually divided. The peritoneum is then mobilized medially to expose the iliac vessels. The round ligament in females is normally divided, while the spermatic cord in males is retracted and preserved. The external iliac artery and vein are dissected free from the surrounding soft tissue with ligation of the overlying lymphatics. Once the vessels are fully mobilized, systemic heparin is given in preparation for the vascular anastomosis.

The renal vessels are next anastomosed to the external iliac vessels. Once the anastomoses are completed, the renal vessels are clamped and blood flow returned to the leg (note, not every surgeon does this). This is an opportunity for the anastomosis to be tested for leaks, allowing the areas to be repaired or revised without comprising the kidney circulation by interrupting reperfusion. Once the anastomoses are determined to be satisfactory, the kidney is then reperfused. Adequate renal perfusion is achieved by inducing a mild hypervolemia and hypertension. The goal systolic blood pressure is about 120–140 mmHg; this may require the use of dopamine and fluid boluses to achieve the desired level. Lasix and mannitol are routinely administered to promote urine production.

After completion of the vascular anastomoses, care is taken to confirm adequate hemostasis. The ureter is then prepared for implantation. Generally, the ureter is spatulated and directly sutured to the bladder mucosa. This is followed by approximation of the bladder muscle wall to create a tunnel over the distal ureter. Ureteral stents are commonly utilized with the belief that they may minimize the incidence of urine leaks or ureteral stenosis. Although not always necessary, a retroperitoneal closed suction drain is placed. Hemostasis is once again confirmed. The wound is carefully closed in layers. The patient is typically extubated in the operating room and transferred to the recovery room or to the ICU.

Early Postoperative Management

In addition to airway management and protection, vital signs are monitored frequently during the immediate postoperative period. Laboratory blood work is typically obtained

in the recovery room, as well as hourly observation and documentation of urine output. Fluid management is of vital importance. Urine output varies from a few drops to greater than 1 L/h, requiring attentive fluid replacement and management. Careful resuscitation with attention to avoiding volume depletion and volume overload is important during this postoperative period. Electrolyte abnormalities can develop and should be monitored and corrected.

Any abrupt cessation of urinary output must be immediately evaluated. This may be due to a clot in the Foley which can be alleviated by simple irrigation. However, it is important to evaluate for an acute renal arterial or venous thrombosis which can manifest in the same fashion. If identified early, a thrombus can (rarely) be removed and the kidney salvaged. If this complication is suspected, the goal is immediate surgical re-exploration.

Postoperative bleeding may present in the setting of hypotension, tachycardia, decreased urine output, or lower-than-expected hemoglobin levels. The drain may reveal a high output of blood. Life-threatening bleeding complications are rare but do occur. This bleeding may be due to loosening of suture on the inferior epigastric vessels or a branch of the renal vein. It can also occur as a rupture of the arterial anastomosis from a mycotic pseudoaneurysm. The retroperitoneal space is usually able to tamponade the bleed; however there can be extensive dissection along the retroperitoneal space resulting in significant blood loss and hemodynamic instability. In addition, the presence of a large hematoma may increase the risk for secondary wound infection and wound breakdown. In this setting, a return to the operating room for exploration is indicated for not only control of the bleed but also evacuation of the hematoma that has accumulated.

Initial pain management is often obtained with a patient-controlled analgesia using intravenous hydromorphone, followed by a transition to oral narcotics during the following days. Once the patient is stable and appropriate, they can be transferred to the floor for ongoing care. Admission to the intensive care unit is not routinely required but may be indicated in the setting of specific complications or institutional protocol.

Postoperative Complications

Patients with low output in the setting of euvolemenia, a normal ultrasound, and no sign of mechanical obstruction may be exhibiting signs of delayed graft function. During this early postoperative period, it is important to monitor for low urine output. Delayed graft function is defined as the need for dialysis within the first week of renal transplantation. This complication is unusual in the setting of living donor kidney transplantation, with an incidence of 0–5 %. In deceased donor transplantation, the incidence is reported to range from 10 to 50 %. In donation after cardiac death, the incidence can range from 50 to 80 % [3, 8]. Renal function typically recovers in most patients but may take as long as several weeks. Certain donor and recipient risk factors are associated with delayed

graft function as outlined in Table 19.9. The management requires careful attention to fluid balance and avoidance of additional kidney injury, especially drug toxicity. Some authors advocate biopsies to be performed on postoperative day 5 and repeated every 7–10 days until onset of graft function to ensure that there is no underlying rejection. A long-term effect of delayed graft function is an increased risk of acute rejection and higher serum creatinine at 1 year. It has also been associated with reduced long-term graft survival [8]. Other postsurgical complications are outlined in Table 19.10.

Table 19.9 Risk factor for delayed graft function [8]

Donor	Recipient
1. Age >60	1. Obesity
2. Hypertension	2. HLA sensitization
3. Requirement of inotropic support	3. Hemodialysis within 24 h prior to surgery
4. DCD	4. Long second warm ischemia time
5. Prolonged cold ischemia time	

Table 19.10 Summary of surgical postoperative complications [3]

Very early	Early	Late
1. Delayed graft function	1. Wound complication	1. Ureteral stenosis
2. Bleeding	2. Urine leak	
3. Acute vascular thrombosis	3. Lymphocele	

Wound complications are associated with significant morbidity, especially in the setting of deep wound infections. This is often associated with abscess formation and can progress to fascial necrosis and dehiscence. Wound complications typically present as drainage. Once identified, the wound should be open and evaluated to rule out a deep wound infection. Superficial wound infections are managed with local care. Wound dehiscence and deep wound infections will require operating room intervention and surgical management, as well as intravenous antibiotics if signs of sepsis develop [3, 8].

Acute arterial thrombosis typically occurs in less than 1 % of all kidney transplants and during the first 24 h post-transplantation. This is typically due to a technical problem or a small embolus resulting in cessation of arterial flow to the graft. Arterial thrombosis should be suspected during the immediate postoperative evaluation when there is an abrupt cessation of urine output in a kidney with an initial brisk diuresis. The renal allograft can (rarely) be salvaged with immediate recognition and reoperation [3, 8].

Venous thrombosis is thought to occur in 2–4 % of renal transplantations. Usually the kidney is unable to be salvaged. The thrombosis can (rarely) extend to the external and common iliac veins and result in deep vein thrombosis and even pulmonary

embolism. This often manifests as sudden onset of bloody urine with unilateral swelling of the ipsilateral lower extremity. Although it can be diagnosed with a Doppler ultrasound demonstrating an absence of venous flow and reversed arterial diastolic flow, suspicion of venous thrombosis should prompt an urgent return to the operating room to attempt graft salvage. The patient should be made aware of the likelihood of a graft nephrectomy in this setting [3, 8].

A urine leak may occur days or weeks after transplantation. It typically occurs at the ureterovesical junction due to necrosis of the tip of the ureter. It may also occur at a ruptured calyx in the setting of an acute ureteral obstruction. It typically presents with symptoms of low urine output, elevated creatinine level, lower abdominal pain, or suprapubic discomfort. Diagnosis is suggested by a fluid collection visible by ultrasound or CT scan. The fluid is sampled percutaneously and sent for BUN and creatinine concentrations to be compared with serum levels. Management involves placement of a Foley catheter as well as a percutaneous nephrostomy and drainage with internal stenting. Leaks that fail conservative management undergo operative intervention with reimplantation of the ureter or an ureteroureterostomy to the ipsilateral native ureter.

Ureteral stenosis is a late complication after transplantation. It typically occurs months to years after transplantation. This is associated with ischemia of the ureter or a tight ureteroneocystostomy. Stenosis presents with elevated creatinine and hydronephrosis and is at times associated with pyelonephritis. Diagnosis is suggested by the presence of an elevated creatinine and moderate-to-severe hydronephrosis. Percutaneous nephrostomy confirms the diagnosis and also provides treatment through placement of an external drain and internal stenting. This may also serve as a means to dilate the stenosis and resolve the issue; however, surgery is occasionally required for persistent or recurrent stenosis. Operative management involves either reimplantation of the transplant ureter, ureteroureterostomy to the native ureter, or ureteropyelostomy.

A lymphocele typically presents weeks to months following transplantation. It is secondary to lymphatic drainage from the recipient lymphatics that were dissected during the time of surgery. Lymphocele can cause compression of the iliac vein with leg swelling and discomfort and compression of the transplant ureter leading to hydronephrosis and renal dysfunction. Ultrasound evaluation will show a perinephric fluid collection. Percutaneous aspiration and analysis of the fluid for white blood cell count differential, BUN, and creatinine will identify the fluid as lymphatic in nature. Management is via intraperitoneal drainage with marsupialization of the lymphocele, either laparoscopically or with an open approach. Care is taken to avoid injury to the allograft renal collecting system and allograft ureter. Percutaneous drainage is a possibility, but it is associated with a lower rate of success and a higher risk of infection [3, 8].

Immunologic Complications

The incidence of hyperacute rejection is very low with the advent of the pretransplant cross-match. It occurs in the presence of circulating preformed cytotoxic anti-donor antibodies against the ABO blood group antigens or the donor HLA class I antigens. Antibodies bind to the antigen expressed on the donor endothelium resulting in complement activation, platelet aggregation, and microvascular obstruction. The pathological findings include interstitial hemorrhage, infiltration of neutrophils, and deposition of antibody on the endothelium. This results in rapid allograft destruction. It may occur within minutes or hours of transplantation. In this setting the renal allograft cannot be salvaged.

Accelerated acute rejection is a rapidly progressive and aggressive reaction typically occurring within the first week of transplantation. The pathologic findings include extensive infiltration of lymphocytes, macrophages, and plasma cells. There is also marked injury to the renal tubules and interstitial capillaries, as well as vascular injury of larger vessels with endothelial swelling. Immediate therapy with anti-T-cell antibodies is indicated as well as pulse corticosteroids. A salvaged allograft is achieved in 50 % of the cases, but long-term function is compromised.

Antibody-mediated rejection is associated with the presence of anti-donor HLA donor-specific antibodies and accounts for approximately 10 % of rejection episodes in the early post-transplant period. Donor-specific antibodies bind to graft endothelial cells, resulting in complement activation and resultant injury. Diagnosis is made based on histologic findings of acute tissue injury, the presence of donor-specific antibody, and positive C4d staining of the endothelial cells. Treatment is removal of donor-specific antibodies in order to decrease further injury and decrease vascular inflammation. This is achieved through plasma exchange, IVIG, rituximab, and bortezomib [8].

Acute T-cell-mediated rejection is the most common type of rejection reaction, with an incidence of about 10–30 % within 1 year post-transplantation. It is T-cell-mediated injury directed at the renal tubules. Histopathologic evaluation reveals T-cell infiltration around the tubules and infiltration within the tubules resulting in tubulitis. Diagnosis is by renal allograft biopsy with management guided by the severity of the histopathological changes seen in biopsy according to the Banff classification system. Mild rejection may be successfully reversed with corticosteroids. Moderate and severe rejections often require the use of anti-T-cell antibody. This type of rejection is reversible in about 95 % of the cases. However late occurrence and repeated episodes are associated with progression to chronic allograft injury [3, 8].

Maintenance Immunosuppression

Several immunosuppressive agents are available for maintenance immunotherapy. They include corticosteroids, cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil/mycophenolic acid, sirolimus, and everolimus. The current trend is for a multi-modality therapy in which two or three agents are used in combination to maximize efficacy and minimize toxicity. There is also a growing trend toward steroid avoidance in order to minimize the side effects associated with chronic steroid use. The majority of kidney recipients are prescribed a combination of a calcineurin inhibitor and an antimetabolite with a rapid corticosteroid taper. A new agent, belatacept, has been approved by the FDA and is used in place of CNIs. It is associated with better renal function but much earlier rejection and a high incidence of lymphoma in EBV seronegative patients.

In addition to the increased risk of malignancy and infection associated with chronic systemic immunosuppression, the calcineurin inhibitors present an additional challenge. Calcineurin inhibitors are nephrotoxic. It is believed to be due to pre-glomerular arteriolar vessel constriction resulting in reduced blood flow and decreased glomerular filtration. This effect is related to the circulating blood levels. Renal dysfunction is reversible if the calcineurin inhibitor blood concentration is reduced. Long-term chronic CNI damage can include striped fibrosis, leading to slow progressive dysfunction. Although drug toxicity presentation is difficult to differentiate from acute rejection, histopathologic findings will show renal tubular vacuolization. If acute rejection has occurred, pathology will show lymphocytic infiltrate of the renal tubules.

Other Considerations

The patient's etiology of renal failure can lead to graft loss due to recurrent disease. Recurrent disease accounts for less than 2 % of all graft losses after kidney transplantation. Primary renal diseases such as membranoproliferative glomerulonephritis and focal segmental glomerulosclerosis are associated with a high risk of recurrence and graft failure. Although some degree of recurrence is seen with membranous glomerulonephritis, IgA nephropathy, and anti-glomerular basement membrane disease, the risk of graft failure is low. In the setting of systemic causes of renal failure, high recurrence rate and graft failure can be observed with oxalosis, hemolytic uremic syndrome, and mixed cryoglobulinemia. As such, awareness of the specific etiology that resulted in renal failure will guide post-transplant monitoring for recurrence. The ultimate goal is an appropriate intervention prior to allograft failure [3].

BK nephropathy is a cause of renal allograft dysfunction in 1–10 % of cases. It is caused by BK virus, a polyomavirus. Reactivation occurs with potent immunosuppression, resulting in renal dysfunction from tubular injury. The diagnosis is suspected when serum creatinine increases. Plasma and urine PCR testing is performed

to detect the presence and quantity of BK virus. Diagnosis is confirmed with renal biopsy. Interstitial infiltrate and tubulitis are seen on light microscopy. Electron microscopy confirms the presence of viral particles. Treatment consists of reducing immunosuppression; however, occasional success has been seen with directed antiviral therapy using agents such as leflunomide, low-dose cidofovir, IVIG, and fluoroquinolones [3].

Chronic graft dysfunction is the result of progressive loss of renal function that begins months to years after transplantation. Graft injury is often multifactorial, with a combination of pre-transplant and post-transplant risk factors playing a role. The pre-transplant factors include pre-existing donor disease, peri-transplant renal injury, ischemia reperfusion injury, prolonged cold ischemia time, age-related GFR loss, hypertension, and vascular disease. Post-transplant factors can be classified as immune-dependent and immune-independent factors. Immune-dependent factors include acute rejection, recurrent glomerulonephritis, interstitial fibrosis and tubular atrophy, and transplant glomerulopathy. Immune-independent factors include hypertension, diabetes, renovascular disease, calcineurin inhibitor toxicity, urinary obstruction, urinary sepsis, CMV nephropathy, and BK nephropathy. Graft injury continues in association with these mechanisms, resulting in progressive renal allograft dysfunction and eventual graft failure [9].

Chronic allograft renal injury is chronic graft dysfunction characterized by interstitial fibrosis and tubular atrophy on biopsy without evidence of a specific etiology. It is a common cause of renal allograft failure, with an incidence of about 25 % at 1 year and 90 % at 10 years. It is clinically characterized by progressive renal dysfunction, hypertension, and variable proteinuria. Unpredictable, with a variable clinical course, there is no current effective management [3, 9].

Chronic antibody-mediated rejection is chronic graft dysfunction characterized by the presence of circulating donor-specific antibodies. There will be positive C4d staining and morphologic evidence of chronic tissue injury on renal allograft biopsy. The particular findings include transplant glomerulopathy, peritubular capillary basement membrane multilayering, interstitial fibrosis, tubular atrophy, and arteriolar fibrous intimal thickening. Risk factors include prior sensitization, donor-specific antibodies, and HLA mismatch. There is no effective management, and its presence is associated with poor graft outcome and resultant allograft failure [9].

Outcomes

Despite the long list of potential complications and challenges with kidney transplant, there has been small but steady improvement in short-term outcomes. In the 2011 OPTN/SRTR annual report on kidney transplantation, it is observed that there is a decrease in the rate of graft failure and return to dialysis. Table 19.11 shows the graft

failure among transplant recipients within 90 days of transplantation, reflecting that decrease in the percentage of early graft failures. Table 19.12 demonstrates the probability of graft failure, return to dialysis, and death with a functioning allograft at the time intervals of 6 months, 1 year, 3 years, 5 years, and 10 years, reflecting an improvement in those outcomes as well. However, the improved 5- and 10-year outcomes have been very small, suggesting that long-term maintenance regimens are inadequate. The report further mentions that as of June 30, 2011, approximately 164,200 patients were surviving with a functioning kidney allograft, which is twice as many as the decade before.

Table 19.11 % Graft failure within 90 days among adult transplant recipients

	All deceased donors	Living donors	SCD donors	ECD donors	DCD donors
2000	5.0	2.4	7.6	4.5	4.9
2001	4.5	2.4	7.6	3.9	4.5
2002	4.5	2.2	8.8	3.7	5.6
2003	4.4	2.3	6.5	3.9	6.5
2004	4.1	1.9	6.4	3.6	6.0
2005	3.7	2.1	5.3	3.3	4.8
2006	3.4	1.5	5.0	3.0	4.2
2007	3.1	1.5	5.6	2.5	3.3
2008	3.2	1.4	4.6	2.8	4.6
2009	2.7	1.4	4.7	2.2	3.6
2010	3.1	1.1	5.1	2.6	3.8
2011	1.9	0.9	2.9	1.7	2.7

Source: OPTN/SRTR 2011 Annual Data Report for Kidney Transplantation

Table 19.12 Outcome probability among deceased donor kidney transplantation [10]

	6 months			1 year			3 years			5 years			10 years	
	Graft failure or death	Return to dialysis	Death with function	Graft failure or death	Return to dialysis	Death with function	Graft failure or death	Return to dialysis	Death with function	Graft failure or death	Return to dialysis	Death with function	Graft failure or death	Re to dia
2000	0.092	0.056	0.036	0.126	0.074	0.053	0.232	0.138	0.094	0.342	0.198	0.144	0.575	0.
2001	0.084	0.051	0.032	0.114	0.068	0.046	0.219	0.123	0.096	0.330	0.181	0.149	0.559	0.
2002	0.084	0.053	0.031	0.114	0.069	0.044	0.220	0.130	0.089	0.325	0.188	0.137		
2003	0.082	0.049	0.033	0.114	0.065	0.049	0.218	0.123	0.095	0.316	0.174	0.142		
2004	0.079	0.049	0.030	0.108	0.064	0.044	0.216	0.126	0.090	0.309	0.176	0.133		
2005	0.075	0.044	0.031	0.107	0.060	0.047	0.203	0.113	0.091	0.296	0.161	0.135		
2006	0.070	0.041	0.029	0.099	0.057	0.042	0.191	0.108	0.083	0.291	0.160	0.131		

2007	0.065	0.039	0.026	0.092	0.052	0.040	0.179	0.101	0.078					
2008	0.063	0.038	0.024	0.086	0.051	0.035	0.170	0.094	0.076					
2009	0.061	0.035	0.026	0.088	0.047	0.040								
2010	0.062	0.037	0.025	0.084	0.048	0.036								
2011	0.049	0.029	0.020											

Conclusion

Kidney transplantation still has potential for growth. Each year is marked by ongoing advances in management, and immunosuppressive protocols. More specific and potentially less toxic immunosuppressive agents and regimens are on the horizon (although not as many as in previous years). There is continuing interest in the idea of inducing tolerance. Waiting time on the transplant list has increased, as has wait list mortality. However, with increased use of extended criteria donors and a growing potential for living donation, an increasing number of patients with end-stage kidney disease will potentially have access to this life-saving procedure.

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20. Preoperative Recipient Evaluation and Preparation (Kidney)

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Introduction

Chronic kidney disease (CKD) has diverse causes and when untreated results in a poor quality of life and decrease in life span. Kidney transplantation can reverse both and make life more meaningful with increase in longevity. Unfortunately, CKD results in comorbid conditions. Therefore, preoperative evaluation for optimization of health status before surgery is essential. This will help in deciding the type of intraoperative monitoring, and help with laying out the best anesthesia care plan [1].

The purpose of preoperative evaluation is to identify risk factors for kidney transplantation and address and correct medical and psychological conditions that may affect transplant outcomes. Referral to a transplant program should be performed early to assess the candidate for a preemptive transplantation (before maintenance dialysis begins). Evaluation of kidney transplant candidates includes medical, surgical, immunologic, and psychosocial evaluations. The patient's individual risks and benefits of transplantation are discussed so that he or she can make an informed decision about whether to proceed with transplantation. After candidates are placed either on the deceased donor list or may be on a list for paired unmatched or good Samaritan donation, a periodic reevaluation is necessary to address new issues that may impact on transplant suitability [2].

Cardiac Evaluation

The most important goal of preoperative cardiac risk evaluation is to reduce the morbidity and mortality related to cardiovascular disease. The high incidence of coronary disease in patients with CKD presents a significant challenge in the care of patients being considered for kidney transplant. In fact, 50 % of all deaths in patients with end-stage renal disease (ESRD) are due to coronary artery disease (CAD) and 36 % of those patients who die after transplantation with a functioning graft are due to cardiac disease [3–5].

According to the Organ Procurement and Transplant Network (OPTN) records, nearly 90,000 candidates were on the waiting list for kidney transplantation as of January 14th 2014. The data from 2011 reveals that amongst the 84,000 candidates awaiting transplantation, 5000 potential recipients died before their kidney transplantation. In 2011, 62 % of kidney transplantation candidates were ≥50 years of age compared with 28.7 % of kidney transplantation candidates in 1991. There is no formal upper age limit at which patients may no longer be accepted for transplantation, although 80 years of age represents a practical biologic limit [6].

The increased aging of candidates necessitates that anesthesiologists be prepared to care for patients with more complex medical conditions.

In addition to evaluation for systemic hypertension, renal recipients will require testing for coronary artery disease. This is usually performed noninvasively by using modalities that include nuclear myocardial perfusion studies and dobutamine stress

echocardiography. These tests provide prognostic value for mortality, but are imperfect for sensitivity and specificity for detecting angiographically defined coronary artery disease in patients with end-stage renal disease. Associations of coronary artery disease with subsequent survival also are inconsistent, likely because plaque instability is more critical for infarction risk than angiographic stenosis [7].

In a survey of 68 transplant centers in 2005, 51 % of program representatives indicated reliance on the initial cardiac evaluation and cardiac history, 7 % used American College of Cardiology (ACC)/American Heart Association (AHA) criteria for noncardiac surgery in the general population to guide cardiac revaluation, and 32 % applied a combination of ACC/AHA criteria, the initial cardiac evaluation, and cardiac history [8].

Because cardiovascular screening and treatment practices of many transplant programs were highly variable and inconsistent with published guidelines, the ACC/AHA worked with representatives of the American Society of Transplant Surgeons (ASTS), the American Society of Transplantation (AST), and the National Kidney Foundation (NKF) to develop a consensus document in 2012 regarding "Cardiac Disease Evaluation and Management Among Kidney and Liver Transplantation Candidates" [9]. See Fig. 20.1 for details of the flow diagram providing some guidelines for cardiac evaluation.

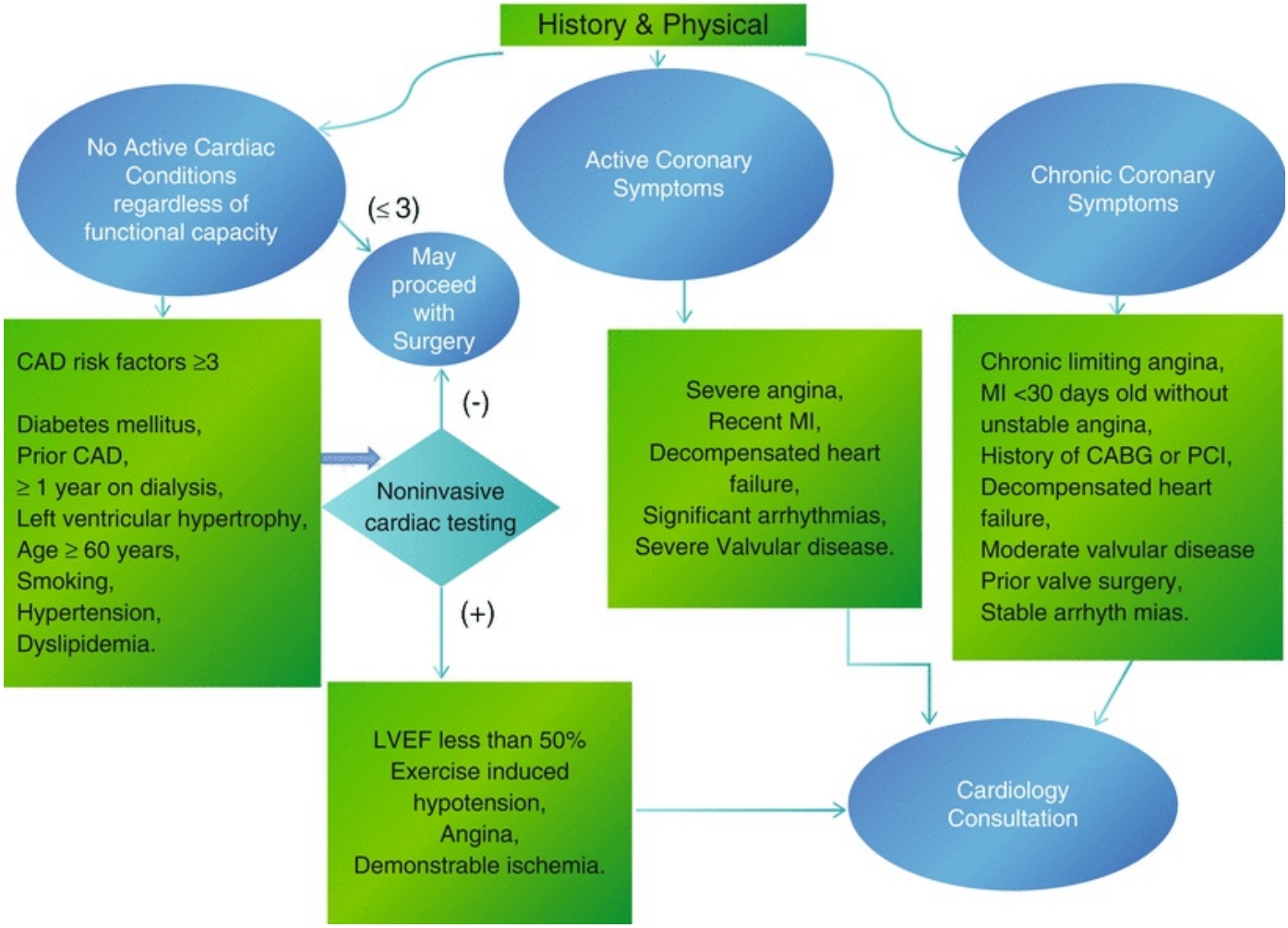

Fig. 20.1 Flow diagram detailing pre-transplant cardiac workup in renal recipients

All renal recipients must have a preoperative ECG during their workup. Abnormal results warrant additional cardiac evaluation. The type of noninvasive cardiac testing (dobutamine stress echocardiography versus myocardial perfusion scintigraphy) is left at the discretion of the perioperative evaluator. There is no evidence for or against surveillance by repeated periodic left ventricular function testing after listing for kidney transplantation as concluded in the 2012 ACC/AHA/AST/AKF consensus report [9].

Echocardiography must be obtained in those with suspected valvular disease or congestive heart failure [2]. More frequent echocardiographic monitoring is also recommended in ESRD patients with moderate aortic stenosis as suggested by Lentine et al. since they usually are "rapid progressors." Patients who show signs of significant pulmonary hypertension during echocardiography require cardiac catheterization. If right-heart catheterization confirms the presence of significant pulmonary arterial hypertension in the absence of an identified secondary cause (e.g., obstructive sleep apnea, left heart disease), referral to a consultant with expertise in pulmonary arterial hypertension management and advanced vasodilator therapies is recommended.

Coronary artery bypass graft (CABG) to improve survival and/or to relieve angina

despite optimal medical therapy may be reasonable for patients with ESRD with significant (>50 %) left main stenosis or significant (≥70 %) stenosis in three major vessels or in the proximal left anterior descending artery plus one other major vessel, regardless of left ventricular systolic function. CABG is recommended in preference to PCI to improve survival in patients with multivessel CAD and diabetes mellitus [9].

NPO (Nothing per Mouth) Guidelines and Preoperative Medications

All patients receiving an elective surgery must abstain from solids or foods by mouth for at least 6 h prior to surgery. Diabetics or those with other medical conditions that impair gastric emptying should have at least 8-h NPO time. Gastric emptying largely depends on vagus nerve function, which can be severely disrupted in patients with DM. The major clinical features of diabetic gastroparesis are early satiety, anorexia, nausea, vomiting, epigastric discomfort, and bloating [10].

Patients should take their scheduled medications with a sip of water or clear juice. In general, the patients should take all of the scheduled medications with the exception of angiotensin system inhibitors and oral hypoglycemic drugs. Angiotensin inhibitors administered immediately before surgery have been associated with a higher incidence of hypotension on induction of general anesthesia [11]. Oral hypoglycemic drugs are withheld on the day of surgery for drugs with a short half-life and up to 48 h preoperatively for long-acting drugs such as chlorpropamide. This is done to avoid reactive hypoglycemia, particularly with sulfonylurea compounds, and associated drug-induced toxicities and interactions [10].

Among patients already taking beta-adrenergic blockers before renal transplantation, continuing these drugs perioperatively is recommended to prevent rebound hypertension and tachycardia. Initiating beta-blocker therapy in beta-blocker-naïve patients the night before and/or the morning of noncardiac surgery is not recommended [9].

Hypertension and Diabetes Mellitus

Patients with CKD have a high prevalence of hypertension and/or diabetes mellitus. Hypertension has been reported to occur in 85–95 % of patients with CKD [12]. Hypertension can be a cause or a consequence of CKD. Approximately one of three adults with diabetes has CKD per 2014 National Chronic Kidney Disease Fact Sheet [13].

In type 2 diabetic patients, modest blood pressure control may be more important than chronic glycemic control [14]. Current recommendations are to target a blood pressure of <130/80 mmHg in hypertensive diabetics. In all diabetics with ESRD,

the type of diabetic disease (type 1 or type 2), method of home monitoring, and usual metabolic control must be studied. It is important to know antidiabetic therapy, such as diet, anti-hyperglycemic agents, or insulin therapy. Serum glucose levels and the glycosylated HbA1c test are useful in evaluating the efficacy of therapeutic control of the diabetic state. HbA1c is not affected by short-term changes in blood glucose levels but, instead, reflects long-term changes in blood glucose levels. Elevated HbA1c is predictive of the presence of microvascular and macrovascular complications associated with DM [10].

The chronic effects of DM can be divided into microvascular (including diabetic retinopathy and nephropathy), neuropathic (autonomic and peripheral), and macrovascular complications (atherosclerotic disease). Perioperative cardiovascular morbidity and mortality are increased two- to threefold in patients with diabetes [15].

There are several items of concern to the anesthesiologist taking care of kidney transplant recipients. Diabetic patients have a list of comorbidities along with their ESRD. These comorbidities will influence anesthetic approach because of gastroparesis, autonomic neuropathy, peripheral neuropathy, cardiovascular disease, and peripheral vascular disease [16]. The major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, pseudo-motor dysfunction, impaired neurovascular function, and hypoglycemic autonomic failure. Determination of the presence of diabetic autonomic neuropathy is based on a battery of autonomic function tests. These include R–R interval variation in the ECG, Valsalva maneuver effects, and postural blood pressure tests to help define the presence of cardiovascular autonomic dysfunction.

Fluid Status and Electrolytes

The immediate preoperative assessment includes identification of disturbances in acid–base balance and electrolytes, as well as an estimation of fluid status, which can range from severe hypovolemic to pronounced hypervolemia in patients undergoing renal transplant surgery. The patient's volume status can be estimated by the frequency of dialysis and when it was last performed. Although further studies are needed, the routine use of hemodialysis immediately prior to surgery cannot be recommended, but should be considered in patients with high serum potassium levels which may be accentuated during graft reperfusion when a significant amount of potassium is released [17, 18].

Most patients have a dialysis shunt in place, which requires special care during positioning for surgery. Its cannulation is reserved for absolute emergencies such as when resuscitation is required but no other vascular access is available. Metabolic acidosis is a common problem in patients with end-stage renal disease. Careful correction of acidosis during surgery is recommended for two reasons. First,

adjustment of acid–base balance with bicarbonate helps to reduce the commonly elevated levels of serum potassium. Second, the function of the transplanted kidney is supported, particularly in terms of maintaining a balanced acid–base state [19]. Other CKD-related comorbid conditions include hypocalcemia, hypophosphatemia, and hyperparathyroidism [20].

Coagulation Studies

There is an increased prevalence of several prothrombotic factors in renal transplant candidates, and thrombophilic patients are at a higher risk for early graft loss. All transplant candidates should have routine coagulation studies performed. Patients who have had a history of thrombosis, including recurrent thrombosis of arteriovenous grafts and fistulas, should have a more extensive coagulation profile performed. This should include screening for activated protein C (APC) resistance, factor V and prothrombin gene mutations, anticardiolipin antibody, lupus anticoagulant, proteins C and S, antithrombin III, and homocystine levels. About 6 % of Caucasians have APC resistance, usually as a result of heterozygosity for the factor V Leiden mutation. They are prone to thrombotic complications and graft loss. All renal transplant candidates with systemic lupus erythematosus should have antiphospholipid antibodies measured. This helps to define the severity of the disease.

Thrombophilia is rarely a contraindication to transplantation, although its recognition should initiate preventive strategies. Therapeutic decisions for long-term anticoagulation need to be individualized with respect to the agent used and the length of treatment. Chronic anticoagulation of dialysis patients with recurrent access thrombosis but without an underlying coagulopathy is often ineffective and should be avoided. Long-standing warfarin administration has been associated with accelerated vascular calcification.

Airway Evaluation

Evaluation of the airway is important especially for diabetic patients requiring kidney transplantation. These patients might require advanced airway equipment for difficult airway management [21].

The cause of increased difficulty with intubation in diabetic patients is not known. One reason might be that abnormal cross-linking of collagen via nonenzymatic glycosylation occurs with chronic hyperglycemia [22]. Patients with long-duration diabetes can develop stiff joints from glycosylation of their connective tissue from their elevated blood glucose levels. Renal insufficiency potentiates this collagen cross-linking [23]. Diabetic patients therefore often develop waxy skin, contractures, and general stiffness of their joints (stiff joint syndrome). Stiff joint syndrome usually

involves the joints of the patient's head and neck, particularly the atlanto-occipital joint, which may limit visualization of the trachea during laryngoscopy. Inability to oppose the palms in diabetic patients is one sign that stiff connective tissue may be present [22].

Anemia

Avoiding transfusions is important for candidates needing kidney transplantation because of the risk of sensitization, with the concomitant possibility of longer wait times, becoming ineligible for a particular live donor, dying while on the waiting list, or having worse outcomes after transplantation [24]. On the other hand, Costa et al. found that during the pre-transplantation period there may be erythropoiesis-stimulating agent hyporesponsiveness. This is associated with increased kidney allograft failure and mortality [25].

Pulmonary Disease

Pulmonary function tests may be required to assess for patients with known lung disease, patients with signs and symptoms suggesting active lung or reactive airways disease, and patients with sleep apnea. Chronic obstructive lung disease and restrictive lung disease recipients have increased post-transplantation infectious complications and mortality. Patients with evidence of chronic lung disease who continue to smoke must stop before transplantation. They should be directed to smoking cessation programs.

Obesity

Obesity is a risk factor for cardiovascular disease and is common before and after transplantation. Although the role of pre-transplant obesity remains uncertain, post-transplant obesity increases the risk of graft failure and mortality. Nutritional intervention is effective in achieving post-transplant weight loss, but the effect on long-term outcomes has not been established [26].

Conclusion

The preoperative workup of renal recipients must be thorough and meaningful. Common associations such as diabetes mellitus, hypertension, and other disorders will require proper definition. This will help to formulate an anesthesia care plan during renal transplantation or other surgery.

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21. Anatomy and Surgical Procedures for Renal and Pancreas Transplantations

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Renal Transplantation

Introduction

The first renal transplant performed in the USA was performed at the Little Company of Mary Hospital in Evergreen Park, IL, on June 17, 1950. As no immunosuppressive agents were used, the graft subsequently failed 10 months later. Several other attempts at renal transplant were an operative success, but met with graft failure due to the lack of immunosuppression [1]. The first successful human renal transplant with long-term function was performed by Murray in 1954 between identical twins [2]. Understanding of immunosuppression and the use of immunosuppressive agents radically changed the field following Murray's 1962 renal transplant with azathioprine, which was the first nonidentical patient with long-term success [3].

The field has undergone major advancement in organ selection, organ preservation, organ allocation, patient selection, and short- and long-term immunosuppressive management. In 2012 in the USA the deceased donor graft failure rate was 1.8 % at 6 months and 2.7 % at 1 year. Currently there are 96,000 patients awaiting renal transplant

in the USA, with 16,526 living and deceased donor transplants performed in the USA in 2012 [4]. Despite the massive strides the field has taken, the procedure of renal allograft implantation remains relatively unchanged for the past 40 years [5].

Anatomy

Several different types of renal transplant allografts are procured for transplantation in the adult patient. These include pediatric en bloc, cadaveric donor, and live donor. Each graft has its own anatomical considerations in the implantation process.

The human kidneys lie in the retroperitoneal space between T12 and L3 with their long axis parallel to the body. The kidneys themselves are encased in perinephric fat, which may differ in quantity reflecting the body mass index and sex. Each kidney is ovoid in shape with an indented medial border that gives rise to the renal pelvis and renal hilum resulting in a bean-shaped appearance. There is no significant difference in size of the right versus left kidney and patient height, width, or weight does not predict size of the graft.

The kidney is covered by a fibrous renal capsule with fibroareolar tissue called the renal fascia. Surrounding this is the perinephric fat. The kidney itself lies on the psoas muscle on both the right and left side. The right kidney abuts superiorly the R lobe of the liver. The duodenum will cross the hilum and the right colon hepatic flexure will often abut the medial border of the inferior pole of the right kidney. The left kidney will have abutting the hilum, the anterior border of the stomach, spleen, pancreas, and splenic flexure of the colon.

The arterial supply of each kidney arises directly from the aorta between L1 and L2. The right renal artery is usually longer as it passes underneath the inferior vena cava. The left renal artery arises slightly lower on the aorta. The renal artery usually divides close to the hilum into five segmental arteries. The venous outflow from each kidney is also very different. Renal veins are direct outflow to the systemic system. The right kidney most commonly has a very short renal vein as it sits adjacent to the inferior vena cava. The left renal vein most commonly passes anterior to the aorta as it drains to the inferior vena cava and drains serve as a tributary for the adrenal vein (superior edge), gonadal vein (inferior edge), and lumbar vein (posteriorly). The left renal vein is most commonly longer in length, in comparison to the right, and is most commonly the preferred organ for procurement, as the transplantation and anastomosis of the renal vein can potentially be technically easier with a significantly longer vein.

Arising from the hilum on both kidneys is a single ureter, which is a thick-walled, muscular duct which carries urine from the renal pelvis to the posterior bladder. Each ureter is approximately 13 cm long and 5 mm wide, with a muscular layer, which has frequent peristalsis. The course of each ureter is generally the anterior surface of the psoas muscle and crossing the external iliac artery. The arterial supply to the ureter

comes from the renal artery and gonadal artery proximally. Preservation of this proximal blood supply remains crucial as the medial and distal arterial supplies will be divided with procurement of the kidney.

Procurement from the cadaveric donor will be described in detail elsewhere in the text. Briefly after organs are flushed with a preservation fluid through a cannula placed in the distal aorta, with a vascular clamp placed at the level of the supraceliac aorta. The fluid is vented through an incision in the distal vena cava or the right heart, until all of the abdominal organs are completely evacuated of blood. After this is completed, the kidneys are generally the last of the solid organs to be removed after the liver and pancreas. The kidneys are most commonly removed en bloc with the segment of aorta and vena cava with ureters cut well beyond the level of the external iliac artery. Once removed from the body the kidneys are separated on the back table. Adrenal glands or partially cut adrenal glands are excised with each kidney. The right kidney vasculature is excised from the en bloc configuration with a renal artery with aortic cuff and renal vein and entire segment of vena cava. This segment of vena cava can later be fashioned to extend the renal vein if needed either with a hand-sewn technique or with a stapled technique. The left kidney on the other hand will include the renal artery with aortic cuff and no vena cava on the renal vein. The procured organ from a laparoscopic or open live donor is different in that the renal veins and renal arteries do not contain cuffs of vena cava or aorta and the adrenal gland is most commonly completely preserved in the donor and not taken with organ. Ureter length in the live donor is often less.

Preoperative Considerations

As the wait time for cadaveric renal transplantation can often extend to 3–7 years depending on blood grouping, antibodies, age, and region, patients' cardiac and perioperative risk factors can dramatically change from their initial listing evaluation. This does require close scrutiny by all members of the transplant team including surgery, medicine, and anesthesia immediately upon the patient's arrival to the hospital. The University of Pittsburgh KP team has a separate Waitlist Clinic to monitor patients on the waitlist and performs yearly cardiac testing to optimize perioperative risk. Frequency of testing and waitlist clinic visits is dictated by patient's age, medical complexity, and functional status. Transplant program's waitlist management varies by center.

The UNOS criteria for listing for a cadaveric renal transplant specify that the patient has eGFR of <20 ml/min. As a result, a patient may or may not have initiated dialysis, which results in a wide range of functional volume and electrolyte status for these patients. ESRD patient undergoing hemodialysis often have this on an alternating day schedule and cadaveric renal transplants performed on Mondays may have patients that have not undergone hemodialysis since the previous Friday. In addition to preoperative

testing, rapid assessment of the patient's volume status, electrolytes, and need for preoperative dialysis must be done immediately upon the patient's arrival to the hospital to ensure that preoperative hemodialysis does not impact the cold ischemic time of the organ.

End-stage renal disease patients have a variety of hemodialysis options and entry points including by way of tunneled hemodialysis catheter, arteriovenous fistula creation, and arteriovenous graft insertion in upper or lower extremities. As it is commonplace, many patients will have multiple fistulas, previous catheters, and central venous stenosis. As all patients will undergo central venous and arterial line placement prior to surgery, it is important that all team members obtain a detailed history and physical examination of all functional and nonfunctional access.

Anesthesia Considerations

After determining adequacy of perioperative testing and dialysis, the patient may be brought back to the operative room for general endotracheal intubation and central venous line placement and arterial line placement. The CVL should be placed using a modified Seldinger technique, with the use of ultrasound guidance. Again, prior to this thorough investigation must be performed of previous catheters, prior imaging demonstrating central venous stenosis, evidence of failed AVF or AVGs, and evidence of central venous varices in the superficial chest and neck. If the guide wire does not easily pass into the right atrium, consider injection of a small amount of dilute contrast under direct fluoroscopy to identify central venous stricture or thrombosis.

Arterial line is usually placed in the wrist or upper arm. Avoid using the ulnar artery in a wrist with a functioning or nonfunctioning radiocephalic fistula as this may represent the only arterial supply to the hand.

Bench Preparation of Renal Allograft

The back table preparation of the renal graft is done prior to skin incision or after start of the case based on staff, graft, and OR availability. The process involves dissecting fat around the renal capsule and mobilization of the renal artery and vein. In addition the ureter is identified and great care is taken to avoid devascularization by minimal dissection and avoidance of dissection of the lower pole of the kidney and the ureter. In preparation for the anastomosis of the renal artery and vein, the renal vein is carefully examined. In the case of the right donor kidney, with a known shorter vein, several options exist to allow for a safe and tension-free anastomosis to the external iliac vein. One option exists of mobilizing the external vein completely and in some cases dividing the internal iliac vein to allow for a tension-free anastomosis. The second involves extending the renal vein by creating a vena caval conduit by oversewing both ends of the cadaveric vena cava after it has been divided above and below the insertion point of the

right renal vein. The opposite side of the vena cava can then be opened for anastomosis.

Renal Transplant Operation

The operation begins after appropriate general endotracheal anesthesia, central venous line placement, and invasive arterial line placement, described previously. Prior to skin incision of vital importance is the operative timeout with identification of the patient, procedure, cadaveric, or live donor organ with laterality and UNOS ID number.

As the heterotopic transplant is performed in the retroperitoneum, the skin incision is curvilinear and extends from 2 cm above the pubis symphysis to a point 2 cm medial to the anterior superior iliac spine. In the event that a simultaneous renal and pancreas transplant is being performed or the patient has previous transplant in both the right and left iliac fossae, a lower midline incision can be used. Surgeons usually prefer the right iliac fossa as the artery and vein are more superficial there. The layers of the abdominal wall are opened in sequence to expose the retroperitoneal space and avoid violation of the peritoneum. This begins with division of the subcutaneous tissue, Scarpa's fascia, external oblique aponeurosis, internal oblique muscle, and transversals fascia. The epigastric artery and veins are identified during the exposure and are initially preserved for possible inflow to a lower pole accessory vessel. If there is no lower pole vessel or the artery is calcified, they can be ligated and divided without consequence. The spermatic cord is also identified and preserved. In rare instances it may be ligated and divided as it impedes with the operation; this is the exception rather than the rule. In female patients the round ligament is ligated and divided.

At this time a retractor system based on surgical preference or availability is put into place. Dissection is then performed of the external iliac artery and vein circumferentially with ligation of any lymphatic structure as to avoid lymphocele formation post-transplantation (Fig. 21.1). Depending on the level of arterial disease or donor graft anatomy the dissection of the iliac artery can be taken proximally to the level of the common iliac artery. The venous dissection can also be taken to the distal vena cava if needed.

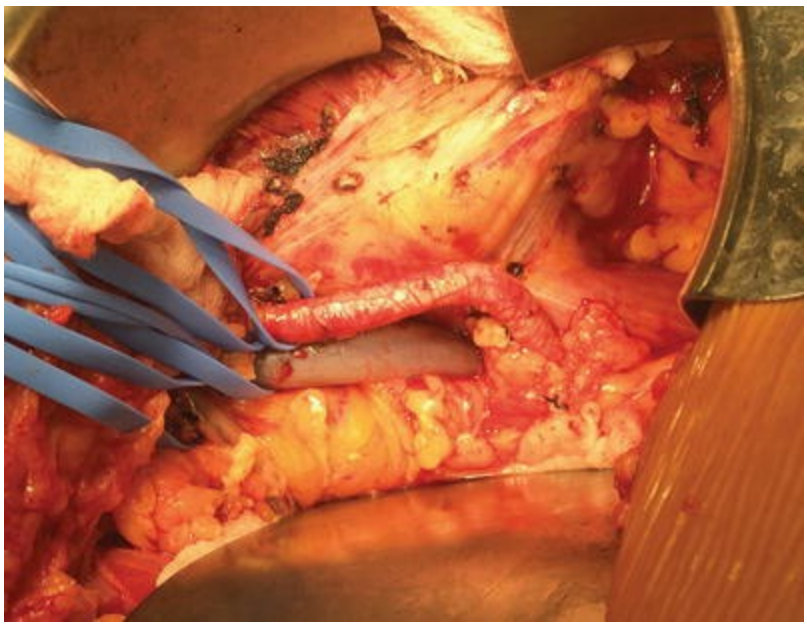

Fig. 21.1 Exposure of the vessels for renal transplantation in the right iliac fossa. Visualized is the external iliac artery and external iliac vein

It should be noted that the renal graft should be kept cool from the time of cross clamp of the arterial inflow in the donor to reperfusion in the recipient. The kidney is packaged in iced preservation fluid during transport and should be maintained in a similar cool solution during the benching process. Throughout the time of the vascular anastomosis the kidney is packed in ice and wrapped in a cool laparotomy sponge.

Prior to initiation of the vascular anastomosis and reperfusion induction agents should have been started and the patient must be hemodynamically stable. Systemic heparin is usually given to patient approximately 3 min prior to the clamping of the iliac artery and vein. The surgeon then proceeds with complete vascular clamping of the external iliac artery and vein. The venous anastomosis is usually completed first. A venotomy is fashioned with an #11 blade and then extended using Potts scissors. The graft renal vein to recipient external iliac vein anastomosis is then completed in a running fashion with 5-0 or 6-0 synthetic, permanent, monofilament suture (Prolene). Care is taken to avoid purse string narrowing of the anastomosis and/or back wall narrowing. If a graft extension is required and no donor vena cava is attached (as is the case with all L kidneys), stored cadaveric vein can be used. Synthetic graft is not recommended due to the very high thrombosis rate.

Next the arterial anastomosis is performed. This is done after vascular clamps are placed on the proximal and distal external iliac artery. After a small arteriotomy is made, it is extended using Potts scissors or a 4 or 6 mm cardiac punch. The anastomosis is done in a running or an interrupted fashion with 5-0 or 6-0 synthetic, permanent, monofilament suture (Prolene). Several options exist with multiple arteries including separate implants on the external iliac artery, creating a common patch prior to

implantation.

The time for completion of the arterial and venous anastomosis is approximately 30–50 min depending on the complexity on the anastomosis. Prior to vascular clamp removal and reperfusion of the graft, the patient is usually given a diuretic (Lasix and/or mannitol) and assessment of appropriate volume status and systolic blood pressure. Clamps are then carefully removed, venous followed by arterial. The renal graft then will quickly regain turgor and a pink color. Deliberate and quick assessment of the renal anastomoses and hilum is undertaken to assess and repair suture line or hilar open vessel bleeding and investigate for thrombosis. This is the most likely time that surgeons will encounter brisk bleeding. In the event that there is thrombosis or uncontrollable bleeding, the option of reclamping the vessels and removing the graft and flushing on the back table does exist.

After the kidney has demonstrated good perfusion, hemostasis has been maintained, and the patient is hemodynamically stable, attention can be focused on the ureter-to-bladder anastomosis. Prior to skin incision a three-way catheter is inserted into the bladder. At this point in time, the Foley catheter tubing to the urine collection bag is clamped and the bladder is distended with antibiotic irrigation until distended adequately. Keep in mind that patients will have different volume of complete bladder distention depending on the amount of urine that they make. Over-distention can result in an extra- or intraperitoneal bladder rupture. The peritoneum is then reflected away from the bladder, and the serosal and detrusor are then divided for a length of 3 cm. The bladder is then entered with an #11 blade or Potts scissors and for 2 cm. The irrigation is aspirated and the Foley catheter clamp removed (Fig. 21.2). The ureter is cut to the appropriate length and the spatulated to match the bladder incision length. The ureter is then anastomosed to the bladder mucosa with 6-0 absorbable suture (Fig. 21.3). A 6 Fr × 12 cm double J closed-tip stent may be placed in the ureter to the pelvis and bladder prior to completion of the anastomosis. The detrusor is gently re-approximated over the anastomosis with interrupted 4-0 absorbable monofilament, with great care taken to avoid compressing the anastomosis.

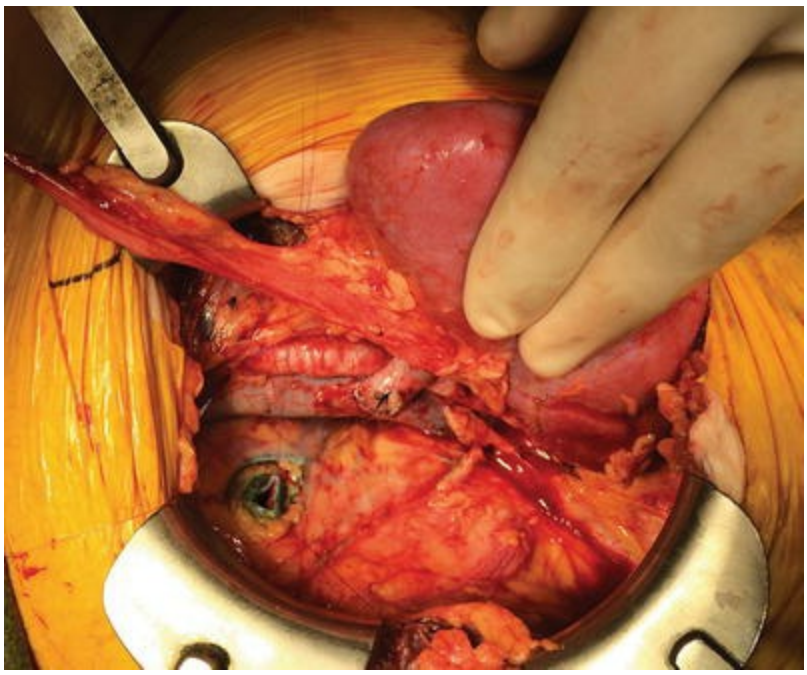

Fig. 21.2 Reperfused renal allograft with visualization of the venous anastomosis. The bladder has been opened in preparation for ureteral implantation

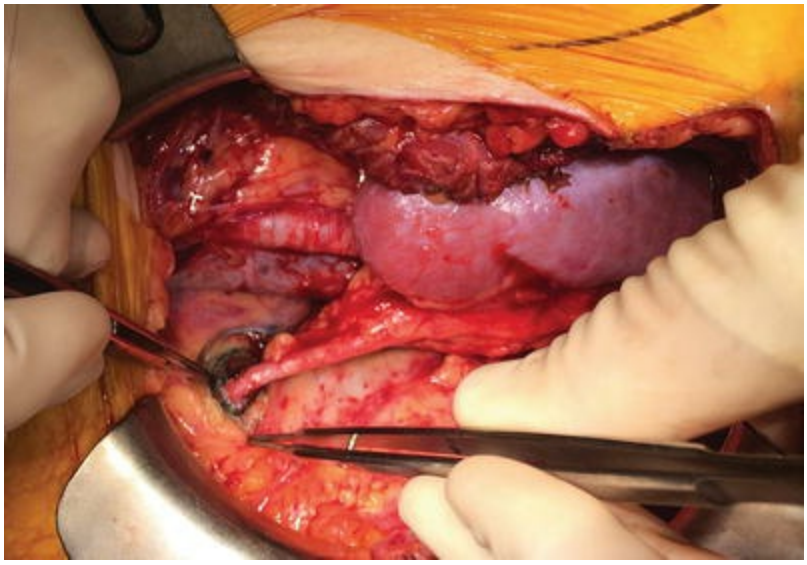

Fig. 21.3 Reperfused renal allograft with completed ureteral anastomosis

At this time thorough inspection of the operative field is undertaken to ensure hemostasis and appropriate positioning of the renal graft to avoid tension, torsion, or pressure on the renal artery or vein. A drain may be left if desired. The external oblique and anterior rectus sheath fascia is then closed in a running fashion. Subcutaneous layer is closed with absorbable suture and the skin with clips.

Pancreas Transplantation

The cadaveric whole-organ pancreas transplant is done as a simultaneous pancreas and kidney transplant, pancreas after kidney transplant (pancreas after previous successful cadaveric or LD renal transplant), or pancreas transplant alone. The transplant is done most commonly through a midline incision. The first successful whole-organ pancreas transplant was performed at the University of Minnesota on December 16, 1966, by William Kelly and Richard Lillehei [6].

The benching of the cadaveric pancreas graft remains one of the most crucial aspects of the transplant. The organ is inspected thoroughly for evidence of trauma, fatty infiltration, or fibrosis. If any of these are found the graft should be discarded. The graft generally comes with duodenum and spleen attached (Fig. 21.4).

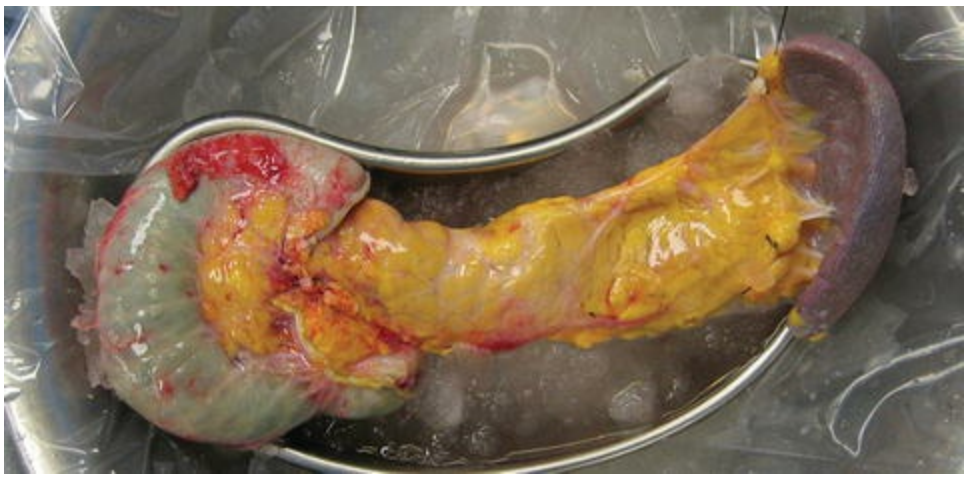

Fig. 21.4 Cadaveric pancreas allograft prior to bench preparation. The staple lines are noted at the borders of the duodenum and the mesentery

The spleen is first carefully dissected off the tail of the pancreas and splenic artery and vein and branches are ligated. Next the proximal and distal duodenal cuff staple lines are inverted with interrupted permanent suture. The root of the mesentery is oversewn with permanent suture in a running locking fashion. Next the superior mesenteric artery (SMA) and splenic artery are then prepped for anastomosis. A Y-graft is then made from the donor common, external, and internal artery. The external and internal iliac arteries of the Y-graft are then anastomosed in an end-to-end fashion with the splenic artery and SMA, respectively. This allows for a single-inflow connection to perfuse the entire pancreas and duodenum. The graft is then tested with iced heparinized preservation fluid and any small venous or arterial branches are ligated (Fig. 21.5). The pancreas is now ready for implantation.

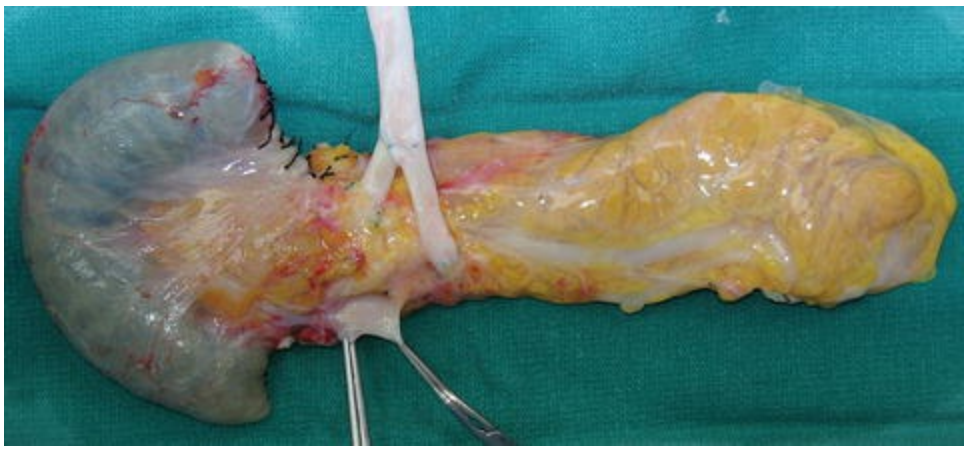

Fig. 21.5 Cadaveric pancreas allograft with bench preparation completed. The vascular clamps are on the portal vein. The ends of the duodenum are oversewn and the extension Y-graft has been fashioned to the splenic artery and superior mesenteric artery. The spleen has also been removed and the splenic vessels have been suture ligated

After appropriate prep and drape, the operation is started with a long midline incision. This is taken through to the fascia and carefully into the peritoneal cavity. Implantation of the kidney in the SPK is performed first if there is minimal cold ischemic time to be placed on the pancreas. The sigmoid colon is mobilized and exposure of the common iliac vein and artery is performed. The renal graft is then anastomosed to the L common iliac artery and vein as described above with permanent monofilament. The ureter is then anastomosed to the bladder in a fashion similar to the isolated renal transplant.

The implantation of the pancreas starts with mobilization of the cecum and the right colon. The distal vena cava and the right common and external iliac vein are identified and dissected free of surrounding tissue (Fig. 21.6). The right internal iliac vein is often ligated and divided to allow for further mobility of the right common and external iliac vein (Fig. 21.7). The distal iliac artery is then dissected. The preferred site of implantation of the pancreas is the graft portal vein to external iliac vein or to distal vena cava and graft Y-conduit to common or external iliac artery. Clamps are placed proximal and distal to the implantation site and most commonly the venous anastomosis is completed first with 6-0 permanent monofilament (Fig. 21.8). In the event of use of the distal vena cava a partial occlusion vascular clamp is placed to allow for adequate venous return. The arterial clamps are then placed and arteriotomy is fashioned and the Y-graft is anastomosed to the R common iliac artery with running 6-0 monofilament permanent suture. Clamps are then removed, arterial after venous. Careful inspection of the anastomoses and the entirety of the pancreas are then undertaken. Suture line bleeding and body and tail bleeder are suture ligated. This portion of the case in general results in the most bleeding if there is going to be any.

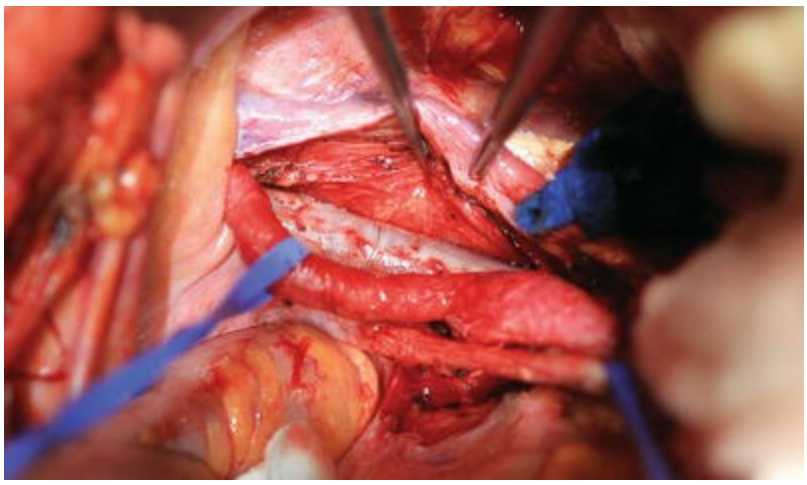

Fig. 21.6 Visualization of the right common and external iliac vein prior to ligation of the internal iliac vein and lateralization

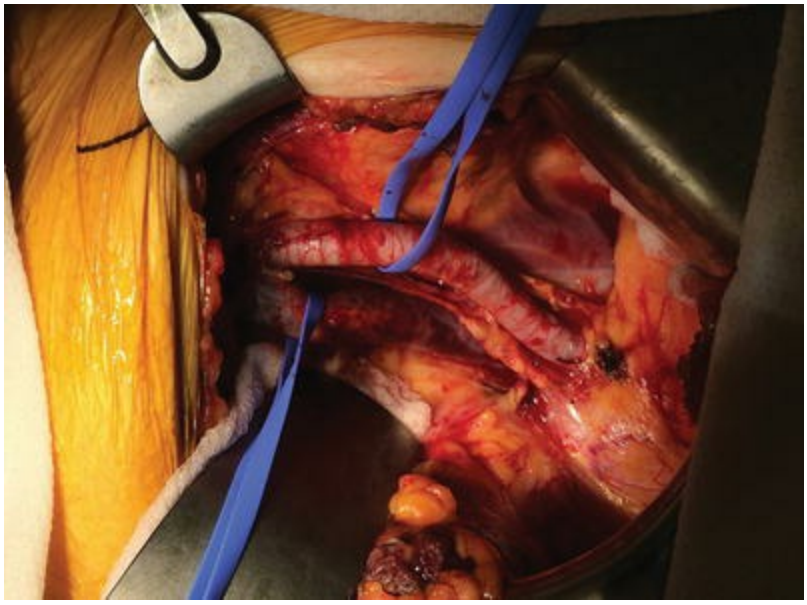

Fig. 21.7 Preparation and lateralization of the right common iliac and right external iliac vein after ligation of all branches of the right internal iliac vein

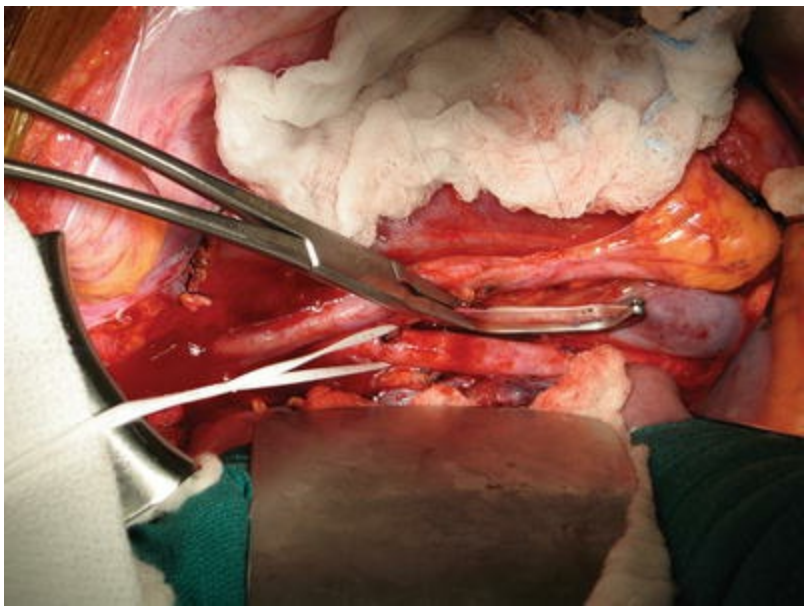

Fig. 21.8 Venous clamping with a partial occlusion clamp of the common iliac vein with 6-0 Prolene proximal and distal corner sutures in place in preparation of the portal vein to common iliac vein anastomosis

The exocrine secretions of the graft are then drained by connection of the graft duodenum to the small bowel of the recipient. The bowel anastomosis can be performed in a hand-sewn fashion or with a stapler. With a hand-sewn technique, a two-layer anastomosis is done, using a nonabsorbable suture for the outer layer and an absorbable suture for the inner layer. Both layers can be performed with a simple running suture technique.

After meticulous inspection for hemostasis as the patient will likely be started on anticoagulation, drains are placed alongside the pancreas and kidney. Fascia is then approximated with running suture. Skin is closed with staples.

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22. Anesthesia and Intraoperative Management of Renal Transplantation

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Introduction

The global epidemic of diabetes and hypertension has resulted in a dramatic increase of chronic kidney disease. Currently, the prevalence of chronic kidney disease varies between 8 and 16 % among different populations in the world [1]. For patients with end-stage renal disease (ESRD), a transplant provides better survival and health-related quality of life than dialysis [2–4]. In addition, transplantation is less resource intensive and more cost effective than dialysis [5, 6].

Renal transplantation is the most commonly performed organ transplantation in the world. In the USA alone approximately 18,000 kidney transplants are done each year. Unfortunately, because of organ shortages the number of transplants is not significantly increasing. The transplant waiting list however continuous to grow with about 4 % per year and has reached 55,371 active status patients on December 31, 2011. The median waiting time for transplantation has now increased to more than 4 years. Consequently,

most patients requiring a renal transplant will not receive one.

In an attempt to alleviate the organ shortage expanded criteria donors and donation after cardiac death (DCD) are alternative strategies to increase the cadaveric donor pool. The long-term survival of single- or dual-kidney grafts from expanded criteria donors older than 60 years of age are excellent, provided that the grafts are evaluated histologically before implantation [7]. With respect to DCD kidneys, initial reports showed higher primary non-function rates. However, in a recent retrospective comparison of post-transplant kidney function there was no difference between DCD kidneys and donation after brain-death kidneys [8].

Ideally, renal transplantation should precede long-term dialysis . The success of transplantation is negatively affected by lengthy pre-transplantation dialysis dependence [9]. Early transplantation however can only be achieved with living donor transplants. The addition of paired kidney exchanges, altruistic donation, and altruistic donor chains to classic direct donation has significantly expanded the number of live donations. Although transplantation between compatible donor recipient combinations remains preferable, in experienced transplant centers HLA- and ABO-incompatible transplantations have become a reasonable alternative for end-stage kidney disease patients with an incompatible live donor.

Preoperative Considerations Relevant to Intraoperative Management

Coronary Artery Disease

Chronic kidney disease is an independent risk factor for coronary artery disease. A cardiovascular event is the most common cause of death in the perioperative period of renal transplantation. Therefore, screening for coronary artery disease is an essential part of the preoperative evaluation for kidney transplant candidates. Knowledge of the severity of cardiac disease will dictate the perioperative management plan. Recently guidelines for the cardiac disease evaluation and management among kidney transplantation candidates have been endorsed and published by the American Society of Transplant Surgeons, American Society of Transplantation, and National Kidney Foundation [10]. The guidelines recommend a thorough history and physical examination in every patient to identify active cardiac conditions. In patients without known cardiovascular disease a resting 12-lead ECG followed by annual ECGs while on the waiting list is recommended. In patients with no active cardiac condition, but with multiple coronary artery disease risk factors, noninvasive stress testing should be considered regardless of functional status. Risk factors are diabetes mellitus, prior cardiovascular disease, more than 1 year on dialysis, left ventricular hypertrophy, age greater than 60 years, smoking, hypertension, and dyslipidemia. The specific number of

risk factors that should be used to prompt testing remains to be determined, but three or more is considered reasonable. In those patients it is also reasonable to perform preoperative assessment of left ventricular function by echocardiography.

Patients with active cardiac disease such as a left ventricular ejection fraction less than 50 %, left ventricular dilation, exercise-induced hypotension, angina, or symptoms of myocardial ischemia should be referred to a cardiologist for evaluation and long-term management according to American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the general population.

For patients who need coronary artery bypass grafting (CABG) a multidisciplinary team on a case-by-case basis must weigh the risk of CABG before renal transplantation, since the CABG procedure may outweigh the risk of transplantation. For patients with multi-vessel coronary artery disease (CAD) plus diabetes mellitus the guidelines state that CABG is preferable to percutaneous coronary intervention (PCI). For patients with significant (>50 %) left main stenosis or significant (≥70 %) stenosis in three major vessels or in the proximal left anterior descending artery plus one other major vessel CABG to improve survival and/or to relieve angina may be reasonable.

In patients in whom coronary revascularization with PCI is appropriate and who are expected to receive a transplant in the subsequent 12 months, balloon angioplasty or bare-metal stent (BMS) placement followed by 4–12 weeks of dual-antiplatelet therapy is probably the best strategy. In patients who have received a drug-eluting stent (DES) it may be reasonable to perform kidney transplantation surgery without interruption of clopidogrel therapy if the risk of bleeding is low. Transplantation surgery within 3 months of BMS placement and within 12 months of DES placement is not recommended, particularly if the anticipated time of post-stent dual-antiplatelet therapy will be shortened. Transplantation surgery is not recommended within 4 weeks of coronary revascularization with balloon angioplasty.

Among patients being considered for renal transplantation with clinical markers of cardiac risk (diabetes mellitus, prior known coronary heart disease, prior heart failure, extra-cardiac atherosclerosis) and those with unequivocal myocardial ischemia on preoperative stress testing, it is reasonable to initiate beta-blockers preoperatively and to continue them postoperatively provided that dose titration is done carefully to avoid bradycardia and hypotension.

Perioperative initiation of beta-blockers in beta-blocker-naive patients may be considered in kidney transplantation candidates with established coronary heart disease or two or more cardiovascular risk markers to protect against perioperative cardiovascular events if dosing is titrated and monitored. However, initiating beta-blocker therapy in beta-blocker-naive patients the night before and/or the morning of surgery is not recommended.

Hypertension

Hypertension is both a cause and a consequence of chronic kidney disease. In patients with end-stage renal disease the prevalence of hypertension is close to 100 %. Adequate blood pressure control in the perioperative period is particularly important due to the increased risk of cardiovascular disease and stroke. For patients taking beta-adrenergic blockers before renal transplantation, continuing the medication perioperatively and postoperatively is recommended to prevent rebound hypertension and tachycardia.

Atrial Fibrillation

The prevalence of atrial fibrillation (AF) in ESRD patients is higher than in the general population and is associated with an increased risk of stroke and mortality [11]. Pre-existing AF is associated with poor post-transplant outcomes [12]. The majority of studies do not support a protective effect for warfarin in ESRD patients with AF.

Pulmonary Hypertension

In dialysis patients the prevalence of pulmonary hypertension is 30–60 % [13]. The pathogenesis is unclear and probably multifactorial. Pulmonary hypertension is associated with increased graft failure and mortality after renal transplantation [13]. It is not evident that the decreased success of renal transplantation is a reflection of poor cardiac function. Kidney transplantation candidates with echocardiographic evidence of significant pulmonary hypertension should be evaluated for underlying causes (e.g., obstructive sleep apnea, left heart disease). Echocardiographic evidence of significant pulmonary hypertension in this population is defined by right ventricular systolic pressure more than 45 mmHg or ancillary evidence of right ventricular pressure overload. Right heart catheterization confirming the presence of significant pulmonary arterial hypertension (as defined by mean pulmonary artery pressure ≥25 mmHg, pulmonary capillary wedge ≤15 mmHg, and pulmonary vascular resistance of >3 Wood units) in the absence of an identified secondary cause (e.g., obstructive sleep apnea, left heart disease) requires referral for pulmonary arterial hypertension management and vasodilator therapy to optimize these patients before transplantation. Patients with significant pulmonary hypertension may benefit from monitoring their pressures with a pulmonary artery catheter and intraoperative transesophageal echocardiography (TEE) to monitor right ventricular function. Following renal transplantation pulmonary artery pressures decrease significantly [14–16].

Heart Failure

In patients with ESRD under dialysis treatment , heart failure is a relatively common finding. No consensus exists on the level of systolic dysfunction at which patients are at

an acceptable risk to undergo renal transplantation. In a retrospective study after transplantation patients with pre-existing left ventricular (LV) dysfunction did have more CHF-related hospitalizations but similar overall survival, graft function, and graft loss when compared with control patients [17]. The vast majority (87 %) of patients with LV dysfunction showed normalization of the left ventricle ejection fraction (LVEF) within 12 months. In another study a cohort of 103 patients with LVEF ≤40 % undergoing renal transplantation showed normalization of LVEF in 69.9 % of the patients within a year [18]. ESRD with significantly depressed ventricular function is not a contraindication to renal transplantation, but it may complicate the anesthetic management. Patients with significant decreased ejection fractions may benefit from intraoperative TEE.

Diabetes Mellitus

Diabetes mellitus is not only the most significant risk factor for the development of ERSD but is also associated with significantly higher rate of graft loss and mortality after transplantation [19]. Cardiovascular events are the cause of mortality in over 60 % of patients. After renal transplantation patients with diabetes have an increased risk of infection. Compared with renal transplant recipients without diabetes infection-related mortality is increased [20]. End-stage renal disease patients with diabetes have a compromised immune system due to impaired neutrophil and monocyte function [21]. Immunosuppression after transplantation further decreases the immunological response. In retrospective studies perioperative hyperglycemia in diabetics and non-diabetics is associated with an increased likelihood of delayed graft function [22, 23]. The usefulness of strict control of blood glucose concentration during the perioperative period is uncertain in patients with diabetes mellitus undergoing kidney transplantation. Tight perioperative glycemic control with intravenous insulin did not decrease the incidence of delayed graft function in diabetics when compared to standard subcutaneous insulin therapy [24].

Anemia

The use of erythropoietin has virtually eliminated the problem of anemia in those with ESRD. The number of blood transfusions has dramatically decreased, and quality of life, cognitive function, exercise tolerance, cardiac function, and, most importantly, survival have increased [25]. In diabetics, maintaining the hematocrit at greater than 30 % is associated with a 24 % reduction in cardiac events in the first 6 months after transplant [26].

Hemostasis Abnormalities

Chronic kidney disease is associated with a prothrombotic tendency in the early stages of the disease. After progression to ESRD, bleeding diathesis by inhibited platelet adhesion to injured vessels is added to the picture [27]. Platelet adhesion to the injured vessel wall is impaired by dysfunction of von Willebrand factor (vWF) , enhanced production of nitric oxide (vasodilator and platelet function inhibitor), and anemia. Correction of anemia in ESRD disease decreases bleeding tendency. The therapeutic effect of anemia correction is explained by enhancing platelet contact to the vessel wall. The increased number of red blood cells distributes more platelets from the center of the blood vessel toward the periphery, increasing platelet contact with and adhesion to injured vessel walls. In addition, the release of ADP (a platelet aggregation inducer) from red blood cells and the scavenging effect exerted by hemoglobin on nitric oxide exert a therapeutic effect [28].

Desmopressin (DDAVP) can be used to promote platelet aggregation by increasing plasma vWF and factor VIII levels. DDAVP can be administered either intravenously or subcutaneously at a dose of 0.3 mg/kg in a single dose. Cryoprecipitate rich in factor VIII and vWF also has a rapid onset of action and its effect is short lived (4–12 h).

Estrogen administration can achieve more prolonged correction of bleeding tendency. Estrogen can either be administered intravenously at a dose of 0.6 mg/kg daily for 5 days or it can be administered transdermally in the form of estradiol, 50–100 mg, twice a week.

The Elderly

The elderly are the fastest growing population with chronic kidney disease. Kidney transplantation can result in improved life expectancy and quality of life in the elderly. Age is no longer considered an absolute contraindication to transplantation. In carefully selected elderly patients the overall outcome after transplantation is excellent [29].

Obesity

The prevalence of obesity (body mass index (BMI) ≥30 kg/m^2) at the time of transplantation among kidney transplant recipients continues to increase inexorably. Although controversial, obesity is considered a predictor of acute rejection and other adverse outcomes after kidney transplantation [30]. Cutoff BMI values above which patients will not be transplanted differ among centers.

Patients with diabetes mellitus and BMI >30 have an increased infection risk and a trend towards decreased survival after transplantation [31]. Total body weight dosing of IV anesthetics in the obese will result in overdosing and ideal body weight dosing will result in underdosing. Lean body weight is the preferred dosing scalar for most IV anesthetic agents in the obese population.

Human Immunodeficiency Virus

Kidney transplantation in human immunodeficiency virus (HIV)-infected recipients is being performed and investigated in select centers. A high incidence of early post-transplant complications such as acute rejection has been observed. The high rejection rates are of serious concern [32].

Anesthetic Management

Adequate venous access should be established because there is a potential for rapid blood loss. Before induction of anesthesia the fluid status of the patient undergoing renal transplant surgery needs to be assessed. Fluid status can range from significant hypovolemia to fluid overload. The patient's volume status can be estimated by the frequency of dialysis and when it was last performed.

Hyperkalemia is a feature of chronic renal insufficiency and probably is an adaptive response that reflects a new set point for potassium hemostasis and excretion [33]. Recognition that mild-to-moderate hyperkalemia is an adaptive response should lead to tolerance of steady-state serum potassium levels of 5.0–5.5 mmol/L. Therefore, serum potassium levels in the 5.0–5.5 mmol/L range should not be a reason to delay surgery. Higher levels or acute increases must be treated.

Gastroparesis is another common feature of ERSD. Gastroparesis is not limited to diabetics with ESRD. The prevalence in patients with all-cause ESRD is reported to range between 36 and 62 % [34, 35]. Therefore, it seems prudent to treat ESRD patients as having a full stomach.

Monitoring

Standard intraoperative monitoring as recommended by the American Society of Anesthesiologists is required for all renal transplant patients. In addition, monitoring should reflect relevant comorbidities and volume status changes that can vary with the time since the last dialysis. A central venous catheter (CVC) aids in the assessment of volume status and can be used for rapid central venous fluid and drug administration. Central venous pressures are the most commonly used metric for assessment of static preload [36]. However, the utility of central venous pressure monitoring in patients with myocardial dysfunction and left-heart failure diminishes. Although seldom required, transesophageal echocardiography (TEE) and pulmonary arterial catheters may be indicated for patients with severe left ventricular dysfunction, valvular abnormalities, or pulmonary hypertension.

Invasive, intra-arterial blood pressure monitoring is the gold standard of blood pressure measurement and has a low complication rate. It is especially useful in patients with significant cardiovascular or lung disease. New devices allow continuous cardiac

output and stroke volume variation to be monitored using mathematical interpretation of the arterial waveform. These metrics have been shown to accurately reflect fluid responsiveness in surgical patients and may be useful in the absence of TEE or pulmonary arterial catheters [37].

Pharmacokinetics and Pharmacodynamics

Chronic kidney disease does not affect only drugs excreted by the kidney. Changes in plasma protein binding associated with chronic kidney disease can profoundly affect hepatic metabolism and distribution. Diminished plasma protein binding increases free fraction of the drug. For example, if total (free plus protein-bound) plasma concentrations are considered, many lipophilic drugs such as diazepam, midazolam, and thiopental appear to have an increased drug distribution and clearance; but if the pharmacokinetics are calculated in terms of free unbound drug, both distribution and clearance remain unchanged [38–40]. The net result is an underlying rate and extent of distribution and elimination much the same as in normal patients.

Cardiac output affects the early pharmacokinetics (front end kinetics) of drug distribution and dilution in the first minutes after administration. A decreased cardiac output increases the fraction of drug distributed to brain, reduces the rate of redistribution, and results in higher concentrations and reduced dose requirements.

An increased cardiac output decreases the fraction of drug distributed to the brain and increases the rate of redistribution, which will result in lower concentrations and increased dose requirement. Anemia associated with renal failure patients may result in a higher cardiac output and as a result an increased dose requirement.

In a study evaluating the induction dose of *propofol* in renal failure patients there was a significant negative correlation of propofol dose with preoperative hemoglobin concentration [41]. End-stage renal disease patients required significantly higher propofol doses to induce loss of (1.42 (0.24) mg/kg versus 0.89 (0.2) mg/kg) in normal renal function patients. Propofol dose required to achieve a BIS of 50 was also higher in ESRD patients (2.03 (0.4) mg/kg versus 1.39 (0.43) mg/kg) in normal renal function patients [41]. The propofol concentration associated with loss of consciousness is similar between healthy subjects and patients with renal failure [42]. In hypovolemic patients or patients with decreased LV function propofol induction dose should be reduced and carefully titrated. There is no difference in the pharmacokinetics for maintenance infusion of propofol between healthy subjects and patients with renal failure [42, 43]. Propofol, a weak acid, is highly bound (98–99 %) to plasma protein, mainly albumin. Protein binding is not different in patients with renal disease [44].

Etomidate may be a useful induction agent in patients with severely compromised cardiac function. However, in a retrospective study etomidate administration for induction of anesthesia has been associated with increased 30-day mortality and

cardiovascular morbidity after non-cardiac surgery [45]. The percentage of unbound (free) plasma etomidate is increased in patients with renal failure (43 % in renal failure patients versus 25 % in healthy subjects) [46].

Currently *thiopental* is not commercially available in the USA. In patients with chronic renal failure, the free fraction of thiopental was almost twice that found in healthy subjects [40]. The reduced plasma protein binding of thiopental in renal failure is related partly to hypoalbuminemia and partly to competitive displacement of thiopental from binding sites by substances present in uremic plasma. In one study, the thiopental induction dose in renal failure patients was similar to normal subjects [47].

When *sevoflurane* is administered the US Food and Drug Administration recommends not to use fresh gas flows <1 L/min and not to exceed 2 MAC hours at fresh gas flow rates between 1 and 2 L/min. For exposures greater than 2 MAC hours fresh gas flows of 2 L/min are required. The safety of sevoflurane in patients with chronic kidney disease has not been established due to remaining concerns about compound A and inorganic fluoride-induced renal toxicity. Degradation of sevoflurane to compound A (fluoromethyl-2,2-difluoro-1-[trifluoromethyl] vinyl ether) occurs by a reaction with strong bases such as barium hydroxide lime or to a lesser extent soda lime which are present in carbon dioxide absorbers of the anesthesia apparatus breathing circuit. Low fresh gas flows and higher temperatures in the breathing circuit increase compound A concentrations. Compound A causes renal injury in rats and is cytotoxic to human kidney-derived HD-2 cells [48–50]. The mechanism of compound A renal toxicity is unclear but is probably related to the renal cysteine conjugate beta-lyase pathway in the biotransformation of compound A. In human studies with compound A exposure as high as 428 ppm/h no evidence of renal toxicity could be demonstrated [51–56]. However, other studies at exposure greater than 160 ppm/h demonstrate renal dysfunction as measured by albuminuria, glucosuria, and enzymuria [57–59]. Fluoride ions are produced by oxidative defluorination of sevoflurane by the cytochrome P450 system in the liver. Deterioration in renal function as demonstrated by increased serum urea nitrogen and creatinine levels at 24 h was detected after peak serum inorganic fluoride concentrations greater than 50 mmol/L [60]. Inorganic fluoride is excreted in the urine at approximately half the glomerular filtration rate. In renal failure patients the half life of fluoride is prolonged [61], thereby increasing the risk for nephrotoxicity. The few studies in patients with renal insufficiency indicate no further worsening of renal function after sevoflurane anesthetics [61–63]. Recognizing the limited safety data in patients with chronic kidney disease it is prudent to use sevoflurane with caution in renal transplant patients.

Isoflurane is not nephrotoxic. Similarly *desflurane* biodegradation does not increase fluoride concentration and worsening renal function has not been observed in patients with or without renal disease [55, 57, 64, 65].

Succinylcholine can be used safely in patients with chronic renal failure, assuming

that the potassium concentration is less than 5.5 mEq/L [66]. The hyperkalemic response after succinylcholine administration is not exaggerated and just as in healthy patients a transient potassium increase of approximately 0.5–1.0 mEq/L is observed. In the presence of conditions that increase the risk of an exaggerated hyperkalemic response (e.g., burns, trauma, tissue ischemia, infections, and neuromuscular disorders including neuropathies), succinylcholine should be avoided. Renal failure can be associated with reduced plasma cholinesterase activity and succinylcholine can cause a prolonged neuromuscular block [67].

Patients with chronic renal failure may require a reduced dose of *mivacurium* . Recovery from mivacurium-induced neuromuscular blockade is slower and correlates with the reduced plasma cholinesterase activity [68]. The clearance of the *cis–cis* isomer, an isomer contributing minimally to the neuromuscular block, is significantly reduced.

In patients with renal failure there is large between-patient variability in pharmacodynamic and pharmacokinetic parameters of *rocuronium* [69]. The major route of rocuronium elimination is by direct liver uptake and excretion in the bile. The liver metabolizes a small portion of rocuronium and some is excreted renally. In renal failure patients the clearance of rocuronium is reduced by 33–39 %, with a 66–84 % increase in the mean residence time. The decreased or absent renal clearance explains the prolonged mean residence time and possible prolongation of effect. When endotracheal intubation and neuromuscular block for a short period of time are needed rocuronium 0.3 mg/kg can provide adequate intubating conditions 4–5 min after administration. Mean recovery times after this dose in patients with and without renal failure are not different. However, there was a significant difference in the variability of the total duration of the block. In the renal failure group the time to spontaneous recovery of the TOF to 70 % ranged from 11 to 95 min [70]. Rocuronium, 1.2 mg/kg, can be used for rapid sequence-induction tracheal intubation but anticipate prolonged recovery from neuromuscular blockade.

The majority of *vecuronium* is excreted in the bile. In a meta-analysis of eight studies it was shown that the duration of action of vecuronium is longer in patients with renal failure [71]. The plasma clearance and elimination half-life are decreased. These findings can be explained by the fact that 20–30 % of administered vecuronium in healthy subjects is excreted by the kidneys. The pharmacokinetics and dynamics of vecuronium are also highly variable in renal failure patients.

The kidneys excrete the majority of *pancuronium* and its active metabolite. The clearance of this long-acting muscle relaxant is significantly decreased in patients undergoing kidney transplantation and therefore shorter acting muscle relaxants are preferred [72].

In chronic kidney disease patients highly variable recovery times for all muscle relaxants have been noted and monitoring the degree of neuromuscular blockade is

advocated.

Neostigmine has a reduced clearance and prolonged half-life in patients with renal failure. When administered at the end of renal transplantation surgery neostigmine pharmacokinetics were not different from patients with normal renal function [73].

Sugammadex is being introduced for the reversal of rocuronium- or vecuronium-induced neuromuscular blockade. After reversal the sugammadex/rocuronium or sugammadex/vecuronium complex is excreted by the kidneys. Further studies are needed before the use of sugammadex in renal failure and renal transplant patients can be recommended.

The pharmacokinetics and pharmacodynamics of *remifentanil* were not altered in patients with renal disease, but the elimination of its principal metabolite, GR90291, was markedly reduced [74]. However, GR90291 after routine clinical use of remifentanil is not likely to produce significant opioid effects [74]. In another study remifentanil blood concentrations were higher and the elimination half-life was prolonged in end-stage renal failure patients when compared to a control group [75]. While statistically significant, these differences do have modest clinical meaning.

In patients undergoing renal transplantation there is large inter-subject variability in the pharmacokinetics of *fentanyl* [76]. Decreases in fentanyl clearance were observed in patients with BUN concentrations above 60 mg/dl. Fentanyl-induced respiratory arrest after tracheal extubation has been reported to occur after a fentanyl dose of 450 µg administered during a 4 h and 30 min renal transplant surgery [77].

Bower and Sear determined the pharmacokinetics of *alfentanil* in ten patients undergoing renal transplantation and eight matched controls. Elimination half-life, mean residence time, and apparent volume of distribution at steady state were not different [78].

Just like for alfentanil, the kinetics of *sufentanil* did not differ between healthy patients undergoing lower abdominal surgery and those with chronic renal failure undergoing renal transplantation [79, 80]. However the degree of interindividual variability was considerably larger in the subjects undergoing renal transplantation. The large variability can result in unexpected high sufentanil concentrations and prolonged respiratory depression [81]. Therefore, sufentanil and all other opioids should be carefully titrated to the need of the individual patient.

Morphine administration to patients with chronic kidney disease has been associated with excessive and prolonged opioid effects. The clearance of morphine and the excretion of its active metabolites are decreased in ESRD. The active metabolites of morphine, morphine-6-glucuronide (M6G) , and to a lesser degree morphine-3-glucuronide (M3G) may exert important clinical effects when accumulating in the plasma of patients with renal failure. M6G is a potent opioid agonist ten times more potent than morphine and M3G is a mild opioid antagonist. Both are poorly excreted in patients with renal failure. Because of the long transfer half-life from blood to effect

compartment, the effects of the metabolites appear only after a significant delay. Patients with renal failure are at increased risk of M6G-induced delayed respiratory depression. Therefore, the use of other opioids should be considered [82]. Renal transplantation normalizes the clearance of morphine and reverses the accumulation of its metabolites [83].

Hydromorphone is 5–10 times more potent than morphine and does not form an active 6-glucuronide metabolite like morphine. For the treatment of acute pain hydromorphone provided significantly better analgesia than morphine [84]. Hydromorphone-3-glucuronide (H3G), the metabolite of hydromorphone, can cause neuro-excitatory symptoms. H3G accumulates between dialysis treatments but is effectively removed during hemodialysis [85]. The safety of hydromorphone in renal failure and renal transplant patients requires substantiation by further studies.

Meperidine's active metabolite normeperidine is renally excreted and will accumulate in renal failure patients and may cause seizures [86].

Intravenous Fluid Therapy

Perioperative fluid management must be optimized in renal transplant recipients as these patients can range from being severely hypervolemic to severely hypovolemic. Knowledge of the patient's preoperative volume status, especially time since last dialysis, is important to guide fluid requirements. Intraoperative volume expansion increases renal blood flow and improves immediate graft function [87–92]. Immediate graft function increases graft survival and lowers patient mortality [92]. Use of central venous pressures can be useful in this regard. Central venous pressure is usually maintained in the range of 10–15 mmHg to achieve this goal. However, close communication between the surgeon and anesthesiologist is necessary when determining maintenance fluid requirement.

Diuretics (furosemide), osmotic agents (mannitol), and sometimes dopamine agonists (dopamine, fenoldopam) are administered to promote diuresis immediately after reperfusion, but only mannitol, when combined with volume expansion, has been shown to decrease the incidence of acute tubular necrosis after transplantation [93, 94]. Administration of dopamine to the kidney transplant recipient is not beneficial for renal allograft function, and administration may be harmful [95]. Hypotension results in decreased graft perfusion. Maintaining an adequate intravascular volume and careful titration of medications are important. Keep in mind that vasopressors, especially alpha agonists, may interfere with renal perfusion.

Generally, isotonic crystalloid solution is given for maintenance therapy, although colloid may be given if volume expansion is necessary. Controversy exists as to the safety of hydroxyethyl starch (HES) solutions in renal transplant recipients. A meta-analysis of 42 studies analyzing the effect of HES solutions on renal function showed

that HES was associated with an increased risk of acute kidney injury and need for renal replacement therapy [96]. In addition, HES has been shown to increase kidney injury and mortality in the intensive care population [97, 98]. A recent study comparing HES to crystalloid in critically ill patients showed that while HES increased the likelihood of renal replacement therapy, its use was associated with decreased cardiovascular organ failure. There was no difference in 90-day mortality between groups [99].

Studies comparing the use of albumin to crystalloid for perioperative volume expansion in renal transplant cases are few. A randomized double-blinded crossover study comparing 5 % albumin to crystalloid for the treatment of intradialytic hypotension found that albumin was not superior to crystalloid [100]. The authors concluded that crystalloid solution should be considered first-choice treatment.

Due to the equivocal nature of the safety or efficacy of colloid solutions for volume expansion, crystalloid solutions should be considered first-line choices for volume resuscitation and for intraoperative maintenance fluid administration in renal transplant recipients. However, in the setting of severe hypovolemia and reduced graft blood flow, colloid solutions may be necessary to rapidly restore blood volume and maintain graft perfusion and should be considered on a case-by-case basis.

Postoperative Analgesia

Many consider the coagulopathy associated with ESRD a relative contraindication for a neuro-axial block. In one study epidural analgesia was effective in the treatment of postoperative pain and no complications were observed [101]. A transversus abdominis plane (TAP) block reduces opioid requirements and pain scores for procedures involving the lower abdominal wall. However, a TAP block using a landmark technique and 20 mL of levobupivacaine 0.375 % did not reduce morphine requirements in the first 24 h after renal transplantation [102]. Intravenous opioid administration by patient-controlled analgesia remains the most commonly used technique to control postoperative pain [103].

Fast Tracking

Hospital stays as short as 48 h in recipients of live donor allografts are feasible and realized in several centers. Preoperative patient optimization and standardized perioperative treatment protocols are considered important factors to decrease hospital stay. Age, gender, and pre-transplant dialysis status did not impact the ability to achieve 48-h admissions [104]. In the future the creation of intensive outpatient units may decrease increased length of hospital stay in patients with significant comorbidities.

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23. Postoperative Care of Renal Transplant Recipients

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Introduction

Renal transplantation is the treatment of choice for patients with end-stage renal disease. It is estimated that renal transplantation saves 25,000 lives annually [1]. In 2010, 16,843 kidney transplants were performed in the USA in patients aged 20 and older [2]; however 98,398 individuals remain on the waitlist for kidney transplantation

(based on OPTN data as of October 18, 2013). Transplant recipients experience a lower mortality than dialysis patients who remain on the waiting list [3]. Moreover those who return to dialysis after a failed allograft experience worse outcomes than waitlisted patients on dialysis [4]. Hence kidney transplantation and graft survival offer a mortality benefit to patients.

Not only does transplantation reduce mortality, but it also substantially improves the quality of life for most patients. However the use of immunosuppression and the presence of many medical comorbidities in these patients make their postoperative management very challenging. Collaboration between transplant surgeons, anesthesiologists, critical care specialists, and transplant nephrologists is essential with each group having its own unique skill sets.

The postoperative period for kidney transplant recipients can typically be divided into early and late postoperative periods. This division helps to narrow down the differential diagnosis of various postoperative complications. The early postoperative period usually encompasses the first 3 months post-transplant. The focus of this chapter is the recognition and management of common immediate postoperative surgical and medical issues in these patients.

Induction Agents

The risk of acute rejection is highest in the first weeks to months after kidney transplantation. Induction therapy is used to reduce this risk by achieving rapid and profound immunosuppression with minimal adverse effects. Agents used for induction include antilymphocyte antibodies (both polyclonal and monoclonal), and interleukin-2 receptor antagonists, which antagonize IL-2-mediated T cell proliferation. The use of induction allows for early steroid withdrawal and the delayed introduction of calcineurin inhibitor initiation if desired when there is concern for slow or delayed graft function. Induction therapy is usually individualized depending on recipient and donor factors and hence prior knowledge of recipient and donor risk factors is useful. The 2009 KDIGO clinical practice guidelines identify patients at high risk when they have one or more of the following: a panel reactive antibody (PRA >0 %), increased number of HLA mismatches, younger recipient and older donor, African-American ethnicity, presence of donor-specific antibodies, ABO incompatibility, delayed onset of graft function, and a cold ischemic time greater than 24 h.

Currently the most commonly used induction agents in the USA are the IL 2 receptor antagonist: basiliximab (Simulect®), polyclonal T cell-depleting agent: rabbit antithymocyte globulin (Thymoglobulin®), and monoclonal T cell-depleting agent: alemtuzumab (Campath-1H®). The type of induction treatment used is important to know for postoperative re-dosing as well as certain medication-associated adverse effects.

Refer to Table 23.1 for dosing and common adverse effects.

Table 23.1 Immunosuppressive agents used for induction

Generic name (brand name)	FDA approved for induction	Dose	Common adverse effects
Rabbit antithymocyte globulin (Thymoglobulin®)	No	1.5 mg/kg IV 3–5 doses. Infused over 6 h if central line or 12 h if peripheral line. Premedicate with acetaminophen, diphenhydramine, and steroids Dose adjustments needed for low WBC counts and thrombocytopenia	Chills, rigors, fever, tachycardia rash, myelosuppression
Alemtuzumab (Campath-1H®)	No	20–30 mg IV × 1–2 doses	Flu-like symptoms, chills, rigor, fever, myelosuppression
Basiliximab (Simulect®)	Yes	20 mg IV × 2 doses (days 0 and 4)	None reported when compared with placebo

Postoperative Assessment

In order to assess the likelihood of delayed graft function information on the status of the donor is useful especially when dealing with a deceased donor transplant. The key data include information on causes/mechanisms of death, donor age, medical history, and cold/warm ischemia time. To monitor urine output a Foley catheter should be inserted; this will also help decompress the bladder. Understanding the patient's hemodynamic status is important. To this end, adequate venous access should be established and an arterial line inserted. Use of a Swan-Ganz catheter is generally not required unless patients have severe left ventricular dysfunction, valvular abnormalities, or known pulmonary hypertension.

Depending on institutional policy, the postoperative care of the patient may take place in an ICU, "step-down" unit, or even the general floor. It is important that the nurses and the physicians taking care of these patients be well acquainted with the patient's prior medical history. Table 23.2 lists common admit orders and protocols.

Table 23.2 Common admit orders and protocols

Admit orders: ICU, step-down, or surgical floor depending on institutional protocol
Protective isolation
Vital signs/monitoring:
CVP monitoring every hour. Transduce with 0.9 % NS pressurized to 150 mmHg
Central line care per clinical care protocol
Central line infection prevention

Pulse oximetry: every hour
Strict intake and output every hour
Vital signs: BP, HR, RR, peripheral pulses to be recorded post-procedure—on arrival, every 15 min for 1 h (or until stable)—followed by every 30 min for 2 h—followed by every hour as needed for 24 h—then unit routine postoperatively
Activity
Ambulate with assistance: three times daily. Start postoperative day 0
Out of bed to chair: three times daily
Notify service:
Name and pager of whom to contact
Temp: ≥38.5 °C
HR: ≥120 ≤ 60 bpm
SBP: ≥180 ≤ 90 mmHg
DBP: ≥110 ≤ 60 mmHg
Pulse Ox: ≤92 %
Urine output: ≤40 ml/h or ≥800 ml/h
Nursing care:
Incentive spirometry: 10 times every hour when awake
Turn/cough/deep breathe
Supplemental oxygen as needed to maintain oxygen saturation ≥92 %
Maintain Foley catheter
Weight daily: standing scale preferred
DVT prophylaxis: apply sequential compression device (SCD), unless contraindicated
: Heparin 5000 units SC tid. Avoid low molecular weight heparin
Diet: NPO except for meds now
Medications:
PCA medications and nursing instructions; dilaudid and fentanyl PCA preferred
Antiemetics:IV Ondansetron 4 mg q6h as needed for nausea and vomiting
Antipruritic: Benadryl 25 mg PO or IV q6h as needed for itching
Bowel regimen: Colace 100 mg po twice daily
IV fluids
Dextrose 2.5 %/0.45 % NaCl with 50 Meq of sodium bicarbonate 1000 ml: intravenous, at 100 ml/h
Orders for 0.9 % NS and 0.45 % NS are also written for replacement protocol given below
Replacement protocol:
If urine output 1–100 ml/h—continue maintenance IV fluids
If urine output 101–400 ml/h—replace urine output with 1:1 0.9 % NS
If urine output 401–800 ml/h—replace urine output 1:1 or 0.5:1 with 0.45 % NS (surgeon preference)
If urine output >800 ml/h—notify HO

PCP prophylaxis: start postoperative day 1. Duration of prophylaxis varies institutionally
Bactrim SS PO daily is the preferred agent
If sulfa allergic and not G-6-PD deficient, select dapsone 100 mg PO daily
If sulfa allergic and G6PD deficient select pentamidine 300 mg NEB every month
Atovaquone 1500 mg po daily
Candida prophylaxis
Fluconazole (DIFLUCAN) tablet: 100 mg po daily: start postoperative day 1. Nystatin swish and swallow can also be used
CMV prophylaxis as follows based on donor and recipient CMV status:
Start postoperative day 1 (*dose adjusted based on renal function*)
IF moderate to high risk (CMV D−/R+, D+/R+, D+/R−)
Valganciclovir 450 mg PO daily
IF low risk (CMV D−/R−)
Acyclovir 400 mg PO every 12 h
Steroid dosing:
Methylprednisolone 200 mg IV postoperative day 1
Methylprednisolone 160 mg IV postoperative day 2
Methylprednisolone 120 mf IV postoperative day 3
Prednisone 80 mg PO postoperative day 4
Prednisone 40 PO postoperative day 5
Prednisone 20 mg PO postoperative day 6 and daily thereafter
Some programs utilize rapid steroid taper (e.g., steroids off by end of first week) or steroid avoidance protocols. PO:IV conversion is 5:4 (prednisone to methylprednisolone)
Antiproliferative agents:
Mycophenolate mofetil 1000 mg po bid, mycophenolic acid 720 mg po twice daily. Oral to IV conversion is 1:1
Calcineurin inhibitor (typically tacrolimus): Monitor 12-h troughs. Goal range is typically 8–12 ng/ml for first 3 months post-transplant. Typical starting dose is 0.05 mg/kg PO every 12 h, but the starting dose may be altered based on the patient's clinical status and/or drug interactions. Due to risk of toxicity, IV calcineurin inhibitors are generally avoided unless absolutely necessary. Sublingual administration of tacrolimus is an option if NPO
Postoperative laboratory orders
Complete blood count with platelets, renal function panel (includes magnesium, phosphorus, serum glucose) every 12 h for 24 h and then every morning unless clinically indicated
Calcineurin inhibitor level (12 h trough) each morning
Liver function tests if indicated, urine culture, and sensitivity

Hemodynamic Status

Maintenance of stable perioperative hemodynamics is of utmost importance and to achieve this goal patients should be monitored carefully. Postoperatively recipients should be in slightly positive fluid balance along with higher blood pressures (we generally prefer SBP ≥ 150 mmHg and DBP ≥ 80 mmHg) to help maintain adequate

perfusion of the newly transplanted organ. Replacement fluids should be given taking into account the patient's urine output, insensible losses (averaging 500–1000 ml/day but varies depending on clinical condition), and volume status. However, care should be taken to gradually decrease the amount of replacement fluid while maintaining stable hemodynamics, as constant full-volume replacement only drives more diuresis. Most centers have their own protocols.

Common causes of postoperative hypotension include bleeding, effect of anesthetic medications, inadequate volume resuscitation, perioperative myocardial infarction with left ventricular dysfunction, aggressive ultrafiltration before transplantation, cytokine release syndrome, and sepsis or other causes of low systemic vascular resistance such as liver disease. If the patient is hypotensive isotonic fluids should be administered rapidly. If anemia is present packed red cells may be given to expand intravascular volume. If a central venous catheter is present the central venous pressures (CVP) (target 7–10 cm H_2O) may help in guiding management of the patient's volume status. Low blood pressures should be avoided to decrease the risk of acute tubular necrosis (ATN) and or risk of delayed graft function (DGF), which is defined as the need for dialysis within the first week of transplantation.

Persistent hypotension, abdominal pain, and a dropping hematocrit are all potential signs/symptoms of intra-abdominal bleeding. Most bleeding is self-limited, but any coagulopathy or thrombocytopenia if present should be reversed. In the event of concerns for a hematoma causing pressure on the ureteral anastomosis and vascular bundle or there is ongoing need for blood product and isotonic fluid infusions to maintain stable hemodynamics, the patient should be taken to the operating room, the bleeding contained, and hematoma evacuated.

Cytokine release syndrome is a rare condition that can be seen from antithymocyte globulin (due to its rabbit origin) generally during the first or second doses that is associated with fevers, chills, rash, myalgias, hypotension, and tachycardia. The treatment is to reduce the infusion rate and this usually resolves the problem. If the above signs and symptoms persist the infusion should be discontinued. Premedication with antihistamines, H2-blockers, and intravenous glucocorticoids can prevent or reduce the severity of symptoms. Since basiliximab and alemtuzumab are humanized monoclonal antibodies infusion reactions are not typically seen.

Aggressive pre-transplant ultrafiltration (usually performed with dialysis) can cause postoperative hypotension. Although there are no specific guidelines on how much pre-transplant volume removal is appropriate, it has been our practice to allow patients receiving pre-transplant dialysis/ultrafiltration to end the treatment 1.0–1.5 kg above their dry weight.

All patients who are candidates for a renal transplantation undergo stringent cardiovascular evaluation per institutional protocol prior to transplantation; hence perioperative acute myocardial infarction is uncommon. The incidence of in-hospital

postoperative myocardial infarction (MI) after renal transplantation was found to be 1.6 % in a recent observational study [5]. In yet another older single-center retrospective study, the overall incidence of cardiac complications in the first 30 days post-transplant was noted to be 6.1 %. Cardiac complications in the latter study included MI (1.6 %), arrhythmia (2.7 %), angina (1.2 %), cardiac arrest (0.5 %), and congestive heart failure (0.1 %) [6]. EKGs should be done if there is a clinical suspicion of MI and cardiac enzymes including CK, CK-MB, and troponins should be sent. A cardiology consultation should be obtained to help with management if cardiac complications are suspected or diagnosed.

Hypertension should be only treated if the blood pressures are very high. We only treat systolic blood pressures greater than 170 and/or diastolic blood pressures greater than 100 after eliminating all potential factors such as pain and nausea. Commonly used intravenous antihypertensive medications include PRN doses of IV hydralazine 5–10 mg every hour as needed or labetalol 10–20 mg IVP over 2 min and can administer 40–80 mg at 10-min intervals with total maximum cumulative dose of 300 mg. Dihydropyridine calcium channel blockers (CCB) are a good oral choice and are our first-line oral antihypertensive medications. We avoid non-dihydropyridine CCBs such as verapamil and diltiazem since they decrease metabolism of tacrolimus and cyclosporine, and can cause nephrotoxicity if the calcineurin inhibitor levels are not closely monitored and adjusted. Awareness of patient's pre-transplant antihypertensive medications is very important. Abrupt cessation of medications such as clonidine can cause rebound hypertension with very high blood pressures. We resume clonidine at smaller doses after transplant unless the patient is hypotensive; this is then weaned off over the next 2–4 weeks. Similar problems can be seen with patients who are on minoxidil and can be avoided by restarting the drug postoperatively and then gradually tapering it off. Wide fluctuations in blood pressure should raise the suspicion of autonomic dysfunction especially in patients with long-standing diabetes and their management can be quite challenging and is generally done in the outpatient setting.

Pain Control

It is our practice to use patient-controlled analgesia (PCA). Opiates remain the mainstay of analgesia and we prefer the use of fentanyl and hydromorphone. Morphine should be avoided in patients with CKD, ESRD, and recent transplantation due to the potential for significant accumulation of morphine-6-β glucuronide which has been reported to cause significant respiratory depression [7]. On the other hand fentanyl is metabolized in the liver to mostly norfentanyl and there is no evidence that any of its metabolites are active. Despite the risk of accumulation in renal failure and potentially respiratory depression, fentanyl has had a good short-term safety profile. Hydromorphone is another drug that can be considered for analgesia in renal failure patients. Although 3-

glucuronide metabolites can accumulate and are neuro-excitatory, it has been used safely in renal failure patients [8].

Postoperative Anemia

Most chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients are anemic as their hemoglobin levels are intentionally maintained no higher than 10–12 g/dl. Postoperatively anemia is thus very common and is likely multifactorial. The causes include postoperative hemodilution due to perioperative positive fluid balance, surgical blood loss, frequent phlebotomy, or bleeding. Although medications and infections may cause anemia this is typically seen later in the post-transplant course and is beyond the intended scope of this chapter. Although there is no "cutoff" for transfusion, we attempt to keep a goal hemoglobin of at least >9 g/dl especially in diabetics and patients with a known history of coronary artery disease (CAD). Transfusions should be avoided if possible since blood exposure may increase the risk of alloimmunization. Postoperative use of erythropoietin-stimulating agents should be considered especially when there are concerns of DGF and slow graft function. After ensuring adequate iron stores, we use erythropoietin at initial doses of 50–100 units/kg three times/week or darbepoetin 0.45 μg/kg weekly.

Leukopenia

Leukopenia can be seen postoperatively and early on is commonly caused by the use of thymoglobulin and may necessitate dose reduction or delayed administration. Other common causes of postoperative leukopenia include mycophenolate mofetil, and trimethoprim/sulfamethoxazole. Other rarer causes include angiotensin-converting enzyme inhibitors/angiotension receptor blockers (ACEI/ARB), proton pump inhibitors and histamine H2-receptor antagonists (H2-blockers).

Postoperative Hyperglycemia

Both diabetics and non-diabetics can have postoperative hyperglycemia and this should be managed with continuous insulin infusion. Once the patient has begun to eat, he or she should be transitioned to subcutaneous insulin with long-acting basal insulin such as insulin glargine or NPH and additional coverage with subcutaneous short-acting insulin such as insulin aspart (NovoLog®). Insulin pumps can be restarted in those who used them preoperatively and consultation with endocrine colleagues should be undertaken. In patients who receive a simultaneous kidney pancreas transplant, glucose should be watched closely as hyperglycemia may signal pancreatic allograft dysfunction. Most centers have their own protocols regarding dosing of steroids Glucocorticoids could be tapered down to 5 mg daily by 1 month or earlier if the kidney is at low risk for

rejection. Likewise in steroid-free protocol patients, steroids are typically tapered off by the end of the first week. All patients should receive diabetic nurse counseling and sometimes an inpatient or outpatient endocrine consult may be appropriate if hyperglycemia is hard to manage.

Allograft Dysfunction

Fluctuations in serum creatinine after transplants are common. However an abrupt increase in creatinine or failure to decrease appropriately should prompt further evaluation. The dysfunction can be categorized as pre-renal, intrinsic renal, and post-renal.

Pre-renal

Pre-renal causes are due to an "effective" reduction in perfusion to the kidney and could be a result of low blood pressures, poor cardiac output, autonomic dysfunction, volume depletion from poor intake or diarrhea, high tacrolimus levels (causing afferent vasoconstriction), renal artery stenosis, and the use of drugs such as ACEI/ARB and nonsteroidal anti-inflammatory drugs (NSAIDs). Efforts should be made to systematically rule out all the possibilities. Low blood pressures should be managed by discontinuation of all antihypertensive mediations and administration of isotonic fluids such as normal saline or packed red blood cell transfusion if indicated. Adequate hydration must be given either by oral route or intravenously if the oral route is not tolerated. The medication list should be reviewed and drugs such as ACEI/ARB or NSAIDs should be discontinued. It is important to remember that certain drugs block the tubular secretion of creatinine (cimetidine, trimethoprim) and their introduction may lead to a rise in serum creatinine which does not reflect a new renal impairment. If the tacrolimus levels are very high, its dose should be held or reduced; typically postoperative tacrolimus trough levels are maintained in the range of 8–12 ng/ml. Finally a Doppler should be done to rule out a renal artery stenosis although this is typically seen later in the post-transplant period.

Intrinsic Renal

Allograft rejection : Hyperacute rejection is a type of antibody-mediated rejection and is rarely seen these days due to improved cross-match techniques and use of induction agents; however it may still occur especially if the patient is very sensitized or in the case of an ABO mismatch. This type of rejection is an antibody-mediated vascular rejection and is characterized by thrombosis of the vessels. Very often these patients will have fever, graft pain, and oliguria to anuria. A renal Doppler may help identify poor flow and in most cases a surgical re-exploration and a renal biopsy are indicated.

However outcomes remain poor.

Cellular rejection : T-cell-mediated rejection can occur rarely within the first week and should be suspected if the creatinine does not improve to the expected level or if there is a rise in creatinine postoperatively. Classic signs such as fever, graft tenderness, and oliguria are typically absent. The diagnosis can be made by biopsy and usually involves lymphocytic infiltration of the interstitium and tubulitis (Fig. 23.1a) or sometimes more severe rejection with arteritis (Fig. 23.1b).

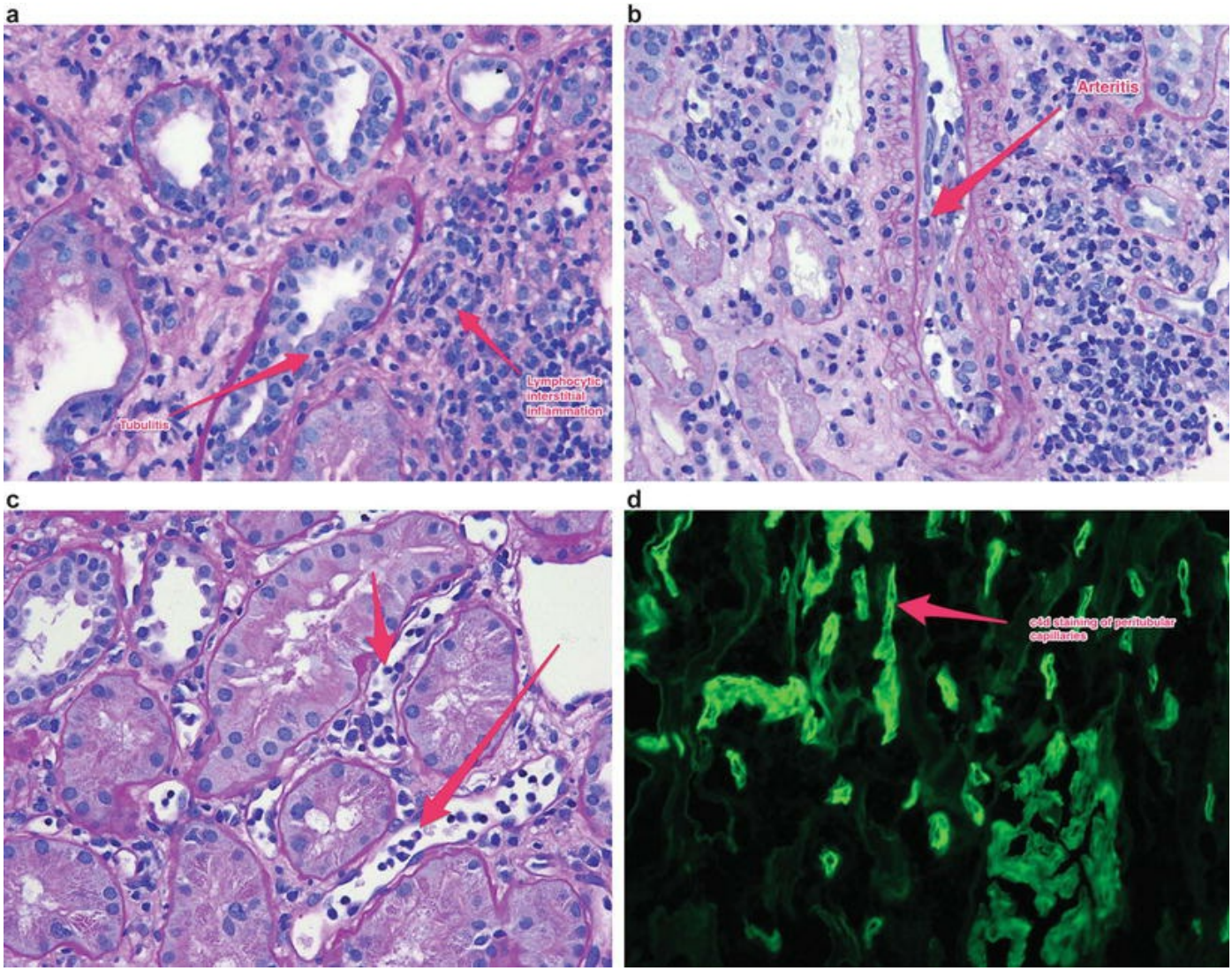

Fig. 23.1 (**a**) Biopsy picture of acute cellular rejection —showing tubulitis and lymphocytic infiltration of the interstitial space. (**b**) Biopsy picture of acute cellular rejection—arteritis suggesting more severe rejection. Tubulitis and interstitial inflammation are also seen. (**c**) Biopsy picture of acute antibody-mediated rejection—with peritubular capillaritis. Neutrophils (see *arrows*) can be seen marginating along the capillary walls. (**d**) Diffuse C4d staining of the peritubular capillaries suggesting an antibody-mediated rejection. C4d is a breakdown product of classical pathway activation and its presence in peritubular capillaries correlates strongly with presence of anti-donor antibodies. However c4d negative antibody mediated rejections are not uncommon

Antibody-mediated rejection : The classic pattern of peritubular capillaritis (Fig.

23.1c) and glomerulitis may sometimes not be seen in early acute antibody-mediated rejection and thus C4d (a by-product of classical complement pathway activation) staining is very useful to identify it. This form of a rejection can sometimes present as acute tubular injury and differentiating it from ATN in the absence of C4d staining may be difficult even for the astute pathologist. Donor-specific antibodies should also be sent and their presence along with positive C4d along the peritubular capillaries (Fig. 23.1d) and glomerular endothelium (glomerulitis) would clinch the diagnosis of antibody-mediated rejection. The treatment of antibody-mediated rejection varies but may include plasma exchange, intravenous immunoglobulin (IVIG), and rituximab.

Recurrence of primary kidney disease can also occur. This is particularly of concern in individuals whose cause of kidney failure is primary focal segmental glomerulosclerosis (FSGS). These patients must be monitored for recurrence as the disease may recur immediately post-transplant and has the potential to quickly destroy the allograft. A spot urine protein-to-creatinine ratio should be measured immediately postoperatively and on a daily basis while the patient is in the hospital to assess for recurrent focal segmental glomerulosclerosis (FSGS). It is good practice to also get a baseline urine protein-to-creatinine ratio in these patients before surgery since many patients may still have intact native kidney function and proteinuria from native kidneys can cloud interpretation of the urinary protein-to-creatinine ratio, as will the presence of many RBCs, and WBCs in the urine. However, a persistent rise in the patient's urine protein-to-creatinine ratio should warrant an urgent kidney allograft biopsy and appropriate therapy (typically plasma exchange) should be instituted if the diagnosis of recurrent FSGS is established.

ATN, resulting from prolonged ischemia, is the most common cause of DGF. The cause of ischemia may be as a result of tubular injury in the donor, prolonged cold or warm ischemia time, or ischemia-reperfusion injury and post-transplant hypotension in the recipient. ATN should be suspected when the creatinine does not improve after transplantation or if there is an initial improvement followed by worsening in serum creatinine. The diagnosis can be relatively easily established with a microscopic urine exam showing tubular epithelial cells or muddy brown casts in a centrifuged urine specimen. Occasionally a biopsy may be needed if the diagnosis is less clear or if there are concerns of ongoing antibody-mediated rejection, which may manifest as acute tubular injury with c4d deposition. Medications can occasionally cause an interstitial nephritis, which may present as white cell casts in the urine and occasionally urine eosinophils. A thorough review of the medications should be done and most common culprits should be discontinued. As ischemic injury upregulates donor HLA and adhesion molecules, the risk of acute rejection is increased and adequate immunosuppression can often be achieved with extended use of T cell-depleting antibodies for induction.

Thrombotic microangiopathy (TMA) can also be seen in the setting of calcineurin

inhibitor (CNI) use, antiphospholipid antibodies, and sometimes in severe antibody-mediated rejection. TMA can be restricted to the allograft and one may not see other classical evidence of hemolysis such as schistocytes in the peripheral smear, lactate dehydrogenase, or thrombocytopenia. A high index of suspicion should be present to diagnose this condition in the absence of classic signs.

Post-renal

The most common causes of post-renal obstruction are benign prostatic hypertrophy (BPH) in men causing urinary retention, clot retained in the Foley catheter, extrinsic compression of the ureter from a blood clot, lymphocele, and urinoma. Treatment involves identifying the cause and treating appropriately. Management of some post-renal causes of allograft has been discussed in the next session on "Monitoring of Urine Output and Urine Leak."

Monitoring of Urine Output and Urine Leak

Robust urine output is most often a sign of good allograft function. Postoperative urine output is typically driven by a combination of perioperative positive fluid balance and solute diuresis. It is good practice to ask the patient about their preoperative urine volumes and this should be taken into account when monitoring urine output as the native kidneys may be contributing to the total volume excreted. An early drop in the patient's urine output should be carefully assessed. A reduction in urine output can be thought of as an issue with "plumbing," vascular inflow/outflow, and renal parenchymal injury or decreased effective arterial circulating volume. Common issues with "plumbing" include presence of bladder clots, dysfunctional bladder (common in diabetics), bladder neck obstruction/narrowing, and extrinsic compression and hence a Foley catheter should be inserted postoperatively for 3–5 days in all the patients. Simple bedside maneuvers may help in establishing the etiology. Flushing the Foley catheter may dislodge clots and allow for free flow of urine. After ensuring adequate intravascular volume, a renal vascular doppler with ultrasound should be performed to ensure good arterial inflow and venous outflow. The ultrasound may also help identify a urinoma or lymphocele, which may cause extrinsic compression of the ureters. If a Doppler is inconclusive, an MAG3 or diethylene pentaacetic acid (DTPA) scan can be used to assess perfusion and possibly even identify an obstruction or urine leak. Most major urologic complications typically originate from the vesicoureteric anastomosis and occur within the first 72 h. The current practice of an extravesical ureteroneocystostomy (Lich-Gregoir) is technically easier than the Leadbetter-Politano (L-P) approach; however the incidence of complications remains at about 3–5 % [9, 10]. A leak can be identified by checking the concentration of creatinine in the fluid from the perinephric drain. In the case of a urine leak, the fluid creatinine should be higher than the blood creatinine. If the fluid creatinine is the same as the blood

creatinine, then a urine leak is unlikely. If a urine leak is identified and the patient has a perinephric drain and a double J ureteral stent, a conservative approach can be taken. If no drain is present a percutaneous nephrostomy tube may have to be inserted to divert the urine and allow for the anastomotic site to heal. If the leak persists or does not heal, re-exploration to implant the ureter may have to be undertaken. Figure 23.2 provides a broad schematic outlay on the management of a low postoperative urine output.

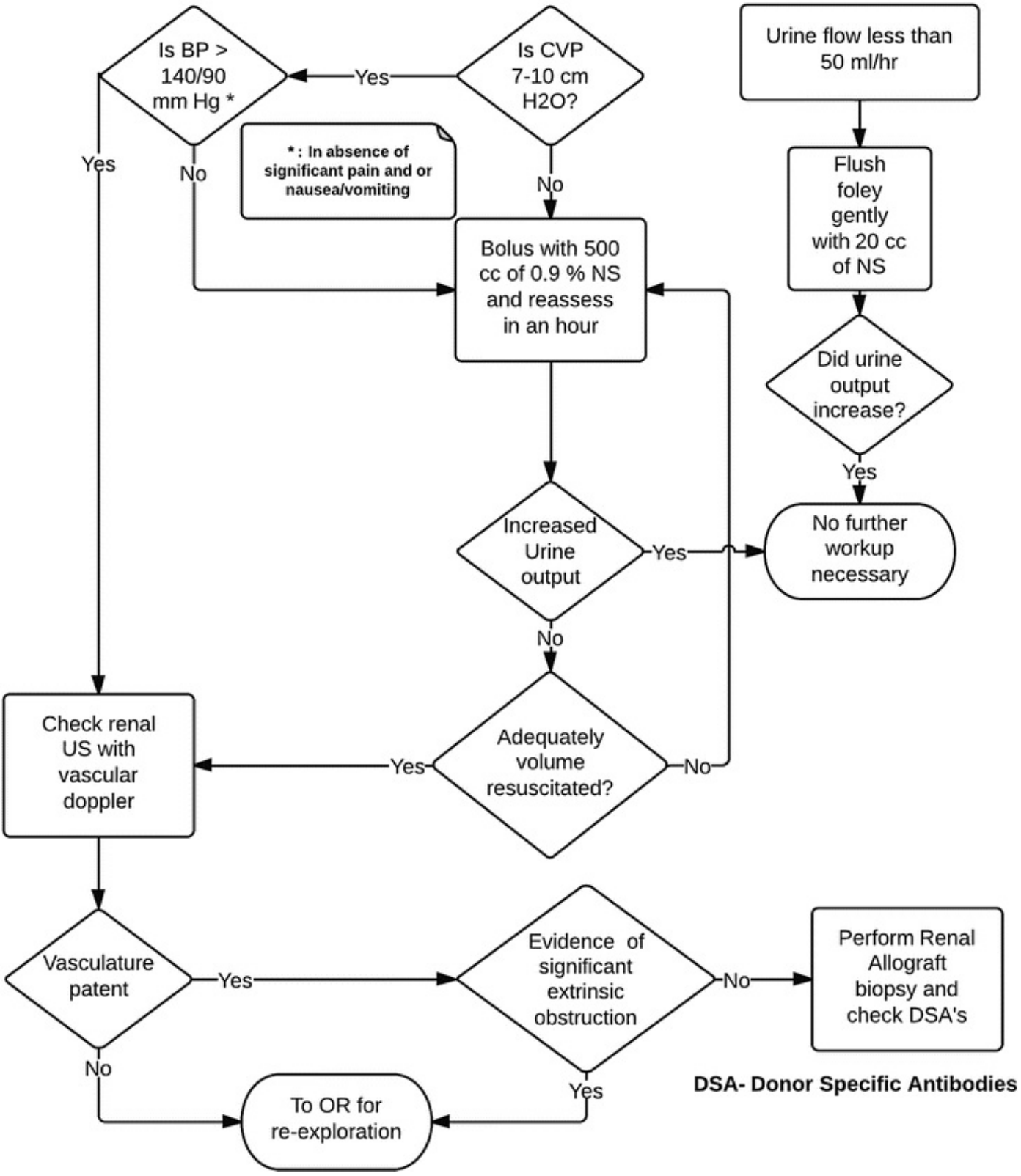

Fig. 23.2 Broad schematic outlay for management of low postoperative urine output. This outlay is not a substitute for clinical judgment

Monitoring of Drains, Ureteral Stents, and Incision Site

Daily monitoring of output from the drains should be recorded. The surgeon should be

asked about the position of each drain (superficial, deep) and the draining organ bed (e.g.: perinephric). The drainage is typically serosanguinous for the first few days; however if gross blood is noted to come out of the drain then the surgeon should be immediately notified. Volume of output from each drain should be recorded. If the output is noted to be increasing then it should be sent for fluid creatinine. Drains are normally removed before discharge unless they continue to drain significantly (generally >60–70 ml daily). When used, ureteral stents are kept in place for about 4–6 weeks to allow the anastomotic site to heal and to keep ureter patent. They are removed via cystoscopy by urologists in the outpatient setting. The incision site should be closely monitored for infections, dehiscence, and drainage. Daily dressing changes are to be done. It is normal to have some serosanguinous drainage from the wound. Staples or sutures are normally removed by the end of the second or third week.

Electrolyte Disorders

Severe electrolyte disturbances can occur post-renal transplant and input of the nephrology or transplant nephrology service should be obtained. Common causes of electrolyte abnormalities are excessive perioperative IV fluids, postoperative solute diuresis, tubular electrolyte wasting, and the effect of some immunosuppressive medications (Table 23.3). Common electrolyte abnormalities include hyperkalemia/hypokalemia, hypophosphatemia, hypercalcemia, hypomagnesemia, and hyponatremia. Labs should be checked every 8–12 h initially to detect and treat abnormalities early.

Table 23.3 Common electrolyte disorders and their management

Disorders	Common causes	Clinical symptoms	Management
Hyperphosphatemia	Renal failure, tissue injury, cell breakdown (e.g., rhabdomyolysis)	Mostly asymptomatic but muscular irritation, carpopedal spasms and tetany if severe associated hypocalcemia	Normally will improve as renal function improves. If patient taking PO and S. phosphorus levels >5.5, use phosphate binders. Rarely hemodialysis is needed. If accompanying symptomatic hypocalcemia—treat accordingly
Hypophosphatemia	High FGF-23, PTH and vitamin D deficiency, ongoing use of phosphate binders, tacrolimus, mTOR, tubular leak	Mostly asymptomatic, but very low levels (<1 mmol) can cause rhabdomyolysis, muscle weakness and respiratory muscle weakness	• Asymptomatic: Oral potassium phosphate–Na phosphate 250 mg tab (8 mmol). Normally 30–60 mmol of elemental phosphate daily in divided doses • Severe or symptomatic cases: Prefer IV route. Transition back to oral once S. phosphorus >1.5 mg/dl. Monitor labs closely
Hypercalcemia	Persistent	Mostly asymptomatic, but high	Cinacalcet or parathyroidectomy, stop

	hyperparathyroidism, normalization of calcitriol production, ongoing vitamin D use	levels can cause dehydration (from furosemide-like effect) and AKI	vitamin D supplementation
Hyperkalemia	Decreased H+ secretion in CCD/MCD. Type 4 RTA, CNIs	Arrhythmias, cardiac arrest, muscle weakness, and paralysis	• Dextrose/insulin • Kayexalate—15–30 g/1–4 times a day orally or rectally. We avoid sorbitol-containing preparations • Loop diuretics if hypervolemic • Sometimes hemodialysis is needed
Hypokalemia	Diarrhea, diuretics, solute diuresis (including hyperglycemia), vomiting, hypomagnesemia	Muscle weakness, rhabdomyolysis, cardiac arrhythmias, ileus, and if very low cardiac arrest. ECG: U waves in lateral precordial leads, sometimes ST depression, and prolongation of QT interval	• PO: KCl or sustained-release potassium chloride tablets. 20–100-mEq daily depending on severity, acid–base status, and chronicity • Potassium phosphate if type 2 RTA or acquired Fanconi syndrome • IV—Rate not to exceed 10 mEq/h except in life-threatening conditions where 20–40 mEq/h has been used • If magnesium low—replace magnesium simultaneously
Hypomagnesemia	Uncontrolled diabetes mellitus, calcineurin inhibitors, alcohol use, volume expansion, familial renal magnesium wasting syndromes	Typically features are neuromuscular excitability, hypocalcaemia, PTH resistance, hypokalemia	• Severe symptoms—tetany, arrhythmias, and seizures: IV route preferred. Magnesium sulfate 1–2 g. Recheck S. magnesium level 6–8 h after dose • No to minimal symptoms: 20–80 mEq of elemental mag in divided doses. We typically use magnesium oxide 800–1600 mg daily in divided doses

Hyperkalemia

Hyperkalemia is very common postoperatively and is initially likely due to tissue injury during surgery, intraoperative blood, and blood product transfusion, and acidosis. Serum potassium of greater than 5.5 mEq/L warrants an electrocardiogram. If peaked T waves are noted insulin and dextrose should be administered to shift the potassium intracellularly and calcium gluconate should be administered to provide cardiac membrane stabilization. However it is important to understand that the use of insulin/dextrose does not decrease total body potassium stores and hence the long-term goal is a reduction in total body potassium stores. This can be done either by administration of sodium polystyrene sulfonate (kayexalate) or the use of diuretics and low-potassium diet. The presence of hyperkalemia should also prompt checking a tacrolimus trough level (if tacrolimus initiated) since it can contribute to hyperkalemia.

ACEI or ARBs should be discontinued. If the patient is hypervolemic a loop diuretic can help decrease serum potassium levels. If the patient is hypovolemic intravenous hydration with 0.9 % NS may help to correct the hyperkalemia. Both diuretics and hydration work by increasing distal sodium delivery and this helps generate the transtubular electrochemical gradient that is needed for potassium excretion. If the kidney is not functioning well enough or at all, dialysis may be required.

Hypokalemia

Hypokalemia can sometimes be seen from excessive postoperative diuresis or patients maintaining their pre-transplant dietary restriction. Hypomagnesemia should be ruled out in patients with refractory hypokalemia.

Hypophosphatemia

Hypophosphatemia is another potential complication due to high levels of serum parathyroid hormone [11] and elevated FGF23 levels [12] as well as phosphorus wasting in the proximal tubule. Close monitoring is essential since profound hypophosphatemia can cause rhabdomyolysis and if critically low even muscle paralysis (including respiratory and cardiac muscles). Care should be taken to ensure that patients discontinue their preoperative phosphate binders and no longer restrict phosphorus in their diet. Occasionally hyperparathyroidism may persist for months after renal transplantation and require further medical interventions with the calcimimetic cinacalcet or surgically via parathyroidectomy. Phosphate levels can be increased by increasing dietary phosphate and by phosphate supplements. However phosphate supplementation can sometimes worsen hyperkalemia due to the potassium in phosphate supplements; in that scenario sodium phosphate should be used. It remains unclear if increasing phosphate in the diet/supplementation increases the risk of formation of calcium phosphate kidney stones.

Hypercalcemia

Another common complication seen post-transplantation is the presence of hypercalcemia. The most common cause is hyperparathyroidism, which may improve with time; however on occasion the parathyroid gland may become “autonomous,” and does not respond to the negative feedback from improved serum phosphates or hypercalcemia. Often the hypercalcemia can be managed with the use of calcimimetics like cinacalcet; we usually start with a dose of 30 mg once a day. One may use loop diuretics if the patient is hypervolemic. Sometimes if hypercalcemia persists due to hyperparathyroidism a referral to an endocrine surgeon for parathyroidectomy may be appropriate.

Hypomagnesemia

Hypomagnesemia is very common in the early post-transplant period and its causes include volume expansion, calcineurin inhibitors, and rarely uncontrolled diabetes mellitus post-transplant [13, 14]. Urinary wasting is very common with both cyclosporine and tacrolimus and although the exact mechanisms remain unclear it is thought to be due to downregulation of epithelial and cytosolic magnesium transporters [15].

The route of administration of magnesium supplementation depends on its severity. In severe cases and in patients who are symptomatic the IV route is preferred (i.e., in patients with neuromuscular disturbances and ventricular arrhythmias). IV route is also preferred in patients with a postoperative ileus since absorption may be impaired. But in patients with no symptoms an oral route is preferred although this can sometimes be limited by side effects like diarrhea or abdominal cramping. Despite aggressive replacement patients can remain mildly hypomagnesemic due to ongoing magnesuria.

Hyponatremia

Occasionally hyponatremia may be seen and is often due to excessive use of hypotonic perioperative fluids in the setting of an elevated antidiuretic hormone (ADH). The excessive ADH release is typically from "non-osmotic" causes such as nausea, vomiting, perioperative pain, and occasionally the use of narcotics. The first step is to decrease the intake of hypotonic fluids and controlling nausea, vomiting, and perioperative pain (which will decrease ADH stimulus). These maneuvers should help correct the hyponatremia by increasing free water excretion in the urine. In severe cases or if the hyponatremia is acute and patient has neurological symptoms then hypertonic saline is indicated. An osmotic/volume stimulus of ADH is generally not seen since most of these patients are well hydrated and have relatively normal serum osmolality preoperatively. If hyponatremia persists an A.M. free cortisol and TSH level should be checked. If pancreatitis is suspected then triglyceride levels should be checked since one may encounter a pseudohyponatremia in this setting.

Discharge

The patient is usually discharged by postoperative day 5. To ensure smooth transition to outpatient care it is very important that the patient receive education on medications including immunosuppression. We use pillboxes at discharge to simplify regimen in the hope of improving compliance. Important contact information of attending surgeons, post-transplant nurses, and transplant nephrologists should be given and the patient should know the role of each provider. It is our practice to see the patient immediately after discharge with increasing intervals between visits in case of patients who follow a

relatively uncomplicated postoperative course. Patients should be instructed to call the medical team before any changes in prescription medications, inpatient admissions, procedures, and even vaccinations.

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24. Anesthetic Management of Patients Undergoing Pancreas Transplantation

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Introduction

The first pancreas transplant performed to treat diabetes mellitus was at the University of Minnesota in 1966 by Kelly et al. In this patient a duct-ligated segmental pancreas graft was transplanted concurrently with a kidney [1]. The success rate for pancreas transplantation was initially very low. However with the development of better surgical techniques, patient selection, and immunosuppressive agents the success rates for both pancreas transplants performed simultaneously with kidney transplants and alone to treat diabetes mellitus have markedly improved. The most recent data from the

International Pancreas Transplant Registry shows that the 3-year patient survival after a simultaneous kidney and pancreas transplant is now 93.2 % with 80 % of patients having pancreas graft function and 87.8 % having kidney function [2].

When successful, pancreas transplantation can provide many benefits for the patient: (1) The need for multiple daily insulin injections is eliminated or reduced. Therefore most patients report a significant improvement in lifestyle. (2) Euglycemia is maintained more effectively than with other pharmacological and mechanical means of insulin administration, including newer insulin formulation (e.g., glargine) and the use of insulin pumps. This may be especially beneficial to those who suffer from multiple, unaware hypoglycemic episodes. (3) Diabetic nephropathy in both native and transplanted kidneys stabilizes or is prevented following successful pancreas transplantation, although it is not completely reversed. As a result the survival rates are much improved in recipients of deceased donor simultaneous kidney-pancreas transplants over recipients of kidney transplants alone 5 and 8 years following surgery. (4) Both autonomic and peripheral neuropathy may be stabilized or reduced following transplantation. The high rate of sudden death in diabetic patients with autonomic neuropathy may be reduced as well. (5) Atherosclerosis can regress in nearly 40 % of patients with a functioning pancreas transplant perhaps because the lipid profile is more favorably altered. Diastolic dysfunction may also reverse or improve following successful pancreas transplantation [3].

Patients are eligible to receive a pancreas transplant if they have disabling or life-threatening hypoglycemic unawareness or have or are likely to develop the secondary complications of diabetes such as nephropathy or neuropathy, and are fit enough to survive the operation. Currently at least 30,000 patients worldwide have received pancreas transplants, the majority in the USA. The majority of transplants done were simultaneous pancreas-kidney transplants (73 %), pancreas after kidney transplants (19 %), followed by pancreas transplants alone (9 %). Currently 90 % of the pancreas transplants done worldwide are done simultaneously due to the excellent results of the combined operation [2].

Patients undergoing pancreas transplantation, either alone or combined with a kidney, present the following challenges to the anesthesiologist:

1. Due to their long-standing diabetes, most of these patients have both peripheral and autonomic neuropathy. Autonomic neuropathy has been associated with sudden death following anesthesia in diabetic patients [4]. Peripheral neuropathy may make nerve injuries due to positioning more likely to occur since the nerves are already damaged.
2. Gastroparesis is also common due to autonomic neuropathy involving the vagus nerve [5]. These patients are therefore at high risk for aspiration in the

perioperative period.

3. Most patients undergoing pancreas transplantation have coronary disease and some have peripheral vascular disease as well. Most of the deaths in pancreas transplant recipients occur from coronary artery disease. In some patients placement of arterial catheters can be hazardous due to poor distal circulation due to peripheral vascular disease. Loss of the pancreas graft due to thrombosis may also occur if perfusion is inadequate due to a low cardiac output state.

4. Most of these patients have renal insufficiency even if they are not in renal failure and receiving a kidney transplant. As a result, most pancreas transplant recipients have long-standing hypertension and all of the morbidities associated with it.

5. Patients undergoing pancreas transplantation almost all have very brittle diabetes that can be difficult to manage. Both hypoglycemia and hyperglycemia may easily occur intraoperatively in these patients. This may be particularly true in patients receiving a pancreas transplant alone specifically because their diabetes is difficult to control [3].

6. Long-standing diabetes may result in stiff joints throughout a patient's body including those in the jaw, neck, and atlanto-occipital joint. This is thought due to abnormal cross-linking of collagen via nonenzymatic glycosylation [6]. Renal insufficiency can potentiate this glycosylation. Tracheal intubation may therefore be difficult in these patients [7]. However despite all these comorbidities, most patients can undergo pancreas transplantation without mortality or significant morbidity [3].

Preoperative Preparation

In most cases pancreas transplantation is performed as a semi-urgent operation as soon as possible after procuring the pancreas because the organ preservation time is less than 24 h. The rare exception is the case of living-related pancreas transplantation where the procedure can be performed electively. In spite of the time constraint it is essential for the anesthesiologist to perform a thorough preoperative evaluation [3].

As noted above, patients undergoing pancreas transplantation with or without a simultaneous kidney transplant often have serious systemic complications resulting from

their long-standing diabetes mellitus. In particular, cardiac disease can affect both graft and patient survival. For example, Gruessner et al. found that the death rate in patients undergoing simultaneous kidney pancreas transplantation in the first year following surgery was 18 % in patients with coronary disease, four times higher than those without [8].

The presence of coronary artery disease is often difficult to determine in diabetic patients because they often will not experience angina despite ischemia due to their autonomic neuropathy. Since it is impossible to thoroughly evaluate a patient's cardiac status in the short interval immediately prior to surgery, most centers involved in pancreas transplantation aggressively screen patients for coronary disease as soon as they become eligible for pancreas transplantation. This may include dobutamine stress tests, dipyridamole thallium scans, and in some cases coronary angiography. In some individuals coronary artery bypass or angioplasty has been performed prior to proceeding with pancreas transplantation. In any event the anesthesiologist must review the cardiac function of the patient, the presence or absence of bypass grafts or stints, and the drug regimen the patients are receiving prior to administering anesthesia for pancreas transplantation [3, 8].

Another important complication from long-standing diabetes that the anesthesiologist should ascertain prior to administering anesthesia for pancreas transplantation is the presence of autonomic neuropathy. Patients with diabetes and autonomic neuropathy are at high risk for developing severe hypotension during the administration of anesthesia due to the impaired function of their autonomic nervous systems. There are case reports of sudden death in the recovery room in patients with diabetes and autonomic neuropathy, perhaps due to the impaired response of these patients to hypoxia [4].

Anesthesiologists should therefore specifically ask about the symptoms of autonomic neuropathy (e.g., dizziness upon standing, hypoglycemic unawareness, hypotension upon initiating dialysis, esophageal motility, nausea, and intermittent diarrhea). Marked orthostatic blood pressure changes without adequate compensation of the heart rate may indicate significant autonomic neuropathy that may increase the risk for hypotension upon induction of general anesthesia. The electrocardiogram should be examined for the presence of resting tachycardia. Resting tachycardia suggests that the vagus nerve is dysfunctional [4].

Dysfunction of the vagus nerve often results in gastroparesis in diabetic patients. Gastroparesis can increase the risk for aspiration upon induction of general anesthesia. Therefore all patients undergoing pancreas transplantation should be asked about the symptoms of gastroparesis and autonomic dysfunction such as heartburn, bloating, and explosive diarrhea [5]. Also because gastroparesis is so common in patients with long-standing diabetes, a non-particulate antacid such as Bicitra prior to surgery is strongly recommended [3].

Peripheral neuropathy is also more common in diabetic patients. Diabetic patients are also more likely to develop postoperative neuropraxias than nondiabetic patients. The anesthesiologist should therefore ask about and document any preexisting neuropathy prior to beginning anesthesia. Patients should be warned that their medical condition predisposes them at risk for postoperative neuropraxia that may not be preventable [9].

Particular attention should also be paid to the examination of the airway prior to inducing anesthesia in pancreas transplant recipients. Beebe et al. found that 13 % of the 55 patients in their study who underwent pancreas transplantation were difficult to tracheally intubate [3]. Hogan et al. found that 1/3 of the 125 patients with long-standing diabetes undergoing either kidney or pancreas transplantation were difficult to tracheally intubate and 2 required an emergency tracheostomy. In contrast less than 3 % of those in their control population were difficult to intubate [6]. Although both of these studies were performed prior to modern video laryngoscopy, which may have improved visualization of the larynx and the success rate for tracheal intubation, anesthesiologists should be aware that patients with long-standing diabetes have stiff tissues and may be challenging to intubate.

Finally the patient's metabolic status and blood sugar should be checked prior to surgery. The type and time of their last insulin administered should be determined. Treatment of hypo- or hyperglycemia is often necessary in the preoperative period and is continued throughout surgery. Occasionally a patient presents for pancreas transplantation whose blood glucose is extremely high (>500 mg/dL). If that is the case arterial blood gases should be obtained and the urine examined for the presence of ketones. The surgery may have to be delayed until the patient stabilizes if ketoacidosis is present [3].

Induction of Anesthesia

Pancreas transplantation with or without concurrent kidney transplantation is a long and arduous procedure. Therefore general anesthesia is used. Anesthesia is usually induced with a small intravenous dose of fentanyl and an intravenous hypnotic agent such as propofol or etomidate. Etomidate is often useful in these patients because it causes minimal myocardial depression and maintains autonomic tone. Therefore hypotension is not seen as often following induction of anesthesia with etomidate compared to propofol or thiopental [3]. Adrenal suppression may occur following induction of general anesthesia with etomidate. There is some evidence that this adrenal suppression may be associated with an increased mortality seen in some studies of patients who had received etomidate for induction of general anesthesia compared to other agents such as propofol [10]. However most transplant recipients receive high doses of corticosteroids anyway as part of their immunosuppression protocol, so adrenal suppression is not a

concern [3]. B blockers such as esmolol or metoprolol are often administered to prevent tachycardia and ischemia form tracheal intubation. Esmolol is better than metoprolol for this purpose. Due to the high incidence of renal insufficiency in this patient population a skeletal muscle relaxant that does not depend on renal excretion such as *cis*-atracurium or rocuronium is administered to facilitate tracheal intubation. Also due to the high incidence of gastroparesis in these patients, a formal rapid-sequence induction (Sellick's maneuver and rapid tracheal intubation following a hypnotic agent and short-acting muscle relaxant such as succinylcholine or rocuronium) is often utilized [3].

Patients with long-standing diabetes as described earlier may often be difficult to tracheally intubate. If the history and physical exam suggest that the patient will be difficult to intubate, an awake, fiber-optic intubation may be performed. Video laryngoscopy with devices such as the C-Mac or Glide-Scope has also been utilized for awake tracheal intubations. Some patients are found to be difficult to intubate only after anesthesia has been induced. In recent years video laryngoscopy has proved to be useful to intubate patients whose tissues are too stiff to be allowing visualization of the larynx using standard laryngoscopy. The laryngeal mask (LMA) is often useful as well in some pancreas transplant recipients because it often provides adequate ventilation if ventilation by mask is difficult. Intubation with a fiber-optic laryngoscope can be performed through a laryngeal mask airway as well while ventilation is provided through the LMA. The Air-Q laryngeal mask airway has been specially designed for intubation with a fiber-optic laryngoscope. The Fastrack LMA has also been designed for tracheal intubation, either blindly through the device or utilizing a bronchoscope. However if after three or four attempts using different techniques the patient still cannot be intubated, he or she should be allowed to awaken from anesthesia and an awake, fiber-optic intubation performed. Persisting with unsuccessful intubation attempts can result in airway edema and tracheal injury. Finally, if ventilation or intubation cannot be achieved by any of these devices trans-tracheal jet ventilation may be required or a surgical airway via a cricothyroidotomy or tracheostomy performed [3].

Maintenance of Anesthesia

After tracheal intubation, anesthesia is usually maintained with either desflurane or isoflurane. Both agents are minimally metabolized and do not harm the kidney. Desflurane allows for earlier awakening than the other agents and is minimally metabolized. However it is an airway irritant and may produce tachycardia. Sevoflurane is not contraindicated for pancreas transplantation. Anesthesiologists often do not use sevoflurane for patients with renal insufficiency because of the concern of nephrotoxicity from a substance called compound A produced by reaction of sevoflurane with the carbon dioxide absorbent used in anesthesia machines [11]. Nitrous oxide is not contraindicated as well and may be used concurrently with either

isoflurane or desflurane. Short-acting narcotics such as fentanyl are administered along with the inhaled agents. Muscle relaxants that do not depend on renal excretion such as *cis*-atracurium or rocuronium are utilized because of the high incidence of renal failure in pancreas transplant recipients [3].

In addition to the anesthetic agents, patients undergoing pancreas transplantation receive a variety of immunosuppressive agents throughout surgery as well as broad-spectrum antibiotics. In addition low-dose heparin (70 units/kg) is given intravenously 5 min before the major vessels are clamped in non-uremic recipients. The heparin is not reversed. Uremic recipients generally do not require anticoagulation. Most patients tolerate immunosuppressive agents without incident. However hypotension, bronchospasm, and pulmonary edema have been reported after administration of monoclonal antibodies used for immunosuppression (e.g., OKT3). Some of these complications can be prevented with proper filtering and administration over 6–7 h. Complications may still occur in spite of these precautions, and occasionally patients may require mechanical ventilation for 12–24 h until the complications resolve [12].

Hemodynamic Monitoring

Patients undergoing pancreas transplantation require the standard monitoring all patients receive (automated blood pressure, pulse oximetry, ECG, end-tidal gas analysis, and core body temperature). In addition, all patients undergoing pancreas transplantation have their central venous pressure monitored, usually via a catheter placed in the internal jugular vein placed after induction of general anesthesia. This allows assessment of volume status as well as providing central venous access for immunosuppressive drugs, blood drawing, and hyperalimentation. Some patients who have required numerous shunts in the arms for dialysis the central venous catheter may be the only vascular access that can be achieved and may have to be placed before general anesthesia is induced [3].

An arterial catheter is also placed, if possible, in patients with a history of cardiac disease or autonomic instability. However often in patients who have received shunts for hemodialysis the circulation is very poor in the extremities. In these patients placement of arterial catheters may be impossible and potentially dangerous to place. Therefore anesthesiologists often have to rely on automated blood pressure monitoring alone [3].

On rare occasions patients undergoing pancreas transplantation require monitoring with a pulmonary artery catheter and/or transesophageal echocardiography. The benefit of the more invasive monitoring is that the cardiac output may be optimized with inotropes and vasodilator therapy, and may result in better graft perfusion. These benefits must be weighed against the risks of the more aggressive monitoring and therapy [3].

Metabolic Monitoring

Patients undergoing pancreas transplantation usually have brittle diabetes. Therefore blood sugars are often difficult to control intraoperatively. Hyperglycemia is very common during pancreas transplantation. Hyperglycemia may be due to the metabolic response to stress, the reduced effect of insulin during anesthesia and surgery, the hyperglycemic effect of corticosteroids or immunosuppressive agents, or the metabolism of lactate from iv fluids. Hyperglycemia may also be induced from glucagon from the perfused pancreas [3, 13, 14].

Islet cell dysfunction and structural lesions have been induced by hyperglycemia in rats, dogs, and cats [15–17]. The growth and function of fetal islet cell isografts in mice are impaired with chronic hyperglycemia [18]. Therefore it seems likely, although it has not been proven, that hyperglycemia would also injure the islet cells in a human allograft. Therefore the serum glucose levels should be measured at least hourly throughout surgery, and every half-hour if significant adjustments are made. Laboratory glucose levels are obtained because of significant error with most point-of-care devices. Table 24.1 lists a glucose management protocol currently in use at the University of Minnesota. Intravenous insulin is infused without dextrose until the blood glucose level is below 150 mg/dL. Low-dose dextrose is added at this point, and may be increased if the glucose level falls. A dextrose infusion helps prevent hypoglycemia and ensures adequate cellular nutrition [3].

Table 24.1 Glucose and insulin management protocol for patients undergoing pancreas transplantation at the University of Minnesota

Blood glucose level (g/dL)	Regular insulin infusion rate (U/h)	D_5W infusion rate (mL/h)
>350	3–5[a]	0
250–350	3[a]	0
150–250	2[a]	0
100–150	2	20
70–100	1–2	20–100
<70	0	100[b]

[a]2 to 5-U boluses of regular insulin may be needed in addition to treat hyperglycemia

[b]5–25 g boluses of dextrose ($D_{50}W$) may be necessary to treat hypoglycemia

Pancreas transplant recipients also often have metabolic acidosis (pH < 7.30). Occasionally this may be due to ketosis. Most often, however, the metabolic acidosis is due to renal insufficiency or failure. Often these patients compensate for their acidosis

by hyperventilating. Therefore the pH should be monitored along with the blood glucose levels. Significant acidosis (pH < 7.30) may require sodium bicarbonate (1–2 mmol/kg) intravenously [3].

Due to the fact that only a low dose of heparin is administered to pancreas transplant recipients, coagulation is usually not monitored in pancreas transplant recipients. However there is evidence that some patients undergoing pancreas transplantation may become hypercoagulable following reperfusion of the allograft. This may result in graft thrombosis. Thromboelastography has been suggested by some authors to determine which patients are at risk for becoming hypercoagulable and administering additional anticoagulation to them [19]. At our institution a heparin drip is usually started 4 h after surgery at 3 units/kg/h and aspirin (81 mg orally per day) is instituted within 48 h of surgery. Heparin is weaned prior to discharge and the low-dose aspirin is continued indefinitely.

Allograft Reperfusion

Figures 24.1 and 24.2 depict the surgical procedure that may result in pancreas drainage either in the bowel or in the bladder. The patient's hemodynamic status must be optimized prior to reperfusion of the pancreatic allograft. Hypotension and inadequate cardiac output during reperfusion may result in poor blood flow to the allograft and cause graft thrombosis. Graft thrombosis is one of the leading causes of graft loss in pancreas transplantation. Systemic hypotension upon reperfusion of the allograft may occur in as many as 20 % of pancreas transplant recipients and probably results from transfusion of the ischemic by-products from the pancreas into the central circulation [3].

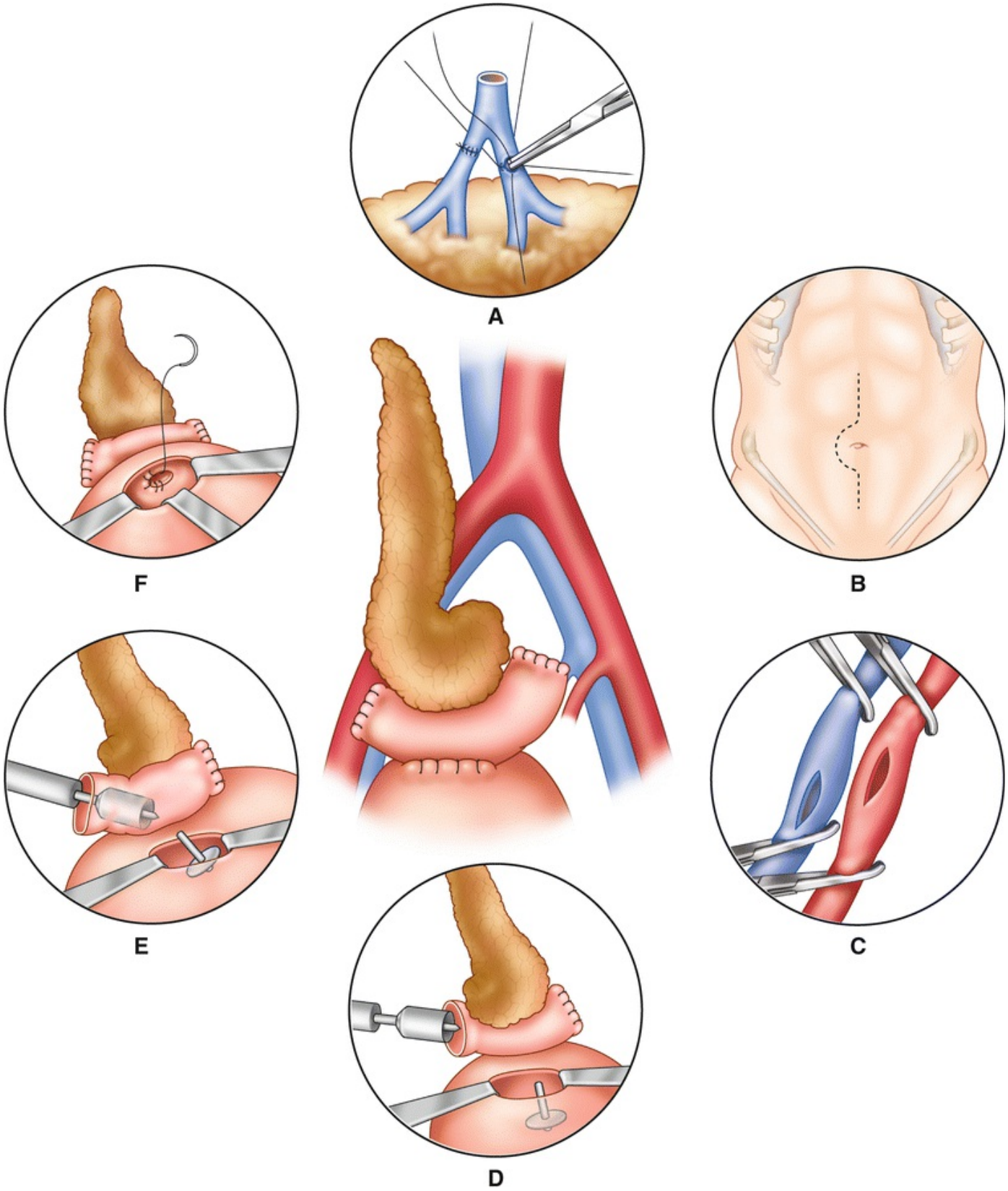

Fig. 24.1 Surgical procedure—diagram demonstrates steps in the procedure with the pancreas allograft being drained into the bowel

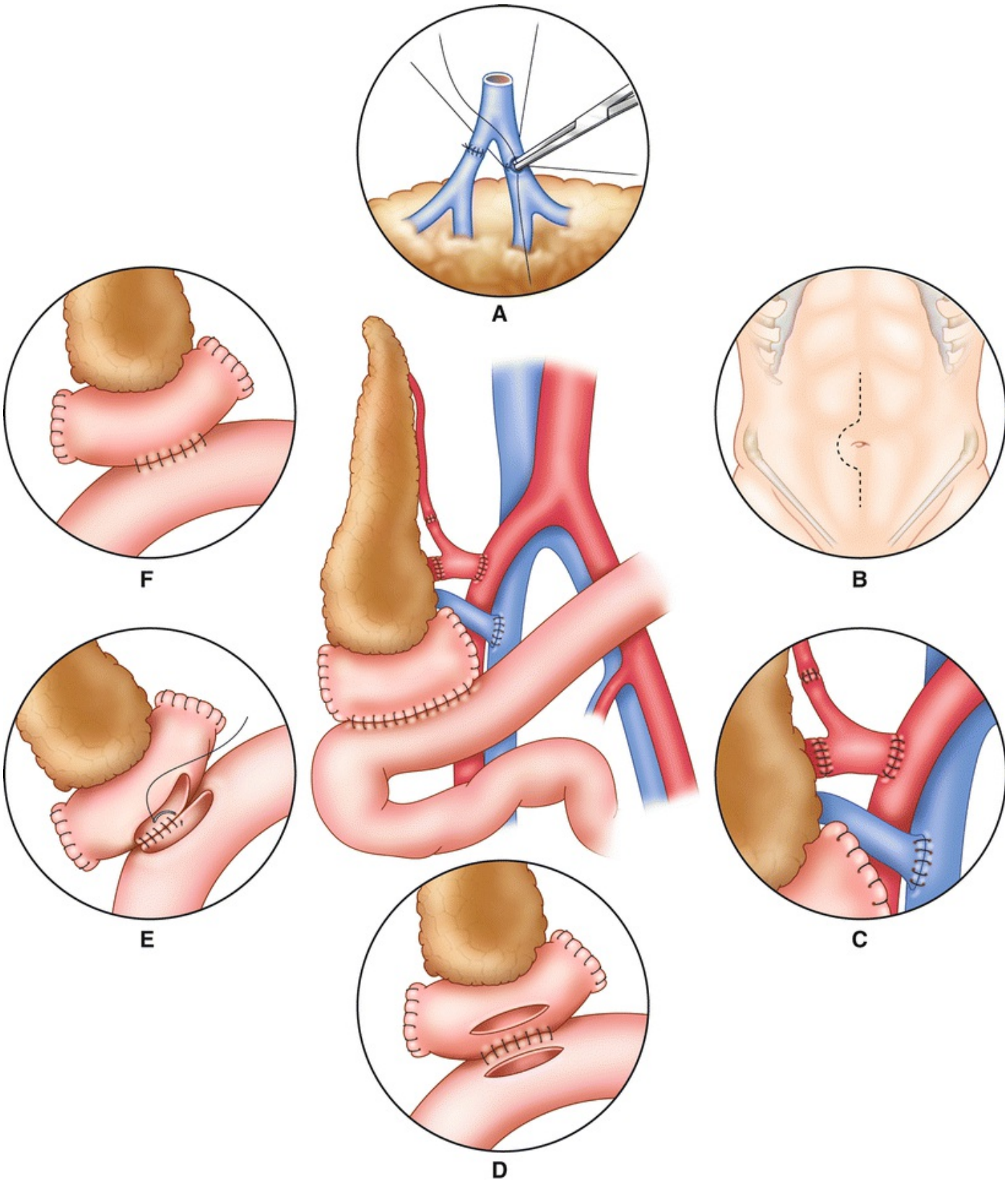

Fig. 24.2 Surgical procedure—diagram demonstrates steps in the procedure with the pancreas allograft being drained into the bladder

To ensure adequate allograft perfusion the patient must have an adequate systemic

blood pressure (120–140 mmHg) and circulating blood volume prior to removing the vascular clamps. This can usually be obtained by administering normal saline, 5 % albumin, or packed red blood cells until the central venous pressure is approximately 14 mmHg. If hypotension still occurs, an inotrope such as ephedrine or dopamine may need to be administered. Pure vasoconstrictors such as phenylephrine are usually avoided, if possible, because of the concern that they may cause vasoconstriction in the transplanted organ. Occasionally inotropic agents may have to be administered at the beginning of surgery in patients with severe cardiac disease to ensure adequate perfusion upon release of the vascular clamps. These patients may benefit from continuous cardiac output monitoring [3].

Edema may develop in the allograft following reperfusion. This may impede circulation in the transplanted pancreas and result in graft thrombosis. An adequate hemoglobin level (>10 g/dL) may help limit edema formation, and some authors recommend that only colloids or blood products be used for volume expansion. Sodium mannitol (25–50 g) administered prior to reperfusion may also help prevent edema formation and prevent graft thrombosis [3].

Postoperative Care

When surgery has been completed most patients can be extubated after reversal of neuromuscular blockade, completely recover motor function, are oxygenating adequately, and are hemodynamically stable. Occasionally patients need to remain intubated overnight if they are not oxygenating adequately due to fluid overload or a reaction to immunosuppressive agents [3]. Blood transfusion may be required in the postoperative period but only if the blood hemoglobin level decreases below 8 g/dL. This will also be helpful in patients experiencing an acute coronary syndrome. If their blood hemoglobin level is below 7 g/dL they should be transfused to improve their hemoglobin level. Setting the transfusion trigger to less than 8 g/dL also helps to decrease allograft thrombosis.

Upon arrival in the recovery room the patient's blood glucose, electrolytes, and hemoglobin concentrations are measured and appropriate treatment begun. Hypertension is quite common in the recovery room and may require treatment with B blockers and vasodilators. The dextrose and insulin infusions are maintained into the postoperative period until the patients begin to take adequate nutrition orally, usually within 10 days after surgery. The insulin infusion is maintained if the serum glucose remains above 150 mg/dL. Usually the serum glucose levels normalize rapidly following reperfusion of the allograft. Occasionally due to the hyperglycemic effects of last doses of corticosteroids or delayed graft function of the allograft, insulin infusions as well as supplemental subcutaneous insulin may be required for a prolonged period of time [3].

Analgesia in the postoperative period is provided with intravenous morphine,

fentanyl, or dilaudid. Epidural analgesia is not utilized routinely in pancreas transplant recipients because heparin is almost always administered to pancreas transplant recipients intraoperatively, and occasionally may be administered to patients postoperatively as well to prevent graft thrombosis. Anticoagulation can increase the risk of epidural hematoma. Although rare, epidural hematomas can result in paralysis even when properly treated [20]. Recently, however, a bilateral transversus abdominis plane (TAP) block has been successfully used to provide analgesia in a pancreas transplant recipient. The TAP block is a superficial, peripheral nerve block that has no risk for epidural hematoma [21].

Summary

Pancreas transplant recipients usually have severe, brittle diabetes and most of the systemic complications associated with the disease. However with careful preoperative evaluation, and intraoperative and postoperative care anesthetic management, most patients can successfully undergo pancreas alone or pancreas with or after kidney transplantation. Anesthesiologists may ensure maximal graft function by optimizing the metabolic and hemodynamic status of patients undergoing this operation.

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Part VI
Liver Transplantation

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25. Liver Transplantation: Historical Perspective

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Introduction

Liver transplantation, which began in the early 1960s, has undergone a remarkable evolution in the past five decades since it was explored by a few inspiring pioneers who dreamed and believed that the replacement of the diseased liver was exactly what was needed for patients with end-stage liver disease (ESLD). They, also, were persistent in experimental models and clinical trials, although success did not come easily.

In this chapter, the historical perspective of liver transplantation is described, with a particular emphasis on anesthesia and perioperative care based on Pittsburgh experience.

Liver Transplantation Surgery

Liver transplantation can be divided into four stages. In the *experiment stage* (1963–1981), the hypothesis of liver transplantation was developed and was carried out in

experimental animal models and limited clinical trials. Immunosuppression was based on steroid and azathioprine. In the *development stage* (1982–1988), many clinical questions were answered, and liver transplantation was accepted as a clinical therapy for patients with ESLD. Cyclosporine replaced azathioprine. The *maturation stage* (1989–2000) begins with another breakthrough with the clinical introduction of FK506 (tacrolimus) and University of Wisconsin organ preservation solution, and many transplantation centers were developed with satisfactory outcome. The *proliferation stage* (2001–present) is characterized by remarkable success in living-donor liver transplantation and introduction of various immunosuppressant adjuncts.

Experimental Stage

The concept of liver transplantation was developed in experimental animal models by transplanting the liver orthotopically by Vittorio Staudacher (1952) and heterotopically by Stuart Welch (1955) and Jack Cannon (1956) with a different short-term outcome [1–3]. This was followed by more systematic experimental animal models by Francis Moore of Peter Bent Brigham Hospital (1959), Thomas Starzl of Northwestern University of Chicago (1960), Rudolf Pichlmayr of Hannover (1967), and Roy Calne of Cambridge (1967) [4–7]. It was recognized that cross-clamping of the inferior vena cava (IVC) and portal vein during hepatectomy imposed a great deal of physiologic stress on recipient animals, and various methods were devised to avoid the low output state and excessive bleeding. Moore used external shunting; Starzl, side-to-side portacaval anastomosis in addition to an external shunt; and Calne, shunting splenic and femoral venous blood into the jugular veins.

A series of three liver transplantations in human were reported by Starzl et al. in 1963, and their early experience was tumultuous at best [8]. Unfortunately, all patients died, one intraoperatively and two within 22 days. A similar fatal outcome was experienced by Demirleau of Paris and Moore [9, 10]. It was not until 1967 when Starzl et al. reported extended survival of three patients after orthotopic liver transplantation [11]. In these patients, donor liver was preserved by balanced electrolyte solution to which low-molecular-weight dextran and heparin were added, and immunosuppression was achieved by prednisone, azathioprine, and heterologous antilymphocyte globulin (ALG). Thereafter, most of the clinical trials were carried out by Starzl and Calne, but their clinical outcome was less than satisfactory due to inadequately preserved cadaveric organs, coagulopathy including fibrinolysis and excessive activation of coagulation, and difficulty in maintaining the balance between immunosuppression and infection control [12]. Their scientific and clinical information is described in detail encompassing all areas of liver transplantation, including surgical technique, rejection and immunosuppression, hemodynamics, blood coagulation, and postoperative care [13, 14]. It is noteworthy that their observation was scientifically sound and became the base

of all future researches and development in liver transplantation.

At the same period, heterotopic liver transplantation was performed by placing the donor organ in the paravertebral gutter without removing the diseased liver. Vascular anastomosis was made utilizing adjacent vessels without portal venous inflow. It was noted that the transplanted liver gradually atrophied possibly from the lack of hepatotropic portal venous flow.

Developmental Stage

This stage began in 1982 when Starzl moved to the University of Pittsburgh, and clinical trial of cyclosporine began by Starzl and Calne. The initial clinical experience in the Pittsburgh program in 1982 was nothing but smooth. This difficulty can be traced to the complex surgical technique and a steep learning curve experienced by the medical center. By the end of 1982, 8 out of 49 patients died intraoperatively due to bleeding in seven and pulmonary embolism in one [15]. A similar difficulty was experienced in the Cambridge program with a 1-year survival of 28 %: 13 % developed major bleeding, and four patients suffered cardiac arrest. Development of the venovenous bypass was an important evolution [16], and cyclosporine improved immunosuppression with lesser infection. A team of dedicated liver transplantation anesthesiologists and intensivists was able to develop a scientific approach. Liver transplantation, finally, became manageable and was adopted as a viable medical therapy for patients with ESLD [17]. Subsequently, liver transplantation centers began to spring all over the world.

Maturation Stage

The next phase of evolution was seen in the following 10 years (1989–2000). The piggyback technique (caval-sparing technique) was reintroduced to achieve hepatectomy with preservation of the IVC and is the most widely used technique today [18]. This technique maintains venous return even without venovenous bypass, and surgical hemostasis is easier due to less raw surface in the hepatic bed.

FK506 (tacrolimus) was introduced to the clinical arena in 1989, and it was shown to be effective in treating rejection refractory to the cyclosporine/prednisolone regimen [19]. Follow-up clinical trials demonstrated that FK506 was superior to cyclosporine with less nephrotoxicity, and it has been the main immunosuppressant up to today.

In the donor organ preservation area, Dr. Belzer of University of Wisconsin developed the University of Wisconsin solution extending the safe cold ischemic preservation period of up to 24 h, a breakthrough compared with 6–8 h with the Euro-Collins solution [20]. Its composition mimics that of intracellular fluid containing potassium lactobionate, KH_2PO_4, $MgSO_4$, raffinose, adenosine, glutathione, allopurinol, and hydroxyethyl starch. University of Wisconsin solution improved the quality of the donor liver and allowed the liver transplantation not a “true emergency” procedure.

Living-related donor liver transplantation was performed in pediatric patients by Broelsh and Strong [21, 22]. The successful living-donor liver transplantation led to an exponential growth in the number of this procedure in years to come both in adults and children, particularly in Asian countries with scarce cadaveric organ donors.

Cluster transplantation or abdominal exenteration with liver transplantation was performed by Starzl (1989) to treat primary malignant tumors of the biliary tract, duodenum, or stomach with secondary involvement of the liver. In this procedure most or all of the stomach, liver, pancreas, spleen, duodenum, proximal jejunum, terminal ileum, and ascending and transverse colon were removed and replaced en bloc [23]. Although this procedure was helpful in only small number of selected patients, this was an appropriate stepping stone in treating malignancies. Of course, this was another challenge for anesthesiologists, because a large quantity of fluids was required due to greater blood loss, third-space fluid loss, and lymphatic fluid loss.

Small bowel transplantation was performed in 1988 in a child with a short gut syndrome and hyperalimentation-induced liver damage [24]. Although the child died of lymphoproliferative disease and sepsis, small bowel transplantation became a viable option for patients with end-stage small bowel disease.

In 1989, Starzl et al. described that liver transplantation was an unfinished product, because hepatitis B and hepatocellular carcinoma were known to recur [25]. Xenograft transplantation was a natural progression, since the baboon's liver may be resistant to hepatitis B virus, and it may alleviate donor organ shortage. The first orthotopic xenotransplantation was performed in 1993 in a patient with hepatitis B and HIV infection using a baboon as a living donor (Fig. 25.1) [26]. Surgical technique was very similar to that of human organ transplantation. Postoperative course was promising: He was awake several hours after surgery and able to eat and walk within 5 days. The liver grew rapidly (from 600 to 1555 g in 24 days), and blood chemistry was essentially normal except hypoalbuminemia. Unfortunately, he died 70 days after transplantation secondary to biliary stasis, infection from aspergillus and candida, antibiotics-induced renal failure, and subarachnoid hemorrhage. After one more unsuccessful xenograft liver transplantation, it was concluded that metabolic incompatibility, complement activation, and rejection were the obstacles in xenotransplantation that can be overcome in near future. They also suggested that transgenic xenotransplantation may be a better alternative.

Fig. 25.1 The first baboon-to-human liver xenotransplantation recipient painted by Sir Roy Calne (with the generous permission of Sir Roy Calne)

Proliferation Stage

In the following 16 years, liver transplantation became a manageable procedure in most major medical centers. Hepatectomy is performed using venovenous bypass, piggyback technique, or simple cross-clamping technique depending on surgeon's preference and anatomy of the patient. Organ allocation practice became more objective by utilizing medical ESLD score (MELD) and pediatric ESLD score (PELD), developed by Wiesner et al. in 2001 [27]. This scoring system, derived from serum creatinine level, international normalization ratio of prothrombin time, and serum bilirubin, predicts the probability of death in patients with ESLD, and has been accepted as an organ allocation guide by the United Network of Organ Sharing (UNOS). The number of

living-donor liver transplantation and small bowel transplantation increased dramatically during this period. Rejection is more controllable with the introduction of newer immunosuppressants (basiliximab, sirolimus, and mycophenolate mofetil) as an induction agent or adjunct to cyclosporine or tacrolimus.

Anesthesiology and Perioperative Care

Experimental Stage

Dr. Jorge Antonio Aldrete was the first anesthesiologist involved in the care of most, if not all, patients at the University of Colorado (Fig. 25.2). He was praised by Starzl as a premier anesthesiologist who "could keep stones alive" and "one of few anesthesiologists who had the skills or determination to handle these difficult cases." His contribution to liver transplantation was extraordinary, although understanding of physiologic care was limited at that time: arterial blood gas analysis was not readily available, and pulmonary artery catheterization was introduced in the 1970s. Aldrete et al. described their clinical experience in liver transplantation in detail [28, 29]. Awake intubation or "crash" induction was used in patients with full stomach, and thiopental and succinylcholine were used in patients with presumably empty stomach. Fluoroxene and nitrous oxide were maintenance agents, and non-depolarizing agents (d-tubo curare or pancuronium) were used for muscle relaxation. Intraoperative monitoring consists of blood pressure, heart rate, central venous pressure, and body temperature. They observed arterial hypotension in practically all patients. Massive blood transfusion was required by many patients (50–350 ml/kg), and blood was replaced based on blood pressure, central venous pressure, and hematocrit values. They noted potential myocardial depression and acidosis associated with transfusion-induced citrate intoxication, metabolic acidosis after hepatectomy, reperfusion hypotension, hypothermia, and altered electrolyte and acid-base balance. They published several more important articles investigating dynamics of body temperature, lidocaine clearance, serum electrolytes, and choline esterase [30–33].

Fig. 25.2 Photos with Dr. Jorge Antonio Aldrete in 1999 at the fifth International Transplantation Society Congress (Pittsburgh, PA). From the *left*, Andre De wolf (Northwestern University), Jorge Antonio Aldrete, William Merritt (John Hopkins University), and Yoogoo Kang (University of Pittsburgh)

On one weekend, Aldrete and Andres Zahler Mayanz, another anesthesiologist, climbed to a mountain to study high-altitude respiratory physiology. On way back home, Mayanz was involved in fatal car accident and became the first physician organ donor in 1968. After his contribution to liver transplantation, Aldrete developed postanesthesia recovery score [34] and is enjoying his pain management practice in Florida.

At the same period, Pappas et al. published their investigation on hemodynamic alterations during liver transplantation in six patients using dye dilution technique to measure cardiac output [35]. They observed a reduction in cardiac index (by 39 %), stroke volume index, and mean arterial pressure (by 18 %), and a rise in peripheral vascular resistance (by 71 %) during the anhepatic stage.

John Farman and Michael Lindop led the liver transplantation anesthesia and intensive care unit at Cambridge, and published their experience of 25 liver transplantations in 1974 [36]. In their report, main anesthetics were nitrous oxide, narcotics, and muscle relaxants. Monitoring consists of ECG, arterial pressure, central venous pressure, and analysis of arterial blood gas and electrolytes. They also observed severe hypotension during the anhepatic stage and on reperfusion of the grafted liver, and reperfusion hyperkalemia. They encountered a significant mortality: two intraoperative deaths (one by excessive bleeding, and another one possibly by air embolism), one by cardiac arrest, one by septic shock, and three by irreversible

hemorrhage. Dr. Dagmar Schaps led the anesthesia group in the Hannover program and published her experience in liver transplantation in 1978 [37].

During this period, clinical hemostatic defects were intensively investigated. Von Kaulla, a German hematologist, investigated coagulation using coagulation profiles and thromboelastography (TEG) [38]. They observed a profound defect in coagulation. In a 3-year-old child, uncontrollable bleeding was followed by severe fibrinolysis, which was reversed by the administration of ε-aminocaproic acid (EACA , 0.1 g/kg). In the second patient, severe fibrinolysis was reversed by EACA. Postoperatively, however, he became thrombophilic and died of multiple arterial thrombosis and pulmonary emboli. In the third patient, fibrinolysis was treated by EACA. Two hours later, he became hypercoagulable, and died of pulmonary embolism in 2 days after surgery. In the fourth patient, fibrinolysis was normalized spontaneously, but he died of pulmonary embolism in the sixth postoperative day. The coagulation defect was not remarkable in the fifth patient, but she died of liver necrosis in the postoperative 23rd day. They suggested that pathologic fibrinolysis was a common occurrence, and it might be caused by anoxia which activated the plasmin-plasminogen system. Additionally, they suggested that the provision of a well-functioning homograft for the anhepatic recipients led to a very rapid correction of the clotting defects. Groth et al. made a similar observation in 1969 [39]. They suggested that moderate bleeding should not be regarded with alarm nor treated pharmacologically since spontaneous improvement can be expected. Further, avoidance of pharmacologic manipulation of hemostasis and omission of an external venous bypass might be helpful in preventing postoperative thromboembolism.

Development Stage

During this period, anesthesia and perioperative care were developed in several centers, namely University of Pittsburgh, Cambridge and King's College of London, University of Minnesota, University of Hannover, and Hospital Cochin of Paris.

At the University of Pittsburgh, the beginning of the liver transplantation program was extremely challenging: Anesthesia care of patients for liver transplantation was relatively unknown at that time, and patients were cared for by the anesthesiologist on call, which diluted the clinical experience of liver transplantation. At the same time, infrastructure of the medical center required a learning period to adapt to the new surgical procedure. Specifically, the need for massive blood transfusion was a major challenge: It was technically difficult, and management of its complications was a daunting task.

In the beginning of 1983, anesthesiologists of the University of Pittsburgh developed a liver transplantation anesthesiology group, and their objective was to develop a patient care guideline through clinical research. John Sassano, a cardiac

anesthesiologist, developed a rapid infusion system with a specific goal of delivering up to 1.5 L of fluid per minute in a controlled fashion while maintaining normothermia (Fig. 25.3) [40]. His ingenious invention utilized readily available various parts. A cardiotomy reservoir (3 L) was attached to a roller pump of a cardiac bypass machine to deliver premixed blood in a rapid rate. A heat exchanger was incorporated to minimize hypothermia associated with massive transfusion. An air bubble detector from a hemodialysis machine was added to avoid accidental air delivery, and all disposable items were assembled at the hospital. This rapid infusion system helped most patients to avoid hypovolemia during liver transplantation as well as patients undergoing cardiac procedures and trauma surgery. The commercial version (Rapid Infusion System® by Haemonetics®, Braintree, MA) was adopted by many liver transplantation centers up to year 2000, and a smaller, improved version is being marketed as a Fluid Management System® (Belmont®, Watertown, MA) [41].

Fig. 25.3 A rapid infusion system designed by Dr. John J Sassano

Douglas Martin, an intensivist and cardiac anesthesiologist, led the research in hemodynamics and electrolyte balance using the pulmonary artery catheter and mixed venous oximetry [42]. They confirmed that the high cardiac output state was associated with low oxygen content secondary to anemia and a moderate decrease in arterial hemoglobin oxygen saturation. Oxygen delivery and oxygen consumption were relatively normal, but arterial-venous oxygen content difference (A-V DO_2) was relatively low, suggesting that patients with ESLD may not be able to utilize oxygen, possibly by the loss of regional vasomotor control resulting in a maldistribution of peripheral flow. They postulated that two anatomically and probably pharmacologically distinct peripheral vascular circuits may exist in parallel; vessels with normal vasoreactivity supplying oxygen to tissues and vessels with a reduced vasoreactivity

behaving as an arteriovenous shunt. They suggested that alpha agonist may increase systemic blood pressure, but may increase shunting by constricting normal nutrient vessels. Further, their studies in electrolyte and fluid balance were foundation of modern anesthesia care [43].

Citrate intoxication had been a well-recognized complication of massive transfusion in the absence of hepatic function. Jose Maquez took charge in the investigation of dynamic changes in ionized calcium level during liver transplantation [44]. The study revealed that ionized hypocalcemia develops in the early stage of liver transplantation, and ionized calcium level and serum citrate level are inversely related during the anhepatic stage. In addition, Dr. Marquez was able to demonstrate the relationship between ionized hypocalcemia and myocardial dysfunction.

Management of blood coagulation was another challenge for the new program. It was evident that patients with ESLD have bleeding tendency secondary to thrombocytopenia, generalized reduction in procoagulants, and activation of the fibrinolytic system. There were two dilemmas in coagulation management: Coagulation profile does not necessarily reflect blood coagulability in the surgical field, and replacement and pharmacologic therapy were guided by clinical impression rather than scientific facts. Yoogoo Kang, who had been in TEG research in obstetrics, reintroduced this technique in liver transplantation [45]. All patients undergoing liver transplantation were monitored by TEG and comprehensive coagulation factor assays. It should be noted that Jessica Lewis (Director, Coagulation Laboratory, University of Pittsburgh) and Franklin Bontempo (coagulation specialist, University of Pittsburgh) were very knowledgeable in TEG and eager supporters of the project. Patients were treated based on TEG findings and coagulation profiles, when available. The study in more than 80 patients demonstrated that all forms of coagulopathy develop during liver transplantation, and they are dilution, excessive activation, fibrinolysis, and heparin effect. Further, blood loss in patients with TEG monitoring was reduced by 50 % compared with that of historic controls [46], although this improvement could have been equally contributed by the use of venovenous bypass and improved anesthesia care.

Management of fibrinolysis was the next focus during this period. Kang et al. observed that severe fibrinolysis was a common occurrence, and it was readily treatable by EACA in vitro. However, EACA was not used clinically to avoid potential thrombotic complications reported by von Kaulla et al. In the first patient who received EACA, severe fibrinolysis, demonstrated on TEG, was treated easily by a small dose of EACA (1 g, IV bolus). Interestingly, the surgeon noticed that oozing stopped approximately 30 min after EACA administration. In their follow-up study, small doses of EACA (<1 g, IV) were found to be effective in treating fibrinolysis documented by a serial TEGs without thrombotic complications [47]. The mechanism of fibrinolysis was studied at the same period. Robert Porte, a medical student from the Dijkzigt university of Rotterdam, measured the level of tissue plasminogen activator (TPA) to investigate

its relationship with fibrinolysis [48], and Mohamed Virji, a clinical chemist, measured the level of TPA and plasminogen activator inhibitor (PAI) to determine their role in fibrinolysis [49]. These two independent studies revealed that severe fibrinolysis is caused by an explosive increase in TPA, which overwhelms PAI on reperfusion of the grafted liver. This is followed by a gradual decrease in TPA and detectable levels of PAI as the grafted liver begins to function.

Several other drugs were tried to improve clot formation or to prevent fibrinolysis during this period. Boylan et al. demonstrated that high-dose tranexamic acid reduced blood loss and transfusion requirement by inhibiting fibrinolysis [50]. Aprotinin was introduced to liver transplantation arena by Neuhaus et al. and Mallett et al. [51, 52]. They reported that high-dose aprotinin reduced the blood loss by more than 50 % while surgical field was dry. It is noteworthy that Carl Groth suggested that aprotinin may be beneficial in treating fibrinolysis in liver transplantation in 1965. Thereafter, many European centers used aprotinin and reported improved coagulation and reduced blood transfusion requirement, although the beneficial effects of aprotinin were not clearly seen in follow-up studies. In the USA, Kang et al. showed that aprotinin inhibits coagulation by inhibiting serine esterase, and its antifibrinolytic activity is weaker than that of the equivalent dose of EACA [53]. They suggested that EACA is more specific toward plasmin and plasminogen, and more economical with less side effects compared with those of aprotinin. Aprotinin was used only in a limited number of liver transplantation centers in the USA. With the combined efforts of clinicians and scientists, blood transfusion requirement decreased from more than 50 units of red blood cells to less than 10 units in a span of 15 years (Fig. 25.4).

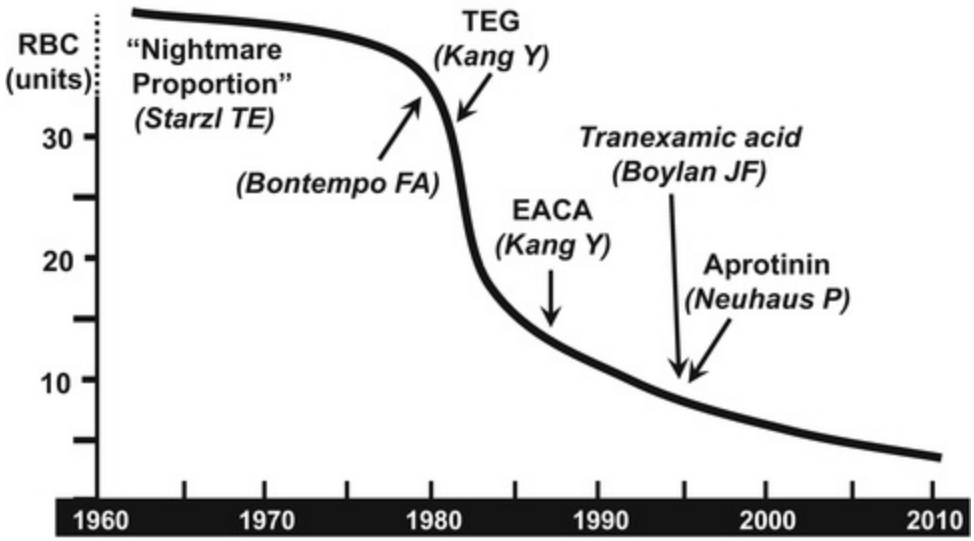

Fig. 25.4 Blood transfusion requirement in 50 years

Clinical application of venovenous bypass played a major role in minimizing surgical complications. Some forms of bypass or shunting techniques had been used in

the 1960s, but results were disappointing owing to the need for systemic heparinization or thrombosis at the cannula site. Starzl and Byer Shaw, with the support of cardiac surgeons (Bart Griffith and Robert Hardesty), developed venovenous bypass utilizing heparinized Gott shunt tubings and Biomedicus centrifugal pump® (Medtronics®, Minneapolis, MN) without systemic heparinization [16]. This technique decompresses the portal vein and IVC by shunting the blood to the left axillary vein to minimize visceral and renal congestion. Consequently, bleeding aggravated by portal hypertension was reduced, and the anhepatic stage became more physiologic by minimizing hypovolemia.

Hypoglycemia expected to occur in patients with severe hepatocellular disease, particularly during the anhepatic stage. However, it was not a clinical concern owing to transfusion of blood products containing dextrose solution. On the contrary, hyperglycemia was a clinical concern after reperfusion of the grafted liver. De Wolf et al. compared blood glucose level of hepatic venous blood and systemic arterial blood in dogs and concluded that reperfusion hyperglycemia was caused by the release of glucose from the hypothermically preserved donor liver via glycogenolysis [54]. Altered glucose metabolism was further investigated by Mallett et al. They observed that persistent hyperglycemia after reperfusion was caused by impaired hepatic reuptake of glucose, and is an indication of the poorly functioning graft liver [55]. Their observation continued with an investigation on hormonal control of glucose metabolism [56].

A similar progress was made in pediatric liver transplantation at the Children's Hospital of University of Pittsburgh led by David Ryan Cook and Lawrence Borland. Their report on the clinical experience of 50 children who underwent 68 liver transplantations has been considered the standard of care of pediatric patients for many years to come [57]. During this period, Goran Klintmalm of Dallas described the role of anesthesiologists in liver transplantation. "The anesthesiologist with specialized training is as important as transplant surgeon. He/she manipulates and corrects the various homeostatic mechanisms of the recipient: blood replacement, correction of coagulation defects and fluid and electrolyte imbalances, monitoring of gas exchange, and preservation of the hemodynamic stability" [58].

Postoperative care of liver transplantation recipients at the intensive care unit underwent a major evolution. The surgical intensive care unit of the Medical Center was primitive by the current standard. Sharing a relatively small intensive care unit by all types of critically ill surgical patients posed a potential for cross-infection, and knowledge base and experience of intensivists were mostly limited to general or cardiac intensive care. Ake Grenvik, an intensivist with surgical background from Sweden, modernized the facility, developed liver intensive care unit, and established the standard for postoperative care [59].

The Central Blood Bank of Pittsburgh, which supplied blood products to 32

regional hospitals, had to make a major adjustment in terms of the need for additional man power, resources and equipment, and development of communication channel not to disrupt blood supply to liver transplantation patients. They were very successful in meeting all challenges, and no patient suffered from hypovolemia and anemia [60]. Another major issue was donor organ procurement and preservation. Mr. Donald Denny, who was the director of procurement agency in Pittsburgh, played a major role in developing the standard for organ procurement [61].

About this time, liver transplantation programs were developed in many parts of the world, and it was necessary to develop a forum of all physicians and scientists involved in liver transplantation. In 1984, anesthesiologists of the University of Pittsburgh hosted the First Symposium on Anesthesia and Perioperative Care in Liver Transplantation. Its specific goal was to present clinical experience and research results of the Pittsburgh program to help others to jump-start their programs. Dr. Starzl began his lecture on "Liver Transplantation" with the following message. "I thought from time to time how really appropriate it was for anesthesiologists to be responsible for the organization of this Symposium. The anesthesiologists are the unsung heroes in the development of liver transplantation. There comes a moment in the life of these patients in which there is a throw of the dice, and their lives fall into the hands of the anesthesiologist. The way in which this group of modern day heroes has responded has really been remarkable. I don't think we can see that illustrated any better than over at the University of Pittsburgh where this year more than 500 liver transplantation surgeries are going to be carried out, a truly staggering total, which I would have thought was the fantasy that cannot be achieved until a few years ago." The symposium was very successful. More than 150 physicians participated in the symposium, and they included anesthesiologists, intensivists, surgeons, hepatologists, blood bankers, coagulation specialists, immunologists, infectious disease specialists, to name a few. The symposium was a media in which multidisciplinary leaders in liver transplantation met face to face to hear experiences and research activities of others. In the anesthesiology field, they were Jorge Estrin and Kruma Belani of University of Minnesota, Steven Rettke and David Plevak of Mayo Clinic, Simon Gelman of University of Alabama, James Chapin of University of Nebraska, William Merritt of Johns Hopkins, Lennard Eleborg of Stockholm, Denise Potter of Kings College of London, and Geroge Khoury of UCLA, to name a few. The proceedings of the symposium were published as a monograph, "Hepatic Transplantation: Anesthetic and Perioperative Management," and it has been the major textbook for the following 30 years. The second symposium held in 1986 evolved into a scientific symposium with presentation of the state-of-the-art clinical and scientific information, together with presentation of research abstracts from all liver transplantation centers. The proceedings were published in Transplantation Proceedings [1987 Aug;19(4 Suppl 3)] with a generous support of Felix Rappaport who was the Editor of the journal. In 1987, Yoogoo Kang and John Farman communicated and agreed

that it was the time to develop an international society related with liver transplantation (Fig. 25.5). The Symposium transformed to the International Society of Perioperative Care in Liver Transplantation, and John Farman developed the Liver Intensive Care Group of Europe. Unfortunately, John Farman passed away shortly after the letter without seeing the one international society. The LICAGE has flourished under the leadership of Michael Lindop, Gilbert Park, and John Klinck.

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7.9.87.

Dear Yoo Goo,

Mike Smith is off to Pittsburgh and has kindly agreed to take a letter with him.

What is the news of the International Liver Transplant Society? We shall be forming a European group, which would be a major contributor.

Our book is still in press, but as soon as it comes out, I will send you a copy. Remember our bargain?

With all good wishes to all of you,

Yours sincerely,

John Farman

Fig. 25.5 A letter from John Farman to Yoogoo Kang in 1987 regarding the formation of the International Liver Transplantation Society

At the first International Society of Perioperative Care in Liver Transplantation held in Pittsburgh, the society transformed again into the International Liver Transplantation Society. The goal of the new multidisciplinary society was to raise the standard of care for patients requiring liver transplantation and to promote education and research by disseminating and exchanging information related to liver transplantation within the medical community, as well as to the public. Many physicians who shared the noble objectives became founding members of the Society: Yoogoo Kang (President, anesthesiology), Russell Wiesner (Vice President, hepatology), William Merritt (Treasurer/Secretary, anesthesiology), and Andre De Wolf (Newsletter, anesthesiology). Founding council members were Jorge Estrin from anesthesiology, Ake Grenvik and David Plevak from critical care medicine, David Van Thiel and Michael Sorrell from hepatology, and William Wall, John Fung, and Robert Gordon from surgery. In 1995, The Society and American Association of Studies in Liver Disease jointly published "Liver Transplantation and Surgery" and Byer Shaw, Michael Sorrell, and Russell Wiesner were instrumental in launching this major joint project. The journal was renamed to "Liver Transplantation" in 2000. The Society has grown leaps and bounds and has been a focal point of liver transplantation. Fortunately, the Society has kept its original goals for the past 25 years.

Maturation Stage

During this period, clinical research continued. In the cardiovascular system, severe reperfusion hypotension leading to cardiac arrest was a major concern. Shushma Aggarwal investigated the hemodynamic changes that occur on reperfusion of the grafted liver, by measuring cardiac output using the dye dilution technique to avoid errors associated with the acute change in blood temperature on reperfusion [62]. They defined the postreperfusion syndrome (PRS) as acute hypotension (<70 % of the baseline value) lasting longer than 1 min within 5 min after reperfusion. They observed that approximately 30 % of patients developed the PRS. Patients with the PRS had lower blood pressure by the study design, more pronounced bradycardia, and lower systemic vascular resistance. Cardiac output was not different between the two groups of patients with and without the PRS, and hyperkalemia, acidosis, and hypothermia were not contributing factors for the PRS. The investigation continued to identify the role of prostaglandin on the PRS by measuring its metabolite (6-keto PGF1 alpha) and thromboxane. The level of 6-keto PGF1 alpha and its relationship with thromboxane were variable in patients with and without the PRS, suggesting that the cause of the PRS is multifactorial and elusive [63].

In 1989, Ellis et al. reported that the PRS could be caused by right-heart dysfunction based on their observation of pulmonary embolism on transesophageal echocardiography [64]. This finding suggested that the PRS could be caused by mechanical derangement in addition to chemical and physical alterations. Right ventricular function on reperfusion of the grafted liver was investigated by De Wolf et al. by determination of right ventricular ejection fraction [65]. Their results indicated that right ventricular function was relatively well preserved in uncomplicated orthotopic liver transplantation.

In the 1990s, medically challenging patients who had been ruled out of transplantation candidacy were considered candidates for liver transplantation, and they were portopulmonary hypertension and hepatopulmonary syndrome. Hughes et al. reported that vasodilator therapy in patients with portopulmonary hypertension was ineffective or unpredictable, and suggested combined heart-lung transplantation for its treatment [66]. This was followed by a successful combined liver-heart-lung transplantation by the Cambridge group in 1987 [67]. In liver transplantation arena, Prager et al. reported a patient whose pulmonary hypertension persisted after liver transplantation [68], and De Wolf et al. reported 80 % mortality, although pulmonary hypertension was normalized in one survivor [69]. They suggested that patients with normal right ventricular function may survive as long as they do not suffer from other medical or surgical complications. Nitric oxide, the most promising drug at that time, was found not to be effective in lowering pulmonary arterial pressure [70, 71]. There had been several sporadic reports on portopulmonary hypertension, but it was not until Susan Mandell of Colorado and Michael Krowka of Mayo Clinic developed a national database to include a large number of patients for a comprehensive investigation [72]. Subsequent studies demonstrated that chronic pulmonary vasodilator therapy before liver transplantation is beneficial to increase survival and improve the course of the disease [73], and many centers developed their own guideline based on published reports [74].

For the hepatopulmonary syndrome , Eriksson et al. reported that six patients with hypoxemia and large shunting improved oxygenation after liver transplantation in 1990 [75]. Scott et al. made a similar observation demonstrating that severe hypoxemia caused by the hepatopulmonary syndrome can be reversed by liver transplantation, although their postoperative course can be prolonged and complicated until the ventilation and perfusion mismatch improves gradually [76]. Hepatopulmonary syndrome was further clarified by Krowka [77], and clinical management of the hepatopulmonary syndrome is promising [78].

Fulminant hepatic failure has been a clinical concern due to difficulties in predicting outcome and in managing cerebral pathology. Keays et al. described their experience in seven patients with fulminant hepatic failure and suggested the clinical importance of intracranial pressure in their outcome [79]. In the early 1990s, Aggarwal et al.

investigated cerebral hemodynamics and metabolism by measurement of cerebral blood flow, intracranial pressure, cerebral oxygen consumption, and cerebral blood flow velocity by transcranial Doppler [80, 81]. They observed depressed cerebral metabolism without evidence of cerebral ischemia, while more than half of patients developed cerebral hyperemia. Hyperemia, per se, did not correlate with outcome, but patients with intractable intracranial hypertension did not survive. This observation strongly suggested the importance of the ICP monitoring in patients with fulminant hepatic failure. Their follow-up study on noninvasive monitoring of cerebral perfusion elucidated that the transcranial Doppler can be a useful adjunct in qualitative assessment of cerebral blood flow and ICP [82]. These observations and suggestions have been the cornerstone of management of fulminant hepatic failure patients and adopted by many liver transplantation centers.

Renal failure or insufficiency is a common occurrence in liver transplantation from the pre-existing hepatorenal syndrome, postoperative renal ischemia, or nephrotoxicity of immunosuppressants [83], and postoperative renal dysfunction is known to be associated with increased morbidity and mortality [84]. In an attempt to minimize renal insult, Planinsic et al. investigated the role of a triple-drug therapy in renal protection in a double-blind study: Dopamine improves renal perfusion, furosemide may reduce renal oxygen consumption, and mannitol is expected to scavenge free radicals and reduce endothelial swelling [85]. In their double-blind study, postoperative renal function determined by urine output and creatinine level and the need for hemodialysis were essentially similar to the control group patients, suggesting that prophylactic renal protection therapy may not be effective in the liver transplantation setting.

Proliferation Stage

In the last 15 years, liver transplantation has become a well-established procedure and been performed in most major medical centers with a 1-year survival of close to 90 %. Living-donor liver transplantation flourished in Asian countries, and it evolved from the use of the left lobe, right lobe and to dual grafts for a single recipient [86–90].

Surgical technique became simpler by using cava-sparing technique (piggyback technique) and possibly by well-trained surgeons. Blood transfusion requirement has been reduced to less than 5–10 units of red blood cells in most centers, and pharmacologic coagulation therapy is not commonly used as severe coagulopathy does not appear to be a common occurrence. The incidence of the PRS appears to be less frequent [91–93]. High-risk group patients are being accepted into the candidacy pool after favorable experiences through evidence-based cardiac evaluation and outcome studies [94, 95]. Transesophageal echocardiography was introduced to the intraoperative care for preload management and detection of cardiac wall motion abnormality, thromboembolism, and other cardiac pathology. Anesthesiologists are

better trained and prepared to tackle a variety of clinical challenges. Postoperative care has improved as more medical centers are equipped with dedicated liver intensive care units and liver intensivists. Renal replacement therapy is instituted in the early stage to prevent renal failure. Immunosuppression and infection control also have played the significant role in the smooth postoperative course and survival.

Conclusion

Liver transplantation has undergone a revolutionary metamorphosis in the past 50 years from an experimental procedure in animal models to xenotransplantation, living-donor liver transplantation, and possibly transgenic transplantation. This progression was made possible by our pioneers who laid a solid scientific foundation, and we are fortunate enough to confirm their observations and take small steps forward. It is humbling that we have had many courageous patients who were very important partners in this journey. Of course, modern liver transplantation could not have been developed without many physicians, scientists, and health care workers who did not mind many sleepless nights.

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26. Preoperative Liver Recipient Evaluation and Preparation

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Introduction

Liver transplantation (LT) is an established mode of treatment for patients with end-stage liver disease (ESLD) and acute liver failure (ALF). Initial challenges in LT included perfection in surgical techniques, organ procurement, and management of immunosuppression post LT. Currently one of the biggest challenges is shortage of donor organs creating a wait list of patients with unique complications of ESLD. These patients need meticulous care which results in significant burden on the health care system. The goal of this chapter is to:

1. Describe indications and contraindications for LT.

2. Discuss medical management of patients on the LT waitlist.

3. Outline the pre liver transplant evaluation process.

Indications for Liver Transplantation

When should medical providers refer patients for LT? The following issues need special consideration when evaluating a patient for LT.

1. *Severity and prognosis of the underlying liver disease.*

2. *Assessment of medical, surgical, and psychosocial issues that may preclude LT.*

3. *Patient and family's wishes and concerns regarding LT.*

It is important to bear in mind that the rate of progression from compensated to decompensated cirrhosis occurs at a rate of 5–8 % per year (Fig. 26.1). Also the cumulative risk of specific complications from ESLD increases with time (Fig. 26.2). Given the overall decreased survival following onset of decompensated cirrhosis a timely referral for LT is clearly warranted. This allows the patient and family access to various multi-disciplinary specialty teams who are well-equipped in helping to navigate the road to a successful outcome following LT.

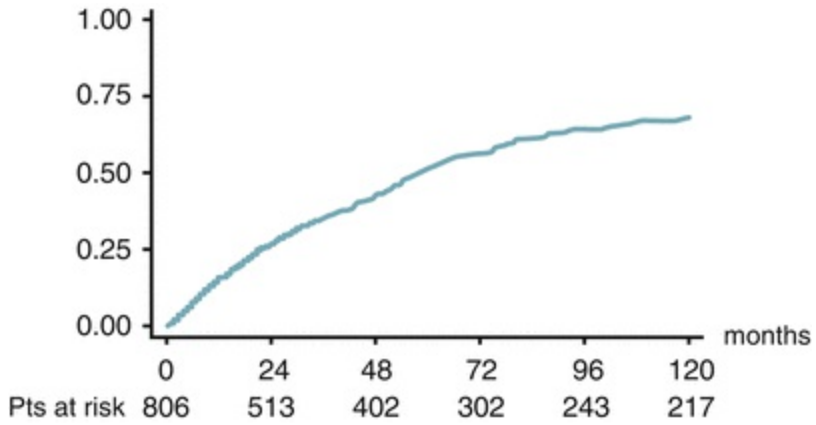


Fig. 26.1 Cumulative proportion of patients transitioning from a compensated to a decompensated stage. Data from D'Amico et al. [83]

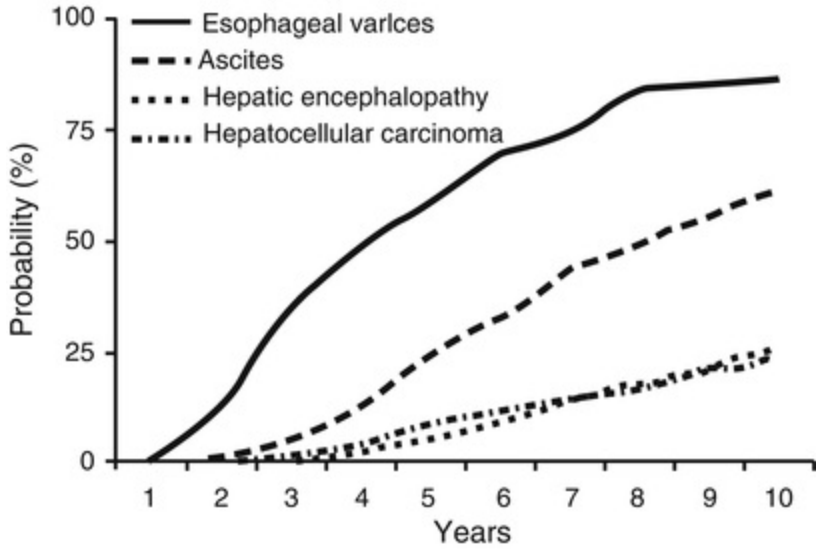


Fig. 26.2 Cumulative risk of complications from cirrhosis over time. Data from Gentilini et al. [84]

Some clinical scenarios in patients with ESLD which should prompt the clinician to initiate the transplant evaluation process include:

1. Development of portal hypertension including bleeding secondary to gastroesophageal varices

2. Development of new ascites or complications related to ascites: refractory ascites (need for large volume paracentesis despite optimal diuretic therapy), spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS)

3. Onset of hepatic encephalopathy (HE).

4. Diagnosis of hepatocellular carcinoma (HCC)

5. Hepatic hydrothorax

6. Other pulmonary complications including portopulmonary hypertension (PPH) and hepatopulmonary syndrome (HPS)

7. Worsening hepatic synthetic function as manifested by low serum albumin and coagulopathy.

One of the objective ways to assess progression of liver disease is calculation of the Child-Turcotte-Pugh [CTP] score [1, 2]. It was originally designed to predict

mortality following surgery and later became a useful parameter to determine severity and prognosis of liver disease. The CTP score was also used to determine candidacy for liver transplantation (score greater than 7) until it was replaced by the Model for End-Stage Liver Disease [MELD] score .

The MELD score is calculated using the serum bilirubin, INR and creatinine level, and was originally developed to predict 30 day mortality in patients with cirrhosis who underwent a procedure such as the transjugular intrahepatic portosystemic shunt [TIPS] [3]. As of 2002 the MELD score is used to prioritize organ allocation for LT.

Common etiologies of liver failure requiring LT may be categorized into acute versus chronic as presented in Table 26.1. Following is a brief description of individual etiologies of LT.

Table 26.1 Common etiologies of liver failure which may require liver transplantation

Acute/fulminant liver failure	
Viral etiologies	Hepatitis A, B, C, HSV, EBV, CMV
Drugs and toxins	Acetaminophen, Mushroom poisoning
Autoimmune Hepatitis	–
Vascular disorders	Budd-Chiari syndrome, Sinusoidal Obstruction Syndrome
Fatty infiltration	Pregnancy related, Rye's syndrome
Inherited disorders	Wilson disease
Chronic liver disease	
Viral etiologies	HBV, HCV
Alcohol induced	–
Hepatocellular carcinoma	Less common liver cancers include hepatoblastoma and fibrolamellar variant of HCC
Cholestatic abnormalities	Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis, separate the pediatric etiologies; this may come in the last section of this table Biliary atresia, Alagille syndrome, Cystic Fibrosis
Autoimmune hepatitis-induced liver cirrhosis	–
Inherited disorders leading to liver cirrhosis	Hemochromatosis, Wilson Disease, Alpha-1-Antitrypsin Deficiency
Vascular disorders	Budd-Chiari syndrome
Metabolic/miscellaneous conditions	Nonalcoholic steatohepatitis (NASH should be separate), cryptogenic cirrhosis, following this should be put in one bucket: amyloidosis, sarcoidosis, hyperoxaluria, urea cycle defects, polycystic liver disease, glycogen storage disease

Acute Liver Failure

Acute liver failure refers to the development of severe acute liver injury with encephalopathy and impaired synthetic function (INR of ≥1.5) in a patient without

cirrhosis or preexisting liver disease [4]. While the time course that differentiates acute liver failure from chronic liver failure varies between reports, a commonly used cut-off is an illness duration of <26 weeks [4].

Acute liver failure may also be diagnosed in patients with previously undiagnosed Wilson disease, vertically acquired hepatitis B virus, or autoimmune hepatitis, in whom underlying cirrhosis may be present, provided the disease has been recognized for <26 weeks [4].

Most patients requiring liver transplant following ALF have good prognosis as long as there is no significant neurologic deficit prior to liver transplant [5]. The King's College Criteria are used to identify patients who are unlikely to recover spontaneously without liver transplant (Table 26.2) [6]. It is imperative to identify these patients to expedite transplant evaluation and listing. In a study conducted at 17 referral centers in US between 1998 and 2001, acetaminophen overdose (39 %) and idiosyncratic drug reactions (13 %) were the most common causes of liver failure [7]. Further the survival of these patients was dependent on etiology (patients with acetaminophen overdose had better outcomes) and neurologic status at presentation [7].

Table 26.2 King's College criteria for liver transplantation in patients with acute liver failure (ALF)

Acetaminophen-induced ALF	Arterial pH < 7.3
–	OR
–	Grade 3 or 4 encephalopathy AND
–	Prothrombin Time >100 s AND
–	Serum creatinine >3.4 mg/dL
Other causes of ALF	Prothrombin time >100 s OR
–	Any three out of the following variables:
–	Age <10 years or >40 years
–	Non-A, Non-B hepatitis, idiosyncratic drug reactions
–	Duration of jaundice before development of encephalopathy greater than 7 days
–	Prothrombin time >50 s
–	Serum bilirubin >18 mg/dL

Presence of intracranial hypertension may be suspected based on assessment of physical signs such as impaired pupillary responses and posturing or may be based on direct measurement of intracranial pressure (ICP). If increased ICP is detected osmotically active agents such as mannitol may be used. In patients with renal insufficiency or those who have resistant intracranial hypertension barbiturates such as thiopental may be used. The potential for liver assist devices as definitive therapy or bridge to transplantation in ALF is an area of active investigation [8].

Alcoholic Liver Disease

Patients with decompensated liver disease secondary to alcohol abuse may benefit from LT since studies have shown similar graft and patient survival in patients with alcoholic liver disease when compared to other indications [9]. This is possible after candidates for LT complete an alcohol rehab program (such as alcoholics anonymous) with documented period of sobriety for at least 6 months. This is to address concerns regarding recidivism and poor compliance to medical therapy following LT. It is important to recognize and treat comorbid psychiatric conditions such as anxiety and depression.

A proportion of patients resume drinking alcohol following liver transplant [10]. A high index of clinical suspicion and periodic alcohol screens on the liver transplant wait list are required since patients may not volunteer this information. Even though there is no conclusive data whether this behavior translates into reduced patient or graft survival it is important to recognize and address alcohol abuse post LT. Another cause for mortality in patient with alcoholic liver disease posttransplantation is related to head, neck, and lung cancer which is a result of high risk behavior such as smoking. This is why all prospective transplant candidates undergo a pre transplant ENT evaluation.

Although controversial, early liver transplantation can improve survival in patients with the first episode of severe acute alcoholic hepatitis (AAH) which is not responding to medical therapy [11]. In this study, severity of AAH was defined as Maddrey's discriminant function of greater than 32. Nonresponse to medical therapy was defined as per the Lille model with a score of more than or equal to 0.45, 7 days after medical treatment, or a continuous increase in the MELD score. Medical therapy constituted of standard treatment of patients with acute liver failure in addition to prednisolone for at least 7 days.

Hepatitis B

Several important developments in prevention of graft reinfection with hepatitis B virus [HBV] has improved graft and patient survival following LT. Initial results of LT for HBV were disappointing because of the development of recurrent HBV infection resulting in death within 12–18 months after the transplant [12, 13]. Perioperative treatment with hepatitis B immune globulin and anti-viral agents has reduced the prevalence and severity of post-liver transplant reinfection with HBV [14, 15]. As a result excellent graft and patient outcomes are now routine and post-transplant survival of patients with HBV exceeds that for other indications.

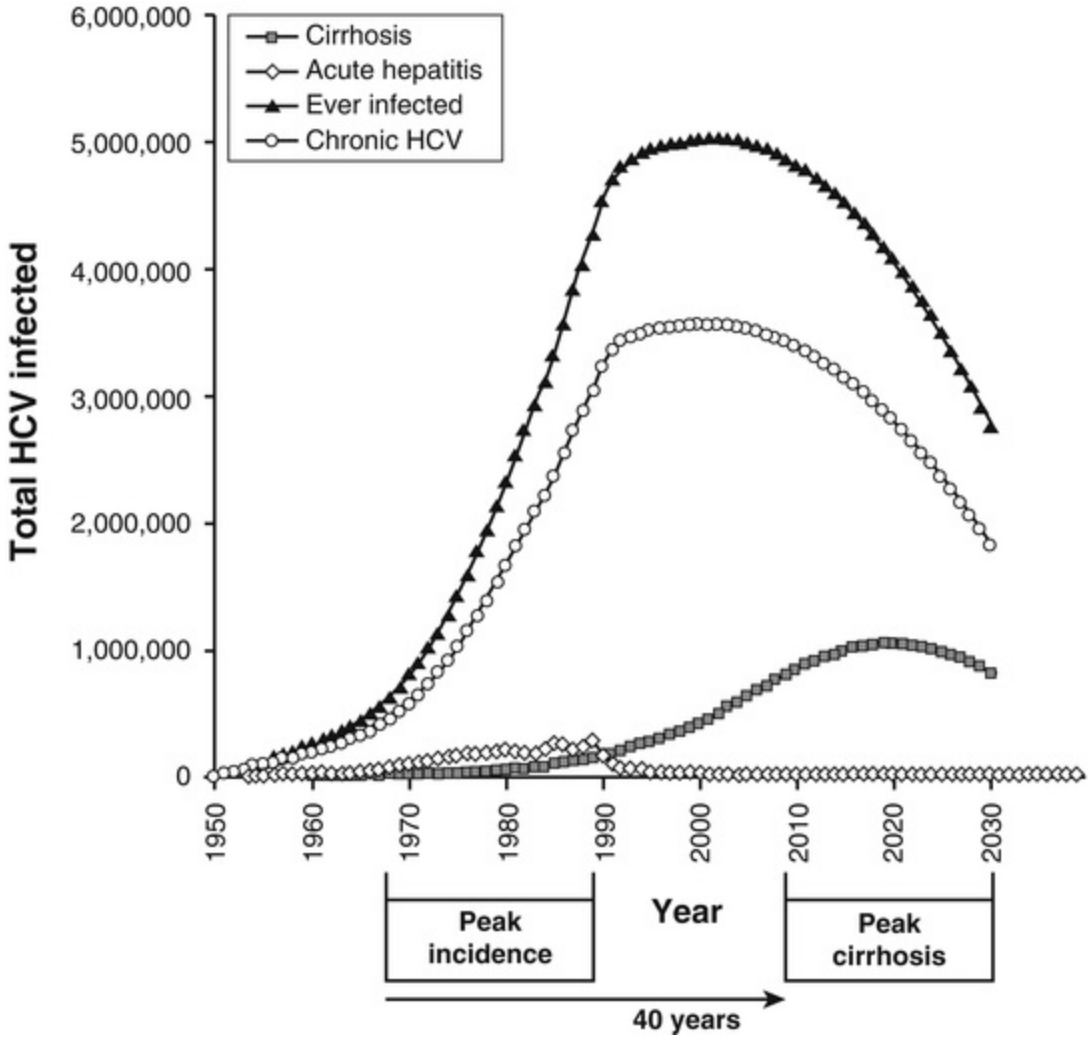
Patients with chronic HBV infection with positive HBV DNA levels should receive optimal duration of anti-viral therapy prior to liver transplantation. Agents available for use include entecavir or tenofovir, the goal being to render the patient HBV DNA

negative prior to liver transplantation, to lower the risk of graft reinfection with HBV.

Recent studies have shown that fewer patients with HBV registered for liver transplantation have ESLD and the increase in HCC is lowest in HBV patients when compared to patients with other indications for LT. This is most likely secondary to widespread use of highly effective antiviral therapy [16].

Hepatitis C

Recent data suggests that prevalence of HCV infection and related complications will continue to increase over the next decade mostly affecting patients over 60 years of age as shown in Fig. 26.3 [17]. Current treatment strategies will likely have little impact on these outcomes. However widespread use of newer anti-HCV agents will significantly reduce the impact of HCV in future [17].



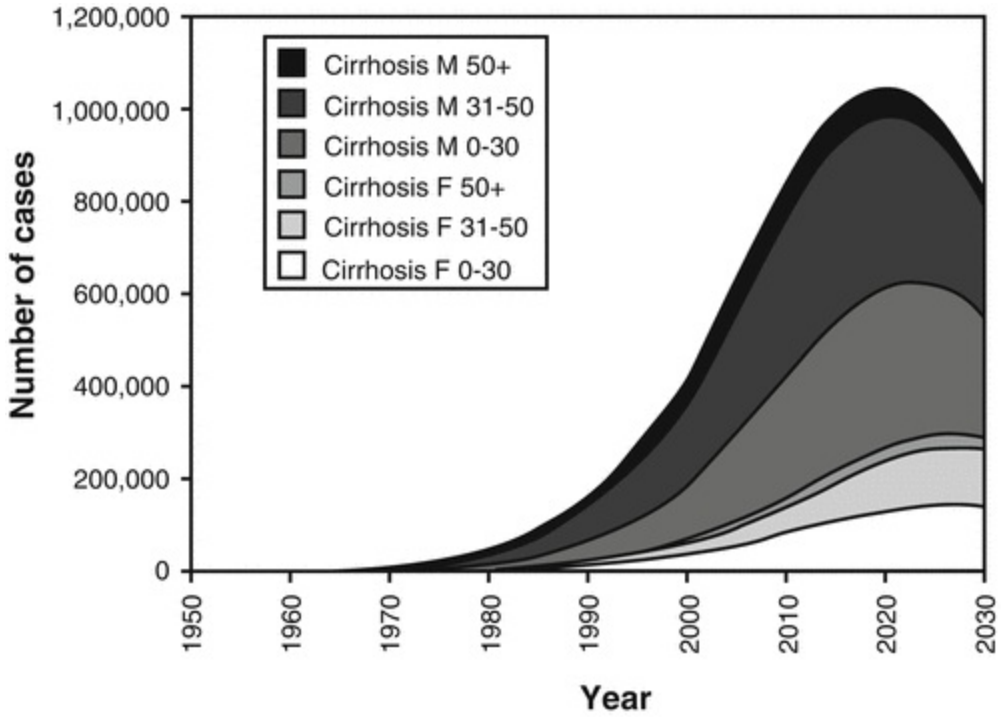


Fig. 26.3 (**a**) Prevalence of HCV infection with respect to year and chronicity of HCV infection. (**b**) Stacked prevalence curves showing prevalence of HCV related cirrhosis according to age and gender at time of initial HCV virus infection. Data from Davis et al. [17]

Given the recent approval of an oral polymerase inhibitor, sofosbuvir for the management of chronic HCV, treatment of patients with HCV prior to LT can prevent HCV recurrence in the majority of patients who become HCV RNA negative at transplantation [18].

Recurrent HCV infection results in reduced patient and graft survival post LT. It is important to identify and treat patients at risk for rapid progression of liver fibrosis. This is because patients with an initial (within 3 years post liver transplant) mild recurrence could progress to cirrhosis within 5 years [19]. Several studies have identified predictors of severe recurrent HCV infection. These include high viral load pre- and post liver transplantation, older deceased donor age, and multiple episodes of acute cellular rejection [19].

Cholestatic Liver Disease

Patients with ESLD secondary to Primary Biliary Cirrhosis [PBC] and Primary Sclerosing Cholangitis [PSC] are candidates for liver transplant with 1 and 3 year survival close to 90 % and 85 % respectively [20]. Patients should be referred for liver transplant evaluation when their survival as predicted by Mayo risk score is less than 95 %.

PBC is a chronic cholestatic disorder most commonly seen in middle aged women and may progress to cirrhosis. Numerous studies have shown survival benefit for

patients who undergo liver transplantation which is evident as early as 3 months after surgery [21]. Most patients have excellent prognosis after liver transplant with 10 year survival close to 70 % [21, 22]. Some patients with PBC who have disabling pruritis and sleep disturbance despite maximal medical therapy may need to be evaluated for liver transplantation due to disabling symptoms.

PSC is a stricturing disease involving the intra and extra-hepatic bile ducts and typically occurs in young men. There is no specific treatment and patients develop liver cirrhosis within 10–15 years. About 75 % of these patients have concomitant inflammatory bowel disease [23]. Liver transplantation has been shown to have survival benefit for patients with PSC [24, 25]. Success after liver transplantation is shown by 3 year survival rates that exceed 90 % [26–28]. Recurrent disease is common after liver transplantation but does not tend to have significant impact on posttransplant survival unless patient is discovered to have cholangiocarcinoma before or during surgery [29]. While awaiting liver transplantation, patients with PSC require surveillance for cholangiocarcinoma, the usual approach being six monthly serum tumor markers—Ca 19-9; CEA and cross-sectional abdominal imaging—MRI abdomen/MRCP.

Hepatic Malignancy

Most cases of primary hepatocellular carcinoma [HCC] occur in the setting of underlying cirrhosis one exception being chronic HBV infection where HCC may develop in the absence of cirrhosis. Certain patient populations such as those with hemochromatosis are also at high risk for HCC.

HCC is one of the primary indications for liver transplantation in the US and currently 20 % of liver transplants are performed for HCC. About half of these are secondary to allocation of exception MELD points for patients who are within MILAN criteria [see definition below]. The survival rate post LT for HCC is similar to those for patients with decompensated cirrhosis without HCC.

Based on the Milan criteria successful LT may be carried out with a single lesion of diameter >2 cm and <5 cm or no more than three lesions provided that the largest is no greater than 3 cm without any vascular invasion, locoregional lymphadenopathy, or distant metastasis [30]. There is recent criticism for Milan criteria to be excessively restrictive and various expanded criteria have been suggested to extend the tumor size and number without compromising patient survival [31]. The UCSF criteria allows LT in patients with a single lesion smaller than 6.5 cm; in patients with three or fewer nodules with the largest being smaller than 4.5 cm, or total diameter less than 8.5 cm without any evidence of vascular invasion [31].

Pre liver transplant evaluation of patients with HCC includes assessment of locally advanced and distant disease. A bone scan and computed tomography (CT) of chest is

obtained to investigate for extra-hepatic spread of the tumor. The current wait times for LT for patients with HCC despite a MELD upgrade vary from 3 to 12 months. Hence strategies need to be devised to provide bridge therapies to LT in this patient population. In addition living donor liver transplantation may be an alternate option for liver transplantation in selected patients.

Recurrent tumor tends to occur in the graft due to micrometastasis in the vascular system. As a result several adjuvant treatments have been devised while awaiting liver transplantation [32]. An important strategy to expand criteria for liver transplantation is to downstage the tumor with the use of loco-regional therapy so that it meets Milan criteria. One such approach is using trans-arterial chemoembolization (TACE) in selected patients with stage III/IV HCC; the tumor can be downstaged with TACE resulting in outcomes similar to stage II HCC [33]. Another strategy is radio-frequency ablation (RFA) which is being increasingly adopted in the management of these patients and has been shown to result in good tumor-free survival rates [34]. Oral therapy with sorafenib is being studied as a possible agent for adjuvant therapy post resection or liver transplantation in patients with HCC [35, 36].

Metabolic Disorders

Metabolic disorders requiring liver transplantation can be divided into disorders that manifest as liver injury (Wilson's disease and Hereditary hemochromatosis) and disorders that do not manifest as obvious liver disease (familial hyperoxaluria and hypercholesterolemia). The two most common indications for liver transplantation in adults are Wilson's disease and hemochromatosis.

- Wilson's disease : Most patients with CLD secondary to Wilson disease have good response to chelating therapy [37]. Some patients who develop ESLD and suffer from complications may become candidates for LT. A small proportion of patients with Wilson disease develops ALF and requires urgent LT. Good long-term survival has been reported for patients with Wilson disease after LT [38]. There is conflicting reports regarding neurologic improvement following LT [38, 39].
- Hereditary Hemochromatosis : Phlebotomy is the primary treatment for patients with hemochromatosis and may result in normal life expectancy. In patients who progress to ESLD with associated complications including HCC the only effective treatment is LT.

Nonalcoholic Fatty Liver Disease (NAFLD)

NAFLD has been projected to become one of the common indications for LT. The post-transplant course of these patients may be complicated by many of the same risk factors which are present prior to LT. These include diabetes, obesity, hypertension, and

hyperlipidemia. These may be worsened post LT under the influence of the immunosuppressive regimen. Recurrence of NAFLD post LT can lead to graft injury however graft loss does not typically occur and 1, 3, and 5 year survival rates are similar when compared to patients who get LT for indications other than NAFLD [40]. Liver Steatosis may represent a late complication of LT in some patients [41]. Management of post transplant NAFLD is similar to pre transplantation and involves dietary and lifestyle intervention and use of lipid lowering therapy. In a recently published case series a select group of patients underwent Roux-en-Y gastric bypass after LT with good outcomes including therapeutic weight loss, better glycemic control, and lower LDL levels [42].

Vascular Disorders

Budd Chiari syndrome (BSC) is characterized by hepatic venous outflow obstruction which in most instances is secondary to thrombosis. This condition is frequently associated with an underlying prothrombotic state. Treatment approaches for this condition range from medical (i.e. anticoagulants and diuretics) to invasive including angioplasty, transjugular intrahepatic portosystemic shunt (TIPS), surgical portosystemic shunts, and LT.

Various scoring systems have been described to support medical decision making in these patients as shown in Table 26.3. The Rotterdam score has been reported to predict survival in patients with BCS at the time of admission [43] whereas the BCS-TIPS prognostic index score predicts transplant-free survival in patients who received TIPS [44]. A large prospective multicenter study validated the Rotterdam score to predict intervention-free survival and BCS-TIPS score for survival [45]. Moreover the authors suggested a step wise approach in the management of patients with BCS from medical to more invasive therapies based on clinical situation [45].

Table 26.3 Scoring systems that may be used in clinical decision making for patients with BCS

Rotterdam score [43]	**BCS-TIPS prognostic index score [44]**
• 1.27 × encephalopathy + 1.04 × ascites + 0.72 × prothrombin time + 0.004 × bilirubin (where ascites was scored as present "1" or absent "0")	• Age (years) × 0.08 + bilirubin (mg/dL) × 0.16 + international normalized ratio (INR) × 0.63
• The 5-year survival rate was 89 % (95 % confidence interval [CI]: 79–99) for class I (good prognosis), 74 % (95 % CI: 65–83) for class II (intermediate prognosis), and 42 % (95 % CI: 28–56) for class III (poor prognosis)	• The cutoff of 7 points had a sensitivity of 58 %, a specificity of 99 %, a positive predictive value of 88 %, and a negative predictive value of 96 % for death or OLT 1 year after TIPS

Autoimmune Hepatitis (AIH)

LT is indicated for patients with AIH who present with ALF or those with ESLD and associated complications who fail to respond to immunosuppression. In patients with

ALF predictors of need for LT despite corticosteroid therapy include MELD score >28, massive necrosis on liver histology, no significant decline in bilirubin and INR values 4 days into treatment, and unchanged MELD-Na score after 1 week of corticosteroids [46, 47]. Once LT is performed patients need combination of prednisolone and calcineurin inhibitor with excellent outcomes. There should be low index of suspicion for recurrence of AIH once steroids are tapered. In such instances treatment with steroids and azathioprine is usually successful [48, 49]. Acute severe AIH or fulminant AIH may also represent an indication for LT.

Absolute and Relative Contraindications of LT

There are several conditions which may present absolute or relative contraindications for LT. Generally patients should be "medically fit" to tolerate the physiological stress on the human body due to LT. One of the aims of pre LT evaluation is to identify patients who do not meet the required medical criteria for LT as described below.

Hepatic and Extra-hepatic Malignancy

HCC is one of the common indications for LT. Some tumor characteristics such as large size (beyond Milan Criteria) present contraindication to LT. Other hepatic tumors such as angiosarcoma have an extremely poor outcome following transplantation and their presence is an absolute contraindication to liver transplantation.

In regard to extra-hepatic malignancies there should be a substantial disease-free duration after curative therapy for a patient to be considered a candidate for LT. This may depend in part on the particular malignancy. Most transplant centers would consider 5 year disease-free survival as appropriate for LT, however, for some cancers such as malignant melanoma a longer duration may be required [50].

Alcohol and Substance Abuse

Current alcohol and illicit drug use is an absolute contraindication to liver transplantation because of concern for compliance to medical treatment following LT. History of narcotic drug use such as methadone is a cause of concern for pain management post LT, however it is not a contraindication for LT [51, 52]. Use of NSAIDs prior to LT should be avoided due to concern for kidney dysfunction and gastrointestinal distress.

Smoking is also prohibited due to risk for potential adverse effects such as hepatic artery thrombosis and malignancy post liver transplantation. In one study on patients with ESLD active smoking was found to be associated with higher mortality post LT and this was primarily related to increased incidence of cardiovascular and sepsis related events [53]. Herbal supplements may be associated with drug interactions so their use

should be avoided in the post LT setting.

Vascular Abnormalities

With advances in surgical techniques vascular abnormalities such as portal vein or superior mesenteric vein thrombosis are no longer a contraindication to performing liver transplantation though it may require more extensive vascular reconstruction. Some patients who cannot undergo vascular reconstruction may need to be considered for multi-visceral transplantation

Cardiovascular Issues

Patients with ESLD have a similar prevalence of coronary artery disease (CAD) when compared with age matched controls [54]. Risk factors for CAD in this patient population include diabetes, hypertension, hyperlipidemia, and obesity. In patients post LT immunosuppression may be a risk factor for hypertension. Patients with NAFLD who undergo LT may be at higher risk for CAD post liver transplantation [55]. All patients undergo cardiac work-up including stress testing prior to LT.

Most patients with ESLD cannot undergo routine exercise stress testing because of poor stamina. These patients usually undergo dobutamine stress echo and in patients selected for LT it has a high negative predictive value for perioperative and long-term cardiac events [56]. Cardiac catheterization with angioplasty and stenting may be performed as clinically indicated however coronary artery bypass surgery may be associated with prohibitive risk in terms of bleeding and postoperative complications. Patients who undergo LT for hemochromatosis may have a higher risk of cardiac arrhythmias in the postoperative setting. Current guidelines mandate updating the stress test on a yearly basis while awaiting transplantation

Pulmonary Issues

Pulmonary evaluation is an important component in the pre liver transplant assessment of patients with ESLD. This is because pulmonary circulation may be affected as a result of cirrhosis and portal hypertension. It is also important to have a low index of suspicion for certain preexisting conditions such as chronic obstructive pulmonary disease and pulmonary fibrosis since these are generally a contraindication for LT.

Hepatopulmonary syndrome (HPS) is a result of dilation of the pulmonary vasculature leading to formation of arteriovenous fistulae. Portopulmonary hypertension (PPH) is a consequence of pulmonary vascular constriction. Both disorders can result in abnormal oxygenation and should be evaluated to determine candidacy for LT.

The hepatopulmonary syndrome (HPS) is characterized by triad of ESLD, intrapulmonary vascular dilations (IPVDs) (with right to left shunting) and hypoxemia

(PaO_2 < 70 mmHg on an ABG in the supine position). The diagnosis of HPS can be confirmed by demonstration of intrapulmonary vascular dilations by contrast enhanced echocardiogram (usually performed with agitated saline). The demonstration of air bubbles in the left atrium within three cardiac beats after visualization of the right atrium is diagnostic of IPVDs. Perfusion lung imaging with ^{99m}Tc-labeled macroaggregated albumin is an alternative technique to investigate for IPVDs but is considered less sensitive than echocardiography [57].

Patients with HPS have a poor prognosis when compared with cirrhotic patients without HPS [58]. The only effective treatment is liver transplantation which has been shown to improve survival in patients with HPS [59]. In majority of patients post LT the hypoxemia will gradually resolve though in some patients a prolonged period of ventilatory support may be required. Since there is potential for improvement post liver transplantation extra MELD points are allocated to patients with HPS.

In contrast porto-pulmonary hypertension (PPH) is an entity seen in patients with portal hypertension in the absence of other diseases associated with pulmonary hypertension. Diagnostic criteria for PPH include resting mean PA pressure >25 mmHg, pulmonary vascular resistance >240 dyn s/cm^5 and pulmonary capillary wedge pressure less than or equal to 15 mmHg on right heart catheterization. Transthoracic echocardiogram with estimation of PA systolic pressure is the recommended screening test for PPH in patients being considered for LT [60]. Patients with PA systolic pressure higher than 50 mmHg in association with right ventricular hypertrophy generally require right heart catheterization for measurement of hemodynamic parameters to confirm diagnosis of PPH. PPH is associated with reduced survival with higher prevalence of postoperative complications following LT [61, 62]. Even with treatment most patients are unable to become candidates for LT [61, 62].

Hepatic hydrothorax is a challenging condition in the management of patients with ESLD. It is characterized by accumulation of transudative fluid in the pleural cavity. The only effective way to control these problems is through reduction of portal hypertension using procedures such as TIPS. Ultimately LT is required so expedited transplant referral should be made for these patients. Chest tube insertion is contraindicated since it is associated with a high prevalence of infection and risk of fistula formation.

Infectious Issues

Patients with ESLD are at high risk for infections (bacterial, viral, and fungal) and should be suspected in any patient with ESLD and unexplained clinical deterioration or hepatic encephalopathy. Sepsis is an absolute contraindication to LT and should be treated with empiric broad-spectrum antibiotics while awaiting culture results. There should be low index of suspicion for spontaneous bacterial peritonitis (SBP).

Some patients have recurrent episodes of SBP which should be adequately treated prior to LT. Guidelines recommend that antibiotic prophylaxis should be administered to the following groups of patients:

1. Cirrhosis and gastrointestinal bleeding

2. Patients with one or more episodes of SBP

3. Patients with cirrhosis and low-protein ascites (<1.5 g/dL) with either poor renal function (serum creatinine ≥1.2 mg/dL, BUN ≥25 mg/dL or serum sodium ≤130 mEq/L) or liver function (defined by Child score ≥9 and serum bilirubin ≥3 mg/dL.

Systemic fungemia is an ominous finding in a debilitated patient with cirrhosis and is an absolute contraindication to performing liver transplant. Since the advent of highly active antiretroviral therapy a larger number of patients with HIV are being referred for LT with acceptable short-term survival [63, 64]. Acquired Immune Deficiency syndrome (AIDS) remains an absolute contraindication for LT.

In addition to receiving age-appropriate vaccinations patients should be routinely vaccinated against HAV and HBV.

Age

There is no clear age restriction in performing liver transplantation; however, older patients tend to be more debilitated, have limited physiological reserves, and may have significant comorbidities precluding liver transplantation.

Renal Issues

Patients with ESLD are at risk for acute or chronic kidney disease which may be a result of multiple risk factors. Cirrhotics who develop acute or chronic kidney disease may require combined liver kidney transplantation. Acute kidney injury (AKI) may result from dehydration, effect of nephrotoxic medications, acute tubular necrosis from hypotension and hepatorenal syndrome. In patients with ESLD renal insufficiency pre liver transplant has been associated with higher risk of chronic kidney disease post liver transplant [65].

In general patients who require dialysis for more than 1 month have low chance of renal recovery. A consequence of this recognition has been the fact that a large proportion of patients now require a combined liver kidney transplant resulting in a decline in the proportion of kidneys available for patients who need isolated deceased donor kidney.

Indications for combined liver kidney transplantation are as follows [66]:

- ESLD patients with ESRD requiring Continuous or Intermittent Renal Replacement Therapy (RRT), or CKD Stage 5.
- ESLD patient with pre-ESRD with MDRD-derived eGFR <30 mL/min for >3 months, or CKD Stage 4.
- ESLD patients with AKI/HRS with RRT duration >8 weeks. Patients should begin the listing evaluation by 6 weeks of RRT and be listed by 8 weeks of RRT.
- ESRD patients listed for kidney transplant with symptomatic liver disease or clinical signs of portal hypertension.
- ESRD patients listed for kidney transplant with asymptomatic biopsy-proven cirrhotic liver disease with >10 mmHg portal-systemic venous pressure gradient.

Another consequence of impaired free water handling in patients with advanced cirrhosis is dilutional hyponatremia. This is associated with higher risk of mortality in patients with chronic liver disease including those on the liver transplant waiting list [67, 68]. In addition post-liver transplant hyponatremia may be associated with calcineurin-induced neurotoxicity [69]. Incorporation of serum sodium level into the MELD model (MELD Na) increases the prognostic accuracy of MELD score especially in patients with relatively low MELD scores [70].

Malnutrition and Deconditioning

Nutritional assessment is an important consideration in pre liver transplant evaluation since 60 % of patients with cirrhosis have protein energy malnutrition (PEM) [71]. Patients with ESLD and malnutrition are at a higher risk for mortality and postoperative complications including liver transplantation [72–74]. In addition patients with malnutrition pre liver transplant are at higher risk for poor short-term outcomes post liver transplant including higher risk for infection, longer ICU and hospital length of stay, and reduced patient and graft survival [75].

Recent research is focused on standardizing new techniques in nutritional assessment for patients with ESLD [76]. This is because routine nutritional assessment based on anthropometrics may be erroneous given ascites and peripheral edema in patients with ESLD.

Various strategies have been adopted to optimize nutritional status of patients with ESLD. This includes initiation of enteral nutrition however success has been limited. A recent meta-analysis concluded that there was insufficient evidence “that oro-enteral nutritional supplementation impacts clinical outcomes” [77]. Clinical trials involving parenteral nutrition in patients with ESLD have not shown clear benefit [78]. Liver transplantation in obese patients presents unique challenges such as cardiovascular disease, diabetes, and wound infections.

In addition cirrhotics have reduced exercise capacity secondary to muscle weakness, cardiomyopathy, and hepatopulmonary syndrome and need an exercise program to limit deleterious consequences of deconditioning [79].

Transplantation Evaluation and Listing

The processes involved in pre liver transplant evaluation may vary from one center to another but the main goals are:

1. To determine whether transplantation is indicated

2. That there are no contraindications to liver transplant

3. To determine that the patient has adequate financial resources and social support to undergo liver transplant and immunosuppression after the transplant is complete.

The first step is obtaining fiscal approval from the patient's insurance provider regarding liver transplant evaluation. Once insurance approval is obtained patients meet the transplant coordinator and social worker who educate the patient and family regarding the transplant process. Patients are also seen by various consultants including:

1. Transplant surgeon: Discuss risks and benefits of the procedure

2. Transplant Hepatologist: Besides discussing risks and benefits of the procedure, confirm underlying diagnosis for ESLD, if applicable, and determine a management plan for complications from ESLD.

3. Psychiatrist and behavioral health: To address substance abuse issues including smoking, drug, and alcohol.

4. Dietitian: Design strategies to optimize nutritional/caloric intake and screen for vitamin deficiencies such as A, D, E, and K.

5. Dentist: To screen for oral cancer and optimize dental/oral health.

6. ENT: in particular alcoholics who are at high risk for oral cancers.

7. Anesthesiologist: This is reserved for patients who are considered high risk for anesthesia due to comorbidities such as porto-pulmonary hypertension or previous complications from general anesthesia.

In addition to a basic history and physical, an updated age-appropriate cancer screening and determination of vaccination status is performed. Patients also undergo evaluation for mycobacterium tuberculosis. Complete lab work is obtained which includes assessment of alternative viral, metabolic, hereditary, and auto-immune etiologies of CLD, ABO-Rh blood typing, liver function tests, tumor markers, urine drug screen, and urinalysis.

Cardiac evaluation includes a transthoracic echo with determination of PA pressure; stress test (usually a dobutamine stress echo) and cardiology consult depending on findings on these studies. Patients with known CAD or more than two risk factors for CAD may benefit from coronary angiography [80]. Patients also undergo abdominal/liver imaging (usually tri-phasic CT or MR) with assessment for HCC and vascular patency. Additional consultations and testing is performed as clinically indicated.

Since 2002 the MELD score has been established as the standard in determining allocation and distribution of donor liver organs for LT. The MELD score is calculated as described above. The range of score is from 6 to 40 and predicts 3-month mortality risk [81]. Donor livers are therefore allocated based on patient's disease severity as opposed to waiting time on the transplant list. Generally patients are considered for listing once MELD score approaches 15. Recent advances in organ allocation are consideration of MELD-Na score since it is a better predictor than MELD score [68, 70, 82].

Certain patients may have conditions which are eligible for exception MELD score since the MELD score is not reflective of the true prognosis of these patients. These include complications from ESLD such as HPS, PPH, and HCC. Other conditions which could receive MELD exception points include familial amyloid polyneuropathy, primary hyperoxaluria, cystic fibrosis with deterioration in pulmonary status and patients with cholangiocarcinoma on a chemotherapy protocol. It may also be reasonable to refer patients with PSC and frequent episodes of cholangitis for LT evaluation.

Once the pre liver transplant evaluation is complete the patient is presented in a multi-disciplinary meeting to discuss candidacy for liver transplant and if approved is listed with UNOS. Patients who are on top of the priority list include those with acute liver failure, hepatic artery thrombosis, or primary graft failure within 1 week of LT (status 1a) and children with life threatening complications from ESLD (status 1b). Otherwise the timing for transplant depends on the patient's calculated or exception MELD score which is reviewed periodically. The frequency of lab testing and

requirement for recertification status has been provided in Table 26.4.

Table 26.4 Frequency of laboratory values and recertification status with respect to MELD score

Status 1A	Status recertification every 7 days	Laboratory values must be no older than 48 h
MELD score 25 or greater	Status recertification every 7 days	Laboratory values must be no older than 48 h
Score ≤24 but >18	Status recertification every 1 month	Laboratory values must be no older than 7 days
Score ≤18 but ≥11	Status recertification every 3 months	Laboratory values must be no older than 14 days
Score ≤10 but >0	Status recertification every 12 months	Laboratory values must be no older than 30 days

Pre liver transplant evaluation involves a multi-disciplinary team approach and requires active participation of the patient and family. It is imperative to select candidates most suited to this treatment. This is because donor organs are a scarce resource and should be allocated wisely. The most equitable means of organ allocation is an area of active investigation.

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27. Anatomy and Surgical Procedures of Liver Transplantation

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Introduction: Liver Anatomy

The liver is a pyramid-shaped organ that fits in the right upper abdominal quadrant beneath the diaphragm with its base towards the right abdominal wall. It is the largest internal organ of the human body and weighs normally around 1500 g (range, 838–2584 g) [1]. It is surrounded cranially by the diaphragm, to the left by the stomach, to the right by the abdominal wall, caudally by the gallbladder, duodenum and inferiorly by the right kidney and the right colon.

The liver has several attachments (Figs. 27.1 and 27.2). Anteriorly there are the falciforme and round ligaments which divide the liver in two unequal-sized lobes. The round ligament houses the remnant of the umbilical vein which is obliterated after birth. An obliterated umbilical vein can sometimes be recanalized as a means for portal vein access as the round ligament ends into the left portal sinus [2]. This recanalization

happens spontaneously in cirrhotic patients with portal hypertensions as means for collateral circulation to bypass the liver. The end of the round ligament is also used as a landmark for left portal vein access in Rex shunt procedures. This is a procedure performed in pediatric patients with normal liver function but left sided portal hypertension secondary to main portal vein thrombosis [3, 4]. Embryologically, the left portal sinus was directly connected to the left hepatic vein by the venous duct of Ariantius which becomes obliterated in later stages to form the ligamentum venosum (Fig. 27.2). This venous ligament defines the posterior border of the left liver lobe from the caudate lobe. Following this ligament towards the diaphragm it will serve as a landmark for finding the left hepatic vein which is useful in left lobe procurement whether as a split or as living donor graft.

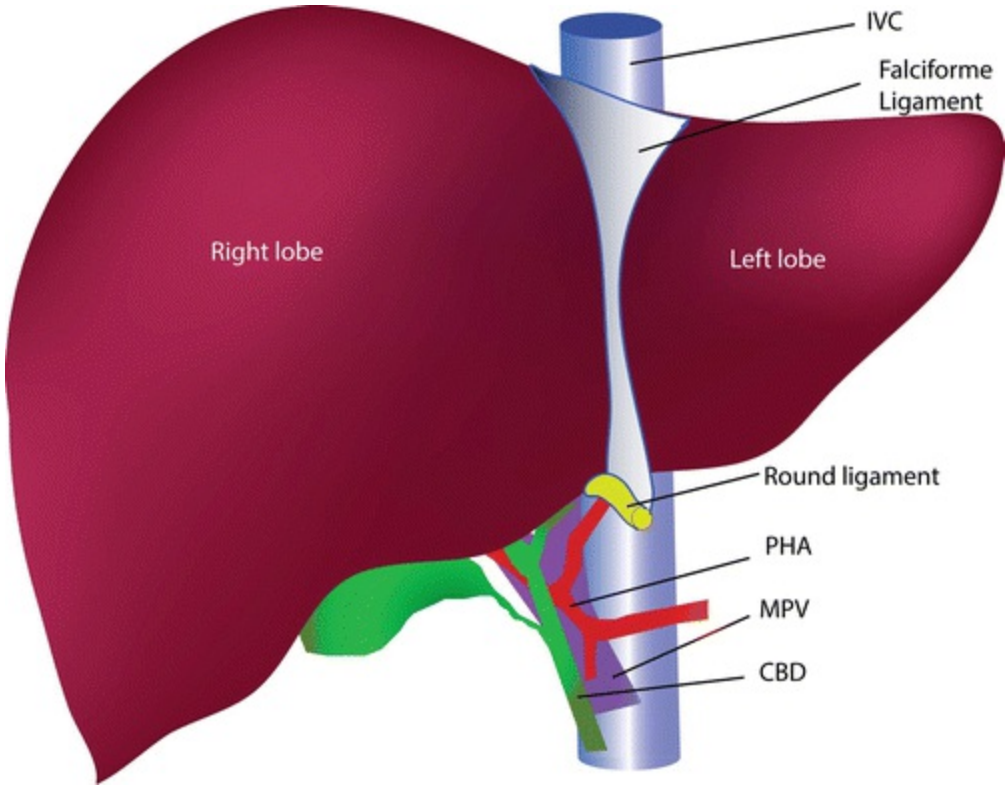

Fig. 27.1 Anterior view of the liver. *IVC* inferior vena cava, *PHA* proper hepatic artery, *MPV* main portal vein, *CBD* common bile duct

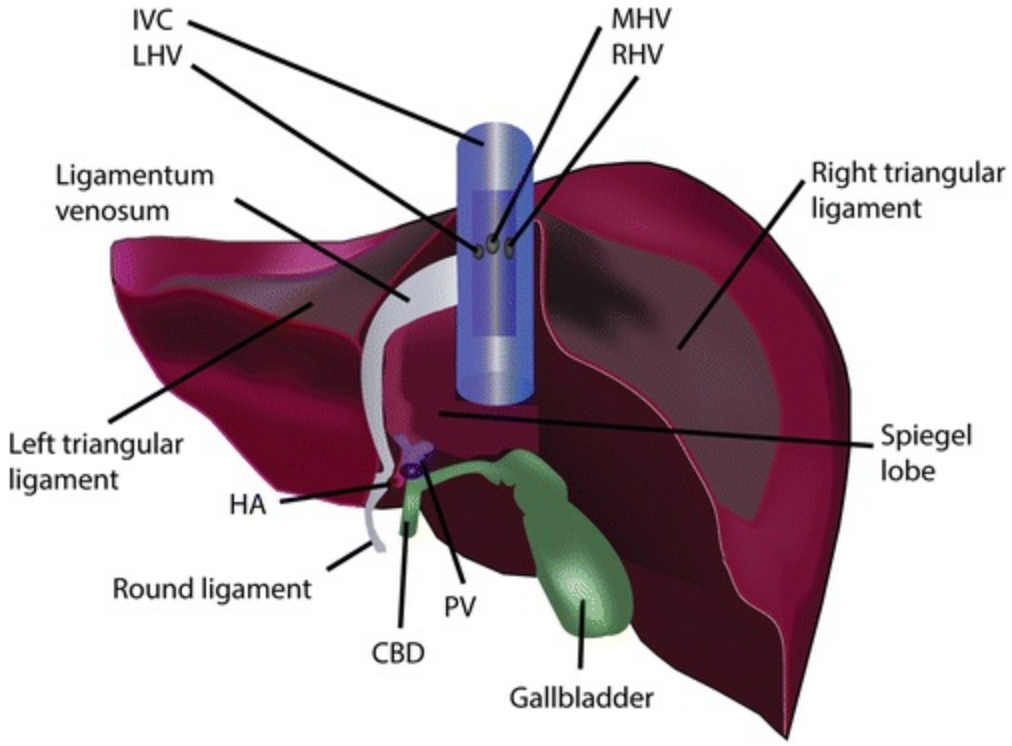

Fig. 27.2 Posterior view of the liver. The ligamentum venosum ends near the left hepatic vein (LHV) and is an important landmark for finding the LHV. *IVC* inferior vena cava, *MHV* middle hepatic vein, *RHV* right hepatic vein, *HA* hepatic artery, *PV* portal vein, *CBD* common bile duct

The ligamentum venosum is connected with the lesser gastric curvature by the lesser omentum in which we sometimes find an accessory left hepatic artery accompanied by the presence of the vagus nerve branch. More caudally the lesser omentum is bordered by the hepatoduodenal ligament. In the hepatoduodenal ligament we encounter the common bile duct at the most right sided border. Proximally towards the liver the common bile duct becomes the common hepatic duct after the insertion of the cystic duct. The common hepatic artery branches off at the left inferior border above the duodenum into a right and left hepatic artery. A middle hepatic artery can sometimes be seen branching off the right hepatic artery before the right hepatic artery dives behind the common hepatic duct. In rare circumstances the right hepatic artery is found anterior to the common hepatic duct. Aberrant arterial variations can occur and are known as accessory when they complement a normal arterial anatomy or as replaced when they replace the normal anatomy. For instance an accessory left hepatic artery from the left gastric artery can be seen in the lesser omentum and this is in coexistence with a normal left hepatic artery. Similarly a replaced right hepatic artery coming from the superior mesenteric artery can be found running behind and parallel to the portal vein on the right side of the hepatoduodenal ligament. The portal vein is usually the most dorsal structure found behind the bile duct and arterial structures. The portal vein is formed by the confluence of the superior mesenteric vein and the splenic vein. The portal vein along with the artery and the bile duct forms the portal triad. The whole triad is surrounded by

a connective tissue known as the glissonean sheath. At the hilum this is also known as the hilar plate. Externally this sheath encapsulates the liver. Cranially it forms the two triangular ligaments attaching it to the diaphragm which in turn form the coronary ligament towards the center. It is only at the bare area between the right and left coronary ligament where the liver is not encapsulated. Underneath the bare area towards the IVC is where the main hepatic veins are found.

Posteriorly the liver wraps around the inferior vena cava (IVC). This is incomplete in most cases with on the left side a protruding lobe known as the Spiegel lobe (Fig. 27.2) and on the right anterior side the paracaval portion. Together the Spiegel and the paracaval portion are known as the caudate lobe. The two portions are connected on the right side of the vena cava by a hepatocaval ligament or in lesser extent by liver parenchyma if the paracaval portion wraps completely around the right side. It is by dividing this ligament during hepatectomy or during right lobe graft procurement that the right hepatic vein becomes exposed. With the exception of the caudate lobe the liver venous drainage into the IVC is by the three hepatic veins at the suprahepatic anterior border: the right hepatic vein (RHV), middle hepatic vein (MHV), and the left hepatic vein (LHV). The caudate lobe drains directly into the IVC by retrohepatic accessory hepatic veins which are usually small. These veins are divided in IVC sparing transplant hepatectomy. Sometimes these caudate lobe branches cover a large enough drainage area in living donors that they need to be reattached in the implantation process in which case they will be labeled as right inferior or accessory hepatic veins.

In 1957 Couinaud published his work on liver anatomy and as of today his work still stands as the basis for functional liver anatomy [5, 6]. He divided the liver into eight segments using the portal and hepatic vein branches. The liver is first divided into two hemi livers by the portal bifurcation. This division can be found in an imaginary line formed from the gallbladder fossa towards the space between the RHV and MHV. This line is known as Cantie's line. It is an important landmark for right lobe hepatectomy as it runs anteriorly towards the MHV. The right liver is then further divided into a right anterior sector supplied by the right anterior portal branch (secondary division) and a right posterior sector supplied by the right posterior branch. Both sectors are separated by the right hepatic vein. Tertiary division of the portal veins will separate the sectors in a superior and inferior part i.e. the right posterior sector is segment VII superiorly and segment VI inferiorly and segment VIII with segment V respectively for the right anterior branch. For the left hemiliver the secondary portal division divides the liver into a medial and a lateral sector. The medial sector being segment IV and the lateral sector being the left lateral lobe consisting of segment II and III. Tertiary division divides Segments IV A superiorly and IV B inferiorly. The same goes for the lateral sector with segment II superior and segment III inferior. Between the right anterior sector and the left medial sector lies the middle hepatic vein. This is an important landmark for right lobe resection in live donor surgery as mentioned earlier.

Thus the middle hepatic vein drains part of segment VIII and V which is often reconstructed in right lobe living donor transplantation without MHV. The aim is to optimize the outflow of the graft and hence prevent a small for size syndrome [7]. The medial sector is divided from the lateral sector by the falciforme ligament and is drained by the left hepatic vein. As mentioned earlier, the caudate lobe or segment 1 lies paracaval and is separated from the rest of the liver by the ligamentum venosum. The segmental numbering follows a clockwise rotation from the left lateral superior position toward right medial superior if looking at the liver from above.

Surgical Procedures

Donor Surgery

The procedure of liver transplant usually starts with the donor procurement. An ideal deceased donor is usually younger than 50 years, has absence of steatosis, is hemodynamically stable, without abdominal trauma and has good renal function with good diuresis. The procedure is usually a multi-organ retrieval with cardiothoracic participation. Donor and recipients are usually matched by ABO types and by size compatibility. Larger grafts can be split for two recipients such as left lateral segment for a pediatric and an extended right lobe for an adult recipient. Two hemi-livers for two adults are also possible but less common due to higher biliary and vascular complications and higher PNF rates [8, 9]. Several reasons have been suggested as cause for these complications and they include the longer cold ischemia time due to the longer procurement time, the smaller artery sizes, and the loss of the segment 4 branch artery during splitting [9].

Deceased Donor Procurement

For the procuring surgeon the most important aspect of donor procurement once the donor organ is deemed suitable for use is to limit and avoid warm ischemia time in cardiac and brain death donors respectively during the procurement. This is achieved by gaining rapid inflow control for cold preservation fluid installation into the donor body as soon as possible. In cardiac death donation the mandatory 5 min wait time after death declaration inevitably adds up to warm ischemia time. Stricter criteria are now being applied for use of organs with prolonged warm ischemia time amongst many centers in an attempt to decrease the incidence of biliary complications.

Routinely the donor procurement is performed through a combined laparotomy and sternotomy. In brain dead donors when the donor is hemodynamically stable, preparatory work prior to cannulation can be done to ensure a fastidious procurement once flushing has started. The liver is first inspected for color, texture, and aberrant arterial anatomy. The left triangular ligament is divided along with the coronary

ligament. This maneuver permits early determination for the presence of an accessory left hepatic artery in the lesser omentum. It also allows proximal supra-celiac aortic clamping in case where lungs are also procured. Next the right hemicolon along with the distal small bowel are freed up from their retroperitoneal attachment from right inferolateral towards left medial. This gesture is known as the Cattell Braasch maneuver and together with duodenal mobilization of the second and third portion (Kocher maneuver) permits complete exposure of the distal aorta and inferior vena cava up to the left renal vein. The right superior mesenteric artery (SMA) is in this way also exposed and an aberrant or replaced right hepatic artery if present can be seen coming off the SMA. The distal aorta is encircled for control after division of the inferior mesenteric artery. The inferior mesenteric vein which runs to the left side of the ligament of Treitz can be isolated and cannulated for portal flushing if necessary.

The hepatoduodenal ligament is then dissected with isolation of the common bile duct . The bile duct and gallbladder if present are flushed at the last minute to minimize bilious contamination of other organs such as heart and lungs. This is done by incising in the gallbladder and dividing the CBD with ligation of the distal stump and injecting 100 ml of physiological serum into the gallbladder forcing it to wash out through the CBD. The CBD is also retrograde flushed with 40 ml of physiological solution. This is done to prevent mucosal autolysis of the biliary system. Some centers dissect the hepatic artery down to the splenic artery in the warm. We routinely perform this in the cold or on the back table when the pancreas is separated from the liver. Next the supraceliac aorta is dissected just beneath the right diaphragmatic cruz and encircled ready for proximal clamping. In cases where no lungs are procured the distal thoracic aorta can be dissected after lifting of the left lung and an open clamp can be placed on the distal aorta just beneath the esophagus.

At this point the abdominal team is ready for aortic cannulation, and in agreement with the cardiothoracic team, 100 U/kg of heparin is given. The distal abdominal aorta is cannulated after 3 min of heparin injection and cold flush fluid is infused. We routinely perform 7 L aortic and 3 L portal flushing with HTK solution. In pediatric donors we use UW solution and the volumes are 4 L and 2 L respectively. Simultaneous proximal aortic clamping is performed by the cardiothoracic and abdominal teams. The cardiothoracic team clamps the ascending thoracic aorta and we usually clamp the supra-celiac or distal thoracic aorta depending on whether the lungs are procured. At the same time the flushing preservative fluid is running through the distal abdominal cannula. The right atrium is then opened to vent the effluent preservation fluid. Care must be made as to have a sufficient suprahepatic IVC when incising the right atrium. This is important for piggyback implantation as discussed further. We prefer venting through the right atrium in order to prevent hepatic congestion. At this point anesthesiology hemodynamic support is halted and topical ice is placed over the organs that will be procured. Abdominal procurement is performed after the cardiothoracic

organs are removed.

The colon is completely mobilized by dividing the mesocolon from the cecum up to the proximal rectum. The mesentery of the small bowel is divided together with the proximal jejunum at roughly 10 cm from the ligament of Treitz. The bowels are retracted out of the body and placed caudally onto the thighs. This provides good exposure for further procurement. The pancreas is first mobilized together with the spleen from its retroperitoneal attachments. The distal stomach is then divided just before the pylorus. The left gastric artery is cut at the lesser curvature and preserved with the lesser omentum. The aorta is cut just below the SMA with care taken to preserve an adequate cuff for the renal arteries. The left diaphragm is incised and the proximal aorta is then divided at that point. The right diaphragm is then incised and the distal IVC is divided above the left renal vein. The liver and pancreas bloc is then removed from the remaining retroperitoneal attachments. The pancreas is then separated from the liver on the back table by dividing the structures in the hepatoduodenal ligament. Once the kidneys are procured, arterial and venous iliac grafts are then removed. One side of each vascular graft is then packed with the liver.

In cardiac death donors the procedure is similar but cannulation of the aorta is given first priority. This is done by sharp dissection through the retroperitoneum just below the ligament of Treitz. It is sometimes difficult to locate the aorta this way since its location cannot be guided by pulsation.

Split and Living Donor Procurement

Splitting the liver from a deceased donor can be performed in vivo or ex situ. In Vivo lessens the cold ischemia time and is reported to have less biliary complication rates due to better visualization of the anatomical structures, but is a burden for the anesthesia management of the donor since blood loss has to be anticipated during the transection of the liver parenchyma with sometimes hemodynamic consequences [10].

Splitting a left lateral segment for living donor donation or from a deceased donor involves parenchymal division at the right side of the falciforme ligament, cutting the left hepatic artery and portal vein at its bifurcation from its respectively right branches. After intraoperative cholangiogram, the bile duct is divided at the insertion onto the main duct. The left hepatic vein is also cut from the IVC. The procedure usually starts by dissecting the hilum and then isolating the left hepatic vein by following the ligamentum venosum as described earlier. No vascular structures are divided until flushing has been completed in split liver transplantation and in living donor after the liver is completely divided. As mentioned earlier the extended right lobe can be used for an adult recipient. Segment IV in these grafts can sometimes become necrotic with biloma formation due to loss of arterial inflow if the middle hepatic artery is sacrificed.

In right lobe adult living donor hepatectomy the right hilar structures are first

dissected out. The right hepatic vein is then dissected out with complete mobilization of the right liver before transection of the liver parenchyma. This occurs at Cantie's line. The middle hepatic vein is usually left in place. The segment 5 and or 8 venous branches to the MHV will need back table reconstruction with a vein graft to minimize vascular congestion and thereby prevent a small for size syndrome [7]. Once the transection is completed, the right hilar structures together with the right hepatic veins are divided with care to preserve further vascularization of the remnant liver.

Splitting a deceased donor liver for two adult recipients is similar to left lobe adult living donor hepatectomy. Here, after dissection of the left hilar structures the transection occurs at Cantie's line with the left lobe retaining the middle hepatic vein. The right lobe subsequently ends up containing the IVC, the proper hepatic artery, and the main portal vein. When using these right lobes the IVC needs to be reconstructed by closing the openings from where the M and LHV used to drain into. This also applies to the left portal venous orifice on the main portal vein.

Recipient Operation

Whole Donor Liver Transplantation

The procedure can be divided into three phases: the pre-anhepatic, anhepatic, and the reperfusion phases. It remains a technically challenging procedure for the whole team. Any technical error can lead to tremendous blood loss, infections, and/or biliary complications. The anesthesiologist has to maintain homeostatic body temperature, hemostasis parameters, fight electrolyte imbalance, and maintain gluconeogenesis while administering muscle relaxant and anesthesia that are not broken down by the liver.

The pre-anhepatic phase comprises removing the native liver and can be the most difficult part of the whole procedure because of major blood loss. The emphasis in the pre-anhepatic phase is to minimize blood loss. Before any liver mobilization is done the inflow is controlled by dissecting the hepatoduodenal ligament and dividing the hepatic arteries and the common bile duct. This is done to limit any bleeding from the liver during mobilization. The portal vein is left in place or if necessary a portal caval shunt is constructed to prevent splachnic venous congestion. Once the liver is disconnected from its inflow the anhepatic phase starts. In selected cases where there is severe portal hypertension with known spontaneous shunting such as splenorenal or large gastric varices, the portal vein can be safely divided without creating a shunt. This will allow a more easier and faster mobilization of the liver because of decreased liver volume and easier exposure of the retrohepatic IVC with its hepatic veins. The liver is mobilized after controlling the inflow with division of the triangular and coronal ligaments. The liver is then dissected off the vena cava with division of the retrohepatic veins. The liver remains only attached with the three hepatic veins and portal vein if no porto-caval shunt or portal vein clamping has been used at the end of the dissection. If

piggyback implantation (Fig. 27.3) is anticipated the veins are kept open. Further dissection of the suprahepatic IVC off the diaphragm is necessary in order to have enough space to put a clamp but more importantly to have enough cuff in order to construct a common cuff from the three separate venous orifices for the hepatic vein anastomosis. If cavo-caval anastomosis (Fig. 27.4) is anticipated the hepatic veins can be closed by a vascular stapler or by running sutures. A new venotomy on the IVC will be used for cavo-caval anastomosis. It is during the anhepatic phase that the patient becomes more acidotic and hypoglycemic. This needs to be corrected by the anesthesiologist. Additionally, during the anhepatic phase , partial clamping of the IVC alters the preload with more fluid demand. The inflow artery and portal vein are first checked to make sure that they are adequate before placing the new liver in the patient and starting the revascularization. If there is evidence of a portal thrombus an eversion thrombectomy can be attempted using forceps clamps to peel the thrombus off the portal vein wall. In extremis, a venous jump graft can be used originating from the superior mesenteric vein. In cases of insufficient arterial inflow the first step is to dissect the artery as far as possible and ligate the gastroduodenal artery in case there is a steal from the gastroduodenal artery. A jump graft from the infraceliac aorta can be constructed using an arterial iliac conduit in cases where the hepatic arterial inflow is inadequate.

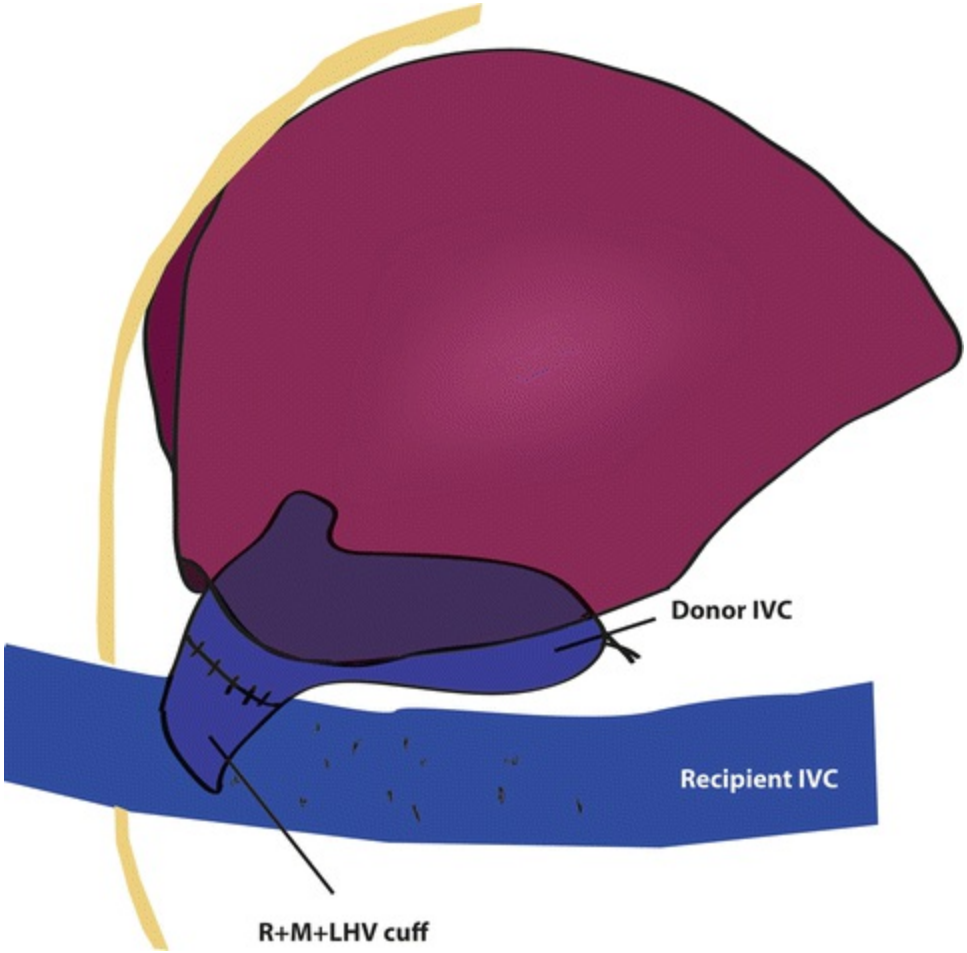

Fig. 27.3 Piggyback venous outflow anastomosis. The donor suprahepatic IVC is attached to the common cuff made by connecting the three separate venous orifices. *IVC* inferior vena cava, *R* right, *MHV* middle, *LHV* left hepatic vein

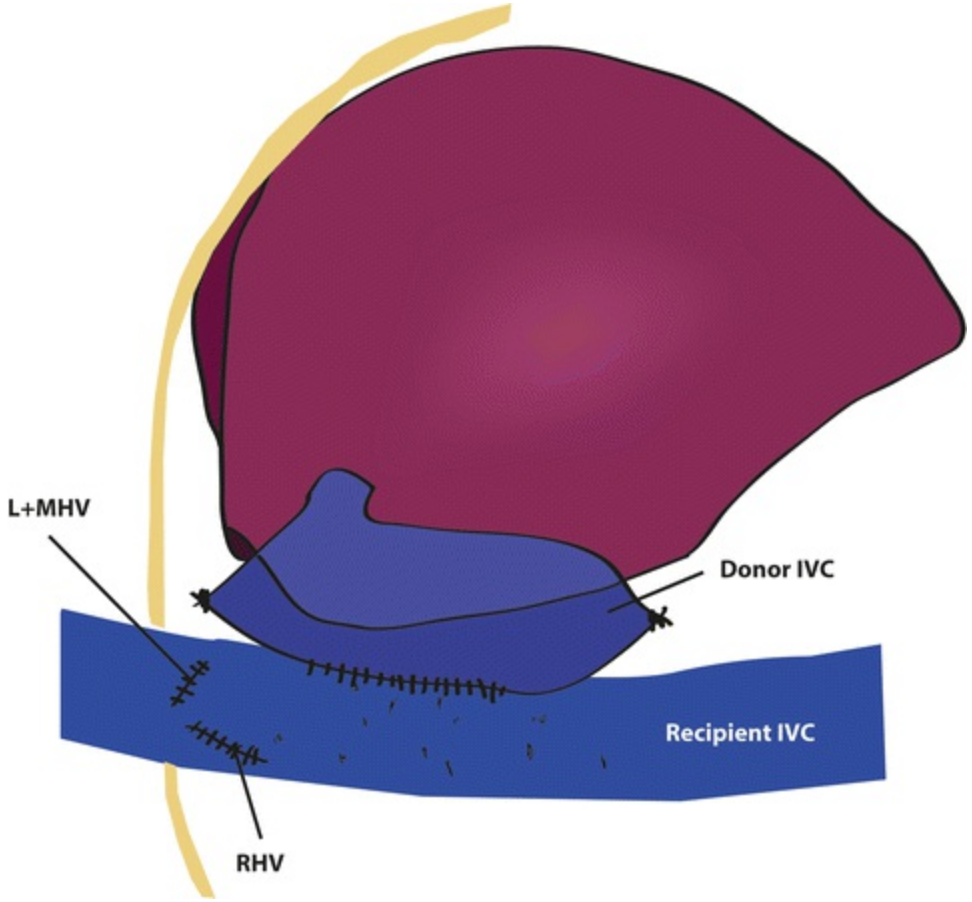

Fig. 27.4 Cavo-caval venous outflow anastomosis. The supra-and infrahepatic openings of the donor inferio vena cava (IVC) are closed. The anastomosis is constructed by two new venotomies on the respective IVC's. *L* left, *MHV* middle hepatic vein, *RHV* right hepatic vein

Standard implantation starts with the hepatic venous anastomosis first and concludes with portal anastomosis. Sometimes in DCD grafts a faster arterial revascularization might be attempted to limit the ischemic biliary injury. Before releasing the clamps we flush the liver with albumin solution and then perform a blood flush to remove any remains of preservation fluid that potentially could contain high concentration of potassium and cause post-reperfusion syndrome. The post-reperfusion syndrome is defined as a decrease in systemic MAP greater than 30 % below baseline for at least 1 min during the first 5 min of liver reperfusion [11] The exact mechanism is not fully understood but it may be explained by the release of cytotoxic metabolic waste products from the liver and the remains of preservation fluids especially with the use of UW preservation solution [12]. Risk factors for post-reperfusion syndrome are longer duration of surgery, longer cold ischemia time, increased blood transfusion, the use of veno-venous bypass and left ventricular dysfunction [13–15]. Also by slowly releasing the outflow clamp or partially unclamping the portal vein this syndrome can be

prevented. If however this occurs the treatment is similar as in treating right heart failure by of starting inotropic support. In our center we further use methylene blue as additional treatment [12, 16, 17].

A quick hemostatic check is made after reperfusion to make sure no dramatic bleeding points are seen before starting the arterial anastomosis if it hasn't been performed yet. Once the arterial anastomosis has been performed we always then perform a thorough hemostasis of the operating field. Packing the liver and waiting for the field to dry up once the newly transplanted liver recovers its coagulation function and the anesthesiologist stabilize the patient before the bile anastomosis is started is a useful technique. We will only start the biliary anastomosis if the field seems adequately dry. This is because the biliary anastomosis is more delicate and does not support too much turning of the liver for hemostasis. In normal liver transplant we routinely perform a duct to duct anastomosis leaving an internal stent through the papilla. Routine T-tube placement has been abandoned because of more complications associated after removal of the T-tube but recent evidence suggests that perhaps less biliary strictures and leakage is associated with the use of T-tubes [18, 19]. In patients with PSC or biliary atresia or redo transplants where the recipient biliary duct can't be used, an end to side hepatico-jejunostomy with a Roux limb is constructed at 40 cm from the ligament of Treitz. The abdomen is closed with two silicon drains one usually behind the right hemi-liver and one behind the inflow anastomosis.

Living Donor or Split Liver Transplantation

The recipient operation is similar to the deceased donor one except the hilar dissection is done as high as possible leaving the portal vein bifurcation; the left and right hepatic artery are usually divided at the hepatic confluence of the hilar plate. In a right lobe graft the right hepatic vein is sewn in to the IVC similar to a cavo-caval anastomosis. The jump graft from V5 to V8 is usually sewn to the recipient left and middle hepatic vein confluence (Fig. 27.5). The rest of the operation is similar to a deceased donor liver transplant.

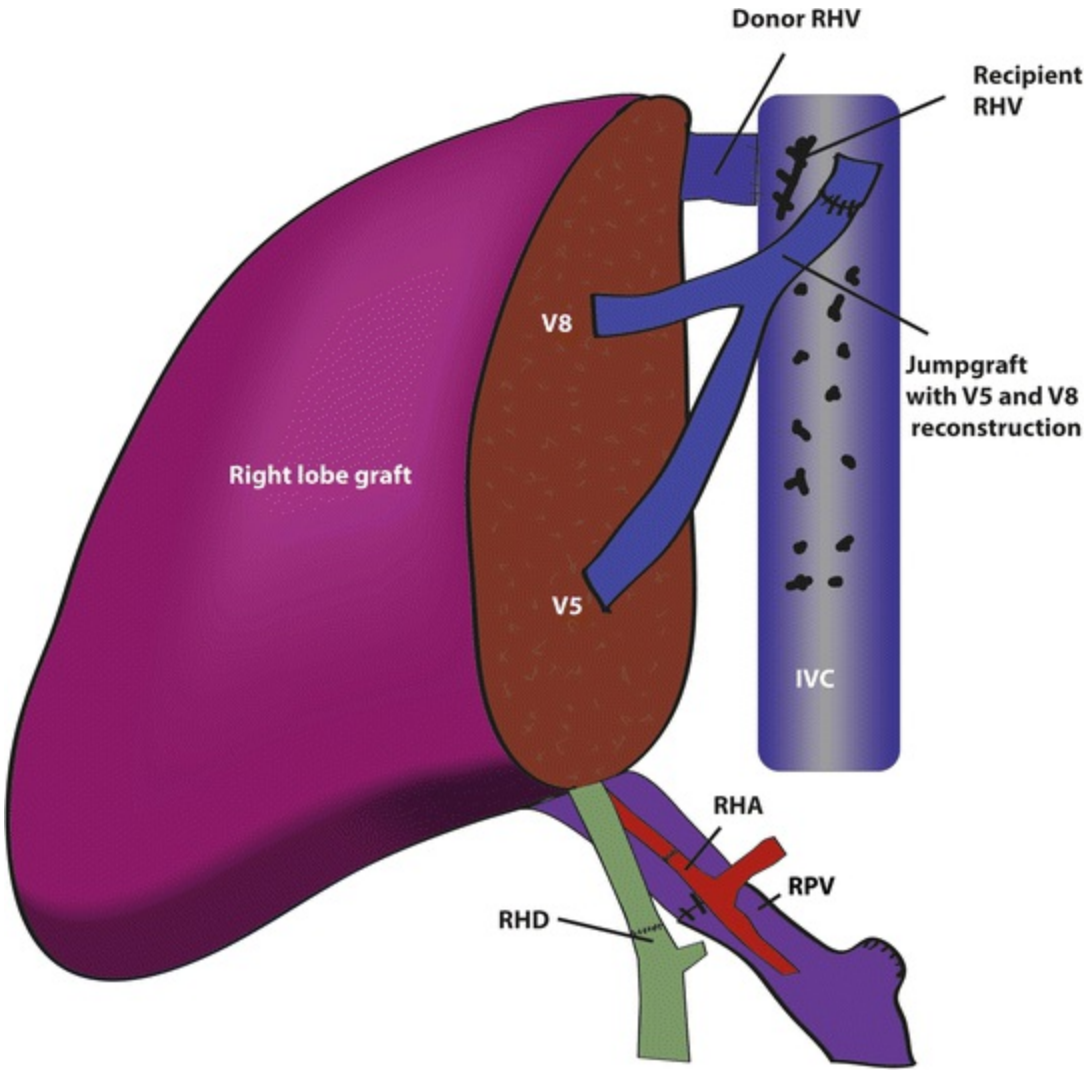

Fig. 27.5 Right lobe living donor liver transplant. The right hepatic vein (RHV) is being contructed on a new recipient venotomy for orientation purposes taking in account the inflow and biliary reconstructions. The jumpgraft can be constructed on separate conduits or as in this case using a reversed arterial or venous graf Y graft with the external and internal iliac on the liver V5 and V8 tributaries. The common iliac limb is then anastomosed on a shortened Left-middle hepatic vein (L-MHV) cuff. *RHA* right hepatic artery, *RPV* right portal vein, *RHD* right hepatic duct

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28. Liver Transplantation Anesthesiology

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Introduction

Liver transplantation has been widely recognized as the ultimate treatment for patients suffering from acute or chronic liver failure. As one of the most challenging noncardiac surgical procedures, successful completion of liver transplantation mandates an anesthesiology team with a special set of knowledge and skills. These include a thorough understanding of systemic manifestations of liver failure, donor types, transplant procedures, and the three stages in the transplant surgical process and related issues. Special attention should be paid to blood transfusion conservation strategies and initiation of induction immunosuppression therapy. The goal of this chapter is to describe this basic knowledge and discuss the anesthetic management of liver transplantation recipients. Practical anesthesia management is described according to the three stages of liver transplantation: Stage I (pre-anhepatic stage), Stage II (anhepatic stage), and Stage III (neo-hepatic stage).

In-depth discussions of special recipients' conditions, including acute hepatic failure (Chap. 34), porto-pulmonary hypertension and hepato-pulmonary syndrome (Chap. 35), and combined organ transplantations including the liver (Chap. 32) are found in each designated chapter in this text book.

Recipients Presenting for Liver Transplantation

Although anesthesiology team members may be introduced to a liver transplantation recipient at a later stage of his or her lengthy pretransplantation workup, the importance of thorough review of the recipient's current medical condition cannot be overemphasized. Patients who have required intensive care prior to transplantation due to decompensating medical conditions especially demand the anesthesiology team's careful reevaluation of the conditions, which may significantly have worsened compared to existing evaluations performed several months prior to transplantation.

In general, isolated liver transplantation is indicated for those who suffer chronic noncholestatic liver disorders, cholestatic liver disorders, metabolic disorders, malignancies of the liver, acute hepatic failure, retransplantation, and miscellaneous conditions (Table 28.1). Among them, end stage liver disease (ESLD) secondary to chronic noncholestatic liver disorders is the most common indication for liver transplantation in adults, accounting for more than 60 % of all transplantations performed annually [1]. In 2011, a total of 5805 adult (18+ years old) liver transplants were performed in the United States, and the etiologies, in descending order, were hepatitis C (23.5 %), hepatic malignancy (20.9 %), alcoholic liver disease (17.6 %), cholestatic disease (9.1 %), acute hepatic failure (4 %), metabolic disease (2.5 %), and others (22.3 %) [1]. Several trends were found among liver transplantation recipients in the United States. Over the past decade, the percentage of recipients aged 50 years or older increased from 58.5 to 77.1 % and the percentage of recipients aged 65 years or older increased from 7.6 % in 2002 to 12.8 % in 2011 [2]. The proportions of recipients with obesity (body mass index > 30) increased to 34.4 % and those with diabetes also increased to 24.7 %. Other notable conditions noted in 2011 in the United States include recipients on life support at the time of transplantation (6.6 %), those with previous abdominal surgery (40.7 %), and those with portal vein thrombosis (8.5 %) or spontaneous bacterial peritonitis (7.6 %).

Table 28.1 Indications for isolated liver transplantation

Non-cholestatic cirrhosis
Hepatitis C
Hepatitis B
Alcoholic liver disease
Autoimmune hepatitis
Cryptogenic cirrhosis
Nonalcoholic steatohepatitis
Others (hepatitis D, hepatitis A, hepatitis coinfection, chronic active hepatitis, other exposure)
Cholestatic liver disease/cirrhosis

Primary biliary cirrhosis
Secondary biliary cirrhosis (Caroli's Disease, Choledochal Cyst, other)
Primary sclerosing cholangitis (ulcerative colitis, Crohn's Disease, no bowel disease, other)
Others
Biliary atresia
Alagille syndrome
Hypoplasia
Extrahepatic
Others
Acute hepatic necrosis
Acute hepatic necrosis (hepatitis, drug, unknown etiology, other)
Hepatitis C: chronic or acute
Hepatitis B: chronic or acute
Metabolic diseases
Alpha-1-antitrypsin deficiency
Hemochromatosis–Hemosiderosis
Other hereditary disorders (Wilson's Disease, tyrosinemia, oxalosis, glycogen storage diseases, others)
Malignant neoplasms
Primary liver malignancy
Hepatocellular carcinoma (with or without cirrhosis)
Cholangiocarcinoma
Hepatoblastoma
Others (fibrolamellar hepatocellular carcinoma, hemangioendothelioma–hemangiosarcoma)
Secondary liver malignancy
Miscellaneous conditions
Budd-Chiari Syndrome, metastatic neuroendocrine tumors, cystic fibrosis, trauma, benign tumors, others)
Retransplantation
Primary nonfunctioning
Acute/chronic rejection
Hepatic artery thrombosis

Chronic Liver Failure: Etiologies, Systemic Manifestations, and Anesthetic Implications

It is important to realize that ESLD causes multiple systemic disorders (Table 28.2). Each systemic manifestation has its significant anesthetic implication during the perioperative period, thus demanding refinement in anesthetic management.

Table 28.2 End-stage liver disease: systemic manifestations

Organ system/manifestation
Cardiovascular-pulmonary systems
Hyperdynamic state
Portal hypertension
Portopulmonary hypertension
Right heart failure
Hepatopulmonary syndrome
Cirrhotic cardiomyopathy
Pleural effusion
Renal-electrolytes system
Hepato-renal syndrome
Hyperkalemia
Metabolic acidosis
Hyponatremia
Hematological system
Coagulopathy
Anemia
Thrombocytopenia
Leukopenia
Spontaneous bacterial peritonitis
Gastrointestinal system
Esophageal varices
Portal hypertensive gastropathy
Mucosal dysfunction of the intestine
Nervous system
Encephalopathy
Endocrine system
Diabetes mellitus
Abnormal sex hormone metabolism
Thyroid disease
Osteoporosis
Adrenal insufficiency

Cardiovascular and Pulmonary Systems

Patients with ESLD undergoing liver transplantation often present with hyperdynamic circulatory conditions, portal hypertension, portopulmonary hypertension, right heart failure, hepatopulmonary syndrome, cardiomyopathy, and pleural effusion. Systemic vasodilatation and formation of collateral veins (e.g., porto-systemic shunts) lead to

hyperdynamic splanchnic and systemic circularity conditions. Persistent endotoxemia, caused by shunting through porto-systemic anastomoses and enhanced endotoxin absorption from the intestine as a result of bile salt deficiency, may contribute to the vasodilation by activation of cascades of secondary mediators. Portal hypertension results from hyperdynamic splanchnic circulation with increased afterload of the portal venous system with intrahepatic cirrhosis. This leads to ascites, splenomegaly, varicose vein formation in the esophagus, portal hypertensive gastropathy, and spontaneous bacterial peritonitis. Portopulmonary hypertension can be categorized as mild (mean pulmonary arterial pressure [MPAP] 25–44 mmHg), moderate (MPAP 45–59 mmHg), and severe (MPAP ≥ 60 mmHg). Moderate to severe portal hypertension is associated with high perioperative mortality in liver transplantation [3] and is considered a contraindication for isolated liver transplantation unless successfully medically managed pretransplant [4]. Right heart failure can be found in patients with pulmonary hypertension. Dilatation of the right ventricle, decreased wall motion of the right ventricle, tricuspid regurgitation, and dilatation of the right atrium are hallmarks of the condition. Hepatopulmonary syndrome (HPS) is characterized by microvascular alterations and dilatation in the pre-capillary and capillary pulmonary arterial circulation. HPS is defined as a widened alveolar-arterial oxygen gradient ($AaPO_2$) on room air in the presence or absence of hypoxemia ($AaPO_2$ = 15 mmHg, or 20 mmHg in patients more than 64 years old) as a result of intrapulmonary vasodilation. HPS can be graded on the basis of the degree of hypoxemia: mild ($PaO_2 \geq 80$ mmHg); moderate (PaO_2 = 61–80 mmHg), severe (PaO_2 = 50–60 mmHg), and very severe ($PaO_2 < 50$ mmHg) [5]. Cirrhotic cardiomyopathy is a recently recognized condition and can be caused by any etiology of ESLD. It presents with systolic incompetence under hemodynamic stress, diastolic dysfunction related to altered diastolic relaxation and electrophysiological abnormalities in the absence of any known cardiac disease. The underlying pathogenetic mechanisms include abnormalities in the β-adrenergic signaling pathway, altered cardiomyocyte membrane fluidity, increased myocardial fibrosis, cardiomyocyte hypertrophy, and ion channel defects with widening of the QRS complex causing prolonged QT intervals. The clinical manifestations of this condition become relevant only in decompensated conditions or immediately after liver donor graft reperfusion with significant volume overload. Pleural effusion can be of a significant amount and may contribute to intraoperative hypoxemia due to atelectasis and decreased ventilation of the affected side of the lung.

Renal and Electrolyte Systems

Hepato-renal syndrome (HRS) [6] results from the cascade of events caused by ESLD with portal hypertension and mesenteric hyperemia; the two conditions cause relative renal hypo-perfusion, resulting in severe renal arterial vasoconstriction and progressive

renal failure. Two types of HRS are observed in clinical practice [7]. Type 1 HRS is an aggressive form with a very poor prognosis, and type 2 HRS develops slowly over weeks; these patients usually have diuretic-resistant ascites and have a slightly better prognosis than those with type 1 HRS.

As a result, hyperkalemia and metabolic acidosis can be seen in patients with ESLD. Hyponatremia is also a common finding in ESLD patients. The pathogenesis is directly related to the vasodilatation and secondary neurohumoral adaptations that occur, including activation of endogenous vasoconstrictors such as antidiuretic hormone. This process leads to an impaired ability to excrete ingested water. Severity of the hyponatremia is related to the severity of ESLD.

Hematologic System

Decreased synthetic function of the liver with ESLD leads to decreased production of procoagulant factors including vitamin K-dependent factors, factor V, and factor XI. Dysfibrinogenemia is caused both by the decreased production and by increased consumption of fibrinogen due to altered production of activators and inhibitors of fibrinolysis, activation of coagulation cascade by endotoxemia, and decreased clearance of fibrinolytic proteins. Of note, traditional laboratory-based coagulation tests, including prothrombin time, partial thromboplastin time, and fibrinogen level, do not necessarily reveal the entire picture of coagulation. This point is important as the coagulation status is a fine balance between these two opposing factors [8]: pro-coagulants and anti-coagulants. Therefore, aggressive correction of coagulation abnormalities measured by these laboratory tests with exogenous coagulation factors and blood products occasionally results in thromboembolic complications at liver transplantation [9]. Thrombocytopenia is a common feature in ESLD. This is primarily due to hypersplenism secondary to portal hypertension, but decreased production of hepatic thrombopoietin synthesis as well as direct bone marrow suppression with alcohol exposure or hepatitis C virus also play a role. Anemia is seen due to a combination of hemorrhage from the gastrointestinal tract, decreased production of red blood cells (bone marrow suppression and/or folate deficiency), and hemodilution due to water retention. Leucopenia can be seen due to bone marrow suppression with viral hepatitis B or C, and excessive alcohol consumption. Together with leukopenia and decreased production of the compliments, patients can be prone to infections including spontaneous bacterial peritonitis.

Gastrointestinal System

Esophageal varices and portal hypertensive gastropathy are primary abnormalities that occur due to ESLD. In general, varices can form at any portion of the alimentary tract from the esophagus to the rectum, but the distal esophagus is the most common site for

varices in ESLD. Esophageal varices result from portal hypertension and often bleed. Child-Pugh score, variceal size, and presence of red wale markings can be used to calculate a prognostic index that quantifies the risk of variceal hemorrhage [10]. An endoscopic banding procedure is occasionally performed during the pretransplantation period either to therapeutically treat bleeding varices or for prophylactic purposes. The timing of this banding procedure and the severity of the varices are important to consider for intraoperative placement of transesophageal echocardiography (TEE) . Portal hypertensive gastropathy [11] has the characteristic endoscopic features of a mosaic pattern with or without red spots. It is most frequently located at the fundus and body of the stomach. Acute bleeding from portal hypertensive gastropathy is usually mild and seen in the presence of severe portal hypertension. Mucosal dysfunction of the intestine due to portal hypertension leads to malabsorption and bacterial translocation [12]. The former leads to malnutrition; the latter leads to bacteremia and spontaneous bacterial peritonitis as well as the main pathogenesis of hepatorenal syndrome due to splanchnic and systemic vasodilation.

Nervous System

Hepatic encephalopathy [13] indicates the spectrum of potentially reversible neuropsychiatric abnormalities observed in patients with liver dysfunction. There are three types of hepatic encephalopathy: Type A is associated with acute liver failure; Type B is associated with portal-systemic bypass and no intrinsic liver disease; and Type C is associated with ESLD. Therefore, hepatic encephalopathy of liver transplant patients are categorized as Type C, and are further subcategorized into those with episodic hepatic encephalopathy, persistent hepatic encephalopathy, and minimal hepatic encephalopathy. In terms of symptom severity, the West Haven criteria [14, 15] for semi-quantitative grading of mental status have been used to score the grade of clinical severity: mild (Grade 1), moderate (Grade 2—lethargy/minimal disorientation/subtle personality change), severe (Grade 3—somnolence/confusion/disorientation), or Grade 4 (coma). Several metabolic factors contribute to the development of hepatic encephalopathy, which include ammonia, inhibitory neurotransmission through gamma-aminobutyric acid receptors in the central nervous system, and changes in central neurotransmitters and circulating amino acids [16].

Endocrine System

Diabetes mellitus is seen in 15–30 % of patients with cirrhosis [17]. Insulin resistance is present in many patients with nonalcoholic steatohepatitis and chronic hepatitis C. Cirrhosis has also been linked to abnormalities in the other endocrine glands, including abnormal sex hormone metabolism, thyroid disease (hypo- and hyperthyroidism),

osteoporosis, and adrenocortical dysfunction.

MELD Score

The Model for End-Stage Liver Disease (MELD) score is a grading system for evaluating the severity of chronic liver diseases for patients age 12 and older. Candidates age 11 and younger are graded with the Pediatric End-Stage Liver Disease (PELD) scoring system . The MELD system was originally developed to predict 3 month-mortality in patients undergoing a transjugular intrahepatic portosystemic shunt (TIPS) procedure [18]. It has been used for the allocation of livers to adults since February 2002 in the United States; this system better predicts liver transplantation outcome compared to the traditional Child-Pugh score. MELD score is calculated based on the three laboratory values (bilirubin, creatinine, and international normalized ratio [INR]): [19]

$$\text{MELD} = 3.8\ [\text{Ln serum bilirubin (mg/dL)}] + 11.2\ [\text{Ln INR}] + 9.6\ [\text{Ln serum creatinine (mg/dL)}] + 6.4$$

where Ln is the natural logarithm.

The United Network for Organ Sharing (UNOS) modifies the currently-used MELD system in two ways. In order to eliminate negative values, the lowest values of each laboratory tests is set at 1.0 (i.e., creatinine of 0.8 mg/dL is automatically changed to 1.0). Therefore, the minimum MELD score becomes 6. In order to avoid giving an unfair advantage to patients with intrinsic renal disease, the maximum serum creatinine level is set at 4.0 mg/dL, which is also the value automatically assigned to patients on dialysis. For allocation purposes, the upper level of the MELD score is capped at 40. Thus, UNOS modified the MELD score for liver transplantation allocation to range from 6 to 40. A higher MELD score indicates increased mortality in the waiting period, thus patients are prioritized for liver transplantation with a higher ranking in the waiting list of a given blood type. MELD scores are updated regularly, especially for patients with severe illness. For example, patients with MELD scores ≥25 have their scores updated weekly. Under the current deceased donor liver allocation system, patients with acute liver failure are exempt from the MELD-based prioritization process outlined above. Patients with acute liver failure are prioritized as UNOS Status 1A or Status 1B. Status 1A patients have a life expectancy of hours to a few days without a liver transplant. Status 1B is reserved for very sick, chronically ill pediatric patients (age less than 18). Also, several conditions receive “Standard MELD Exceptions ”; they receive a higher than calculated MELD score due to higher mortality. These conditions include hepatocellular carcinoma (HCC), hepatopulmonary syndrome, portopulmonary hypertension, familial amyloid polyneuropathy, primary hyperoxaluria, cystic fibrosis, and hilar cholangiocarcinoma. The anesthesia team should be well aware of patients’ MELD scores, since patients with high MELD score have been demonstrated to have a higher incidence of complications and mortality at liver transplantation.

The PELD system is calculated using parameters including bilirubin, INR, albumin, growth failure, and age (less than 1 year old or not).

Other Recipient Conditions

The following recipient conditions warrant special anesthetic considerations from the anesthesiologist team. Fulminant hepatic failure is defined as acute liver necrosis without any preexisting liver disease. This condition is one of the MELD-exempt conditions; the severity and priority for liver transplantation would be gauged with another grading system (i.e., King's College Criteria [20]). In addition to rapidly progressing coagulopathy, renal failure, metabolic acidosis, and respiratory failure, increased intracranial pressure can be an important challenge to successful perioperative anesthetic management (Chap. ##). Patients with hepatopulmonary syndrome or portopulmonary hypertension also receive MELD-exception treatment. Severe intraoperative hypoxemia or acute right heart failure could be major challenges in the care of these patients during the peri-transplantation period. These conditions are discussed further in Chap. ##. Emergent retransplantation is indicated for a primary nonfunctioning liver graft. Primary nonfunctioning is defined as an aggravated form of reperfusion injury resulting in irreversible graft failure without detectable technical or immunological problems [21, 22]. It is the most common reason for early retransplantation [23], with a reported incidence of 4–8 % [24]. These patients present at the ICU after recent liver transplantation with or without hepatectomy of the nonfunctioning liver graft. These patients are transferred from the ICU to the operating room with full monitoring and vascular accesses and the retransplantation is performed with a minimal dissection stage; however, a prolonged "anhepatic state" due to graft failure often causes severe coagulopathy and metabolic derangement including hyperkalemia and metabolic acidosis. Retransplantation for chronic rejection is often associated with adhesion and a prolonged dissection phase with surgical bleeding and incurred risk of massive transfusion. Budd-Chiari syndrome is a rare cause of portal hypertension and liver failure, which often results from hypercoagulable states induced by polycythemia vera, essential thrombocytosis, and myeloid metaplasia [25, 26]. These patients can present for liver transplantation with or without porto-systemic shunt surgeries or transjugular intrahepatic porto-systemic shunts (TIPS). Intraoperatively, establishment of vascular accesses could be challenging and a thorough review of the preoperative venography is important for planning.

Types of Liver Grafts and Their Implications

A liver transplantation involves the whole liver or a reduced-sized liver (a split graft or a liver segment). Transplantation of the latter would allow two liver recipients to

receive a liver from one deceased donor or allow for living donor liver donation. A reduced-size liver transplant may result if the donor liver is too large for the recipient. Liver grafts can be donated from either deceased or living donors. The former can be categorized into donation after brain death (DBD) donors and donation after circulatory (or cardiac) death (DCD) donors . Living donor grafts consist of right lobe donations for mainly adult recipients or left lobe donations for mainly pediatric recipients. In 2011 in the United States, 5805 adult liver transplants were performed, which included transplant of 5351 livers from DBD donors, 266 from DCD donors, and 188 from living donors [1]. Concerns about donor safety has decreased the enthusiasm for living donor liver transplantation in the United States, and recently the number of donations from living donors plateaued at about 250 annually. For deceased donors, extended (or expanded) criteria donation (ECD) liver grafts have been utilized increasingly due to the shortage of donors with standard criteria donation (SCD) . The definition of ECD has been defined well in kidney transplantation; however for liver transplantation, the criteria are not necessarily unanimous and are defined per transplantation center [27].

The course of anesthesia for liver transplantation is often dictated by the category and the quality of the donor liver graft. For example, living donor liver transplantation for an adult recipient usually takes place alongside donor hepatectomy; therefore, coordination of the timing of two operations (donor and recipient) is important. In general, the cold ischemic time in living donor liver transplantation is markedly shorter than that in deceased donor liver transplantation. Liver transplantation using ECD graft [28, 29] or grafts with higher donor risk indexes [30] may result in primary nonfunctioning and delayed functioning. These conditions can present with significant hemodynamic derangement post re-perfusion with refractory coagulopathy and lactic acidosis.

Surgical Methods and Their Anesthetic Implications

Discussion with the transplant surgical team regarding the surgical method of the liver transplantation is crucial as each surgical team and institution has its own method. Basically, the liver graft is implanted either with preservation of the retrohepatic inferior vena cava (IVC) (the so-called “piggyback” method) or the traditional retrohepatic caval resection (the so-called “standard” method). The piggyback method , first described by Tzakis et al. in 1989 [31], has become widely adopted and is the contemporary technique of choice for liver transplantation [32]. This technique preserves the venous return from the lower body via the IVC with application of a side clamp on the IVC to exclude the hepatic vein for circulatory system for hepatectomy of the diseased liver. In such a way, the venous stasis of the lower body and the kidneys is avoided and the preload of the heart during the anhepatic stage can be maintained. On the other hand, the retrohepatic caval resection technique was described as the original

method of liver transplantation hepatectomy [33]. Clamping at the supra-hepatic IVC as well as at the infra-hepatic IVC are required to exclude the liver from the circulation for hepatectomy, which often results in venous stasis in the lower body as well as the kidneys; venous return is compromised and the preload of the heart is decreased. When venous collateral vessels are well established, this drawback can be minimized. Prior to the procedure, the surgical team may test hemodynamic conditions with a test application of the IVC clamp. Therefore, the anesthesiology team should prepare for potential hypotension after the application of the IVC clamping, which requires inotropes with judicious usage of volume infusion. Alternatively, to minimize the drawbacks associated with the IVC clamping as well as minimize the venous stasis of the portal system, veno-venous bypass (VVB) was developed [34] and has been used in selected centers. The idea is to insert drainage cannula both in the portal vein and the femoral vein and return the venous blood to the upper body venous system using a centrifugal pump. Traditionally, the return cannulas are placed in the axillary vein with a surgical cut down technique; however, the percutaneous technique using the internal jugular vein is advocated to avoid wound complications by axillary cut down (infection, seroma, or nerve damage). The anesthesiology team may be asked to place the return cannula via the internal jugular vein and play a major role in the VVB initiation and termination [35].

Intraoperative Anesthetic Management

Induction and Maintenance of General Anesthesia and Anesthetic Agents of Choice

The recipients' preoperative condition is reviewed and examined for any further changes; any sign of deterioration of the condition compared to the pretransplantation workup should be investigated. Judicious use of anxiolytics is recommended to avoid oversedation prior to the induction of general anesthesia, as the bioavailability of benzodiazepine usually high due to low serum albumin. Given the urgency of the transplantation and possible delayed gastric emptying due to ESLD, the patient should be treated as if they have a full stomach and rapid sequence induction to secure the airway is warranted; however, routine use of succinylcholine in this scenario should be avoided due to a concern for acute hyperkalemia associated with this agent. Intravenous induction agents including propofol or etomidate can be safely used. When post induction hypotension is a concern, the latter agent may be preferred. Potential adrenal suppression with etomidate may be mitigated by the glucocorticoid administration for immunosuppression regimen. Maintenance of anesthesia can be easily achieved with the balanced technique using inhalational agents, nondepolarizing muscle relaxants, and opioids. If fast track anesthesia is planned to remove the endotracheal tube early in the

postoperative period, the rapid offset agents can be selected, including sevoflurane or desflurane, rocuronium if sugammadex as a reversal agent is available, and remifentanil infusion.

Several inotropes of choice (epinephrine, dopamine, or norepinephrine) should be prepared for any unexpected hemodynamic changes. Vasopressin should also be available in case of refractory hypotension. A cell salvage device and a rapid infusion system should also be available in the operating room and ready for use if indicated. Prophylactic antibiotics (a third generation cephalosporin of choice) should be given prior to the skin incision and timely re-dosing during the operation. In case of massive bleeding, the timing of re-dosing should be shortened to maintain the effective plasma concentration of antibiotics. For intraoperative fluid maintenance, any isotonic-potassium and glucose-free crystalloids should be adequate. Excessive usage of normal saline solution should be avoided, since a sudden increase in serum sodium level may result in acute central pontine myelinolysis [36].

Vascular Accesses and Monitoring

The degrees of cardiovascular and pulmonary system involvement in ESLD as well as the invasiveness of the surgical transplant method dictate selection of invasive hemodynamic monitoring. However, each transplantation institution has its own institutional guidelines based on its philosophy and historical practice [37]. These institutional practices can vary significantly from a minimalist approach (one arterial line, several large bore intravenous lines with or without central venous line) to a maximalist approach (two arterial lines, two central lines with a pulmonary arterial [PA] catheter with continuous cardiac output measurement and TEE). The advocates of two arterial lines (one radial arterial line and the other via a central arterial system: contralateral side of the brachial artery or the femoral artery) are based on observations that a central arterial line would better represent the central arterial pressure than a radial artery, especially under hypotensive conditions, would serve as a failsafe measure during the surgery, and would allow continuous monitoring during phlebotomy via the other arterial line. The two central lines may assure the two independent rapid infusion sites of blood and fluid at the time of hemodynamic disaster, while allowing placement of a PA catheter. A PA catheter provides direct measurement of right-sided pressures as well as pulmonary arterial pressure, which is crucial when the recipient has preexisting pulmonary arterial hypertension. The catheter can provide continuous monitoring of pulmonary arterial pressure postoperatively in the ICU. TEE can be especially useful to evaluate right ventricular function that demonstrates pulmonary hypertension to rapidly diagnose the potential cause of cardiac collapse (hypovolemia, myocardial depression, and clot/air embolism), and to evaluate the performance of VVB. If VVB placement using the axillary cut down technique is anticipated, a venous

access on the ipsilateral side of the arm should be discouraged, since infusion via the distal site of the same side of the axillary cut down will be obliterated.

These invasive monitors should be placed under a well-established safety protocol. Ultrasound-guided insertion of the central lines would be recommended and the tube transducing method [38] assures the venous site prior to the insertion of a dilator. Use of a smaller diameter arterial catheter may minimize postoperative hematoma formation. The arterial puncture of the femoral artery should be performed with great caution since the site is prone to postoperative hematoma formation, which could occasionally warrant surgical evacuation and pseudoaneurysm repair. A TEE probe can be safely placed and maintained intraoperatively; however, insertion of a probe into a patient who had recent banding of esophageal varicose veins can result in gastrointestinal bleeding. A recent review of the complications associated with invasive monitoring, including VVB cannulation, showed a relatively low incidence overall; however, vascular complications at the femoral vascular sites (arterial and venous) were rather striking [39].

Stage I (Pre-anhepatic) Management

The anesthesia team should be aware that there are three distinctive stages in liver transplantation. Each stage is defined by surgical feature, which inevitably demands specific anesthetic management and could potentially lead to specific complications. Stage I starts at the surgical incision and ends with the termination of the blood flow to the recipient's diseased liver.

During this stage, the surgical team performs dissection of the liver and its hilum, which may take longer in those who undergo redo-liver transplantation, have histories of upper abdominal surgery, or have histories of recurrent spontaneous bacterial peritonitis. A large amount of surgical bleeding can be encountered when recipients have severe portal hypertension with numerous porto-systemic venous shunting in the abdominal walls and peritoneal tissues. On the other hand, the duration of this stage can be very short for those who undergo redo liver transplantation for primary nonfunctioning due to completed dissection with minimum adhesion. Therefore, the primary goal of anesthetic management during Stage I is to maintain the volume status. A potential risk of sudden surgical bleeding during Stage I should be determined preoperatively to plan vascular accesses and to prepare blood products. When the risk is high, a rapid infusion device should be prepared. Maintenance of low central venous pressure (CVP) may reduce venous bleeding during hepatectomy [40, 41], although the evidence for using low CVP in liver transplantation is conflicting [42, 43]. For patients with severe portal hypertension, octreotide infusion may be indicated to reduce the portal venous pressure.

Aggressive normalization of the coagulation abnormality based on traditional

laboratory-based coagulation tests and/or point of care coagulation tests (thrombelastography or thromboelastometry) may not be warranted or even could be detrimental [44]. On the other hand, a systematic review indicates that the benefit of prophylactic use of tranexamic acid and aprotinin both reduced the need for allogeneic blood products in liver transplantation. No increased risk for hepatic artery thrombosis, venous thromboembolic events, or perioperative mortality was observed for any of the investigated drugs [45]. Currently, aprotinin is not used due to widely publicized concern for thromboembolic complications observed in the field of cardiac surgeries [46].

Stage II (Anhepatic) Management

Stage II starts when blood circulation to the diseased liver is terminated, which is achieved by clamping the portal vein, the hepatic artery, and the hepatic vein. Hepatic venous drainage to the systemic circulation is achieved either by application of a spoon-clamp at the junction of the hepatic vein to the IVC or by application of straight clamps both above and below the retrohepatic IVC. The former clamping technique is required for the surgical team to perform the retrohepatic caval preservation technique or the piggyback technique. Stage II ends when the liver graft is reperfused in the recipient's circulation system. During this stage, the surgical team performs a hepatectomy of the recipient's diseased liver, ensures hemostasis of the liver bed, establishes the venous outflow of the liver graft, and anastomoses one of the two blood inflows to the liver graft (the portal venous system or rarely the hepatic arterial system). In a few selective cases with severe intra-operative hemodynamic instability, the application of VVB is still justifiable and it is initiated to aid the surgical procedures at this stage [47]. Occasionally, VVB is initiated to aid the dissection procedure when the surgical team encounters difficulty.

During Stage II, the patient is anhepatic, which is the hallmark of this phase. Despite preexisting dysfunction of the diseased liver, complete loss of whatever liver function remains leads to striking changes in the recipient's system. Coagulopathy is often observed due to accumulation of tissue plasminogen activator (tPA) and other anti-coagulation products, including a heparinoid product [48] which is normally metabolized by the liver. Drug metabolism relying on hepatic function ceases. The level of serum lactate is elevated. Hemodynamic changes at the time of initiation of the stage can be profound. In this setting, aggressive correction of coagulation derangement should not be indicated, since the changes are temporary phenomena and accumulated tPA and other endogenous anti-coagulants will normally be quickly metabolized after liver graft reperfusion. Sudden hemodynamic derangement should be anticipated at the temporal termination of the hepatic venous drainage, which often results in decreased cardiac output because of the reduced preload. This is especially commonly observed at

the clamping of the IVC for the standard procedure or overzealous side clamping of the IVB for the piggyback procedure. Well-developed collateral venous circulation formation due to long standing ESLD may minimize this incidence; otherwise, VVB should be indicated when the patient cannot tolerate the clamping of the IVC. Sequestration of the venous blood in the portal venous system may lead to hypotension. In this case, porto-systemic shunting with a temporal surgical shunting procedure or porto-systemic VVB can be performed. Of note, the hypotension occurring in this stage is better treated with aggressive administration of vasopressors rather than fluid replacement, since aggressive volume administration may result in volume overload at graft re-perfusion, which could lead to right heart failure, or venous congestion of the liver graft which is detrimental for its function. Preparation for graft reperfusion at Stage III should be initiated; serum potassium level should be aggressively managed to less than 4 mEq/L, metabolic acidosis should be corrected, and inotropes should be readily available.

Stage III (Neohepatic) Management

Stage III starts at graft reperfusion and ends at completion of the liver transplantation procedure. This stage is further subdivided into the time period within 5 min after the graft reperfusion and the rest of the period, since the initial 5 min after the graft reperfusion is the most volatile period regarding hemodynamic condition. After completion of anastomosis of hepatic outflow and one of the hepatic inflows (mainly the portal vein, rarely the hepatic artery), the surgical team is ready to reperfuse the liver graft. During the graft reperfusion, all the sequestrated venous blood in the portal venous system and in the venous system in the lower body returns to the heart if VVB has not been used. Preservative solution with high potassium concentration remained in the liver graft and endogenous metabolites with accumulated in the vascular system of the liver graft during cold and warm ischemic stages are also returned to the heart. Sudden overloading of the heart with this venous volume, potassium, and endogenous metabolites can result in systemic vascular dilatation with depressed cardiac function as well as pulmonary vascular constriction; systemic arterial hypotension, decreased cardiac output, bradycardia, and pulmonary arterial hypertension are often observed and even prolonged sinus arrest or pulseless electrical activity cardiac arrest could occur [49]. The systemic hypotension associated with liver graft reperfusion is coined as post reperfusion syndrome (PRS). PRS, first described by Aggarwal et al. in 1987 [50], is a syndrome of cardiovascular collapse related to systemic vasodilatation due to the release of vasoactive substances from the reperfused liver, acidosis, hyperkalemia, hypercarbia, and hypothermia. The original definition of PRS is prolonged hypotension (over 1 min) which occurs within 5 min after the reperfusion of the liver graft. Hypotension is defined as the decrease of systemic mean arterial pressure of more than

30 % from base line pre-reperfusion.

The anesthetic management of this critical stage is preparation for such cardiac dysfunction and timely management of cardiac conditions. For preparation, aggressive treatment of serum potassium should be initiated during Stages I–II. The methods include insulin and glucose administration, loop diuretics, treatment of metabolic acidosis with bicarbonate (50 mEq IV) or tromethamine infusion. A 100-mL of the latter solution contains tromethamine 3.6 g (30 mEq) in water, which is hypertonic 389 mOsmol/L and pH 8.6 (8.4–8.7). This solution does not contain sodium ions, which is beneficial for unwanted sodium load for recipients with hyponatremia. Intravenous administration of calcium chloride (1–2 g) should be considered immediately prior to the graft reperfusion for cardiac membrane stabilization. In order to decrease exogenous potassium load, allogeneic red blood cells can be processed with a cell salvage device. Uncontrollable hyperkalemia, when encountered, should be aggressively treated with intraoperative hemodialysis using the existing hemodialysis catheter or newly established central venous access. “Pretreatment” to counteract the anticipated cardiac depression can be initiated prior to graft reperfusion using infusion of inotropes (e.g., epinephrine), intravenous calcium chloride (1 g), intravenous bicarbonate (50 mEq), and intravenous methylene blue (100 mg). Maintaining 100 % inspiratory oxygenation concentration to increase oxygen stores in the system and decreasing inhalation agent to minimize vasodilator effect of the agent should be considered.

At graft reperfusion, further aggressive treatment should be indicated upon any initial sign of cardiac dysfunction: bolus administration of epinephrine and vasopressin and/or atropine (0.4–1 mg). When cardiac arrest occurs, the surgical team should initiate immediate cardiac compression. This is achieved best by direct cardiac massages via the incision of the left diaphragm. For differential diagnosis of cardiac arrest, TEE is very useful. When intracardiac clots are witnessed, heparin administration (3000–5000 IU) via the central line to prevent further expansion of the clot can be considered. A low-dose administration of recombinant tissue plasminogen activators (0.5–4 mg) has been reported to be effective in the treatment of pulmonary thromboembolism in liver transplantation [51].

When stable hemodynamic status is achieved after reperfusion of the liver graft, the surgical team proceeds to complete the other inflow vessel anastomosis. At this stage, close monitoring of the coagulation status is very important, since reasonable surgical hemostasis should be achieved prior to reconstruction of the biliary system following the vessel anastomosis. Coagulation status monitoring at 30 min after the graft reperfusion should best guide further coagulation management, since a reasonable improvement of coagulation parameters is expected at this stage. Conversely, poor graft function should be anticipated when ongoing coagulopathy is observed at coagulation monitoring at 30 min post reperfusion.

At the end of the procedure, a return VVB cannula, if it was used, is removed and a

purse string stich is applied at the insertion site to minimize hematoma formation. If the patient's condition is stable, the liver graft is functioning, and the blood transfusion is minimal, fast track anesthesia can be considered and early termination of the mechanical ventilation and removal of the endotracheal tube can be achieved either in the operating room or the ICU [52].

Strategies for Blood Transfusion Conservation

Complications related to allogeneic blood transplantation in liver transplantation have been documented. Therefore, it is prudent for the anesthesia team to exercise conservation strategies to minimize exposure of the patients to allogeneic blood products. A number of strategies have been demonstrated to achieve the goal. These include maintenance of low CVP, acute hemodilution and autologous blood return, and cell salvaging. The theoretical rationale for maintaining low CVP is to minimize surgical venous bleeding with reduction of systemic venous pressure. This technique seems to be particularly useful during Stage I. The techniques include phlebotomy and pharmacological systemic vasodilation with an inhalational agent as well as veno-dilators [53]. Acute hemodilution and autologous blood return at the beginning of Stage I can achieve not only reduction of the CVP but also preserve autologous blood for auto-transfusion in a later stage of transplant surgery. The rationale of this technique is that platelets and coagulation factors can be well preserved in the autologous blood and aid hemostasis upon auto-transfusion. This technique can be indicated only for patients with hemodynamic stability and higher hemoglobin levels. Red blood cell (RBC) salvage using a cell salvage device is a well-established technique and has widely been used. Contraindications for the technique include infected materials in the surgical field and malignant lesions. Some studies, however, suggest the properly washed shed blood were free from malignant cells [54]. By combining these strategies, some transplantation centers have achieved non-RBC transfusion liver transplantation [53].

Point-of-care coagulation monitors have been widely used to diagnose coagulopathy or fibrinolysis and to direct transfusion therapy [55]. Unlike the conventional plasma coagulation tests (including prothrombin time, partial thromboplastin time, INR, platelet count, or fibrinogen level), these point-of-care coagulation monitoring devices can provide the anesthesiology team with relatively whole blood coagulation conditions [56], except for temperature (the default temperature of 37.0 °C at the measurement) and endothelial function (the cup and the torsion pin are made of steel) in a relatively short period of time. Currently, thromboelastometry and thromboelastography are widely available as point-of-care coagulation monitors. Thromboelastometry (ROTEM, TEM®, Tem Innovations GmbH, Munich, Germany) is an established method testing viscoelastic hemostasis in whole blood [57]. Its multiple assays can provide information regarding extrinsic and intrinsic coagulation conditions as well as heparin

effect, fibrinolysis, and fibrinogen contribution. Thromboelastography has also been used widely [58] and provides information on the activity of the plasma coagulation system, platelet function, and fibrinolysis [59]. Recently, several new TEG variants have been utilized to provide faster assessment of coagulation condition as well as estimation of fibrinogen level.

Special Agents Administered at Transplantation

Glucocorticoid is a very common agent to be started intraoperatively; it is administered intravenously (methylprednisolone of 500 mg–1 g) immediately prior to or at the time of graft reperfusion. Anesthetic implication of intraoperative glucocorticoid administration is mainly hyperglycemia. The standard initial immunosuppressive regimen for most liver transplant recipients is tacrolimus and mycophenolate mofetil, commonly in conjunction with glucocorticoid. By 1 year after transplant, most patients are no longer taking glucocorticoid and are taking tacrolimus with or without mycophenolate mofetil. With these immunosuppressive regiments, acute rejection occurs in less than 20 % of recipients during the first year.

Currently, induction agents for lymphoid depletion have infrequently been used in liver transplantation; however, they have an important role as calcineurin inhibitor-sparing agents in the immediate post-transplant period. These induction agents include polyclonal antibodies (e.g., antithymocyte globulin and antilymphocyte globulin) and monoclonal antibodies such as muromonab-CD3 (or OKT3) which is directed against the CD3-antigen complex on mature T-cells or humanized monoclonal antibodies against the interleukin-2 receptor (e.g., basiliximab and daclizumab). Other experimental induction agents may also be used, including belatacept, which is a high-affinity fusion protein that binds CD80/86 on antigen-presenting cells; efalizumab, which is a humanized monoclonal antibody against leukocyte function-associated antigen-1; or alemtuzumab, which is a humanized monoclonal, complement-fixing, anti-CD52 antibody that is expressed on the surface of immune cells. If these induction agents were used in the operating room, the anesthesiology team should be vigilant for potential complications associated with these agents including fever, rash, hypotension, bronchospasm, pulmonary edema, or thrombocytopenia. Premedications with corticosteroid, histamine 1 receptor blocker, histamine 2 receptor blocker, and acetaminophen should be administered prior to the initiation of these agents. Any side-effects should be promptly treated with termination or slowing-down of the infusion rate of an induction agent.

Hepatitis B hyper immunoglobulin is often indicated for patients with hepatitis B receiving hepatitis B-negative donor graft. This product is made from human plasma; therefore, the patient should be watched for any sign of allergic reaction.

Octreotide is occasionally indicated for recipients with severe portal hypertension

to decrease portal venous pressure and flow during transplantation. The reported hemodynamic impact of this agent includes increase of systemic and pulmonary vascular resistance and resultant increase of systemic and pulmonary arterial pressures with bradycardia and decreased cardiac output.

Recognition and Formation of a Liver Transplantation Anesthesiologist Team

Recruitment of dedicated liver transplantation anesthesiology team members has been advocated to increase the consistency of the practice and potentially safer transplantation results [60]. A number of large transplantation centers have adopted such a practice [61]. Unfortunately, anesthesiologists or intensivists are not specifically mentioned or recognized in the statement in the glossary of the Health Resources and Services (HRHS) Administration Organ Procurement and Transplantation Network (OPTN) web site (http://optn.transplant.hrsa.gov/resources/glossary.asp). The stated definition of "Transplant Team" only includes clinical transplant coordinators, transplant physicians (mainly indicates hepatologists), transplant surgeons, financial coordinators, and social workers. As an effort to establish the transplantation anesthesiology team, a proposal has been created and is under review with the American Society of Anesthesiologists (ASA) (Table 28.3) [62].

Table 28.3 Guidelines for director of liver transplant anesthesia Committee of Origin: Transplant Anesthesia (Approved by the ASA House of Delegates on October 21, 2009)

Liver transplant programs shall designate a Director of Liver Transplant Anesthesia.
The Director of Liver Transplant Anesthesia shall be a Diplomate of the American Board of Anesthesiology (or hold an equivalent foreign certification). Applicants who are not Board certified shall attain this status within 2 years of their approval as Director of Liver Transplant Anesthesia.
The Director of Liver Transplant Anesthesia shall have one of the following:
1. Fellowship training in Critical Care Medicine, Cardiac Anesthesiology and/or Pediatric Anesthesiology that includes the perioperative care of at least 10 liver transplant recipients, or
2. Within the last 5 years, experience in the perioperative care of at least 20 liver transplant recipients in the operating room and/or intensive care unit. Experience acquired during postgraduate (residency) training shall not count for this purpose.
The Director of Liver Transplant Anesthesia shall earn a minimum of 8 h of ACCME Category I CME credit in transplant-related educational activities within the most recent 3-year period.

(Adapted from United Network for Organ Sharing. Attachment I to Appendix B of UNOS Bylaws: XIII. Tranplant Programs. Available at https://www.unos.org/wp-content/uploads/unos/Appendix_B_AttachI_XIII.pdf; accessed 9/15/2015.)

Conclusions

The liver transplantation anesthesiology team should be well-trained and specialized to provide safe and reliable management. Since patients with ESLD present with various degrees of systemic manifestations and these conditions have significant implications in anesthetic course, preoperative evaluation and planning of anesthesia management is crucial. Occasionally, transplantation-specific procedures should be requested, including VVB management and TEE placement and evaluation. Intraoperative coagulation management should be stage-specific. Intraoperative compilations sometimes require the anesthesiology team's best abilities to treat cardiac demise and massive bleeding and its treatment with transfusion.

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29. Postoperative Care of the Liver Transplant Recipient

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Introduction

Liver transplantation for both acute and chronic liver failure results in excellent outcomes. Patient and graft outcomes are closely monitored on a national level and 1-year survival is between 80 and 92 % (http://optn.transplant.hrsa.gov/latestData/rptStrat.asp accessed 10/19/13). Perhaps more than with any other surgical program, graft and patient outcomes for liver transplantation reflect the combined efforts of several interrelated services. The success stems from a multidisciplinary approach with close involvement of gastroenterologists, anesthesiologists, surgeons, and intensivists. This chapter will review the concerns related to postoperative care of the liver transplant patient in the intensive care unit. Existing evidence on potential early concerns such as hemodynamic monitoring, respiratory failure, neurologic management, electrolyte and glucose correction, coagulation management, systemic immunosuppression, graft function and rejection, and technical problems will be reviewed. The chapter will conclude with brief mention of long-term complications related to recurrence of disease that may lead to future ICU admissions.

Monitoring Hemodynamics

Monitoring hemodynamics after liver transplantation is critical in the postoperative setting. Acute changes in hemodynamics that are not properly diagnosed or treated can result in impaired graft function, prolonged ICU stay, and increased mortality. Postoperative management of hemodynamics begins with a thorough understanding of the underlying pathophysiology. End-stage liver disease typically results in high cardiac output and low systemic vascular resistance. Following successful transplantation this process begins to reverse, leading to a reduction in cardiac output and an increase in systemic vascular resistance with improved maintenance of systolic blood pressure [1].

Blood Pressure and Fluid Status Measurement

Real-time monitoring of blood pressure in the postoperative setting is crucial and invasive hemodynamic monitoring should be maintained for at least the first 24 h following transplant. Hemodynamic monitoring for liver transplantation should include arterial and central venous catheters at a minimum. Beyond central venous pressure (CVP) monitoring, utilization of a pulmonary artery catheter (PAC), echocardiography, or noninvasive continuous cardiac output [2] has been described. The type of monitoring differs among transplant centers and is determined by individual or institutional practice. For example, Schumann et al. surveyed 62 transplant centers in the United States and found that PACs were used in 30 % and transesophageal echocardiography was used in 11.3 % during the intra-operative period [3].

The PAC had previously been the standard for fluid monitoring for liver transplantation at most centers. Evidence that PACs fail to improve outcomes in critical care [4, 5], and their potential to induce ventricular arrhythmias [6] has led to less-invasive monitoring for the orthotopic liver transplant (OLT) patient. An increasing number of transplant centers now rely on CVP monitoring alone with only selective PAC usage, while others continue to routinely use PAC monitoring for all their patients.

Due to limitations of central venous and pulmonary artery catheters, the use of dynamic methods of fluid responsiveness is currently being explored. Presumably dynamic measurements based on physiologic responses will be more accurate than static indicators [7]. The measurements, including systolic pressure variations (SPV) and pulse pressure variations (PPV) , are derived from algorithms that abstract data from an arterial line and allow beat-to-beat monitoring for the purpose of predicting fluid responsiveness. Although the data are promising under anesthesia [8, 9], these monitors have not been validated in the ICU. Furthermore, in order to obtain accurate calculations, patients must be in sinus rhythm, have a closed chest, have normal intra-abdominal pressures, and be on controlled ventilation with positive end expiratory pressure (PEEP) of 0–5 cm H_2O [10]. Perhaps the most prudent approach from all this

data is to base management on clinical examination findings and appropriately titrate fluid according to the patient's hemodynamic trends. The preferred choice of monitoring tool (central venous line, PAC, or echocardiography) remains controversial due to the lack of evidence indicating a difference in patient outcomes. Overall choice of monitoring for cardiac function and fluid status is probably best decided based on the expertise of the center and the familiarity and ease of access to different options.

Portopulmonary Hypertension

A detailed discussion of the underlying etiology of pulmonary hypertension in the liver transplant patient can be found in other chapters, but a discussion of their management deserves quick mentioning here.

Portopulmonary syndrome is defined as pulmonary hypertension in association with portal hypertension. Diagnostic criteria vary, but it is important to note that pulmonary pressures should be verified with right heart catheterization pre-transplant if suspicion for pulmonary hypertension arises on echocardiography [11]. Prevalence of portopulmonary syndrome in liver transplant is approximately 6 % as found in a prospective study evaluating 165 patients [12]. Due to the effect on postoperative mortality, most patients with portopulmonary hypertension will have been identified in the preoperative setting; this information is vital to the physician caring for the patient postoperatively. Of particular importance are both the severity of disease and treatments the patient received prior to transplant. Disease severity is a predictor of postoperative mortality. Severe portopulmonary hypertension (mean pulmonary artery pressure > 45 mmHg) is associated with a perioperative mortality of 40 % [13]. Mild pulmonary hypertension (mean pulmonary artery pressure < 35 mmHg) is not associated with decreased survival and current case series suggest that if pulmonary pressures can be reduced medically to less than 35 mmHg, then outcomes are acceptable [14].

If evidence of pulmonary hypertension is identified on echocardiography, then fluid status should be optimized, as volume overload can be an exacerbating factor. Inotropic support and inhaled agents for pulmonary hypertension, for example dobutamine, milrinone, and inhaled nitric oxide, can be used for more severe cases, particularly if the patient was requiring these agents prior to transplantation. Right heart function should be improved if possible, because prolonged failure will impair graft perfusion and lead to graft failure due to decreased left heart output (secondary to decreased left ventricular filling) and worsened venous congestion from right heart failure.

Randomized clinical trials for the treatment of portopulmonary hypertension are lacking and most therapies are derived from known treatments for primary pulmonary hypertension. These include epoprostenol (prostacyclin), endothelin receptor antagonists such as bosentan, and phosphodiesterase-5 inhibitors such as sildenafil. While definitive data in the liver transplant setting does not exist, these agents are

frequently used to improve a patient's pulmonary hemodynamics so that the patient can be considered for transplant [15]. The continuation of pulmonary vasodilators is critical in the postoperative setting. Additionally, repeat echocardiography and/or a pulmonary artery catheterization may be beneficial in directing further therapy if right ventricular failure develops in the ICU.

Respiratory Issues

Pulmonary complications can be very common in the postoperative setting. Many liver transplant patients will have a tenuous respiratory status requiring care ranging from close observation to prolonged mechanical ventilation. While the incidence varies, prompt recognition and treatment is essential to improve the patient's outcome [16]. Predisposing factors in the pre-operative setting include underlying pulmonary disease (in particular a restrictive pattern on pulmonary function tests) and smoking [17]. In addition, patients intubated pre-operatively are at risk for mechanical ventilation needs postoperatively due to the underlying disease.

Early Extubation

Early extubation after liver transplant is often possible due to improvements in both surgical and anesthetic techniques. The concept of early postoperative tracheal extubation began with cardiac surgery and was applied to select liver transplant patients in the late 1990s [18]. Proponents argued that early extubation reduced the risk of ventilator-associated pneumonia and improved both splanchnic and hepatic blood flow. Early extubation has been shown to decrease ICU length of stay and resource utilization [19]. In some centers, early extubation is performed in as many as 70–80 % of cases [20]. Although these results are promising, extubation immediately following OLT is not a routine practice at all transplant centers.

Variables predictive of delayed tracheal extubation include: primary graft dysfunction, renal and/or cardiovascular failure, serious neurological impairment, transfusion of more than 12 units of intraoperative red blood cells and pulmonary edema [21]. Interestingly, severity of liver disease, duration of surgery, and duration of cold ischemia did not predict prolonged intubations. Glanemann and colleagues demonstrated that patients that were extubated immediately following surgery actually had a lower rate of reintubation when compared with patients who were extubated on average 5 h postoperatively, or those requiring prolonged mechanical ventilation of more than 24 h [22]. In a multicenter trial conducted to evaluate the safety of early extubation [23], extubation rates varied from 5 to 67 % despite a uniform set of extubation criteria. The authors concluded that there were likely institutional-specific practices that were not measured or controlled by the study. The differences in outcomes

among the centers revealed that variability persists despite efforts to provide protocolized care.

At this time, there is no consensus among transplant centers regarding early extubation following OLT, and whether it should be a therapeutic goal remains debatable [24, 25]. However, for the correctly selected patient, this can be a valid strategy to reduce hospital costs and ICU length of stay (Table 29.1). Patients that are good candidates for extubation are hemodynamically stable, demonstrate low risk for surgical re-exploration, and have received few intraoperative blood products. Additional trials are required to establish indications for early extubation.

Table 29.1 Data on early extubation after liver transplantation

Study	Type	Comment
Glanemann et al. [154]	Retrospective analysis	546 patients analyzed, immediate extubation in 18.7 %. No increased incidence of reintubation when compared with patients successfully extubated later.
Mandell et al. [19]	Prospective trial	147 sequential patients, 111 successfully extubated immediately. 83 patients transferred directly to surgical ward. 1 day ICU reduction in 75.5 % of patients with no problems reported with patient safety.
Biancofiore et al. [155]	Prospective trial	207 out of 354 patients extubated immediately, two re-intubated. In the final year of the study 82.5 % of patients were successfully extubated immediately.
Mandell et al. [23]	Multicenter prospective trial	391 patients who met criteria for early extubation. Complication rate of 7.7 %, however was skewed as two institutions had higher complication rates. Removing these two centers the complication rate fell to 3.6 %. This difference may be related to a center's experience with early extubation.

Mechanical Ventilation Management

Liver transplant patients who are not candidates for early extubation in the operating room are common, particularly among patients with pre-existing pulmonary pathology. A subset of patients will require prolonged mechanical ventilation and may develop additional pulmonary complications in the postoperative period. It is critical for the intensivist to recognize these patients and work to prevent ventilator associated lung injury.

Post-liver transplant patients in the ICU may develop acute respiratory distress syndrome [26]. The differential for ARDS is broad and includes infection [including ventilator-associated pneumonia (VAP)], systemic reperfusion injury, transfusion reaction, or graft failure. Patients who meet criteria for ARDS should be placed on low tidal volume ventilation [27]. While patients with severe liver disease were excluded from the ARDSNet study, there currently is no evidence to suggest that low tidal volume ventilation is harmful. In fact, recent studies have shown expanded benefit of low tidal volume ventilation even in patients who do not have ARDS [28].

The data in regards to other forms of mechanical ventilation are minimal for all critical care patients, and nonexistent for the post-OLT patient with ARDS. Airway

pressure release ventilation [29], high-frequency oscillatory ventilation [30, 31], prone ventilation [32], inhaled nitric oxide [33], neuromuscular blocking agents [34], and recruitment maneuvers [35] have all been studied, but for most randomized studies, patients with cirrhosis and liver failure were excluded. All the studies have shown the ability to improve oxygenation; some have shown a mortality benefit, but none have been as definitive as ARDSnet . Lung-protective mechanical ventilation should be the underlying ventilator support strategy of post-liver transplant patients with ARDS requiring mechanical ventilation.

Several theoretical concerns related to liver transplant patients and ARDSNet ventilation exist. In the ARDSNet protocol, permissive hypercapnia is used. There is some concern that this elevated PCO_2 may affect graft function, but there is currently no significant data addressing this potential complication. A second concern has been the administration of positive end-expiratory pressure (PEEP) and the corresponding increase in intrathoracic pressure, which in turn may impede venous return from the new liver. No studies have addressed high PEEP, but there is published evidence that PEEP up to 10 cm H_2O does not adversely affect graft function [36].

A subset of posttransplant patients will be difficult to wean from ventilator support and can prove challenging. Liver transplant patients should be treated like other patients who are mechanically ventilated and when feasible, given daily sedation holidays and spontaneous breathing trials in an effort to evaluate readiness for extubation. For patients with prolonged ventilation requirements, tracheostomy should be considered as with other intubated patients in the ICU setting.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome is a complication of cirrhosis that adds unique concerns to the postoperative course. The presence of hepatopulmonary syndrome can lead to increased postoperative mortality, particularly for severe cases of hepatopulmonary syndrome ($PaO_2 < 50$ mmHg on room air) [37]. Diagnosis and intra-operative management of hepatopulmonary syndrome is covered in other chapters.

The complication most commonly seen in patients with hepatopulmonary syndrome is prolonged hypoxia in the postoperative setting. Management of hypoxia is important, as prolonged mechanical ventilation in these immunosuppressed patients is associated with an increased risk of adverse events. There have been case reports of using nitric oxide to improve oxygenation, but no randomized trials exist to demonstrate the efficacy of this therapy [38]. In some patients with severe hepatopulmonary syndrome, the recovery of oxygenation may be prolonged. Recent data from two Canadian centers reported a mean rate of increase in PaO_2 of 3.1 ± 2.3 mmHg/month, and mean time to resolution of the intrapulmonary shunt of 4.5–18 months (median 11 months posttransplant) [39]. For these patients, prolonged mechanical ventilation may not be the

most appropriate therapy and it may be appropriate to consider extubation with administration of supplemental oxygen or noninvasive ventilation. This strategy can be effective in reducing ventilator related complications and will allow for a postoperative patient to leave the ICU and avoid a prolonged stay. Further studies will be necessary to determine the feasibility of this approach.

Neurologic Issues

Sedation

Sedation of the mechanically ventilated patient is challenging; this is especially true in the post-liver transplant patient. Mental status changes can be an early clue to graft dysfunction and efforts should be made to avoid excessive sedation. Benzodiazepines are not recommended as they have been shown to increase delirium in the ICU setting [40]. Propofol and dexmedetomidine have become popular sedatives due to their favorable pharmacokinetics. A recent meta-analysis suggested that use of dexmedetomidine or propofol infusions rather than a benzodiazepine infusion in critically ill adults reduced ICU length of stay and duration of mechanical ventilation [41]. There have been only a few recent case reports of safe use of dexmedetomidine infusions in post-liver transplant patients [42, 43]. The short acting agents have a favorable profile and allow for serial neurologic exams while still providing adequate sedation and anxiolysis.

Pain Management

Liver transplant is a major surgical procedure and may be accompanied by significant postoperative surgical pain. Pain control intra- and postoperatively is usually achieved with fentanyl, via infusion or intermittent bolus. Other opioids such as morphine and hydromorphone are avoided if possible due to their prolonged half-lives in liver failure. Fentanyl derivatives such as sufentanil, alfentanil, and remifentanil have superior pharmacokinetic properties but are not routinely used in the postoperative setting due to higher cost, insufficient staff experience, and lack of data showing improved efficacy. Some patients may require use of a patient controlled analgesia (PCA) pump along with longer acting agents, or transition to around-the-clock oral medications if pain persists.

Thoracic epidurals are beneficial for pain control following abdominal surgery [44], however they are not routine for liver transplant patients. The varied coagulation status of posttransplant patients raises concerns regarding the use of thoracic epidurals for postoperative analgesia. Hypotension from the epidural also raises concern that graft function may be compromised, particularly in posttransplant patients who have complex hemodynamic indices. For certain patients, other than transplant recipients (i.e.: hepatectomy patients) thoracic epidurals may be an acceptable option for postoperative

analgesia.

Non-opioid adjuncts for pain control have received significant attention. While there have been few studies examining these agents in liver transplant patients, some generalizations can be made. Nonsteroidal anti-inflammatory drugs (NSAIDs) , while efficacious for pain, should probably be avoided in the setting of increased bleeding risk and potential renal insufficiency. Acetaminophen is usually given at lower doses (2 g/day) for liver failure patients and should be avoided in the immediate postoperative period. However, for patients with functioning grafts, it is reasonable to consider acetaminophen administration due to its synergy with opioids.

Unfortunately there does not exist a one-size-fits all approach to pain management in the liver transplant patients. Each patient's individual risk for postoperative pain must be weighed against potential side effects. At this point, opioids such as fentanyl remain the mainstay of therapy until further studies are completed that can validate the safety of other interventions.

Hepatic Encephalopathy

Patients with liver failure often suffer from hepatic encephalopathy . The underlying etiology of hepatic encephalopathy is not entirely understood but current theories suggest that increased ammonia in the systemic circulation crosses the blood brain barrier where it is converted into glutamine by astrocytes. The glutamine causes swelling of the astrocytes, which impairs neurotransmission regulation. Interestingly, the level of ammonia does not correlate with neurologic symptom severity, so trending ammonia levels may not be helpful. In the postoperative period, a patient with a newly functioning liver should have steady clearance of toxins and a continual improvement in mental status. If there is no improvement or mental status declines, then a workup for graft nonfunction and infection should be undertaken and electrolyte imbalances corrected. Given the extreme changes in coagulation status, there should also be a low threshold to obtain imaging if there is concern for intracranial hemorrhage.

Osmotic Demyelination Syndrome

Hyponatremia in the setting of liver failure will be discussed below. However, it is important to note a potential neurologic complication that is associated with rapid correction of hyponatremia: central pontine myelinolysis or osmotic demyelination syndrome. The exact etiology of osmotic demyelination syndrome is unknown. The symptoms are usually seen 1–6 days after the insult of rapid sodium correction [45]. The most common clinical manifestation is fluctuations in consciousness. Eventually, pseudobulbar palsy and quariparesis may develop. If a patient is known to be hyponatremic preoperatively, then clinicians must closely monitor electrolytes and choose intravenous fluids appropriately to avoid rapid over correction postoperatively.

Electrolyte and Endocrine Issues

Adequate management of electrolytes can be challenging in posttransplant patients. The patients often have numerous abnormalities that should be closely monitored and corrected. Treatment of the more common electrolyte abnormalities found in posttransplant patients will be discussed below.

Sodium Homeostasis

Alterations in sodium levels are very common in pre- and posttransplant patients. In fact, there is clinical evidence to suggest that adding serum sodium to model for ESLD (MELD) scoring improves mortality prediction [46]. The first step in management is to determine the acuity of the situation. Patients with acute hyponatremia (development in under 48 h) are at risk for developing neurologic impairment and, consequently, require prompt correction of serum sodium levels. Administration of a hypertonic (3 %) saline infusion may be necessary for this situation. In patients with more chronic hyponatremia (development in over 48 h), rapid correction of hyponatremia is an independent risk factor for the development of posttransplant neurological complications [47]. Serum sodium correction should be performed in a controlled manner in this instance. The goal is usually 1–2 mmol/L per hour for the first 48 h. If the level rises too quickly, then hypotonic intravenous fluids should be started to restore the goal correction rate.

Hypernatremia is a less-frequent complication associated with liver transplant patients. The etiology is frequently related to excessive loss of free water in patients using an osmotic laxative (such as lactulose) to reduce hepatic encephalopathy. These patients are unable to adequately regulate their own free water balance due to impaired thirst mechanisms. This derangement may continue into the postoperative setting. As the mental status improves, the patient should begin to appropriately regulate water intake. For a hypernatremic patient who is unable to tolerate oral free water boluses, hypotonic maintenance fluids are recommended with close monitoring of electrolytes.

Hyperkalemia

Hyperkalemia may be the most lethal electrolyte abnormality due to the rapid progression of arrhythmias and death. The causes of hyperkalemia in the posttransplant patient are often multifactorial. Many liver transplant patients either have pre-existing renal dysfunction [48] or will develop transient renal dysfunction in the perioperative period which can impair mechanisms of potassium homeostasis.

For patients that had significant blood loss and transfusion requirements during the operation, there may be a significant potassium burden in the form of lysed cells from aged units that are transfused. Many liver transplant centers have a high usage rate of blood products and will often be assigned aged units by the blood bank because they are

unlikely to be wasted. While this is an excellent use of resources, these units contain less-functional cells and correspondingly represent a higher potassium load to the patient. Washing the cells before transfusion can partially attenuate the hyperkalemia, but frequent potassium monitoring remains necessary.

Hyperkalemia can be exacerbated acutely by reperfusion of the preserved graft and release of a significant potassium load from ischemic tissues. This is often managed with temporizing measures such as administration of calcium, sodium bicarbonate, and insulin with glucose, but the total body potassium may continue to be elevated in the postoperative setting. Dialysis may be needed if renal insufficiency and hyperkalemia persist in the ICU.

Hypocalcemia

Hypocalcemia is frequently identified in liver transplant patients. However, it is important to remember that these patients often have low albumin levels and the total calcium is not necessarily reflective of free calcium levels [49]. Ionized calcium levels are more accurate in this situation. Low calcium levels can result from chelation with the anticoagulant citrate, found in blood products and renal replacement therapy infusions. Hypocalcemia should be suspected in a patient with hypotension despite adequate resuscitation. Calcium gluconate or calcium chloride can be used for replacement.

Glucose Levels

Glucose levels following liver transplantation have significant implications for both prognosis and complications. Hypoglycemia in the postoperative period may be a marker for sepsis or poor graft function [2]. Hyperglycemia, which is much more common in the postoperative setting, may be a reflection of underlying diabetes, stress response, or steroid administration. Severe hyperglycemia (glucose > 200 mg/dL) is associated with an increased risk of liver allograft rejection [50], surgical site infection [51], and increased mortality [52]. Hyperglycemia is known to aggravate ischemia reperfusion injury in several organ systems.

Although hyperglycemia has complications, tight glucose control (between 80 and 120 mg/dL) is not recommended due to poor outcomes in the ICU setting [53, 54]. The best approach is to achieve modest glucose control (150–180 mg/dL), which is consistent with current ICU guidelines. In the immediate postoperative setting, an insulin infusion with frequent blood glucose checks is often required, as fluctuations in the stress response make steady state dosing difficult.

Renal Complications

Renal insufficiency following liver transplant is a common occurrence. Some studies report up to a 50 % incidence, though numbers vary widely due to the lack of a uniform definition. Acute ischemic tubular necrosis (ATN) is the most common cause of early renal failure following liver transplant [55]. A number of contributing factors increase the risk of renal dysfunction postoperatively. They include: hepatorenal syndrome, hepatitis C, diabetes mellitus, intraoperative and postoperative hemodynamic instability, massive transfusion, vasopressor infusions, infections, frequent radiologic studies, and nephrotoxic immunosuppressants and antibiotics [56, 57]. Management usually includes judicious fluid management, medication dose reductions based on creatinine clearance, and avoidance of further renal insults.

Eight to seventeen percent of patients with posttransplant acute kidney injury go on to require renal replacement therapy despite supportive care [2]. Risk factors for renal replacement therapy (RRT) following transplant include preoperative serum creatinine (Cr) greater than 1.9 mg/dL, blood urea nitrogen (BUN) greater than 27 mg/dL, ICU duration of greater than 3 days, and MELD score greater than 21 [55]. Some patients will progress to end stage renal disease (ESRD) and require kidney transplantation in the future. One percent of all kidney transplant patients in the United States are prior liver transplant patients with ESRD. The risk for kidney injury is further increased in recipients of living donor liver transplantation. These patients may develop small for size syndrome (see section below), which worsens fluid and hemodynamic derangements [58].

Hepatorenal syndrome (HRS) involves severe vasoconstriction of the renal vasculature and renal hypoperfusion in the presence of decreased systemic vascular resistance and normal renal parenchyma [59, 60]. Patients with HRS pre-liver transplant have been found to require longer ICU stays postoperatively and more dialysis, and are more likely to progress to ESRD following transplant than patients without HRS. Calcineurin inhibitor (CNI) initiation should be withheld for the first several days following transplantation to allow for reversal of HRS physiology and recovery of renal function [56].

Monitoring renal function in liver transplant patients is challenging, as elevations in serum creatinine are late indicators of renal insufficiency and proteinuria may not develop in the presence of calcineurin inhibitors [61]. A formula for calculating glomerular filtration rate should be utilized for the detection of renal dysfunction, but the results may be less reliable in patients with liver disease. A recent study suggested that cystatin C levels in the immediate posttransplant period are superior to creatinine based equations for estimation of GFR and may be useful as a confirmatory test for kidney injury [62]. Although it may be more accurate, cystatin C is not universally available, and it is more expensive. Until better markers are discovered and validated, serum creatinine will remain the main criterion used for the diagnosis of AKI.

Calcineurin-Induced Nephropathy

Once renal failure begins to develop, nephrotoxic immunosuppressants, namely CNIs, should be withdrawn, and immunosuppression should be maintained with renal-sparing protocols. CNI-induced nephropathy results from afferent arteriolar vasoconstriction and subsequent decrease in renal perfusion [63]. Using a reduced dose of cyclosporine, or replacing cyclosporine with mycophenolate mofetil (MMF) and sirolimus reduces the incidence of CNI-induced renal injury [64]. While CNI-induced nephropathy was reduced with MMF and sirolimus, the incidence of biopsy-proven acute rejection in the liver increased. Fortunately, this was not associated with increased rates of graft loss. A recently conducted Cochrane review of the literature surrounding CNI toxicity did not reach a conclusion regarding the role of CNI minimization in preventing nephrotoxicity in liver transplant patients [65]. Many centers now delay the administration of these drugs following surgery. The dosages used today are also substantially lower than those prescribed in the past in order to reduce the subsequent risk of chronic kidney disease [56].

Infectious Complications

Infections are the leading cause of morbidity and mortality after liver transplantation. The early posttransplant course (first month) is often complicated by surgical site infections and infections related to hospitalization including urinary tract infections, pneumonias, blood stream infections, and pseudomembranous colitis [66]. Patients post-liver transplant are at particular risk for developing bacterial infections of the liver and surgical site including abscesses, cholangitis, and peritonitis. Standard perioperative antibiotic prophylaxis with third generation cephalosporins should be used to reduce the risk of infections [67]. Although prior studies had suggested that selective bowel decontamination with prolonged antibiotic use prior to transplantation may help reduce the occurrence of infections, a Cochrane Database analysis concluded that there was no clear benefit of this intervention, and that decontamination may in fact increase the risk of infection and length of hospital stay [68]. Prebiotics and probiotics may provide some benefit, and should be further studied.

Opportunistic Infections

Opportunistic infections generally occur in the second through sixth months, when immunosuppression is most profound. Trimethoprim/sulfamethoxazole (TMP-SMX) prophylaxis for Pneumocystis jirovecii should be instituted for the first 6 months following transplant, and continued in patients requiring monoclonal OKT3 antibodies for rejection and in patients with graft dysfunction. An additional benefit of TMP-SMX administration is prophylaxis for Toxoplasma gondii, Listeria monocytogenes, and

Nocardia asteroids [66].

CMV infection is notable for its association with increased opportunistic infections in liver transplant patients, including fungemia and bacteremia, and its association with transplant rejection [69]. Infection with CMV within the first year of transplant is associated with increased mortality. Effective prophylaxis can be provided with ganciclovir or valganciclovir for 3 months following transplant [70]. Herpes simplex virus (HSV) reactivation may occur posttransplantation, but antivirals used for CMV prophylaxis should also be effective in these patients. If the patient is not receiving CMV prophylaxis, acyclovir can be used for the prevention of HSV. Varicella vaccination should be administered prior to transplantation. Beyond 6 months, patients are no longer at risk for most opportunistic infections if the level of immunosuppression has been reduced.

Candida is the most common fungal pathogen following liver transplantation and accounts for nearly 80 % of postoperative fungal infections, followed by Aspergillus. Most fungal infections occur within the first 2 months following transplantation. Risk factors for opportunistic fungal infections are retransplantation, renal failure, and reoperation involving the thoracic or abdominal cavity [71]. The use of antifungal prophylaxis is highly variable between liver transplant centers, and can include nystatin suspension, fluconazole, amphotericin B, or no empiric prophylaxis [72].

Hematologic Issues

Transfusion Triggers

Blood transfusions for bleeding are indicated to maintain adequate oxygen delivery. No firm transfusion threshold exists, but evidence in other patient populations suggests that a more restrictive strategy is appropriate. In the most recent clinical practice guidelines published, the taskforce, comprised of surgeons, anesthesiologists, and intensivists, felt there was good evidence to recommend a restrictive strategy of red blood cell (RBC) transfusion (hemoglobin < 7 g/dL) in critically ill patients with hemodynamically stable anemia [73]. Acute blood loss with hemodynamic instability should probably be addressed by more aggressive resuscitation with blood products. Further trials testing rigorous transfusion protocols are necessary, but the trend has been toward more restrictive transfusion practices.

Colloid Versus Crystalloid

No evidence for the superiority of albumin over crystalloid has been found in the critical care literature, but it is important to note that liver transplant patients were excluded from the trial [74]. Either crystalloid or colloid can be used effectively when administered in bolus doses for hypotension. In a patient with significant ascites,

colloids may be the fluid of choice for resuscitation. It does appear that among colloids, albumin may be safer than hydroxyethyl starchs because of the lower incidence of anaphylactic reactions, coagulation disorders, renal or liver failure, pruritus, and better hemodynamic stability [75]. Hydroxyethyl starch has also been found to increase the need for renal replacement therapy when compared with normal saline [76] and lactate ringers [77].

Thoughtful selection of crystalloid is essential as significant electrolyte derangements may be present in the postoperative setting. Boniatti and colleagues showed recently that hyperchloremia, possibly due to the administration of normal saline, is the primary cause of metabolic acidosis in liver transplant recipients [78]. Among critically ill patients with sepsis, large chloride loads from saline resuscitation have been associated with increased renal failure [79], and hospital mortality [80]. While this has not been exhaustively studied in the posttransplant setting, this concept may translate to the care of liver transplant patients as well. Future studies are needed to assess the utility of various balanced salt solutions in the care of patients post-OLT.

Coagulation Deficits

Coagulopathy does not resolve immediately after transplantation and often persists into the postoperative ICU period. The etiology is multifactorial and can involve hyperfibrinolysis, disseminated intravascular coagulopathy, platelet activation, platelet sequestration within the graft, and the presence of heparin-like effect (HLE). Some patients are actually hypercoagulable posttransplant, which further complicates the evaluation of their coagulation status [81]. The cause of this hypercoagulability is not entirely clear but maybe due to impaired synthesis of antithrombin by the liver.

As the new graft improves in function, synthesis of coagulation factors should improve and laboratory values should return to baseline. While laboratory value correction may not correlate well with bleeding risk, it does correlate with improved graft function. Failure to see improvement in coagulopathy should prompt a work up for graft nonfunction and infection, two serious causes of impaired coagulation in the postoperative setting. Routine transfusion for laboratory abnormalities is not indicated unless there is evidence for ongoing bleeding and hemostatic problems [82]. Aggressive transfusion can worsen cardiac function and consequently graft perfusion, so it should be reserved as therapy for clinically significant bleeding.

Fibrinolysis

In addition to hypofibrinogenemia from transfusions and blood loss, the new graft releases t-PA and tissue factor, which results in an accelerated fibrinolytic state that frequently causes significant consumption of fibrinogen in the post-reperfusion setting [83, 84]. Refractory bleeding should prompt an investigation for low fibrinogen and

fibrinolysis. Administration of antifibrinolytic drugs has shown benefit in reduction of transfusion requirements, and with the small number of patients studied so far, there does not appear to be an increased risk in thrombotic events (Table 29.2). Due to the lack of definitive data, it is not routine practice to administer antifibrinolytics, but practice patterns may change with further results.

Table 29.2 Trials on use of antifibrinolytic agents in liver transplantation

Study	Type	Drug	Comments
Boylan et al. [156]	Randomized controlled trial	Tranexemic Acid	TXA: 25 patients, Controls: 20 patients. Statistically significant reduction in intraoperative blood loss (20.5 units vs. 43.5 units). No difference in hepatic artery or portal venous thrombosis.
Kaspar et al. [157]	Randomized controlled trial	Tranexemic Acid	32 patients randomized to TXA or control. No difference in transfusion, but decreased fibrinolysis seen on TEG
Dalmau et al. [158]	Randomized controlled trial	Tranexemic Acid/ε-Aminocaproic Acid	132 patients randomized to TXA, ε-aminocaproic acid, or placebo. Statistically significant reduction in intraoperative transfusion for TXA, not for ε-aminocaproic acid. No differences in thrombotic events or post-operative transfusion.
Dalmau et al. [159]	Randomized controlled trial	Tranexemic Acid/Aprotinin	127 patients randomized to TXA or Aprotinin. No difference in transfusion requirements or thrombotic complications.
Ickx et al. [160]	Randomized controlled trial	Tranexemic Acid/Aprotinin	51 patients randomized to TXA or Aprotinin. No difference between intraoperative blood loss or transfusion requirements.
Molenaar et al. [161]	Meta-analysis	TXA/Aprotinin/ε-Aminocaproic Acid	Meta-analysis including the above trials showing no increased risk of thrombotic complications with antifibrinolytic agents.
Gurusamy et al. [162]	Meta-analysis	TXA/Aprotinin (additionally looked at other interventions to reduce blood loss)	Only aprotinin may reduce blood transfusion requirements. No difference seen between TXA and controls; no difference seen between aprotinin and TXA (only 3 trials included comparing the two).

TXA tranexemic acid, *TEG* thromboelastography

Heparin-Like Effect (HLE)

The prevalence of HLE in patients undergoing liver transplant is not uncommon, and can range from 25 to 95 % of cases [85]. Patients who have acute liver failure, primary nonfunction of the liver graft or require retransplant have a higher prevalence of HLE. The problem appears to be worse in patients with acute liver failure; however, the problem can persist in the posttransplant period regardless of the etiology of the liver failure [86].

The HLE can come from an exogenous source as well as an endogenous source. Residual heparin bound to the endothelium of the donor liver, which is perfused with

heparin before clamping, is the exogenous source of heparin. The endogenous source comes from substances known as heparinoids. The increased release of heparinoids is thought to occur from activation of macrophages or hepatocytes following ischemic injury to the liver. There is currently no evidence for reversing the HLE and supportive care is the best treatment option. An infusion of protamine sulfate has been attempted, but did not result in reduced bleeding or transfusion requirements [87]. If impaired coagulation persists several days into the postoperative period, then a sepsis workup is indicated as infection can worsen the production of these heparin-like molecules.

Thrombocytopenia

Low platelet counts are a commonly seen abnormality in the posttransplant patient. The etiology for the thrombocytopenia is varied but is related to decreased circulation and decreased production. With severe cirrhosis, there is often significant sequestration of platelets in the spleen due to portal hypertension, and the new graft will also sequester platelets. There is decreased platelet production because of low thrombopoietin levels in liver failure patients [88]. In the postoperative period, massive blood transfusions can result in a dilutional thrombocytopenia. Finally, even if the platelet count is adequate, platelets in a patient with liver disease may have decreased function because of adenosine diphosphate-induced and collagen-induced aggregation [89]. Platelet function may be further impaired by uremia in the setting of coexistent renal dysfunction. Thromboelastography (TEG) may be beneficial in measuring platelet function [90], but definitive studies relating use of TEG in liver transplant patients are needed.

Coagulation Factor Deficiencies

All coagulation factors except for factor VIII and von Willebrand factor are synthesized by the liver and are therefore decreased in the setting of severe hepatic impairment. Fresh frozen plasma (FFP) can replace these factors, but administration of plasma carries the risk of transfusion reactions and large volumes are often needed to reverse the laboratory coagulopathy [91].

For patients with refractory bleeding, many clinicians have used recombinant activated factor VII (rFVIIa) [92]. No randomized clinical trials have been conducted in postoperative liver transplant patients; however, case series have shown some benefit. There are risks associated with the off-label use of rFVIIa. Mayer and colleagues demonstrated increased risk of thrombosis with rFVIIa administration in patients presenting with intracerebral hemorrhages [77]. The exact role of rFVIIa in liver transplantation is unclear due to lack of data. Given the uncertainty, recommendations are that rFVIIa should be used only as “rescue therapy” in patients with severe life-threatening bleeding where other therapies have failed.

Immunosuppression

Posttransplant immunosuppression is necessary to prevent rejection of the donor organ. However, immunosuppression must be balanced with the maintenance of other immunologic functions, especially the prevention or recurrence of infection and malignancy. Fortunately, the rejection of transplanted livers occurs less frequently than in other organs [93], so lower dosages can be used. Side effects and complications can still occur in the postoperative period, so the intensivist should be familiar with the indications and side effects of immunosuppressants (Table 29.3).

Table 29.3 Immunosuppressants : their mechanisms of action and side effects

Class	Name	Mechanism of action	Side effects
Corticosteroids	– Prednisone	Reduce antigen presentation and lymphocyte activation	– HCV recurrence – HCC recurrence – Metabolic effects – Hepatic fibrosis
Calcineurin inhibitors	– Cyclosporine – Tacrolimus	Reduce IL-2-mediated T cell activation	– Nephrotoxicity – Neurotoxicity – Metabolic effects – HCC recurrence – PTLD
Mycophenolic acid	– Mycophenolate mofetil	Inhibit DNA synthesis	– GI distress – Bone marrow suppression
mTOR inhibitors	– Sirolimus – Everolimus	Reduce IL-2-mediated T cell activation	– Bone marrow suppression – Pneumonitis – Delayed wound healing

The immunosuppressive effects of corticosteroids include a decrease in IL-1-induced lymphocyte activation, a decrease in CD4+ T-cells, and a decrease in antigen presentation by dendritic cells [94]. Steroids are used for induction and maintenance during the first year following transplant, and also for treating episodes of acute rejection. Concern exists for the use of high-dose corticosteroids accelerating rates of HCV recurrence, HCC recurrence, and hepatic fibrosis. However, the avoidance of steroids in immunosuppression has not been shown to be beneficial in HCV positive transplant recipients [95]. Commonly seen acute side effects from high-dose steroids include: hypertension, glucose intolerance, agitation/insomnia, infection risk, and poor wound healing. Most of the signs and symptoms can be managed, so corticosteroid cessation is rare.

The calcineurin inhibtors (CNIs) , cyclosporine and tacrolimus, are used frequently

in order to prevent rejection. Calcineurin inhibition results in a decrease in the pro-inflammatory cytokine IL-2 and subsequent decrease in T-cell activation. Both CNIs undergo metabolism by the cytochrome P450 system, and require careful monitoring of levels, especially when used in conjunction with other medications that induce or inhibit cytochrome P450 [93]. Common side effects of CNIs include nephrotoxicity and neurotoxicity, including seizures, delirium, cognitive impairment, neuropathy, and coma. If a posttransplant patient develops concerning neurologic symptoms, tacrolimus levels should be checked. Unfortunately, neurologic symptoms can develop even at therapeutic levels of tacrolimus. Treatment is largely supportive as there is no way to acutely lower tacrolimus levels other than dose adjustment. A strategy of using low dose CNI for maintenance of immunosuppression has been suggested in order to minimize renal dysfunction [96, 97]. Additional side effects from CNIs include hypertension, hyperlipidemia, metabolic acidosis, and diabetes. CNIs have also been found to increase levels of the transcription factor TGF-beta, which may increase the risk of hepatocellular carcinoma recurrence or posttransplant lymphoproliferative disorder [93, 94].

Mycophenolate mofetil (MMF) undergoes metabolism into mycophenolic acid (MPA). MPA inhibits the synthesis of guanosine nucleotides, necessary for DNA transcription, and subsequently decreases lymphocyte proliferation [93]. Side effects of MMF include gastrointestinal distress and bone marrow suppression. An advantage of MMF is its lack of renal toxicity, and MMF levels do not need to be regularly monitored. Unfortunately, monotherapy with MMF is associated with higher rates of rejection, so the combination of MMF with a low dose CNI has been proposed as a strategy for reducing renal dysfunction and graft rejection [98].

The mammalian target of rapamycin (mTOR) inhibitors , sirolimus and everolimus, are similar to the CNIs in many ways. They too inhibit IL-2-mediated activation of T-cells, and are metabolized by the cytochrome P450 system [93]. There is some concern for increased risk of hepatic artery thrombosis [32] with sirolimus when used as de novo therapy [99], and the FDA has issued a black-box warning in regards to this risk. Side effects of the mTOR inhibitors include bone marrow suppression, interstitial pneumonitis, edema, and delayed wound healing. In patients with CNI-induced nephrotoxicity, early conversion to sirolimus helps to prevent kidney damage. However, the recently published PROTECT trial did not demonstrate any benefit with the early substitution of everolimus for CNI in patients with a normal baseline renal function [100].

The role of mTOR inhibitors versus CNIs in patients with HCV remains controversial [101, 102]. Antiangiogenic properties of mTOR inhibitors may prevent recurrence of HCC, when used in conjunction with systemic chemotherapy posttransplant [103]. The data are strong enough that the American Association for the Study of Liver Diseases recommended patients undergoing transplant for hepatocellular

carcinoma (HCC) receive sirolimus for immunosuppression [61].

Rejection

After liver transplantation, there are many types of graft rejection that may occur. Rejection of the allograft can be hyperacute, acute, chronic, or graft-versus-host (GVHD). Since chronic rejection is not usually an issue for the ICU patient, it will not be covered in this chapter.

Hyperacute rejection, mediated by antibodies, occurs within minutes to hours after the transplant procedure. Sixty percent of the cases of hyperacute rejection are due to ABO-incompatible allografts. In the presence of ABO-incompatible transplants, plasmapheresis, splenectomy, and the CD20 monoclonal antibody, rituximab, have been reported to prevent hyperacute rejection [104], but immediate retransplantation is often the only lasting option. Because antibody-mediated rejection with ABO-compatible allografts is so rare, due to the liver's relative resistance to the humoral immune system, a positive crossmatch does not necessarily preclude liver transplantation. However, evidence does suggest that the presence of preformed donor-specific HLA-antibodies can increase the risk of acute cellular rejection and chronic rejection [26].

Unlike hyperacute rejection, which is B cell mediated, acute rejection is mediated by T cells. Acute rejection is usually seen within days or weeks of the transplant and occurs in 36–75 % of liver transplant patients. Acute rejection is characterized by mononuclear inflammation and active cell damage, and episodes refractory to antirejection medications (usually high-dose steroids) can progress to chronic rejection [105]. Risk factors for the development of steroid unresponsive acute rejection include pre-liver transplant steroid administration, ABO incompatibility, recurrent rejection, low serum cyclosporine levels, and high liver function tests. A rising or persistent elevation of alanine aminotransferase (ALT) levels should prompt a biopsy to exclude rejection. Treatment options for a positive biopsy depend on the severity and include: optimization of maintenance immunosuppression for mild rejection, steroid pulses for moderate or severe rejection, and T cell depletion therapies for severe rejection.

GVHD occurs in 1–2 % of liver transplant recipients and is associated with an 85 % mortality rate. In the case of solid organ transplant, donor lymphocytes remaining in the parenchyma become detectable in the recipient weeks after transplant. These immunocompetent cells react against the different cellular antigens found in the host. A humoral response leading to hemolysis can also occur due to organ ABO incompatibility [106]. GVHD is divided between acute (occurring within 100 days of transplant) and chronic (after 100 days) presentations. Risk factors associated with the development of GVHD include alcoholic liver disease, hepatocellular carcinoma, and diabetes mellitus. It has also been suggested that GVHD is more likely to occur in the setting of close HLA matching and autoimmune hepatitis. Symptoms usually develop 2–

6 weeks posttransplant, and include fever, diarrhea, rash, and pancytopenia. Similar to treatment for acute rejection, treatment of GVHD includes administration of corticosteroids, increasing the current immunosuppressant regimen, or administration of medications for the antagonism of T cells. Mortality following the development of GVHD can be as high as 85 % [107]. Prevention includes limiting recipient exposure to donor lymphocytes, such as graft irradiation or treatment with monoclonal antibodies, and limitation of blood products to those that have been leukocyte reduced and irradiated.

Surgical Concerns

Aside from the medical complications discussed above, there are some posttransplant complications that occur secondary to surgical technique. Successful liver transplant services have close collaboration between the internists, surgeons, and intensivists. Complications that necessitate relisting the patient or urgent return to the operating room are discussed among the services and the risks and benefits are weighed carefully.

Primary Nonfunction

Primary nonfunction occurs in 4–8 % of deceased-donor liver transplants. Although uncommon, it is the most serious and life threatening condition in the immediate postoperative period and can be the most challenging for the transplant service. It is caused by reperfusion injury of the new liver, and results in irreversible graft failure. The diagnosis of primary nonfunction can only be made in the absence of technical or immunologic causes for graft dysfunction [108]. The acute destruction of hepatocytes results in decreased bile production, coagulopathy, encephalopathy, hypoglycemia, lactic acidosis, and hemodynamic instability. Signs often are present intraoperatively, but correction of the metabolic disturbances will need to be aggressively continued in the intensive care unit. The risk factors for primary nonfunction are numerous, and include: prolonged cold ischemic time, increased donor age, donor hypernatremia, donor length of stay in the ICU, male recipients with female donors, reduced graft size, racial mismatch between donors, retransplantation, and hepatic steatosis [109–111].

The only treatment for primary nonfunction is early retransplantation, and primary nonfunction is the most common reason for early retransplantation [110]. Without retransplantation, mortality is high. In addition to the complications from liver failure, cardiovascular, renal, and respiratory failure can often result from the release of vasoactive mediators from the nonfunctioning liver. Often times, removal of the failing graft can lead to a dramatic improvement in the patient's clinical status. In the absence of an immediately available liver, a rescue hepatectomy with portocaval anastomosis can be performed with subsequent liver transplantation occurring 24–48 h following

hepatectomy [112].

The effect of iloprost, a synthetic PGI_2 analogue, is currently being evaluated for its utility in preventing reperfusion injury and reducing the rate of primary allograft nonfunction [113]. Artificial liver support systems can theoretically be used to provide temporary support to patients as they await retransplantation. Artificial support systems provide hemodialysis combined with adsorption by albumin or charcoal in order to remove toxic metabolites. Bioartificial systems additionally use hepatocytes to provide synthetic function. Unfortunately, a meta-analysis of these systems did not demonstrate a mortality benefit in patients with severe liver failure. Furthermore, these systems can be associated with serious side effects, including bleeding, disseminated intravascular coagulopathy, fever, shock, and acute renal failure [114]. They also have not been studied specifically for use in patients with primary nonfunction.

Patients that undergo retransplantation for PNF demonstrate a 57 % survival if retransplantation occurs within the first 3 days of transplant (presumably before multiorgan failure occurs). Retransplantation between postoperative days 8–30 is associated with worse prognosis [115]. The principal issues that determine feasibility of retransplant include the extent of advanced liver failure and its comorbid conditions, such as brain herniation, refractory sepsis, or severe hemodynamic impairment. As little data exist to guide decisions for retransplant in such settings, the decision is based on the experience and judgment of the surgical team. Patients who require a second or third retransplant for primary nonfunction have poor survival (57 % mortality), and the feasibility of allocating another organ to the patient needs to be weighed against organ shortages.

Initial Poor Graft Function

Initial poor graft function (IPGF) is a poorly defined entity occurring in approximately 20 % of OLTs. It can result in decreased graft survival, renal failure, severe bleeding, sepsis, and progression to primary nonfunction of the graft. Risk factors for the development of initial poor function include the quality of the graft, ischemic time, primary disease, and operative techniques [116]. Definitions of IPGF vary, but include findings of transaminitis and coagulopathy within 7 days of transplant [117]. Although graft and recipient outcome after IPGF remains unpredictable [118], early identification does allow for close monitoring and a low threshold to return for exploratory laparotomy. The monitoring of static serum lactate levels does not predict liver function after transplantation, but Wu et al. studied lactate clearance, which has been suggested as an alternative biomarker for the development of IPGF [119]. Patients with early lactate clearance less than 24.6 % had a higher rate of IPGF (OR = 169). Further studies are necessary to determine if poor lactate clearance can prompt intensivists and surgeons to institute more aggressive interventions and improve mortality.

Hepatic Artery Thrombosis

Hepatic artery thrombosis occurs in up to 5 % of transplanted patients, with a higher incidence in pediatric patients, and is associated with a high rate of graft failure and mortality [32]. It is the most common vascular complication of liver transplantation and the second most common cause of liver graft failure after primary nonfunction [120]. Risk factors for the development of hepatic artery thrombosis include unmatched vessels, vascular damage during anastomosis construction, retransplantation, low recipient weight, and anatomic variance. Nonsurgical risk factors include diabetes, hypercoaguable state, CMV mismatch, primary sclerosing cholangitis, and donor age [121].

The clinical presentation depends on the time of onset of HAT and the existence of collateral vessels. Early HAT can present with biliary tract necrosis followed by sepsis, altered mental status, and coagulopathy. Late HAT usually presents as biliary tract complications leading to necrosis and abscess formation and liver ischemia. The key is early diagnosis so that treatment can be initiated in order to avoid graft loss. Posttransplant grafts can be monitored with Doppler ultrasound to detect presence or absence of hepatic artery flow, and definitive diagnosis is made with angiography or surgical exploration. If the diagnosis is made early, and there is no liver graft damage, surgical reconstruction of the hepatic artery is the best treatment [122]. Retransplant may be necessary if there is accompanying biliary tract damage and parenchymal necrosis.

Portal Vein Thrombosis

Portal vein thrombosis is rare in adults, occurring in only 0.5–15 % of liver transplants, and usually in the early transplant period [67]. Patients with portal vein thrombosis can present with transaminitis, ascites, portal hypertension, and graft failure. Risk factors for the development of portal vein thrombosis include technical difficulties during surgery, pretransplant portal vein thrombosis, small portal vein size, prior splenectomy, and the use of venous conduits [123]. Surgical treatments include thrombectomy and anastomotic revision, or retransplantation. Thrombolysis in interventional radiology is generally not recommended because of the risk of re-occlusion and concern for anastomotic disruption.

Hepatic Vein and Inferior Vena Cava Thrombosis

Hepatic vein and inferior vena cava (IVC) thrombosis are also rare, occurring in 1–6 % of transplants [124]. Symptoms include lower extremity edema, portal hypertension, and ascites. Surgical technique, which may result in narrow vessels and decrease flow into the IVC, and underlying hypercoagulability are risk factors. Percutaneous angioplasty is

the treatment for thrombosis, but may be complicated by restenosis and repeat procedures may be necessary [125]. Stenting may also be considered. Retransplantation may be necessary if there is massive necrosis. Unfortunately, there is no provision for priority listing for patients with portal vein or hepatic vein thrombosis from UNOS. Most centers will start long-term anticoagulation after revision or retransplantation for vascular thrombosis [67].

Biliary Tract Stenosis

Biliary tract complications are the most common technical problem after OLT and occur in 5–20 % of patients post-liver transplant [126]. They are often referred to as the "Achilles heel" of liver transplantation. These can be complicated by graft dysfunction or secondary infection. Strictures and leaks are the most common cause of complications. While leaks can occur early, strictures usually occur late following transplantation (after 3 months). Risk factors include vascular insufficiency, ischemia/reperfusion injury, or poor surgical technique. The rate of anastomotic stricture is higher in patients undergoing living donor transplants [127]. Non-anastomotic leaks can also occur as a result of vascular, infectious, or immune-mediated dysfunction. These usually present earlier than anastomotic leaks and are associated with worse outcomes.

Evaluation for biliary irregularities can be difficult as elevations in bilirubin, alkaline phosphatase, and gamma glutamyl transferase can be nonspecific. Endoscopic retrograde cholangiopancreatography (ERCP) with dilation and stent placement is generally the initial approach to treating biliary anastomotic strictures. ERCP has a high success rate (75 %) in the treatment of biliary strictures. In the event of ERCP failure, percutanoues transhepatic biliary drainage or surgical reconstruction with a Roux-en-Y hepaticojejeunostomy can be performed [128]. Intraoperative placement of a T-tube to stent the biliary tract may help to prevent stricture formation, monitor bile output and perform cholangiography [129]; however, the increased risk of peritonitis and cholangitis limits the utility of T-tubes.

Small-for-Size Syndrome

Compared with cadaveric transplantation, living donor transplantation is complicated with a unique set of concerns—including donor safety, graft size, technical difficulties with biliary tree and outflow tract repairs, and of course ethical considerations. The liver volume required to avoid small-for-size syndrome (SFSS) is characterized by a graft-to-recipient weight ratio of 0.8. Small for size grafts are grafts that are less than 0.8–1 % of the recipient's weight, or less than 30–50 % of the expected full sized liver [130]. Although its exact mechanism is unknown, SFSS appears to result from portal hypoperfusion and inadequate hepatocellular regeneration. SFSS results in delayed

synthetic function and decreased graft survival. Severe cases may progress to liver failure within weeks of transplant. Strategies to decrease portal hypertension may be effective treatments for SFSS such as splenic artery embolization, transjugular intrahepatic portosystemic shunt, or mesocaval or portocaval shunts [131, 132].

Long-Term Complications

Because outcomes in the early posttransplant period continue to improve, management of complications in the later posttransplant period is becoming even more integral to the overall care of the liver transplant patient. These late complications are largely related to the consequences of prolonged immunosuppression, but recurrence of the original disease (HBV, HCV, HCC) remains of concern. The intensivist should be aware of the treatments and indications so that these important therapies are not missed in the immediate postoperative period.

Hepatitis B Virus

Hepatitis B virus (HBV) recurs nearly universally in previously infected liver transplant patients. HBV recurrence contributed significantly to post-liver transplant mortality and followed a particularly aggressive course, including rapidly progressing cirrhosis or fulminant hepatitis, prior to the introduction of current prophylaxis regimens. Consequently, HBV infection had previously been a relative contraindication to liver transplantation at certain transplant centers [109]. The risk of HBV recurrence is increased depending on the type of pretransplant disease. For instance, the presence of HBV DNA seropositivity or HBV-associated cirrhosis prior to transplant results in an increased risk of HBV recurrence. Patients with fulminant hepatitis or a superimposed delta virus have a lower risk of reinfection [133].

The introduction of anti-hepatitis B surface antigen (anti-HBs) immune globulin, or HBIG, has reduced the recurrence of HBV following liver transplantation from 80 to 20 % [134]. Specifically, long-term treatment with HBIG (greater than 6 months) afforded a longer time to recurrence, decreased rate of recurrence, and increased rate of survival [133]. Although the mechanism for this protective action has not yet been elucidated, the goal for treatment with HBIG is HBsAb greater than 500 IU/L for the first 6 months following transplant [135, 136]. Unfortunately, the long-term use of HBIG is associated with high costs, and HBIG has been less effective in patients with high viral loads [134].

For patients at high risk of HBV recurrence (those with high viral load and pretransplant viral replication), a nucleoside analogue antiviral should also be considered [135]. The combination of HBIG and antivirals has improved 5 year survival to greater than 90 % in patients undergoing OLT for HBV [137]. Lamivudine is

often used in the pretransplant period to lower HBV load prior to transplant. However, a HBV polymerase mutation, YMDD, has limited the utility of lamivudine [138]. In the presence of lamivudine resistance, alternative antivirals such as adefovir, entecavir, or tenofovir may be considered. Monotherapy with antivirals posttransplant has not been found to be as effective in preventing the recurrence of disease. Currently, there are two strategies for discontinuing HBIG postoperatively. The first is HBIG withdrawal after initial combination therapy, and addition of a second oral antiviral agent. The second is a completely HBIG-free regimen using one or two oral antiviral agents [139].

Hepatitis C Virus

Hepatitis C recurrence posttransplantion follows a particularly aggressive course. Up to 30 % of all patients with disease recurrence will progress to cirrhosis of the allograft within 5 years of transplant [109]. Factors that may contribute to more aggressive disease course include donor age, graft steatosis, ischemia/reperfusion injury, diabetes, immunosuppression, and cold ischemic time [61, 140]. Low viral load prior to transplant has been demonstrated to reduce the risk of severe HCV recurrence. Unlike with HBV, no role for hepatitis C virus immune globulin has been found for the treatment of these patients [137].

Following transplant, there is no role for prophylactic antiviral therapy. High levels of immunosuppression make antiviral therapy ineffective, and these treatments are poorly tolerated. Antivirals should be used in patients with severe inflammation or mild to moderate fibrosis on biopsy [61]. Currently, pegylated interferon and ribavirin are being used, and new protease inhibitors are being evaluated for their utility in treating HCV.

Historically, retransplantation for liver failure secondary to recurrent HCV infection has been associated with a particularly poor survival [141], but there are conflicting results in the literature [142]. The current practice is not to perform retransplant for recurrent HCV, but this controversy remains to be decided, and perhaps will be influenced by advances in antiviral therapy.

Posttransplant Cancers

OLT recipients are at least twice as likely to develop cancer as the matched population, and cancer accounts for approximately 11 % of all deaths after transplant [143]. Most posttransplant malignancies are cutaneous. Of the noncutaneous malignancies, risk was increased in patients with primary sclerosing cholangitis (PSC) and alcoholic liver disease (ALD). The intensivist should be aware of the treatment for recurrent hepatocellular carcinoma or posttransplant lymphoproliferative disease since patients may return to the ICU due to failing graft function.

Hepatocellular Carcinoma

An increasing number of patients with hepatocellular carcinoma (HCC) undergo liver transplantation. This trend has occurred due to the UNOS organ allocation protocol, which allows exception to the MELD score for patients with HCC, giving them priority for liver transplantation beyond that determined by the degree of liver dysfunction [144, 145]. The rates of recurrence for patients with limited disease (with the Milan Criteria) are 10 %, while patients with more aggressive disease demonstrate recurrence rates of 40–60 % [146]. The risk of tumor recurrence in these patients is augmented by the use of immunosuppressants, and early discontinuation of calcineurin inhibitors may help to prevent disease recurrence. Uncontrolled pilot trials and retrospective analyses have suggested that sirolimus was associated with lower tumor recurrence and improved survival after liver transplantation [147]. These results have not been confirmed in an RCT and no recommendation can be made regarding use of mTOR inhibitors to reduce HCC recurrence outside of clinical trials.

Staging systems, such as the Milan Criteria or UCSF Criteria, can be used to predict the recurrence of HCC following liver transplant [148]. Risk factors for the development of recurrence include initial lesion size, number of lesions, and age of donor. AFP level, waiting time until transplant, and use of therapy to decrease disease burden prior to transplant did not affect the rate of recurrence [144]. While most disease recurs within the first 1–2 years following transplant, late disease recurrence is not uncommon [149]. Surveillance methods following transplant should include serial chest and abdominal imaging for 3 years following transplant. AFP levels may be trended as well. Once disease recurrence occurs, radiofrequency ablation or lesion resections are the treatments of choice. Liver retransplantation is not recommended for recurrent HCC [150].

Posttransplant Lymphoproliferative Disease

Posttransplant lymphoproliferative disease (PTLD) has an incidence of 2–5 % following liver transplantation. Risk factors for the development of PTLD include Epstein-Barr virus (EBV) infection, young recipient age, cytomegalovirus (CMV) mismatch, and the use of thymoglobulin [151]. Early occurrence frequently occurs in the setting of EBV infection, while later occurrence is not associated with EBV. EBV status should be determined prior to transplantation in order to identify high-risk individuals. Patients with high viral loads should be considered for early preemptive therapy, including the use of antivirals or monoclonal B cell antibodies. The signs of PTLD development include lymphadenopathy, microcytic anemia, electrolyte disturbances, and abnormal liver or kidney function. The diagnosis relies on histopathology. Once PTLD has been diagnosed, a reduction or cessation of immunosuppression should be considered [151]. The anti CD20 antibody rituximab, chemotherapy, radiation therapy,

and surgical debulking are effective in the treatment of PTLD [152, 153]. Though not often seen in the ICU, some of these patients may be admitted due to complications from tumor growth or chemotherapy.

Conclusion

Post-liver transplant patients require ongoing medical management to both avoid and treat potential complications (Table 29.4). Optimal medical management encompasses all organ systems and requires close collaboration among the multidisciplinary physicians, nurses, and ancillary staff in the ICU. Many complications cannot be managed just medically, and will require relisting the patient or return to the operating room. Even after the immediate surgical period, many patients will require readmission to the ICU due to long-term complications. The intensivist must be knowledgeable about the immediate and long-term care related to liver transplantation.

Table 29.4 Common complications after OLT: their risk factors and treatment options

Post-op complication	Incidence	Risk factors	Treatment options
Poor Graft Function			
Primary nonfunction	4–8 %	Ischemic time, donor age, graft size, retransplantation, graft steatosis	– Retransplantation – Temporizing measures: rescue hepatectomy, artificial liver support, iloprost
Initial poor function	20 %	Graft quality, ischemic time, primary disease, operative techniques	– Supportive care
Vascular complications			
Hepatic artery	5 %	Unmatched vessels, vascular damage, retransplantation, diabetes, hypercoagulable state, CMV mismatch, PSC, donor age	– Surgical reconstruction – Retransplantation
Portal vein	0.5–15 %	Small size, pretransplant portal vein thrombosis, prior splenectomy, use of venous conduits	– Thrombectomy and reconstruction – Retransplantation
Hepatic vein	1–6 %	Surgical technique, budd-chiari syndrome	– Angioplasty – Stenting
Biliary complications	5–20 %	Vascular insufficiency, reperfusion injury, surgical technique	ERCP with dilation and stenting, percutaneous transhepatic biliary drainage, surgical reconstruction
Rejection			
Acute	36–75 %	Prior steroid use, ABO incompatibility, recurrent rejection, low cyclosporine levels, elevated LFTs	– High-dose steroids – Anti-thymocyte antibodies
Chronic	3–5 %	Poor monitoring, noncompliance with immunosuppressives, multiple episodes of	– Retransplantation

		rejection	
Graft vs. host disease	1–2 %	Alcoholic liver disease, HCC, diabetes	– High-dose steroids – Increased immunosuppression – Anti-T cell regimens
Recurrence of Disease			
HCC	10 % (within Milan criteria)	Immunosuppression, number and size of lesions, donor age	– Radiofrequency ablation – Resection of recurrent lesion
HBV	20 %	HBV DNA seropositivity, HBV associated cirrhosis	– HBIG – Antivirals
HCV	100 % (30 % develop cirrhosis in 5 years)	High doses of immunosuppression, donor age, ischemic time, reperfusion injury, graft steatosis, diabetes	– Pegylated interferon – Ribivarin – Direct acting antivirals

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30. Multiorgan Transplantation Including the Liver

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Introduction

The evolution of such a complex operative procedure as orthotopic liver transplantation (OLT) has been breathtaking. Over a brief two decades, this life saving procedure has been universally applied throughout the world. Now available on every continent, liver transplantation has evolved to become the preferred treatment for acute and chronic liver failure. With this evolution, advances have been observed in patient selection, donor identification, perioperative care, and recipient survival. The refinement of hepatic transplantation has coincided with similar developments in other solid-organ transplant specialties to create the opportunity for multiorgan transplantation. The natural progression of success in treating single-organ failure to the realm of multiorgan transplantation is demonstrated in Fig. 30.1 [1].

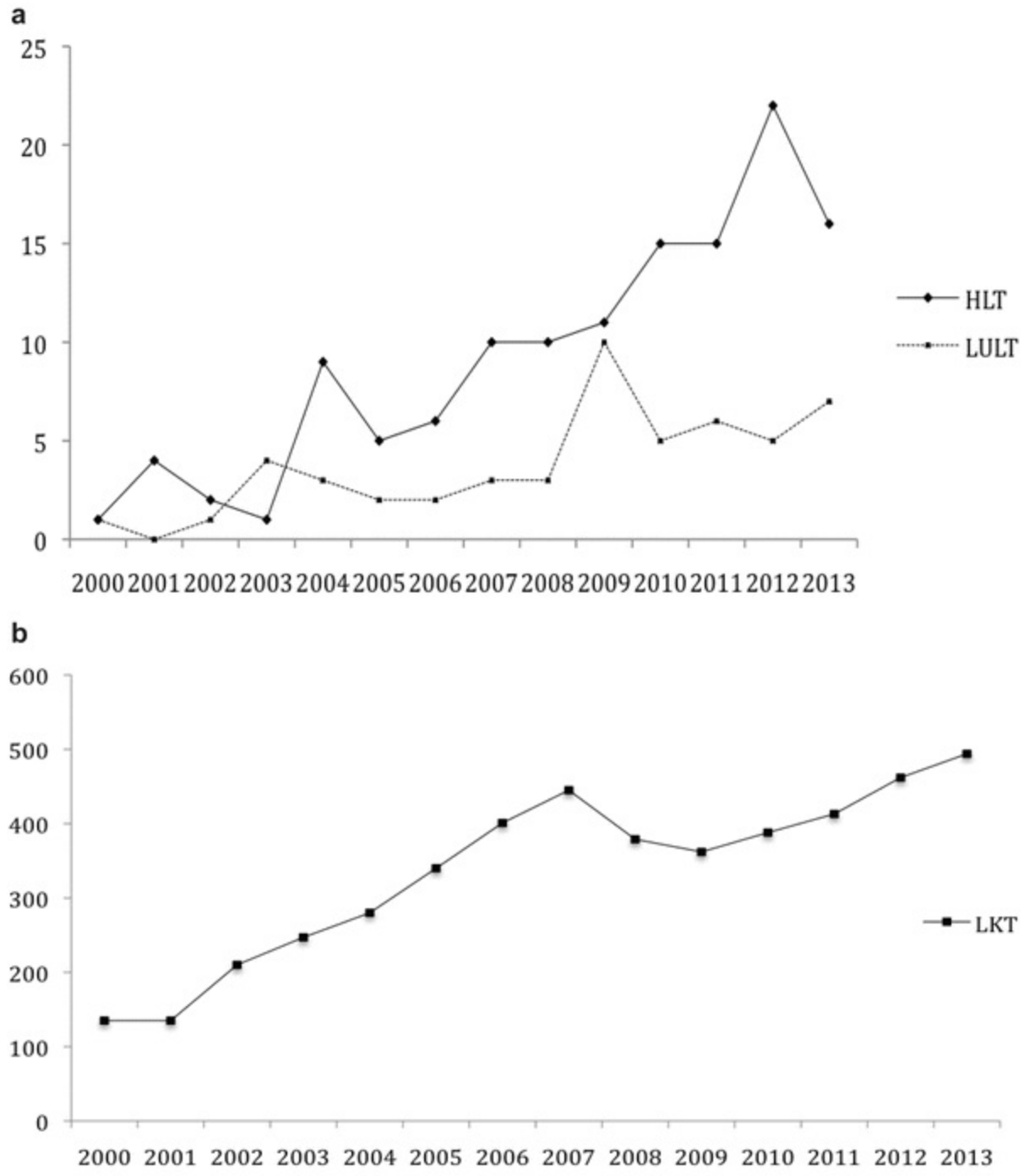

Fig. 30.1 Annual performance of multiorgan transplantation including the liver. (**a**) Annual incidence of heart–liver (HLT) and lung–liver transplantation (LULT) in the United States. (**b**) Annual incidence of liver–kidney (LKT) transplantation in the United States. (Data from United Network for Organ Sharing [1].)

Multiorgan transplantation is a unique challenge to the anesthesiologist due to the complex physiology of multiple impaired organ systems and potential conflicting management goals for each transplanted allograft. This chapter will discuss anesthetic considerations of combined organ transplantation including liver–kidney transplantation (LKT), heart–liver transplantation (HLT), and lung–liver transplantation (LULT).

Combined Liver–Kidney Transplantation (LKT)

The adoption of the model for end-stage liver disease (MELD) score in 2002 as the basis for liver allograft allocation has resulted in an increase in the annual incidence of LKT (Fig. 30.1) [1–3]. Renal insufficiency is common, occurring in approximately 30 % of patients awaiting OLT [4, 5]. Renal insufficiency in the setting of end-stage liver disease can be broadly categorized as: (a) acute kidney injury (AKI) secondary to prerenal azotemia, hepatorenal syndrome, or acute tubular necrosis, and (b) chronic kidney disease (CKD) secondary to glomerulonephritis, polycystic kidney disease, and primary hyperoxaluria [6].

The duration and degree of renal insufficiency prior to OLT correlate with posttransplant renal dysfunction [5, 7, 8]. Northup et al. analyzed a large cohort of OLT recipients who received renal replacement therapy while waiting for transplantation between 2002 and 2007 to identify predictors of spontaneous recovery of renal function following transplantation [5]. Pretransplant variables independently associated with recovery of renal function included short duration of therapy, lower recipient age, absence of diabetes, and younger donor age. Of these, pretransplant duration of hemodialysis was the most predictive of spontaneous renal recovery as recipients requiring <30 days of renal replacement therapy were likely to experience spontaneous recovery while those requiring >90 days were unlikely to recover [5]. Unfortunately, the vast majority of patients fall between these two extremes with few data available to support evidence-based recommendations.

Post-OLT renal dysfunction, particularly the need for hemodialysis, significantly increases morbidity and mortality [4, 9]. An SRTR analysis of cirrhotics with renal failure who received either OLT or LKT between 2002 and 2008, demonstrated significantly greater graft and patient survival among LKT recipients; particularly LKT for renal failure secondary to hepatorenal syndrome [10]. However, LKT remains controversial because of insufficient data to formulate consistent guidelines on identification of candidates who will derive benefit.

The International Liver Transplantation Society hosted a consensus conference on renal insufficiency among OLT candidates that proposed specific criteria for LKT (Table 30.1) [6]. Despite these recommendations, variability continues among centers with respect to the length of time AKI is tolerated prior to listing for LKT.

Table 30.1 Criteria for simultaneous liver–kidney transplantation [6]

1. End-stage renal disease and dialysis
2. No dialysis with a glomerular filtration rate <30 mL/min and proteinuria >3 g/day with a 24-h urine protein/creatinine ratio >3
3. Acute kidney injury and a requirement for dialysis at least 2 times per week for more than 6 weeks

From Charlton et al.; with permission

The decision to list a patient for LKT who has previously been an isolated OLT candidate is a clinical dilemma with significant ramifications. Avoiding chronic hemodialysis is obviously beneficial as hemodialysis, either pre or posttransplant, are each independent predictors of post-OLT mortality [4, 9, 11]. However, the addition of a renal allograft for LKT reduces the available donor pool, increases wait-list mortality, and denies renal transplant candidates an opportunity.

Preoperative Preparation

Detailed preoperative evaluation focusing upon the etiology of hepatic and renal failure is prerequisite to accurate prediction of the need for LKT. In these complex patients, clinical investigation of renal function should focus upon the last documentation of adequate glomerular filtration rate, abdominal imaging of the kidneys, and evidence of proteinuria as a renal biopsy is often precluded by the patient's underlying coagulopathy. Deterioration of renal function in a candidate with a history of renal insufficiency, ultrasound evidence of abnormal renal anatomy, or significant proteinuria prompts earlier consideration of LKT. As these patients demonstrate dual organ system failure with a significantly higher probability of wait-list mortality, the astute practitioner should perform thorough surveys of additional organ involvement including neurologic, cardiac, pulmonary, and hematologic pathology.

Vascular access may be difficult due to previous or preexisting central venous catheters, arteriovenous fistulas, or lack of venous access. Preoperative venous mapping utilizing magnetic resonance imaging is superior to computed tomography and ultrasound for the evaluation of venous patency, anatomy, and the presence of stenoses. Ultrasound guidance at central venous cannulation is recommended, particularly in the presence of a coagulopathy or atypical vascular anatomy. For the liver transplant procedure, femoral arterial cannulation for monitoring and femoral venous access for veno-venous bypass (VVB) or continuous renal replacement therapy (CRRT) may be necessary. Prior to any catheter placement involving the femoral vessels, the intended site for renal allograft implantation should be verified and protected [12].

Pretransplant hemodialysis to optimize electrolyte concentrations prior to the large-volume resuscitation, blood transfusions, and electrolyte shifts expected during OLT is recommended. Electrolyte stability during OLT is enhanced further by intraoperative CRRT and packed red blood cell mass washing prior to transfusion [13, 14].

Intraoperative Considerations

The operative sequence is determined by the allograft with the lowest tolerance to cold ischemia. In LKT, implantation of the liver precedes the kidney. In general, the

anesthetic considerations of LKT are similar to OLT but LKT recipients can be expected to display greater variation in volume status and electrolyte imbalance. Long-standing renal failure also portends a higher incidence of cardiac and peripheral vascular disease.

Patient preparation for LKT is similar to OLT. Patient positioning should be meticulous with special attention to avoiding compression of an arteriovenous fistula or hemodialysis access graft [15]. Verification of the incision and location for renal transplantation prior to performing the operation by anesthesiologists, surgeons, and nursing is prerequisite to avoid unwanted skin incisions, drain placements, or venous catheter insertions that may compromise the renal transplant procedure.

Rapid sequence induction is recommended due to the increased risk of aspiration from uremia and ascites. Hypotension during anesthetic induction may result from intravascular volume depletion secondary to hemodialysis or chronic diuretic therapy for the management of ascites. Judicious volume loading prior to induction, principally through the administration of blood products to offset the recipient's coagulopathy, improves hemodynamics while optimizing the recipient for intraoperative monitor placement. Typical intraoperative monitoring and access include a radial arterial catheter, a femoral arterial catheter, two large bore peripheral veins, and a central venous high flow conduit. In addition, the patient should have a pulmonary artery catheter (PAC) or intraoperative transesophageal echocardiogram (TEE) for evaluation of volume status and assessment of cardiac function. Early establishment of adequate monitoring is essential to optimize these patients' precarious physiology.

Fluid management is challenging in the setting of renal failure as large-volume blood replacement and rapid electrolyte shifts occur during OLT. Crystalloid administration should be tempered as targeted blood and blood product administration form the mainstay of infusion therapy. Observation of the surgical field, as well as communication with the surgeon as to the amount of ascitic drainage and the formation of thrombus avert acute hypovolemia and facilitate resuscitation. Fluid management is further guided by acid-base data from arterial blood gases, lactate levels, PAC pressures, or TEE data.

Electrolyte abnormalities are inevitable in the performance of major surgery and the ability of the anesthesiologist to address issues other than the short-term correction of hyperkalemia, hypocalcemia, and hypomagnesemia is limited. Frequent laboratory analysis and monitoring of serum sodium is critical as crystalloid and colloid solutions utilized in resuscitation contain significant amount of sodium, and acute increases in sodium may result in central pontine myelinolysis [16]. Sodium bicarbonate may be required intraoperatively to treat acidosis and hyperkalemia during liver allograft reperfusion; however, these ampules may contain as much as 1000 mEq/L of sodium that can accelerate hypernatremia. Hyperkalemia is frequent in the setting of renal insufficiency and may be problematic during liver transplantation as a result of large-

volume blood transfusion and ischemia/reperfusion injury. In our center, the perfusionist is able to "wash" blood products to minimize the amount of potassium administered during blood transfusion. Intraoperative CRRT is useful in promoting electrolyte stability during LKT [13, 14].

During renal transplantation, fluid resuscitation is the mainstay for the treatment of hypotension as the use of vasopressors potentiates renal allograft vasoconstriction. However, overzealous fluid infusion may precipitate hepatic venous congestion and parenchymal dysfunction. Isotonic crystalloid solutions are the first choice for volume restoration in renal transplantation, but in the setting of severe hypovolemia, colloid solutions are ideal in restoring intravascular volume and tissue perfusion [17]. Hypotension refractory to adequate fluid therapy and blood transfusion may respond to dopamine [15]. Diuretics such as mannitol and furosemide are frequently administered during renal allograft reperfusion; however, their use in LKT should be tempered to avoid overdiuresis that can promote portal vein thrombosis.

Postponing kidney transplantation to promote stabilization and resuscitation of the patient in the intensive care unit following liver transplantation can be a distinct advantage in scenarios where the patient is profoundly coagulopathic, hemodynamically unstable, or requires excessive vasopressor support upon completion of liver transplantation. In these situations, a 6–12 h delay to optimize the recipient's physiology through improved hemostasis and reduced vasopressor requirements is unlikely to affect long-term renal function.

Postoperative Management

The postoperative course for the LKT recipient is dependent upon the duration of surgery as well as early allograft function. Communication among the various teams is essential as the management and goals of care for each specific organ-system may not be parallel. Hepatic allograft dysfunction manifests as refractory acidemia, coagulopathy, hypoglycemia, and encephalopathy with subsequent acute kidney injury. Renal allograft dysfunction manifests as oliguria with subsequent electrolyte imbalance. Doppler ultrasound evaluation of the transplanted allografts in the setting of early dysfunction may demonstrate vascular abnormalities that could trigger reexploration [18].

Hypotension in the postoperative period is typically the result of hypovolemia or hemorrhage but may be secondary to arrhythmias from electrolyte imbalance, acidemia, or vasodilatory shock. Frequent assessment of abdominal drains and laboratory analyses are essential. In the setting of refractory hypotension, an echocardiogram to supplement PAC data can guide treatment. In general, maintaining a target urine output may not be appropriate in the setting of LKT as the practice of large-volume crystalloid boluses to enhance renal perfusion followed by high dose diuretic administration to promote urine production can be harmful to the hepatic allograft as high central venous

pressures precipitate hepatic congestion with subsequent hepatocyte dysfunction. Conversely, overdiuresis results in hypotension, reduced portal venous flow, and a potentially hypercoagulable state that may precipitate portal venous thrombosis. LKT recipients may require a brief period of hemodialysis until the transplanted kidney assumes sufficient function.

Immunosuppression will vary according to the recipient's indication for LKT and any previous history of a preexisting solid-organ transplant. In general, immunosuppressive regimens are guided by the liver allograft and typically avoid the antibody induction regimens commonly employed in renal transplantation.

Combined Heart–Liver Transplantation

Combined heart and liver transplantation (HLT), originally described by Thomas Starzl in 1984, has been increasingly accepted as a therapeutic option for patients suffering from concomitant cardiac and hepatic failure as well as certain metabolic disorders [19]. While HLT remains an infrequent procedure, its incidence has steadily risen with excellent outcomes reported (Fig. 30.1) [19–23]. In fact, HLT recipient 1- and 5-year survival are comparable to recipients of isolated cardiac or liver transplantation, reflecting precise identification of appropriate HLT candidates and restriction of the procedure to centers with robust cardiac and hepatic transplantation programs [20].

HLT candidates can be fundamentally divided into two categories: those candidates where the liver is being replaced to support cardiac function and those candidates who demonstrate true dual organ failure [12] (Table 30.2). Metabolic diseases, such as familial amyloidosis and familial hypercholesterolemia, involve a genetic defect of the liver that results in cardiac failure [20]. For these indications, the role of the hepatic allograft in HLT is to provide a gene product to support the newly transplanted cardiac allograft. Explanted livers from metabolic disease candidates appear normal and these candidates do not exhibit manifestations of end-stage liver disease. The absence of coagulopathy, thrombocytopenia, or portal hypertension simplifies the liver transplant procedure and facilitates recovery. These candidates are distinctly different from the true dual organ failure population where portal hypertension and its complications are present, resulting in a patient who is significantly more debilitated at the time of HLT.

Table 30.2 Indications for combined heart liver transplantation

I. Metabolic diseases
Familial amyloidosis
Familial hypercholesterolemia
II. Dual-organ failure
Cardiac diagnosis
Restrictive cardiomyopathy

Congenital heart disease
Idiopathic dilated cardiomyopathy
Ischemic dilated cardiomyopathy
Hypertrophic cardiomyopathy
Hemochromatosis
Hepatic diagnosis
Cardiac cirrhosis
Hepatitis-induced cirrhosis
Cryptogenic cirrhosis
Alcoholic cirrhosis
Hemochromatosis

HLT candidates are currently underserved by United Network for Organ Sharing (UNOS) allocation policy that prohibits cardiac and liver allografts from allocation as a single unit [24, 25]. As a result, HLT waitlist mortality is greater than predicted by the sum of MELD and cardiac status scores with fewer than 30 % of patients listed nationally for HLT receiving transplantation [24].

Preoperative Preparation

Meticulous preoperative preparation for HLT is essential as time is limited when organs are available. Ideally, this occurs among the cardiac and liver transplant teams at the time of listing with periodic review. The preoperative evaluation should include extra-cardiac and extra-hepatic organ system assessment, recent laboratories, vasoactive medications including infusions, the presence of an implantable cardioverter-defibrillator or an intra-aortic balloon pump. A thorough understanding of the indications for HLT provides guidance in candidate assessment with respect to the operative strategy and anticipated difficulty.

Patients with coexisting cardiac and hepatic disease are predisposed to pulmonary hypertension which may manifest as a result of ischemic, idiopathic, or cirrhotic cardiomyopathy, hepatopulmonary syndrome, or portopulmonary hypertension. In assessing cardiac function, recent testing, including an echocardiogram and cardiac catheterization to determine pulmonary vascular resistance and reversibility of pulmonary hypertension, is critical. Irreversible or “fixed” pulmonary hypertension is a contraindication to HLT because of the high risk of right heart failure and early morbidity [26].

Intraoperative Considerations

The physiology of cirrhosis and cardiac failure complicates the anesthetic management

of HLT [27]. Catheter derived pressures supplemented by TEE are useful in guiding therapy. Standard patient monitoring includes: arterial catheter, PAC, and TEE. Rapid sequence induction is indicated for a variety of reasons including inadequate NPO status, gastroparesis, dysmotility, and ascites. Hypotension at induction may result from a preexisting cardiomyopathy or decreased systemic vascular resistance that is characteristic of the hyperdynamic cardiac physiology observed in cirrhotics [28]. Balanced anesthesia utilizing opioids, muscle relaxants, and low dose volatile anesthetics minimizes vasopressor requirements.

HLT begins with implantation of the cardiac allograft as the heart demonstrates the least tolerance to cold ischemia and improved cardiac function supports early hepatic allograft function. Numerous HLT operative strategies have been reported and range widely from complete cardiac transplantation with sternal closure before proceeding with abdominal dissection to maximal abdominal dissection before initiating cardiopulmonary bypass (CPB) [29, 30]. The key to evaluating an operative strategy is recognition of the two fundamentally different HLT patient populations as the aim should be to minimize the duration of extracorporeal circulation with its associated complications of coagulopathy, hypothermia, and metabolic abnormalities [31].

The most reported surgical approach is cardiac transplantation performed first followed by interruption of extracorporeal circulation and heparin neutralization [20, 21, 23]. With the mediastinum open, liver transplantation is performed by caval sparing hepatectomy (piggyback technique) or caval excision with or without veno-venous bypass (VVB) [20, 21, 23, 30, 32]. Sternotomy closure is delayed until the risk of tamponade is minimal. Advantages of this technique include short periods of cardiac allograft ischemia and a decreased length of CPB, thereby reducing blood loss and transfusion requirements. While this technique reduces the period of anticoagulation, it increases hepatic allograft cold ischemia.

Alternatively, the performance of both cardiac and hepatic transplantation while on CPB has been advocated [22]. In this technique, the cardiac and hepatic dissections are concomitantly performed with exposure of the hepatic vasculature. CPB is initiated and the cardiac transplant completed. With the newly transplanted heart beating and CPB maintained, the liver transplant procedure is performed. The patient is then weaned from CPB and the chest is closed. The procedure concludes with the biliary anastomosis and abdominal closure. The authors noted decreased blood transfusion requirements despite CPB but required high doses of anti-fibrinolytic therapy. Potential advantages of this approach include decreased hepatic cold ischemia and improved hemodynamic stability by avoidance of hepatic reperfusion upon the transplanted heart [22].

While no superior approach has emerged, it is critical that coordination between the cardiothoracic anesthesiologist, liver transplant anesthesiologist, cardiothoracic surgeon, liver transplant surgeon, and perfusionist occurs prior to and throughout the

surgery. Discussions should include surgical sequence, CPB, use of VVB, placement of bypass cannulas, central venous catheters, arterial catheters, and heparin utilization.

Thrombocytopenia, thrombocytopathy, impaired vitamin K metabolism, clotting factor deficiency, qualitative and quantitative fibrinogen abnormalities, as well as hyperfibrinolysis each contribute to the coagulopathy observed in patients with liver failure [33]. Continuous clinical assessment of the surgical field, coagulation laboratories, activated clotting time, and thromboelastography form the foundation guiding transfusion practice for both components of HLT.

HLT recipients typically require inotropic and vasopressor support for separation from CPB and augmentation of ventricular function. An intra-aortic balloon pump or a mechanical assist device may also be indicated upon conclusion of the cardiac transplant. While an intra-aortic balloon pump or mechanical assist device theoretically increases the risk of vascular thrombosis secondary to disrupted arterial flow and hypotension, we have not seen these concerns materialize. Following cardiac implantation, the pulmonary artery catheter should be repositioned with the TEE probe maintained for hemodynamic monitoring during the liver transplant procedure. Careful titration of vasoactive infusions with weaning of vasopressors is a priority to optimize the recipient's physiology for hepatic implantation.

Liver transplantation incurs unique demands upon the newly transplanted heart. Transplanted cardiac allografts demonstrate a normal Starling relationship between end-diastolic pressure and cardiac output [34]. Therefore, cardiac allografts are preload dependent and limited in their tolerance of sudden reductions in total venous return as would occur with occlusion of the inferior vena cava [27]. The utilization of VVB decreases the hemodynamic stress upon the transplanted heart by attenuating sudden declines in venous return and hemodynamic instability secondary to allograft reperfusion [35]. An alternative technique is preservation of inferior vena caval blood flow (piggyback technique) which eliminates the need for VVB and shortens the anhepatic period by lowering the number of required anastomoses [36]. However, the ability to achieve an adequate hepatic venous cuff to preserve continuous caval flow is variable and often requires significant dissection within the hepatic parenchyma.

Reperfusion of the hepatic allograft is associated with electrolyte abnormalities, acidosis, hypothermia, and ischemia/reperfusion injury [37]. The "cytokine storm" triggered by ischemia/reperfusion increases cardiac demand and may precipitate arrhythmias in the transplanted heart as the allograft is not conditioned to tolerate sudden fluid and electrolyte shifts.

Acute elevation in pulmonary arterial pressures and right ventricular dysfunction are common during reperfusion of the hepatic allograft and can precipitate right ventricular failure of the transplant heart. The result is a vicious cycle of decreased cardiac output, systemic hypotension, and further right ventricular ischemia. Right ventricular failure also results in hepatic allograft congestion and dysfunction. Pulmonary arterial

catheterization permits immediate recognition of pulmonary hypertension and guides treatment with pulmonary vasodilators, while TEE is useful in real-time evaluation of right ventricular function.

Goals in the management of right-sided heart failure include preservation of coronary perfusion by maintaining systemic mean arterial pressure, optimizing right ventricular preload, decreasing pulmonary vascular resistance, limiting pulmonary vasoconstriction through optimal ventilation, and supporting right ventricular function [31]. Successful outcome after placement of a right ventricular assist device has been reported in HLT [38].

Postoperative Considerations

The postoperative course of the HLT recipient is a result of the patient's pretransplant functional status, the occurrence of an intraoperative complication, and the immediate function of both allografts. Successful recovery requires meticulous, coordinated care balancing the concerns of the cardiac and hepatic transplant teams.

Early cardiac and hepatic allograft function are inter-related. The newly transplanted hepatic allograft depends upon cardiac function as right ventricular failure secondary to prolonged CPB, ischemia/reperfusion injury, or increased pulmonary vascular resistance precipitates hepatic congestion and allograft dysfunction. Biventricular failure results in systemic hypotension with increased vasopressor requirements that are deleterious to the hepatic allograft.

Similarly, the newly transplanted cardiac allograft requires hepatic function to maintain acid/base balance and normothermia. In the presence of hepatocyte injury, the release of cytokines/toxins from the injured hepatic allograft is immediately transported to the cardiac allograft where the result is cardiac arrhythmias. Furthermore, persistent coagulopathy from CPB and hepatic dysfunction precipitates abdominal and thoracic hemorrhage. Cardiac tamponade must be suspected in the setting of acute hypotension, elevation with equalization of diastolic pressures, or decreased chest tube output [39].

Hemodynamics should be monitored utilizing a PAC and arterial catheter. Transthoracic or transesophageal echocardiograms supplement these data and should be obtained as necessary. PAC pressures, mixed venous oxygen saturation, arterial pressures, liver function tests, and urine output are principal determinants for discontinuing inotropic and vasopressor support. Chest tube output must be monitored closely with frequent laboratory analysis including arterial blood gas, lactate, liver function tests, complete blood count, and coagulation panel. Hepatic Doppler ultrasound evaluates vascular flow and patency within the allograft. Integration, communication, and a precise treatment plan for nurses and intensivists are essential.

Combined Lung–Liver Transplantation

Of all multiorgan transplant procedures involving the liver, the performance of combined lung with liver transplantation remains the least defined. While the incidence of LULT over the past decade has increased (Fig. 30.1), the available clinical data on indications, candidate selection, surgical technique, and posttransplant management of LULT remain sparse compared to LKT and HLT [1]. Similar to HLT, LULT candidates demonstrate higher waitlist mortality than isolated lung or liver candidates and are not afforded UNOS allocation priority [40]. The absence of a defined allocation strategy has resulted in the lung allocation score being the typical driver of donor allografts over the MELD score; however, the efficacy of this practice versus a combined disease severity score or MELD-based allocation has not been validated [41, 42]. Nevertheless, unique considerations in candidate selection and recipient management are emerging [42, 43].

LULT has evolved over the past decade from a procedure performed primarily in children and young adults with cystic fibrosis to a procedure employed over a much larger etiologic spectrum in older adults [40, 42–47]. Indications for LULT can be broadly categorized into three groups to assist in candidate selection, operative strategy, and posttransplant management. The first is end-stage pulmonary and hepatic disease from a single etiology, as in cystic fibrosis, alpha-1-antitrypsin deficiency, and sarcoidosis. This is the traditional indication for LULT for which there is the most literature and a history of outcomes comparable to single-organ transplantation [47]. The second indication is concomitant pulmonary and hepatic failure from different etiologies, as found in idiopathic pulmonary fibrosis with concomitant cirrhosis secondary to hepatitis C. The third group is patients exhibiting end-stage liver disease with secondarily compromised lung function such as portopulmonary hypertension. Of the three groups, the latter group is the greatest clinical challenge.

Preoperative Preparation

As with the performance of all multiorgan transplant procedures involving the liver, the three principles of precise understanding of the etiology of multiorgan failure, astute recipient selection, and continuing coordination among the applicable care teams is essential for optimal outcomes. When considering a LULT candidate, etiologic classification according to the above algorithm clarifies key physiologic concerns and potentially successful operative strategies. Three physiologic concerns that require particular attention in the assessment of LULT candidates are nutritional status, cardiac performance, and preexisting bacterial or fungal colonization.

Low body mass index (BMI) as a result of inadequate nutrition is common in patients with respiratory and hepatic failure. Respiratory failure increases the work of

breathing and overall energy expenditure by the body. As respiratory failure progresses, exercise tolerance decreases leading to skeletal muscle atrophy that promotes further disuse. Concomitantly, liver failure manifests malnutrition through disrupted protein/glucose metabolism, impaired gastric motility secondary to ascites and electrolyte anomalies, and cachexia secondary to chronic sepsis or subclinical hemorrhage. Available data have not identified a threshold BMI to predict outcomes; however, careful attention to nutritional status throughout the evaluation process as determined by stable weight, plasma protein concentrations, skeletal muscle mass, and enteral tolerance is essential as one approaches transplantation [42, 46]. Nutritional failure, as manifest by the inability to prevent catabolic physiology through enteral feeding is a contraindication to LULT.

Cardiac function is paramount in the evaluation of all candidates for solid-organ transplantation; however, in the performance of LULT, right heart function requires meticulous assessment as the incidence of right ventricular failure is higher in LULT and its consequences catastrophic [30, 43]. As the indications for LULT are relaxed, more candidates are presenting with portopulmonary hypertension. In the presence of moderate to severe right heart dysfunction, as evaluated by echocardiography, LULT should be deferred and medical therapy continued to promote cardiac conditioning. If cardiac dysfunction persists or further medical management is not practical, the only potential option is heart, lung, and liver transplantation [43]. The most challenging situation is when cardiac conditioning occurs with near complete resolution of right ventricular dysfunction as there are currently no specific criteria to predict how the heart will respond to sudden additional pressure changes associated with allograft reperfusion.

Lastly, bacterial and fungal colonization, including molds, are becoming more prevalent [47]. Often, these bacteria can demonstrate multidrug resistance. Bacterial colonization does not preclude LULT provided the patient does not demonstrate septic physiology or is decompensated [42]. Data on the presence of a mold that does not demonstrate tissue invasion pretransplant are absent. Therefore, it is reasonable to proceed provided the patient appears optimized for transplantation and extended antibiotic or antifungal therapy is expected [48]. In these settings, the LAS is helpful in providing guidance as to the candidates' tolerance for surgery. A threshold LAS between 45 and 55 is emerging as a poor prognostic indicator for LULT but has not been validated [42].

Intraoperative Management

Lung transplantation is performed prior to liver transplantation. Multiple surgical sequences have been reported including: integrated, concomitant dissection of the chest and abdomen prior to CPB, initiation of CPB followed by thoracic and liver

transplantation [49], thoracic organ transplantation during CPB with discontinuation of CPB prior to OLT [44], and abdominal dissection before lung and liver implantation without CPB [42]. This latest technique has been reported to minimize cold ischemic times, transfusion requirements, fluid resuscitation, and pulmonary edema in the newly transplanted lung [42].

Hemodynamic monitoring includes an arterial catheter, pulmonary arterial catheter, and TEE. The PAC is positioned only to the central venous position during the initial placement, and further relocated into a pulmonary artery after reperfusion. Balanced anesthesia with opioids and volatile agents provide hemodynamic stability.

CPB and VVB are not required for LULT. One advantage of CPB is reduced stress on the right ventricle during single-lung ventilation; however, CPB in candidates with liver failure promotes dilutional coagulopathy and platelet dysfunction [50, 51]. VVB during liver transplantation also supports right ventricular function and should be instituted when the patient demonstrates right ventricular dysfunction on TEE or hemodynamic instability upon caval interruption.

Acute right heart failure is a frequent cause of morbidity and mortality in LULT [30, 46]. This typically occurs upon reperfusion of the hepatic allograft as a result of sudden increases in pulmonary arterial pressure. TEE is essential in monitoring as are the availability of pulmonary vasodilators and inodilator agents. In addition, prompt treatment of acute acidosis and electrolyte perturbations is critical during the period of hepatic allograft reperfusion.

Postoperative Management

The postoperative management of LULT recipients is particularly challenging as the goals of care between the lung and liver teams may be discordant. Typically, lung transplant recipients receive restrictive fluid management with liberal use of diuretics to achieve low central venous pressures. In this setting, vasopressors are employed to maintain acceptable mean arterial pressures. The clinical aims are to prevent pulmonary edema, optimize oxygenation in the newly transplanted lung, and facilitate early extubation. Unfortunately, the presence of vasopressors and hypovolemia can result in hypoperfusion, biliary ischemia, and hepatic allograft dysfunction. Indeed, multiple authors report a high incidence of biliary and septic complications among LULT recipients [40, 42]. Frequent laboratory assessment of each allograft, including arterial blood gas, lactate, and liver function tests are required. Doppler ultrasound interrogation of the hepatic allograft and bronchoscopic assessment of the lung allograft should be performed when clinically indicated. Careful monitoring of cardiac pressures, acid base status, mixed venous oxygen saturation, urine output, and echocardiography guide intravascular volume status assessment and diuretic management to prevent pulmonary edema. Continuing discussions between the

pulmonary and transplant teams based upon real-time data on pulmonary and hepatic allograft performance is critical to a successful outcome as the acceptable parameters for each organ pair will be unique.

The frequency and morbidity of pulmonary allograft dysfunction are greater than hepatic allograft dysfunction. Pulmonary allograft dysfunction occurs within the first 72 h after lung transplantation and manifests as impaired gas exchange as a result of alveolar damage and increased capillary permeability [52]. Following supportive care with lung protective ventilation strategies and diuretic therapy, inhaled nitric oxide or prostacyclin are typically utilized to mediate pulmonary allograft dysfunction and ischemia/reperfusion injury [53]. The application of each has not been demonstrated to affect hepatic function. In select scenarios, veno-venous extracorporeal membrane oxygenation is indicated; hereto, our experience suggest this is well-tolerated by the liver.

Lastly, sepsis secondary to allograft failure is the most common cause of morbidity and mortality [42, 46]. A unique dilemma to LULT is management of colonized bacteria or fungi, including molds. Active bacterial or fungal sepsis, in addition to clinically invasive molds, is a contra-indication to LULT. When transplantation is performed with active colonization, prolonged antibiotic prophylaxis on the order of months is indicated [42]. In the presence of mold colonization, prophylaxis should be extended for at least 1 year and considered indefinitely.

Conclusion

Multiorgan transplantation represents the pinnacle of clinical solid-organ transplantation. Successful outcomes are dependent upon a clear understanding of the indications for transplantation, discriminating candidate selection, meticulous preparation, and constant communication between all involved parties as to operative technique and posttransplant care.

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31. General Anesthesia for the Patient with End-Stage Liver Disease and Post Liver Transplantation

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Introduction

An aging population and medical advances over the past decades have led to an increasing number of patients with chronic liver disease (CLD) and end-stage liver disease (ESLD) presenting for nontransplant surgery [1–4]. The same applies to a rising number of older and more comorbid patients undergoing liver transplantation (LT) combined with a steadily increasing time of survival after transplantation [5]. As a direct consequence for the anesthesia care personnel, there is nowadays a very high probability to manage ESDL or post-LT patients for elective or emergency nontransplant surgery in and outside of transplant centers.

The following chapter provides a comprehensive summary for anesthesia care in both patient populations. The chapter is divided into two parts: a summary of anesthetic care in CLD/ESLD patients in part one and for anesthesia in liver transplanted patients in part two.

General Anesthesia for the Patient with End-Stage Liver Disease

The therapeutic options and thus survival of patients with liver disease is continuously improving [2–4]. These patients might therefore be subjected to several types of surgery including minor and major procedures. As in non-liver disease patients, preoperative evaluation will determine the choice of anesthetic regimen and intraoperative management.

Preoperative Evaluation

See also Chap. 26

The preoperative anesthesia evaluation of the patient with liver disease must include an *assessment of the liver function* and a list of *liver disease-related organ dysfunctions* that additionally alter the risk for anesthesia and surgery. Many of these issues are detailed in other chapters of this book and have been reviewed recently, i.e., hepatic encephalopathy [6], portopulmonary hypertension and hepatopulmonary syndrome [7], hepatorenal syndrome [8], cirrhotic cardiomyopathy [9], and coagulopathy [10, 11]. Therefore, the following sections describe the most important anesthesia relevant issues.

Risk of Surgery and Scoring

Up to date, no specific marker or score allowed for the prediction of perioperative morbidity and mortality in hepatic patients. This might be explained by the patient's individual risk which is highly dependent on the degree of liver dysfunction, presence of comorbidities, type of surgery, estimation of residual hepatic function in liver resection surgery, and finally the anesthesiologists' experience and resources [12]. Scoring systems help to estimate the anesthesia-related risk in liver failure patients.

- *Classification of the American Society of Anesthesiologist* (*ASA*) (Table 31.1): The ASA score is associated with perioperative morbidity in CLD and an ASA ≥ IV reflects an independent risk factor for 90 day mortality [13, 14].

Table 31.1 American Society of Anesthesiologists physical status classification system (ASA)

Classification	Physical status
ASA 1	Healthy person
ASA 2	Mild systemic disease
ASA 3	Severe systemic disease, not incapacitating
ASA 4	Severe systemic disease that is a constant threat to life
ASA 5	A moribund person who is not expected to survive without operation

ASA 6	A declared brain-dead person whose organs are being removed for transplantation

- *Child-Turgcotte-Pugh classification* (*CTP*) (Table 31.2): The significance of the Child-Pugh classification was heavily debated. However, the classification has been shown to correlate with mortality in patients with liver dysfunction who underwent different types of surgery. Thus, it still might serve as additional information for the risk and risk-management of these patients [1, 15–17]. In this respect, patients with a CTP < 8 seem relatively save for most types of surgery [18].

Table 31.2 Child-Turcotte-Pugh's classification (CTP)

Parameter	**1 Point**	**2 Points**	**3 Points**
Total bilirubin (mg/dL)	<2	2–3	>3
Serum-albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (s. prolonged) or Prothrombin time (INR)	<4 <1.7	4–6 1.7–2.3	>6 >2.3
Ascites	Absent	Mild	Moderate
Hepatic encephalopathy (grade)	None	1–2	3–4
CTP-Class	*A*	*B*	*C*
Points	5–6	7–9	10–15

- *Model of end-stage liver disease* (*MELD* , Table 31.3): MELD scores correlate with mortality in patients with liver cirrhosis subjected to different types of surgery [19–22]. In liver diseased nontransplanted or post-LT patients, an increased MELD additionally hints towards cardiac or renal malfunction [23, 24]. A range between 8 and 14 points were suggested, below which anesthesia and surgery should be relatively safe [18, 20, 21, 25]. In my opinion, the wide range of MELD score proposed would suggest that no clear MELD score cut-off exists that would reliably predict the patients' individual risk for a certain anesthetic or surgical procedure. Certainly, the type of surgery and experience of the medical team are of great importance.

Table 31.3 Model of end-stage liver disease score (MELD) : calculation

MELD = [0.957 × (log s-creatinine) + 0.378 × (log s-bilirubin) + 1.120 × (log INR) + 0.643] × 10

Liver Function

Patients with suspected liver dysfunction scheduled for anesthesia and surgery need to receive a thorough *medical history* and *physical examination* in order to detect

preexisting liver disease and related problems [1, 26, 27]. Fatigue, nausea and vomiting, hematemesis, pruritus, jaundice, hemorrhagic diathesis, abdominal distension, or altered mental status can represent clinical signs of liver dysfunction [28]. Additionally, taking a *drug history* is essential in order to uncover drug-induced liver failure [29]. In particular paracetamol or antimicrobial drugs represent potential candidates for drug induced liver dysfunction [30, 31].

Neurologic Function

Hepatic encephalopathy exemplifies one of the main neurological complications in liver disease. Ammonia is thought to be of particular importance in its pathophysiology. Typical symptoms are ranging from apraxia and behavioral changes to decerebrate posturing and coma. Several aggravating and *reversible factors* should be avoided or minimized during anesthesia, such as: hypokalemia, alkalemia, hypoglycemia, hypovolemia, and administration of benzodiazepines [1, 6, 28].

Pulmonary Function

See also Chap. 33

It is interesting to note that pulmonary symptoms might be the first signs of liver dysfunction which may occur even before liver disease is diagnosed [4]. Pulmonary complications include lung restriction, pulmonary shunting, and portopulmonary hypertension:

- *Lung volume restriction* can develop due to the presence of ascites and pleural effusion [32, 33]. To determine the quantity of pleural effusion and whether it needs preoperative drainage, pleural sonography is easier to perform and more specific as compared to chest X-ray [32, 34].
- The *hepatopulmonary syndrome* predicates at least in part on imbalanced nitric oxide and endothelin production and endothelin receptors. Dilatation of pulmonary vessels in low ventilated areas results in a right to left shunt. The anesthesiologist must bear in mind that oxygen can improve hypoxemia, but mechanical ventilation during general anesthesia can even aggravate intrapulmonary shunting [35].
- *Portopulmonary hypertension* develops due to a decreased clearance of vascular regulating mediators, e.g., serotonin, bradykinine, thromboxane, or neuropeptides. These mediators can activate vascular constriction, remodeling, and thrombosis in lung vessels [36]. Portopulmonary hypertension should be ruled out prior to anesthesia and surgery, because it is associated with increased mortality [37]. While mild forms of pulmonary hypertension might not be diagnosed, echocardiography can detect moderate to severe pulmonary hypertension [38]. As potential treatment, prostacyclin analogues or endothelin receptor antagonist have

been proposed recently [39–41].

Cardiovascular Function

See also Chap. 35

Severe liver disease can be associated with a hyperdynamic circulation, increased cardiac output, and reduced systemic vascular resistance. Furthermore, patients with CLD and ESLD show a high incidence of cardiac comorbidities:

- *Cirrhotic cardiomyopathy* is defined as decreased cardiac contractility in hepatic patients [9, 23]. As a consequence during general anesthesia, the compensatory inotropic and chronotropic response to surgical stress is impaired. Thus, intraoperative hemorrhage, hypoxemia, or hypotension exacerbate hemodynamic instability and increase the risk of intra- and postoperative liver dysfunction.
- *Coronary artery disease* is more prevalent in patients with ESLD [42]. A 12-lead electrocardiogram should be routinely performed if not assessed recently. Furthermore, ECG-monitoring during anesthesia can detect intraoperative ischemic events.

Renal Function

See also Chap. 34

Hypoperfusion and/or ischemia play an important role in the development of the *hepatorenal syndrome*. It correlates with poor prognosis. Loop diuretics, aldosterone antagonists, and the use of vasoconstrictors appear to be important in these patients [8]. In this regard, dopamine is not beneficial. As a first line therapy, vasopressin analogues, e.g., terlipressin, are recommended [8].

Coagulation Function

See also Chap. 36

The liver produces most coagulation factors. As a result of liver dysfunction or even liver failure, coagulation is impaired. In addition, splenic congestion as well as a decreased hepatic release of thrombopoietin can lead to low and *dysfunctional platelets*. Low preoperative platelet count reflects an independent risk factor on perioperative complications in liver surgery [43]. Therefore, a thoroughly *bleeding history* should be taken prior to anesthesia and surgery. In case of intraoperative suspicion of diffuse bleeding, application of desmopressin before transfusion of thrombocytes should be considered [44].

Laboratory Testing

Routine liver enzyme testing of *alanine aminotransferase* (*ALT*) or *aspartate aminotransferase* (*AST*) in CLD or ESDL patients is of little value and therefore not recommended, and should better depend on clinical suspicion of liver dysfunction [45]. ALT as well as AST are markers of hepatocellular integrity and do not reflect hepatic function. Moreover, the remaining intact hepatocytes in severe liver cell damage can be low and result in a reduced release of cytosolic transaminases.

Albumin (half-life of 2–3 weeks) is probably a better marker of impaired liver function as compared to ALT or AST. To detect more acute alterations in hepatic function, *prealbumin* (half-life 2 days) can be of value.

Not only but especially when a history of bleeding exists, coagulation status should be assessed. *Prothrombin time* (*PT*), *international normalized ratio* (*INR*), *and partial thromboplastin time* (*PTT*) are of value. In addition, a *complete blood count* serves to determine possible thrombocytopenia and anemia [28].

Finally, testing *electrolytes* seems important, because imbalances are common in hepatic disease and need to be corrected in order to prevent cardiac arrhythmias, worsening of hepatic encephalopathy, or coagulation disorders.

Other than the above mentioned, markers of liver disease should be addressed according to the medical history and physical examination.

Anesthetic Management

Anesthetics

Alterations in hepatic blood flow, hypoalbuminaemia, volume of distribution, and changes in pharmacokinetics as well as pharmacodynamics are often seen in ESLD. Many anesthetics are metabolized in the liver. Liver dysfunction or liver insufficiency therefore impairs their metabolization. Combined with a higher susceptibility to narcotic drugs of the patient with ESLD, the requirement of anesthetics is lower [46–48]. In order not to overdose drugs or to risk awareness, the use of *bispectral index monitoring* to monitor depth of anesthesia in hepatic patients might be beneficial [49–51]. The metabolization and course of action of anesthetics might differ significantly in ESLD:

- *Opioids* need dose adjustment and titration if applied continuously or repetitively. These drugs have prolonged half-lives in liver dysfunction. Single doses of fentanyl or sufentanil and continuous application of remifentanil is regarded safe in the hepatic patient.
- With the exception of oxazepam and temazepam, *benzodiazepines* should be used with great caution. A decreased hepatic clearance for these drugs, lead to a longer elimination half-life and a prolonged recovery [52]. Another disadvantage of benzodiazepines is reflected by the fact that stimulation of central GABA-receptors

can worsen preexisting hepatic encephalopathy.

- At the moment, *propofol* represents the best choice of intravenous narcotics. Its usage for sedation as well as induction of anesthesia seems save. It displays no significant pharmacokinetic alteration in cirrhosis, a normal recovery time, and minimal effects on preexisting encephalopathy [52–54].
- *Volatile anesthetics* can be applied in order to maintain anesthesia. The use of halothane is discouraged, because of known hepatotoxic effects. If inhalational induction of anesthesia is necessary, sevoflurane should be used. Based on existing knowledge of modern volatile anesthetics, there is no major advantage or disadvantage between the different substances [55, 56]. Whether volatile anesthetics are a useful tool to especially sedate hepatic patients in the intensive care setting remains to be investigated [57].
- Hepatic metabolized *muscular blocking agents* should be avoided. Because of extra-hepatic and extra-renal elimination, *cis*-atracurium seems best.

The possibility of employing *regional anesthesia* as an anesthetic technique in hepatic patients has been reviewed recently [12]. Regional anesthesia might be applied under certain circumstances. However, up to date no evidence exist supporting better survival in this population with regional anesthesia.

Monitoring

Standardization of monitoring has not been fully established for ESLD or liver failure patients undergoing anesthesia. The decision for invasive monitoring should depend on the general constitution of the patient and the planned extend of surgery. In expectation of increased blood loss, large bore venous access is mandatory. The placement of arterial lines, central venous lines, or pulmonary artery catheters has not yet proven to count for improved outcome. During major surgery, monitoring of pH, lactate, glucose, sodium, potassium, calcium, and urine output is helpful.

Recovery from Anesthesia

Whether a patient with ESLD needs to be transferred to an intensive care unit depends on the type of surgery, risk of postoperative bleeding, and comorbidities of the patient.

In the recovery room and as mentioned above, benzodiazepines should be avoided and opioids for pain management should be titrated to effect.

General Anesthesia for the Patient Post Liver Transplantation

Patients who have undergone liver transplantation in the past often display symptoms

related to the transplant operation or to immunosuppressive therapy on presentation in the emergency department. Hepatic, biliary and intestinal disorders, infections, or rejection are common diagnosis [58]. Given the increasing survival and age of transplant recipients, this population might also develop diseases not related to liver transplantation. Taken together, a large proportion of patients post LT undergo some type of nontransplant surgery in the following years [59]. While in the early posttransplant-stage abdominal surgery is needed, ENT, urology, gynecology, orthopedic, cardiac, and many other operations are scheduled later after LT [60–62].

With sufficient graft function, elective procedures including major cardiac surgery seem quite safe, and a higher incidence of complications are unlikely [59, 62]. However, in emergency operations, complication rate rises as compared to the nontransplanted population [59]. Depending on the type of operation and the number of reoperations, the anesthesiologist should keep in mind that a difficult surgical approach could occur and that abdominal surgery is associated with increased blood loss and longer duration of operation [63].

Preoperative Evaluation

See also Chap. 26

In the preoperative evaluation of post-LT patients several issues should be considered:

- *Preexisting diseases initiated by liver dysfunction* might still be evident despite LT, e.g., left ventricular outflow obstruction, renal impairment, pulmonary affections, etc. [64].
- The *underlying disease* that led to LT might reoccur, e.g., autoimmune disease, hepatitis, primary biliary cirrhosis, sclerosis, alcohol consumption, etc. [65, 66].
- *Concomitant diseases* in LT-patients persist despite LT, e.g., coronary artery disease [67, 68].
- *Perioperative complications* and *immunosuppression-related disorders* might have developed, e.g., infection, rejection, vasculopathy, renal impairment, diabetes, systemic hypertension, neurotoxicity, malignancies, etc. [69].

The increase in survival of liver graft recipients has resulted in greater prevalence of complications. Most important with respect to post-LT morbidity and mortality are posttransplant cardiovascular and chronic kidney diseases, but also include diabetes, metabolic syndrome, systemic hypertension, and many others [70, 71]. Therefore, the focus during the preoperative evaluation should not be restricted to liver graft function, but must be expanded to all possible complications by thoroughly taking the medical history and evaluating the physical capacity of the patient. The preoperative assessment

must include questions regarding recent changes in weight, fever, malaise, etc. The following most important issues should be ruled out prior to anesthesia and surgery:

- *Graft function* and potential *rejection*
- *Infection*
- *Organ systems*, that might have been influenced by the underlying disease as well as the potential complication after liver transplantation
- State of *immunosuppression*

Likewise, preoperative evaluation of pediatric liver transplant recipients should focus on side effects of immunosuppressive therapy, risk of infection, and the potential of rejection [72]. Especially in children, but also to a lesser extend in adults, the anesthesiologist should carefully assess the airway. Post-LT *lymphoproliferative diseases* might have developed, affecting the tonsils, and complicating airway management [73, 74].

Differences Between Transplanted and Normal Liver

Some physiological responses relevant to anesthesia change with a transplanted liver as compared to a normal liver. Most importantly, the transplanted liver is denervated, thus, physiological responses of the liver might be blunted [60, 75]. For instance, patients are unable to feel liver capsule pain and typical clinical symptoms of liver pathologies may be absent. Another issue regards *autonomic regulation*. At least within the first year, it seems unlikely that sympathetic denervation is restored by re-innervation post LT, and catecholamine levels in the liver remain lower than normal [75]. Soon after LT, total *liver blood flow* is elevated, firstly, due to the lack of vasomotor control and secondly, due to continued preexisting and abnormal splanchnic hemodynamics that might last for several months [76, 77]. Later after LT, liver allograft function and liver blood flow do not appear to be significantly impaired as a result of denervation under physiological conditions [75]. Nevertheless, two points should be considered by the anesthesia care giver:

- Experimental data suggest that *catecholamine treatment* , i.e., epinephrine and norepinephrine, act different in the transplanted liver as compared to normal liver. Here, macro- and microcirculation seems to be more decreased after LT in response to catecholamine therapy [78]. Some authors recommend continuous administration of prostaglandin E to maintain sufficient hepatic perfusion in the allograft [79].
- In shock, the normal *liver serves as a blood pool* by vasoconstricting its vessels. This mechanism can be impaired in denervated grafts and adequate blood

redistribution might lack appropriate blood redistribution [77, 80].

Most regulations of metabolism, metabolization, and protein synthesis seem to recover post-LT [75]. Glucose metabolism and insulin resistance can be affected especially during the first months after LT. Immunosuppressive therapy appears to play a major role. Despite reduction of immunosuppressive drug dosing over time and the potential of normalization in glucose metabolism, post-LT diabetes represents a common side effect (see below) [81, 82].

Immunosuppression

The transplantation itself, the sometimes poor clinical condition of patients, and immunosuppressive therapy compromise the immune function of post-LT patients. Even if the immunosuppressive therapy can be reduced over time, most patients have to continue some form of immunosuppression lifelong [83]. The choice of drugs for immunosuppressive therapy after liver transplantation varies between centers. Despite standardization, immunosuppressive regimens are additionally tailored to patients' individual risk characteristics and primary indication for liver transplantation. Furthermore, the course of immunosuppressive therapy might change over time, including dose modification as well as switch of drugs according to side effect profile or allograft rejection [71, 83]. Commonly used immunosuppressive therapy after liver transplantation includes:

- *Calcineurin inhibitors* (e.g., cyclosporine A, tacrolimus)
- *Antimetabolites* (e.g., mycophenolate mofetil, mycophenolate sodium, azathioprine)
- *Mammalian target of rapamycin* (*mTOR*) *inhibitors* (e.g., sirolimus, everolimus)
- *Anti-body based drugs* (e.g., anti-thymocyte globulin, anti-lymphocyte globulin, muromonab-CD3 antibody, basiliximab, daclizumab)
- *Corticosteroids*

The combination of these drugs aim to target different sites of the T-cell activation cascade and to minimize side effects [83]. Stopping immunosuppression might result in fatal rejection of the transplanted organ [84]. Therefore, it is more than important to *continue immunosuppressive therapy* in post-LT patients during the perioperative period of subsequent surgery or even pregnancy [4, 85]. The dose, schedule, and route of administration should be continued as before surgery and no dose should be withheld [59]. If possible, a switch from oral administration to an intravenous route should be avoided. In case that oral intake cannot be continued, the transplantation center or the transplant team should be contacted regarding dosage advice [69, 84]. This is

especially true, when sepsis or other severe disease might impact the gastrointestinal uptake of the drug [59].

Whether *corticosteroid therapy* needs additional intraoperative substitution, remains a matter of debate [60, 61]. Minor surgery after LT without signs of allograft rejection, most likely does not require additional cortisone applications. A routine use of stress dose has not been recommended [60, 84]. However, in major surgery and with a high degree of stress estimated for the patient, cortisone substitution might be considered.

Some immunosuppressive drugs are administered according to their blood concentration (e.g., cyclosporine A or tacrolimus) [69]. Because of bleeding-induced hemodilution during post-LT operations and drug–drug interactions, these concentrations may vary. Therefore, *daily monitoring of blood levels* through the perioperative period and adjustment of dose are recommended [72, 85, 86].

The immunosuppressive therapy can exert *significant side effects* including neurotoxicity, nephrotoxicity, hyperkalemia, hypertension, diabetes, thrombocytopenia, leucopenia, etc. In the pediatric post-LT population, immunosuppression might further lead to growth retardation, hirsutism, serum electrolyte abnormalities, Cushing, obesity, pathological fractures, malignancies, and rarely hypertrophic obstructive cardiomyopathy [72]. As mentioned above, the preoperative anesthesia evaluation needs to rule out all potential side effects of immunosuppressive therapy.

Immunosuppressants are extensively metabolized by hepatic cytochrome P450. Thus, *multiple drug–drug interactions* might occur and become unpredictable when several medications are administered at the same time. Calcineurin and mTOR inhibitors are of special interest regarding potential drug–drug interactions [84]. With respect to anesthetic drugs used for induction and maintenance of anesthesia, human data is very limited. However, the characteristics of drugs administered during anesthesia might be altered on one hand, and anesthetics might alter blood concentrations of immunosuppressants on the other hand [69, 85]. An updated extended list on several drug–drug interactions with immunosuppressants can be found online [84].

- *Calcium channel inhibitors* , in particular diltiazem, can elevate cyclosporine levels. This becomes evident if these drugs are given repetitively over days. A single bolus administration has probably no effect [69].
- *Propofol* does not seem to alter cyclosporine levels nor is its action being altered by immunosuppressants [87].
- Recovery from *neuromuscular relaxants* , e.g., vecuronium and pancuronium might be prolonged in patients receiving cyclosporine, and lower does might be necessary [88, 89]. In contrast to cyclosporine, azathioprine seems not to interact with neuromuscular relaxants [85]. It is highly recommended that neuromuscular monitoring is employed in all patients on an immunosuppressive regimen.

- Blood concentrations of *benzodiazepines* can be moderately increased if coadministered with cyclosporine. Application to effect has been recommended [84].
- Most *anti-infectives* increase either the immunosuppressant concentration or their toxic side effects [84].

Time after Liver Transplantation

After successful transplantation the function of the allograft and subsequently of extra hepatic organs normalizes with time. It has been proposed *grouping the time course post-LT in stages*: e.g., perioperative, mid-term, and long-term [79].

Shortly after transplantation , direct consequences of the transplantation might be most prominent: poor clinical condition of the patient, pulmonary infections and effusion, insufficient liver function, acid base imbalances, anemia, coagulation disorders, and others. During this period, abdominal surgery might occur more often, e.g., re-exploration, revision of the bile duct system, revision of vascular complications, drainage of abscess or hematoma [79]. If the patient requires a reoperation, the anesthesiologist may be confronted with increased intraoperative blood loss and severe hypotension. The latter can impair graft function and should be avoided as good as possible. Therefore, blood pressure, acid base and coagulation imbalances must be tightly monitored and corrected.

Later after transplantation and with restored liver function, the side effects of immunosuppression are predominant. For instance, hyperglycemia or renal dysfunction can develop and need attention from the anesthesiologist [79].

Liver Graft Function

The risk of allograft dysfunction in nontransplant surgery following LT remains low [59]. But a potential rejection of the transplanted liver should always be ruled out prior to elective surgery and anesthesia [79]. Of note, routine operations during graft rejection increase perioperative morbidity. Clinical signs of acute rejection involve cholestatic jaundice, increased liver enzymes, failure of hepatic synthetic function, eosinophilia, lymphocytosis, and nonspecific symptoms, e.g., poor appetite, irritability, fatigue [72]. If suspicious signs of rejection are discovered, the patient should first undergo diagnostic and appropriate treatment in cowork with the transplant team or transplant center, before being scheduled for elective surgery. Finally and in case of living-related liver transplantation, the “small for size” liver syndrome and related graft insufficiency needs to be assessed prior to surgery [90, 91].

Neurologic Function

The neurological status might be impaired post-LT and represents a significant risk for morbidity and mortality [92]. The prevalence of neurological symptoms or disorders after LT ranges from 11 to 42 % [93]. Remarkably, patients diagnosed with hepatic encephalopathy before transplantation are at high risk developing neurological symptoms post-LT [94].

Most neurological complications occur in the early phase after LT [95]. Here, seizures, encephalopathy, and mental confusion are predominant [92, 95, 96]. Later in the course after transplantation, encephalopathy and mental confusion are still of major impact [92]. Cerebrovascular events, particularly in the early phase after LT, represent most severe complications that are associated with high mortality [97].

It appears difficult or almost impossible to find specific causes for neurological dysfunction after LT. Preexisting alcoholism, hepatitis, or malnutrition add to post-LT neurological malfunction [93]. Other peri- or postoperative factors comprise for instance infections, side effects of immunosuppressive therapy, electrolyte dysbalances, and many others [92, 96]. Most likely, the orchestration of several pre-, intra-, and postoperative factors leads to neurological dysfunction post-LT.

Why are neurological malfunctions important to the anesthesiologist? First, morbidity and mortality are increased in these patients. Second, patients might present with seizures, thus, anesthetics which lower the seizure threshold and intraoperative hyperventilation should be avoided in these patients. Third, patients might not be fully aware of the planned procedure and may be incompliant to preoperative orders or unable to give consent to the anesthesia procedure.

Pulmonary Function

As denoted in the first part of this chapter, pulmonary affections in hepatic patients and gas exchange abnormalities are common in liver transplant patients. Early after LT, postoperative hypoventilation, pleural effusions, disturbed diaphragm movements, and atelectasis impair lung function. As the graft function is sufficient, gas exchange generally improves after liver transplantation with time [98]. However, diffusion capacity of the lung mostly remains reduced to approximately 70–80 % [69, 98]. A preexisting hepatopulmonary syndrome might continue despite sufficient transplant function and even worsen during subsequent pregnancy [4].

Cardiovascular Function

See also Chap. 35

Patients receiving a liver graft suffer with a higher incidence from *ischemic heart disease* and *cardiomyopathy* [42]. These diseases continue to be a problem post-LT. Additionally and even if pretransplant cardiac work up has been without pathological findings, *cirrhotic cardiomyopathy* can appear after LT [99, 100]. This might be owed

to a low systemic vascular resistance before the transplantation that rises significantly post-LT [76].

The low systemic vascular resistance, low blood pressure, and *hyperdynamic circulation* in hepatic patients continue in the early phase after transplantation [79]. In this stage, patients require most likely higher levels of vasopressor therapy during surgery. Over time post-LT, hyperdynamic circulation and intrapulmonary shunting decreases [76].

A preexisting *autonomic dysfunction* is very common in ESLD. The majority of these patients improve posttransplantation. However, it needs to be kept in mind that a portion of these patients fail to recover, and disturbed autonomic function continues post-LT [101, 102].

Hepatic artery thrombosis can occur within the first weeks post LT especially in children and thus, the anesthesiologist should maintain blood pressure in a normal range and avoid hemoconcentration [85].

Renal Function

See also Chap. 34

Many patients post LT show impaired renal function. During the early stage it can be caused by intraoperative ischemia-reperfusion injury [103]. *Acute renal failure* occurs in 12 % posttransplant, but 97 % recover within 1 month [104]. The above mentioned MELD-Score serves as a predictor for the development of acute kidney injury for the first days after LT [105]. However, the usefulness of the score with respect to evaluating kidney function in the transplanted patient has never been addressed.

Later after the transplantation, renal dysfunction is mostly triggered by *immunosuppressive therapy* [59, 60]. For instance, cyclosporine and tacrolimus dose-dependently decrease renal blood flow and glomerular filtration due to vasoconstriction [85]. Serum creatinine is a late and insensitive indicator of kidney disease. It has been recommended to employ an estimating equation to evaluate glomerular filtration rate [71]. Renal eliminated drugs should be adjusted for a clearance of 40–50 mL/min [59].

Coagulation Function

See also Chap. 36

With good allograft function, a preexisting plasmatic coagulopathy normalizes within days to weeks. If significant splenomegaly preexisted, e.g., in cirrhotic liver disease, platelets might continue to malfunction over several months. Hence, it seems reasonable that platelets and plasmatic coagulation are tested prior to nontransplant surgery. For intraoperative monitoring of coagulopathy, thrombelastography can be employed if available [106].

Infection

See also Chap. 2

Based on the magnitude of transplant procedure and the often poor clinical condition of the patient shortly after LT, as well as continuous immunosuppressive therapy, the *risk of infection is increased* post LT. The high infection rate is a major transplant-related problem and most patients post LT are expected to develop at least one clinical infection episode [58, 61, 72]. The period between the third and the sixth month after transplantation tends to be of particular risk for opportunistic infection. That includes herpes viruses, fungi, unusual bacterial, and protozoa [71]. Long-term and with reduced immunosuppressive drug dosage, the risk of infection decreases [71].

It is important to *assess possible infections* prior to elective surgery, because it reflects a significant cause of morbidity and mortality after transplantation. Immunocompromised patients might not present typical clinical signs of infection, e.g., fever, leukocytosis, or peritonitis, and a low white blood cell count can easily mislead [58, 69]. If infection is present before elective surgery, the procedure should be rescheduled. Reduction or yet discontinuation of immunosuppressive therapy clearly increases the risk of rejection and is discouraged [85]. In doubt, contacting the transplant team or center for cowork might be a good choice.

Diabetes Mellitus

Corticosteroids and other immunosuppressants are considered diabetogenic and cause insulin resistance [65]. Much of the risk for posttransplant diabetes mellitus is connected to calcineurin inhibitors and steroid treatment [107]. The incidence of new onset of diabetes mellitus after LT is about 26 % and develops typically during the first year [108].

Laboratory Testing

Recommendations for laboratory testing in post-LT patients for nontransplant surgery are sparse and differ significantly. Some authors recommend in order to survey graft function and major side effects of immunosuppression complete laboratory testing including complete blood count, coagulation, electrolytes, standard liver and renal function test [63]. However, there is a clear lack of clinical evidence on which laboratory tests reduce the risk of perioperative morbidity in this population. Laboratory testing should depend on the time of the last checkup, the magnitude of expected surgery, the medical history, the physical examination, and the general condition of the patient. Given the above mentioned possible complications, the following tests might be options:

- *Glucose* measurement appears reasonable because of frequent hyperglycemia post

LT [79].

- A panel of *electrolytes* might be useful, especially potassium, because of potential renal impairment.
- *Liver enzymes are of some value* in suspicion of rejection [58]. AST and ALT can be elevated up to a year post LT. Without signs of liver dysfunction, testing liver enzymes for minor surgery are of questionable value. Anesthesia seems not to influence liver enzymes when pre- and postop values were compared [60]. The question remains what to do with abnormal liver tests, since the reasons for abnormality are manifold [71]. Therapeutic consequences depend on the persistence and the severity of abnormalities. At least to repeat the test and in doubt contact the transplant team might be an approach for the anesthesiologist.
- *Cholestatic parameters* : alkaline phosphatase and bilirubin might be of some value, if the patient presents clinical signs of cholestasis. Bilirubin readings normalize within 3 months post LT. Afterwards, increased bilirubin levels might be a sign of rejection, obstruction, or hepatitis.
- *Albumin and/or prealbumin* can be measured in suspicion of allograft rejection. Despite the fact that low albumin levels correlate with higher morbidity in nontransplant surgery, there is no data whether the knowledge of low albumin levels lead to any consequence or improvement of patient's management [59].
- *Plasmatic coagulation* : a coagulation status should be assessed in case of major surgical procedures, neuroaxial anesthesia, and suspicion of liver or renal dysfunction [59]. Prothrombin time and partial thromboplastin time have been suggested [69]. Based on a similar bleeding risk of transplanted and nontransplanted patients for nontransplant surgery, coagulation tests are of little value in minor surgery with normal graft function.
- *Complete blood count* : with respect to platelet count and possible anemia, at least for major surgery, a complete blood count appears important.

Anesthetic Management

Which anesthetic management serves best for post-LT patients remains unknown. There is virtually no evidence and most recommendations are based on very small clinical trials, case reports, and expert opinion.

Regional anesthesia alone or in the combination with general anesthesia is not contraindicated in patients receiving continued immunosuppression after LT if coagulation is within normal range. For instance, regional procedures might work well in obstetric anesthesia post LT and with coexisting pulmonary disease [4]. A strict aseptic technique is mandatory, because patients are immunocompromised.

In case of allograft malfunction, considerations of choice of anesthetics are comparable to the anesthetic management of patients with end-stage liver disease (s. above).

Premedication

Given the potential drug–drug interactions with maintained *immunosuppressive substances* and the possibility that blood levels of immunosuppressants can change, it is important that patient's regular medication is maintained if no contraindications exist [69]. As mentioned above, it is essential to continue the exact dose and time schedule of immunosuppressive drugs. If the transplant works sufficiently, no specific recommendation can be given with respect to *anxiolytics* or standard premedication.

Anesthetics

In the early stag e after LT, anesthetics that minimally influence hepatic or splanchnic perfusion are preferred. That applies to opioids and most volatile anesthetics. With sufficient liver and renal function, there is no contraindication to use any anesthetic [60, 72].

- *Opioids* : fentanyl, sufentanil, alfentanil, and remifentanil can be used as usual without any restrictions in dosing.
- *Hypnotics* : *propofol*, *thiopental*, and *etomidate* can be used as usual. The safety and feasibility of using *ketamine* post LT seems uncertain at this point. Only case reports exist showing uneventful administration but also seizure activity in children on cyclosporine. The latter is known to exert neurotoxicity including lowering the seizure threshold. Depending on the pharmakodynamic and thus the time frame between administration of cyclosporine and subsequently ketamine, the combinaton might enhance seizure activity. Based on existing knowledge, coadministration of cyclosporine and ketamine cannot be recommended.
- *Volatile anesthetics* : *isoflurane* and *sevoflurane* can be used safely. *Desflurane* might decrease hepatic blood flow to some extend [109]. Whether this might affect the transplanted liver remains unknown. *Halothane* should not be used in either adult or pediatric patients after liver transplantation. If inhalational induction of anesthesia is required, sevoflurane is the better option.
- *Neuromuscular blocking agents* : *atracurium* or *cis-atracurium* are a good choice as they are spontaneously degraded by Hofmann reaction [59, 72]. As mentioned above, potential interference with immunosuppressive drugs must be considered when choosing the neuromuscular relaxant [110]. *Succinylcholine* should be handled with care, because of potential renal impairment and associated

hyperkalemia.

Monitoring

No specific monitoring is required in post-LT patients, if the transplant functions satisfactorily. In general and besides standard monitoring, the choice of invasive measurement has to be rather attributed to the patient's clinical condition, underlying diseases, and magnitude of the planned surgery than to the fact that the liver has been transplanted. *Invasive monitoring* should be restricted to a minimum because of potential infections and only installed after a risk-benefit discussion. If the decision is made to apply invasive monitoring, it is more than important to guarantee strict aseptic techniques as the use of gowns and gloves has been proved to reduce infections [72, 111, 112]. If available, using *trans-esophageal echocardiography* or *pulse contour analysis* instead of pulmonary catheters for cardiac monitoring might be superior in posttransplant patients as it avoids the invasive procedures-related risk of infection [63].

Intraoperative Management

Perioperative single shot antibiotics should be administered as in nontransplanted patients [61, 72].

With respect to *airway management* and because of the higher risk of infections in post LT, nasal intubation should be avoided as far as possible and oral intubation is preferred. For the same reason, early extubation might prevent ventilation associated pneumonia [69, 72]. Laryngeal mask airway can be used without problems considering the limitations as usual.

For intraoperative *ventilation strategy* , it is important not to hyperventilate the patient, since cyclosporine and tacrolimus therapy can lower the seizure threshold. The ventilator should be set in order to prevent atelectasis, and positive end-expiratory pressure can be applied. Aggressive mechanical ventilation impairs vena cava blood flow and hepatic blood circulation [113]. Thus, low tidal volumes and adequate positive end-expiratory pressure or even spontaneous breathing patterns might be advantageous. In this context, early extubation seems not only favorable with respect to the risk of ventilator associated infections but also to optimize liver blood circulation postoperatively.

The *hemodynamic management* should be adjusted to preexisting cardiovascular diseases and preservation of graft function. This is to provide adequate perfusion to the heart and the transplanted liver without risking hypotension during induction and maintenance of anesthesia [106]. Appropriate volume replacement has been suggested to optimize hepatic perfusion [60]. The risk for *hepatic artery thrombosis* concerns specially the pediatric patient early after transplantation. The mean arterial pressure

should be in the upper normal range. In this context, the question of optimal blood viscosity and whether hematocrit should be lower than 28–30 % remains unanswered [114, 115]. Convincing clinical data is absent, but as with all patients, overtransfusion must be avoided. Perioperative *hypertension* can be corrected with all common vasodilators.

Regarding the type of *volume replacement* , no evidence can suggest specific solutions. Crystalloids have been recommended by some authors [60]. If transfusion is required, leukocyte-poor, irradiated blood products should be administered in all patients post transplant [69].

Recovery from Anesthesia

The *postoperative management* depends on the general constitution and type of surgery. The fact that a patient had a liver transplantation in the past is not per se an indication for transfer to the intensive care unit. Patients undergoing minor operations and in good clinical condition can be transferred to the recovery room and subsequently to the general ward. However, patients with insufficient transplant function, poor clinical condition, and major surgery should be transferred to a higher dependency ward, e.g., intermediate care or intensive care unit.

For *postoperative pain control*, using *nonsteroidal anti-inflammatory* are discouraged. These drugs increase the risk of nephrotoxicity when cyclosporine or tacrolimus are coadministered. Furthermore, blood concentrations of nonsteroidal anti-inflammatory can significantly increase in the presence of immunosuppressants [116]. *Opioids* such as morphine and pethidine has been suggested in post-LT patients [59]. With sufficient allograft function, oxycodone might also work, but its elimination can be prolonged in the case of graft insufficiency [117]. Finally, *local wound infiltration* lowers opioid consumption during the early postoperative phase. Bupivacaine and ropivacaine can safely be used in post-LT patients.

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Part VII
Special Issues in Liver Transplantation

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32. Acute Liver Failure: Perioperative Management

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Introduction

Acute Liver Failure (ALF) as the name suggest is a disease of rapid onset and progression. It has a high mortality (>80 % without transplantation) that depends on age, etiology, and other factors such as prothrombin time, serum bilirubin level, and stage of encephalopathy at the time of admission. Estimates of acute liver failure in the US are

approximately 2000 cases per year. Proper monitoring, aggressive treatment, and timely transplantation significantly reduce mortality.

Numerous attempts have been made to characterize ALF. The most commonly used definition of acute liver failure is: onset of encephalopathy within 8 weeks of the onset of jaundice without preexisting liver disease [1]. This definition has been modified by Bernuau et al. who divided acute liver failure into acute, subacute, and late onset. They suggested that the absence of preexisting liver disease is a common denominator; however it is the onset of encephalopathy in relation to jaundice that characterizes these patients into acute (<2 weeks), subacute (2–8 weeks), and late onset liver failure (8–24 weeks) [2]. This definition has also been used to predict the prognosis.

Etiology of Acute Liver Failure

Identification of etiology in individual cases is important because of the implications for prognosis and therapy (Table 32.1). Some of the etiologies include viral (hepatitis A, hepatitis B, herpes, CMV, EBV), vascular (Budd-Chiari syndrome, right heart failure, shock liver), metabolic (Wilson's disease, HELLP) [3], Acute fatty liver of pregnancy, tyrosinemia), drugs and toxins (acetaminophen, Amanita phalliodes, Bacillus cereus toxin, herbal remedies), and miscellaneous/indeterminate (malignant infiltration, autoimmune hepatitis, sepsis). Viral hepatitis is overall the primary cause of ALF; of all the viral etiologies hepatitis B, A virus is more prevalent [4]. Hepatitis C virus is a rare cause of ALF. Acetaminophen toxicity is the leading cause of ALF in the US, accounting for approximately 40 % of cases [5–11]. Acetaminophen hepatic toxicity has also been reported after therapeutic doses in patients with a history of chronic alcohol consumption, and those on a simultaneous regimen of hepatic enzyme inducing drugs, like phenytoin [12]. About 20 % patients fall in the category of unknown etiology. The groups with the highest spontaneous survival reported are those afflicted by acetaminophen toxicity (57 %), and hepatitis A virus (40 %), with the lowest survival in those afflicted by Wilson's disease [11].

Table 32.1 Fulminant hepatic failure—etiologies

Viral hepatitis
Hepatitis A, B, D, and E (HAV, HBV, HDV, HEV respectively).
Herpes Simplex virus Hepatitis
Epstein Barr virus Hepatitis
Yellow fever
Q fever
Drug toxicity
Acetaminiphen

Halothane
Isoniazid
Sodium valproate
Antimicrobials: ampicillin with clavulinic acid, erythromycin, tetracycline, ciprofloxacin
Troglitazone
Cyclophoshamide
Loratadine
Antabuse
Propylthioviacil
Ketoconazole
Phenytoin
Tricyclics
Ecstasy
Other toxins
Amanita phalloides
Organic solvents
Herbal medicine (ginseng, penny royal oil, and teucrium polium)
Bacterial toxins (E. bacillus and cyanobacteria cereus)
Miscellaneous
Reye's syndrome
Eclampsia
Autoimmune hepatitis
Acute fat liver of pregnancy
Heat stroke
Budd-Chiari syndrome
Cardiac failure
Leukemia
Lymphoma
Malaria
Ischemia
Lecithin-cholesterol acyl transferase deficiency
Wilson's disease
Portal vein thrombosis
Cardiac tamponade

Pathophysiologic Changes and Monitoring in Acute Liver Failure

ALF patients have heterogeneous clinical presentation, but they do share common disease process of acute hepatocyte loss and its sequelae. Presenting symptoms are often nonspecific, including fatigue, malaise, anorexia, nausea, abdominal pain, fever, and jaundice [5]. Often these symptoms progress to severe coagulopathy and encephalopathy and/or coma. Clinical deterioration is often rapid and any worsening in the patient's condition should warrant urgent referral to a transplant center. Acute liver failure affects multiple organ systems in the body including the central nervous system, the cardiovascular, pulmonary, renal, metabolic, and coagulation systems [13]. Monitoring the patient with ALF will involve appropriate assessment of all these organ systems.

Central Nervous System

In adult patients encephalopathy is the hall mark of acute liver failure. Several mechanisms have been implicated [14, 15]: (1) impaired ammonia metabolism in the Astrocytes, (2) ionic shift, (3) abnormal energy metabolism, (4) impaired neurotransmission. Inadequate metabolism of ammonia in the liver triggers a multilayered neurometabolic cascade of physiologic changes that affects the cerebral hemodynamics. Encephalopathy is divided into four grades [16] with grade 4 being most severe. Interestingly, the grades of encephalopathy may fluctuate from one level to the other especially in the early part of the illness and is not a good determinant of the cerebral hemodynamic state.

In acute liver failure the typical signs and symptoms of increased intracranial pressure like nausea, vomiting, and papilledema are absent. The changes in the central nervous system can only be assessed by determining cerebral hemodynamic and metabolic changes. The cerebral hemodynamic parameters and techniques to be considered for monitoring are: Cerebral blood flow (CBF), Cerebral metabolic rate of oxygen consumption ($CMRO_2$), arterial-jugular venous oxygen content ($AJDO_2$) difference, CO_2 reactivity, intracranial pressure (ICP), cerebral vascular resistance (CVR), computerized tomography (CT scan), and determination of cerebral blood flow velocity using transcranial Doppler Ultrasonography (TCD).

The compliance of the brain progressively decreases as the cerebral blood volume increases from normal to high and eventually the intracranial pressure is so high that the brain either herniates or is in a state of impending herniation as schematically represented in Fig. 32.1 [17–19].

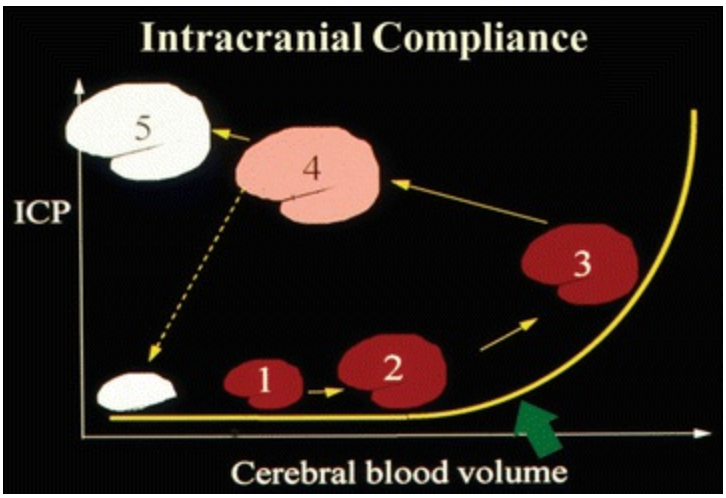

Fig. 32.1 Change in intracranial compliance in acute liver failure. Relationship between cerebral blood volume and intracranial pressure (ICP) as patient advances from Phase 1–5

Five Phases of Cerebral Hemodynamic and Metabolic Changes

The cerebral hemodynamic and metabolic changes observed in acute liver failure are divided into five different phases and are presented in Fig. 32.2 [20]. These phases are independent of the grades of encephalopathy. They are characterized as follows:

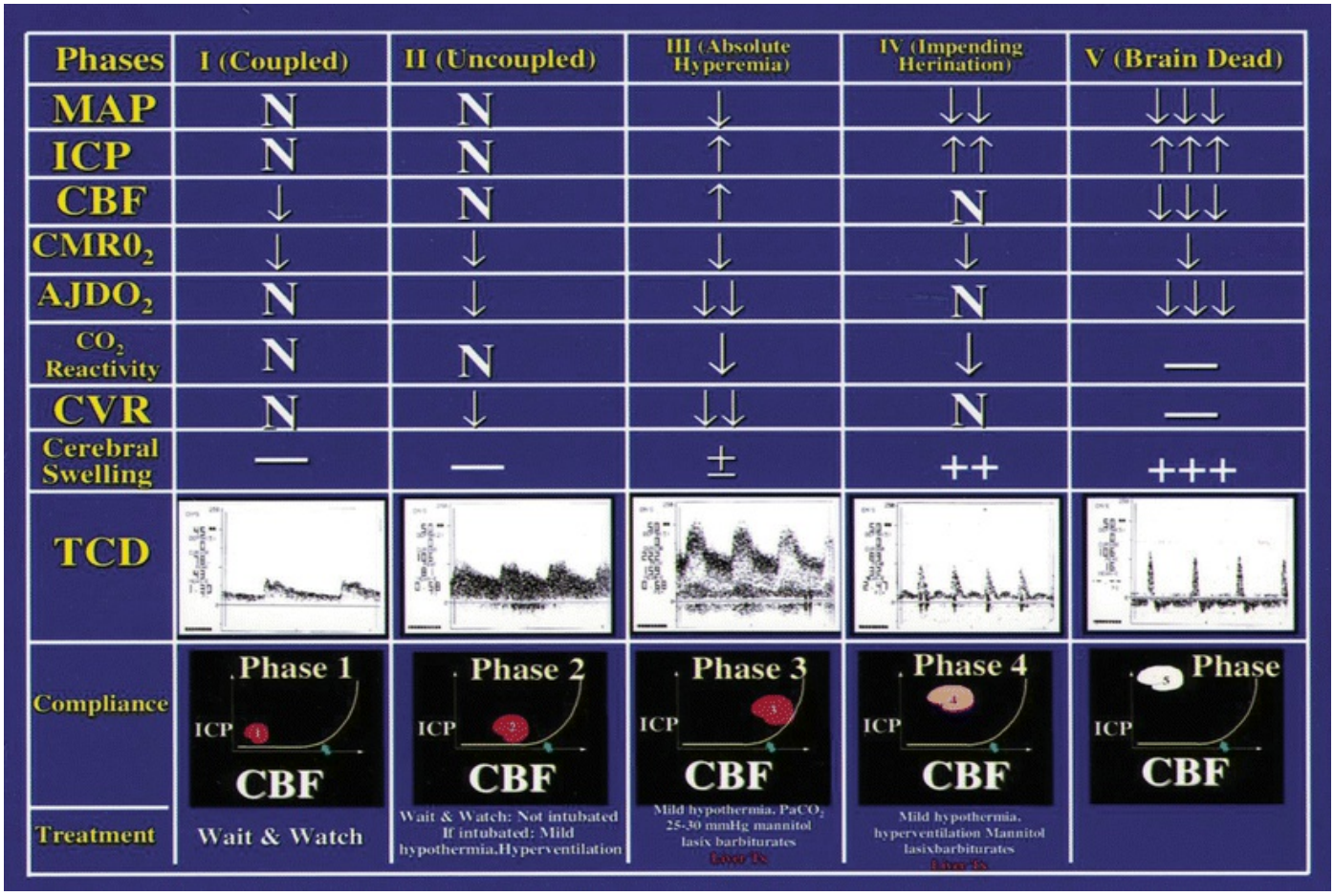

Fig. 32.2 Cerebral hemodynamics and metabolic changes and treatments in phases 1–5 in patients with acute liver failure. *MAP* mean arteryl pressure, *ICP* intracranial pressure, *CBF* cerebral blood flow, *CMRO* $_2$ cerebral metabolic rate of oxygen consumption, *AJDO* $_2$ arterial jugular venous oxygen content difference, *CVR* cerebral vascular resistance, *TCD* transcranial Doppler ultrasonography

Phase 1 (*Coupled*): Demand ($CMRO_2$) and supply (CBF) are matched as demonstrated by normal $AJDO_2$ difference. In this phase the ICP is normal, response of CBF to arterial CO_2 changes (CO_2 reactivity) is intact. Cerebral vascular resistance is normal and there is no brain swelling.

Phase 2 (*Uncoupled*): Demand ($CMRO_2$) is low but the supply (CBF) in spite of being low, is more than the demand of the brain (relative hyperemia) as demonstrated by narrow $AJDO_2$. In this phase ICP is still normal and CO_2 reactivity is still intact. However, cerebral vascular resistance is decreased although there is still no brain swelling.

Phase 3 (*Uncoupled*): Demand ($CMRO_2$) is low but the supply (CBF) is high (absolute hyperemia) as demonstrated by narrower $AJDO_2$. CO_2 reactivity, although reduced, is still intact. However, ICP is high, cerebral vascular resistance is further decreased and brain swelling may be present.

Phase 4: Demand ($CMRO_2$) is low and the supply is low (CBF), as demonstrated by normal $AJDO_2$. The $AJDO_2$ is deceptively normal. Supply is low because of very high ICP and the blood flow to the brain is reduced because of extramural compression of the cerebral vessels by cerebral swelling. CO_2 reactivity is markedly reduced. Cerebral vascular resistance is normal and the brain is swollen. These observations confirm that ICP monitoring is extremely important in management of these patients. It is ICP which distinguishes coupled Phase 1 from the seemingly coupled Phase 4, which is close to herniation.

Phase 5 (*Impending herniation or herniation*): Shows minimal CBF with very high ICP.

It is uncommon to see all five phases in one patient, because (1) the natural disease progression is highly variable. The phases may change from one to the other within hours, or in days, depending on the etiology and other compounding factors like other organ system involvement; (2) impact and timing of liver transplantation; and (3) the phase at which the patient was referred, as the patient may have already passed through some of the phases prior to being transferred to the hospital. The first four phases of cerebral hemodynamic changes are reversible. Therefore, it is crucial to monitor the cerebral hemodynamics in order to institute proper therapy before irreversible changes occur.

Cerebral Blood Flow (CBF)

CBF can be determined using the intravenous Xe-133 clearance technique [21] and/or stable xenon-CT scan method [22]. The intravenous Xe-133 clearance technique is the preferred method as (1) it can be determined at the bed side, and the risks associated with moving a hemodynamically unstable patient from intensive care unit setting to radiology suite can be eliminated; and (2) this technique can be performed more frequently. The limitation of this technique is that it solely measures CBF. Stable xenon-CT scan determinations of CBF also provide information regarding intracranial pathology which may help to determine the cause of the coma; i.e. cerebral swelling, space occupying lesion, and cerebral hemorrhage. However, to determine CBF by this technique the patient has to be transported to the CT scanner. It may be dangerous to transport a critically ill patient. Therefore, this technique should only be used in select circumstances.

Since acute liver failure is a metabolic disorder, the CBF changes are global. Interestingly, low CBF can even be seen in higher grades of coma (grade 3 and 4) [23–25]. Low CBF most often is not ischemia, as these patients have very low $CMRO_2$. Usually, low blood flow is coupled and is a good prognostic sign unless the patient is in phase 4 of cerebral hemodynamic and metabolic changes of the brain, where blood flow is low because of massive swelling and intracranial hypertension [20]. High cerebral

blood flows, which are usually seen in grade 4 coma, are associated with cerebral swelling and intracranial hypertension and have a poor outcome [23, 26].

Arterial-Jugular Oxygen Content Difference ($AJDO_2$)

$AJDO_2$ is determined by analyzing the difference in oxygen content of systemic arterial blood and the jugular venous blood. Jugular venous samples can be obtained by inserting a catheter in the internal jugular vein [27, 28]. The position of the catheter tip must be confirmed by lateral roentgenogram of the head and neck. If the tip of the catheter is not at the level of jugular bulb, the blood samples can be contaminated by extra cranial blood and will give false results. Blood samples can also be contaminated if the blood samples are drawn rapidly.

$AJDO_2$ is a good bed side clinical tool to determine (1) changes in global cerebral blood flow and (2) the adequacy of CBF in relation to cerebral metabolic rate of oxygen consumption ($CMRO_2$). This is only applicable if the $CMRO_2$ remains unchanged. Since $AJDO_2 = CMRO_2/CBF$, monitoring and managing the $AJDO_2$ can eliminate repeated determination of CBF [29].

At a $PaCO_2$ of 40 mmHg, the normal $AJDO_2$ range is 5.1–8.3 vol.%. The normal $AJDO_2$ range for other levels of $PaCO_2$ can be calculated by increasing the $AJDO_2$ range by 3 % for a decrease of each mm Hg in $PaCO_2$ and vice-versa. A normal $AJDO_2$ indicates that the supply of CBF is closely coupled with the cerebral metabolic demand of the oxygen. $AJDO_2$ below the normal range demonstrates uncoupling, showing cerebral hyperperfusion relative to $CMRO_2$ (cerebral luxury perfusion), whereas values above the normal range, which also indicate uncoupling, are consistent with cerebral hypoperfusion relative to $CMRO_2$.

In acute liver failure, very few patients have normal $AJDO_2$ (coupling). A majority of patients have low $AJDO_2$ (uncoupling) which is most likely caused by depressed cerebral metabolism. Moreover, if the $AJDO_2$ and CBF both are very low, this may indicate minimal extraction of oxygen and irreversible brain injury as seen in phase 5 [20, 29].

Cerebral Metabolic Rate of Oxygen Consumption ($CMRO_2$)

$CMRO_2$ is calculated as product of CBF × $AJDO_2/100$. In acute liver failure $CMRO_2$ is depressed even in early phases of the disease. It is usually less than 50 % of normal [23, 24]. In some instances it can even be as low as 25 % of normal, and still the patients may recover without apparent neurological deficit. Low $CMRO_2$ may very well be an indication of the depressed active and basal metabolism of the brain. Unlike in

head injury [29], $CMRO_2$ is not a predictor of outcome in acute liver failure [23, 24].

CO_2 Reactivity

CO_2 Reactivity is the response of CBF to changes in arterial CO_2 tension. The normal response is 3 % CBF change per mm Hg change in $PaCO_2$. It is a relatively noninvasive technique. The response of CBF changes to CO_2 alterations provides a tool to predict the efficacy of hypo or hyperventilation from both the therapeutic and prognostic points of view [20]. In determining CO_2 reactivity certain precautions must be observed: (1) Systemic mean arterial pressure must be maintained (2) An observable change in CBF requires a minimum of 5 mmHg alteration in CO_2 (3) Prior to determining CO_2 reactivity, a baseline CBF needs to be assessed in order to ensure that a patient with low CBF is not hyperventilated and that a patient with high CBF is not hypoventilated.

CO_2 reactivity is well preserved in early phases (phase 1, 2) for hyper and hypoventilation [17, 20, 30]. However, in phase 3 and 4, although the vascular response to changes in $PaCO_2$ is preserved for hyperventilation, it is reduced for hypoventilation. This change in response suggests that as patients move towards higher phases, the vessels become more dilated and lose their vasomotor tone for further dilatation. It should be noted that hyperventilation can still be an effective therapy for reducing CBF in late phases as shown in Fig. 32.3.

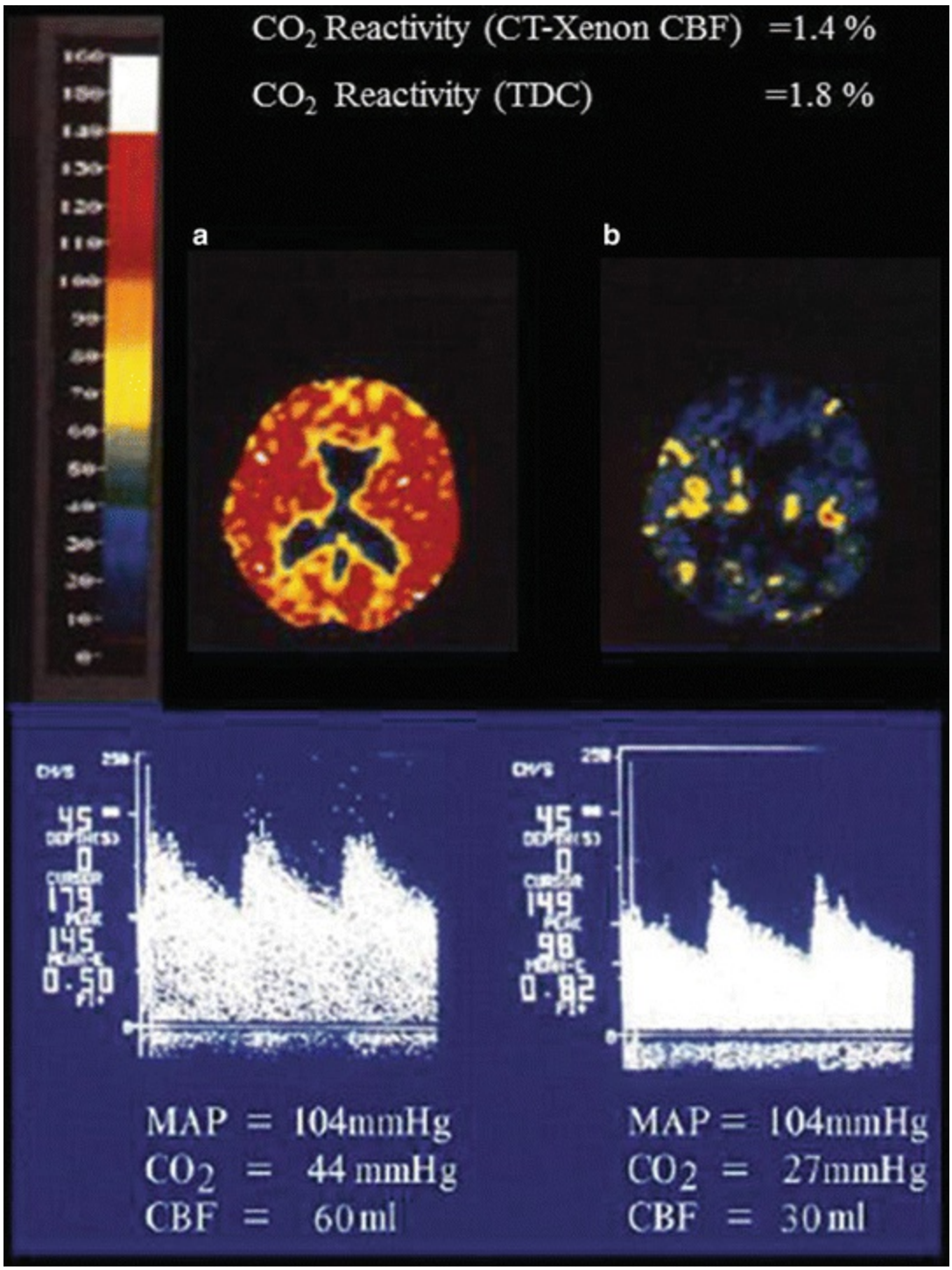

Fig. 32.3 CO_2 reactivity in a patient with acute liver failure. (**a**) Cerebral blood flow (CBF) determined by CT-Xenon method and cerebral blood flow velocity (CBFV) determined by Transcranial Doppler ultrasonography (TCD) at $PaCO_2$ of 44 mmHg, mean artery pressure (MAP) of 104 mmHg. (**b**) Cerebral blood flow (CBF) determined by CT-Xenon method and cerebral blood flow velocity (CBFV) determined by Transcranial Doppler ultrasonography (TCD) at $PaCO_2$ of 27 mmHg, mean artery pressure (MAP) of 104 mmHg

Cerebral Vascular Resistance (CVR)

CVR is calculated as (MAP − ICP)/CBF (normal = 3.6 mmHg/ml/100 g) CVR is normal

in phase 1. When the cerebral vessels dilate the vascular resistance reduces as in phase 2. In phase 3, cerebral vascular resistance reduces further, however, increase in cerebral blood volume causes a rise in ICP [19]. In phase 4, because of cerebral swelling, CVR is increased to a point that the CBF is reduced [20].

Intracranial Pressure (ICP)

ICP is one of the most important parameters to be monitored in acute liver failure. This is because 40 % of mortalities in this population are from brain herniation [31]. An ICP monitoring device should be inserted as soon as patient is intubated. It is challenging to insert an ICP monitoring device because of the coagulopathy associated with liver failure.

Prior to inserting an ICP monitor (1) computed tomography (CT scan) of the head should be performed in order to rule out any adverse intracranial pathology; (2) coagulation status must be optimized after evaluation by either following the conventional coagulation parameters (prothrombin time, partial thromboplastin time, platelet count, and fibrinogen degradation products) and/or thromboelastography (reaction time >6 min, alpha angle >50°, maximum amplitude >50 mm, and whole blood clot lysis time >300 min) [32, 33]; and (3) the airway must be secured.

There are three different sites for inserting intracranial pressure monitoring devices: epidural, subdural, and parenchymal. Out of these three sites, epidural placement is the most popular because of lowest incidence of hemorrhage (<4 %), and infection (<1 %) [34, 35]. Parenchymal placement has the highest incidence of both hemorrhage (13 %) and infection (4 %). While, the drawback of an epidural monitoring device is its unreliability in obtaining absolute ICP values, it does measure changes in ICP consistently.

The etiology of intracranial hypertension in ALF is unknown. However, it appears that toxins lead to cerebral vasodilation, which increases cerebral blood volume, followed by an increase in intracranial pressure, and increased capillary leak (vasogenic cerebral edema). Cerebral edema further compounds the intracranial pressure. Initially, the ICP increase precedes the development of cerebral swelling. Later, the increase in ICP is compounded by cerebral swelling. An increase in ICP is seen when the CBF is high and cerebral vascular resistance is low indicating increase in cerebral blood volume [36]. The precipitating factors for cerebral vasodilation and increase in cerebral blood volume are: (1) anemia and episodes of hypotension [37]; (2) hypoxia caused by pulmonary congestion; and (3) lactic acidosis [24].

It is interesting that, in acute liver failure, papilledema has not been reported to be observed in conjunction with intracranial hypertension. In acute liver failure patients, high ICP's (>40 mm H_2O) are tolerated much better in comparison to patients with head injury [38]. Once intracranial hypertension sets in, it is difficult to control unless and

until the diseased liver is replaced by a normal functioning liver. With every new episode of intracranial hypertension, it becomes increasingly difficult to bring the ICP to its baseline value and the subsequent fluctuations are more pronounced. Unequal and dilated pupils are seen with extremely high ICP's, but, fortunately, these can be reversed by aggressive medical management.

Computed Tomography of the Head

It is very difficult to transport these patients to a computed tomography (CT) scanner, as they may be (1) hemodynamically unstable, (2) on assisted ventilation, and (3) require multiple vasopressor infusions. However, it is essential to obtain a CT scan of the head in order to: (1) to establish baseline condition of the brain on admission to intensive care unit; (2) prior to insertion of ICP monitor; and (3) in any acute change in neurological status, particularly a sharp rise in ICP.

It is interesting that cerebral swelling appears mostly in phase 3 and 4 and is associated with very high blood volume [20, 23, 24, 37, 39, 40]. Presence of cerebral swelling in conjunction with high CBF indicates a poor prognosis [41]. Likewise loss of the gray–white matter interface signifies a poor prognosis. During these phases, if cardiovascular status becomes very unstable, liver transplantation may become contra-indicated.

Cerebral Blood Flow Velocity (CBFV)

CBFV can be measured by using transcranial Doppler ultrasonography (TCD) . TCD consists of a pulsed Doppler instrument operating at a low frequency (2 MHz), coupled with a computer that performs Fourier transformation of the complex waveform data for real-time spectral display. This technique is noninvasive, can be used at the bedside to determine CBFV in all the major intracranial vessels [42, 43].

TCD variables (Fig. 32.4) include systolic cerebral blood flow velocity (SFV), diastolic cerebral blood flow velocity (DFV), mean cerebral blood flow velocity (MFV), or [(SFV + DFV)/2]), and pulsatility index (PI), or [(SFV − DFV)/MFV]). Every variable of the waveform is important, however, diastolic cerebral blood flow velocity determines the period during which the brain receives its blood flow. Pulsatility index is believed to reflect cerebrovascular resistance and thus shows exponential correlation with ICP. In TCD monitoring, the observed trends over time are more revealing than any single set of measurements [44].

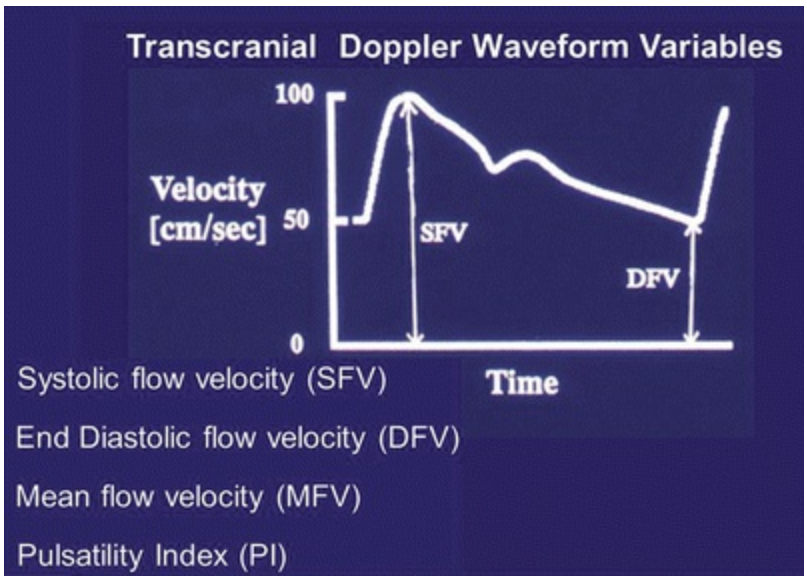

Fig. 32.4 Variables of Transcranial Doppler ultrasonography waveform. *SFV* systolic blood flow velocity, *DFV* diastolic blood flow velocity, *MFV* mean blood flow velocity, *PI* pulsatility index

TCD can be used to estimate: (1) cerebral blood flow, (2) ICP, (3) CO_2 reactivity, and (4) effect of various therapeutic modalities on CBF, ICP, and CO_2 reactivity [45, 46]. Figure 32.2, shows sequential changes in TCD patterns of a patient with acute hepatic failure [47]. Phase 1: Decreased systolic cerebral blood flow velocity (normal = 61 cm/s), normal pulsatility index (normal = 0.90 ± 0.24). Phase 2: Normal systolic cerebral blood flow velocity with low pulsatility index. Phase 3: Increased systolic cerebral blood flow velocity with low pulsatility index. Phase 4: Decreased systolic cerebral blood flow velocity, with high pulsatility index. Phase 5: Negative diastolic flow or retrograde CBF (brain death). Figure 32.3 shows the effects of hyperventilation on TCD patterns of a patient with acute liver failure. It shows that as the patient is hyperventilated and the $PaCO_2$ is decreased from 44 to 27 mmHg the mean cerebral blood flow velocity reduces from 145 to 98 cm/s and at the same time the CBF determined by CT-xenon method also shows reduction from 80 to 60 ml/100 g. This indicates that; (1) the CO_2 reactivity demonstrated by TCD compares very well with the CT-xenon CBF determination method, (2) CO_2 reactivity is preserved even at very high CBF, though 50 % of normal (CO_2 reactivity 1.4 %) [48–50] demonstrating that hyperventilation is an effective therapeutic modality in reducing CBF. The diminished CO_2 reactivity is secondary to the vessels developing vasoparalysis. Figure 32.5 shows the effects of barbiturates on TCD patterns of a patient with acute liver failure. In a patient with high intracranial pressure (ICP = 34 mmHg, PI = 1.92) when barbiturates are administered, the ICP (28 mmHg) and PI (1.27) are reduced, provided the mean arterial pressure (MAP) is maintained at normal level (>80 mmHg). If the MAP reduces as an effect of barbiturates then ICP may further increase and cerebral perfusion may

reduce to dangerously low levels. MAP should be maintained by administering vasopressors, alone or in conjunction with increased fluid volume

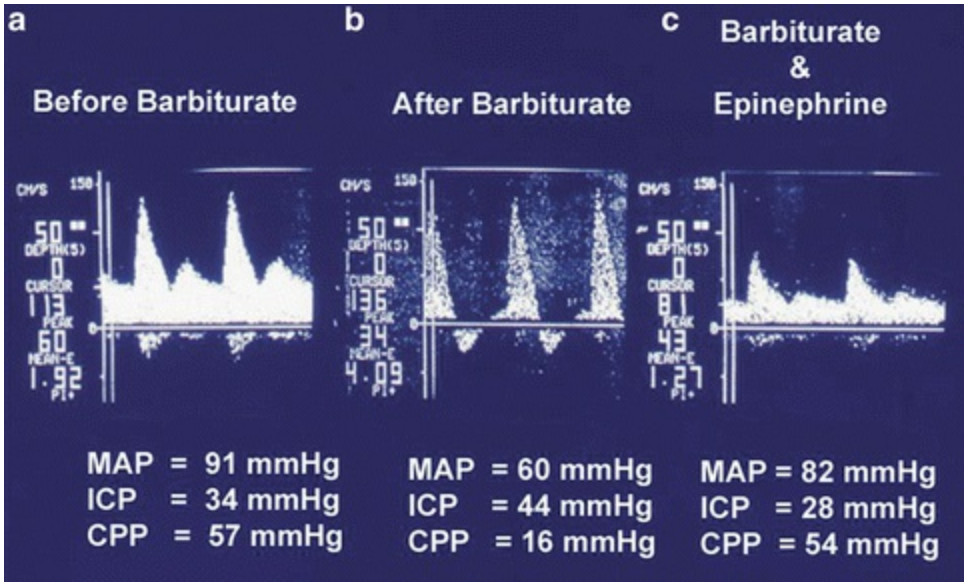

Fig. 32.5 Effect of Intravenous Barbiturate administration on Cerebral Blood Flow Velocity in an Acute Liver Failure patient with intracranial hypertension. (**a**) Cerebral Blood flow velocity in a patient with increased intracranial pressure (ICP). (**b**) Effect of barbiturates on ICP during hypotension (MAP = 60 mmHg), Cerebral Blood flow velocity shows loss of diastolic flow velocity and increase in ICP to 44 mmHg. (**c**) Effect of Barbiturate on ICP after restoration of mean artery pressure (MAP = 82 mmHg) by Epinephrine infusion. Cerebral Blood flow velocity shows restoration of diastolic flow velocity, and decrease in ICP to 28 mmHg

Cardiovascular System

Acute liver failure has varied hemodynamic manifestations depending on the etiology and the severity of the illness. It is essential that pulmonary artery catheter be placed so that appropriate diagnosis and treatment be made. Often in early phases of the disease (phase 1 and 2) these patients show a normal cardiac hemodynamic profile Fig. 32.2. As the disease progresses, they develop characteristics similar to those observed in septic shock (low systemic vascular resistance, high cardiac output, tachycardia, hypotension, and high mixed venous oxygen saturation of hemoglobin). Eventually (phase 4 and 5) [20], the hemodynamic status becomes very unstable and high doses of vasopressors are required for patient survival.

It is not unusual to observe pulmonary edema [51]. Most often, it is noncardiogenic in origin but in patients with viral etiology of ALF, myocarditis may cause cardiac failure and pulmonary edema. ST segment elevation on ECG is a rare occurrence and is observed without the presence of elevated myocardial enzymes levels (CPK) and abnormalities in serum electrolytes [52]. It is possible that increased intracranial pressure may cause ST segment elevation and be misinterpreted for myocardial ischemia.

Cardiac arrhythmias (supraventricular tachycardia, sinus bradycardia, premature ventricular contraction, and premature arterial contractions) are commonly seen in acute liver failure cases [53]. The etiology is not always known. However, viral myocarditis, accumulation of bilirubin, bile acids, acid-base and electrolyte imbalance and potentially other toxic metabolites may be the possible cause of the majority of arrhythmias. Sinus bradycardia in conjunction with episodic systemic hypertension (Cushing's phenomenon) is a sign of impending brain herniation.

In addition to cardiac changes, there is tissue hypoxia in the presence of adequate oxygen delivery as demonstrated by high oxygen saturation in mixed venous blood and high serum lactate level [54].

Respiratory System

Patients often hyperventilate and develop a respiratory alkalosis before a metabolic acidosis as liver failure progresses [10]. Arterial hypoxemia is of common occurrence, especially when patients are in grade 3 and 4 coma. The etiology of hypoxemia appears to be multifactorial: The risk of (1) Aspiration of gastric contents due to loss of airway reflexes from progressive encephalopathy requires airway protection in early grades of coma, (2) Atelectasis from shallow rapid breathing provides potential foci for pulmonary infection and pneumonia, (3) Intrapulmonary shunting, (4) Pulmonary edema which, in these instances, is usually non cardiogenic in origin. It is normally associated with generalized capillary membrane leak and, therefore, can be part of the same phenomenon [55, 56]. However, these patients also have a potential for neurogenic pulmonary edema, especially in the phase of cerebral decomposition.

Renal System

Since acute tubular necrosis (ATN) is the most common cause of renal failure (reported incidence varying from 40 to 85 %, It is often multifactorial, with prerenal azotemia, renal ischemia, acute tubular necrosis, and hepatorenal syndrome as common causes [57, 58]. Avoidance of nephrotoxins and adequate intravascular volume is important in maintaining renal function.

Hepatic Metabolism

The liver is the primary site for carbohydrate metabolism. Therefore, as the liver fails acutely, patients develop hypoglycemia caused by depletion of glycogen stores and decreased gluconeogenesis. Monitoring of blood glucose level is important as the glucose levels can fall to life threatening levels in a very short period of time [59, 60]. Upper GI bleeding is a recognized complication and is often stress related. Histamine-2 receptor blocking agents and proton pump inhibitors have been shown to be efficacious

in several trials [61].

Many clinicians believe that it is important to determine the extent of hepatic necrosis by either open liver biopsy or by transjugular biopsy. Transjugular biopsy of the liver is a relatively noninvasive technique and is performed under radiological guidance. It is a very useful technique and provides significant information [23, 62–64]. The one disadvantage of this technique is that since ALF may involve the liver in a heterogeneous way, there may be significant sample variability [65]. The liver biopsy information coupled with the patient's clinical information and status should be evaluated continually in order to decide indications for transplant. Although a liver biopsy at the time of transplant can be made intra-operatively at the time of an available liver donor, ideally this decision is made before bringing the patient to the operating room.

Coagulation System

The primary hematologic derangements seen in ALF include platelet dysfunction and thrombocytopenia, reduced fibrinogen, and a prolonged prothrombin time [5, 61]. Because the liver is the primary site for the synthesis of coagulation factors (factor V, VII, IX, and X; partially factor VIII, XI, and XII), it is not surprising to see severe coagulopathy in patients with acute liver failure. Antithrombin III (AT III), a major inhibitor of coagulation, is also decreased. Out of all the coagulation factors, factor V decreases most rapidly followed by factor II, IX, and X. In contrast to other factors, factor VIII is increased, however the etiology of its increase is unknown [66].

Coagulopathy can be assessed using conventional coagulation profile (prothrombin time, partial thromboplastin time, serum fibrinogen level, fibrinogen degradation products, and platelet count) and/or by thromboelastography (TEG) .

Prothrombin time is greatly increased when acute liver failure is caused by a paracetamol overdose as opposed to viral hepatitis [67]. The prothrombin time (PT) is used as a prognostic indicator as well as a way to follow the progress of the liver injury and correction of the PT is not routinely done unless there is clinical bleeding or an invasive procedure is planned [68].

Electrolyte and the Acid–Base State

Electrolyte imbalance is common. Hypernatremia is often seen because of (1) renal dysfunction and (2) use of sodium bicarbonate to treat metabolic acidosis. Hypernatremia is difficult to treat and, its presence can be a factor in potentiating cerebral swelling [58]. Hyponatremia , although rare, requires extreme caution as rapid correction of serum sodium levels can predispose the patient for central pontine mylenolysis. Hyponatremia can also promote cerebral swelling. Hyperkalemia may be seen in the presence of renal failure. Ionized hypocalcemia and hypomagnesemia are

rarely present. Metabolic acidosis is invariably present. The magnitude of acidosis depends on tissue perfusion, hepatic necrosis, and core body temperature. It is imperative to correct metabolic acidosis in order to avoid adverse effects on heart and brain. Hyperosmolarity is commonly seen in acute liver failure, which can be from hypernatremia. Presence of hyperosmolality hinders the beneficial effects of mannitol on the brain.

Management of Acute Liver Failure

The key for success in this group of patients is a team approach of dedicated anesthesiologists, gastroenterologists, intensivists, and surgeons. The gastroenterologist should take the responsibility of educating the physicians in local hospitals to identify these patients early in the course of illness and transfer them to a liver intensive care unit.

As the patient is referred, the team of physician must be alerted and work distributed, which includes: arrangement for CT scanner for CBF studies, placement of PA catheter, jugular bulb catheter, and endotracheal intubation if needed. After the preliminary examination is completed and monitoring is established, the management plan must be discussed. Since this is a multi organ disease, the management has to be focused on all the affected organs and the combined effect of multiorgan dysfunction. Evaluation of etiology of disease and decision regarding transplantation status also must occur concurrently.

Central Nervous System (Fig. 32.2)

In phase 1, the brain is in the flat portion of the pressure–volume curve (compliant), and the supply (CBF) and demand ($CMRO_2$) are coupled. Airway protection should be determined based on clinical indications. In phase 2, the brain is still in the flat portion of the pressure–volume curve. However, there is an uncoupling between the supply (CBF) and demand ($CMRO_2$). Mild hyperventilation is required to correct this. In phase 3, the patient is at the knee of the pressure–volume curve and has absolute hyperemia; ICP increases and there may be cerebral swelling. In this phase patient's head of the bed should be raised 30° so that there is a gravity support in reducing ICP [69, 70]. In this phase aggressive treatment with a combination of mild hypothermia (33–34 °C) [71, 72], hyperventilation [73–75] and diuretics [61] and barbiturate infusion [76] may be required. Furosamide is effective in reducing cerebral swelling especially when combined with mannitol. Caution must be observed in using mannitol by itself, as these patients may have serum osmolality >320, at which level the mannitol may not be very effective and secondly, the initial response to mannitol may be further cerebral vasodilation, increase in CBF and increase in ICP. Barbiturates are very effective in

reducing intracranial hypertension by causing cerebral vasoconstriction and thereby reducing CBF [76]. However, barbiturates also reduce systemic arterial pressure especially in the presence of hyovolemia. If systemic hypotension develops during barbiturate infusion, vasopressors or fluid must be infused promptly to avoid hypotension. Systemic hypotension is counterproductive in producing the desired effect of barbiturate on ICP. As a matter of fact, ICP may increase further as shown in a TCD tracing of a patient with acute liver failure (Fig. 32.5).

Hypothermia is an effective mode of treatment in reducing CBF and, thereby, reducing the intracranial pressure [72]. It has been shown that mild hypothermia (32–34 °C) is effective. Caution is advised during the cooling process because the temperature may drop to a level below the target point, when there is a propensity for the occurrence of cardiac arrhythmias [77]. The advantage of this temperature zone (32–34 °C), is that cardiac arrhythmias are seldom seen at this level of body temperature. The possible mechanisms of reduction of ICP by hypothermia may be a combination of: (1) reduction in uptake of ammonia by the brain [78, 79]; (2) reduction in inflammatory response [80–83]; (3) reduction in both active and basal metabolism of the brain thereby causing reflex vasoconstriction; and (4) direct cerebral vasoconstriction.

Phase 4 management is crucial. During this phase ICP is extremely high and the CBF is low. In this phase, because of the reduced compliance of the brain, all the treatment modalities mentioned above are needed—only more frequently. In phase 3 and 4, every effort should be made to replace the native liver as soon as possible [20].

Cardiovascular System

The major changes in the cardiovascular system include hypotension, decreased systemic vascular resistance [84], high cardiac index, arrhythmias and ST-segment changes [52]. During the first two phases (1 and 2), if hypotension develops, it responds to volume infusion and seldom needs vasopressor support. In phase 3, vasopressor infusion is often needed. Adrenaline or nor-adrenaline infusion is more effective in contrast to dopamine and/or dobutamine. In phase 4, the cardiovascular hemodynamics are unstable. Large doses of vasopressors are required and patients may develop hypotension even when the intravascular volume status is adequate [85, 86]. In late phase 4, arrhythmias and ST-segment changes are seen. ST-segment changes are shown to be non-ischemic in origin and do not respond to nitroglycerine infusion. ST-segment changes appear to be a sign of poor prognosis. Arrhythmias are commonly seen in acute liver failure. If they are from acid base and electrolyte imbalance, they respond well to the treatment of underlying etiology. In late phase 4 and phase 5, episodes of hypertension and bradycardia may develop as terminal signs of impending brain herniation.

Respiratory System

Since these patients are encephalopathic, the airway has to be controlled for prevention of aspiration as well as for pulmonary ventilation when they reach grade 3 coma and, sometimes, even as early as in grade 2 coma. Arterial hypoxemia is common and higher positive end expiratory pressure, PEEP (>10 cm H_2O) and/or high inspired oxygen tension may be required in conjunction with mechanical ventilation. High PEEP may be detrimental for intracranial hypertension. In circumstances where the intracranial pressure is elevated, high frequency ventilation may alleviate the need for PEEP [87]. Fiber optic bronchoscopy and suctioning is often required to identify the site of atelectasis and to remove secretions. Pulmonary edema is a sign of poor prognosis. Since it is non cardiogenic in origin, it is unresponsive to medical treatment. Urgent transplantation, if the patient is otherwise transplantable, is the only option. Use of high PEEP and low volume high frequency jet ventilation is effective only for short durations [88]. In selected patients, prone ventilation is shown to be effective. It should only be used when the ICP monitoring is in place [89].

Renal System

Since acute tubular necrosis (ATN) is the most common cause of renal failure, adequate fluid volume status should be established. In some instances, continuous veno-venous hemofiltration (CVVH) or hemodialysis (CVVHD) is required as a supportive measure [90, 91]. Caution should be observed, as too fast a withdrawal of volume during continuous venous filtration may lead to hypotension. For this reason, intermittent hemodialysis is not recommended in patients with ALF [92]. CVVHD may be continued intra-operatively if needed to allow optimal fluid management during transplantation.

Hepatic System

Hypoglycemia is aggressively corrected by infusing 5 % dextrose in water solution [93]. Electrolytes should be supplemented and followed closely. Enteral nutrition should be started early when feasible [94].

Coagulation System

Correction of coagulopathy is difficult, as there is increased peripheral consumption and reduced synthesis of coagulation products by the liver. Coagulation is basically maintained by exogenous replacement of factors and platelets. Replacement of factors is essential to avoid spontaneous bleeding, especially, prior to and, after the placement of an intracranial pressure monitor. It has been shown that administration of Recombinant factor VIIa (40–80 μg/kg intravenous bolus) prior to insertion of ICP monitor is beneficial in optimizing coagulopathy and therefore volume overload from

administration of fresh frozen plasma can be avoided [95]. Prior to placing an ICP monitor, baseline TEG and coagulation profile is obtained and is brought to as near normal levels as possible. For maintenance, fresh frozen plasma and platelets are used. Plasmapheresis can also be used as an adjunct to minimize coagulopathy.

Electrolyte and the Acid–Base State

Hypernatremia can be minimized by use of tris (hydroxymymethyl)-aminomethane, THAM, (0.3 M THAM [ml] = body weight [kg] × base deficit [mmol/kg]), for treatment of metabolic acidosis. THAM is a better choice of buffer in patients with acute liver failure, since it does not cause an increase in serum osmolality, or sodium or an increase in carbon dioxide production. However, THAM is a weak buffer and needs to be supplemented with sodium bicarbonate in correcting base excess >6. THAM is relatively contraindicated in renal failure.

Sodium bicarbonate is a strong buffer but causes high osmolality, hypercarbia, and hypernatremia which are all undesirable in acute liver failure. Hyperkalemia can be readily observed in the presence of renal failure. Infusion of glucose and insulin is generally effective in lowering the levels of serum potassium. If hyperkalemia persists, renal support with CVVHD can be considered. Hypokalemia, although rare, is corrected by potassium supplements.

Infection Management in ALF

The most common pathogens are Staphylococcal species, streptococcal species, and gram negative rods [5]. Fungal infections (particularly Candida albicans) occur in up to one-third of ALF with the risk factors of renal failure and prolonged antibiotic therapy for existing bacterial infections (Sass, Saito, Doyle). Common sites of infection include pneumonias (50 %), bacteremia (20 %), and urinary tract infections (25 %) (Boudouin). Most centers recommend prophylactic gram negative coverage and fluconazole therapy [96, 97].

Determining the Need for Transplantation: Criteria and Prognostic Factors

Since at least 20 % of the patients with ALF may survive without transplantation, extensive studies of prognostic factors have been done to identify patients who should be urgently transplanted. Currently the most widely applied are those described as the King's College Criteria (Table 32.2). In the group with acetaminophen toxicity, the PT, serum creatinine level, (patients with encephalopathy grade III–IV), or pH <7.3 irrespective of encephalopathy had a predictive value for poor outcome [98]. In non-

acetaminophen patients, criteria were not dependent on stage of encephalopathy and of an INR > 6.5 or any three of the following variables (age <10 or >40 years, etiology of non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions, duration of jaundice before encephalopathy >7 days, INR > 3.5, serum bilirubin level of >17.5 mg/dl) were associated with mortality without transplant.

Table 32.2 Transplantation criteria at King's College Hospital

Acetaminophen group
• pH < 7.3 (encephalopathy grade independent) 24 h or more from overdose, after correction of hypovolemic status
• Or clusters of the next three parameters
– Encephalopathy stage III–IV
– PT > 100 s (INR > 6.5)
– Serum creatinine > 300 mmol/L (3.4 mg/dL)
No acetaminophen group
• PT > 100 s (INR > 6.5) (Encephalopathy grade independent)
• Or any of the next parameters
– Age <10 or >40 years
– Etiology: hepatitis non-A non-B, halothane, idiosyncratic reaction to drugs, Wilson's disease
– Jaundice length >7 days before encephalopathy appearance
– PT > 50 s (INR > 3.5)
– Serum bilirubin > 300 mmol/L (17 mg/dl)
– PT > 50 s (INR > 3.5)

While these criteria have a high predictive value when present, other investigators have cautioned that they may fail to identify those patients with low risk to die [99, 100]. The Clichy, France group analyzed 115 patients with FHF due to HBV and found coagulation factor V level, patient age, absence of HBV surface antigen, and serum alpha-fetoprotein level to be independent predictors of survival [101].

Other criteria have been developed to increase prognostic ability such as definition of hepatic parenchyma histology, and hepatocyte volume by liver biopsy [102]. Biopsy is useful in cases of indeterminant cause, to rule out chronic disease as well as to assess potential for recovery. Because of coagulopathy biopsies are generally obtained by the transjugular approach [63]. Less than 50 % viable hepatocytes have been reported to correlate with poor prognosis without transplantation. However the lack of homogeneity is a limitation [62].

Other prognostic criteria have included hepatic volume less than 700 cc on abdominal CT scan, poor results on functional assessment of the hepatic mass via galactose elimination test [103, 104], a significantly reduced arterial ketone (acetoacetate/Beta-hidroxybutirate) body/ratio [105], and low coagulation factor V and

factor V/VIII ratio (Factor V level <10 % and ratio of factor VIII/V >30 % is a indicator of poor outcome) [66]. The APACHE II System had a predictive value similar in efficacy to the King's College criteria in patients with acetaminophen toxicity.

Clinical criteria for transplantation are primarily based on worsening encephalopathy and uncorrectable coagulopathy [106]. Persistent increase in ICP is a poor prognostic sign; as the patient crosses phase 2, OLT is necessary to reverse the process [20].

Once a decision for transplantation is made, multimodality treatment continues as described above. This usually includes respiratory support, renal support with CVVHD, and coaguloapthy control with plasmapheresis or factor replacement.

Intraoperative Management

In the operating room, the same intensity of care has to be continued as provided in the intensive care unit. Cerebral perfusion pressure is maintained and increments in ICP are avoided by maintaining delicate balance of mean arterial pressure and ICP. Inhalation anesthetic agents are avoided to prevent further cerebral vasodilation and mycocardial depression. Clamping the inferior vena cava and the portal vein may be poorly tolerated; this has led to the routine use of veno-veno bypass using the axillary vein. The use of a temporary portocaval shunt is another available option [107].

Transplantation Options in Acute Liver Failure

Patients who are transplant candidates require timely transplantation to achieve a good outcome [108]. Every effort should be made to avoid progressive cerebral edema, systemic infection, and severe hemodynamic instability because this may preclude the candidacy for liver transplantation. Although optimal results are obtained with transplantation with a whole deceased donor liver, other liver replacement strategies employed include living related split liver transplantation, auxiliary liver transplantation [109], and experimental approaches such as hepatocyte transplantation [110], xenotransplantation [111], and support with bioartificial liver assist devices [112]. Extended criteria deceased donors including donors after cardiac death and ABO incompatible graft may also be considered, based on the clinical condition of the patient.

Properly timed liver transplantation in ALF increases survival from 20 % to over 70 % in both children [113] and adults [114, 115]. Long-term survival after liver transplant is not as optimal as for nonviral, nonmalignant indications for reasons that may be related to an underlying immune defect [116] in patients with ALF.

Extracorporeal Assistance in Acute Liver Failure

Among current approaches in providing extracorporeal assistance to the acutely failing liver, non biologic support such as plasma exchange and bound solute dialysis are most common. Cellular bioreactor-based therapies [117, 118] have undergone clinical evaluation in the past but are currently not routinely available.

Liver Support with No Biological Component

For almost half a century, extracorporeal therapy has been under intense investigation as a alternate method for the support of the failing liver. Approaches such as hemodialysis, hemoperfusion through charcoal resin [119], and combined nonbiologic methods with hemofiltration and plasma exchange [120], have all been utilized with ALF.

Plasma Exchange

This method , designed to reduce the level of circulating toxins and replace essential proteins such as clotting factors may be useful in supporting patients with ALF.

This method has been enhanced with a high-volume exchange technique where 8 L or more (15 % of the body weight) of plasma are exchanged for fresh frozen plasma per treatment. This method has shown a positive impact with increase in systemic vascular resistance, mean arterial pressure, and decrease in cardiac output and ammonia level [121].

Bound Solute Dialysis: Albumin-Dialysis (MARS)

The selective removal of water-soluble and albumin-bound substances is the target of the Molecular Adsorbent Recirculating System (MARS) [122]. It uses human serum albumin as a shuttle between a blood-sided dialysis membrane and a remote set of sorbent columns (charcoal and anion exchanger) and a conventional dialysis unit on the other [123]. A meta-analysis of four randomized controlled trials of MARS in liver failure failed to show any survival benefit. However MARS improves encephalopathy and serum bilirubin level. Hence MARS is useful as a bridge to stabilize the patient while waiting for new liver to be available for transplantation.

Liver Support Systems with Biological Components

Devices with biological properties use bioreactors loaded with isolated cells from different origin [124]. Design and maintenance of a long-term three-dimensional culture are key features for successful performance in a bioreactor, maintaining functions such oxidative detoxification (P 450 enzyme system), biotransformation (e.g. urea synthesis, gluconuridation, and sulfation), excretion (bile system), synthesis of protein and

macromolecules, intermediate metabolism (gluconeogenesis, fatty acids, and aminoacids), and modulation of the immune and hormonal system [124]. Porcline cells have been widely used as well as transformed human hepatoblostoma (C3A) cell lines. Safety issues for the application of these devices include the risks of xenozoonotic infection and leakage of immobilized cells with a subsequent malignancy risk [125]. Loading of liver cells in the extraluminal space of hollow-fiber cartridge is the basis for many of the biologic liver support devises in clinical trial.

Bioartificial Liver (BAL)

The HepatAssist study was performed in USA and Europe [126]. The device consists of a hollow fiber cartridge containing 50 g of cryopreserved primary porcine hepatocytes seeded onto collagen-coated dextran beads prior to placement in the bioreactor, coupled with charcoal in a plasma perfused circuit. The BAL uses a centrifugal plasma separator that supplies the plasma perfusion circuit. This system is shown to be safe and demonstrated possible survival advantage in fulminant/subfulminant hepatic failure.

Extracorporeal Liver Assist Device (ELAD)

Another extracorporeal liver assist device was developed in 1992 [127], and was introduced to the clinical arena in 1993 as the Extracorporeal Liver Assist Device (ELAD) [128, 129]. The system uses the C3A cell line derived from human hepatoblastoma cells housed in the extracapillary space of a hollow fiber dialysis cartridge, which then is perfused with an ultrafiltrate of the patient's blood. The system has been modified to accommodate a larger number of cartridges and cells to a total of four cartridges each one loaded with 100 g of cells. The system is being tested in patients with ALF in a multicenter trial, and has shown to improve ammonia, bilirubin, and encephalopathy, without a clear survival benefit [130].

Other systems, including a bioartificial liver support system [131], isolated hepatocyte transplantation [132] and extracorporeal liver perfusion (human or xenogenic) have also been utilized.

Conclusion

The successful management of patients with ALF requires a multidisciplinary approach with intensive monitoring and intervention to achieve a successful outcome. Until the proven demonstration of alternative therapies, timely transplantation remains the treatment of choice in those at high risk of mortality.

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33. Portopulmonary Hypertension and Hepatopulmonary Syndrome

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Introduction

Liver disease and portal hypertension may have a deleterious effect on the pulmonary microcirculation. Vasoactive molecules damage the vascular endothelium. The endothelial dysfunction may cause two clinically distinct pathologies: vasodilatation and shunt formation that result in hypoxia and the hepatopulmonary syndrome , and vasoconstriction and increased vascular resistance that cause pulmonary hypertension. Both entities are progressive diseases and result in shortness of breath and if untreated will lead to early mortality. Hepatopulmonary syndrome causes progressive hypoxia but may be reversed by liver transplantation. The more severe the hypoxia at the time of liver transplantation the higher the risk of the procedure and the more prolonged the recovery in the intensive care unit and the hospital.

Portopulmonary hypertension is also a progressive disease with increasing resistance to flow in the pulmonary microcirculation with medial hyperplasia and eventual fibrosis. The increasing rise in pulmonary vascular resistance causes right heart dysfunction and eventual failure. Portopulmonary hypertension requires intensive medical therapy to control the hypertension and to allow the right ventricle to adjust to

the extra work. Liver transplantation may reverse portopulmonary hypertension but it may progress after transplantation or remain static. Continued medical therapy is often required after transplantation. The risk for undergoing a liver transplant increases as the pulmonary vascular resistance increases and the right ventricular function is compromised. If there is significant pulmonary fibrosis then a double-lung transplant together with a liver transplant may be indicated.

Pulmonary Vascular Endothelium

The vascular endothelium is the largest dynamic organ in the body. It is a monolayer of cells that line the blood vessel lumen and plays an integral role in vascular tone and blood flow, maintaining the fluidity of the blood by its anticoagulant surface. The endothelium also is responsible for the selective permeability of nutrients and cells to the tissues. The nitric oxide produced by the healthy endothelium is essential for the regulation of vasomotor tone, permeability, and integrity of this cellular layer [1]. The vasodilator substances produced by the endothelium are nitric oxide and prostacyclin and the vasoconstrictor molecules are mainly endothelin-1 (Fig. 33.1) [2].

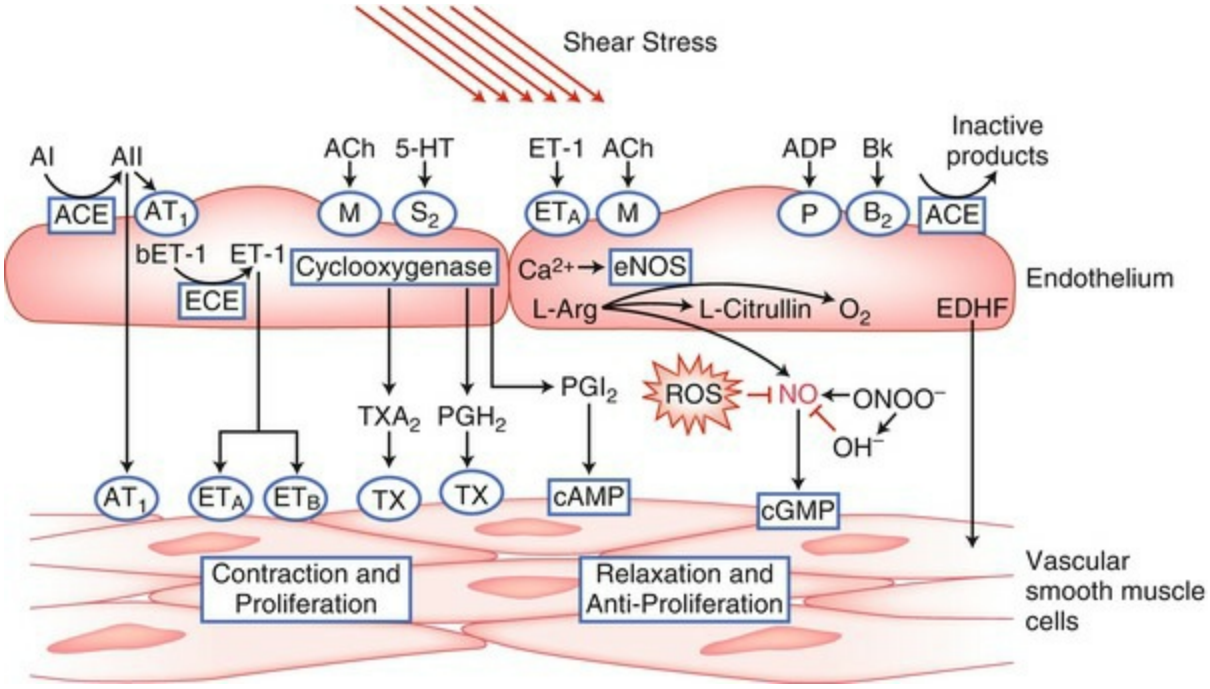

Fig. 33.1 Normal endothelium with endothelium-derived vasoactive substances. Sheer stress leads to a release of nitric oxide and other vasoactive molecules. [*NO* nitric oxide, *ACE* angiotensin-converting enzyme, *Ach* acetylcholine, *AI* angiotensin, *A11* angiotensin II, *ATI* angiotensin I receptor, *Bk* bradykinin]

Portal hypertension , with or without liver disease, causes oxidative stress, and together with the exposure of the endothelium to inflammatory cytokines causes an interruption of the nitric oxide integrity, which results in endothelial dysfunction. This

may result in vasoconstriction, microthrombosis, hyperplasia of the vascular muscle layers, and eventual fibrosis. This causes the clinical condition of portopulmonary hypertension. An excess of vasodilatory molecules, nitric oxide, and prostacyclins results in the dilatation of blood vessels, shunt, and aneurysm formation that present as the clinical conditions of hepatopulmonary syndrome.

Portopulmonary Hypertension

Portopulmonary hypertension (POPH) is characterized by an increased pulmonary artery pressure caused by an increase in pulmonary vascular resistance that is the result of portal hypertension usually associated with liver disease [3]. The increase in pulmonary artery resistance involves the presence of an excess of endothelin-1, and other vasoconstrictors such as vasoactive intestinal peptide (Fig. 33.2) [4].

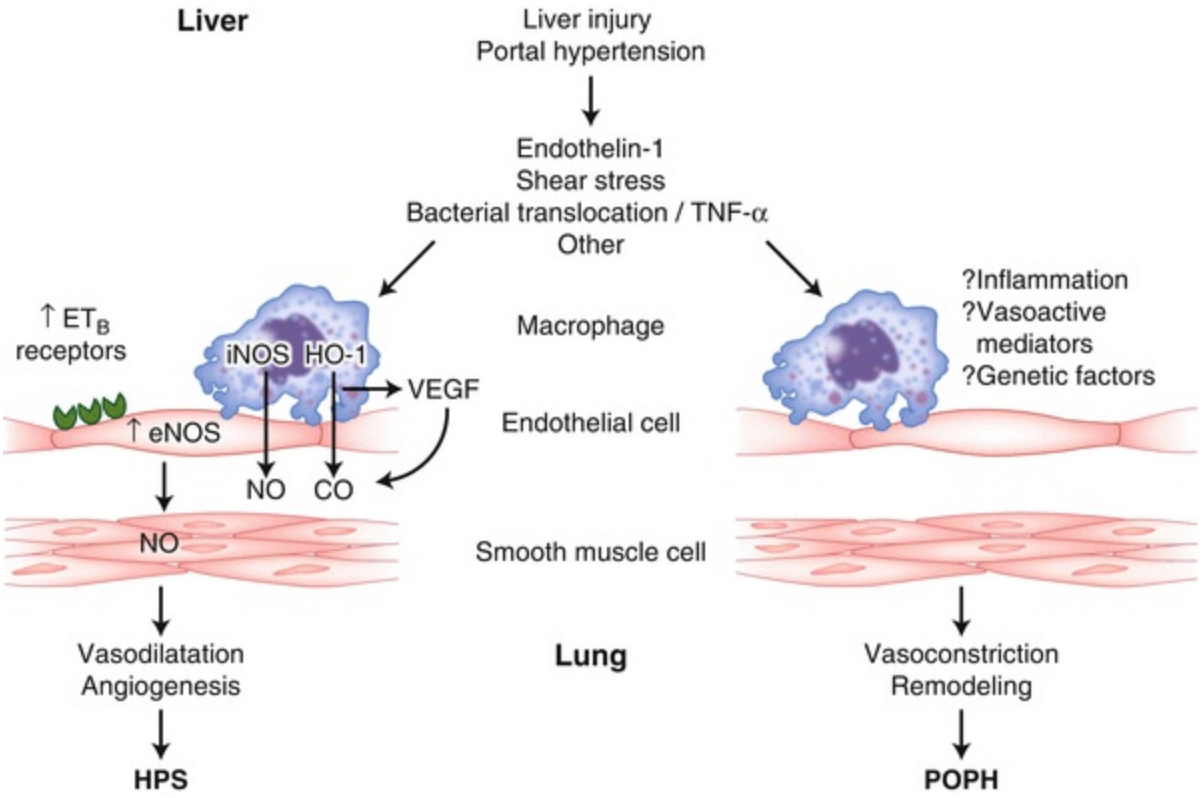

Fig. 33.2 Pathophysiology of hepatopulmonary syndrome (HPS, microvascular dilatation, and angiogenesis) and portopulmonary hypertension (POPH, vasoconstriction, and remodeling in resistance vessels)

There is also development of smooth muscle hyperplasia, hypertrophy, plexogenic arteriopathy, and microthrombi that may be found. Eventually some areas of the microvasculature will progress to fibrosis. All these pathological changes result in an increase in pulmonary vascular resistance that may be reversible by vasodilatation and later remodeling, but areas of fibrosis will result in a fixed defect (Fig. 33.3) [5].

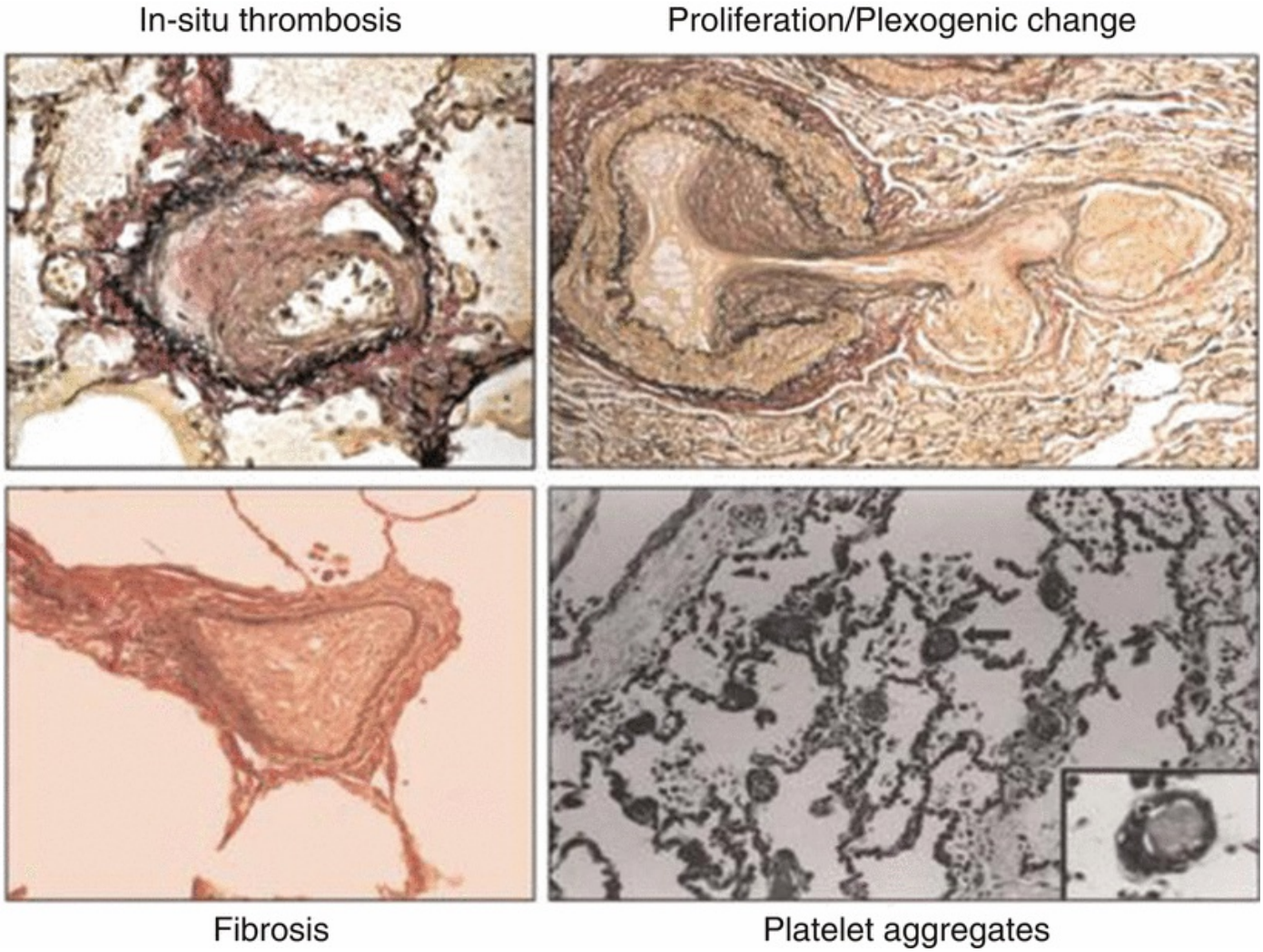

Fig. 33.3 Pulmonary arteriole pathological changes causing an increased resistance to blood flow resulting in portopulmonary hypertension . These images demonstrate intimal thickening, cellular proliferation, fibrosis, and intralumenal microemboli

Portopulmonary hypertension was initially described in 1951 [6]. It is defined as pulmonary arterial hypertension associated with portal hypertension. The portal hypertension is usually associated with liver disease but not always. The diagnosis is made from the hemodynamic data obtained from a right heart catheterization (RHC) . A mean pulmonary artery pressure (MPAP) greater than 25 mmHg at rest and 30 mmHg with exercise, and an elevated pulmonary vascular resistance (PVR) greater than 240 dyn s/cm^5, with a transpulmonary gradient greater than 12 mmHg, is pathognomonic of POPH [3, 5]. In many definitions a pulmonary capillary wedge pressure of less than 15 mmHg is included but in patients with severe liver disease this number may be elevated by a very increased cardiac output and volume overload. Therefore, the vascular resistance must be measured by RHC to confirm POPH. See Table 33.1 for a summary of diagnostic criteria for portopulmonary hypertension.

Table 33.1 Diagnostic criteria for portopulmonary hypertension

1. Presence of portal hypertension
2. Mean pulmonary artery pressure >25 mmHg
3. Pulmonary vascular resistance >240 dyn s/cm^5
4. Transpulmonary gradient >12 mmHg

The incidence of POPH in patients presenting for liver transplantation has been reported to be between 5 and 8.5 % [7–9]. The incidence of pulmonary hypertension in liver candidates is close to 20 % but this is caused by high cardiac output, volume overload, or cirrhotic cardiomyopathy. Mean pulmonary artery pressures of 40–45 mmHg may be found as a result of increased cardiac output, pulmonary venous hypertension, and congestion but on RHC the PVR is found to be normal and the PCWP may be elevated [5]. The resistance across the pulmonary vasculature is not elevated in these patients and therefore it is not POPH [3]. Table 33.2 provides case presentations of pulmonary hypertension in liver transplant recipients as shown by Krowka [5]. Patients #3 and #4 are the only ones with true POPH as they have the elevated pulmonary vascular resistance. Potential causes of pulmonary hypertension are shown in Fig. 33.4 [10].

Table 33.2 Pulmonary hypertension presentations in liver transplant recipients

				Pt #4	
	Pt #1	**Pt #2**	**Pt #3**	**Before treatment**	**After treatment**
RVSP (echo) (mmHg)	69	66	99	70	50
MPAP (mmHg)	33	36	63	50	38
PCWP (mmHg)	7	25	19	15	15
CO (L/min)	11.9	9.3	6.1	6.3	9.3
PVR (dyn s/cm^5)	175	95	577	444	197

RSVP right ventricular systolic pressure, *MPAP* mean pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *CO* cardiac output, *PVR* pulmonary vascular resistance

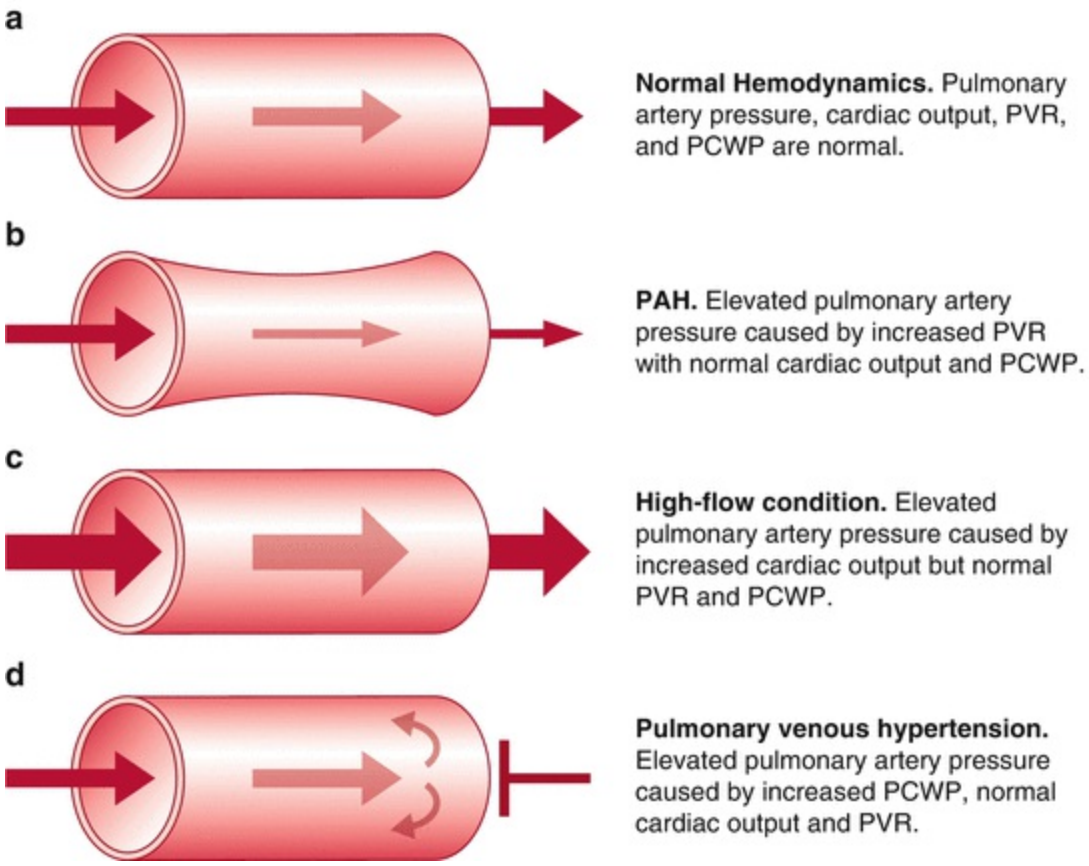

Fig. 33.4 Potential causes of an elevated mean pulmonary artery pressure in the patient with liver cirrhosis

Diagnosis of Portopulmonary Hypertension

The clinical presentation of POPH is increasing fatigue, dyspnea on exertion, syncope, and occasional chest pain, and sudden death. In two series of patients with POPH the 4-year and 5-year survivals were 4 % and 14 %, respectively [11, 12]. The most common physical findings are an accentuated pulmonary component of the second heart sound and a systolic murmur. Therefore, on routine clinical assessment these patients are difficult to diagnose, although signs of right ventricular failure may be present. The electrocardiogram may reveal right heart strain. The chest X-ray may show right heart enlargement and failure with dilatation of the pulmonary arteries.

POPH may be precipitated by the increase in cardiac output that may follow a transjugular intrahepatic shunt formation (TIPS) [13].

The most important screening tool is the transthoracic echocardiograph. All patients presenting for liver transplantation should be screened for POPH by transthoracic echocardiography . The right ventricular systolic pressure (RVSP) is estimated based on the velocity of tricuspid regurgitation (TR) using the modified Bernoulli equation RVSP mm Hg = 4 × (TR m/s)^2 + right atrial pressure. The tricuspid regurgitant jet flow may not be present in all patients negating this diagnostic tool. In this case a careful assessment of right ventricular function should be made, preferably by transesophageal

echocardiography and an estimation of PVR made. One test reporting a sensitivity and negative predictive value of 100 % utilizes the ratio of peak tricuspid regurgitant velocity (TRV) to right ventricular outflow tract velocity time (VTI_{RVOT}) [14]. To confirm the diagnosis an RHC should be performed to clearly characterize the pulmonary hemodynamics.

The Right Ventricle

Assessing right ventricular performance still remains a challenge. The right ventricle (RV) is a complex structure that cannot be approximated by a simple geometric form. It functions in a low-impedance system; therefore it is sensitive to pressure overload. Along with contractility and loading conditions, ventricular interactions play an important part in right ventricular function and failure. Right ventricular dysfunction or failure may result in liver graft congestion and failure and may result in total loss of the newly implanted liver graft and also the recipient. Therefore careful evaluation of the right heart must be made in the pretransplant workup of these patients and a careful assessment of the severity of the POPH must also be made. Most institutions will make an RSVP of >50 mmHg a necessity for an RHC. However, it is not the absolute number of the RVSP or the MPAP that should be the trigger but the function of the RV must be included in this decision. Careful examination by TEE must be made for systolic and diastolic dysfunction of the RV. The RV faced with an increasing pressure overload adapts through hypertrophy and dilatation but eventually will fail. The diagnostic features of RV dysfunction are an E/A ratio <1, a prolonged deceleration time >200 ms, a prolonged isovolumetric relaxation time >80 ms, enlarged right chambers, abnormal pattern of contractility, and a prolonged ratio of pre-ejection period to LV ejection time >0.44 s [15]. Figure 33.5 shows transthoracic echocardiographic images of a patient with portopulmonary hypertension [16].

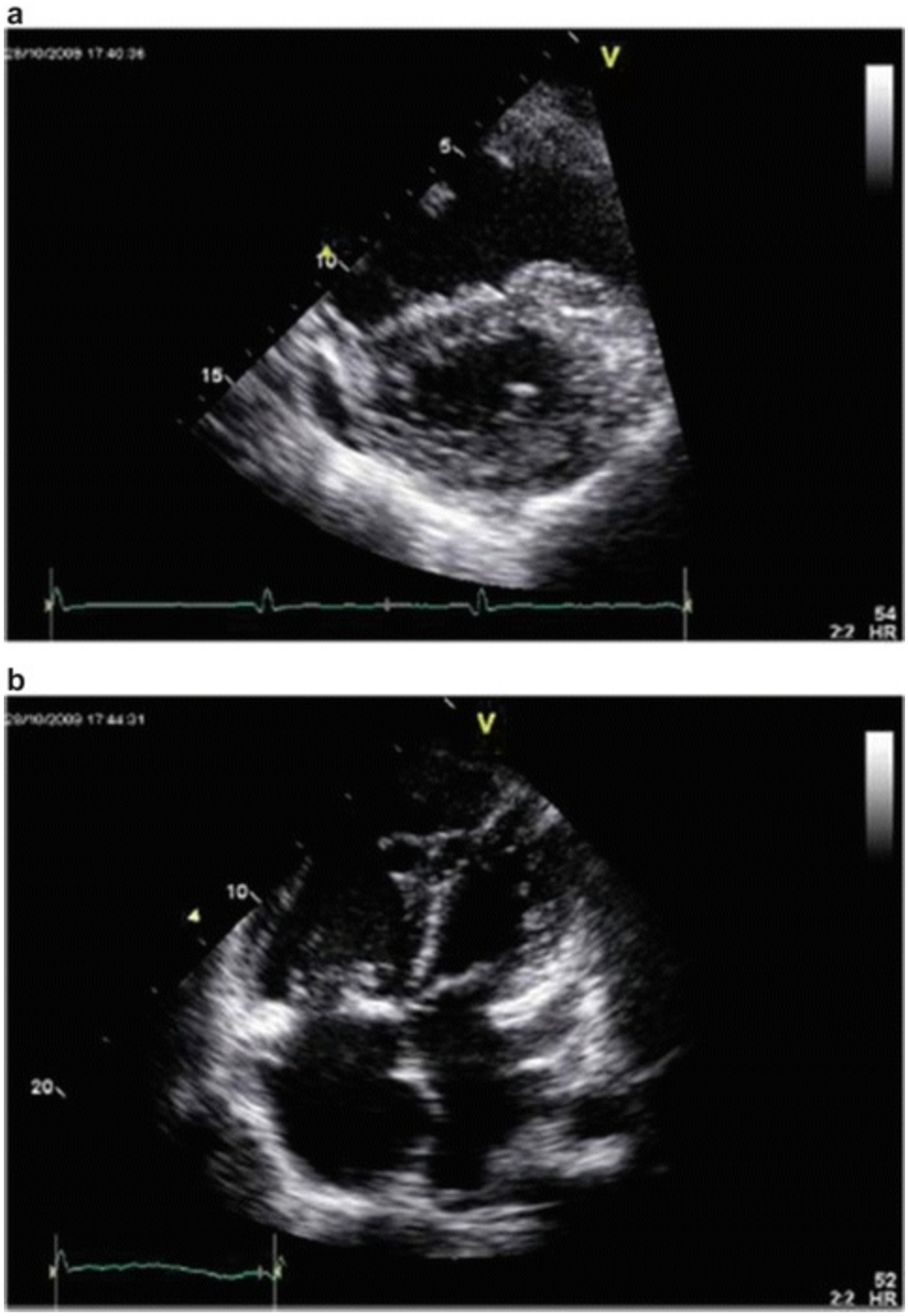

Fig. 33.5 Transthoracic echocardiographic images of a patient with portopulmonary hypertension. Note the D-shaped left ventricle in the short-axis view (**a**) and a severely dilated right ventricle in the four-chamber view (**b**)

The typical patient with liver cirrhosis has a hyperdynamic circulation with a low systemic vascular resistance that may mask a significant cirrhotic cardiomyopathy, which can lead to a false sense of security when managing these patients. Most patients with liver cirrhosis will have some manifestations of a cardiomyopathy even if it is just a prolonged QT interval on the electrocardiogram or a downregulation of the beta receptors [17]. This must be taken into consideration when assessing the right heart

function in a patient with POPH.

Implications for Liver Transplantation

The key questions that need to be answered are the following: (1) Is it safe for patient and graft to transplant with POPH? (2) Will the POPH resolve after liver transplantation?

Is It Safe to Transplant with POPH?

The data available would suggest that a patient with an MPAP of 25–35 mmHg can safely undergo liver transplantation. Once the MPAP increases above 35 mmHg the mortality increases significantly both for transplantation and on the waiting list for transplantation [18, 19]. A review of the right heart and pulmonary hemodynamics should be made just prior to transplantation to be sure that significant progression of POPH has not occurred since the last evaluation [20]. However, the key to the success of the transplant is the function of the right heart and not the value of the MPAP or PVR. A patient with an MPAP of 30 mmHg with an elevated PVR and poor RV function is at higher risk than the patient with an MPAP of 40 mmHg and elevated PVR but good functioning RV. These patients with right heart dysfunction should be deferred from surgery and have pulmonary vasodilator therapy initiated, and then reevaluated later to assess right heart improvement. Table 33.3 outlines an assessment screening and action plan for patients with portopulmonary hypertension.

Table 33.3 Assessment screen and action plan for portopulmonary hypertension

1. All liver transplant candidates screened with TTE: RVSP > 50 mmHg or RV function questionable; RHC. If MPAP > 25 mmHg and PVR > 240 dyn s/cm^5 then TEE to assess right heart function.
2. MPAP 25–35 mmHg PVR > 240 dyn s/cm^5: Good right heart function start pulmonary vasodilator therapy, place on transplant list, and reassess every 6 months.
3. MPAP 35–40 mmHg PVR > 240 dyn s/cm^5: If RV function poor defer transplant and start pulmonary vasodilator therapy and reassess in 6 months. If RV function good then stress RV with dobutamine and fluid challenge; if still good then place on transplant list and start pulmonary vasodilator therapy.
4. MPAP > 40 mmHg and PVR > 240 dyn s/cm^5: Defer transplant and start on vasodilator therapy and reassess in 6 months.

If liver disease increases urgency of transplant then only proceed if RV function is very good and patient withstands a stress test. If RV is not excellent, then consider liver double-lung transplant

Does Portopulmonary Hypertension Resolve After Liver

Transplantation?

It might seem impossible for patients in whom the intrapulmonary pathology has progressed to fibrosis to have reversal of primary pulmonary hypertension after liver transplantation or with vasodilator therapy. However, there is good evidence that patients who have responded to pulmonary vasodilators will over months after a successful transplant resolve their pulmonary hypertension [21–23].

Intraoperative Management of the Patient with POPH

Those patients that have been assessed to have good RV function and proceed to transplantation still have the potential rigors of a major procedure to undergo and the potential to withstand a 300 % increase in cardiac output after liver graft reperfusion (Fig. 33.6) [20].

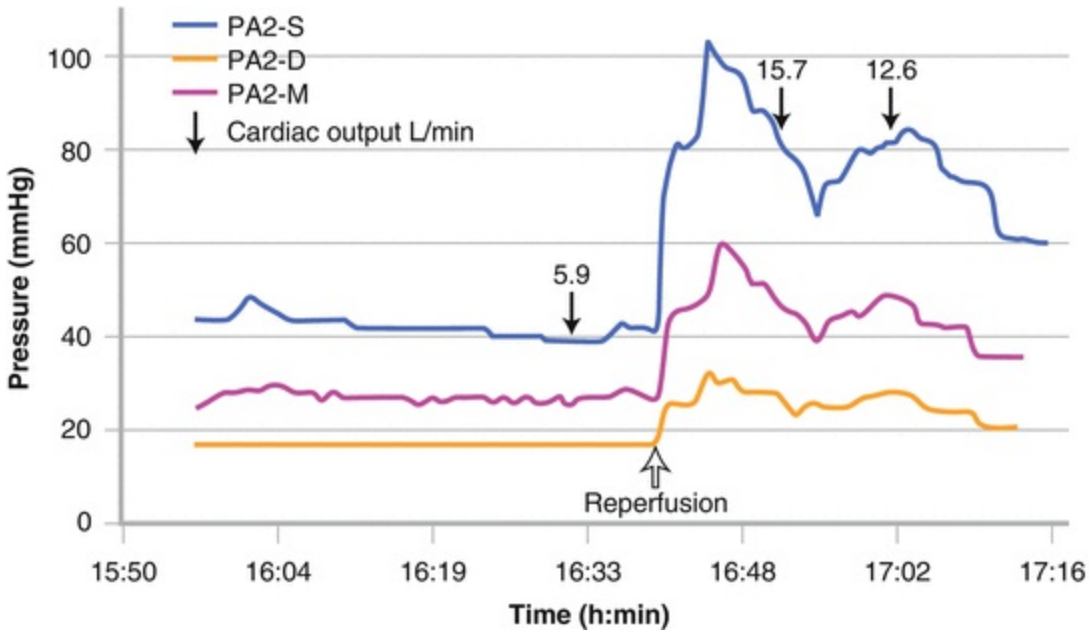

Fig. 33.6 A threefold increase in cardiac output at the time of reperfusion resulting in severe pulmonary hypertension

There is no reliable way to protect the RV and the liver graft if this scenario occurs. Inhaled nitric oxide may be effective in some patients in reversing or moderating this acute rise in pulmonary artery pressure [24]. Consideration for extracorporeal right heart bypass should be given to assist in unloading the RV [25]. Right ventricular assist devices are unlikely to be successful when the RV failure is the result of afterload resistance. Pumping blood into the pulmonary artery will result in increasing pulmonary artery pressure and lung injury [26].

Pulmonary Vasodilator Therapy

Initially the prostacyclins were administered to reduce PVR. However, these drugs had to be given by long-term intravenous therapy (epoprostenol) or by inhalation (inhaled iloprost) [21–23]. Then oral preparations of phosphodiesterase inhibitors, namely sildenafil, became available with promising results [27, 28]. Now two newer drugs, bosentan and ambrisentan, that are endothelin receptor antagonists have been shown to be effective in selected patients [29, 30]. Despite these therapies there are case reports of patients wherein the pulmonary hypertension has progressed after a successful liver transplantation [31]. Perhaps these patients were misdiagnosed with POPH and really had primary pulmonary hypertension in the face of portal hypertension and liver disease.

MELD Exception

Candidates with POPH will be eligible for an MELD exception. Diagnosis should include initial MPAP and PVR levels, documentation of treatment, and post-treatment MPAP < 35 mmHg and PVR < 400 dyn s/cm^5. Transpulmonary gradient should be required for initial diagnosis to correct for volume overload [32].

Hepatopulmonary Syndrome

Definition, Incidence, and Clinical Features

In 1884 Flückiger [33] described a female patient with cyanosis finger clubbing and liver cirrhosis. The association between cyanosis and liver disease continued to be observed and a new syndrome termed the hepatopulmonary syndrome was coined to reflect the arterial hypoxemia which occurs in about one-third of patients with liver cirrhosis in the absence of detectable cardiorespiratory disease (Fig. 33.7).

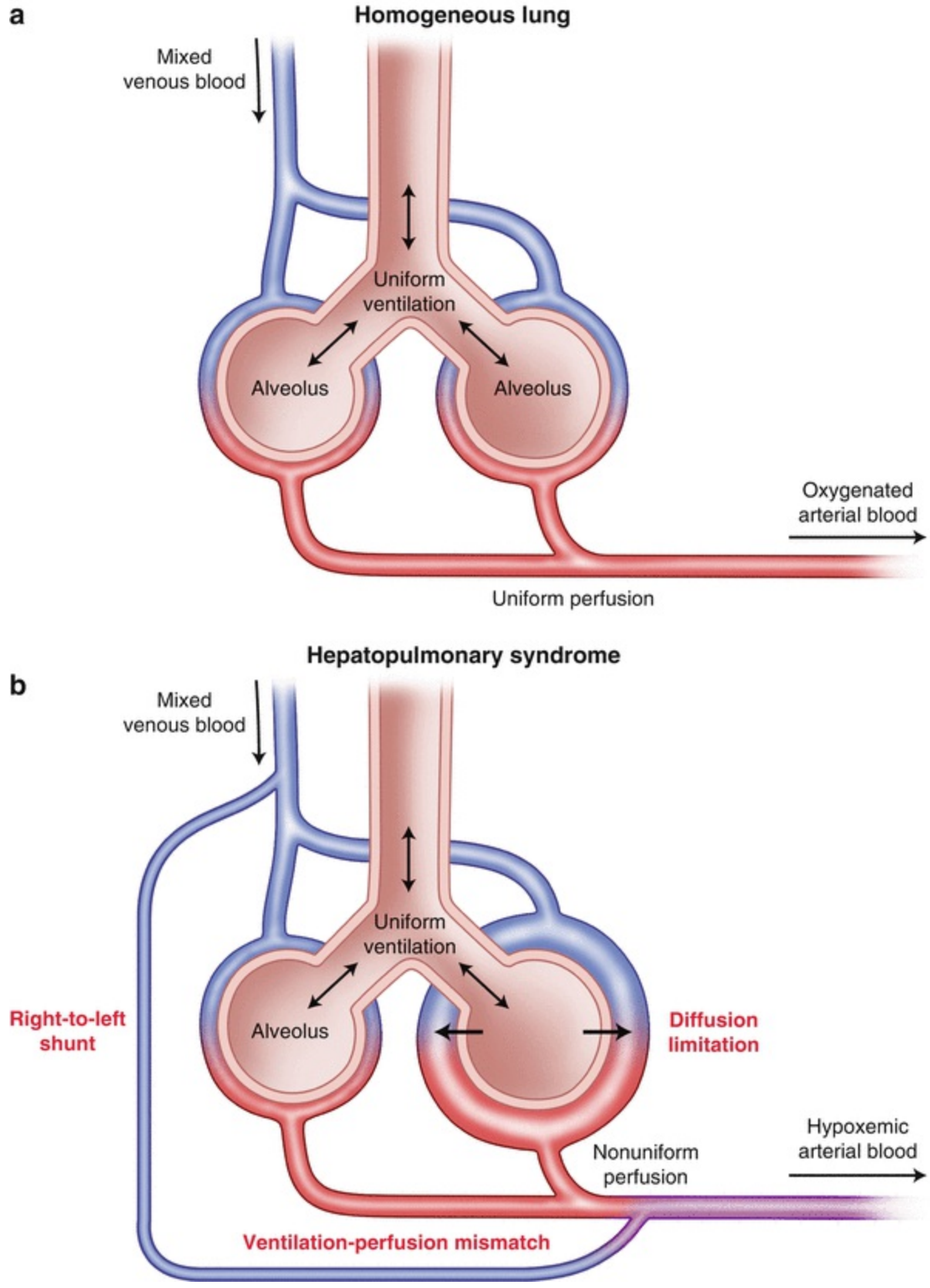

Fig. 33.7 (**a**) Normal pulmonary alveolar perfusion and diffusion; (**b**) three mechanisms of arterial hypoxemia in hepatopulmonary syndrome: Right to left shunt; diffusion limitation; ventilation-perfusion mismatch

The hepatopulmonary syndrome (HPS) is defined as the triad of liver disease and/or portal hypertension together with an increased alveolar-arterial gradient on room air, together with intrapulmonary microvascular vasodilatation [34, 35]. The intrapulmonary vascular dilatations result in a positive contrast echocardiogram, with echogenic material formed from agitated saline when injected intravenously passing from the right side of the heart to the left side with a 4–6-beat delay (Fig. 33.8) [34]. If the contrast crosses over to the left side faster than this then a septal defect should be considered.

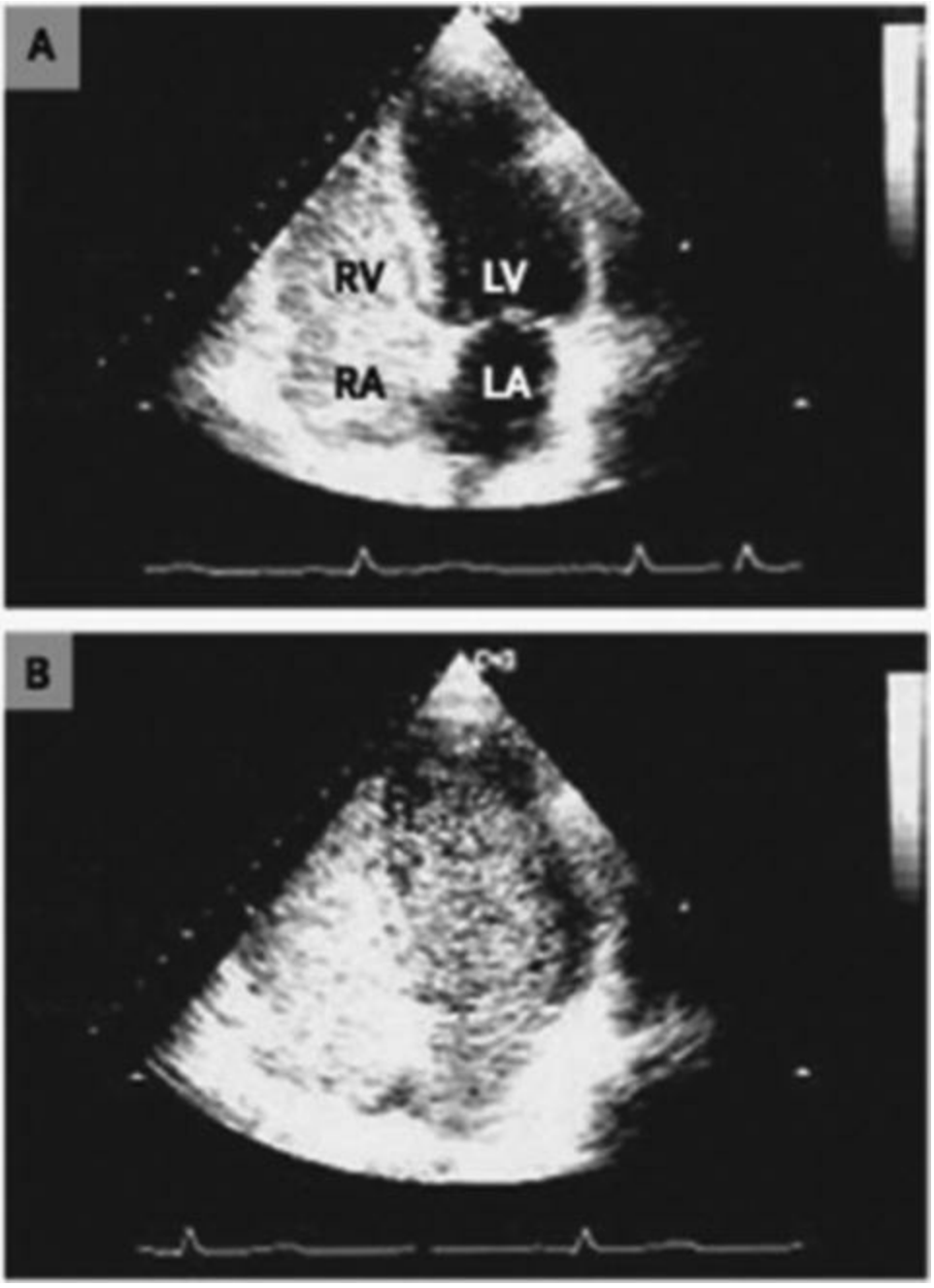

Fig. 33.8 Transthoracic echocardiogram demonstrating a delayed passage—5 to 6 beats—of echogenic material from the injection intravenously of agitated saline, from right to left heart

The impairment in oxygenation that occurs with HPS in some patients may be found to worsen upon standing. This is termed orthodeoxia and is a strong indicator of HPS [36, 37]. It is the result of preferential perfusion of the lung bases in a standing patient. Some patients with HPS also exhibit platypnea which is shortness of breath that is made worse by sitting up from the lying posture. This is the opposite of most other pulmonary conditions in which the patient breathes better on sitting up. Criteria defining HPS are outlined in Table 33.4 [34, 38]. Figure 33.9 shows albumin uptake in the lung, brain, and kidneys in a patient with hepatopulmonary syndrome [34].

Table 33.4 HPS criteria

1. Liver disease often cirrhosis and portal hypertension
2. Alveolar-arterial oxygen gradient >15 mmHg while breathing room air
3. Intrapulmonary vascular dilatations demonstrated by (a) contrast-enhanced echocardiography revealing a delayed passage (4–6 heart beats) of echogenic material (agitated saline) from right to left heart; (b) abnormal brain uptake >6 % after technetium-99m-labeled macroaggregated albumin lung perfusion scan

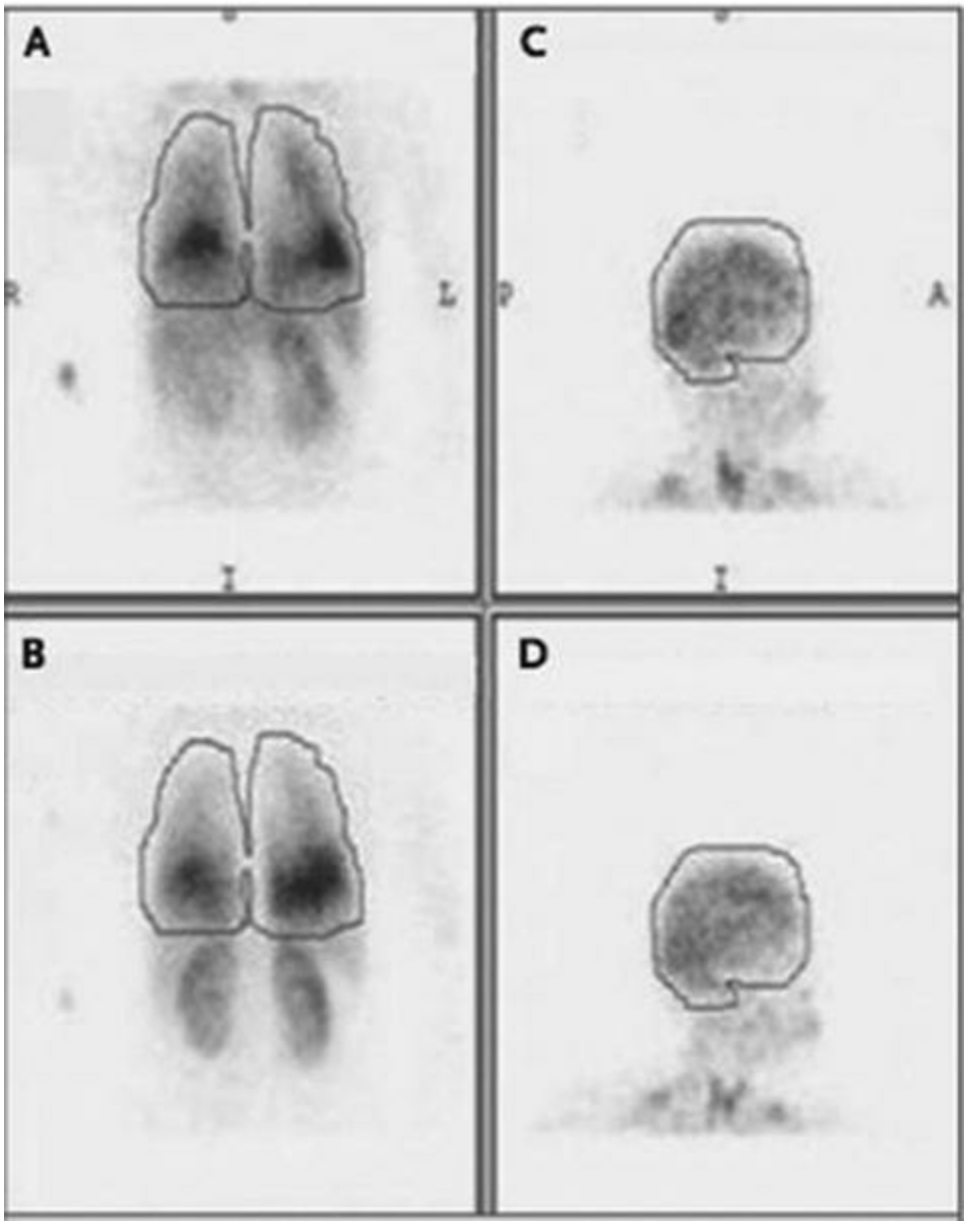

Fig. 33.9 Lung, brain, and kidney scans using technetium-99m-labeled macroaggregated albumin in a patient with hepatopulmonary syndrome. (**a**) Uptake in anterior lung fields; (**b**) uptake in posterior lung fields and kidneys; (**c**) and (**d**) uptake in right and left cerebrums

All patients presenting for liver transplantation should be screened with pulse oximetry while breathing room air both in the sitting and supine positions [39]. With a threshold value of <96 %, pulse oximetry had a sensitivity and specificity of 100 % and 88 %, respectively, for detecting patients with a PaO_2 of <60 mmHg [40].

Finger clubbing together with marked cyanosis may be seen in some patients with severe HPS (Fig. 33.10) [34]. However, more nonspecific symptoms such as shortness of breath at rest or exertion may be noted. Orthodeoxia may be elicited in some patients with HPS when the PaO_2 decreases by 5 % on raising up from the supine position and simultaneously platypnea—increasing shortness of breath—may be found. A decrease in

the diffusing capacity for carbon monoxide in a single breathe test is also found [41].

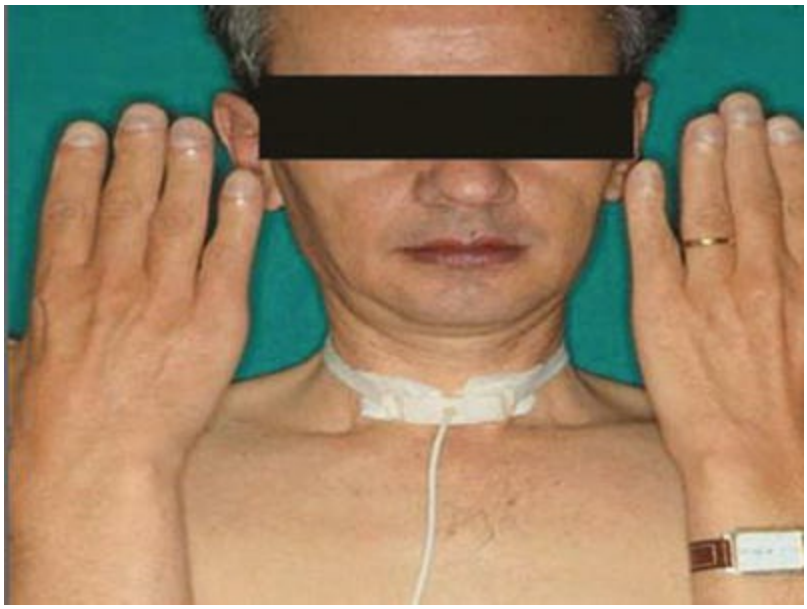

Fig. 33.10 Classical physical signs of a patient with severe HPS

The severity of HPS is not related to the severity of the liver disease [42]. The prevalence of HPS depends on how routine the screening for it is in patients presenting for liver transplantation. In centers where screening is routine HPS is found in around 30 % of patients [43].

Pathophysiology

Intrapulmonary vascular dilatations are the key pathology of HPS. Red blood cells usually travel through the pulmonary capillaries in single file and pick up oxygen. The dilation of the vessels causes the transit time of the red cells to increase and also the number of cells passing through together to increase. This results in less oxygen being taken up by each red cell. A large shunt may develop as a discreet vessel and this may be amenable to coiling. The etiology of this effect on the intrapulmonary vasculature is the production of excess vasodilating molecules such as nitric oxide. This is supported by increased levels of exhaled nitric oxide that may be detected in some patients with HPS and its absence when the HPS has resolved [44].

An experimental example exists to replicate HPS and this is a common bile duct-ligated rat model (Fig. 33.11) [45]. This model has demonstrated an overexpression of endothelin-B receptors that increases vasodilation and endothelin-1 [46]. Angiogenesis is stimulated by increased levels of vascular endothelial growth factor in this model [47]. A genetic predisposition to developing HPS has been suggested in human studies [43].

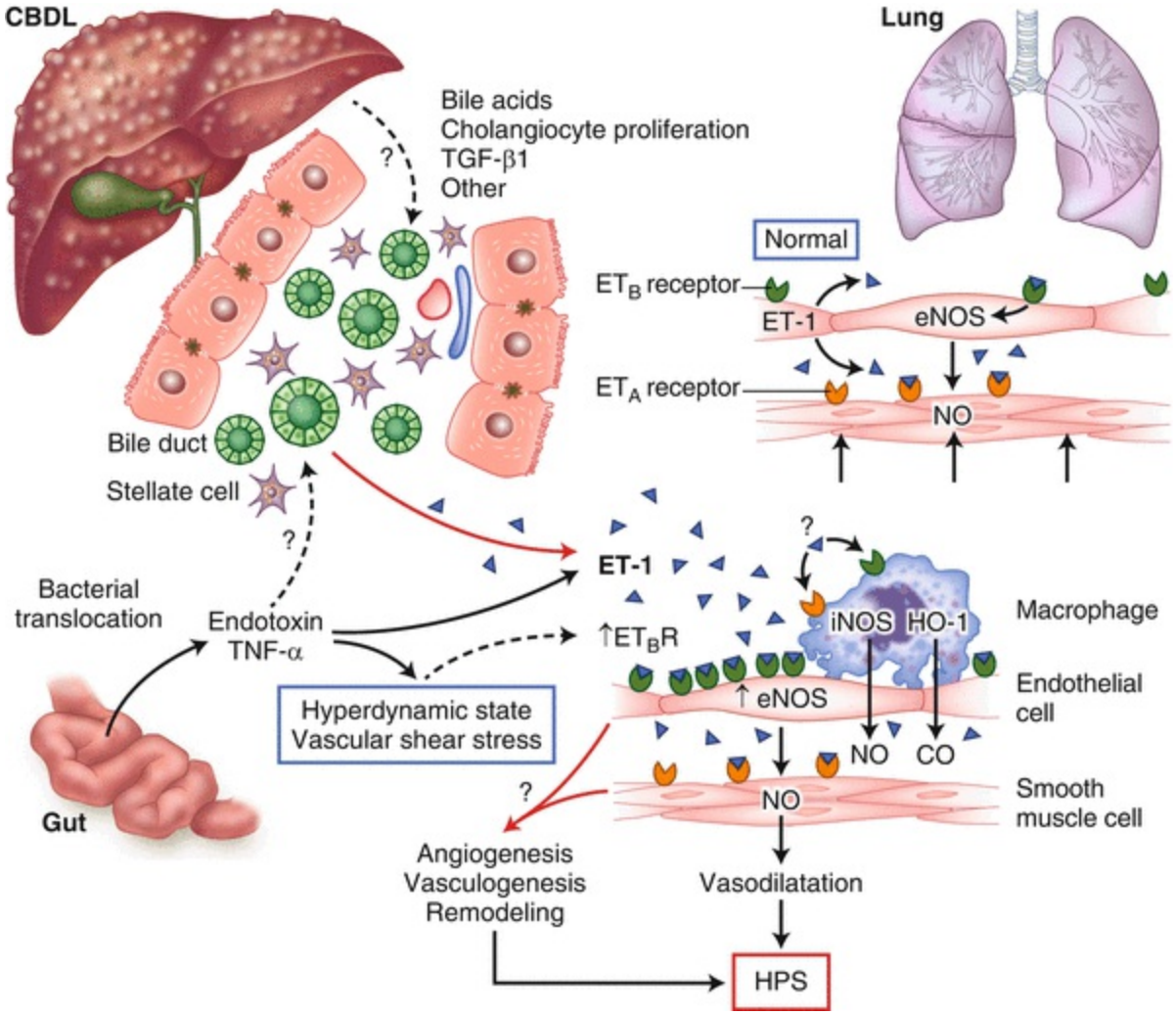

Fig. 33.11 Potential mechanism of hepatopulmonary syndrome in an experimental rat model. *ET-1* endothelin-1, *HO-1* heme oxygenase 1, *iNOS* inducible nitric oxide synthase, *eNOS* endothelial nitric oxide synthase, *NO* nitric oxide, *CO* carbon monoxide, *TNFα* tumor necrosis factor α, *TGF-β1* transforming growth factor

Perioperative Management

The 5-year survival for patients with HPS who do not receive a liver transplant is 23 %, compared to 88 % if they receive a liver transplant [48]. Liver transplantation is the only curative treatment for HPS and this condition is an indication for transplantation. In those patients with severe HPS defined as room air PaO_2 of <60 mmHg the post-transplant morbidity may be significantly increased [3, 49].

The intraoperative management of patients with HPS is to maintain oxygenation, which is usually attainable by increasing the inspired oxygen and adding positive end-expired pressure. The continuous monitoring of mixed venous oxygen saturation (SvO_2) may assist in the adjustment of oxygen delivery to prevent organ hypoxia [50]. The mixed venous oxygen saturation may be used as a guide to determine the need for portosystemic venovenous bypass during liver transplantation. If the SvO_2 falls below

65 % on vascular exclusion of the liver bypass may be beneficial [51]. Careful attention to detail is essential to avoid venous air emboli or thromboemboli as there is increased likelihood of transfer over to the systemic circulation. Patients with severe HPS undergoing liver transplantation may require prolonged postoperative critical care and hospitalization, but there overall survival should match those patients without HPS [48, 49]. Noninvasive ventilation following tracheal extubation is more effective at maintaining oxygenation than oxygen delivered via a face mask [52]. Careful attention to fluid therapy is mandatory to prevent volume overload and pulmonary dysfunction. Goal-directed fluid therapy based on stroke volume variation has been demonstrated to be effective in this patient population [53, 54].

Hepatopulmonary syndrome is a progressive disease of increasing hypoxia resulting from intrapulmonary vascular dilatations in the presence of liver disease. Liver transplantation is the only definitive therapy after which the hypoxia and shunts will eventually resolve (Fig. 33.12) [49, 50, 55].

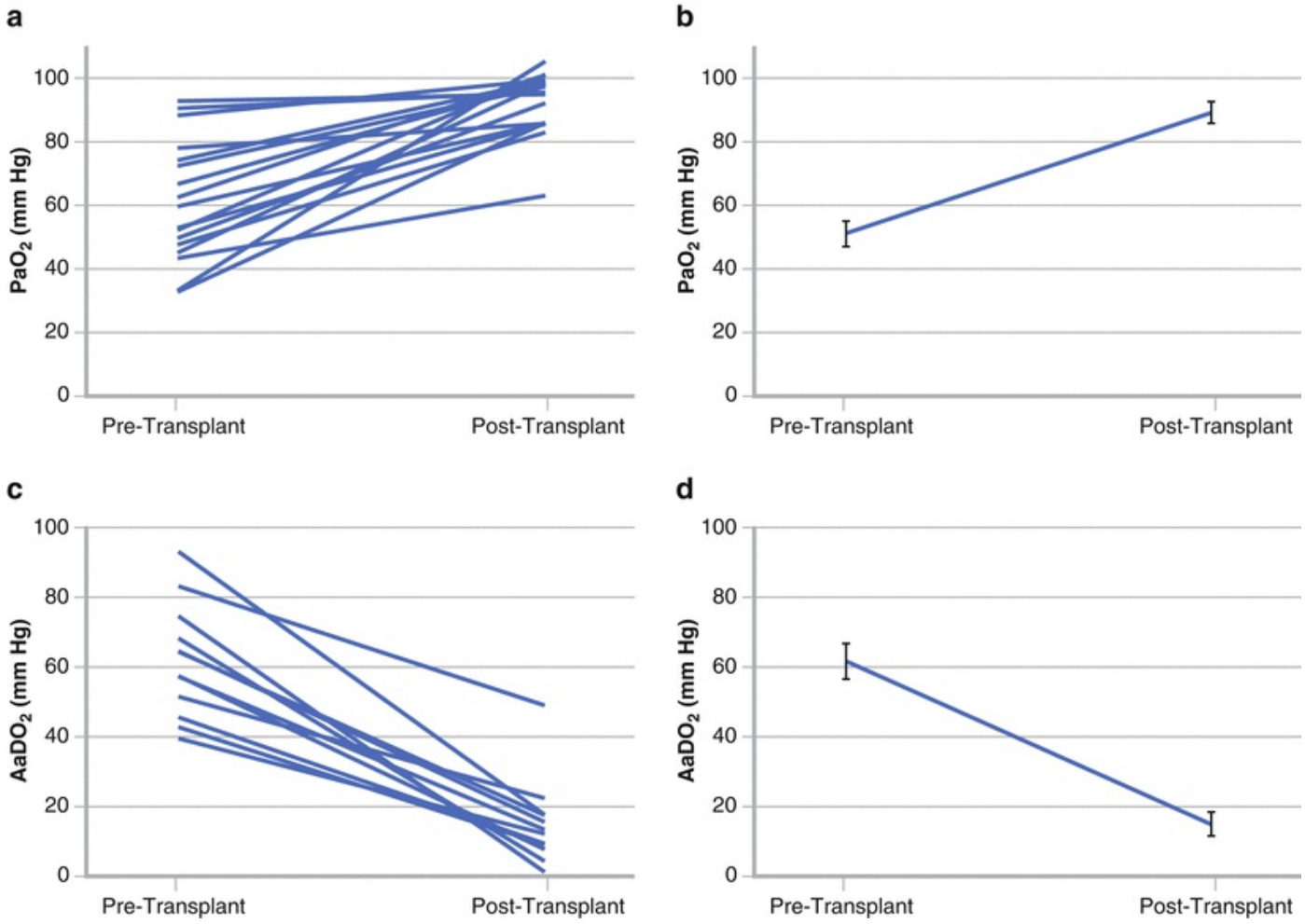

Fig. 33.12 Improved oxygenation and reduced A-a gradients after liver transplantation. (**a** and **c**) are the change in PaO_2 and A-a gradients in a cohort of 29 patients from pretransplant to a range of 4 months to 2.6 years post-liver transplant. (**b** and **d**) are mean changes of all the recipients

The survival of patients with severe HPS takes the support of excellent perioperative care [56, 57]. Those patients who are severely hypoxic postoperatively following complications during the transplant may be assisted by extracorporeal membrane oxygenation (Fig. 33.13) [58, 59]. This can reduce the need for mechanical ventilation and avoid the potential for ventilator-associated pneumonia and potential barotrauma.

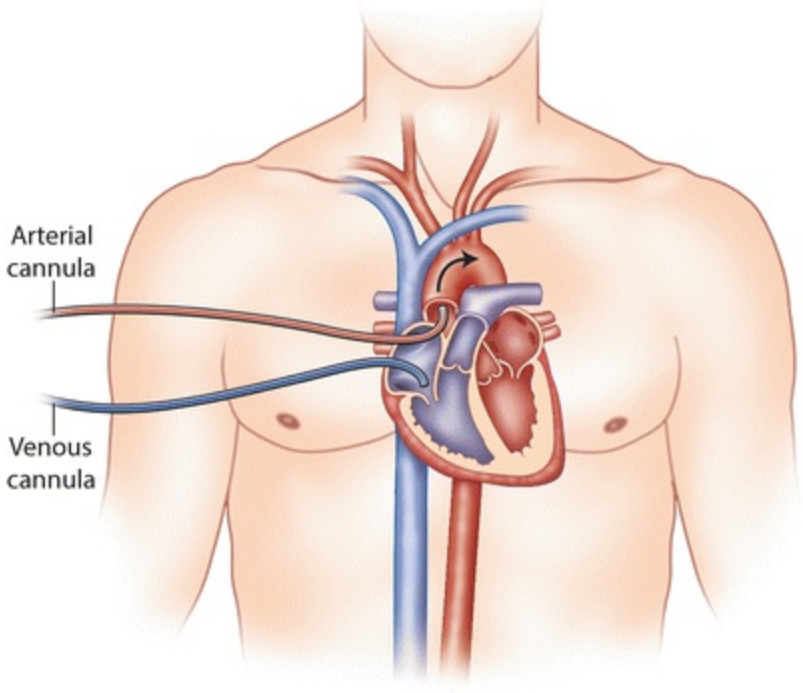

Fig. 33.13 Central extracorporeal membrane oxygenation cannulation

Extracorporeal membrane oxygenation may also be used as a bridge to liver transplantation in a patient with acute respiratory distress syndrome-induced life-threatening hypoxemia aggravated by HPS [60].

MELD Exception

Candidates with a clinical evidence of portal hypertension, evidence of a shunt, and a $PaO_2 < 60$ mmHg on room air will be listed at an MELD score of 22. There will be an increase in points every 3 months if the candidate's PaO_2 stays below 60 mmHg. Candidates should have no significant clinical evidence of underlying primary pulmonary disease [32].

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34. Renal Dysfunction in Hepatic Failure

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Introduction

Renal function impairment is a frequent occurrence in chronic or acute hepatic failure. The consequences of renal involvement can adversely impact patient outcomes and can affect the functions of distant organs and may further worsen the hepatic function. The majority of cirrhotic patients especially those with ascites suffered one form or another of renal impairment [1]. In this chapter we discuss the etiology, pathophysiology, diagnosis, and types of renal involvement in patients with end-stage liver disease (ESLD).

Definition of Acute Kidney Injury in Liver Disease

In 2004 the Acute Dialysis Quality Initiative (ADQI) proposed the use of RIFLE criteria (risk, injury, failure, loss, end-stage renal failure) to define and stratify the acute kidney injury (AKI) (Table 34.1) [2]. This definition stratified the AKI into grades of severities that relayed on the changes in the SCr levels and/or urine output. The clinical applications of RIFLE criteria proved to predict patient outcomes with increasing mortality and morbidity at a higher RIFLE scores. However, the Kidney Disease

Improving Global Outcomes (KDIGO) [3] improvised and simplified the definition but still using the SCr and urine output criteria as indictors for renal function. However, the Acute Kidney Injury Network (AKIN) and in an effort to broaden the scope of the definition of the AKI, they came up with new definition [4] for AKI that was in 2011 and they recommended to use SCr as the only indictor for renal function due to unreliability of urine output in the setting of liver disease (Table 34.2).

Table 34.1 RIFLE criteria

Stage	GFR criteria	Urine output criteria	Probability
Risk	SCr increased ×1.5 GFR decreased >25 %	<0.5 mL/kg/h for >6 h	High sensitivity (risk > injury > failure)
Injury	SCr increased ×2 GFR decreased >50 %	<0.5 mL/kg/h for >12 h	
Failure	SCr increased ×3 GFR decreased 75 % SCr ≥4 mg/dL	>0.3 mL/kg/h ×24 Oliguria Anuria × 12 h	
Loss	Complete loss of renal function >4 weeks		High specificity
ESRD	Complete loss of renal function >12 weeks		

Table 34.2 The proposed diagnostic criteria for AKI in cirrhosis

Diagnosis	Definition
Acute kidney injury	Rise in Scr of ≥50 % from baseline or by ≥0.3 mg/dL in <48 h. HRS-1 is a specific form of AKI
Chronic kidney disease	GFR of <60 mL/min for >3 months calculated using MDRD6 formula. HRS-2 is a specific form of CKD
Acute-on-chronic kidney disease	Rise in SCr ≥50 % from the baseline or rise in SCr ≥0.3 mg/dL in <48 h in patients with cirrhosis with GFR <60 mL/min for >3 months calculated using MDRD6 formula

The AKIN definition included an absolute increase in SCr of ≥0.3 mg/dL within 48 h or 50 % increase of SCr from the baseline value within 24 h and that is irrespective to the etiology of the AKI. This definition of AKI will cover a wide spectrum of renal diseases in patients with acute or chronic hepatic failure. Accordingly, the presence of chronic renal failure will be defined as continuous renal impairment beyond the 3-month cutoff period. However, patients with ESLD and with the application of either these two definitions will result in fewer cases to be qualified to have the HRS-1 and the rest will fall within the definition scope of AKI. Accordingly, the ADQI proposed to use the terminology of hepatorenal disorders to define all types of AKI that accompanied ESLD and leaving the HRS-1 to be considered in small percentage of patients when they meet certain diagnostic criteria [5]. CKD is defined when the GFR dropped below a cutoff limit of 60 mL/min/1.73 m^2 for more than 3 months. In patients with ESLD there is

difficulty to accurately measure the GFR due to the fact that most of the equations that are used to calculate the GFR are relayed on the SCr which is not a sensitive marker for renal function especially in ESLD [6]. The most widely used formula to calculate the GFR in patients with ESLD is the abbreviated modification of diet in renal disease (aMDRD) in which eGFR is equal to 186 × (SCre mg/dL) − 1.154 × age − 0.203 × 0.742 if patient is female ×1.21 if patient is African-American [7]. By using this formula and with the applying of definition of CKD, it is acceptable to consider HRS-2 as CKD when the GFR is <60/mL/min which is corresponding to SCr of 1.5 mg/dL. Acute deterioration of renal function in patients with baseline CKD or HRS-2 (acute on chronic) is still defined by the percentage changes of SCr from the baseline.

Hepatorenal Connections

The pathophysiological changes in cirrhosis are mostly associated with systemic vasodilatation and splanchnic hyperemia which is accompanied by reflex stimulation of the sympathetic system to maintain hemodynamic stability [8, 9]. As a result there is an increase in the circulating catecholamine and activation of the renin-angiotensin system (RAS) . The role of renal sympathetic nervous system stimulation in the etiology of intrarenal vasoconstriction is at best a contributing factor since renal sympathetic denervation did not reverse the vasoconstrictor response that was demonstrated in HRS [10].

The activation of RAS may play a serious role in the etiology of intrarenal vasoconstriction and eventful renal damage as well as in the propagation of hepatic fibrosis with further deterioration of hepatic function [11, 12]. Recent studies indicated that angiotensin II can activate the contraction of the hepatic stellate cells which results in increased intrahepatic resistance to portal blood flow with the development of portal hypertension. The clinical values of ACE inhibitors and/or angiotensin receptor blockers (ARB) in cirrhotic patients are still required to be evaluated since the results of recent clinical trials are not very promising [13, 14]. The issues related to the use of ARBs and ACE inhibitors in cirrhotic patients are related to the development of systemic hypotension which can further compromise renal perfusion and blood flow. A new scientific discovery of the presence of a homolog of ACE that is present in the heart, kidneys, and testis which can convert angiotensin II into angiotensin (1–7 and 1–9) both can oppose the effects of the parent agent on the vascular resistance and on the hepatic cells. The clinical applications of these agents may pave the way for new therapeutic interventions to prevent renal injury in liver cirrhosis [15].

The presence of cirrhotic cardiomyopathy in patients with ESLD is a well-documented phenomena which can be detected in all kinds of cirrhosis not only in alcohol-induced cirrhosis. The severity of cardiac involvement is clearly related to the severity of liver disease and it tends to improve within 6–12 months after successful

liver transplantation [16]. The cardiac dysfunction can be partially explained by high plasma levels of brain natriuretic peptide in the presence of relative hypovolemia or low preload (due to vasodilatation) and it correlates very well with the severity of liver disease [17].

The contribution of high levels of circulating catecholamine in the etiology of cardiomyopathy in ESLD is undeniable and can lead to myocardial growth and myocardial fibrosis with impairment of myocardial relaxation. The hyperactivity of sympathetic system can result in beta-adrenergic receptor down-regulation and abnormality of the signal transduction with overall reduction in the response to sympathomimetic agents [18]. Recently, endogenous cannabinoids (EC) which are lipid-signaling molecules have been recently found to be upregulated in liver disease and considered to be a factor not only in pathogenesis of liver cirrhosis but also in cirrhosis-induced hyperdynamic circulation and/or cirrhotic cardiomyopathy [19].

In ESLD there is breakdown of intestinal mucosal barrier which results in translocation of bacteria and endotoxin from the intestinal tract to the systemic circulation by passing the hepatic filter through the porta-systemic shunting or due to impairment of hepatic de-toxification function. The presence of chronic low levels of endotoxemia in patients with ESLD is the underlying mechanism of the chronic inflammatory response and the resultant splanchnic and systemic vasodilatation [20]. The increased production of pro-inflammatory cytokines (TNF-α, IL-18) which is coupled with excessive production of nitric oxide (NO) can further impair the cardiac dysfunction. The contribution of cardiomyopathy to the pathogenesis of AKI and especially to HRS is still controversial, but cirrhotic patients demonstrate that an inability to increase cardiac output during stress (sepsis, surgery) may further impede the already compromised renal blood flow and lead to AKI. The presence of excessive vasoactive mediators in ESLD can lead directly or indirectly through activation of secondary mediators to low SVR and high intrarenal vascular resistance. These agents include endotoxin, NO, TNF-α, IL-18, endothelin, glucagon, and prostaglandins. The increased production of NO is due to up-regulation of the inducible nitric oxide synthase (iNOS) , possibly induced by high shear stress on the vascular beds of both systemic and splanchnic and the presence of access of endotoxin. The high levels of NO are not only related to increased production but also decreased NO removal. In a recent study by Serna et al. [21] the investigators demonstrated the presence of high dimethylarginine dimethylaminohydrolases (DDAHs) which indicates an increased breakdown of asymmetric dimethylarginine (ADMA) , the natural NOS inhibitor which results in further increased NO production with sustained mesenteric vasodilatation. A new theory is emerging to explain in the intrarenal vasospasm while there is widespread systemic and splanchnic vasodilatation, in which ADMA plays the pivotal role in the inhibition of intrarenal NO production resulting in the vasoconstriction [22, 23].

Other known mediators of the intrarenal vasodilatory response are PGs, which are normally increased whenever there is intrarenal vasoconstriction as demonstrated by increase in urinary excretion of these PGs, except in patients with HRS [24]. The finding that there is a low level of vasodilatory PGs prompted the administration of these agents to patients with HRS; however, the results are still disappointing and may be due to further deterioration in the SVR and decrease in renal perfusion pressure or simply they play minor role in the pathophysiology of AKI of ESLD.

The Spectrum of AKI in ESLD

The most common AKI in patients with ESLD is acute tubular necrosis (ATN) 35 % and prerenal azotemia 32 %, HRS-1 20 %, and HRS-2 6.6 % and the rest are miscellaneous causes.

Prerenal Azotemia

It is defined as functional derangement of kidneys that can be caused by an array of causes which operate or start outside the kidneys. The most common etiology is preload reduction due to hypovolemic and hemorrhagic shock. Another etiology is related to low cardiac output that can be caused by multiple factors such as cardiogenic shock, septic shock, and hypovolemic shock. Prerenal azotemia is a common etiology for AKI in ESLD and caused mostly by relative hypovolemia (induced by low SVR), paracentesis and aggressive diuretic therapy, low cardiac output due to cirrhotic cardiomyopathy, and sepsis. Once the prerenal azotemia is set in and if not treated appropriately it can lead to intrinsic renal injury and can set the motion for ATN or HRS.

Acute Tubular Necrosis

The etiology of acute tubular necrosis (ATN) in patients of ESLD is mostly related to preload reduction as in hemorrhagic shock, hypovolemic conditions mostly due to aggressive diuretic therapy, septic shock (bacterial peritonitis), and use of nephrotoxic agents. The differentiation between ATN and HRS-1 is difficult to establish due to overlap in presentation and in the precipitating factors. HRS-1 mostly responds to preload optimization and/or vasoactive agents with the removal of the precipitating factors (sepsis, diuretics, nephrotoxic drugs) or by liver transplantation [25, 26]. However in ATN there are many pathological and structural damages within the renal tubules that are attributed to ischemia and will require long time for regeneration and repair process (average 1–3 weeks).

Analysis of urine can be helpful in the differential diagnosis such as urine osmolality which is high in HRS-1, urine sodium which is high in ATN, and the

presence of cellular casts, hemoglobin, and myoglobin are mostly associated with ATN. Doppler ultrasound can be used to confirm the presence of intrarenal vasoconstriction which is the hallmark of HRS and can exclude other etiologies for the AKI [26]. Recently, the role of certain urinary biomarkers in the differential diagnosis of HRS-1 and ATN started to emerge as specific and accurate diagnostic tests. Although still not commonly used in clinical practice but the possibility for future use is there, such biomarkers include kidney-injury molecule-1 (KIM-1), interleukin-18 (ILT-18), and neutrophil-gelatinase-associated-lipocalin (NGAL) [27].

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is defined as reversible renal functional derangement in patients with ESLD. The diagnosis is usually established by the exclusion of other causes for renal impairment and failure to respond to volume resuscitation. Certain diagnostic criteria were established by International Ascites Club (IAC) in 2007 to confirm the diagnosis of HRS and to differentiate from other causes of AKI in ESLD (Table 34.3) [1, 28]. HRS is characterized by progressive decrease in GFR and renal blood flow with marked intrarenal vasoconstriction in the presence of systemic vasodilatation. There are two types of HRS, type I and type 2; typical HRS-1 is the rapidly progressive AKI with 100 % increase in SCr to a level of >2.5 mg/dL or to 50 % decrease in GFR to a level of <20 mL/min within less than 2-week period. Type-2 HRS which is considered as a form of CKD is mostly observed in patients with ESLD and ascites which is slowly progressive AKI with SCr of >1.5 mg/dL [29]. Although the exact etiology of HRS is still not fully understood, there are multiple factors that operate together in the development of the HRS. These factors are systemic vasodilatation with hyperdynamic circulation, stimulation of renal sympathetic system and activation of RAS, low renal perfusion pressure due to possible cirrhotic cardiomyopathy, and finally the role of different pro-inflammatory cytokines on renal blood flow and renal function.

Table 34.3 Diagnostic criteria of HRS (IAC)

Major criteria: Only one major criterion is required to establish the diagnosis of HRS
1. Low GFR, as indicated by SCr >1.5 mg/dL or 24-h creatinine clearance <40 mL/min
2. Absence of shock, ongoing bacterial infection, fluid losses, and current treatment with nephrotoxic drugs
3. No sustained improvement in renal function (decrease in serum creatinine to ≤1.5 mg/dL or increase in creatinine clearance to ≥40 mL/min) after diuretic withdrawal and expansion of plasma volume with 1.5 L of a plasma expander
4. Proteinuria <500 mg/day and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease
Additional criteria
1. Urine volume <500 mL/day
2. Urine sodium <10 mEq/L

3. Urine osmolality greater than plasma osmolality
4. Urine red blood cells <50/high-power field
5. Serum sodium concentration <130 mEq/L

Overall, the development of HRS-1 is usually due to precipitating factors such sepsis, aggressive paracentesis, GI bleed, or surgery [30]. These factors can lead to further deterioration of cardiac output and renal blood flow as well as excessive production of multiple mediators that further compromised the delicate renal hemodynamics with the end result of HRS-1. However, in HRS-2 or CKD there is no clear precipitating factor but overall slow-progressive deterioration of the renal function coupled with gradual increase in renal vascular resistance [28, 29]. According to the IAC definition of HRS-1 to establish the diagnosis of HRS-1, three major criteria are required (Table 34.3). However, to differentiate the HRS-1 from ATN by relying on the urinary sodium excretion or presence of proteinuria indices can be unreliable. The prognosis of HRS-1 is very poor with almost 80 % mortality within 4 weeks. HRS-2 has much better prognosis with the median survival rate around 6 months. The prognosis of both types is dependent on the severity of liver diseases (high MELD or Child-Pugh scores) as well as the presence of the precipitating factors [26, 31].

Intrinsic Renal Diseases

Nephrotoxic Agents

The aminoglycoside antibiotics are notorious for causing renal damage through their effects on renal tubules and glomeruli [32]. The aminoglycoside-induced renal toxicity is characterized by non-oliguric or polyuric renal failure with increased urinary loss of glucose, protein, and electrolytes. As expected aminoglycoside nephrotoxicity is more frequent and severe in patients with ESLD due to underling AKI. Other antibiotics that are implicated in nephrotoxicity include penicillin, acyclovir, and amphotericin [33].

The contrast-induced nephropathy (CIN) is a well-known complication following any diagnostic or therapeutic interventions where the CIN is used. The etiology of CIN is probably multifactorial, either direct toxic effects on the renal tubules or renal vascular spasm due to hyperosmolality and high viscosity and/or through the release of toxic free radicals. CIN tends to occur in patients who are at high risk to develop AKI as in diabetic patients, old age, and ESLD or in any patient with underlying kidney disease. Recently, the incidence of CIN is reduced since the introduction of nonionic iso-osmolal or low osmolal agents and with the use of smaller doses of the agent. In patients with ESLD, the use of the contrast media should be restricted or completely avoided unless it is extremely necessary and only in cirrhotic patients with normal renal function [34].

Chronic Glomerulonephritis

Viral hepatitis and in particular hepatitis C cirrhosis are leading causes of glomerular pathology. Hepatitis B cirrhosis can cause glomerulonephritis which is seen mostly in endemic areas and where the HBV surface antigen carrier state is fairly common. In both types of viral hepatitis the glomerular involvement shows a wide spectrum of pathological changes that can affect the glomerular membrane or the vascular parts of the glomerulus [35, 36].

IgA Nephropathy

The primary form of IgA nephropathy is usually presented with proteinuria and hematuria due to deposit of the globular IgA in the renal mesangium and in the glomerular capillaries. In patients with ESLD and especially in alcoholic cirrhosis there is high level of serum IgA and the development of subclinical IgA nephropathy is fairly common. The possible explanation for IgA nephropathy in patients with ESLD may be related to decreased hepatic clearance of the protein complex and impaired phagocytic function of Kupffer cells [37].

Diabetic Nephropathy

Diabetes type 1 and 2 are common etiologies for nephropathy and in patients with ESLD there is high prevalence of glucose intolerance and diabetes especially in patients with nonalcoholic steatohepatitis. Diabetic nephropathy is commonly diagnosed in patients with ESLD as part of metabolic syndrome which is related to obesity [38].

Postrenal Insufficiency

The etiology of postrenal renal failure in cirrhotic patients is not different in incidence or in etiology from what is seen in general population. The common causes include stones, iatrogenic injuries, tumors, and prostatic hypertrophy in males.

The Role of Renal Biomarkers in the Diagnosis of AKI

Although SCr is commonly used to define and diagnose AKI, it is not a perfect marker due to delayed rise in its serum level which may hinder the early diagnosis of AKI. SCr may not accurately reflect the renal function as it is affected by food, race, gender, muscle mass, and laboratory method that is used to measure SCr. In cirrhotic patients the use of SCr will overestimate the GFR due to reduced production (low muscle mass) and dilutional hypervolemia [39]. To minimize the effects of these factors on the SCr measurements when used to calculate the GFR in patients with ESLD a lower cutoff value of SCr is used (0.97 mg/dL) [40].

Recently the National Kidney Disease Education Program (NKDEP) Laboratory Working Group reviewed the problems related to the use of SCr to estimate the GFR and suggested to standardize the method of SCr measurement. The NKDEP reported that due to the current variability in SCr laboratory measurements, it is reflected on the accuracy of all GFR estimation by any kinds of equations that rely on SCr value. The NKDEP recommended to seriously address this problem to reduce the analytical bias in SCr measurement [6, 41].

Due to the shortcoming of SCr measurement as a marker for renal performance, multiple new biomarkers have been suggested to replace SCr. NGAL is one of these biomarkers that were extensively studied in patients with ESLD and in post-liver transplant population. NGAL is a protein that is up-regulated after renal injury and can be detected in the plasma and urine especially in HRS and can be used to establish the diagnosis of HRS [42].

Cystatin-C is another biomarker that was used to diagnose AKI in liver transplant recipients. Cystatin-C is a small protein molecule that is produced by all living cells and completely removed by glomerular filtration and it is not affected by the factors that affect SCr [43]. The urinary L-type fatty acid-binding protein (L-FABP) is another biomarker that showed some promising results in the diagnosis and prediction of AKI while kidney injury molecule-1 (KIM-1) was found to be useful in the diagnosis of AKI due to tubular injuries [44, 45].

Although these biomarkers have been studied and evaluated in multiple studies, their clinical applications are still needed to be evaluated especially when considering the different etiologies of AKI in different patient's population.

Therapeutic Interventions in AKI

In general the therapeutic interventions will include the following:

1. Preload optimization through fluid administration, reversal of negative inotropic state, and management of the afterload

2. Holt all diuretics and nephrotoxic agents

3. Treatment of the underlying etiology of AKI that includes sepsis or GI bleeding

4. Evaluation for transjugular intrahepatic portosystemic shunt (TIPS), renal replacement therapy (RRT), or liver transplantation

Pharmacologic Interventions

The aim of the pharmacologic interventions is to reverse or at least ameliorate the renal damage while waiting for the definitive treatment which can be the liver transplantation as the only option to prevent mortality. The main agents that are in use in ESLD-associated AKI are the following:

1. Systemic vasoconstrictors: The use of these agents will in theory reverse the main triggering mechanism for the AKI which is systemic and splanchnic vasodilatation. Some of these agents showed promising results in clinical trials by ameliorating the triggering factors and increasing the renal perfusion pressure and eventually improving renal function. These drugs that were studied extensively include norepinephrine, vasopressin, and vasopressin analogues (terlipressin) [46] and somatostatin and its analogue (octreotide). Terlipressin was studied and used in both types of HRS and showed that it can improve the renal blood flow and GFR with significant reduction in the SCr especially when combined with proper preload management.

2. Renal vasodilators: The data about the use of direct renal vasodilators such as dopamine, fenoldopam [47, 48], or prostaglandins showed conflicting results but overall no clear proof that they can be effective [49]. The main reason for their failure in clinical practice is probably related to their effects on the systemic vascular resistance and systemic blood pressure which further comprises the renal perfusion and neutralizes any direct renal effects. ACE inhibitors and endothelin receptor blockers, in spite of their direct renal vasodilatory effects, were unable to resolve the AKI due to deterioration in the renal blood flow that resulted from their effects on the systemic vascular resistance.

Transjugular Intrahepatic Portosystemic Shunt

It is a widely used technique to lower the portal pressure in patients with ESLD especially in the presence of refractory ascites. TIPS by lowering the portal pressure is supposed to shut off the biochemical, hemodynamic, and neurohumoral escalations in the cirrhotic patients. However, such action is not nearly complete as it is hoped for and it is not without the possibility of serious complications. TIPS apart from being an invasive procedure can lead to acute hepatic decompensation with acute hepatic encephalopathy. TIPS can cause serious tribulation on the systemic hemodynamics with acute heart failure due to volume overload and/or passage of toxic mediators into the systemic circulation [50]. Careful patient selection is warranted when TIPS is planned to prevent life-threatening complications. The improvement of renal function does not

happen immediately after the TIPS procedure and can take up to 4 weeks before any significant benefit can be detected. To achieve better results and improve the outcomes a combination of therapeutic interventions that include volume optimization (usually with albumin solution) and vasoactive agents, whether renal vasodilators or systemic vasoconstrictors, with removal of any precipitating factors should be considered.

Renal Replacement Therapy

The use of RRT in patient with ESLD and AKI especially in HRS-1 is justified as a bridging intervention while waiting for liver transplantation. The application of continuous RRT or intermittent hemodialysis (HD) depends on the patient hemodynamic status and the tolerability of the particular procedure [51]. Intermittent HD is appropriate for ambulatory patients while continuous form of RRT is preserved for patients with delicate hemodynamic status and managed in critical care unit. Intermittent HD can lead to chronic inflammatory status with high levels of pro-inflammatory cytokines and microvascular angiopathy with end-organ damages and can seriously impact patient outcomes.

Recently the wide application of molecular adsorbent recirculating system (MARS) is gaining popularity in ESLD patients with AKI. MARS is able to remove albumin-bound, water-soluble toxins and vasoactive agents and it tends to have benign effects on the patient hemodynamics. Such substances that can be cleared by MARS include NO, TNF-α, IL-6, and many other toxic mediators. MARS can be used as a bridging therapy until liver transplantation or until the precipitating factors for the AKI can be dealt with appropriately [52].

Liver Transplantation

This is the ultimate therapy for ESLD and the ESLD-induced AKI, but still not without caveats since the procedure itself carries very high risk for AKI and renal failure. After successful liver transplantation the renal function will show a significant improvement within the 30 days but it can take as long as 1 year for all the renal indices to go back to normal. The use of the MELD score to prioritize the organ allocation offers some benefits to the patients with ESLD and AKI due to the incorporation of the SCr in the score. The patients with HRS-1 have a higher mortality on the waiting list than patients with a comparable MELD score; this may point out the ineffectiveness of MELD score in risk stratification in HRS-1 patients [53].

The incidence of AKI after liver transplantation is extremely high and depending on the methods that are used to define the post-transplant AKI it can be as high as 80 %. The development of AKI can negatively impact the patient and graft outcome [54] and can consume extensive financial resources and manpower. The etiology of early post-transplant AKI is multifactorial and related to high level of free radicals, blood

transfusion, sepsis, ischemia reperfusion injury, and nephrotoxic agents. Later in the post-transplant period, other factors will operate; these include the direct nephrotoxicity of the immunosuppressant agents, sepsis, and development of hypertension and diabetes mellitus as consequence of prolonged use of immunosuppressant agents. Most patients who developed early or late post-transplant AKI will end up with some degree of CKD and eventually chronic renal failure that will require RRT or renal transplantation.

Prognosis of AKI

In general AKI is a common complication in critically ill patients and after major surgical procedures as in open heart surgery, organ transplantation, trauma, and systemic sepsis. The availability of sophisticated pharmacological interventions MARS and RRT application did not result in significant improvement in mortality and morbidity. This may be related to the far-reaching effects of AKI on most body organs with the induction of structural and/or functional damages. The prevention of AKI or early detection and treatment if it can be achieved will be the best therapeutic intervention. Understanding the mechanism of distant organ damages that are induced by AKI and the underlying pathological communication between the diseased kidneys and other organs may solve the mystery of poor outcome in AKI [55, 56].

Recent finding that the development of AKI can cause hepatic vascular congestion, increased vascular permeability, neutrophil infiltration, and elevated liver enzymes may point out to one of the devastating effects of AKI. Animal experiments showed that AKI can induce hepatic proinflammatory cytokines, increase the toxic free radicals, and stimulate apoptosis with end result of hepatic dysfunction. The role of RAS in the production of hepatic fibrosis in patients with AKI is becoming clear which is related to the stimulation of hepatic stellate cells by angiotensin II and further escalation of the portal pressure. All these findings helped to complete the picture of the AKI and its impact on distant body organs and the result of high morbidity and mortality when it sets in motion.

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35. Cirrhotic Cardiomyopathy and Liver Transplantation

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Abbreviations

BNP Brain natriuretic peptide

Ca^{2+} Calcium

cAMP Adenylyl cyclase

K^{+} Potassium

MELD Model for end-stage liver disease

Na^{+} Sodium

NO Nitric oxide

proBNP Pro-brain natriuretic peptide

TDI Tissue Doppler imaging

TIPS Transjugular intrahepatic portosystemic shunt

VO_2 Maximal oxygen consumption

Introduction

The studies on this new nosological entity, whose term and characteristics were defined only several years later, began more than 50 years ago on a group of alcoholic cirrhotics in which increased cardiac output and other electrocardiographic abnormalities (prolongation of the QT interval, bundle branch block, T wave inversion, depression of the S-T segment, multiple extrasystoles) were observed [1–3]. An impaired thiamine utilization and/or the presence of an endogenous vasodilator were believed to be the precipitating cause [1, 2].

A subsequent study, based on autopsy series of alcoholic and nonalcoholic cirrhotics, showed the presence of cardiac hypertrophy and cardiomyocyte edema in the absence of coronary artery disease, hypertension, or valvular disease [4]. Subsequently, clinical and animal studies described an impaired hemodynamic response to physiologic stress (exercise), or pharmacologic stress (catecholamines) or increase preload (volume expansion) despite a high-resting cardiac output [5–7]. Additional animal and human studies confirmed these findings and found that they were due to a decreased myocardial contractile function [8].

In the workshop of Montreal (2005), all these findings were summarized in a syndrome termed “cirrhotic cardiomyopathy” and defined as “chronic cardiac dysfunction in patients with cirrhosis, characterized by blunted contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities, in the absence of known cardiac disease.”

Now, it is formally accepted that cirrhotic cardiomyopathy is characterized by intrinsic alterations in myocardial function, is related to both portal hypertension and cirrhosis, and is irrespective of the causes of cirrhosis, although some etiologies (e.g., iron overload and alcohol consumption) may have an impact on myocardial structure and function [9].

Epidemiology

The exact prevalence of cirrhotic cardiomyopathy is unknown. As explained, the cardiomyopathy is often clinically silent until intercurrent changes in demand occur (i.e., infection) or after transplantation, when abnormalities in cardiac diastolic and systolic reserve are seen.

A prolongation of the QT interval [9–13] and elevation in circulating concentrations of brain natriuretic peptide (BNP) [14] have been suggested to be the earliest signs of cirrhotic cardiomyopathy. BNP levels are elevated in decompensated cirrhosis and in some patients with compensated cirrhosis, suggesting that not all cirrhotics, but only those with cardiac dysfunction, have cirrhotic cardiomyopathy [15]. BNP levels have demonstrated to well correlate with the presence of diastolic dysfunction [15].

The prevalence of QT interval prolongation in cirrhosis is greater than in the general population, and increases with the severity of the disease (25 % in cirrhosis Child-Pugh class A vs. 51 % in Child-Pugh class B, vs. 60 % in Child-Pugh class C) [13].

Natural History

Cirrhotic cardiomyopathy is undoubtedly well tolerated and asymptomatic for months to years, especially in the early phase of cirrhosis and the lack of clear symptoms masks and delays its diagnosis. The natural history of the disease is therefore not entirely characterized. Considering that the diagnosis of cirrhotic cardiomyopathy usually occurs during a phase of decompensation or as a complication after liver transplantation, it is understood that this diagnosis carries an unfavorable prognostic implication and often occurs late in the course of the cirrhosis.

While the incidence and progression of the cirrhotic cardiomyopathy are considered to be related to the stage of liver cirrhosis and to the presence of portal hypertension, the correlation is often not linear. The enhanced level of several substances with potential cardiotoxic effects (endotoxins, cytokines, bile salts, and insulin) [13], that directly act on the membrane potential of cardiomyocyte, are the pivotal cause of the prolongation of QT interval in cirrhosis, and they do not linearly correlate with the severity of cirrhosis.

In the initial phases of the disease, the presence of a blunted cardiac response in cirrhotics is masked by the splanchnic arterial vasodilation that unloads the ventricle and hides the presence of cardiac insufficiency [9]. The contemporary presence of the autonomic dysfunction, impaired volume, and baroreceptor reflexes also contributes to the blunted cardiac response [9].

Since there are no targeted treatments, the management of cirrhotic cardiomyopathy is empirical [16] and it is not known whether therapy impacts on the natural history of the disease. Similarly, the treatment of cirrhosis complications such as ascites, hepatic encephalopathy, and esophageal varices appears to have no impact on the natural history of cirrhotic cardiomyopathy. Conversely, the natural history is influenced by transjugular intrahepatic portosystemic shunt (TIPS) and liver transplantation. The reason for this is the development of heart failure and pulmonary hypertension after a rapid increase in venous return, occurring after both procedures, unmasking the

presence of cirrhotic cardiomyopathy.

Clinical Presentation

Cardiac function is modulated by the afterload, namely arterial compliance, and preload, venous return. Cirrhotics have a reduced arteriolar and venular tone and therefore have low systemic vascular resistance (vasodilation leading to reduced afterload) and impaired venous return (blood pooling leading to reduced preload) while still being clinically volume overloaded. Functional capacity in cirrhotics is often impaired by low arterial pressure (related to reduced vascular resistances). Clinically these patients have impaired exercise tolerance and fatigue. The mean arterial pressure is indeed a product of cardiac output divided by systemic vascular resistance: the reduction in vascular resistance dramatically reduces the mean arterial pressure. As a compensatory mechanism cardiac output is generally increased in cirrhosis to compensate for the reduced vascular resistance. When cirrhotic cardiomyopathy develops, the impaired cardiac function, resulting in a blunted cardiac response, leads to further reduction in mean arterial pressure during exertion or increased demand, and leads to further reduction of the mean arterial pressure and amplifications of the symptoms of exercise intolerance and fatigue. It is however very difficult from a clinical standpoint to differentiate whether the worsening in symptoms is due to a further reduction in systemic vascular resistance or to a new reduction in the cardiac response. Relative renal hypoperfusion is present in cirrhosis and is worsened when the cardiomyopathy ensues; this may lead to further aggravation of volume overload. Due to peripheral pooling from the splanchnic arterial vasodilation and reduced venular tone, pulmonary congestion is rarely seen in cirrhotics, even when cirrhotic cardiomyopathy is present. The occurrence of pulmonary congestion following TIPS or liver transplantation is highly indicative of underlying cirrhotic cardiomyopathy.

Due to the lack of specificity of management and cardiac monitoring of symptoms related to the incidence of cirrhotic cardiomyopathy, it is advisable that cardiac abnormalities are sought for to determine whether a cardiomyopathy is present. The cirrhotic cardiomyopathy is indeed characterized by a broad spectrum of cardiac alterations that cause a high-output heart failure [17, 18]. Considering that the vast majority of patients evaluated for cardiomyopathy or heart failure have reduced cardiac output, it is clear that this cardiomyopathy differs from other forms (i.e., dilated cardiomyopathy) and may require a more focused approach. An echocardiography may, indeed, often show a normal cardiac systolic function even in decompensated cirrhotics, thus potentially falsely leading away from a diagnosis of cardiomyopathy. If one were to approach the decompensated cirrhotic patient with the expectation to find a higher than normal cardiac output, the finding of a normal output would certainly not rule out the cardiomyopathy but rather make it more likely (Table 35.1).

Table 35.1 Clinical and diagnostic comparison between cirrhotics with and without cardiomyopathy, at rest, during exercise, after TIPS, after liver transplant

Patients	Cirrhotics without cardiomyopathy	Cirrhotics with cardiomyopathy
At rest	• Clinical findings: Hyperdynamic state (few patients) • Echocardiography: 1. Prolonged isovolumetric relaxation time (mild) • Electrocardiogram: QT prolongation (few patients)	• Clinical findings: Hyperdynamic state (many patients) • Echocardiography: 1. Prolonged isovolumetric relaxation time 2. Diastolic dysfunction (E/A ratio of ≤1) (systolic dysfunction [rare]) 3. Left atrial enlargement 4. Left ventricular Hypertrophy • Electrocardiogram: 1. QT prolongation (many patients) 2. Bundle branch block and or ST-segment depression (some patients)
During exercise	• Clinical findings: 1. Normal cardiac output increase 2. Reduction in systemic vascular resistance and mean arterial pressure 3. Impairment in aerobic capacity (peak oxygen consumption) 4. Hyperdynamic circulatory state	• Clinical findings: 1. Impaired cardiac output increase 2. Severe reduction in systemic vascular resistance and mean arterial pressure 3. Chronotropic incompetence 4. Abnormal autonomic reflex 5. Severe impairment in aerobic capacity (peak oxygen consumption) 6. Severe hyperdynamic circulatory state
After TIPS	• Clinical findings: 1. Heart failure (rare, and mild) 2. Ascites (rare) 3. Liver and renal failure (rare) 4. Death (extremely rare)	• Clinical findings: 1. Heart failure (more frequent) 2. Ascites (more frequent) 3. Liver and renal failure (more frequent) 4. Death (more frequent) 5. Further prolongation QT interval
After liver transplant	• Clinical findings: 1. Normalization of portal-hepatic hemodynamics 2. Amelioration of cardiac autonomic function after 12 postoperative months • Electrocardiogram: Normalizaton of QT prolungation in 50 % of subjects within 12 months	• Clinical findings: 1. Normalization of portal-hepatic hemodynamics 2. Early myocardial depression 3. Early drop in cardiac index and oxygen delivery 4. Normalization of cardiac structure and function by 9–12 postoperative months • Electrocardiogram: Normalization of QT prolongation in 50 % of subjects within 12 months

Pathophysiology of Systemic Vascular Resistance and Cardiac Dysfunction

Chronological sequence in which cardiac alterations impact on cardiomyocyte is not fully defined. Multiple electrical abnormalities play a role in the onset of cirrhotic cardiomyopathy (QT interval abnormalities, electrical and mechanical dissociation, chronotropic incompetence) whose development is also linked to autonomic dysfunction (defects in the sympathetic nervous system and vagal impairment) [9, 19].

Prehepatic Sinusoidal Portal Hypertension

Experimental rat model of pre-portal hypertension has elucidated that vasoactive substances (such as ammonia, endotoxin, prostacyclin, serotonin) are released from the intestine when portal pressure is increased, leading to splanchnic vasodilation and further increase in portal pressure [20]. These substances released in the plasma mediate an altered basal contractility and response to beta-adrenoceptor activation in the heart. The presence of portosystemic shunting, further limiting the degradation of these substances by the liver, significantly worsened cardiac performance [21].

Hepatic and Posthepatic Sinusoidal Portal Hypertension

Liver cirrhosis is the result of a series of phenotypic changes in the hepatic stellate cells that make them activated, transformed, and able to produce extracellular matrix components and vasoconstrictive mediators and, finally, to promote liver fibrosis and increased vascular resistance in portal microcirculation, thus causing portal hypertension [22, 23].

In cirrhosis, two fundamental aspects are present: (a) an increased vascular intrahepatic resistance, due to a dramatic decrease of nitric oxide (NO) production in the sinusoidal and postsinusoidal areas [24], and (b) a marked peripheral arterial vasodilation, principally due to an increased amount of vasodilators (NO, prostacyclin, and others) and a decreased amount of vasoconstrictors, in these same vascular districts [25–27]. The marked peripheral arterial vasodilation is initially compensated by an increase in heart rate and cardiac output (hyperdynamic circulation). Indeed, in the early stages of cirrhosis, the sympathetic nervous system and the renin–angiotensin–aldosterone system are greatly activated to compensate arterial vasodilation but, in the late stages, this compensation is lost and the reduced preload (relative hypovolemia) prevails [28, 29].

This is associated with a process of vascular remodeling in the conductive vessels, consisting in a decrease in the thickness and the total area of the vascular wall and in a reduction in the vessel ability to contract, as demonstrated in animal models of cirrhosis [30].

These vascular changes, influencing the afterload, may mask a blunted cardiac response and the diagnosis of cirrhotic cardiomyopathy may be delayed.

The Blunted Cardiac Response

As previously said, in liver cirrhosis, the marked peripheral arterial vasodilatation is compensated through an enhanced activity of the sympathetic nervous system [28, 29]. It is well known that although short-term sympathetic overdrive increases cardiac performance, prolonged stimulation leads to the occurrence of a cardiomyopathy [9]. This causes profound myocardial remodeling and left ventricular hypertrophy characterized by a desensitization of the beta-adrenergic receptor, pro-apoptotic signaling in cardiomyocytes and pro-fibrotic signaling in fibroblasts. The consequence is that in the early phase of cirrhosis, there is an increased cardiac output and a hyperdynamic circulation, whereas in the advanced phases, systolic and diastolic dysfunction with detrimental cardiac consequences ensue [9].

Changes in sympathetic tone and autonomic function affect not only the heart but also the vasculature, the kidneys, and the lungs. Impaired autonomic dysfunction affects about 80 % of cirrhotics impairing renal perfusion and worsening cardiovascular adaptation, especially in those with decompensated liver disease [31, 32]; however, other clinical abnormalities are crucial in determining the blunted cardiac response (Fig. 35.1).

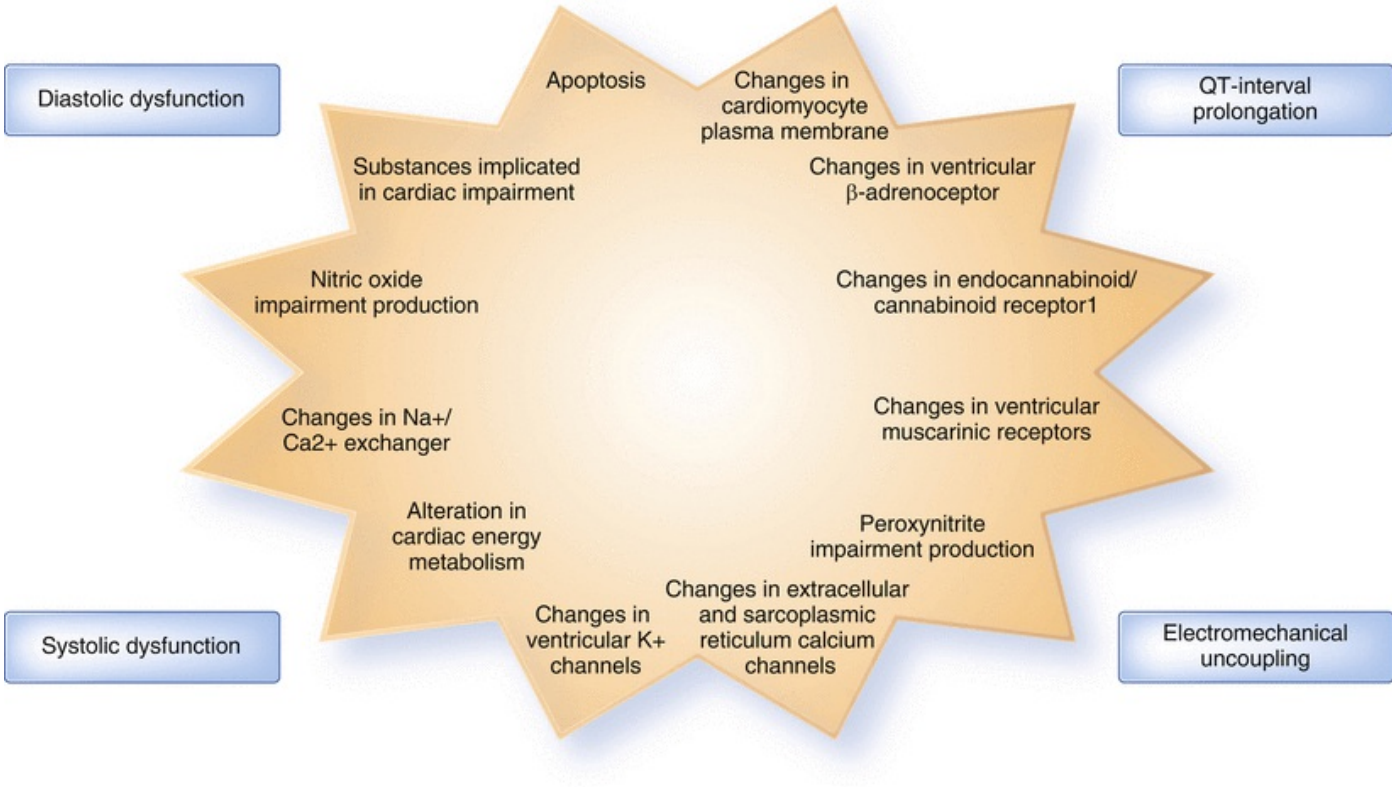

Fig. 35.1 Clinical and pathological basis of cirrhotic cardiomyopathy

QT Interval Prolongation

Prolongation of the QT interval (≥0.44 s), a condition associated with an increased risk

for ventricular tachyarrhythmias, is frequently the first abnormality seen in cirrhotics and noncirrhotics with portal hypertension [12]. The length of QT interval also correlates with the degree of liver dysfunction and circulating plasma noradrenaline [12]. K^+ channel abnormalities and sympathoadrenergic hyperactivity are both implicated in delaying cardiomyocyte repolarization. Diurnal and nocturnal modifications in autonomic tone circulatory status, and respiratory and oxygen demand, also influence the length of QT interval [33]. After liver transplantation, the QT interval is corrected in nearly 50 % of patients [12].

Electrical and Mechanical Dissociation

Whether QT prolongation mediates the cardiomyopathy or is a marker for the cardiomyopathy is not entirely true. Electromechanical uncoupling has been observed in cirrhotics with QT interval prolongation and it is proposed to be due to defective K^+ channel function in ventricular cardiomyocytes [34]. As described above, chronic overstimulation of the beta-adrenergic receptor leads to inotropic and chronotropic incompetence which further promotes electrical/mechanical dissociation [35]. Cardiac diastole is the filling of the heart which occurs as passive flow from the atria to the ventricle during ventricular relaxation: abnormalities in ventricular relaxation, which is an active process, or increased myocardial stiffness, which is a passive process, may lead to diastolic dysfunction. Impaired calcium signaling in cardiomyocyte is seen in cirrhotic [9], and leads to a manifestation of chemical and mechanical molecular changes leading to impaired relaxation. Left ventricular hypertrophy and myocardial fibrosis may lead to increased myocardial stiffness [36, 37].

Cardiac hypertrophy is indeed often seen in cirrhosis and is a result of the hypertrophy of the cardiomyocytes and an increase in the extracellular collagen content and fibrotic reaction [36], and the severity of the hypertrophic response correlates closely with the magnitude of the increased cardiac output [36].

The ratio of early (E wave) to late (A wave) diastolic filling (E/A ratio) and the deceleration time of the E wave are useful echocardiographic Doppler signs measuring the transmitral flow able to evidence diastolic condition after physiological or pharmacological stress test. Unfortunately, the E/A ratio is strongly dependent on preload and in decompensated cirrhotics this may be a disadvantage; furthermore, since diastolic dysfunction may disappear from 6 to 12 months after liver transplantation and cirrhotics with more severe diastolic dysfunction are more likely to have heart failure after liver transplantation [17, 38], it is advisable, in pretransplant phase, to use echocardiographic machines equipped with tissue-Doppler-based algorithm, to obtain more accuracy in detecting diastolic dysfunction, at rest [39].

Although, in several cases of cirrhosis, diastolic dysfunction is of mild degree and does not increase the pulmonary artery systolic pressure to abnormal levels [40],

nevertheless it is an independent predictor of mortality and its knowledge helps plan supporting measures to avoid or make more mild the onset of post-liver transplant heart failure [41].

Systolic dysfunction has been associated with alterations in preload, afterload, and diastolic dysfunction. A reduced myocardial reserve, an impaired oxygen extraction (probably due to the local imbalanced NO production and function), and a negative inotropic effect of endocannabinoids participate in causing it [17, 42, 43]. Prolongation in total electromechanical association in systole due to the lengthening of systolic time intervals is the crucial electrical abnormality present in this condition [11]. Cirrhotics may be affected by this condition as demonstrated after pharmacologic or exercise-induced increase in afterload or heart rate in which left ventricular ejection fraction did not change [17, 44].

The echocardiographic evaluation of left ventricular systolic function using new systems as speckle-tracking imaging promises to early identify cirrhotics with functional ventricular impairment [39]. According to some authors, pretransplant risk factors may predict post-liver transplant heart failure. In cirrhotics undergoing liver transplantation, the postoperative onset of systolic heart failure is considered an independent predictor of mortality [41], and identifying these patients before transplantation may optimize perioperative management.

Several pathogenic mechanisms impact on cardiomyocyte membrane and receptor function and give their contribution in causing an impaired myocardial response.

- *Alteration in cardiac energy metabolism*:

  Disturbances in substrate utilization seem to have a pivotal role in the pathophysiology of cardiac function. It seems that metabolic changes may precede structural and functional changes in the heart [45]. Dysregulation in cardiac energetics is viewed as one of the potential mechanisms underlying cirrhotic cardiomyopathy [46].

- *Substances implicated in cardiac impairment*:

  Carbon monoxide, hemoxygenase, NO, and endogenous cannabinoid bile acids in concert with other circulating molecules (cytokines, endotoxin, chemokines, lipids, for example) have a strong role in impairing cirrhotic heart, thus contributing to induce cardiac changes viewed in cirrhotic cardiomyopathy [47].

- *Changes in cardiomyocyte plasma membrane*:

  Changes in the membrane result in the increase in cholesterol content and in the cholesterol-to-phospholipid molar ratio; the principal effect, observed in rat models of cirrhosis but not in portal hypertensive rats, is the reduction of membrane fluidity, the increase of its stiffness, and the lower cAMP production in response to adrenergic stimulation [48, 49] (Fig. 35.2a).

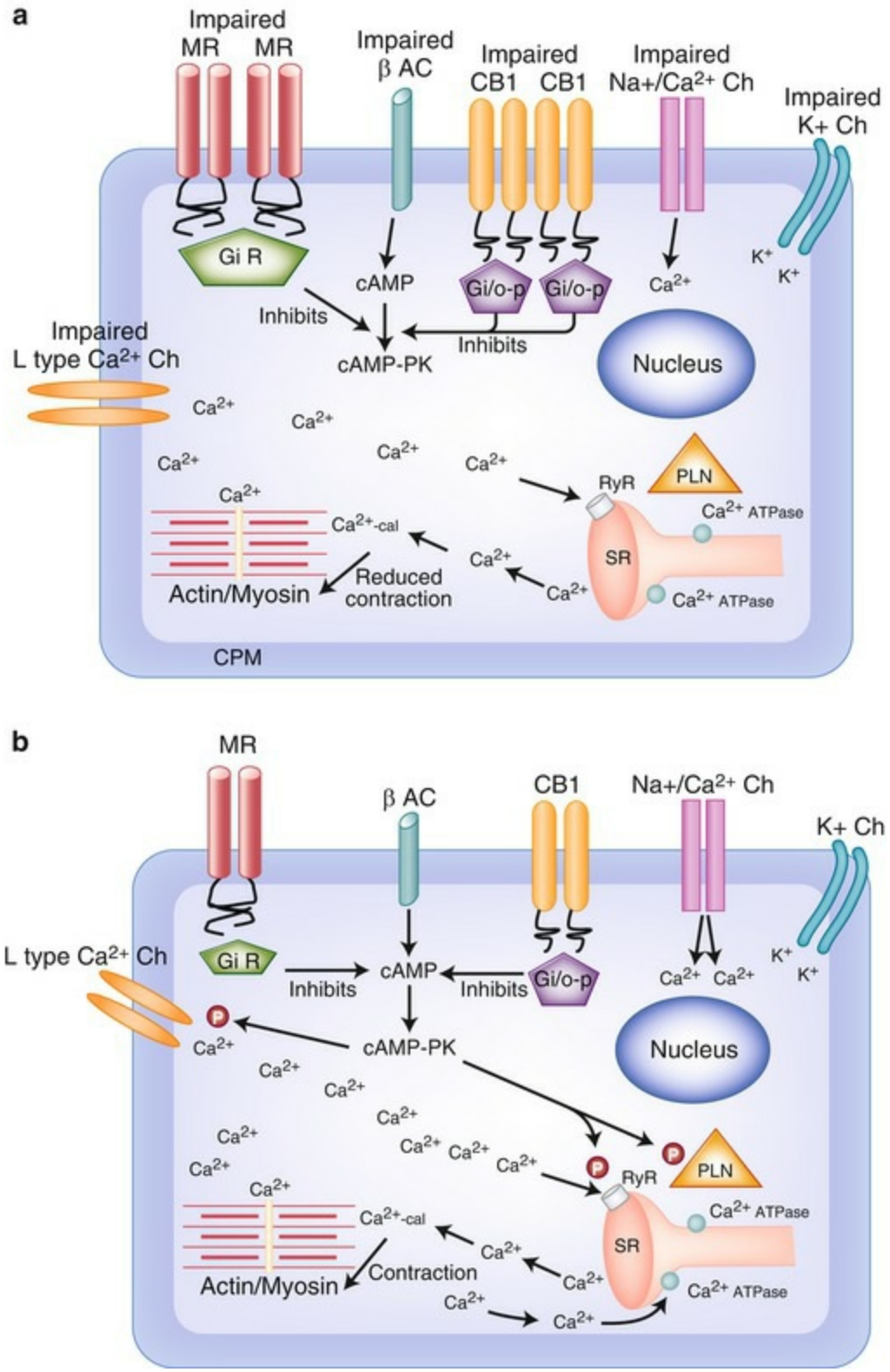

Fig. 35.2 (**a**) Impaired function of cardiomyocyte in cirrhotic cardiomyopathy . The entry of Ca^{2+} through L-type Ca^{2+} channels, in the cardiomyocyte, is imbalanced. The trigger of Ca^{2} to release Ca^{2+} from intracellular stores by ryanodine receptor (RyR) in the sarcoplasmic reticulum is low. The contraction is reduced. B-adrenergic receptor is imbalanced and does not contribute to stimulate Ca^{2+} influx. Reduced Ca^{2+} influx through L-type Ca^{2+} channels causes decreased Ca^{2+} entry and SR load resulting in smaller Ca^{2+} transients

that causes a decrease in contractile force. *Abbreviations*: *β AC* β-adrenoceptor, *Ca $^{2+}$ -cal* Ca^{2+}-calmodulin, *cAMP* adenylyl cyclase, *cAMP-PK* cAMP-dependent protein kinase, *CB1* cannabinoid receptor 1, *CPM* cardiomyocyte plasma membrane, *Gi/o-p* $G_{i/o}$ proteins, *K $^{+}$* potassium, *K $^{+}$ Ch* potassium channels, *L-type Ca $^{2+}$ Ch* L-type Ca^{2+} channels, *MR* muscarinic receptor, *Na $^{+}$ /Ca $^{2+}$ Ch* Na^{+}/Ca^{2+} channels, *N* nucleus, *P* phosphorylation, *PLN* phospholamban, *RyR* ryanodine receptor, *SR* sarcoplasmic reticulum. (**b**) Normal function of cardiomyocyte. Ca^{2+} influx enters through L-type Ca^{2+} channels in the cardiomyocyte. Ca^{2} triggers a further release of Ca^{2+} from intracellular stores by ryanodine receptor (RyR) in the sarcoplasmic reticulum. Ca^{2+} influx and released Ca^{2+} directly favor the contraction. Contraction is terminated by the rapid uptake into the SR by SR Ca^{2+} ATPases. β-Adrenergic receptor stimulation increases inotropy by phosphorylation (P) of PLN and L-type Ca^{2+} channels through cAMP-PK-stimulating Ca^{2+} influx and Ca^{2+}-pump activity. This increases the load of Ca^{2+} in the SR stores and leads to enhanced Ca^{2+} transients upon depolarization. *Abbreviations*: *β AC* β-adrenoceptor, *Ca $^{2+}$ -cal* Ca^{2+}-calmodulin, *cAMP* adenylyl cyclase, *cAMP-PK* cAMP-dependent protein kinase, *CB1* cannabinoid receptor 1, *CPM* cardiomyocyte plasma membrane, *Gi/o-p* $G_{i/o}$ proteins, *K $^{+}$* potassium, *K $^{+}$ Ch* potassium channels, *L-type Ca $^{2+}$ Ch* L-type Ca^{2+} channels, *MR* muscarinic receptor, *Na $^{+}$ /Ca $^{2+}$ Ch* Na^{+}/Ca^{2+} channels, *N* nucleus, *P* phosphorylation, *PLN* phospholamban, *RyR* ryanodine receptor, *SR* sarcoplasmic reticulum

- *Changes in ventricular β-adrenoceptor*:

  Rat models of cirrhotic cardiomyopathy have demonstrated to have a blunted cardiac response due to a decreased membrane fluidity and to an attenuation of the portion of the beta-adrenergic receptor signaling pathway upstream of adenylyl cyclase [50, 51] (Fig. 35.2a).

- *Changes in ventricular muscarinic receptors*:

  In rat models of cirrhosis, blunted muscarinic (M2) responsiveness and defective signal transduction to cAMP are reported; interestingly, this was not caused by receptor down-regulation but by changes in postreceptor system of cardiomyocyte [52].

- *Changes in ventricular K^{+} channels*:

  Activation of ventricular K^{+} channels promotes hyperpolarization and relaxation, whereas inhibition causes depolarization and contraction. A decreased K^{+} current density for the three types of K^{+} channels present in ventricular myocytes was found in a rat model of cirrhosis [53]. These rats exhibited a longer duration of baseline action potential as compared with ventricular myocytes of sham-operated rats [53]; the QT interval prolongation present in cirrhotics was hypothesized to be a direct consequence of these changes [9]. In another animal study, it was ascertained that the altered inotropic effect was due to changes in K^{+} channels able to modify resting membrane potential and action potential waveform and thus the intracellular Ca^{2+} concentration, the key driver of the myocardial contractility [54].

- *Changes in membrane and sarcoplasmic reticulum calcium channels*:
  Cardiac myocytes of a rat model of cirrhosis were demonstrated to have a decreased cardiac contractility, due to a decrease in initial plasmalemma Ca^{2+} entry (through L-type Ca^{2+}) as well as a decreased Ca^{2+}-stimulated Ca^{2+} release, whereas intracellular systems were showed to be intact [55] (Fig. 35.2a).
- *Changes in Na^{+}/Ca^{2+} exchanger*:
  Na^{+}/Ca^{2+} is responsible for maintenance of a steady-state intracellular free Ca^{2+} concentration and its impairment may thus contribute to the onset of cirrhotic cardiomyopathy [56, 57].
- *Changes in endocannabinoid/cannabinoid receptor1*:
  Studies in vitro and on rat models of cirrhosis indicated that the increased activity of cannabinoid receptor1 may be responsible for myocardial contractility dysfunction [42, 58].
- *NO impairment production*:
  An overproduction of NO is cardiodepressant, but inducing a splanchnic arterial vasodilation and a hyperdynamic circulation in cirrhosis masks the presence of blunted cardiac function [59] (Fig. 35.2a).
- *Peroxynitrite impairment production*:
  An overproduction of peroxynitrite depresses cardiac function through nitration (or S-nitrosation) of cardiac contractile proteins, such as actin [60].
- *Apoptosis*:
  Cardiomyocyte apoptosis may play a pivotal role in myocardial remodeling in heart failure [61]. Several lines of evidence indicate that also a mild increase of the apoptotic rate may induce cardiac dysfunction; changes in mRNA and protein expression levels of tubulin and collagen characterize this phase [62]. Interestingly, apoptosis (cardiac damage and fibrosis) has been appreciated in experimental animal models in preclinical cardiac failure [62].

Treatment and Prognosis

Cirrhosis is a life-threatening condition with an overall unfavorable prognosis if liver transplant is not safely performed. Impaired cardiac reserve is an additional condition that may worsen the prognosis especially in the setting of acute decompensated cirrhosis. Increased cardiac output, indeed, serves as an important compensatory mechanism in cirrhosis, and loss of the compensation may be critical in determining patient discharge in conditions of further reduction in systemic vascular resistance (such as sepsis) or reduced intravascular volume (such as hemorrhage) [63]. The inability to

increase cardiac output, favoring a decrease in renal perfusion, likely contributes to the pathogenesis of hepatorenal syndrome driving to unfavorable outcomes [11, 64]. The ensuing sympathetic activation increases cardiac contractility but also stimulates renal sodium and water retention through the activation of the renin–angiotensin–aldosterone system. Overactivation of the sympathetic tone and the renin–angiotensin–aldosterone systems contributes to worsening cardiac and renal remodeling and dysfunction, thus, negatively, affecting the prognosis [65]. Liver transplant, completely changing the natural history of the disease, may be the cure for cirrhosis and the associated cardiomyopathy [9].

There are no specific treatments for cirrhotic cardiomyopathy. In the absence of dedicated studies, general knowledge and considerations used for heart failure have been considered, with some exceptions. Angiotensin-converting enzyme inhibitors (and vasodilators in general) are a mainstay in the treatment of systolic heart failure, but they likely have little or no role in the cirrhotic cardiomyopathy, a condition with which there is severe systemic vasodilation. Beta-adrenergic blockers have also shown to reduce mortality in patients with systolic heart failure. Data on beta-adrenergic blockers in patients with heart failure and preserved ejection fraction are not available; yet such drugs are often used. There is a clear rationale to use beta-adrenergic blockers in patients with cirrhotic cardiomyopathy since their sympathetic overdrive is the key feature of the disease process; the use of these drugs is sometimes hindered by hypotension, though needed for the prevention of recurrent variceal bleed. A selective beta-blocker (beta1 and beta2) without alpha-blocking activity may be preferred to avoid further vasodilation, although some experimental studies show favorable data with carvedilol, a nonselective alpha-beta1/2 blocker. Appropriately sized controlled trials with beta-blockers in this disease are however lacking. Diuretics including loop-diuretics and aldosterone antagonists are often used to treat hypervolemia in cirrhotics with and without cardiomyopathy, but whether such treatment affects the outcome is unknown [9].

After liver transplantation, there is both a rapid hemodynamic change and an increased filling pressure that may worsen a pre-existing congestive heart failure. Some studies demonstrated cardiovascular complications in almost 25 % of patients undergoing liver transplant and a higher risk for postoperative pulmonary edema in patients with an abnormal heart function [66, 67]. Since conflicting results exist on the correlation between cirrhotic cardiomyopathy and severity of liver disease [63, 68, 69], all cirrhotics, independently of their Child-Pugh-Turcotte or model for end-stage liver disease (MELD) classifications, should be screened to evaluate the presence of cardiac abnormalities in pretransplant phase. An interesting study performed on 64 cirrhotics screened before liver transplant demonstrated that 23 % (15 patients) was affected by cirrhotic cardiomyopathy [68].

The fact that an amelioration of cardiac function has been observed after liver

transplant corroborates the concept that the cardiomyopathy is truly cirrhotic in origin [38] and that pretransplant evaluation of cardiac function is necessary to better plan the management of the patients and their long-term outcome.

Pretransplant Investigation of Cirrhotic Cardiomyopathy

Comorbid conditions of the recipient influence the outcome of liver transplant [70]. Increasing rates of cardiovascular complications after liver transplantation have been observed. They affect over 70 % of liver allograft recipients but cardiovascular mortality is reported to be less than 7–15 % [71]. Child-Pugh or MELD classifications are able to evaluate the severity of liver disease but fail to predict the post-liver transplant outcome [72]. Therefore, cardiac evaluation may be an additional screening tool to predict cardiovascular complications in the post-transplant period. The New York Heart Association (NYHA) and the Framingham score are useful tools to identify cirrhotics with heart failure but do not provide specific recommendations for the pretransplant assessment of liver transplant candidates.

It is known that the presence of an hyperdynamic circulation in cirrhosis is directly related to the severity of hepatic disease [73]. In conditions of marked vasodilation, if a high cardiac output cannot be maintained by a good cardiac function, the prognosis is grave [73]. Monitoring cardiac function may therefore be useful, and several noninvasive assessment tools exist. Electrocardiography and echocardiography are performed in most transplant liver centers to identify individual characteristics and cardiac compliance to liver transplant. The presence of cardiovascular complication after liver transplantation raised also the question of the underlying reasons for heart failure and electrical abnormalities. Cirrhotic cardiomyopathy with overt left ventricular failure has emerged as an important cause of perioperative morbidity and mortality for liver transplant recipients [16].

Cirrhotic cardiomyopathy (variably defined) is present in up to 50 % of the patients undergoing liver transplant. The cardiomyopathy is primarily characterized by electrophysiological abnormalities, a normal cardiac function at rest, and a blunted cardiac response to stimuli and systolic and diastolic dysfunction. The QT interval prolongation is one of the major electrophysiological abnormalities and is related to the severity of the liver disease and the degree of portal hypertension; it may be associated with an increased risk of ventricular arrhythmias but its more severe complication (sudden death) is not a frequent event in cirrhotics [74]. Prolonged QT interval should be evaluated in order to correct the reversible causes, such as electrolyte disturbance or the use of QT interval-prolonging drugs [75].

In spite of different opinions on the relation of cirrhotic cardiomyopathy with the severity of liver disease [63, 68, 69], a consensus exists about its linkage with the hemodynamic changes associated with portal hypertension; the subsequent

hyperdynamic circulation impacts on cardiac load and makes more difficult an accurate evaluation of systolic and diastolic function through the conventional echocardiography [74]. Therefore, since systolic and diastolic functions deeply depend on changes in cardiac load, interpretation of conventional echocardiographic images can be challenging. However, a preoperative conventional echocardiography should be performed routinely to evaluate left and right ventricles and valvular function. The American Association for the Study of Liver Diseases recommends transthoracic echocardiography with Doppler for all liver transplant candidates.

A prevalence of left ventricular hypertrophy was appreciated in 30 % of subjects before liver transplant [76]. An interesting echocardiographic study before and within 6 months after liver transplant showed that the presence of diastolic dysfunction (defined as E/A ratio of ≤1) in pre-liver transplant recipients was associated with an excess risk of heart failure and was able to predict post-liver transplant survival [77]. In pretransplant phase, the presence of heart failure should be monitored and optimization of therapy, using beta-blockers and diuretics (including aldosterone antagonists), should be made. Angiotensin-converting enzyme inhibitors should be used sparingly before transplantation and added gradually after transplantation. Successful liver transplant in patients with ejection fraction as low as 10 % has been obtained after aggressive medical management [78].

Tissue Doppler imaging (TDI) , directly measuring the velocity of myocardial displacement, overcomes the impaired preload and afterload present in cirrhotics with hyperdynamic circulation and is considered the most sensitive and reproducible echocardiographic technique for assessing left ventricular filling dynamics; the tissue velocity, measured at the basal part of the lateral and septal left ventricular wall during early filling (E′), is primarily determined by the relaxation of the left ventricle. TDI velocities have significant correlation with invasive indices of the left ventricular relaxation and the E/E′ index is considered the most important parameter of the left ventricular diastolic function [79, 80]. Exercise tests, reproducing a condition of stress as that induced by liver transplantation, may disclose abnormal cardiac reserve or reveal comorbid conditions.

Dobutamine stress-induced echocardiography , combining the evaluation of function with perfusion, although used especially in excluding patients at risk for perioperative cardiac events, related to obstructive coronary artery disease [81], may be another useful tool to give information about ventricle function in stress condition; however, when utilized to predict the development of adverse cardiac events following liver transplant, it demonstrated to have a low predictive value [81].

Cardiopulmonary exercise testing , by measuring maximal oxygen consumption at peak exercise, while the workload is progressively increased on a cycle ergometer, is the most commonly used method to assess exercise capacity in clinical practice [82]; it is also considered a strong and independent predictor of death from any cause and

accurately identifies patients at high risk of post-liver transplant mortality [82]. Cardiopulmonary exercise testing is an important test that can unmask the presence of a severe cirrhotic cardiomyopathy, since cardiac dysfunction is a potential cause for the persistent alteration of aerobic capacity. Six-minute walk test is considered a good alternative to cardiopulmonary exercise testing; it may assess global functional reserve of a cirrhotic patient [82]. Unfortunately, the inability of cirrhotics to reach the predicted maximal cardiac frequency limits the value of all these exercise testing; chronotropic incompetence, a sign of cirrhotic cardiomyopathy, silent at rest but unmasked by exercise, might be the right explanation, but also the presence of gas exchange abnormalities, beta-blocker treatment, or deconditioning might impede to cirrhotics to reach their predicted maximal heart rate at exercise [82].

Cardiovascular magnetic resonance is recognized to be an important method for assessing cardiac morphology and function, to exclude the presence of cardiomyopathy although costs associated with the procedure are not irrelevant [83]. Due to the lack of radiation and its noninvasive character, cardiovascular magnetic resonance may be repeated more times without contraindications. However, its exact role in detecting the presence of cirrhotic cardiomyopathy has to be determined [84].

ProBNP (a cardiac hormone secreted from the ventricle in response to pressure or volume overload) is evaluated in cirrhotics before liver transplantation and is considered to be useful to describe hemodynamic and cardiac profiles [85, 86]; according to some authors, elevated concentrations of proBNP indicate the presence of hyperdynamic syndrome with cardiac dysfunction [85].

According to some authors, global pre- and post-liver transplant mortality, as well as adverse events immediately after liver transplant, is not significantly different in cirrhotics with or without cardiomyopathy [68].

Liver Transplantation

Cirrhotic cardiomyopathy has recently gained interest because of the success of liver transplantation. The surgical procedure produces significant cardiovascular stress for the patient with cirrhosis since it induces significant changes in preload and afterload, and favors the release of cytokines and vasoactive mediators into the systemic circulation. Liver transplant, as all surgeries, poses stress on the heart due to the hemodynamic and fluid changes seen with anesthesia and hemorrhage. The simple clamping of the hepatic vein, inducing a considerable reduction of the amount of blood that reaches the heart, causes a great impairment of hemodynamic stability [87]. Moreover, liver transplant with the “new” liver causes an increase in the cardiac afterload and preload subsequently leading to cardiac volume and pressure overload. All of these changes may affect the heart unmasking myocardial contractile responsiveness and, thus, reveal the presence of cirrhotic cardiomyopathy.

Pulmonary edema is the most frequent cardiovascular complication within the first few days of liver transplant [88]. Therefore, prompt fluid management and cardiac monitoring are necessary. Transesophageal echocardiography and/or pulmonary artery catheterization are considered to be useful intraoperatively to allow for real-time hemodynamic monitoring and volume management. A number of cirrhotics undergoing liver transplant have an abnormal cardiac response during the surgical procedure after reperfusion without baseline echocardiographic parameters being able to predict it [66]. The presence of an abnormal cardiac response during liver transplant has a clinical relevance since an abnormal heart function during the surgery can complicate the liver transplant surgery and influence the early postoperative period. The pathophysiological mechanism includes a rise of pulmonary wedge capillary pressure above 15 mmHg that causes an inadequate management of increasing volemia. The Frank–Starling mechanism indicates that in a normal heart, an increase in preload induces an increase in the stroke work; however, patients with cirrhotic cardiomyopathy show an abnormal cardiac response characterized by a decrease in stroke work in spite of an increase in pulmonary wedge capillary pressure [66].

A number of studies demonstrated the presence of an abnormal cardiac performance, several minutes after reperfusion that is considered the most cardiovascular stressful moment during liver transplant [66, 87–91]. Interestingly, the only variables able to predict the development of the abnormal heart response were the presence of hyponatremia and hemodynamic data [66, 89–91].

According to some authors a significant decrease of heart rate and an increase of mean arterial pressure occur within the first few days after liver transplant [92], whereas other authors suggest that these changes occur over a period of 2 weeks to 2 months, or even >6 months post-transplantation [93]. A recent study comparing hemodynamic changes in alcohol vs. viral-induced cirrhosis in the immediate postoperative period showed that patients with viral-related cirrhosis had a rapid improvement in systemic hemodynamics, whereas these changes were lacking in the alcohol group [94]. However, the prevalent opinion is of a great accordance on the fact that liver transplantation results in correction of portal hypertension and reversal of hyperdynamic circulation [95–97].

Post-transplant Evaluation of Cirrhotic Cardiomyopathy

It is known that poor preoperative cardiac reserve causes postoperative myocardial depression, poor cardiac output, hypoxemia, and mortality [98, 99]. Therefore, postoperative fluid management is a very crucial and useful option to avoid hypovolemia (due to hemorrhage, third space losses, and ongoing ascite formation) or fluid overload, which can be detrimental to the heart. In the immediate postoperative period, the metabolic derangement (due to acidosis, hypothermia, and electrolyte

disturbance), impairing the cardiac contractility, may result in significant swings in the systemic hemodynamics, as well as the rapid improvement of systemic vasodilation that can cause a sudden increase in the afterload, adding extra stress to the heart. Massive transfusion, as well as postreperfusion syndrome, characterized by a marked decrease in systemic blood pressure following unclamping of the portal vein and liver reperfusion, may also cause hemodynamic depression.

Up to 70 % of patients may undergo cardiac or subclinical complications following liver transplant (pulmonary edema is the most common complication, then followed by overt heart failure, arrhythmia, pulmonary arterial hypertension, pericardial effusion, and cardiac thrombus formation) [71, 100]. According to some authors, none of the pretransplant investigations would be able to accurately predict postoperative cardiac complications [100]. The first study examining cardiac function before and after liver transplant on 30 patients for a mean period of 21 months showed that left ventricular sizes did not significantly change whereas diastolic function deteriorated (it showed a decreased E/A ratio that fell significantly from 1.32 to 1.01) [101]. Subsequently, an interesting prospective randomized study evaluating cardiac function after liver transplant showed severe stresses on the cardiovascular system, hypotension, and bradycardia at the time of graft reperfusion in two patients with cirrhotic cardiomyopathy that subsequently died [102]. It was also observed that left ventricular dysfunction worsened and there was a mild increase in ventricular wall thickness in the first 3 months after liver transplant, whereas BNP levels were high for the first 2 months only [102]. However, the main limit of this study was to restrict the cardiac control in up to 3 months after liver transplant (information was lacking on subsequent months), without any comparison with a control group.

In another study in which BNP levels were evaluated in cirrhotics following liver transplant, these levels were increased from the first postoperative day and returned to normal values after 1 week [103]. The limit of this study was that patients with acute liver failure, retransplantation within 30 days, perioperative major cardiovascular events, or troponin I levels ≥1 ng/ml were excluded [103]. In such a study, echocardiography was always able to reveal diastolic dysfunction on examination of liver transplant recipients that had BNP levels >391 pg/ml, indicating the presence of cirrhotic cardiomyopathy. Another study demonstrated an improvement of electrophysiological abnormalities with a decrease in QT interval time at 3 months after liver transplant [104]. A further study evaluating 15 cirrhotics with echocardiography and stress radionuclide ventriculography before and with echocardiography 6 months after liver transplant showed a significant improvement in wall thickness, in diastolic function, and in systolic response and exercise capacity during stress [38]. It was hypothesized that before liver transplant, the continuous need of maintaining for a long time a high cardiac output with an intense systolic contraction, because of the presence of hyperdynamic circulation, was the cause of cardiac hypertrophy that regressed after

amelioration of mechanical stress and when hyperdynamic state disappeared as occurred after liver transplant [38]. A retrospective study on 86 liver transplant recipients who preoperatively performed both transthoracic echocardiography and right-side heart catheterization showed that systolic heart failure was significantly more likely to develop in patients with preoperative elevated pulmonary artery or right heart pressures [105]. This significant cardiovascular complication was attributed to the underlying cardiomyopathy condition. All survivor and nonsurvivor liver transplant recipients had early myocardial depression, but nonsurvivors preoperatively showed less cardiac reserve and postoperatively a very early drop in cardiac index and oxygen delivery [105]. The authors concluded that patients with preoperative elevated right-sided cardiac pressures, as well as older patients, could have a great risk for developing heart failure after liver transplantation [105]. Unfortunately, all these studies suffer from the evident limit that echocardiographic indices may be difficult to interpret, given the changes in load, following liver transplant; however echocardiographic indices have proven to have the ability to adequately inform on the cardiac function of the patients.

Very interesting was a recent study on infants or children with cirrhosis due to biliary atresia in which significant increases were demonstrated in several echocardiographic parameters such as left ventricle wall thickness (23 % increase), left ventricular mass indexed to body surface area (51 % increase), and left ventricular shortening fraction (8 % increase) in >70 % of this population [106]. According to these authors, abnormal pretransplant echocardiography was able to predict disease severity and clinical status in post-transplant phase [106].

It is known that liver transplant recipients commonly have a severely impaired aerobic capacity; therefore, another limit of the studies on cardiac function after liver transplant is the lack of a precise measure of VO_2 (maximal oxygen consumption) during exercise [79]. Indeed, VO_2 may be influenced by, as well as may influence, cardiac function [79]. In the future, it is desirable that further studies measure VO_2 during an exercise performance after liver transplant. Although apparent conflicting results emerge from the studies on cardiac function after liver transplant, it is common opinion that after initial cardiac problems following liver transplant, there is a recovery of cardiac function and principally of diastolic function (Fig. 35.2b). According to some authors, this recovery might result from a reduction of levels of (yet unidentified) cardiodepressant metabolites, following the recovery of liver graft function [46]. Finally, other clinical trials are needed to better comprehend the complex hemodynamic changes that occur during and following liver transplant.

Conclusions

A significant number of patients with liver cirrhosis (~50 %) have normal resting cardiac function but abnormal cardiac responses after exercise or stress, TIPS, or liver transplantation consistent with the presence of cirrhotic cardiomyopathy [9]. Cirrhotic cardiomyopathy should be sought for in cirrhotics undergoing liver transplant to risk stratify the patient for the worsening of hemodynamics in post-transplant phase. Although overt congestive heart failure is transient in many cases, with the hyperdynamic circulation reversing after liver transplant, heart failure is still among the most common complications of liver transplant leading to prolonged hospital stay and an increase in mortality rate. A correct fluid management and a more close monitoring during liver transplant aimed at avoiding decompensation should be planned, as it may be of help in the management. The prognosis of liver transplant recipients will depend on the control of cirrhotic cardiomyopathy as well as of the other comorbidities. In the absence of evidence specific for cirrhotic cardiomyopathy, the recommendations of the American College of Cardiology/American Heart Association guidelines for the treatment of patients with heart failure should be considered for the management of cirrhotic cardiomyopathy [107], with consideration for special conditions such as markedly reduced systemic vascular resistance, a feature rarely encountered in heart failure.

Special effort should be made in order to guide an evidence-based management of liver transplant recipients. In this way, a precise identification of high-risk patients of cirrhotic cardiomyopathy, using all tools of investigations in pretransplant phase, will help establish the best approach for the management of their hepatic disease, taking into account cardiovascular risks during the liver transplant surgery and in the period following liver transplant.

Further studies will hopefully give information on the molecular pathways involved in the contractile dysfunction of the cardiomyocyte, potentially providing novel and specific therapeutic approaches, and potentially improving the care of patients with cirrhosis, especially during and after liver transplant.

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36. Coagulation Abnormality and Its Management

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Introduction

Liver transplantation (LTx) continues to result in significant transfusion requirements, although less so than in previous decades. Blood transfusion is associated with increased morbidity and mortality, emphasizing the need to further reduce the need for blood product transfusion [1]. The current almost ubiquitous use of the piggyback technique and overall better surgical techniques [2–4], and the recently introduced restrictive use of fluids to avoid increases in central venous pressure [5], have helped to reduce blood loss, but better management of hemostasis should allow a further reduction of transfusion requirements. Not surprisingly, there is significant inter-institutional variability in the need for blood transfusion, with some patients requiring no blood product transfusion at all [6].

Liver disease has for a long time been the prime example of acquired coagulopathy. However, this view is changing rapidly because it is now realized that the consequences of severe liver disease on the coagulation system are more complex than previously thought. There is now growing evidence that the coagulopathy is not as severe as the traditional coagulation tests suggest [7, 8]. Instead, the current view is that there is a

new precarious balance between the pro- and anticoagulant systems [9–11].

Since the traditional coagulation tests give an incomplete picture of the overall coagulability, we will have to adjust our interpretation of these tests. While all LTx centers use intraoperative coagulation monitoring based on traditional coagulation tests, many centers also use viscoelastic tests of clot kinetics since the introduction of thromboelastography into clinical practice by Kang in the early 1980s [12]. The interpretation of these viscoelastic tests allows for a better coagulation management, including a more optimal use of blood products and a more directed pharmacologic intervention such as the use of antifibrinolytics to correct hyperfibrinolysis.

Hypercoagulability is now recognized as a potential problem in patients with severe liver disease. For example, anticoagulants are now considered in an attempt to prevent and/or treat portal vein thrombosis despite prolonged prothrombin time [11, 13–16]. However, hypercoagulability has also been observed during LTx, sometimes resulting in intracardiac thrombosis (ICT) , an uncommon but frequently lethal complication [17]. The viscoelastic tests allow the early detection of hypercoagulability, and therefore guide us in the prevention and/or treatment of ICT during LTx.

Brief Review of Hemostasis

Hemostasis is essential to stop blood loss from a damaged vessel, and consists of vasoconstriction, platelet plug formation, and blood coagulation. The platelet plug formation and blood clot formation are closely tied together, potentiate each other, and occur simultaneously. In other words, this is an intricate interplay between platelets, coagulation factors, and components of the vessel wall [18–20]. Summarized, damage to blood vessel and/or endothelium results not only in the exposure of tissue factor (thromboplastin; expressed by fibroblasts and smooth muscle cells and under pathologic conditions [e.g., endotoxemia] also by endothelial cells and leukocytes), leading to activation of factor VII (factor VIIa; extrinsic pathway), but also in platelet adhesion to the subendothelial tissue by the von Willebrand factor (vWF, produced by endothelial cells, megakaryocytes, and subendothelial connective tissue) that binds to the platelet at the glycoprotein Ib/IX receptors, while there is also direct binding of platelets to subendothelial tissue through binding of glycoprotein Ia/IIa receptors to collagen (Figs. 36.1 and 36.2). Platelet activation follows, resulting in a change in its shape (increase in surface area), the development of pseudopods, the shedding of microparticles expressing tissue factor and procoagulant phospholipids, the increased expression of membrane receptors, and the release of procoagulant factors from alpha granules (fibrinogen, vWF, thrombospondin [a platelet aggregate stabilizer]) and dense granules (ADP, serotonin, calcium) (Fig. 36.2). Thrombin and collagen intensely and massively activate platelets; this results in the further release of thromboxane A_2 (vasoconstrictor as well as platelet activator) functioning as a positive feedback loop in the activation of

platelets. Moderate platelet activators include ADP and thromboxane A_2, while weak platelet activators include epinephrine, PGE_2, serotonin, and ATP [20]. Aggregation of platelets is the result of fibrinogen, fibronectin, vitronectin, and vWF bridges between glycoprotein IIb/IIIa receptors on adjacent activated platelets. In addition, factor XII is activated (intrinsic pathway) by exposure to subendothelial tissue (collagen) especially in the presence of activated platelets through their release of polyphosphate, resulting again in activation of factor X and further production of thrombin (Fig. 36.1). Thrombin not only results in the activation of fibrinogen and platelets but also of factors V and VIII (positive feedback loop). The result is platelet plug formation and the promotion of clot formation (conversion of fibrinogen to fibrin) [11, 18, 20]. Finally factor XIII is activated by thrombin and enhances platelet adhesion to damaged endothelium, stabilizes the formed fibrin clot through cross-links increasing its resistance to lysis, and stimulates tissue granulation and eventually repair.

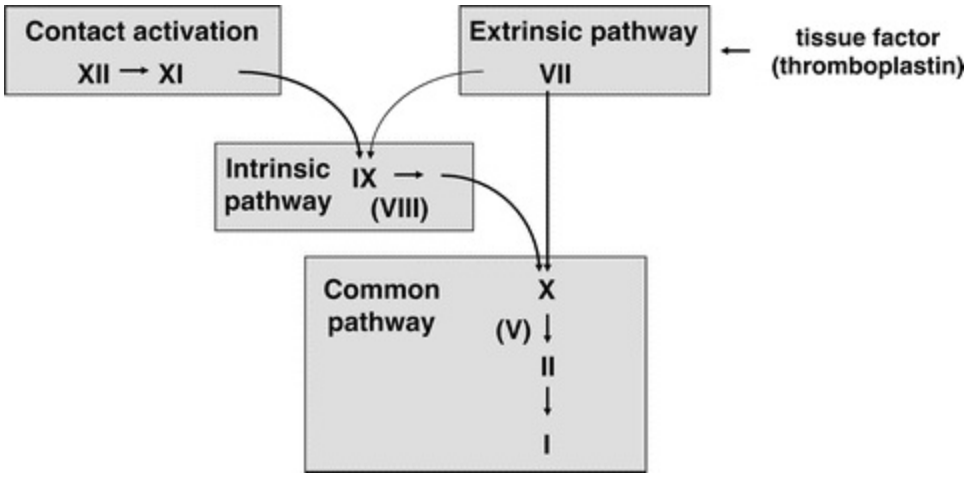


Fig. 36.1 Coagulation pathways . Activation of the extrinsic pathway (through activation of factor VII by tissue factor) and the intrinsic pathway (through contact activation of factor XII) ultimately results in the formation of fibrin (factor I), the building block of the clot. Most steps require the presence of Ca^{++} and platelet phospholipid. See text for details

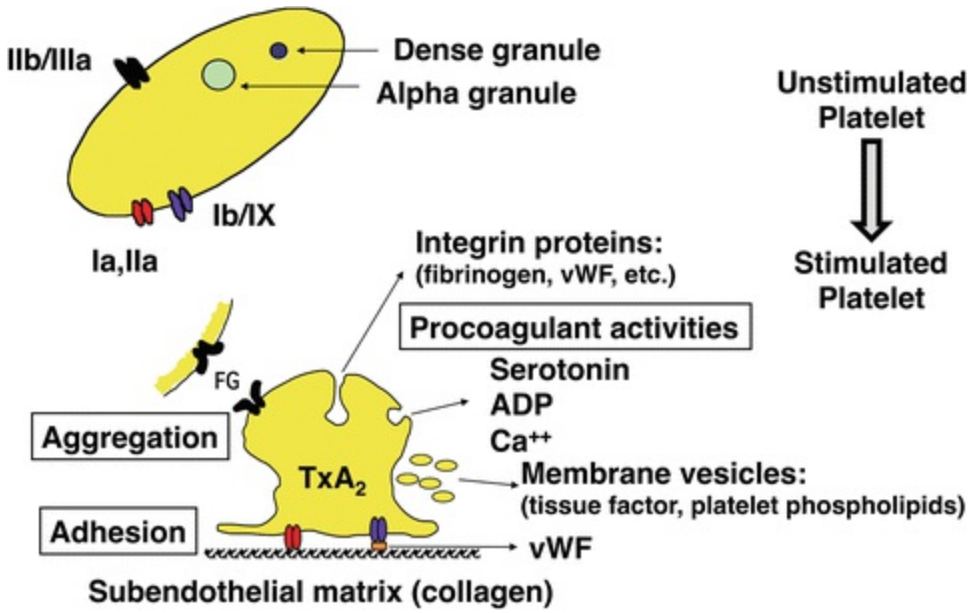


Fig. 36.2 Platelet activation . Platelet activation results in aggregation of platelets and several procoagulant activities. See text for details

The processes described in the previous paragraph are quite complex and are influenced by procoagulant as well as anticoagulant factors while there are also feedback mechanisms with amplifying and inhibiting loops. Although it is clear that clot formation has to be efficient, it is important that these processes are localized and regulated at the same time in order to limit clotting to the site of vessel injury. Indeed, this is essential in order to preserve life because clot formation that goes unchecked would result in massive intravascular clotting. There are several potent mechanisms that normally limit the clot formation to the site of vascular injury, preventing thrombosis in healthy vessels (Fig. 36.3). When thrombin is formed near healthy endothelium, it binds to thrombomodulin expressed on endothelium and thereby activates protein C. With protein S as a cofactor, protein C (both synthesized in the liver and vitamin K dependent) then inactivates factors Va and VIIIa. Protein S has other anticoagulant activities as well [20]. Antithrombin (AT) neutralizes most of the enzymes generated during activation of the clotting cascade, especially thrombin and factors Xa and IXa. The irreversible complex that is formed by the binding of AT and thrombin is thrombin-antithrombin (TAT) and is a sensitive marker of thrombosis. Heparin increases the activity of AT by at least 1000-fold. Heparinoids and heparan (expressed by healthy endothelium) have similar effects as heparin. Prostacyclin and nitric oxide, released by healthy endothelium, inhibit platelet activation, and tissue factor pathway inhibitor (TFPI) , secreted by and expressed by endothelial cells, inhibits factors VIIa and Xa. Finally, plasminogen is activated to plasmin by the release of tissue plasminogen activator (tPA) by healthy endothelium (activated protein C promotes this), and by thrombin, fibrin, and factor XIIa, lysing any fibrin that would have been produced in

healthy vessels. Plasmin not only lyses fibrin but also inactivates factors Va, VIIIa, and XIIa. Thus, normal endothelium prevents clot formation by the expression of heparan (activating AT), thrombomodulin (activating protein C), and TFPI, and by the release of prostacyclin, tPA, and TFPI (Fig. 36.3). ADAMTS13 (a disintegrin-like and metalloproteinase with thrombospondin type-1 motifs), synthetized in hepatic stellate cells, cleaves the very large ("hyperactive") vWF multimers. Deficiency of ADAMTS13 (as a result of severe liver disease or consumption) results in increased platelet activity and various microangiopathies [21]. Disturbances in this complex hemostatic balance can result in hypocoagulation or hypercoagulation.

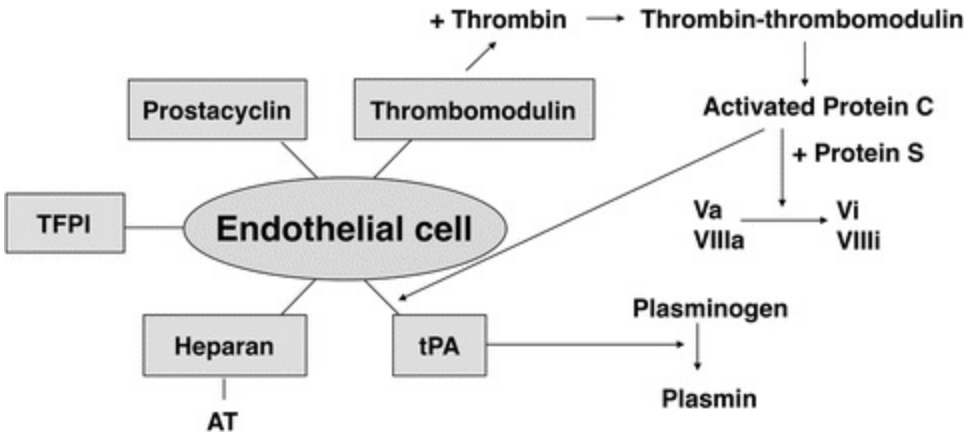


Fig. 36.3 Anticoagulant pathways . The normal endothelial cell plays a crucial role in limiting the clot formation to the site of vessel injury. See text for details. *TFPI* tissue factor pathway inhibitor; *AT* antithrombin; *tPA* tissue plasminogen activator

Fibrinolysis of the formed clot is essential in the eventual restoration of blood flow. This is done through the activation of plasminogen into plasmin, and this process is also controlled by various activators and inhibitors (Fig. 36.4). Activators include tPA, urokinase plasminogen activator, and factor XIIa, and inhibitors include tPA inhibitor (plasminogen activator inhibitor or PAI, released by endothelium), plasmin inhibitor, and thrombin-activatable fibrinolysis inhibitor (TAFI) . Here too, disturbances of this balance may result in hyperfibrinolysis (hemorrhage), or hypofibrinolysis (increased risk of thrombosis).

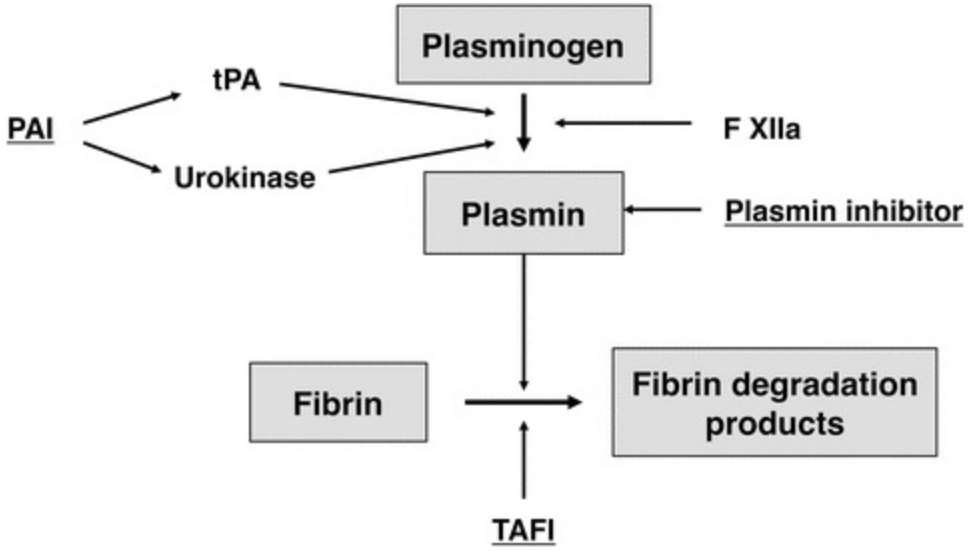


Fig. 36.4 Fibrinolytic system . Activators and inhibitors of the fibrinolytic system. Inhibiting factors are underlined. *PAI* plasminogen activator inhibitor; *tPA* tissue plasminogen activator, *TAFI* thrombin-activatable fibrinolysis inhibitor. See text for details

Coagulation Changes in Chronic Liver Disease (Cirrhosis)

For many years, the impaired synthesis of clotting factors (factors I, II, V, VII, IX, X, XI, XII) by the dysfunctional liver and thrombocytopenia has been considered to result in severe coagulopathy [22]. Vitamin K malabsorption contributes to the coagulopathy through impaired production of factors II, VII, IX, and X. The platelet count is reduced mainly due to splenic sequestration, decreased production (reduced synthesis of thrombopoietin in the liver, hepatitis C infection, folic acid deficiency, and chronic alcohol abuse), and thrombin-mediated platelet consumption [9, 11, 23–25]. There is some evidence of impaired platelet aggregation, reduced adhesiveness, and impaired procoagulant properties of platelets as a result of reduced production of thromboxane A_2 and defective signal transduction [26]. Others however have found no evidence of platelet dysfunction [27, 28]. Reduced concentration of factor XIII is seen in a minority of patients with severe liver disease (21 %), and may contribute to increased bleeding [29]. Also, low factor XIII concentration has been associated with increased mortality [29]. The clinical significance of fibrinogen abnormalities (dysfibrinogenemia) is currently unclear [24].

On the other hand, there are changes that enhance thrombus formation: there is a reduction in the concentration of inhibitors of the coagulation system such as protein C, protein S, AT, and tissue factor pathway inhibitor (TFPI) [9, 11, 30, 31], and elevated levels of factor VIII (produced by endothelial cells in kidney, spleen, lungs, and brain) and vWF [32, 33]. Deficiency of ADAMTS13 as a result of severe liver disease results in increased platelet clumping [21]. ADAMTS13 is present in fresh frozen plasma,

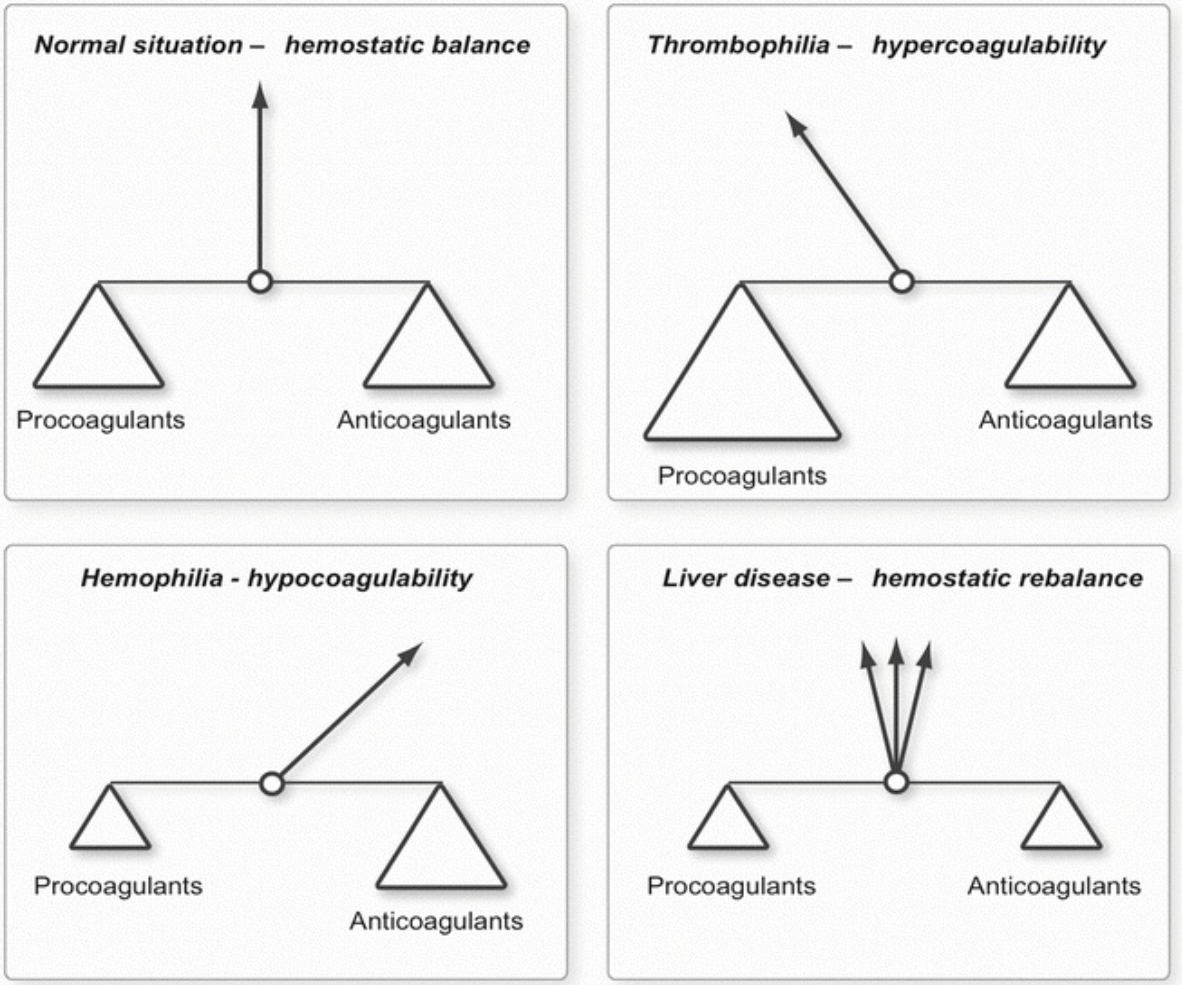
which is the only available source of ADAMTS13. Here too the increased vWF concentration and reduced ADAMTS13 are rebalanced by a reduction in platelet count (and possibly reduction in platelet function); therefore platelet transfusion should only be done based on bleeding complications, NOT on platelet count [34]. There is evidence for adequate thrombin generation in patients with severe liver disease or undergoing LTx, validating the concept of the rebalancing of the pro- and anticoagulant systems [8, 35].

Changes in the fibrinolytic system mimic the changes in the coagulation system. There is a reduction of both pro- and antifibrinolytic factors: there are decreased levels of plasminogen and alpha$_2$-antiplasmin, but increased levels of tPA and its inhibitor PAI [36]. Although tPA is synthesized by endothelial cells, it is metabolized by the liver, resulting in increased concentrations in liver disease [11, 37]. In most patients this results in a new balance, but in a minority of patients there is increased tPA activity. Some feel that a hyperfibrinolytic state in chronic liver disease, at least in part due to a decrease in thrombin activatable fibrinolysis inhibitor (TAFI, synthetized in the liver) concentration, may contribute to bleeding [38]. Bacterial infection plays a role by stimulating the release of tPA, contributing to a hyperfibrinolytic state [39]. The hyperfibrinolytic state can be documented by the presence of D-dimers [40].

Overall, the simultaneous and opposing changes in both the coagulation and fibrinolytic systems in patients with liver disease are now felt to result in a new balance (Fig. 36.5) [31, 41, 42]. This fragile coagulation balance can be tipped into a state of severe hemorrhage or, less frequently, thrombosis. We have all observed that patients with severe liver disease have episodes of hemorrhage, most frequently intestinal hemorrhage mainly caused by portal hypertension. Also, bleeding may be provoked by stressing factors such as infection or renal failure [42, 43]. In addition, endogenous heparinoids may be released from the endothelium in the presence of bacterial endotoxins, and their clearance may be reduced [44]. Similarly, a state of hyperfibrinolysis can be triggered by inflammatory mediators and endotoxins. However, patients with cirrhosis also have a higher incidence of peripheral thrombosis with thromboembolism and portal vein thrombosis despite abnormal PT or INR [24, 42, 45, 46]. Obviously reduced flow in the portal vein contributes to this complication, but under the right circumstances and with the right triggers, some of these patients become truly hypercoagulable; after all these patients have reduced concentrations of the inhibitors of the coagulation system and increased concentrations of vWF and factor VIII. The release of platelet-derived microparticles by endotoxemia or systemic inflammation may be such a trigger and result in a procoagulant effect by expressing phospholipids and tissue factor; this process is associated with systemic complications and adverse outcome in patients with acute liver failure [47–50]. Intracardiac thrombosis (ICT) has been observed during LTx, reflecting a state of hypercoagulability [17]. It is important to recognize that these patients are not “autoanticoagulated,” as

frequently thought in the past [11, 42]. Also, certain types of liver disease are associated with a prothrombotic state. In patients with hepatocellular carcinoma this may be the result of hyperhomocysteinemia [51]. Patients with mild or moderate chronic cholestatic liver disease (primary biliary cirrhosis, primary sclerosing cholangitis) have a mild hypercoagulable state, likely the result of better platelet function (enhanced gpIb/V/IX expression), higher fibrinogen concentrations, and lower degree of hyperfibrinolysis [26, 52].

a



b

Hemostatic changes promoting bleeding	'Rebalance'	Hemostatic changes promoting thrombosis
• Thrombocytopenia platelet function defects • Enhanced production of nitric oxide and prostacyclin	Primary hemostasis	• Elevated levels of VWF • Decreased levels of ADAMTS-13
• Low levels of coagulation factors II, V, VII, IX, X, and XI • Vitamin K deficiency • Dysfibrinogenemia	Secondary hemostasis	• Elevated levels of FVIII • Decreased levels of protein C, protein S, antithrombin, α2-macroglobulin, and heparin cofactor II
• Low levels of α2-antiplasmin, factor XIII, and TAFI • Elevated tPA levels	Fibrinolysis	• Low levels of plasminogen

Fig. 36.5 (**a**) New balance of coagulation in liver disease . Severe liver disease results in a new but more fragile balance of the coagulation system. Relatively small stimuli can result in a state of severe coagulopathy or in hypercoagulability. (**b**) Changes in pro- and anticoagulant factors in liver disease. Concentrations in both pro- and anticoagulant factors are changed, resulting in a new balance of the hemostatic system

Patients with severe liver disease may have, at the same time, grossly abnormal coagulation tests, signs of accelerated intravascular coagulation, and evidence of fibrinolysis [42]. Although tests frequently suggest the presence of disseminated intravascular coagulation (DIC) , clinically evident DIC is rarely seen, and autopsy results indicate that fibrin depositions are uncommon [53]. It is possible that the high concentrations of D-dimers are the result of the formation of fibrin clot that is more susceptible to fibrinolysis, the increased levels or tPA, or the presence of abnormal fibrinogen; once again, endotoxemia may play a significant role [24, 54, 55].

So, the combination of the reduced concentration of coagulation factors, thrombocytopenia, changes that enhance thrombus formation, and the complex changes in the fibrinolytic system results in a new fragile equilibrium (Fig. 36.5). What are the clinical implications of this new understanding? First, there is a poor relationship between the degree of coagulopathy as determined by the traditional laboratory tests and the occurrence of gastrointestinal bleeding or duration of bleeding after liver biopsy [11, 56]. It is now felt that bleeding from esophageal varices is to a large degree related to a mechanical cause (portal hypertension), while coagulopathy does contribute. Also, blood loss during LTx is poorly related to the degree of abnormality of the traditional coagulation tests [57]. In addition, administration of recombinant factor VIIa shortens the PT results but has minimal clinical benefit during LTx [58]. Thus, coagulation management is better guided by the clinical picture and non-conventional coagulation tests than by the traditional coagulation tests.

Changes in Traditional Coagulation Tests in Severe Liver Disease

The *prothrombin time (PT)* tests the extrinsic pathway of the coagulation system: it measures the time for the plasma to clot after addition of tissue factor of different origins. PT depends on factors I, II, V, VII, and X, and is a good indicator of severity of liver disease (especially acute liver disease because the extrinsic pathway is dependent on factor VII that has a short half-life). The international normalized ratio (INR) was meant to standardize the effect of the added tissue factor, but there is still inter-laboratory variability. The reduced synthesis of coagulation factors in severe liver disease is reflected in the prolongation of the PT, which is used as an independent marker of severity of liver disease and as a prognostic indicator. The *activated partial*

thromboplastin time (aPTT) tests the contact activation (intrinsic) pathway; it is initiated by activation of the contact factors of plasma. The aPTT is also prolonged in patients with severe liver disease, but usually not as much as the PT. However, both PT and aPTT are poor predictors of bleeding in these patients because of the presence of compensatory mechanisms [41]. Also, these tests are not very sensitive regarding the effects of reduced concentrations of anticoagulants such as AT, protein C, and protein S, and don't take into account the interactions of the coagulation factors with platelets and the reduced concentration of factor XIII.

Platelet count is reduced in patients with severe liver disease, a result of diminished production in the bone marrow (bone marrow depression and altered thrombopoietin metabolism) and hypersplenism. *Platelet function* has been assessed by several tests in vitro, but their clinical usefulness has been disappointing [59]. *Bleeding time* assesses platelet function in vivo, but is highly influenced by factors such as vascular smooth muscle dysfunction in liver disease as well as by variability among those who perform the test. Thus, prolonged bleeding time is observed in up to 40 % of patients with cirrhosis [60], but its clinical relevance remains unclear [9, 28].

Measurements of *individual coagulation factors* can help in obtaining a more accurate diagnosis, but only the measurement of fibrinogen is of clinical significance to most anesthesiologists. *Fibrin degradation products and D-dimers* are present in both severe liver disease (as a result of a hyperfibrinolytic state and reduced clearance) and disseminated intravascular coagulation (DIC).

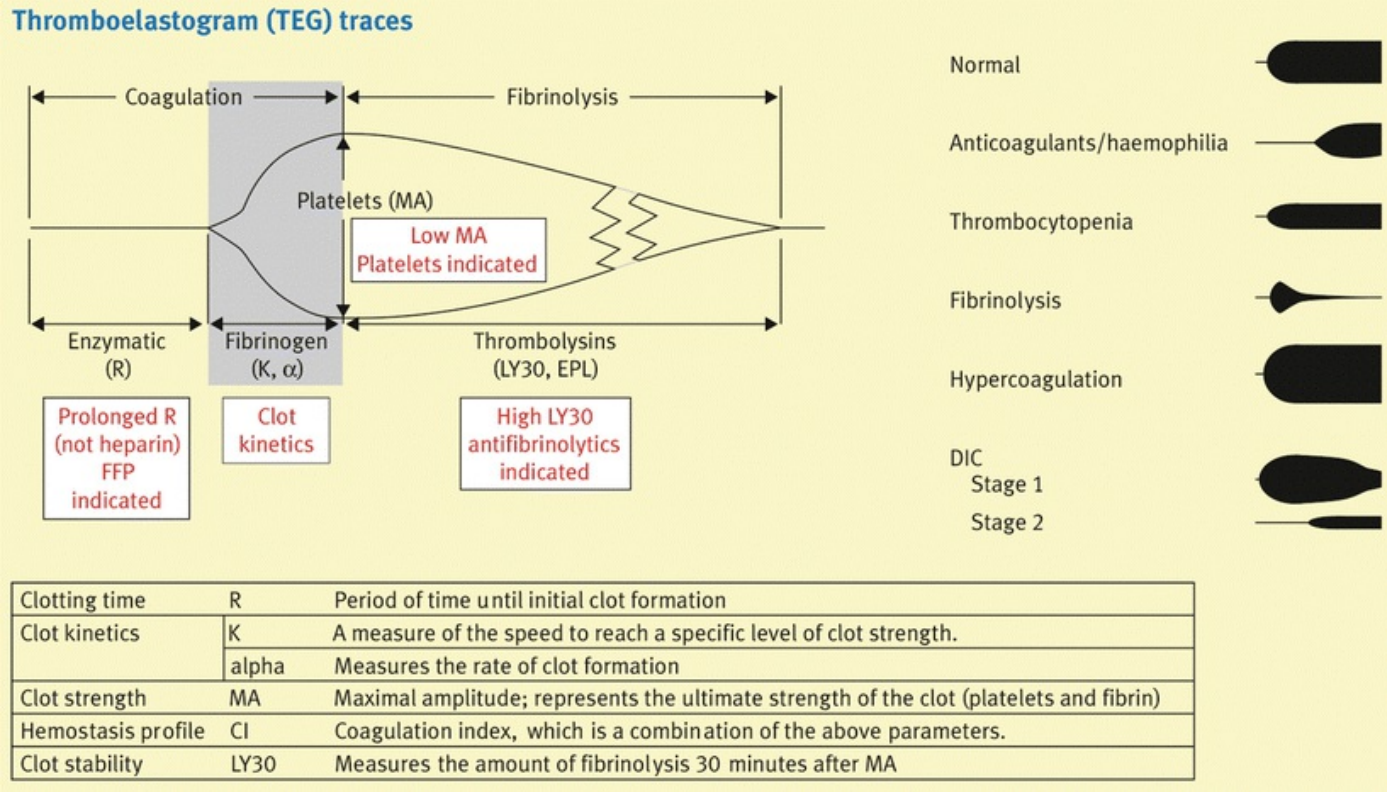
Overall, the conventional coagulation tests (PT, aPTT, INR, platelet count) do not reflect the compensatory mechanisms that play a major role. Therefore, despite abnormal coagulation tests, these patients do not necessarily bleed excessively clinically. Consequently, interventions attempting to normalize these tests may not be required before invasive procedures and during LTx [9].

Monitoring of the Coagulation System During Liver Transplantation

Routine coagulation tests are performed at all transplant centers during LTx, and include at least PT, aPTT, platelet count, and fibrinogen concentration. Many centers use additional tests based on viscoelasticity measurements of clot strength to obtain a better, more complete view of the coagulation system; these tests include thromboelastography (TEG®), thromboelastometry (ROTEM®), and Sonoclot® [61–63]. The main advantage of these viscoelastic tests is that they monitor the coagulation from fibrin formation to clot retraction and fibrinolysis. In addition, these tests are performed on whole blood, allowing the interaction between the plasmatic pathways and platelets, and they can demonstrate the presence of hypercoagulability [64, 65]. TEG® and ROTEM®, and

probably also Sonoclot®, provide valuable information on the fibrinolytic process [66].

TEG® and ROTEM® are clotting tests that determine the overall whole-blood coagulability by analyzing the viscoelasticity of the clot during its formation and dissolution [64, 65]. The TEG® analysis includes the effects of most of the factors that affect clot formation, with the endothelium as the only exception. The TEG® tracing displays the torque on a pin that is dropped in a cup containing whole blood that is oscillated 4° 45′ in either direction every 4.5 s at 37 °C (Fig. 36.6). Without clot, the oscillation of the cup has no effect on the torsion wire, and the result is a straight line on the TEG® tracing. When there is clot formation, the maximum rotation of the torsion wire is recorded as the TEG® outline (thromboelastogram). Derived parameters include reaction time (*r* time; time to 2 mm amplitude, normal range 5–7 min), clotting time (*k* time; time from 2 to 20 mm amplitude, normal range 1.5–3 min), speed of clot propagation (angle, α, normal range 54–67°), maximum amplitude (MA, normal range 55–73 mm), and clot lysis index (amplitude 60 min after MA is achieved divided by MA, expressed in %). MA reflects the strength of the clot, and a gradual, small reduction in amplitude occurs following the development of the MA and reflects clot retraction, the result of fibrin-platelet interaction in which the platelet's actin cytoskeleton plays a major role. Clot retraction should be distinguished from hyperfibrinolysis, the result of premature breakdown of the clot by plasmin [67, 68]. The principles of the ROTEM® technique are similar except for a stationary cup and rotating pin, an optical detector system, and the inclusion of an electronic pipette [64, 65]. However, the terminology to describe the tracings is different. Also, because of the different materials that are used, the reference ranges of the TEG® and ROTEM® tracings are not the same [64, 65].



Clotting time	R	Period of time until initial clot formation
Clot kinetics	K	A measure of the speed to reach a specific level of clot strength.
	alpha	Measures the rate of clot formation
Clot strength	MA	Maximal amplitude; represents the ultimate strength of the clot (platelets and fibrin)
Hemostasis profile	CI	Coagulation index, which is a combination of the above parameters.
Clot stability	LY30	Measures the amount of fibrinolysis 30 minutes after MA

Fig. 36.6 Basics of TEG . Typical thromboelastography tracings for several coagulation abnormalities are presented, and specific therapeutic options for certain TEG abnormalities are suggested

TEG® and ROTEM® allow global assessment of the coagulation system within 20–30 min, including clot initiation (platelet aggregation, platelet-fibrin interaction, fibrin cross-linkage), clot strengthening, clot stability, and eventually clot lysis [69]. Just by looking at the TEG® tracings it can be determined whether the patient has a normal coagulation profile or has hypocoagulability, hypercoagulability, or hyperfibrinolysis. A prolongation of *r* usually indicates inadequate coagulation factor concentration; a decreased α is usually the result of low fibrinogen and to a lesser degree platelet count or function; and a decreased MA mainly reflects inadequate platelet count or function and to a lesser degree low fibrinogen. Hypercoagulability is reflected by short *r* time, increased α angle, and increased MA. Hyperfibrinolysis is seen as the rapid narrowing of the TEG tracing (Fig. 36.6). The interpretation of the TEG® can be improved by the addition of specific agents: hyperfibrinolysis in the blood sample can be blocked by adding a small dose of epsilon-aminocaproic acid, while heparin effect can be eliminated by adding heparinase or protamine; the resulting TEG® tracings can then be compared to the native TEG® tracing, allowing detection of hyperfibrinolysis or heparin effect in the patient. The clotting process can be accelerated by adding activators such as celite or tissue factor, and this allows a faster assessment of the coagulation system. However, the interpretation of the test then has to be based on adjusted normal ranges. Celite acts as a contact surface, activating factor XII, and platelets.

Several studies have investigated the relationships between TEG® parameters and traditional coagulation tests; overall the results have been poor [70, 71]. This is to be expected because of the completely different technologies that are used (tests on plasma or isolated platelets vs. whole blood); for example, PT and PTT tests end when fibrin starts to develop. However, when TEG® analysis is performed on platelet-inhibited whole blood or purified fibrinogen solutions, good relationships are found between clot strength (TEG® variable MA) and fibrinogen concentration [72]. Management of the coagulation system has to be based not just on traditional coagulation tests and viscoelastic tests, but should be driven by the clinical need to intervene. Although TEG® and ROTEM® results do not always correlate well with the impression obtained from the surgical field, TEG® and ROTEM® are particularly helpful in determining how to improve clinical coagulopathy.

The viscoelastic tests have several advantages. These are rapid tests, providing us with a good overview of overall coagulability in 20–30 min. They allow the rapid detection of factor deficiency or inadequate platelet count or function, fibrinolysis, and heparin effect. Another advantage is that TEG® includes the effects of factor XIII on clot formation rate and strength (r, α, MA) while the traditional coagulation tests do not [73]. TEG® also allows us to determine the presence of hypercoagulability that cannot be discovered by traditional coagulation tests [70]. Finally, an increase in clot formation rate (as documented by a shortening of the r time on TEG®) has been observed as a result of reduced AT concentration, supporting the concept of the establishment of a new coagulation balance in patients with severe liver disease [74].

Another viscoelastic test is the Sonoclot® . A hollow, open-ended plastic probe is placed in a cuvette with the blood sample. The probe then oscillates vertically in the sample, and the clotting process is reflected in the gradually increasing impedance to movement [64]. Cuvettes with activators or inhibitors are available. Overall there is less experience with the Sonoclot® than with the other viscoelastic tests during LTx [66, 75, 76].

Intraoperative Changes in Coagulation and Their Management

The main causes of bleeding during LTx include portal hypertension, inadequate surgical hemostasis, hypothermia, dilutional and/or consumption coagulopathy, hyperfibrinolysis, effects of synthetic colloids, and release of heparin-like substances and inflammatory mediators from the graft and other tissues. Clamping of portal vein and inferior vena cava (complete or partial) results in an increase in hydrostatic pressure distally in these vessels, contributing to blood loss. The concentration of platelets and most factors affecting coagulation (including fibrinolytic system and inhibitors) will reduce as a result of dilution and/or consumption. It seems logical that

severity of liver disease influences transfusion requirements, related to more severe portal hypertension and coagulopathy. However, there is conflicting information on this [77, 78]. A lower transfusion requirement was observed in patients undergoing living donation LTx compared to cadaveric donation LTx, although many factors besides MELD score and degree of coagulopathy could be responsible for this, such as better quality of the graft [79].

Proper coagulation monitoring is essential to manage the coagulation system perioperatively. Certain coagulation problems are associated with the stage of the LTx procedure. For example, surgical bleeding is more common in stages I and II, while hyperfibrinolysis is seen especially towards the end of stage II and early stage III. The most important blood products that are used to correct coagulopathy during LTx include platelets, fresh frozen plasma, and cryoprecipitate. There is limited experience with other blood products such as prothrombin complex and fibrinogen concentrates [80].

Immediate Preoperative Management and Stage I (Dissection)

Because the bleeding risk is not nearly as bad as suggested by the traditional coagulation tests, it is not recommended to attempt to correct abnormal traditional coagulation tests immediately preoperatively or at the beginning of the LTx procedure. To the contrary, the routine administration of fresh frozen plasma, cryoprecipitate, or platelets at that time is expected to increase central venous and portal venous pressure, resulting in increased bleeding caused by increased hydrostatic pressure in the transected vessels [57, 78, 81]. Rather, a low CVP management is chosen by some, necessitating the use of vasoconstrictors to maintain systemic blood pressure [82]. Most anesthesiologists, myself included, however prefer to maintain normovolemia in order to maintain hemodynamic stability, thereby reducing the risk of renal impairment by maintaining its perfusion [83, 84]. Gradual correction of the coagulopathy should be started when intraoperative bleeding occurs and should be guided by coagulation monitoring. If bleeding occurs without evidence of oozing, i.e., surgical bleeding, an argument can be made for the administration of FFP in equivalent amounts to the administration of red blood cells to restore normovolemia and to maintain the fragile, new coagulation balance. Fresh frozen plasma contains not only coagulation factors but also inhibitors of the coagulation system (protein C, protein S, AT, TFPI). Platelet and cryoprecipitate administration are infrequently necessary at this stage, although their administration should be guided by platelet count, TEG/ROTEM, and observation of the surgical field. There is limited experience with prothrombin complex concentrate in liver transplantation [80]. This purified concentrate contains not just factors II, VII, IX, and X, but also protein C, protein S, and AT. Although the administration of prothrombin complex concentrate can normalize PT in patients with liver disease, its efficacy and safety during LTx have not yet been established [80]. Its main potential advantage would

be its low volume.

Management of Hyperfibrinolysis

Hyperfibrinolysis is usually seen towards the end of stage II and early stage III and is the direct result of increased concentrations of tPA in the presence of decreased concentrations of its inhibitors. tPA is released by the graft and mesenteric vessels on reperfusion, possibly related to ischemic damage of the endothelial cells [40, 85]. Although some centers routinely use prophylactic antifibrinolytics during LTx, others only administer antifibrinolytics when fibrinolysis is clearly present on TEG and there is evidence of significant oozing in the surgical field [86, 87]. Small doses are usually sufficient (e.g., ε-aminocaproic acid 250–500 μg) but mild fibrinolysis in the absence of clinical bleeding does not require pharmacological intervention because it is usually self-limiting. The prophylactic use of antifibrinolytic agents has resulted in reduced transfusion requirements; most experience has been obtained with aprotinin, but since its withdrawal from the market in 2007 (due to renal toxicity and increased incidence of myocardial infarction), there is less interest in this practice. There seems to be a shift away from prophylactic use of antifibrinolytics towards a practice of administration of antifibrinolytic agents when fibrinolysis is clearly documented by TEG/ROTEM and when there is evidence of oozing in the field [88].

Management of Heparin Effect

Heparin effect may be seen after graft reperfusion and is usually caused by the release of heparin that was part of the preservation solution [89]. If it is felt to result in clinical oozing, it can be antagonized with a small dose of protamine (25–50 mg or 1 mg/kg) [90].

Use of Factor VIIa

Although VIIa administration improves PT and INR, there is no evidence that it results in a reduction in transfusion requirements; however it could be of value as a rescue therapy in uncontrollable bleeding [58, 91].

Management of Hypercoagulability and Intracardiac Thrombosis (ICT)

Massive intracardiac thrombosis (ICT) has been documented during LTx, initially early after graft reperfusion, but later during all stages [17, 92, 93]. Remarkably this complication in the form of pulmonary thromboembolism during LTx associated with a hypercoagulable TEG had already been described by von Kaulla in 1966, although it is

not clear whether this was truly ICT [94]. The estimated incidence is about 1–4 %, and the mortality is likely about 50 % [17, 93, 95]. ICT has to be differentiated from peripheral venous thrombosis with embolism to the heart: monitoring with transesophageal echocardiography has made it clear that during the development of ICT there is de novo clot formation in the heart, usually attached to the valves and pulmonary artery catheter (Fig. 36.7), but in extreme cases clots can be observed attached to the mitral or aortic valve, clearly not a result of embolization [17, 95]. Although the initial report on ICT described its occurrence immediately after graft reperfusion, it is now clear that ICT can happen unexpectedly at any time during LTx [17, 95, 96]. Sometimes the ICT spontaneously disappears, probably the result of secondary fibrinolysis [97].

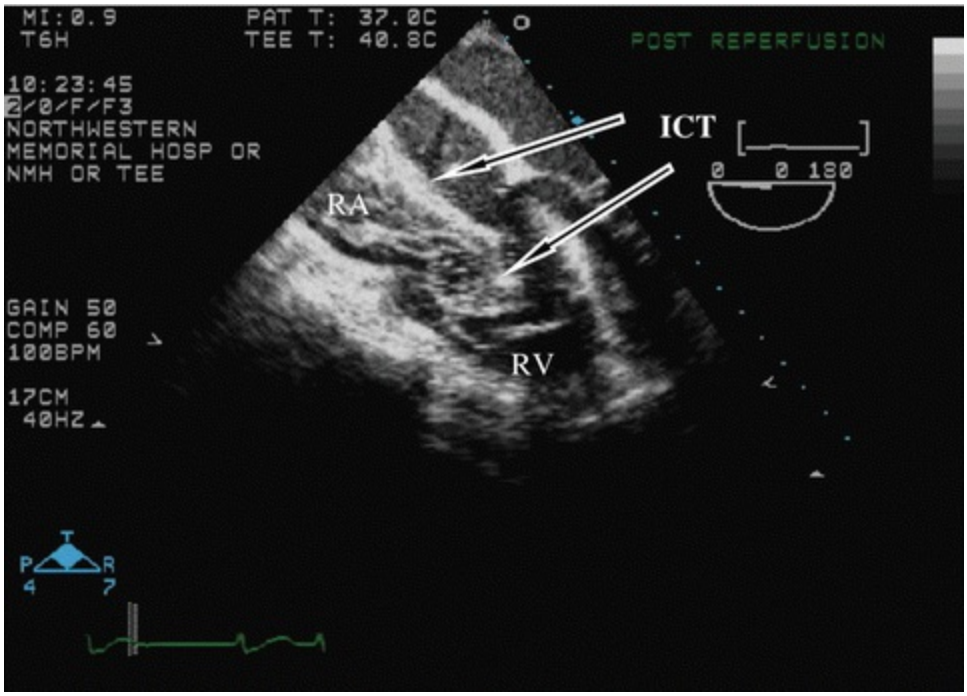


Fig. 36.7 TEE of intracardiac thrombosis (ICT) . Transesophageal echocardiography (four-chamber view) in a patient with ICT. Clots can be observed in the right atrium (RA) and right ventricle (RV). Note the leftward shift of the interatrial and interventricular septa (from Boone et al. [92], with permission)

It has been discussed already that in general clot formation in patients with severe liver disease is better than suggested by traditional coagulation tests (reduced concentrations of protein C, protein S, and AT, and increased concentrations of vWF and factor VIII). However, some patients become overtly hypercoagulable in the presence of the right triggers especially because of the fragile balance of the coagulation system. Extensive surgery may release an overwhelming amount of tissue factor, with the diseased or absent liver unable to clear tissue factor or other activated coagulation factors. Release of endotoxins, possibly related to an ischemic insult to the intestines during portal vein clamping, and release of activators from leukocytes may further activate the coagulation system [98]. It is known that endotoxemia and severe systemic

inflammation cause the expression of tissue factor on circulating monocytes, microparticles, and endothelial cells in the microvascular system, resulting in widespread activation of the coagulation system [20]. Despite some case reports linking the use of antifibrinolytics to ICT, there is no convincing evidence that their use increases the risk of ICT [95, 99].

A hypercoagulable TEG tracing (very short reaction time, wide maximum amplitude), clotting of the TEG blood sample before it could be analyzed, and even clotting of a heparinized blood sample (indicating very low AT concentrations) have all been observed in several of these patients [17, 93]. However, ICT has been observed in the absence of hypercoagulability on TEG, probably because the patient can suddenly and at any time become hypercoagulable [100]. A flat-line TEG is, in my opinion, likely the result of hypercoagulability followed by severe secondary fibrinolysis [93, 101]. Early and correct diagnosis of ICT depends on routine transesophageal echocardiography and pulmonary artery pressure monitoring [92]. Early diagnosis allows immediate intervention with low-dose tPA (2–4 mg) that may be effective because it is administered very early in the clotting process before solidification of the clots [92]. Usually a small dose of heparin is administered as well. The potential for rapid lysis of intracardiac clots is supported by a case report where the ICT was not present anymore during autopsy [102]. Higher dose tPA may be successful also but may be associated with more significant blood loss [103–105]. Supportive therapy consists of the administration of routine resuscitation drugs, including epinephrine, and cardiac compression [17, 93]. Thrombectomy has been tried, although it is frequently but not always futile [17, 96, 105]. In my opinion, prevention may include the use of low-dose heparin (3000–5000 U) in combination with FFP administration before clamping of the major vessels or whenever hypercoagulability is observed on TEG. Hypercoagulability has also been observed in other critically ill patients such as during ARDS, multiple organ failure, and severe tissue trauma, and is associated with increased tissue factor concentrations [70, 106].

Management of Coagulopathy in Acute Liver Failure

Overall, the coagulation changes seen in patients with acute liver failure are similar to those seen in cirrhosis, with a proportional reduction (re-balancing) of procoagulant and anticoagulant proteins (Fig. 36.8) [107–109]. As a result, recent studies suggest that hemostasis in most of those patients is well preserved, despite abnormal traditional coagulation tests [108, 110, 111]. One exception is the reduced fibrinolytic potential in acute liver failure, the result of increased levels of PAI [108]. However, because PT and other conventional coagulation tests suggest significant coagulopathy, invasive procedures are frequently preceded by the administration of fresh frozen plasma and platelets. While these transfusions may not be needed at all, it may actually worsen

intracranial hypertension as a result of an increase in central venous pressure. Some therefore prefer recombinant factor VIIa, although it remains unclear whether this reduces the risk of bleeding [112]. Nevertheless, it is understandable that correction of coagulopathy is attempted before doing a high-risk procedure (placement of intracranial pressure monitor) because of the devastating consequences of intracranial bleeding [28].

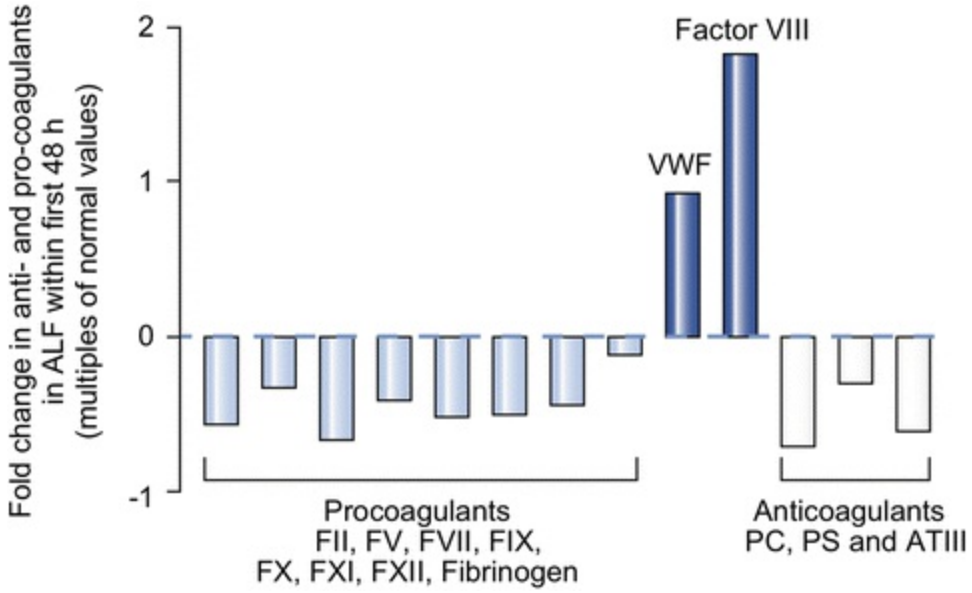


Fig. 36.8 Changes in concentration of pro- and anticoagulants in acute liver failure. Both procoagulants and anticoagulants are reduced to a similar extent, while vWF and factor VIII are elevated, resulting in a re-balancing of the coagulation system

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37. Simulation: In Anesthesia for Liver Transplantation

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Keywords Anesthesia management – Liver transplantation – End-stage liver disease – Simulation – Critical thinking – Problem solving – Debriefing

Abbreviations

ALT Anesthesia for liver transplantation

ESLD End-stage liver disease

LTx Liver transplantation

OR Operating room

TEG Thromboelastogram

Introduction

Simulation is an effective teaching method for medical students, nurses, and residents [1, 2]. Anesthesiologists have been in the forefront of simulation training as an adjunct to clinical or classroom teaching. Anesthesia for Liver Transplantation (ALT) is a subspecialty course designed to prepare trainees who have a basic knowledge of anesthesia to manage patients who have end-stage liver disease and are undergoing liver transplantation (LTx).

The simulated environment offers many opportunities to learners that extend beyond traditional lectures, tutorials, and problem-based learning discussions (PBLD) [3]. It has the potential to provide learners with an opportunity to take on new roles, to learn by doing, to take risks, and to solve problems; it permits time and autonomy to make decisions without the pressure of accountability. It is as close as one can get to the real work place but with learning as the primary goal; because there is no actual patient placed at risk, the goal of patient outcome is addressed indirectly when learned lessons are later applied in clinical practice. In simulation the interaction is only between the educator and the learner therefore the education can be focused without distractions from other involved parties.

Making use of the full potential of simulation requires the planning of curriculum, execution of teaching sessions and scenarios, and the follow up to implementation in clinical practice [4]. In planning a curriculum there should be a basic outline that can be customized for the capability of the learner because not all learners have similar skills. The educator has to have a clear understanding of his role to direct the learner.

Role of Educators

The educator should: (1) Create learning objectives; (2) Provide reading material for medical knowledge; (3) Provide an opportunity for preoperative assessment; (4) Transform learning objectives into clinical scenarios; (5) Prepare the clinical scenarios; (6) Create an appropriate learning environment; (7) Tailor general learning outcomes to the needs of the individual learner; (8) Help the learner reflect on the experience of the clinical scenario; (9) Provide appropriate feedback; (10) Review the session to consolidate learning.

Role of Learner

The learner should: (1) be self-motivated; (2) come prepared for the simulation; (3) have a working knowledge of basic anesthesia skills (should be in clinical anesthesia year 3, 4, or advanced training).

Why Simulation Education in Liver Transplantation

Anesthesiology?

Because the number of liver transplant centers has increased more than the supply of suitable organs, fewer transplants are performed per center. Simulation is a good way to strengthen the experience of practitioners who will be faced with caring for transplant patients. It may also be helpful in the credentialing of team members [5].

Simulation has the potential to standardize the learning experience. In real life, the issues for anesthesia are imposed by the patient's condition and vary from patient to patient providing an inconsistent learning environment over which we have little control. Years of practice and countless patient encounters may be needed before the clinician experiences the set of challenges that can be presented in simulation scenarios. In a simulated environment it is the educator who determines the complexity of scenario and thus the learning experience can be predetermined and consistent.

Simulation prepares learners to prevent crisis rather than to just react to events that have already occurred. Learners should be aware of resources and anticipate predictable events. For example, a patient with significant bleeding can be managed without too much difficulty if there is clear communication with the surgeon and blood bank, the blood products are available and the vascular access and equipment to rapidly transfuse blood have been prepared. Requisite skills include the ability to recognize the situation, predict its evolution and engaged or recruit assistance to solve the problem.

Simulation helps to build Confidence. Once the learners have gone through the simulation course of ALT, they can be emotionally better prepared for the real-life liver transplantation (LTx) experience; as a result they are less anxious when they are performing their first LTx and therefore may make better medical choices.

Simulation helps to prevent fixation errors. Persistent fixation on a problem that the learner understands poorly and failure to revise diagnoses are common problems [6]. In some cases secondary issues receive more attention than the primary problem (treating hypotension rather than hypovolemia).

Simulation teaches learners to use all sources of information and cross check so that potential for inaccurate, incomplete, and erroneous information be minimized.

Learning Objectives

By the end of the session the trainee should be able to:

1. Obtain a thorough preoperative history and physical examination for patient with end-stage liver disease undergoing LTx. Learners should be able to understand the special medical issues and be able to coordinate different specialties to maximally optimize the condition of the patient for surgery.

2. Understand the urgency of the use of blood and various blood products and be able to administer them as need arises. Learners should be able to set up as well as trouble shoot various devices to administer fluid rapidly and safely into the patient.

3. Understand the importance of intraoperative invasive monitoring including the insertion of arterial lines, central lines, and pulmonary artery catheters.

4. Recognize coagulation changes and their management with blood products and pharmacological intervention using thromboelastography as a guide.

5. Understand the use of veno-veno bypass, and alternate techniques when bypass is not used.

6. Manage acid base and electrolyte abnormalities.

7. Recognize and assess Post reperfusion injury.

8. Communicate effectively with the transplant surgical team concerning issues that arise during surgery. Learners must communicate effectively with other individuals involved in the anesthetic care of the patient including blood bank, laboratory, and other technical support [5].

Reading Material for Medical Knowledge

In the Pre-Simulation Session the trainee is provided with reference material. Advance preparation is one of the keys for a successful simulation course, especially if the learner has not been previously exposed to liver transplantation anesthesia. Prior to any simulation session background medical knowledge is essential. Back ground knowledge can be augmented by providing reading material on a web-based format that participants read at their own pace (Fig. 37.1) and reviewing and discussing a multiple choice questionnaire. After reading the material participants should understand the pathophysiological changes of end-stage liver diseases and how these changes will influence the anesthetic management during liver transplantation. The unique hemodynamic, metabolic, and coagulation profile of each stage (pre-anhepatic, anhepatic, and neohepatic) should be emphasized. After pre-course preparation, the quiz can be taken at the start of the learning session and can be used to assess knowledge and understanding of the concepts presented in the pre-course material. Debriefing the

answers of each question can serve as a platform for more in-depth discussion. This process of thinking and talking is helpful to confirm and build understanding of the medical knowledge, as well as to correct any misunderstandings which have been revealed. This should take place in a small group and in a friendly environment. Brief power-point presentations on special topics (for example acute liver failure, porto-pulmonary hypertension, hepato-pulmonary syndrome) can assist the learners in achieving a higher level of knowledge.

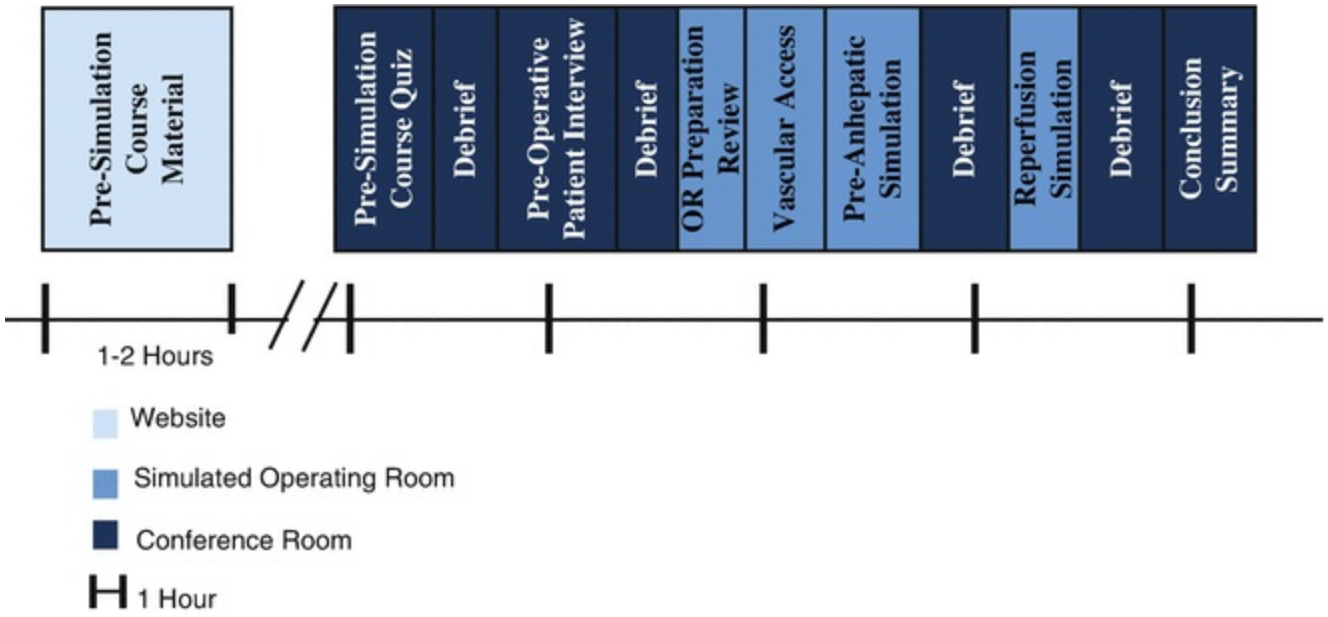


Fig. 37.1 Simulation course timeline . Timeline showing simulation course components. Physical resources are color-coded. Pre-class material is viewed on the website which occurs before the day that the simulation takes place, as indicated by the interrupted timeline. The simulator course requires the use of a conference room and a simulated operating room

Interviewing End-Stage Liver Disease Patient

It is important for the anesthesiologist to be a part of the team assessing ESLD patients for liver transplantation. Therefore, a mock preoperative interview of a potential candidate for liver transplantation, impersonated by one of the instructors gives the opportunity to focus on the history and physical condition of the patient and how to optimize the condition of the patient prior to surgery [7]. In addition it also permits the learners to deal with delicate social issues such as Hepatitis C, HIV, and the special requirements of Jehovah's Witness patients. This session takes about 20–45 min. The learner is given the stem patient, for example: 52 year old male with ESLD due to Alcoholism for OLTX. Debriefing after the preoperative interview is helpful in emphasizing unique points pertinent to this patient population [5, 8].

Setting Up the Environment of the Operating Room

At this point the participants should be able to test their abilities with the high-fidelity simulated clinical scenarios [9]. It is very important to create an environment that is as close as possible to the operating room (Fig. 37.2, Table 37.1.) Props provide a sense of place and tools to perform the expected action. The goal is to provide enough stimuli and generate enough data to engage the learner and thus promote the interactions needed to achieve the learning objectives. The checklist for the room set-up should be provided in the pre-course material, this way the participant can anticipate how the simulated operating room will look. Creating a sense of familiarity decreases the level of anxiety during the clinical scenarios while encouraging engagement. It might not be feasible to provide a working trans-esophageal echocardiography machine (TEE), thromboelastography (TEG), or rapid infusion system due to cost, but having similar looking equipment and projecting the virtual data on a screen is cost effective and a reasonable facsimile to the OR experience of LTx (Fig. 37.3). Blood products can be made available in the form of bags filled with red colored liquid for packed red cells and yellow colored liquid for fresh frozen plasma. The bags should be labeled with identification numbers and blood group, placed in a cooler and made available upon request. Details, such as presence of a phone to make simulated phone calls to the blood bank, laboratory and attending for advice should not be overlooked. One of the instructors plays the role of the surgeon and use this opportunity to interact with the participants during the clinical scenario, helping to provide clues to the differential diagnosis: “I have drained six liter of ascites” or “this liver is old, long cold ischemia time” or creating some tension: “liver is congested I cannot manipulate it, do something about it.” All these statements are meant to help participants integrate the input from the surgical team and assess how well they can communicate. The presence of an anesthesia technician will help to assess how well the participants can use the resources at hand.

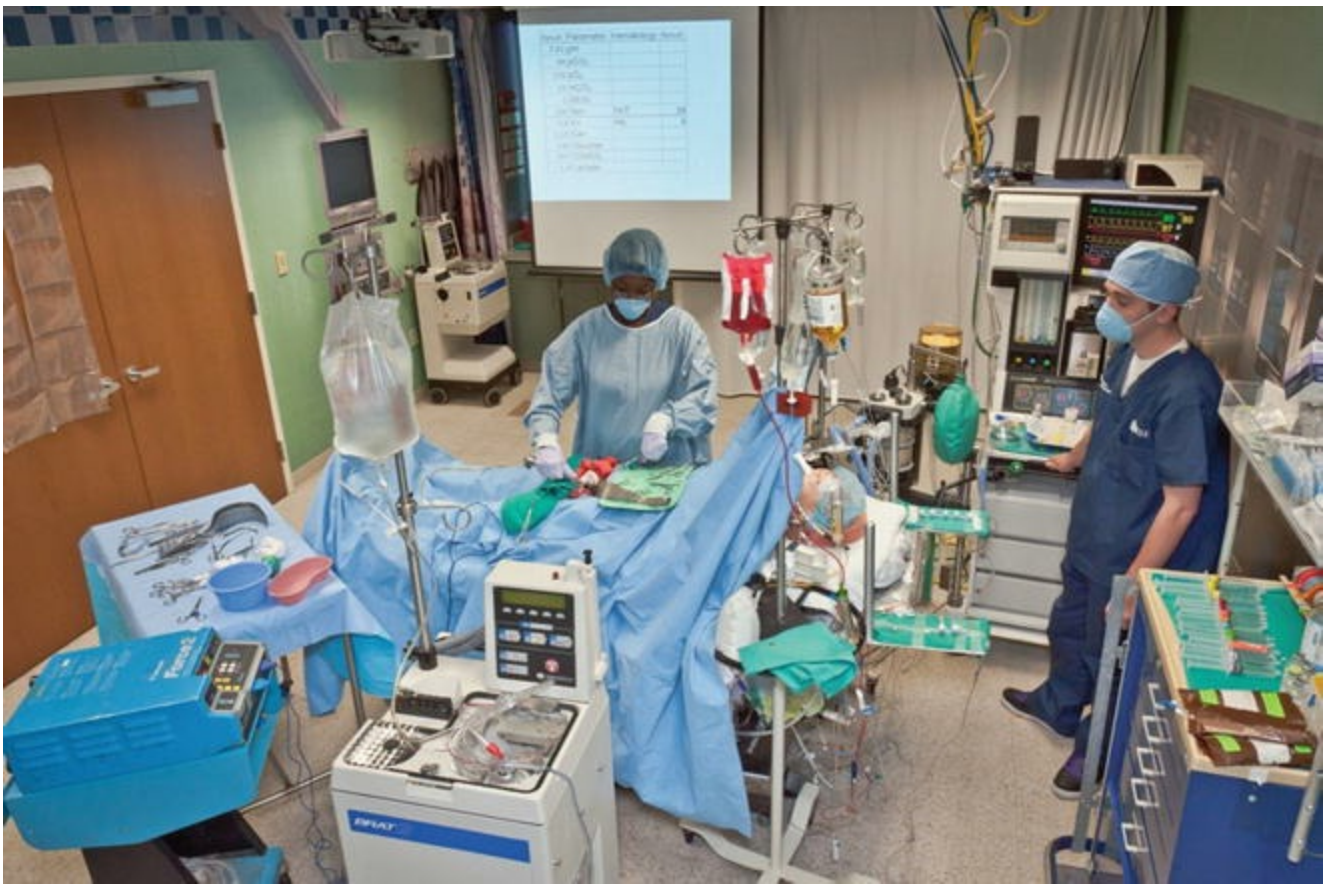


Fig. 37.2 Simulated operating room for liver transplantation

Table 37.1 Props present in the simulated operating room

Simulated environment	
Equipment	High-fidelity simulation mannequin
	Anesthesia cart with common OR set-up and medication
	Anesthesia machine
	High-fidelity monitor (EKG, blood pressure, CVP, pulmonary pressure, SpO2, ETCO2, temperature) Fig. 37.2
	Rapid Infusion System
	Transesophageal echocardiography probe/machine
Projector screen for additional data	SvO_2 and cardiac output
	Arterial blood gas results
	TEE video-loops
	TEG images
Additional material	Telephone
	Blood products
Personnel	Surgeon
	Anesthesia technician

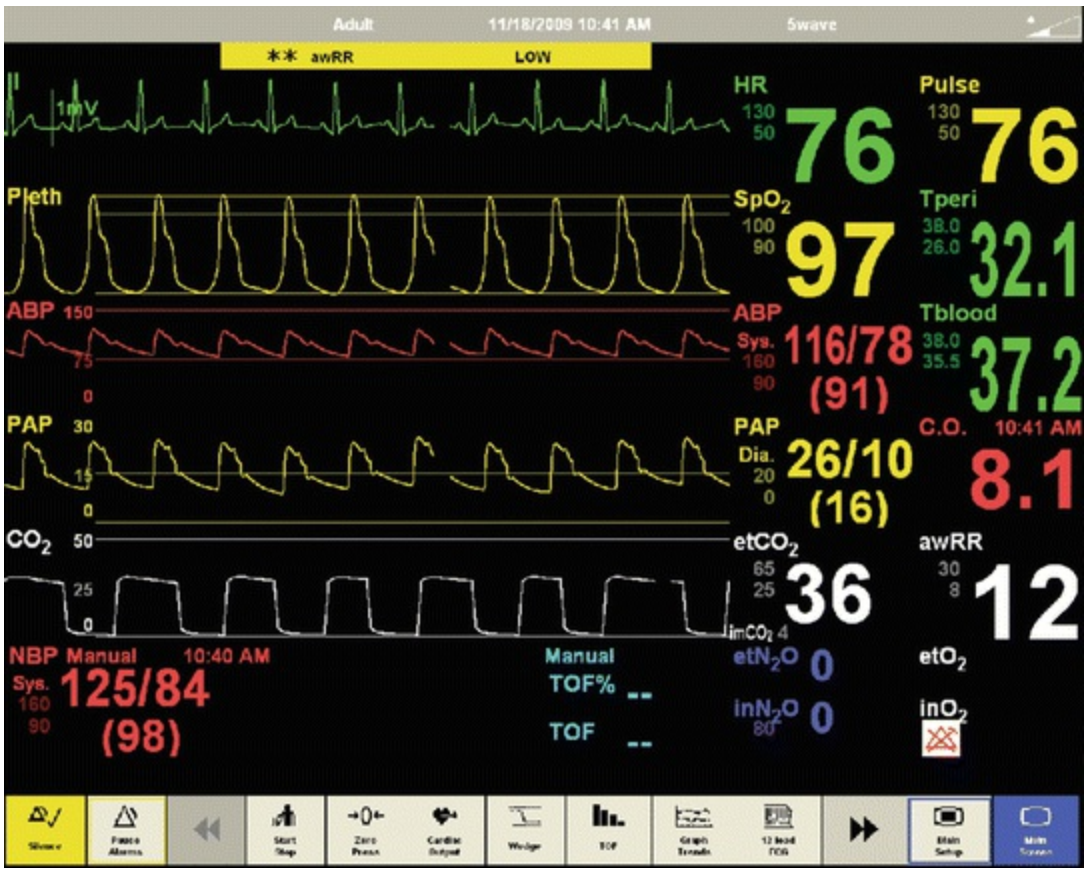


Fig. 37.3 Anesthesia machine monitor display for the high-fidelity simulation of a liver transplant patient

The environment created should be such that learners are challenged in their thinking and action but never intimidated. The teacher should raise relevant topics and the learners should reflect on those topics. In the beginning of the course the learners can be reassured that perfection is not the expectation of this course but that this is an environment for learning by interaction.

Central Venous Line Placement

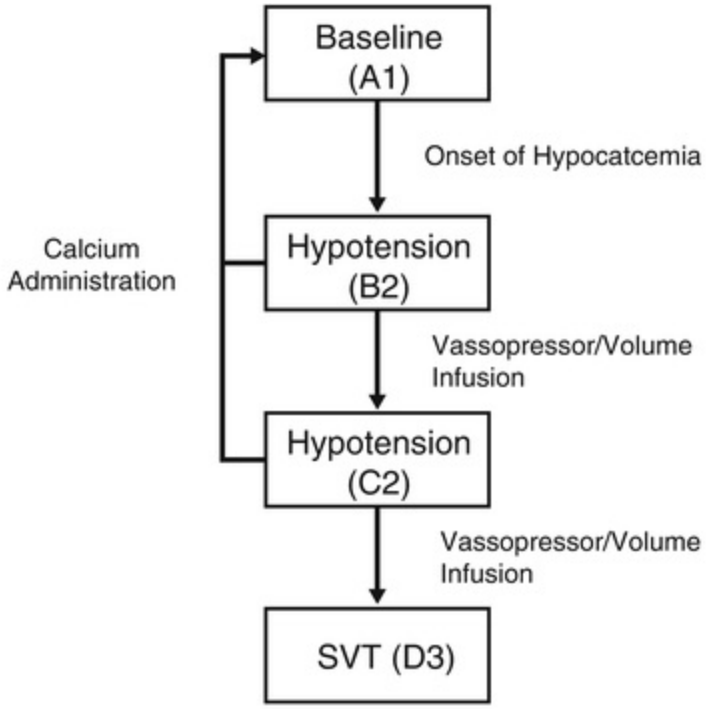
By the time most participants are assigned for a liver transplant anesthesia rotation they are in the 3rd or 4th year of anesthesia residency and should be experienced in placing central venous lines. The goal of central venous line placement simulation is to understand the necessary vascular access, the options and risks associated with each line and special risks in ESLD patients who are often coagulopathic. The placement of a veno-venous bypass cannula (# 18 Fr) is unique to liver transplant anesthesia and malposition is disastrous [10, 11]. Emphasis is placed on how to set up the procedure tray, patient preparation, identification of landmarks, insertion and confirmation of the guide wire location, dilation of the tissue path and finally confirmation of placement. Other topics include: how to avoid air embolism, detection of inadvertent

malplacement, and the procedures to initiate and terminate veno-venous bypass.

Simulation Session

The clinical scenarios are held with high-fidelity mannequin-based simulation. The goal of the clinical scenario is to engage the learner in the scenario so that they will have the experience of recognizing problems, identifying available resources, and making decisions. Advanced learners become bored if presented with overly simple problems that fail to challenge their skill sets. The scenario must reflect clinical events that would move the learner toward the final goals of understanding the events of liver transplantation and being able to anticipate responses to their actions. For example, during the pre-anhepatic stage of liver transplantation hypotension is common and the etiology invariably is hypovolemia or hypocalcemia. Creating a scenario of simple hypovolemia will be easily recognized and corrected, however it may lead to a discussion of atypical causes of hypotension. Ultimately, through the simulated clinical scenarios the participants should have the opportunity to make a differential diagnosis and take action based on data presented or that they should have known to request. They should also be able to judge the effectiveness of their intervention and change the intervention accordingly. If the initial problem is properly managed, the scenario moves to a second problem; however, if the participant fails to identify and address the initial problem the patient will spiral down and not survive. Thus the scenario could be terminated after covering one or two challenging medical issues, depending on the participants' performance. Either way, the learning objective would be accomplished and reinforced during the debriefing session following the scenario.

For example, one of the scenarios may be set during the pre-anhepatic stage [5]. As mentioned above, hypotension is a common problem encountered at this time. Initially hypotension is secondary to hypovolemia after the surgeon announces that he is draining 6 l of ascites. If appropriate action is taken for fluid resuscitation, the hypotension resolves briefly but later persistent hypotension secondary to hypocalcemia occurs. The hemodynamic profile is similar to fluid overload and failure to suspect hypocalemia may lead to inappropriate interventions. Unless an arterial blood gas is requested and the actual problem is identified there is more hemodynamic instability. Administration of calcium solves the problem; failure to identify the issue leads to a poor outcome and. the scenarios is terminated (Fig. 37.4).



Hemodynamic Parameters

	HR	CO	BP	PA	CVP	SvO2	EICO
A	78	8	110/70	25/10	10	100	34
B	90	5	85/50	35/20	15	100	34
C	130	6	94/60	35/20	15	100	34
D	150	2	50/20	50/20	30	60	25

Arterial Blood Gas Values

	pH	PaCO	PaO	HCO	BE	Na	K	Ca	Osmol	Lactate
1	7.41	34	176	22	-2	138	3.8	1.02	297	1.8
2	7.4	34	176	22	-2	138	3.8	0.86	297	1.8
3	7.28	34	140	20	-7	138	3.8	0.7	297	3

Fig. 37.4 Preanhepatic stage , clinical scenario. Flowchart showing the progression through the pre-anhepatic phase hypocalcemia scenario. The letter in each box of the flowchart corresponds to the hemodynamic parameters at that stage of the scenario, while the number refers to the arterial blood gas (ABG) values shown in the tables. Arrows indicate flow through the scenario starting with baseline hemodynamics and ABG values (A1). With the onset of hypocalcemia the monitor displays hypotension with a corresponding ABG that has low ionized calcium (B2). At any point if the resident administers calcium chloride then the hemodynamics and ABG return to baseline values. If vasopressors or fluids are inappropriately administered then the scenario progresses with worsening hemodynamics (C2) eventually progressing to supraventricular tachycardia (SVT) and evidence of tissue hypoperfusion (D3). *HR* heart rate, *CO* cardiac output, *BP* arterial blood pressure, *PA* pulmonary artery pressure, *CVP* central venous pressure, *SvO2* mixed venous oxygen saturation, *ETCO2* endtidal carbon dioxide, *PaCO2* arterial partial pressure of carbon dioxide, *PaO2* arterial partial pressure of oxygen, *HCO3* serum bicarbonate, *BE* base excess, *Na* serum sodium, *K* serum potassium, *Ca* serum ionized calcium, *Osmol* serum osmolality

A second scenario can be created for reperfusion of the graft liver. During reperfusion hypotension can arise from graft nonfunction, hyperkalemia, or pulmonary embolism. All three causes of hypotension differ in their patterns of hemodynamic, metabolic, and coagulation changes and the learner must identify the etiology by using

monitoring variables in order to provide appropriate management. This scenario emphasizes urgency and quickness to make medical choices.

Debriefing

Debriefing is one of the most crucial portions of simulation. Criticism should be constructive and specific [12–16]. Remember to critique the performance and not the performer. This period is structured, and discussion and feedback between the teacher and the learner consolidates lessons learned. Debriefing includes the gathering of information (G), analysis (A), and summarization (S) to promote retention of learning [17]. This is collectively named as GAS Methodology. It is usually appropriate to move to a separate room from the simulation operating room. A change of location permits a more objective assessment of what happened and a moment to solidify mental images. It gives opportunity to the learners to vent and change perspective. This can be initiated by asking the participant to discuss the events in the scenario. "What happened?"A re-telling of the sequence of events permits the learners to identify what parts of the scenario were especially memorable to them. Facilitator comments should be nonjudgmental in the "gathering" phase of debriefing. Recall of events, timeline, and the emotions that were triggered by the scenario are all important. Notes or recordings of the sessions, while not essential, can assist recall especially if there is a discrepancy between what the learners remember and what the facilitators observed. This can be resolved by playing a video.

During the analysis phase of debriefing the Educator directs the flow of discussion, and where possible, links the discussion to memorable events [18]. Give opportunity to the learners to recognize errors that occurred in their management and also direction to find the means to correct them. The intention is that learners will do most of the talking. This can be promoted by asking "What went well and why." Stressing inappropriate action makes the learners defensive and only promotes passivity. It is important that the learners can say why they did what they did based on their situational awareness during the simulation. Inappropriate management usually results from failure to correctly identify the underlying problem. The learners should be able to offer differential diagnoses some of which may not have occurred to them during the rapidly evolving scenario. The Educator can direct the discussion of how to confirm clinical possibilities. "What made you decide that the patient is volume overloaded?" "When would hypotension not respond to volume?" Once the target pathology is correctly identified, it is appropriate to consider what will happen if it is left untreated. Building upon prior knowledge and a mental construct of the liver failure patient permits thought experiments that predict physiologic changes brought about by surgical and anesthetic manipulations. Management decisions can then be considered. "What can you do differently to avoid this from happening in the future?"

Write down algorithms of hemodynamic changes and coagulation changes for further discussion. A whiteboard or other visual display can be helpful. Session should ideally reflect common patterns that may be observed during liver transplantation procedures with emphasis on the physiologic changes that are distinct to transplantation physiology. The instructors must be able to explain the physiologic consequences of inappropriate clinical decisions based on physiologic principles presented during the lecture portion of the simulation session. Themes for discussion include: the mesenteric and systemic vasodilation accompanying chronic liver failure; the focal nature of this vasodilation (with unresponsiveness to alpha vasoconstrictors by vasoplegic vessels), treatment of vasodilated shock by increasing cardiac output to adequately supply both vasodilated and normal vascular beds; The importance of right ventricular function; the altered response to medications due to distribution and/or responsiveness (unpredictably heightened preoperative sedation in the presence of encephalopathy); the need for robust, even redundant, vascular access and monitoring to identify and immediately correct volume status; correction of metabolic variables such as potassium, ionized calcium, and base deficit, to targeted values (rather than acceptable ranges) in anticipation of reperfusion; blood component therapy based on volume status and TEG rather than estimates of blood loss.

Because multiple physiologic alternations occur simultaneously during liver transplantation, learners can become overwhelmed. Summarizing the lesson before going to a second issue provides time for incorporating the lesson into both conscious and emotional memory. Using this approach, each physiologic alternation can be approached sequentially and pace of the discussion can be made suitable to the individual learner.

The debriefing both reinforces and consolidates lessons. Questions during the debriefing session ideally build upon lessons and facts previously learned; rote memorization is a poor teaching method, is unlikely to be retained over long periods and may be remembered incorrectly during actual crisis in the clinical arena. Ongoing feedback can improve behavior in simulation and also in clinical practice.

Assessment and Evaluation

Appropriate performance in a simulated environment does not guarantee clinical outcomes in the OR where multiple patient and environmental variables may impact patient care. The aim of the course is to ensure a baseline understanding of the patients and issues unique to LTx surgery and to provide the learner with appropriate management tools. Evaluation of the learner's performance should rarely be presented as a pass/fail decision. Rarely, the discovery of deficits of knowledge or judgment may be severe enough to recommend very close supervision or remedial training prior to caring for LTx patients. Nonetheless most trainees find the course to be both helpful and

reassuring when completed prior to being scheduled to care for a patient undergoing LTx.

The impact of simulation course on the performance of the learner can be determined by observing the progress of the learner during the course. Instructors can see the change in confidence, anxiety level, and the medical decisions as the simulation session progress. It is useful to ask direct questions to the learner such as: Was the reading material easy to understand and applicable to the anesthesia for liver transplantation? Do you feel comfortable in setting up the necessary equipment and drugs for liver transplantation anesthesia? Do you feel reasonably confident in your ability to provide anesthesia for a liver transplant patient? A confidential and anonymous survey at the end of the course should ask for suggestions for improvement in the course material and presentation.

Instructors should note the attitude of the learner; positive comments that have been made include: Thank you so much. This course is extremely helpful, thanks for putting this together for us. I wish other subspecialties have similar course.

Conclusion

Anesthesia management of liver transplantation patients presents unique challenges because of the complexity of the surgery and the pathophysiology of end-stage liver disease. Experience obtained in this simulation course provides learner with the ability to strengthen their medical knowledge, improve both clinical skills and confidence while reducing anxiety. It promotes both critical thinking and problem solving helping a learner to evolve from resident to consultant level.

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Part VIII
Multivisceral Transplantation

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38. The Historic Evolution of Intestinal and Multivisceral Transplantation

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Keywords Multivisceral transplantation – Intestine transplantation – Immunosuppression – Graft function – Recipient preconditioning – Health-related quality of life (HRQOL)

Introduction

Although the intestine was one of the first organs to be transplanted in animals, it was the last to be successfully transplanted in humans [1]. Such a significant delay reflects the organ structural and immunologic complexity. For many decades, the intestine was considered a forbidden organ because of the enigma of graft-versus-host disease (GVHD) [2, 3]. With extensive preclinical studies, clinical introduction of various immunosuppressive drugs, and more recently better understanding of gut immunity, intestinal transplantation has become technically feasible with increased practicality and durability over the last three decades [4].

This chapter focuses on the multifaceted historic evolution of visceral transplantation with special reference to the pioneer experimental and clinical work triggered by the introduction of new premises, availability of novel immunosuppressive

drugs, and innovation of surgical techniques. In addition, the current status of the different types of visceral transplantation is highlighted with new insights for future consideration.

Experimental Visceral Transplantation

Traced back to the pioneer experimental work of the 1912 Nobel Prize winner Alexis Carrel (Fig. 38.1a), the modern history of bowel transplantation was signaled by the innovative experimental work of Lillehei (Fig. 38.1b) and Starzl (Fig. 38.1c) that was published more than half a century ago [5, 6]. Most of the technical aspects of these canine procedures were the same as those in clinical use today (Fig. 38.2). These experimental models also highlighted some of the immunological and metabolic behavior of the visceral allograft as intestine alone or combined en bloc with other abdominal organs including the liver.

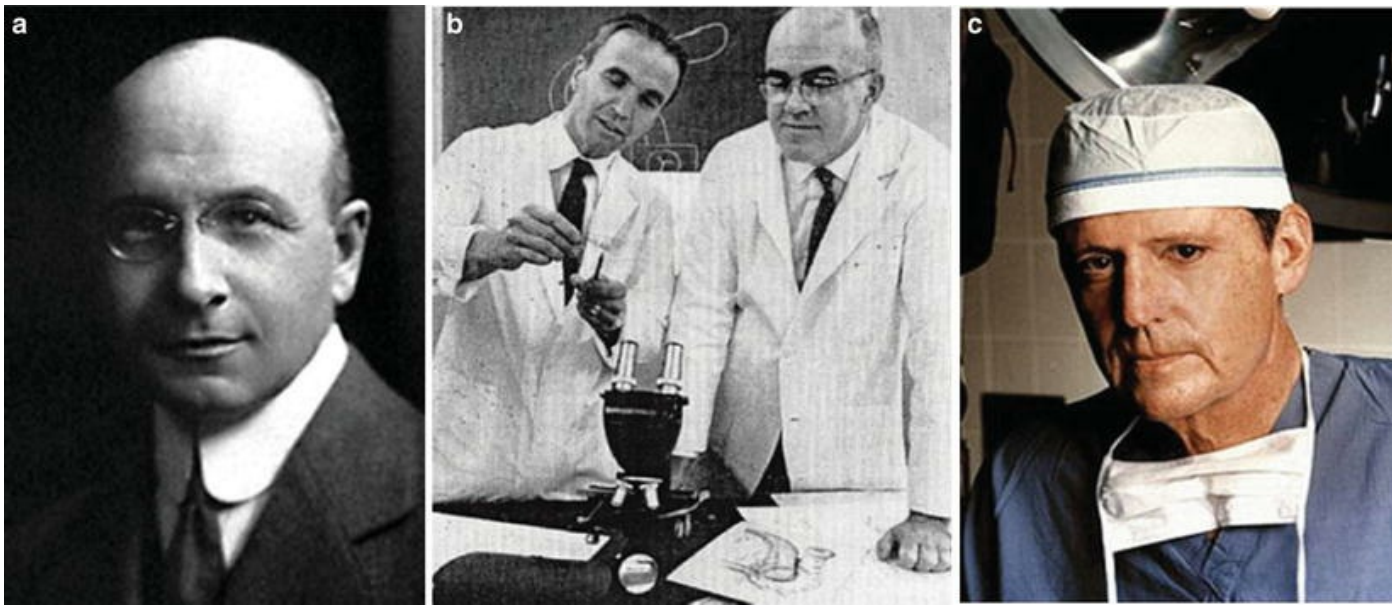

Fig. 38.1 (**a**) Alexis Carrel, (**b**) Richard Lillehei (*left*) and William Kelly (*right*), (**c**) Thomas Starzl

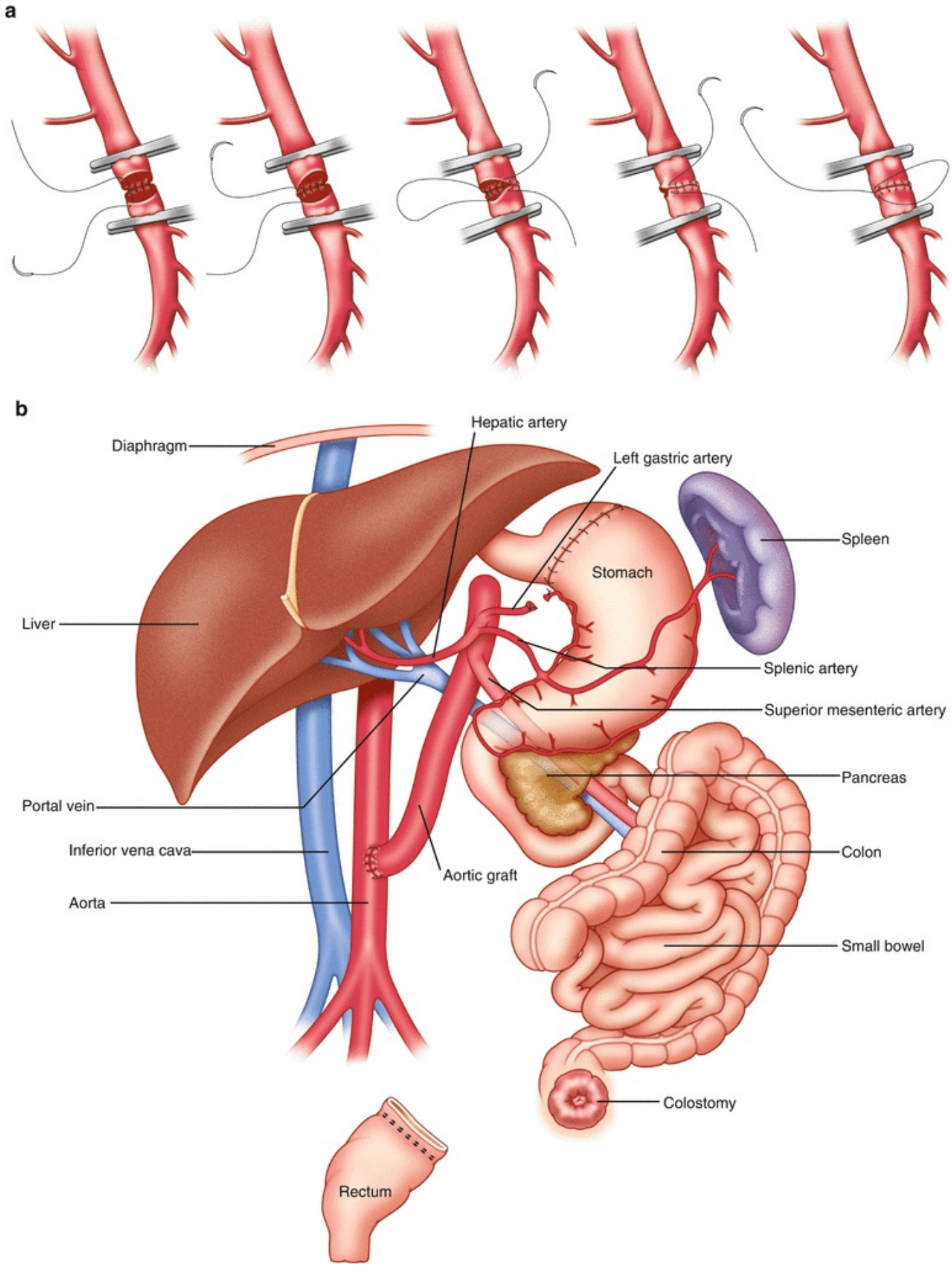
a
b
Diaphragm
Hepatic artery
Left gastric artery
Spleen
Stomach
Liver
Splenic artery
Superior mesenteric artery
Pancreas
Portal vein
Inferior vena cava
Aortic graft
Colon
Aorta
Small bowel
Colostomy
Rectum

Fig. 38.2 (**a**) Technique for anastomosing the superior mesenteric vessels [5]. (**b**) Schematic view of the transplanted tissues and their anatomic relation to the host

The Carrel's successful implantation of vascular grafts and performance of several autotransplantations were behind the landmark initial experiment of Lillehei and his colleagues at the University of Minnesota. The designed animal model assessed the physiological response of different degrees of small bowel ischemia. The technical feasibility of re-implantation as an auto or visceral allograft was also examined with special focus on patency of the venous and arterial vasculature [5].

The Starzl's model of "mass homotransplantations of abdominal organs" was introduced to study the behavior of a large denervated homograft in which the lymphatic drainage was interrupted. The boldness of the concept was evident in the cataclysmic postoperative course with a longest survival of 9 days among 19 dogs. However, the experiment observed a great degree of functional preservation of the liver that suggests mitigation of the rejection process. The same observation has been recently documented in humans by the senior author [4, 7–9].

Visceral Transplantation in Humans

Isolated Intestine Transplantation

The successful development of clinical intestinal and multivisceral transplantation is one of the most important milestones in modern history of organ transplantation. Five years after the Lillehei experiment, Deterling at the Boston Floating Hospital [10] performed the first small bowel transplant in an infant by using a segment of the mother's ileum. Another intestinal transplant in a child was also declared for the first time by Deterling during the discussion of Alican's first clinical case at the eleventh annual meeting of the society for surgery of the alimentary tract in 1970 [10]. With azathioprine (Imuran) being the primary immunosuppressive agent, the attempts of these innovative surgeons and others across the globe (Fig. 38.3) were short lived with a patient survival ranging from 12 h to a few weeks (Table 38.1) [10–14].

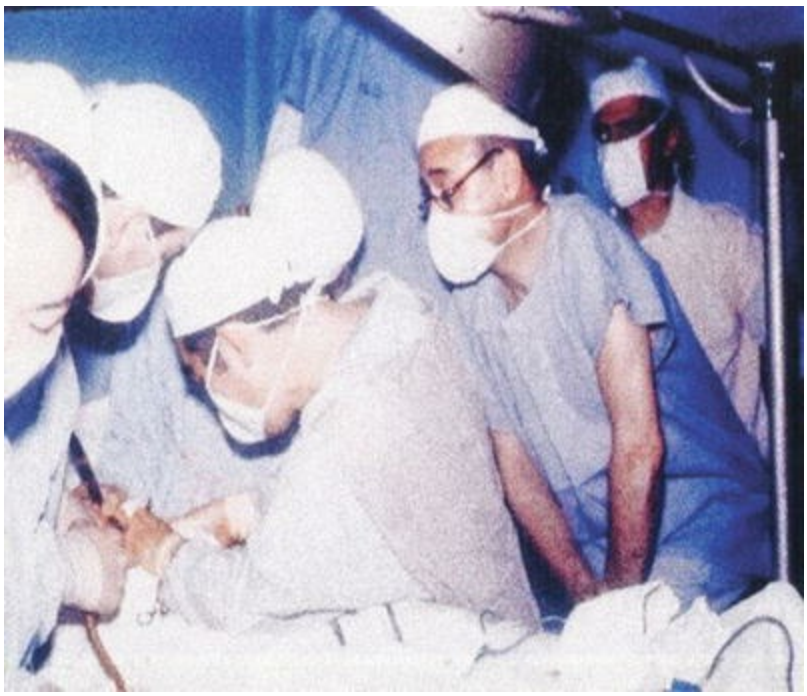

Fig. 38.3 Masayuki Okumura performing the first small bowel transplant in Latin America at the University Hospital of Sao Paulo Brazil in 1968

Table 38.1 Clinical intestinal transplantation in the azathioprine era

Year	Author	Institution	Etiology of intestinal failure	Graft survival
1964	Deterling [10]	Boston Floating Hospital	Mesenteric thrombosis	12 h
1964	Deterling [10]	Boston Floating Hospital	Mesenteric thrombosis	2 Days
1967	Lillehei [11]	University of Minnesota	Intestinal infarction	A few hours
1968	Okumura [12]	University Hospital-Sao Paulo Brazil	Mesenteric thrombosis	10 Days
1969	Olivier [14]	Hôtel-Dieu de Paris	Gardner's syndrome	23 Days
1969	Alican [10]	University of Mississippi	Strangulation by a mesenteric band	9 Days
1969	Okumura [12]	University Hospital-Sao Paulo Brazil	Volvulus	5 Days
1970	Fortner [13]	Memorial Sloan Kettering	Gardner's syndrome	79 Days

With the late 1970s arrival of cyclosporine, further worldwide attempts were made in humans after good results in rodent animal models. With 13 publications in the English literature (Table 38.2) [13, 15–21], better survival was observed compared to the azathioprine era. Of these recipients, only one patient is currently alive with fully functioning graft for nearly 25 years.

Table 38.2 Clinical intestinal transplantation in the cyclosporine era

Year	Author	Institution	Etiology of intestinal failure	Graft survival
1985	Cohen [13]	Toronto General Hospital	Gardner syndrome	10 Days
1987	Tattersall [15]	Rush University, Chicago, USA	Short bowel syndrome	13 Days

1987	Goulet [16]	Hôpital Necker-Enfants Malades, Paris, France	Neonatal volvulous	8 h
1987	Goulet [16]	Hôpital Necker-Enfants Malades, Paris, France	Volvulous	6 Month
1987	Deltz [17]	University of Kiel, Federal Republic of Germany	Volvulous	12 Days
1988	Goulet [16]	Hôpital Necker-Enfants Malades, Paris, France	Volvulous	17 Months
1988	Grant [18]	University of Western Ontario, London, Canada	Intestinal pseudo-obstruction	14 Days
1988	Deltz [19]	University of Kiel, Federal Republic of Germany	SMV thrombosis	49 Month
1989	Goulet [20]	Hôpital Necker-Enfants Malades, Paris, France	Neonatal volvulous	
1989	Goulet [20]	Hôpital Necker-Enfants Malades, Paris, France	Neonatal volvulous	2 Months
1989	Goulet [20]	Hôpital Necker-Enfants Malades, Paris, France	Neonatal volvulous	24 Days
1989	Wallander [21]	University Hospital, Uppsala, Sweden	Aganglionosis	8 Weeks
1990	Goulet [20]	Hôpital Necker-Enfants Malades, Paris, France	Intestinal atresia	7 Months

The clinical introduction of FK-506 (currently known as tacrolimus) in 1989 refueled the interest of the transplant community in the field of intestinal transplantation. The early successful outcome with the first isolated intestinal transplantation and subsequent cases under tacrolimus-steroid-based immunosuppression proved the technical feasibility and practicality of intestinal transplantation under tacrolimus as a powerful immunosuppressive agent [22]. The initial encouraging results and continual improvement in outcome will be further discussed under current status of the procedure.

Composite Visceral Transplant

Twenty years after his first successful canine multivisceral transplant experiment, Starzl performed the first multivisceral transplant in humans in 1983 with en bloc inclusion of the stomach, duodenum, pancreas, intestine, and liver [23]. His enthusiasm was stimulated by the clinical availability of cyclosporine as a better immunosuppressive drug. Despite the painful operative experience with the first case, the recipient of the second transplant survived more than 6 months with fully functioning graft to die from progressive post-transplant lymphoproliferative disease (PTLD) . Similar attempts were made worldwide under cyclosporine with a patient survival ranging from 7.5 to 66 months (Table 38.3) [23–26]. The procedure has been increasingly utilized in the tacrolimus era [4, 27].

Table 38.3 Clinical transplantation of composite visceral grafts

Year	Author	Institution	Etiology of intestinal failure	Graft survival
1983	Starzl [23]	University of Pittsburgh Medical Center	Short bowel syndrome + liver failure	A few hours
1986	Williams [25]	Rush-Presbyterian-St Luke's Medical Center	Gastroschisis + liver failure	4 Days

1987	Starzl [23]	University of Pittsburgh Medical Center	Neonatal volvulus + liver failure	192 Days
1988	Williams [25]	Rush-Presbyterian-St Luke's Medical Center	Volvulus + liver failure	109 Days
1988	Grant [24]	University of Western Ontario	Short bowel syndrome	
1989	Margreiter [26]	Innsbruck Medical University	Cancer (head of the pancreas)	8 Months

Shortly before the clinical introduction of tacrolimus, Grant et al. published the first case of successful combined liver and intestinal transplantation under cyclosporine in humans [24]. To overcome the observed prohibitive risk of intestinal allograft rejection under cyclosporine, the Ontario group transplanted both the liver and intestine from the same donor to a recipient with normal native liver. Such a successful outcome combined with the clinical introduction of tacrolimus stimulated a wave of enthusiasm that increased the utilization of the different types of intestinal transplantation for patients with irreversible intestinal failure and complex abdominal pathology.

Evolution of Immunosuppression

The clinical introduction of tacrolimus ushered in a new era in the field of intestinal and multivisceral transplantation. Soon after the initiation of the clinical trial with tacrolimus and steroid-based immunosuppression (type I), most centers experienced prohibitive risk of allograft rejections. During such an exciting era, different novel approaches were also introduced due to the introduction of new immunosuppressive agents with new insights into the mechanism of allograft acceptance and transplant tolerance.

With more emphasis on the difficulty of clinical care rather than survival, induction therapy with cyclophosphamide and daclizumab was introduced as part of multiple-drug immunosuppression including different cellular and molecular targets (type II) (Fig. 38.3). With better control of rejection, the overall survival has improved at major centers and according to the Intestinal Transplant Registry (ITR) [4, 28–30]. Unfortunately, updated results confirmed the long-term detrimental effect of chronic multiple-drug maintenance immunosuppression with erosion of the observed early survival benefits beyond the 10-year post-transplant landmark [4] (Fig. 38.4a).

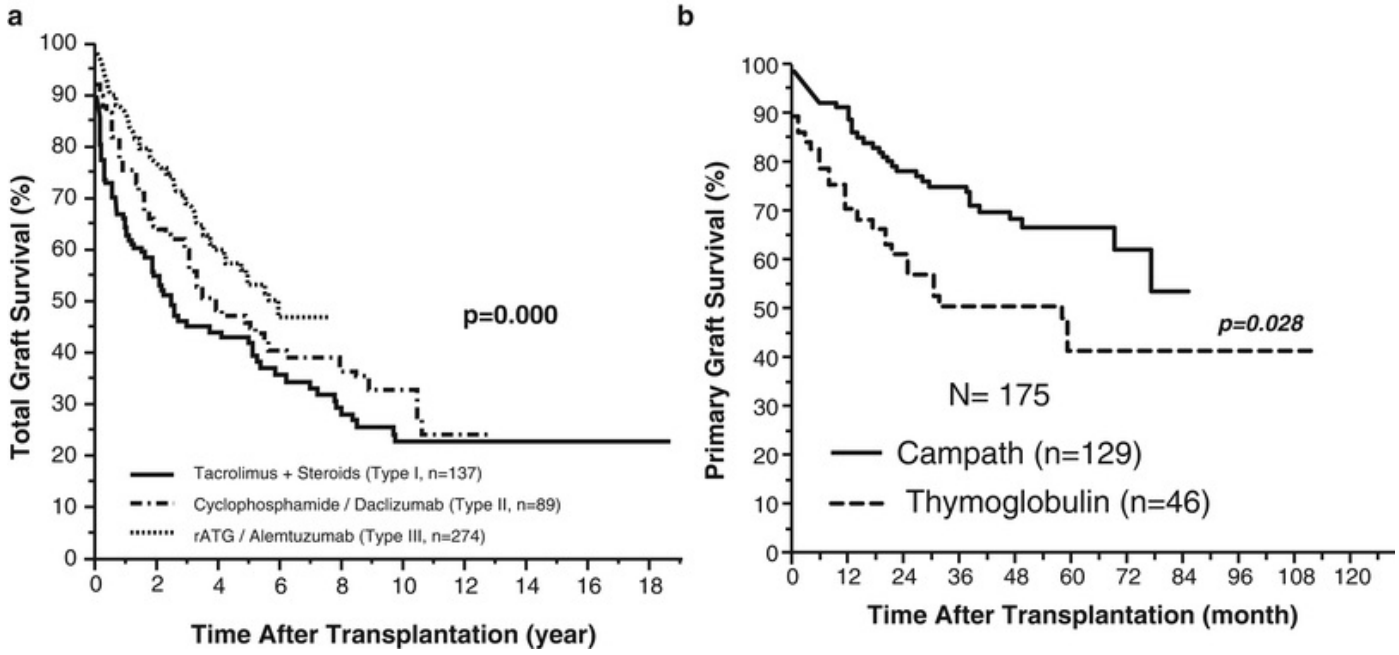

Fig. 38.4 (**a**) Improvement of visceral allograft survival according to the type of immunosuppression. (**b**) Better graft survival in patients pretreated with alemtuzumab (Campath-1H) compared to those pretreated with antithymocyte globulin (thymoglobulin) (data from Abu-Elmagd KM, Costa G, Bond GJ, et al. Five hundred intestinal and multivisceral transplantations at a single center: major advances with new challenges. Ann Surg 2009;250(4):567–81; and Abu-Elmagd KM, Costa G, Bond GJ, et al. A decade of experience with a single dose of rabbit antithymocyte globulin or alemtuzumab pretreatment for intestinal and multivisceral transplantation. Clin Transpl 2012:155–66)

With new insights into the mechanism of allograft acceptance and transplant tolerance, recipient preconditioning using thymoglobulin or alemtuzumab (Campath-1H) (Fig. 38.4b) with post-transplant minimal immunosuppression was introduced (type III) with the aim to improve allograft stability and reduce the need for long-term post-transplant immunosuppression at the University of Pittsburgh [31–33]. With perioperative partial depletion of the recipient lymphoid cells, amelioration of the initial donor-specific immune response is expected. Jointly application of minimal post-transplant immunosuppression has the potential to avoid the possible erosion of the alloengraftment mechanism of clonal exhaustion-deletion without high penalty of destructive immune response [32, 33]. The Pittsburgh intestinal and multivisceral recipients were the first to receive such a novel protocol with further improvement in overall outcome [4]. Reduction in the total incidence of intractable rejection and fatal infections partially contributed to better overall survival. Equally encouraging is the concomitant reduction in risk and fatality of PTLD despite the depletion of recipient lymphoid cells. With such a novel protocol, further improvement in outcome was achieved with more survival advantage utilizing alemtuzumab compared to rabbit antithymocyte globulin (thymoglobulin) (Fig. 38.5) [9]. A similar protocol has been reported by the Miami group utilizing alemtuzumab as an induction and not a pretreatment agent with multiple perioperative doses with no attempts to space out the

tacrolimus maintenance dosage [34, 35].

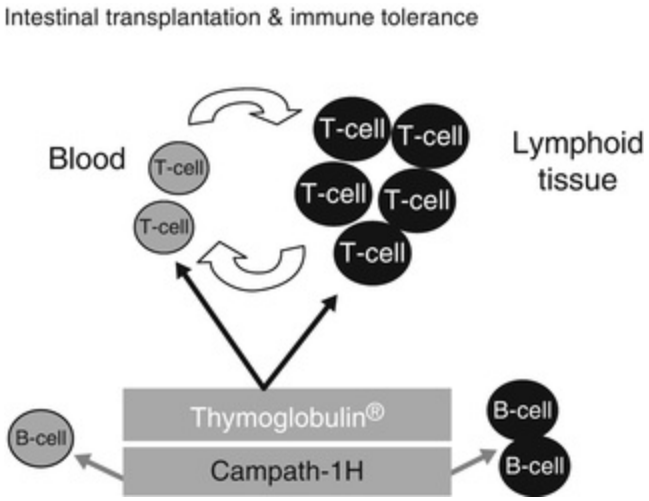

Fig. 38.5 This illustration depicts the dynamics of the lymphocyte depletion by both thymoglobulin (rATG) and Campath-1H (alemtuzumab). Note that both agents are effective in depleting both the intravascular and tissue T-lymphocytes. However, only Campath-1H is effective against the B-lymphocytes

The demonstrated striking ability to further reduce maintenance immunosuppression with recipient pretreatment supports Pittsburgh's hypothesis of successful induction of partial tolerance in these immunologically challenging recipients. With the unprecedented successful achievement of spaced doses of tacrolimus up to 8 years, partial tolerance is achievable and drug-free long-term engraftment is within reach despite the high intestinal allograft immunogenicity [4, 9].

Improved Outcome

Survival

The cumulative worldwide clinical experience demonstrated steady improvement in one and five actuarial graft survival [32]. However, a time series analysis of conditional 5-year actuarial survival showed only slight improvement over time [36]. Beyond the 5-year milestone, the conditional survival of Pittsburgh series showed a patient survival rate of 75 % at 10 years and 61 % at 15 years, with a graft survival of 59 and 50 %, respectively (Fig. 38.6) [37]. Graft failure and various complications including immunosuppression-related organ injury continued to impact the patient long-term survival with rejection, infection, and renal failure [4].

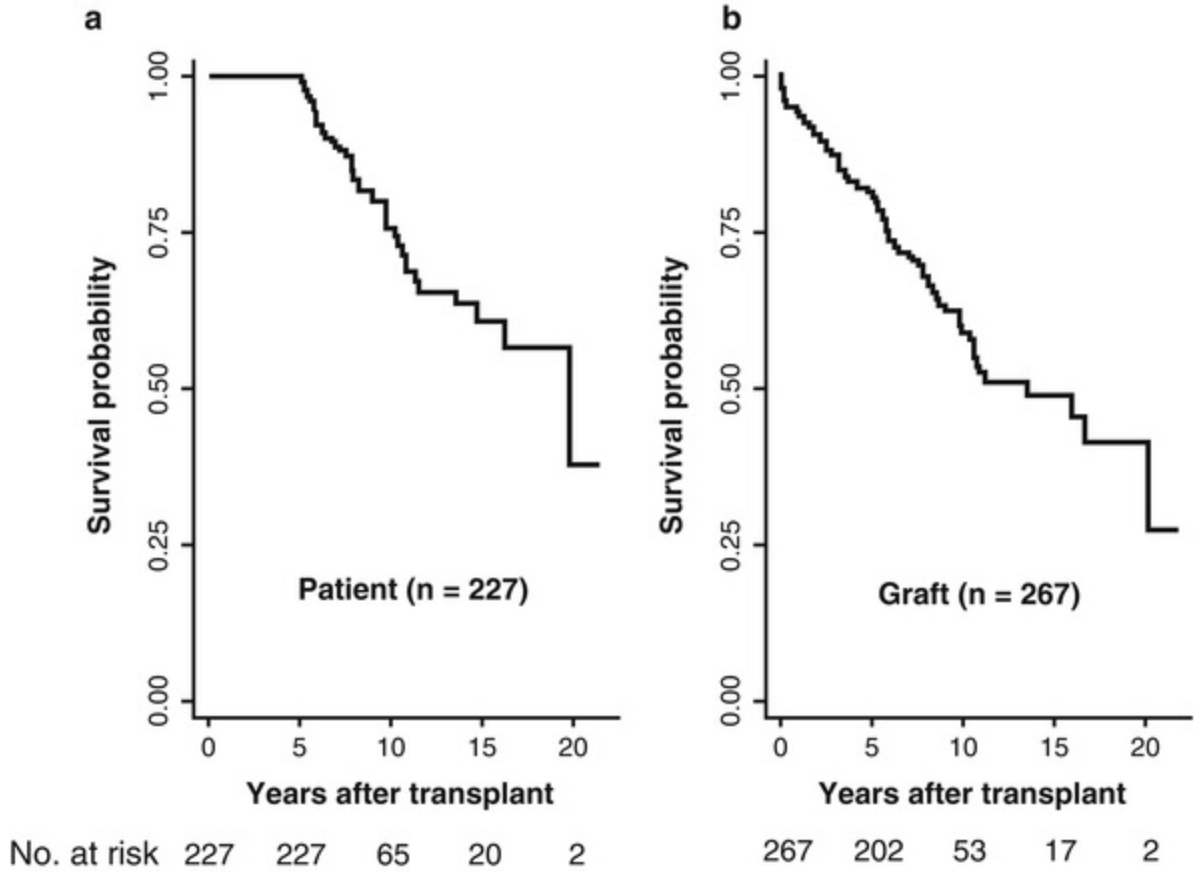

Fig. 38.6 Survival curves for conditional patient (**a**) and graft (**b**) survival after visceral transplantation. The analysis excluded patients who demised before the 5-year post-transplant landmark (data from Abu-Elmagd KM, Kosmach-Park B, Costa G, et al. Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation. Ann Surg 2012;256(3):494–508)

The long-term survival risk factors are summarized in Table 38.4. Nonfunctional social support and non-inclusion of the liver as part of the visceral allograft were the most significant risk factors of patient survival and graft failure (Fig. 38.7). Non-inclusion of the liver continued to be the most significant predictor of late graft loss since Pittsburg group reported the immune-protective effect of the liver in 1998 [4, 7, 8]. Other significant predictors include early rejection, female recipient, older recipient age, splenectomy, and retransplantation.

Table 38.4 Long-term patient and graft survival risk factors

	p	Hazard ratio	95 % Confidence interval
Patient			
Lack of social support	0.000	6.132	3.370–11.160
Rejection ≤90 days	0.016	2.363	1.172–4.765
Female recipient	0.025	1.992	1.089–3.646
Recipient age ≥20 years	0.025	2.014	1.093–3.711
Re-transplantation	0.026	2.053	1.089–3.873

No preconditioning	0.046	2.013	1.013–4.997
Graft			
Liver-free allograft	0.000	3.224	2.026–5.132
Splenectomy	0.001	2.212	1.396–3.506
HLA mismatch	0.040	1.258	1.011–1.565
Rejection ≤90 days	0.046	1.601	1.008–2.541
PTLD	0.085	1.638	0.934–2.872

HLA human leukocyte antigen, *PTLD* post-transplant lymphoproliferative disease
Modified from Abu-Elmagd KM, Kosmach-Park B, Costa G, et al. Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation. Ann Surg 2012;256(3): 494–508, with permission

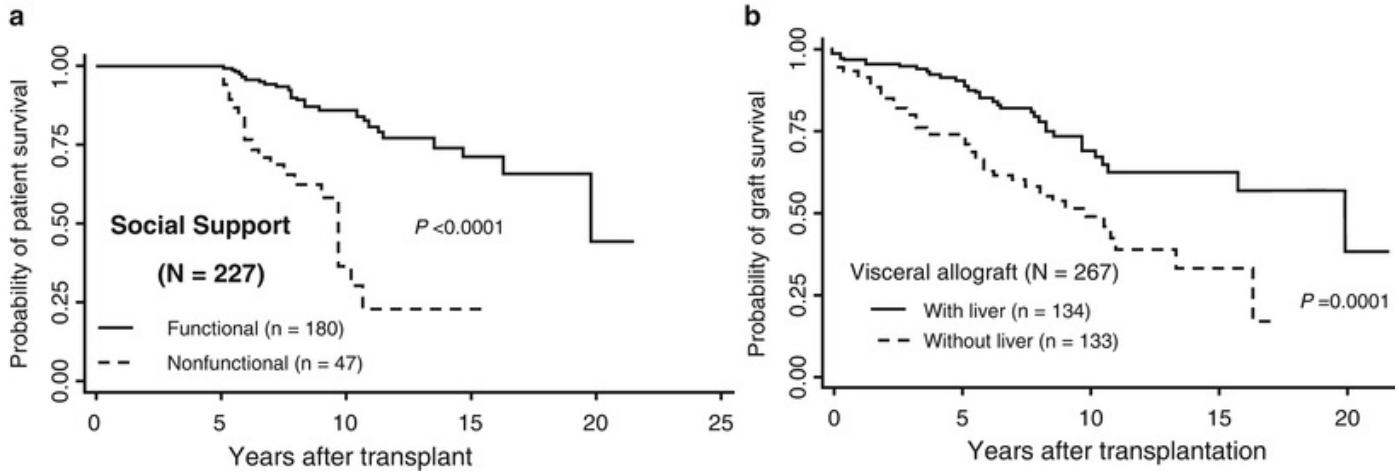

Fig. 38.7 Long-term conditional survival probability for patients according to social support status (**a**) and overall cumulative graft survival according to allograft type, with special reference to inclusion of the liver (**b**). Both variables were the most significant predictors of long-term patient and graft survival, respectively (data from Abu-Elmagd KM, Kosmach-Park B, Costa G, et al. Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation. Ann Surg 2012;256(3):494–508)

Graft Function

The ability to restore nutritional autonomy and other graft functions is the important metric to assess therapeutic efficacy [4]. The reported high rate of long-term nutritional autonomy without intravenous nutrition and the improved body mass index (BMI) with sustained serum albumin levels higher than that before transplantation are testimony of excellent allograft function (Fig. 38.8). In a recently published cross-sectional study on pediatric recipients, positive growth was observed in the majority of cases, particularly those with steroid-free immunosuppression but with limited catch-up [38]. The failure to achieve full functional recovery includes the sustained gut dysmotility and fat malabsorption. These are due to the result of denervation and lymphatic disruption of

the visceral allograft, respectively [39].

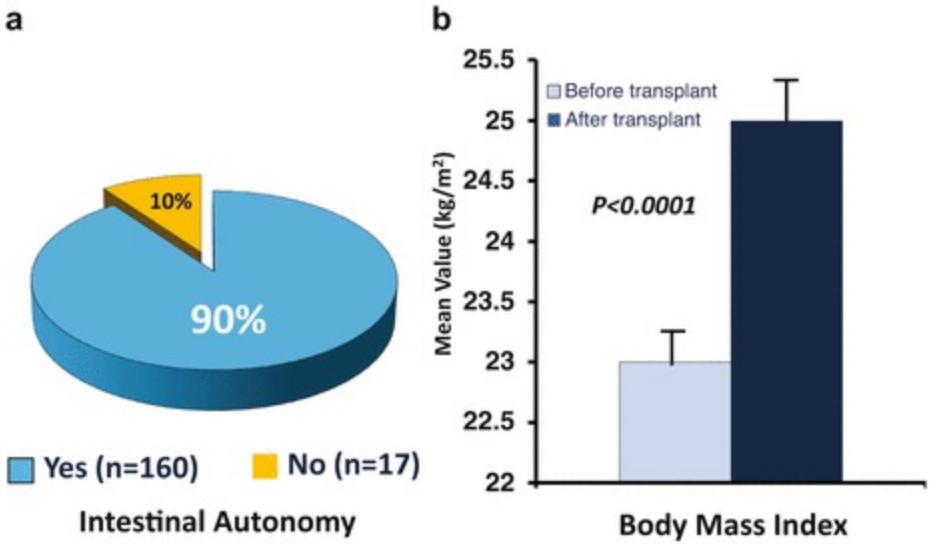

Fig. 38.8 Long-term graft function of 177 visceral allograft recipients who survived beyond 5 years at the University of Pittsburgh Medical Center. (**a**) Achievement of enteric autonomy defined by freedom from intravenous nutrition and fluid supplement. (**b**) Body mass index before and after transplantation

Quality of Life

With the continual improvement in survival outcome, the health-related quality of life (HRQOL) issues have become an important primary therapeutic index. The relatively young clinical age of the field with its multifaceted complexity has limited the validity of the currently available tools to assess HRQOL in this unique population. In addition, the utilization of the procedure as a rescue therapy has negatively biased most of the quality of life measurements.

Several studies addressed the HRQOL following visceral transplantation among both children and adults using different study instruments [4, 28, 37, 40–45]. With the use of the child health questionnaire, two well-designed studies demonstrated physical and psychosocial functions similar to healthy normal children [40, 41]. However, the parental proxy assessments were different from the recipients, with lower response in multiple categories including physical health and social functioning. In addition, lower values among the school functioning subcategories and psychological health summary score were also reported [41].

The HRQOL was addressed in five series of adult recipients that were published in peer-reviewed journals with dedicated study design [37, 43, 45–47]. All of these studies demonstrated improvement in many of the quality of life domains, with a better overall rehabilitative index than HPN including the use of treatment-specific questionnaires [47]. With the exception of depression and increased financial demands, successful transplantation offsets the deprived effect of HPN on most of the QOL

domains and resolves the chronicity of the primary disease [37, 46].

The multidimensional quality of life aspects in both adults and children have been recently addressed in a comprehensive single report reflecting the largest single-center experience with more than two decades of follow-up [37]. The study identified, for the first time, a spectrum of different developmental, psycho-neurological, and behavioral disorders among visceral allograft recipients, particularly children, including autism, developmental delay, attention-deficit/hyperactivity disorders, and deafness at a relatively higher rate than the general population [37]. The authors attributed these observations to organic brain dysfunctions that occurred due to intestinal failure during the early phases of neuronal, emotional, and physical development. The disease process is also compounded by the pre-transplant HPN-associated complications and morbidities that may occur after transplant. Of the documented pathologic changes are brain atrophy, cerebral vascular insufficiency due to multiple septic emboli, micronutrient deficiencies, trace element toxicities, and liver failure-induced metabolic encephalopathy [48–54]. Accordingly, early consideration for gut rehabilitation including transplantation is recommended with the aim to reduce the risk of such devastating irreversible deficits particularly among the pediatric population.

The long-term rehabilitative efficacy of visceral transplantation was recently accessed utilizing the socioeconomic milestones [37]. A high education index was reported among all respective age group with sustained cognitive, psychosocial, and physical functions after all types of visceral transplantation. In addition, the ability to create a nuclear family, having children, and becoming a productive citizen is another valid indicator of a high rehabilitative index after visceral transplantation. Equally important is that most recipients scored high on the Lansky and Karnofsky performance scales, with normal functional activities in 88 % of current survivors [55] (Fig. 38.9).

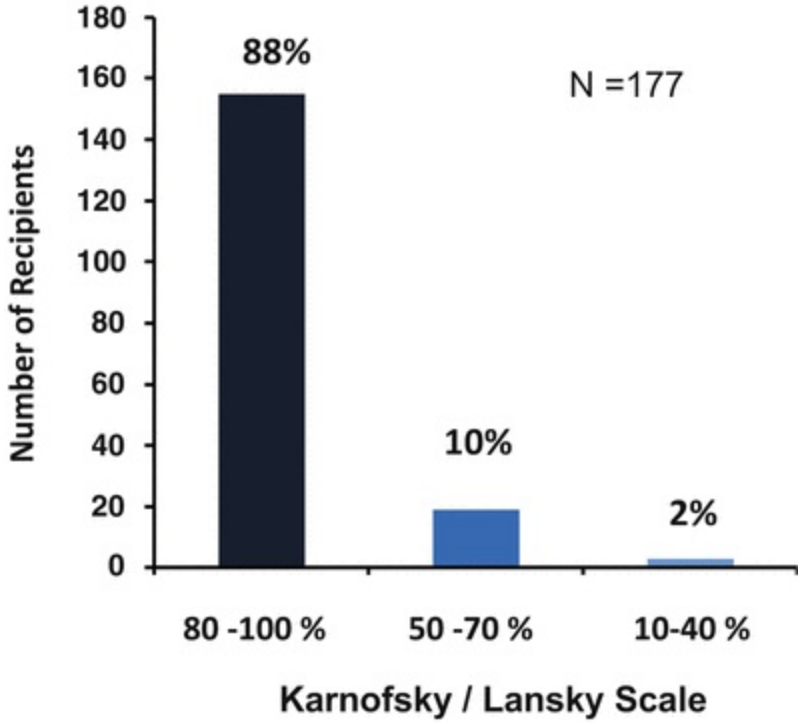

Fig. 38.9 One hundred and fifty-six of 177 (88 %) visceral allograft recipients in University of Pittsburgh Medical Center who survived beyond the 5-year milestone scored 80–100 % on the Lansky/Karnofsky performance scale

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39. Technical Innovation and Visceral Transplantation

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Introduction

The improvement of outcomes after intestinal and multivisceral transplantation over the last two decades is due to multiple factors including innovations in surgical techniques [1–3]. With increased practicality, visceral transplantation has been successfully used for patients with different varieties of irreversible gastrointestinal failure. Accordingly, different combinations of en bloc abdominal visceral organ transplant have been more frequently utilized [4, 5].

All different types of small bowel containing transplants can be categorized into three main prototypes: “isolated intestinal,” “liver-intestinal,” and “multivisceral” transplantation s. Historically, the terms “isolated intestinal” and “multivisceral” transplantation originated more than half a century ago from the pioneer respective work of Lelihie and Starzl et al. and the third prototype “liver-intestinal” has been recently introduced by Grant et al. [5, 6] (Fig. 39.1). Because of continual technical advances

there has been some confusion concerning the nomenclature of these allograft combinations [7].

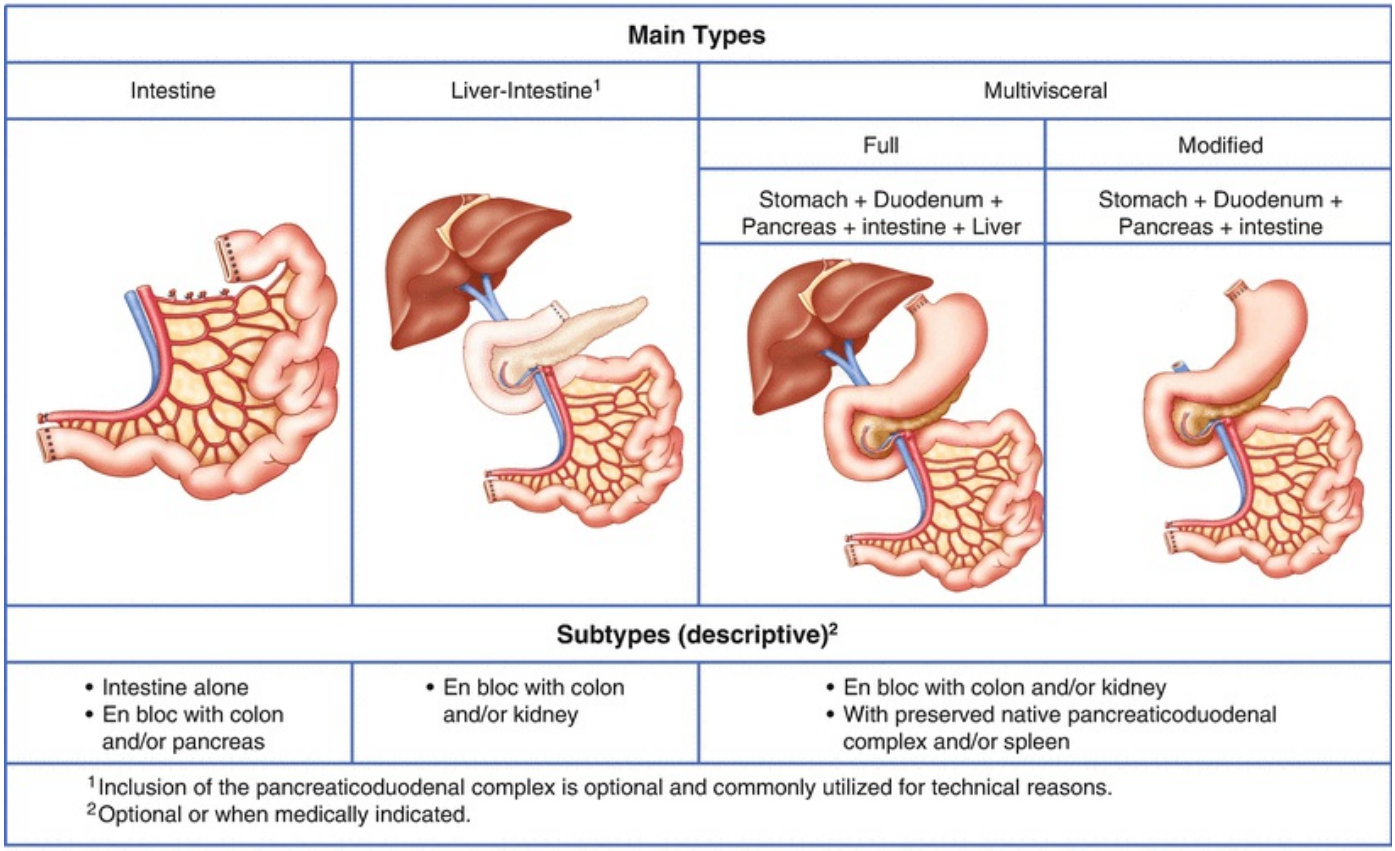


Fig. 39.1 The prototypes and the subtypes of visceral transplantation

While intestine being the central core of visceral allograft, the term "multivisceral" is a distinctive nomenclature for stomach-contained visceral allograft. Among multivisceral transplant, "full" contains liver allograft while "modified" does not. Secondary organs include colon and the pancreaticoduodenal complex with or without spleen. Colon can be retained with any three types of visceral allografts. The pancreaticoduodenal complex is routinely part of liver-intestinal graft and can be added to intestinal grafts for the patients who need combined intestine and pancreas transplant [8, 9].

We describe herein these three main prototypes of visceral transplantation and discuss the most relevant technical modifications in both donor and recipient procedures.

Choice of Visceral Transplant Allograft

Isolated Intestine

Isolated intestinal transplantation is the proper choice for patients with intestinal failure without liver cirrhosis. Mild-to-moderate liver dysfunction with periportal hepatic fibrosis is not contraindication for isolated intestinal transplant particularly in patients without synthetic or vascular decompensation. Isolated intestinal graft has been more frequently used with a higher incidence in adults (55%) than children (37%) [2]. This could be partly due to the greater need for a combined liver-intestinal transplant in children as a result of a higher incidence of end-stage liver disease associated with total parenteral nutrition in this age group.

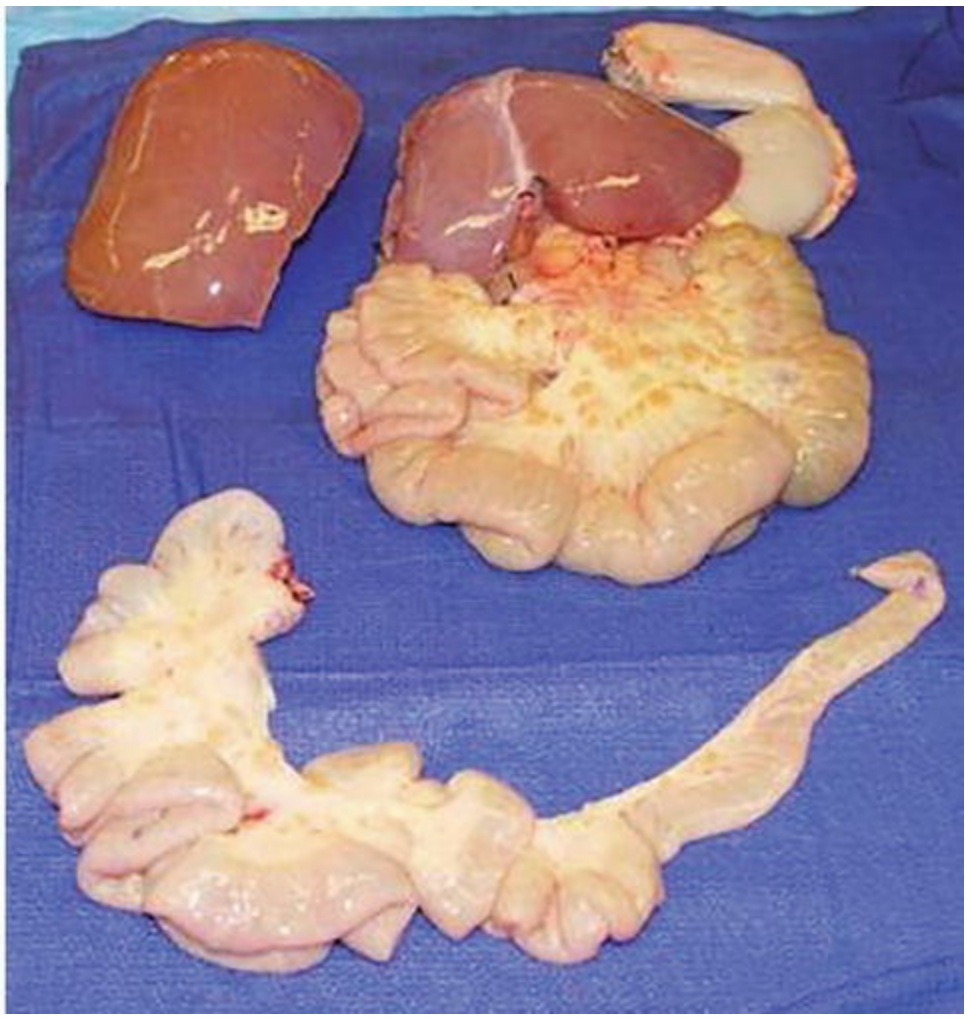
The indications for this type of transplant can be collectively divided into short bowel syndrome, motility disorders, malabsorption syndromes, and gastrointestinal neoplastic disorders. In patients with concomitant pancreatic insufficiency and intestinal failure, such as patients with cystic fibrosis, chronic pancreatitis, or diabetes mellitus, an en bloc intestine and pancreas transplant may be considered [10].

Combined Liver-Intestine

The combined liver-intestine transplantation is usually indicated for patients with intestinal failure who developed end-stage liver disease due to long-term parenteral nutrition [10, 11]. The procedure may also be indicated for patients with liver failure combined with portomesenteric venous thrombosis when isolated liver transplantation is not technically feasible.

The organs can be transplanted in a simultaneous or consequent fashion. The en bloc allograft includes the pancreaticoduodenal axis along with liver and small bowel to maintain continuity of gastrointestinal tract and integrity of axial blood supply. Pediatric or small candidates requiring combined liver and intestinal transplants may benefit from a “reduced-size liver”—small bowel graft [12] which may include left, right, or extended right lobes of the liver (Fig. 39.2).

a



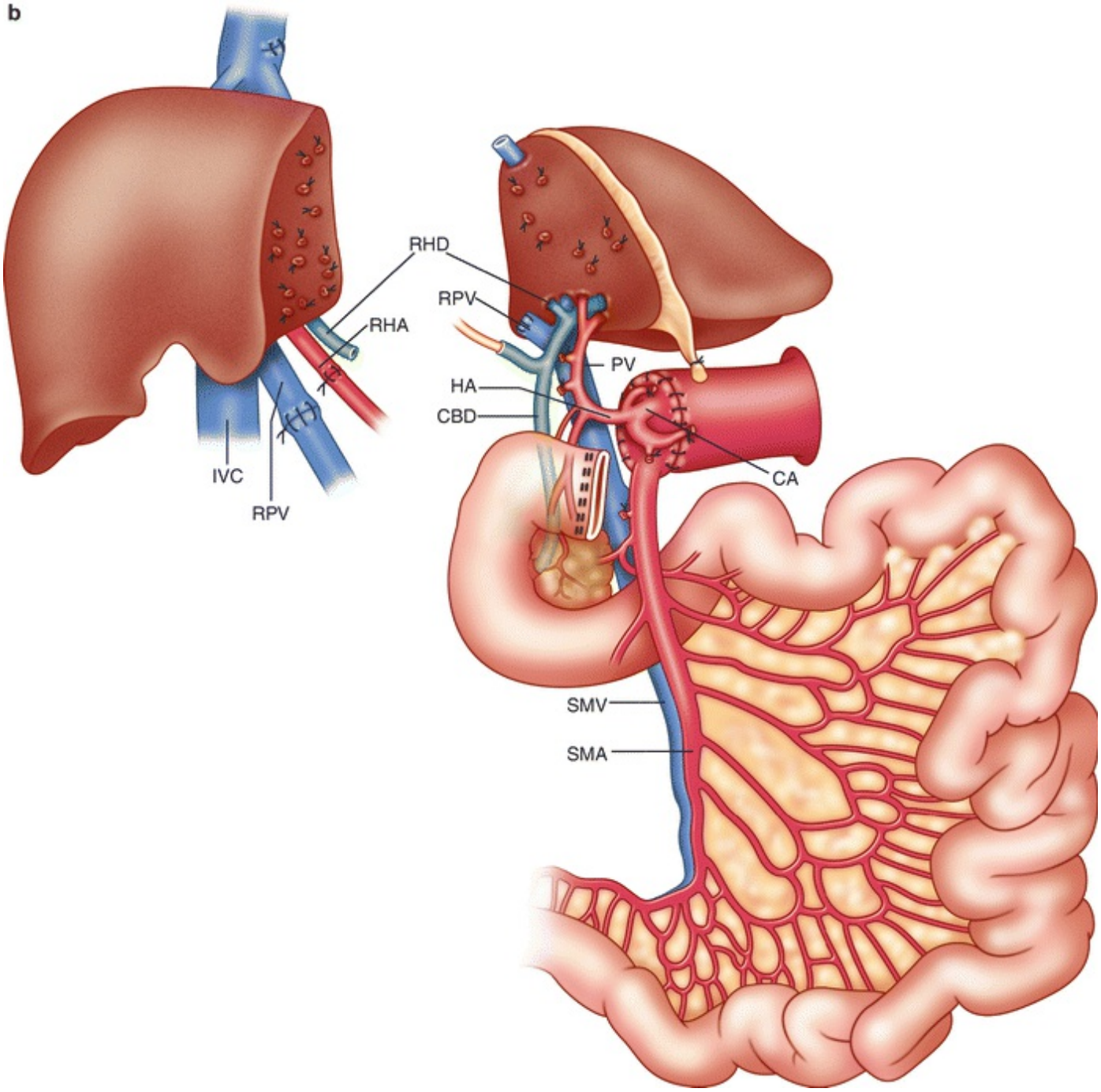


Fig. 39.2 (**a**) A split right hepatic graft and a reduced-size multivisceral graft that contains left hepatic lobe, and reduced small intestine. (**b**) A split right trisegment hepatic graft and an en bloc composite left lateral hepatic segment and intestinal graft with a single Carrel patch of superior mesenteric and celiac arteries. The single Carrel patch is anastomosed to a conduit of donor thoracic aorta at the back table. Separate arterial and venous grafts to the right trisegment hepatic lobe. *IVC* inferior vena cava, *RPV* right portal vein, *RHA* right hepatic artery, *RHD* right hepatic duct, *CBD* common bile duct, *PV* portal vein, *HA* hepatic artery, *CA* celiac artery, *SMA* superior mesenteric artery, *SMV* superior mesenteric vein

In 2009, the senior author [3] proposed and implemented a “domino transplant procedure ” in which patients with recurrent chronic rejection after isolated intestinal

transplantation would receive a combined liver-intestine graft from the same donor even if they have a fully functioning native liver. The recipient native liver will be given to another candidate of liver-only transplant.

Multivisceral

Full or modified multivisceral transplantation comprises nearly 24 % of adult and 13 % of pediatric intestinal transplants [10, 13]. It is indicated for patients with complex abdominal pathology including massive gastrointestinal polyposis, traumatic loss of the abdominal viscera, extensive abdominal desmoid tumors, locally aggressive non-metastasizing neoplasms, advanced generalized hollow visceral myopathy/neuropathy, and complete thrombosis of the splanchnic arterial or portomesenteric venous systems with hepatic decompensation [3].

From an immunological standpoint, multivisceral or combined liver-intestine transplant may have an advantage over isolated intestine transplant. The achieved better long-term engraftment with liver-contained graft compared to liver-free graft was reported by the senior author [3]. The improved outcome is mostly related to the immunoprotective effect of the concomitantly transplanted liver. This observation can be partially explained by the recently published data showing that liver-contained allografts were associated with significant clearance of preformed alloantibody and low induction of de novo donor-specific antibodies along with better survival in liver-contained allografts [14]. The study also demonstrated the important role of alloantibody in chronic visceral allograft injury and the liver can be immunoprotective with less favorable outcome in recipients with persistent alloantibodies.

Donor Surgery

Donor Criteria

Optimal donor selection is imperative to successful transplant outcome in intestine-contained transplantation. Prolonged downtime and the requirement for high-dose or multiple inotropes compromise the quality of visceral grafts. Other important factors include size disparity especially for recipients who lost the abdominal domain or large component of the abdominal wall. Allograft reduction in conjunction with efforts to increase abdominal domain including abdominal wall transplant and pre-transplant implementation of tissue expander in subcutaneous layer have been performed to facilitate graft coverage with newly created abdominal wall [12, 15, 16]. It is imperative to obtain arterial and venous vascular segments from the same donor to facilitate visceral allograft implantation. Accordingly, prompt initiation of communication with other abdominal organ-sharing programs is essential to facilitate smooth retrieval.

Surgical Procedure

With an increase in the gap between organ donation and demand, a procurement procedure is needed that permits multiple-organ retrievals for separate recipients waiting for liver, pancreas, and intestinal allografts [4]. A recent advance in organ retrieval technique made it feasible to share these organs among three different recipients (Fig. 39.3). When multivisceral transplantation is required for patients with preserved liver function, modification of the technique made it possible to utilize the donor liver for one recipient and the remaining visceral organs to a second patient (Fig. 39.4). The term "modified' multivisceral transplantation was first introduced in 1993 and recently published by the senior author [17–19].

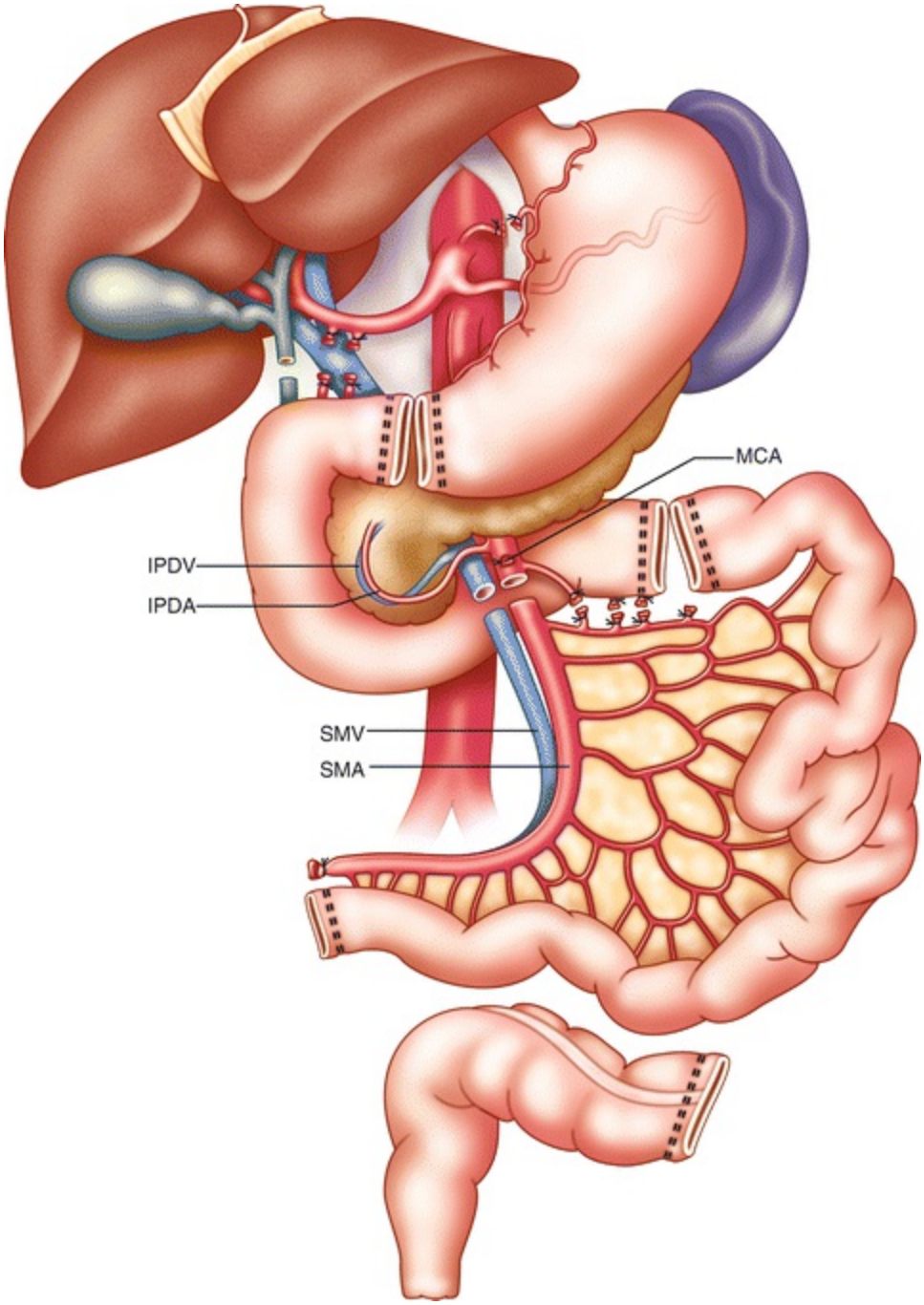


Fig. 39.3 In situ separation of the intestinal graft and dissection of the superior mesenteric pedicle. Note preservation of both the inferior pancreaticoduodenal artery (IPDA) and inferior pancreaticoduodenal vein (IPDV) with the pancreatic graft by limiting the dissection of the superior mesenteric vessels (SMV, SMA) below the level of the ligated middle colic artery (MCA)

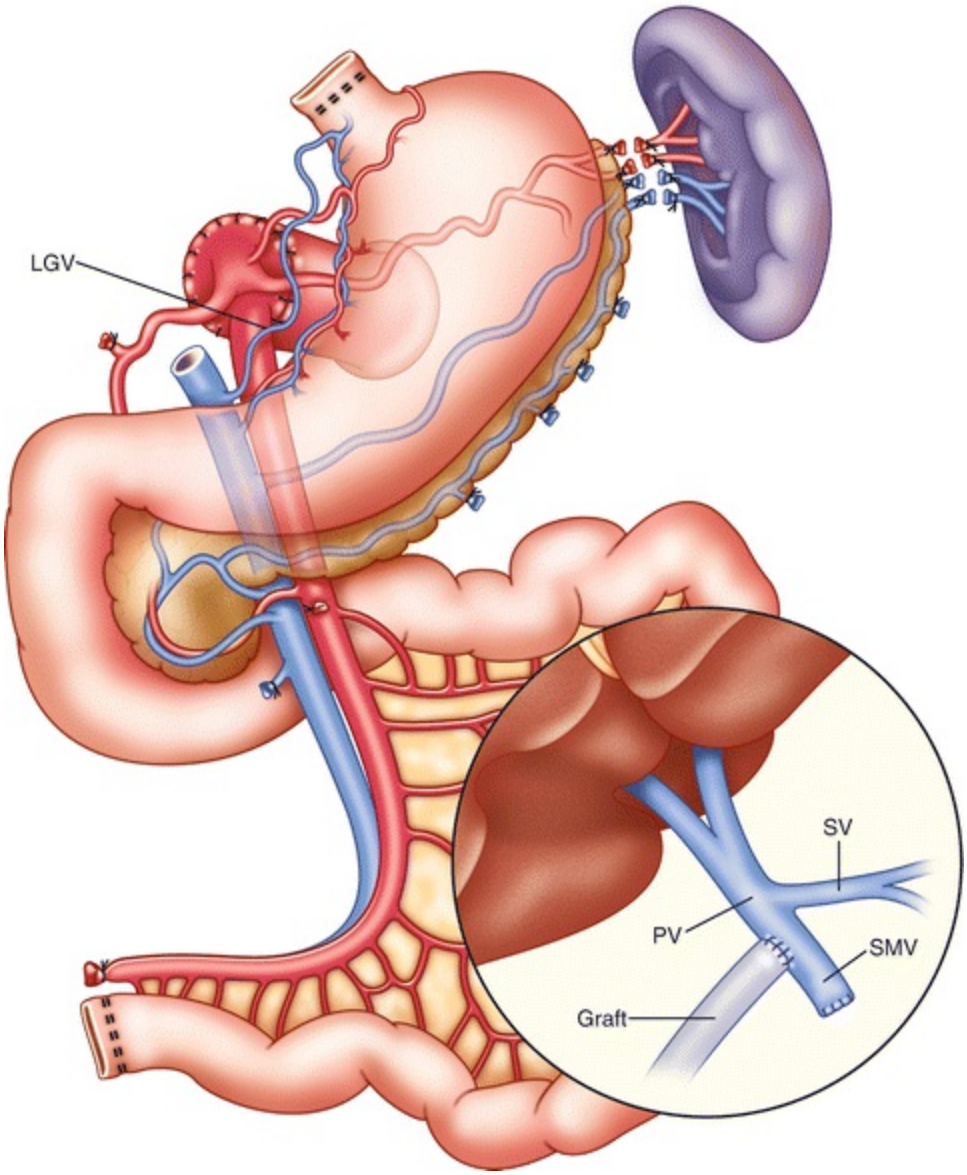


Fig. 39.4 Modified multivisceral graft that contains stomach, duodenum, pancreas, and small intestine. Note preservation of the gastroepiploic arcade and left gastric pedicle including the left gastric vein (LGV). Inset: Venous drainage of the composite visceral graft to the side of the recipient superior mesenteric vein (SMV) stump by using the donor common iliac vein as an extension graft without compromising the recipient portal venous flow during graft implantation. PV, portal vein; SV splenic vein

Upon entering the abdominal cavity, the intestine should be carefully examined. Thin mesentery with less adipose tissue is preferable because fat component is susceptible to ischemic-reperfusion injury, resulting in fat necrosis and subsequent mesenteric sclerosis after transplantation. Intestine with pneumatosis or portal venous gas is unacceptable for transplant. Iliac arteries and veins are accessed for the suitability for interposition grafts. Once quality of organ(s) is found to be satisfactory for transplant, direct communication between donor and recipient team prompts the recipient operation to minimize the cold ischemic time.

The first step of organ retrieval is performing the organ dissection with Cattel maneuver to mobilize small bowel and right colon that facilitates exposure of the vena cava and aorta [20, 21]. The left renal vein is identified with isolation of the SMA origin. Then the abdominal aorta is encircled distally for the eventual insertion of an infusion cannula. The supraceliac aorta is also encircled for later cross clamp.

After the colon and intestine are mobilized from retroperitoneum, the ileum is divided with the gastrointestinal stapler near the ileocecal valve when donor colon is not procured with the visceral organs. Right and transverse colons are detached from ileocolic vessels by taking down right and middle colic vessels. The remaining steps of the procedure are dictated by the type of required visceral allograft.

Isolated Intestinal Graft

The proximal jejunum is transected at the Treitz ligament after an interruption of the inferior mesenteric vein. At this juncture, the intestine is attached to the donor only by the superior mesenteric vascular pedicle, containing the superior mesenteric artery (SMA) and vein (SMV). These vessels are exposed by transversely dividing the anterior peritoneal sheath of the mesenteric root, distal to the level of the ligated middle colic vessels.

When the pancreas is procured for another recipient, the inferior pancreaticoduodenal artery needs to be preserved for the pancreatic graft, which originates just proximal to the origin of the middle colic artery [4]. Because the gastroduodenal artery is transected when donor liver graft is removed, injury of the inferior pancreaticoduodenal artery will devascularize the head of the pancreas. In order to maintain sufficient arterial flow to the head of the pancreas, the SMA will be divided distal to the origin of inferior pancreaticoduodenal artery. Since the first couple of jejunal arterial branches may originate from the SMA proximal to inferior pancreaticoduodenal artery, these proximal jejunal branches may need to be sacrificed.

When the pancreas is not procured, numerous small venous and arterial pancreatic branches from superior mesenteric vessels can be divided to obtain more length of the main trunk of mesenteric vessels. Further meticulous dissection leads to the splenomesenteric confluence of the portal vein. After cross clamp and cold flushing, SMA is transected at its origin, and the SMV is transected at the splenomesenteric confluence.

Liver-Intestinal Graft

During the initial phase of retrieval with intact circulation, the liver and small intestine should be carefully manipulated and dissected en bloc with their central vascular structure [6, 22, 23]. The proximal end of allograft was transected at the bulb of duodenum just distal to the pylorus. Full preservation of the donor pancreaticoduodenal

complex en bloc with the combined liver-intestinal graft was adopted to eliminate the need for biliary reconstruction and maintain continuity of the axial blood supply.

During the cold phase of dissection, the crucial final step in liver-intestine graft retrieval is excision of a large Carrel patch that contains both the celiac axis and SMA from anterior aortic wall without compromising the renal arteries [4]. By carefully opening the anterior wall of the aorta from its caudal portion to the root of SMA, the origins of the celiac axis and SMA and the two renal arteries can be readily visualized from inside the aortic lumen. After clear identification and protection of both renal arteries, the large Carrel patch can be fashioned safely.

Full Multivisceral Organ

En bloc dissection of the liver, stomach, duodenum, intestine, pancreas, and spleen from the diaphragm and retroperitoneum is performed. The graft to be retrieved can be modified according to patient's need with exclusion of the liver or inclusion of the kidney. After dividing the diaphragmatic crura, the abdominal esophagus is stapled. A long segment of thoracic and abdominal aorta is retrieved in continuity with a Carrel patch containing celiac axis and SMA.

Modified Multivisceral Organ

The procurement of modified multivisceral grafts can be aborted because of arterial anomalies that could potentially compromise the vascular inflow to the isolated liver allograft [19]. For proper cost-effective planning, CT angiogram may be considered at the time of donor evaluation. However, the decision to proceed with retrieval of the liver and the modified multivisceral graft to be given to two different recipients currently takes place in the donor operating room in most cases. In the presence of replaced or accessory right and/or left hepatic artery, the decision is based on liver surgeon's decision whether the accessory hepatic artery can be sacrificed or reconstructed on the back table with a branch of the main hepatic artery. Preoperative CT angiogram or intraoperative ultrasound withclamping of the accessory vessels could facilitate the decision.

Similar to the full multivisceral organ retrieval, en bloc dissection of abdominal organs is carried out followed by transection of abdominal esophagus. The liver graft is separated in situ or on the back table. The hepatic artery is transected at the level of the common hepatic artery and the gastroduodenal artery is also divided. The bile duct is transected 5–10 mm above the duodenum to allow duct-to-duct reconstruction in the recipient who undergoes native pancreaticoduodenectomy. The portal vein is transected 5–10 mm above the splenomesenteric confluence to allow portal vein anastomosis in the recipient [4]. Allograft splenectomy is performed on the back table. Great attention must be directed to avoid injury of the pancreatic tail during allograft splenectomy.

Preservation of the donor spleen en bloc with the composite allograft has been advocated by others [9, 24].

Interposition Vessel Grafts

It is imperative, after completion of visceral organ retrieval, to obtain adequate arterial and venous grafts [6, 20, 21]. An iliac vein is commonly used as an interposition venous graft that is anastomosed to donor SMV for venous drainage. Iliac and carotid arteries are ideal conduit to be placed on the recipient's aorta for implantation of isolated intestinal graft.

With combined liver-intestinal or multivisceral transplantation, a long segment of the thoracic/abdominal aorta is retrieved in continuity with the origin of both celiac axis and SMA. A segment of the back table prepared aortic conduit will be placed on recipient aorta, and the other segment is utilized on the back table as a single arterial conduit anastomosed to the common Carrel patch of both the celiac trunk and SMA.

Recipient Surgery

Two-Stage Approach

In preparation for visceral transplantation, a first stage surgical exploration has been increasingly utilized. The primary purpose of the approach is to eradicate intra-abdominal infections by surgical methods including debridgement, repair of fistulae, and restoration of gastrointestinal continuity. Upon referral, these patients often have intra-abdominal infection with enteric leak, abscesses, enterocutaneous fistulas, infected foreign materials including ventral hernia mesh, and venting tube drainage with colonized multidrug-resistant organisms. Because of the need for heavy maintenance immunosuppression after visceral transplant, successful treatment of these infections is necessary for successful outcome.

Another valuable purpose of the initial surgical exploration is to restore gastrointestinal continuity. Foregut and midgut reconstruction, particulary in patients with prior bariatric surgery, reduces the need for composite visceral allograft by salvaging the native stomach and may eliminate the need for isolated intestinal transplantation in selected cases after successful rehabilitative surgery including bowel lengthening.

When such an ambitious goal of achieving natural autonomy is not reached, restoration of upper gastrointestinal continuity temporally improves quality of life and more importantly reduce the number of required visceral organs with the need in most cases for intestine-only allograft (Fig. 39.5). Accordingly, the pancreatic gland from the same donor can be retrieved and utilized for another recipient. Another important advantage of the technique is utilizing the native conduit as an end stoma in patients who

require allograft enterectomy due to graft failure.

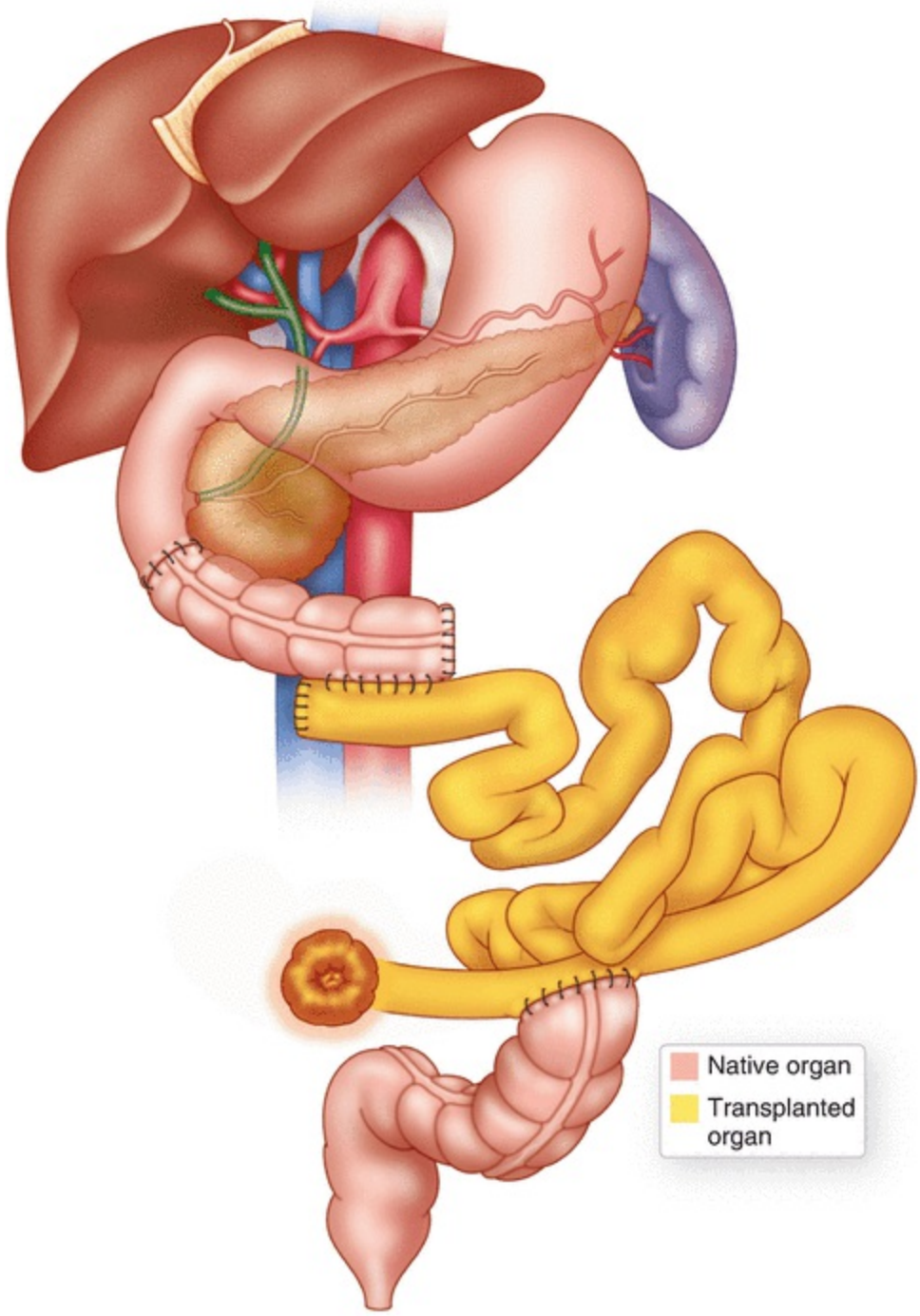


Fig. 39.5 Colonic interposition and intestinal transplantation . A patient who developed midgut volvulus and underwent total enterectomy with leaking duodenal stump. Upon referral, a duodenocolic anastomosis was performed in close proximity to the duodenal papilla. After recovery, the patient underwent a transplant with an isolated intestine without the need for gastric or duodenum-contained allograft utilizing a segment of the native colon as a visceral conduit between native duodenum and proximal allograft jejunum. The allograft terminal ileum is then anastomosed to the distal end of the remaining native colon

Evisceration of Native Organs

Evisceration of the diseased native organs is the initial step of the recipient transplant operation and is primarily determined by the extent of the underlying visceral pathology.

At the time of transplant, with the exception of motility disorders, most recipients have already lost most of the native intestine but may require completion enterectomy. In addition, recipients receiving liver and intestinal transplantation require total hepatectomy. Following dissection of the portal vein, a portocaval shunt is created to decompress the remaining left upper abdominal native organs including stomach, duodenum, pancreas and spleen. With modified or full multivisceral transplantation, the native organs can be removed en bloc or in a piecemeal fashion. The commonly used piecemeal evisceration technique consists of the following steps [19]:

1. Completion enterectomy with surgical excision of residual small intestineand colon if indicated. With modified multivisceral transplantation, preservation of the blood supply to the native liver is crucial with avoidance of injury to any vascular anomalies including replaced right hepatic artery that may arise from the SMA.

2. With multivisceral transplantation, subtotal gastrectomy is performed with transection of the stomach 3–5 cm below the esophagogastric junction. With modified multivisceral transplantation, the left accessory hepatic artery that may originate from left gastric artery should be preserved by careful dissection close to the gastric wall.

3. With the need for native pancreaticoduodenectomy,with and without preservation of the spleen, the pancreaticoduodenal complex is mobilized from the retroperitoneum. The common bile duct and gastroduodenal artery are then dissected and transected. The splenic artery and vein are separately ligated for complete removal of duodenum, pancreas, and spleen. For spleen-preserving pancreaticoduodenectomy (SPPD), the head of the pancreas is transected anterior to the confluence of the portal vein. Subsequently both segments of pancreas are removed with individual ligation of all tributaries of both the splenic artery and vein.

4. With full multivisceral transplantation, hepatectomy is performed in a piggyback technique by ligating and dividing all short hepatic veins. Hepatic artery and portal vein are preserved until the back table procedure is completed to minimize the time of the anhepatic phase.

Transplantation of the Visceral Graft

Vascular Reconstruction

Interposition Vascular Grafts

The initial in situ placement of a free donor arterial and venous conduit in the recipient before bringing the visceral allograft to the operative field is introduced by the senior author and later utilized by others. The technique avoids having to work in a confined space around the bulky visceral organs. The technique facilitates a safe vascular reconstruction with shorter implantation time of the visceral allograft [6] (Fig. 39.6).

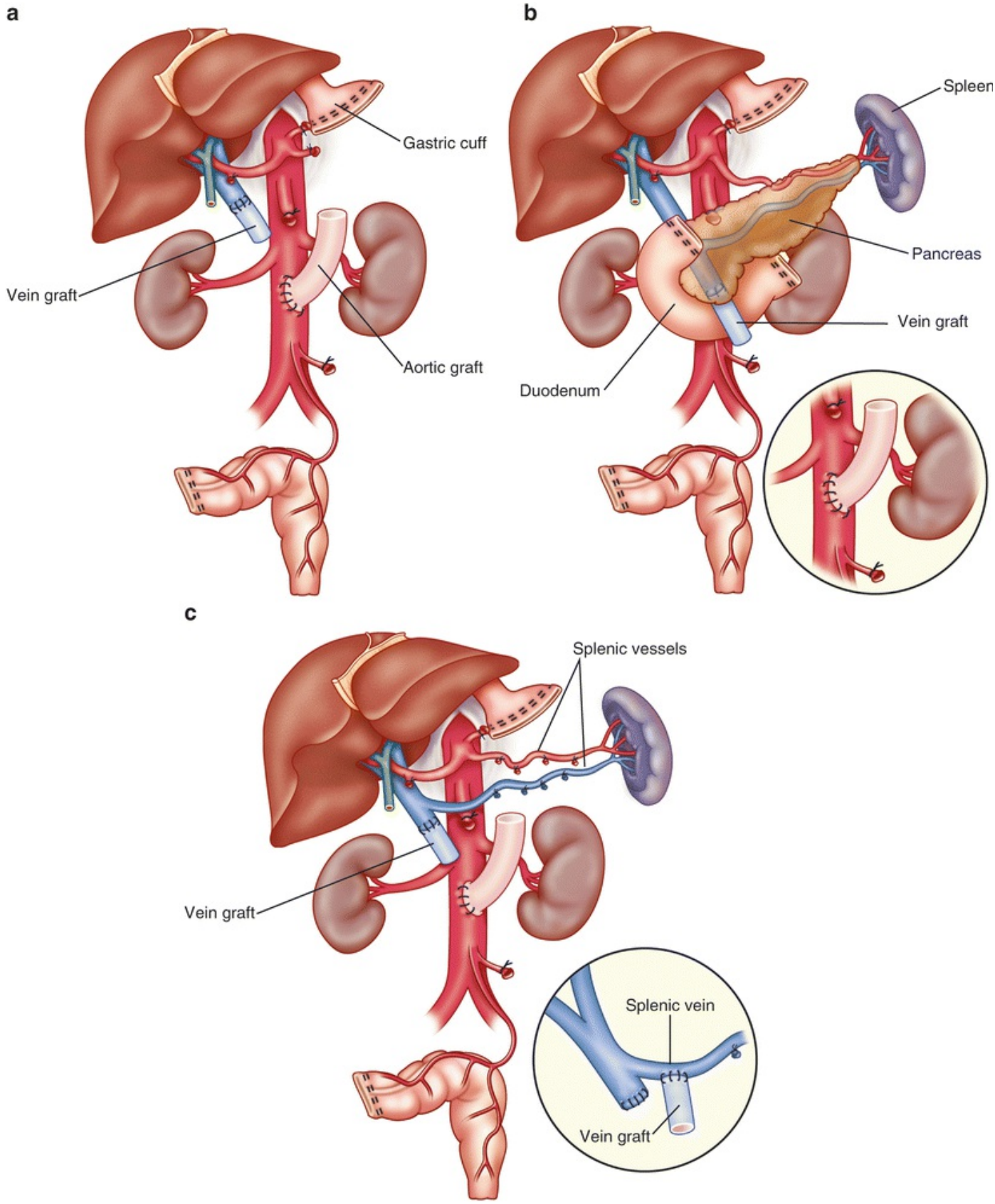


Fig. 39.6 The recipient operation with complete or partial removal of the native left upper abdominal organs and placement of interposition vascular grafts for modified multivisceral transplantation . (**a**) Major evisceration with near-total gastrectomy, total enterectomy, and pancreaticoduodenectomy. (**b**) Preservation of the splenopancreaticoduodenal

complex. (**c**) Pancreaticoduodenectomy with preservation of the native spleen

Arterial Inflow

With isolate intestine, iliac or carotid arterial graft is placed on the native aorta in an end-to-side fashion. During implantation of the intestine, the arterial graft is anastomosed to the SMA of the intestine.

With composite visceral grafts, the aortic origin of both the celiac and superior mesenteric artery are retrieved en bloc and constructed as a single Carrel patch. The Carrel patch is then anastomosed on the back table to a single arterial conduit utilizing a segment of the donor thoracic aorta. Under certain circumstances, a bifurcated common iliac arterial graft is anastomosed to the splenic and superior mesenteric artery of the visceral graft on the back table for en bloc intestine and pancreas transplant (Fig. 39.7). Before implantation of the visceral organs, another donor aortic conduit is anastomosed to the recipient supraceliac or infrarenal aorta in an end-to-side fashion. Finally the arterial reconstruction is completed by anastomosing the two aortic conduits (Fig. 39.8).

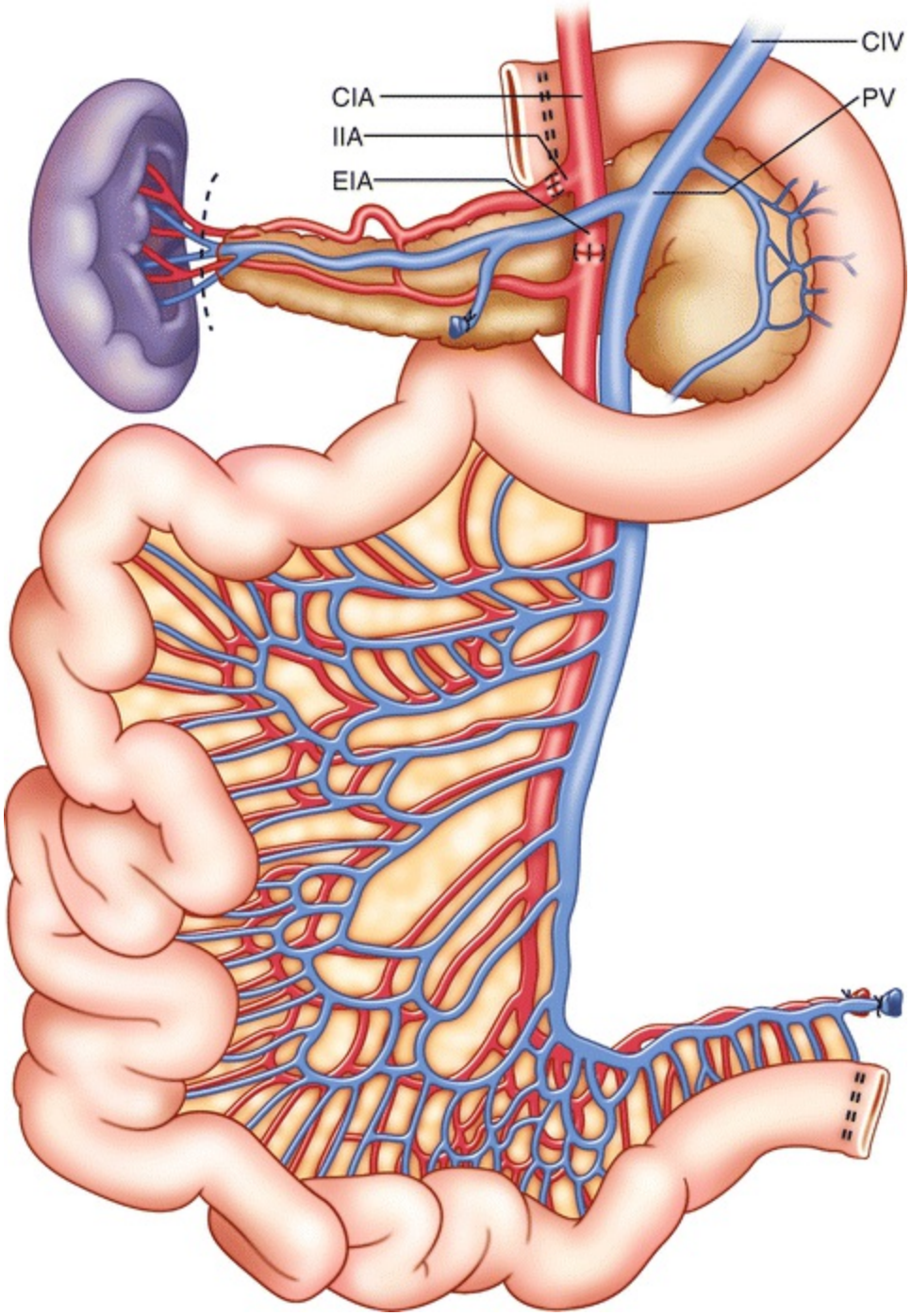


Fig. 39.7 Back table vascular reconstruction of a composite intestinal-pancreatic allograft with a bifurcated iliac arterial graft and common iliac vein graft. *CIA* common iliac artery, *CIV* common iliac vein, *EIA* external iliac artery, *IIA* internal iliac artery, *PV* portal vein

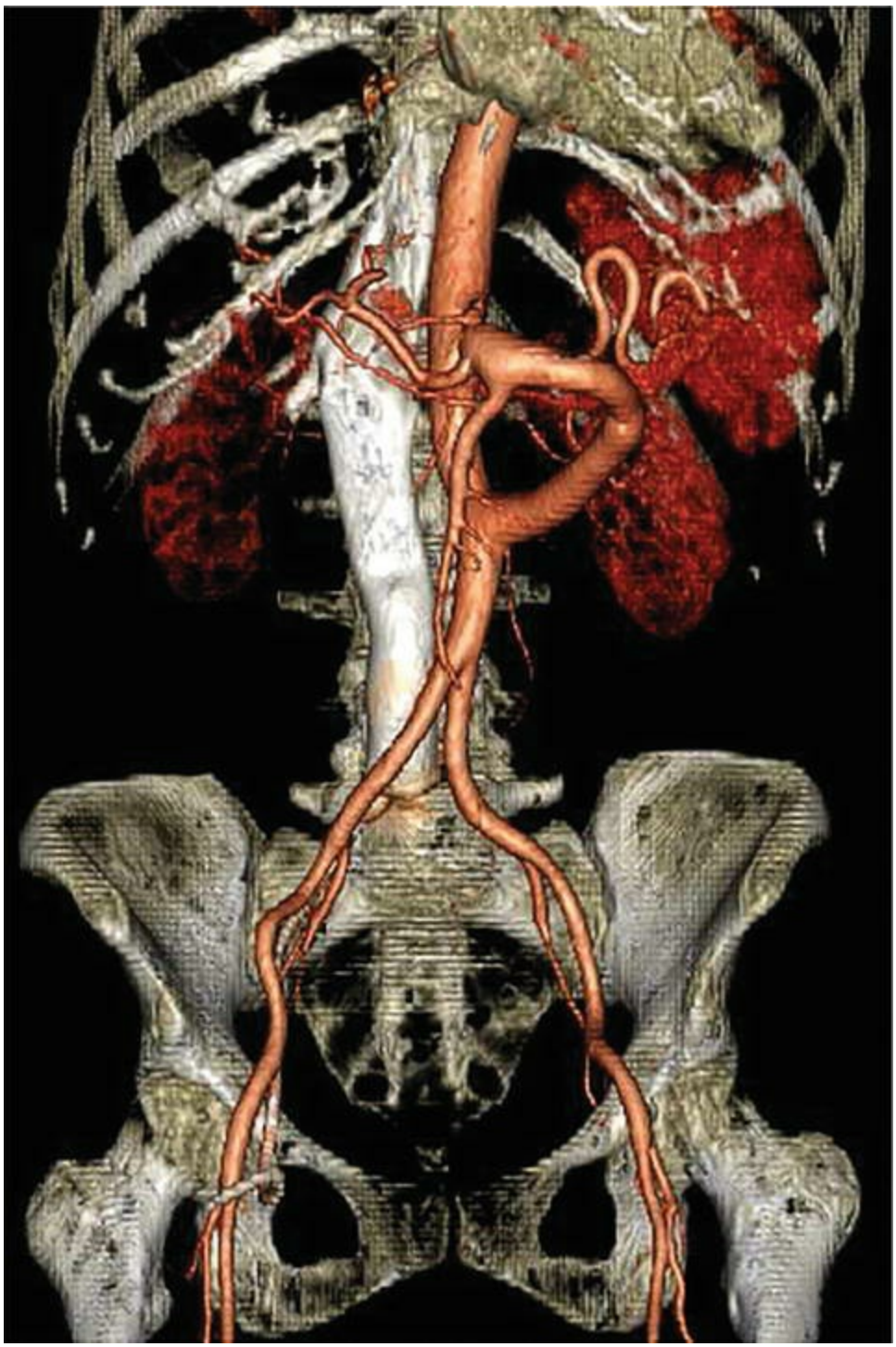


Fig. 39.8 3-D computed tomography of an infrarenal aortic graft with a single common conduit of a Carrel patch containing both the celiac artery and SMA

Venous Outflow

Venous outflow from liver-free visceral grafts such as isolated intestine and modified multivisceral can be established with either portal or systemic drainage. Portal drainage had been considered to be more physiologic than caval drainage, supported by various animal models that showed optimum liver structure and function depending on hormones

(especially insulin), nutrients, and other substances from splanchnic venous blood [25]. As a result, diverting the portal flow with its hepatotrophic factors from the liver can cause hepatic atrophy and impaired liver function. Accordingly, it is our practice to attempt portal drainage if technically feasible.

Iliac vein is commonly used as an interposition graft in end-to-end or end-to-side to the recipient portal vein in the hepatic hilum, SMV or splenic vein. For caval drainage, interposition venous graft is placed to the recipient infrarenal vena cava, renal, or iliac veins.

With visceral allograft contained liver, venous outflow is created between recipient and donor vena cava mostly with piggyback technique. With combined liver-intestinal transplantation, a permenant portocaval shunt is performed between the native portal vein and inferior vena cava.

Restoration of Gastrointestinal Continuity

With isolated intestinal transplantation, the proximal anastomosis is performed between the distal end of residual native intestine and transplanted jejunum. With full or modified multivisceral transplant, the residual recipient gastric cuff or abdominal esophagus is anastomosed to the anterior wall of the donor stomach. Pyloroplasty is performed because of gastric denervation. With liver-intestine transplantation and en bloc preservation of the pancreaticoduodenal complex, the native duodenum or jejunum is anastomosed to the allograft jejunum just distal to the duodenojejunal junction. Reconstruction of the hind gut is established in recipients with residual colorectal segment with creation of chimney ileostomy or simple loop ileostomy. Patients with previous proctocolectomy receive an end ileostomy.

Restoration of gastrointestinal continuity has received various modifications. With modified multivisceral transplantation, the duct-to-duct biliary reconstruction is required for recipients who undergo complete evisceration or spleen-preserving pancreaticoduodenectomy (SPPD) . For patients with preserved native duodenopancreatic complex the native and transplanted duodenum are anastomosed in a piggyback fashion [18]. The technique is indicated for patients with pseudo-obstruction syndrome who had end-stage dysmotility of both intestine and stomach. The preserved duodenum is shortened to avoid segmental dysmotility.

An innovative sphincter-preserving pull-through technique was recently introduced by the senior author. The procedure was performed in a Crohn's disease patient with prior total proctocolectomy and preserved anal sphincter utilizing an en bloc colon and small bowel transplantation [26, 27] (Fig. 39.9). The colon is procured en bloc with small intestine with preservation of the middle colic and ligation of the inferior mesenteric artery close to its origin. It is essential to preserve the right colic artery and the colonic marginal arterial arcades to maintain adequate blood supply to the distal end

of colonic graft. Twenty four to 48 hours after transplantation, the pull-through operation is completed by transanal dissection of the rectum with preservation of the internal and external anal sphincter. The anastomosis is established between the allograft colon and the recipient anal verge. The technique has the potential to improve allograft absorptive function and quality of life in patients with preserved anal sphincter.

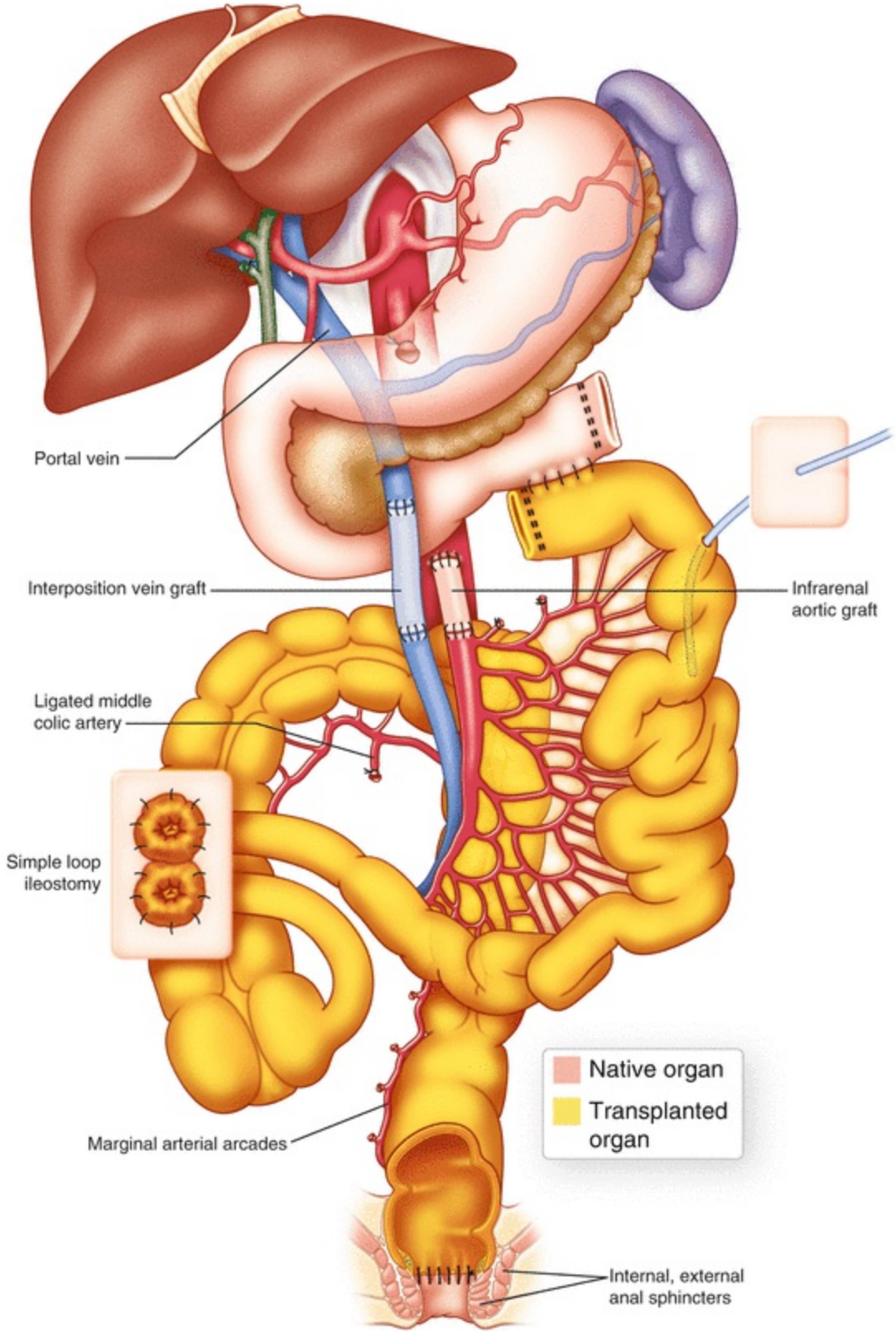


Fig. 39.9 Hind gut pull-through reconstruction with en bloc colon and intestinal transplantation

Abdominal Wall Reconstruction

Abdominal wall closure is one of the most challenging technical problems in visceral

transplantation [6, 16, 17, 28]. The extreme difficulty in facing complete closure of the abdominal wall is due to significant loss of the abdominal domain because of previous multiple abdominal surgeries with total enterectomy, coexistence of multiple enterocutaneous fistulae, and abdominal wall resection due to desmoid tumors. The failure to close the abdominal wall results in high mobility and mortality.

Before transplantation, implantation of tissue expander can be helpful to increase the surface area of the abdominal wall skin [15]. At the time of transplantation [15], a proportionally smaller organ donor, graft reduction, skin closure with or without component separation techniques, myocutaneous flap, and fascial closure with mesh or other tissue can be entertained. As a nonvascularized tissue allograft, the use of fascia of the rectus muscle from the same donor is also reported [29].

One of the novel approaches in abdominal wall closure is the simultaneous abdominal wall transplantation [28, 30]. Abdominal wall graft with rectus abdominis muscles is procured with external iliac vessels. Implantation of abdominal wall is initiated after revascularization of the visceral allograft. Blood supply of abdominal wall is derived from the donor epigastric artery that can be anastomosed to recipient epigastric artery using microscope [30] (Fig. 39.10a). Alternatively, donor epigastric vessels are brought to the field in continuity with the external iliac vessels that are implanted into the recipient's common iliac vessels [28] (Fig. 39.10b).

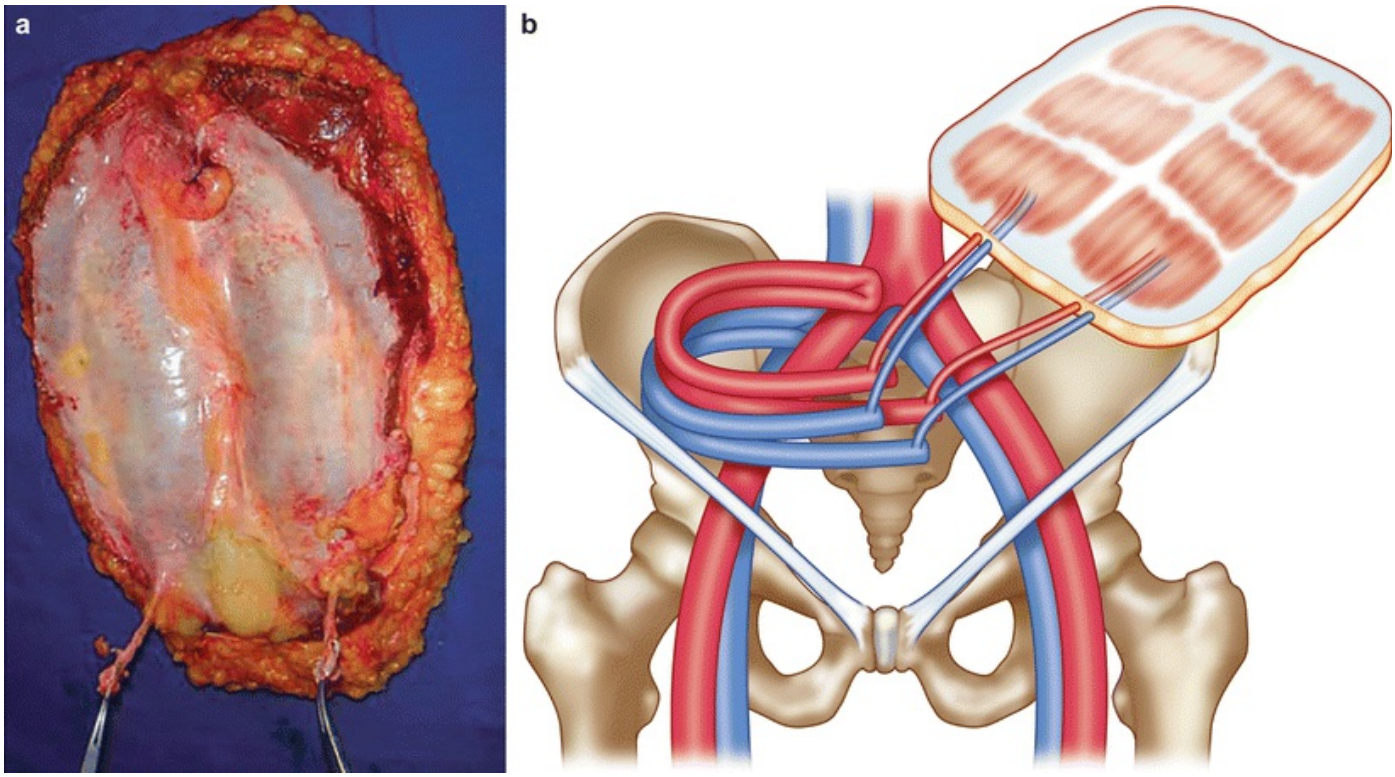


Fig. 39.10 (**a**) The abdominal wall graft isolated with bilateral epigastric pedicles (reprinted from Cipriani R, Contedini F, Santoli M, et al. Abdominal wall transplantation with microsurgical technique. Am J Transplant 2007:7:1304–7; with permission). (**b**) Donor epigastric vessels retrieved in continuity with the external iliac vessels that

are anastomosed into the recipient's common iliac vessels

Abdominal wall transplantation is a novel and feasible technique, but has not gained popularity in the community because of its technical complexity and potential postoperative complications. In many high-volume centers, most of the visceral allograft transplants are done without the need for major autologous or allo-abdominal wall reconstruction by the good selection of smaller size donors and judicious intraoperative intravenous fluid resuscitation with simple abdominal wall skin closure [3].

Therapeutic Advantages of the surgical modifications

The technical modifications have improved the therapeutic efficacy of the different types of visceral transplant. With modified multivisceral transplantation, donor liver is utilized for another recipient with end-stage liver disease. Preservation of the native spleen with pancreaticoduodenal complex improved survival with reduced risk of PTLD [19, 31–33] (Fig. 39.11). Another important advantage of preserving the pancreaticoduodenal complex is to improve the technical feasibility and safety of the procedure and to augment long-term advantages. By preserving the duodenal sweep, biliary drainage is easily established with a piggyback fashion between native duodenum and allograft duodenum or jejunum. As a result, biliary complications were eliminated. In addition, the islet cell mass is increased with reduced risk of calcineurin inhibitor and steroid-induced diabetes. With the adoption of portal venous drainage of the liver-free allograft, proper delivery of the hepatotropic factors to the native liver is maintained with different physiologic and immunologic benefits.

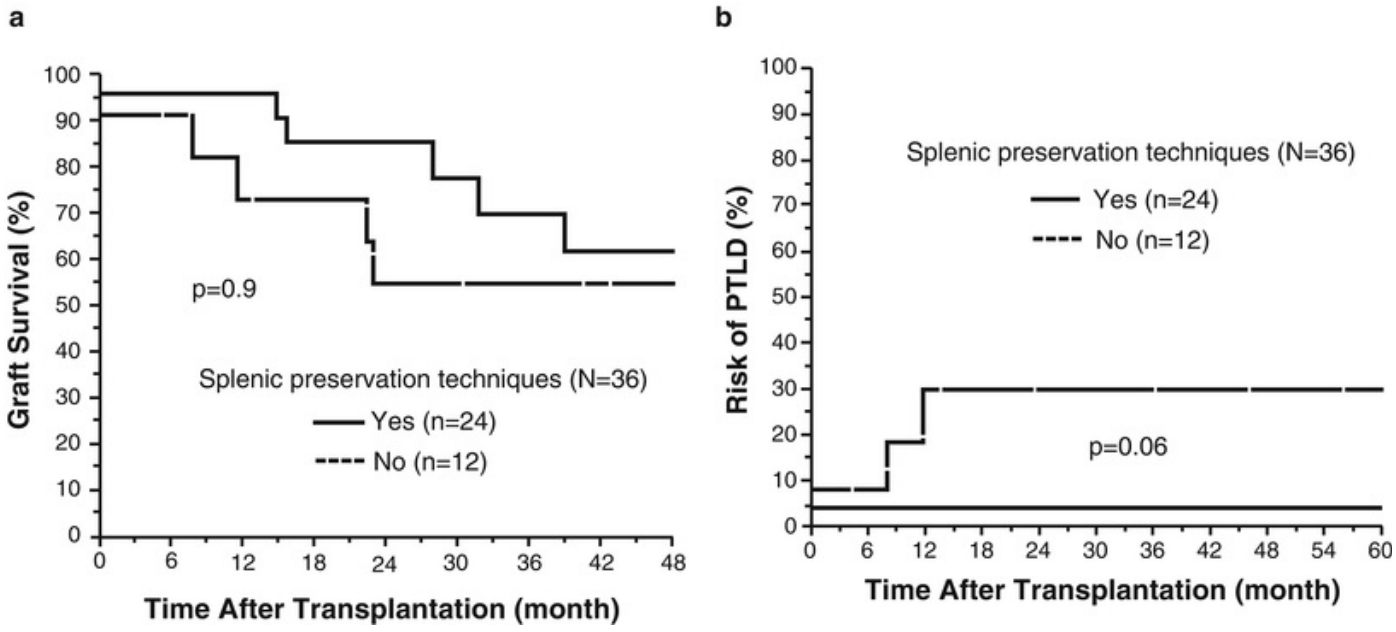


Fig. 39.11 (**a**) Kaplan–Meier graft survival according to the type of the recipient operation shows better short- and

long-term survival in the splenic preserving techniques. (**b**) Cumulative risk of post-transplant lymphoproliferative disorders (PTLD) in patients with and without preservation of the native spleen. Note the lower risk of PTLD with splenic preservation (data from Cruz RJ Jr, Costa G, Bond G, et al. Modified "liver-sparing" multivisceral transplant with preserved native spleen, pancreas, and duodenum: technique and long-term outcome. J Gastrointest Surg 2010;14(11):1709–21)

For those who required pancreaticoduodenectomy including patients with Gardner's syndrome who have duodenal adenoma(s) with severe dysplasia [18, 34–37], it is our common practice to preserve the native spleen [32, 33] (Fig. 39.6c). The published data demonstrated improved patient survival with reduced risk of PTLD and GVHD (Fig. 39.12). Efforts should always be made to preserve native spleen with all types of visceral transplantation because of its physiologic and immunologic therapeutic advantages.

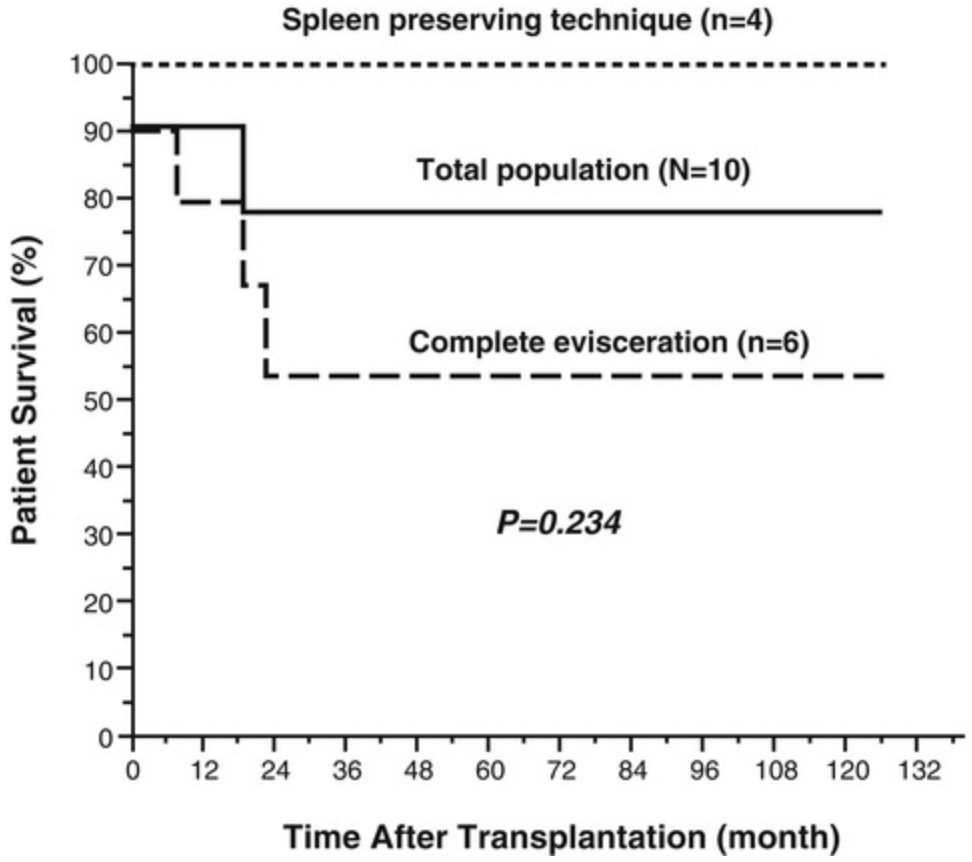


Fig. 39.12 Patient survival following modified multivisceral transplantation for Gardner's syndrome patients according to the type of evisceration technique (data from Cruz RJ Jr, Costa G, Bond G, et al. Modified multivisceral transplant with spleen-preserving pancreaticoduodenectomy for patients with familial adenomatous poplyposis "Gardner's syndrome." Transplantation 2011;91(12):1417–23)

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40. Preoperative Recipient Evaluation for Visceral (Intestine, Intestine/Liver, Multivisceral) Transplantation

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Keywords Multivisceral – Graft – Intestinal failure – Liver cirrhosis – Mesoportal thrombosis

Introduction

Patients who require intestine-containing grafts are diverse and can be categorized into the following three groups:

1. Patients who need an isolated intestinal transplant or a modified multi-visceral transplant including stomach, duodenum, pancreas, small intestine for gut failure (Group 1).

2. Patients who need both an intestine and liver transplant for intestinal failure with total parenteral nutrition (TPN) and liver disease (Group 2).

3. Patients with liver cirrhosis/complete mesoportal thrombosis who need either an intestine/liver transplant or a full multivisceral transplant (Group 3).

Group 1 patients are TPN-dependent and tend to become chronically dehydrated. Renal dysfunction is not uncommon. Sometimes they need simultaneous kidney transplantation. Because of their long history of parenteral nutrition (TPN) use, their line access tends to be limited and line infections need to be checked.

Group 2 consists of the Group 1 population with liver disease. They are much sicker than Group 1. Patients who have short gut syndrome with TPN-associated liver disease may not present signs of portal hypertension until their liver becomes more cirrhotic than regular cirrhosis patients, as portal flow is decreased due to short gut syndrome. Therefore, we treat these patients carefully once they develop ascites and portal hypertension.

Group 3 is made up of essentially the same as patients who undergo (isolated) liver transplantation. Liver/intestine or full multivisceral transplantation is needed because of difficulty securing inflow to the liver (portal vein flow). Therefore, preoperative evaluation and preparation of patients in this group is the same as that for liver transplant patients.

Indications and Contraindications for Visceral Transplantation

Indications

Visceral transplantation is indicated for the patients with (1) irreversible and permanent intestinal failure, and (2) presence or onset of life-threatening complications from TPN.

The onset of liver disease or central venous catheter-related complications such as recurrent or potentially fatal sepsis/fungemia and loss of venous access sites are life-threatening complications from TPN, as well as Medicare-approved criteria for visceral transplantation. Preemptive visceral transplantation (before the patient develops TPN-related complications) is still a controversial issue, as it has not been approved by Medicare or most insurance carriers [1, 2]. In addition to the indications above, patients with liver cirrhosis and mesoportal thrombosis (Group 3) are indicated for liver/intestine or full multivisceral transplantation.

Contraindications

Contraindications to visceral transplantation are similar to those for transplantation of other solid organs due to malignancy, severe systemic disease, etc. They may be even more absolute because of the considerable morbidity and mortality following this procedure. Thus, patients with multiple severe congenital anomalies, recent extra-

abdominal malignancy, or severe neurologic disability are not appropriate candidates for transplantation. Recent line infections could be a frequent dilemma for visceral transplant patients. However, the patient can undergo transplantation if a line infection is treated at least for a few days, and the patient is not bacteremic at the time of the procedure. Multisystem autoimmune diseases such as scleroderma and severe immune deficiencies are also relative contraindications to visceral transplantation [1–3].

Pretransplantation Recipient Evaluations

Neurological Evaluation

Patients frequently suffer subclinical cerebrovascular events, especially in the setting of hypotension, due to sepsis and ischemic bowel or systemic atherosclerosis. Therefore, our program performs a routine head computerized tomography (CT) scan at the time of outpatient evaluation. Anti-epilepsy drugs need to be checked prior to transplantation since many of them interact with tacrolimus (Prograf). Pretransplant consultation with the neurology service and switching anti-seizure medication to levetiracetam (Keppra) should be considered.

Psychiatric/Social Support Evaluation

Many Group 1 and 2 patients have received numerous surgeries. Some of them undergo 20–30 surgeries prior to coming to a transplant center. Many may have depression and anxiety disorders. Evaluation of patients by a designated psychiatrist who is familiar with intestinal failure and transplantation is essential. It is also not uncommon that patients use narcotics regularly for chronic abdominal pain and have high narcotic tolerance, factors which are extremely challenging in the perioperative setting. Preoperative evaluation by a chronic pain specialist to reduce narcotic use using alternative techniques is important. We prefer transdermal pain management while patients are on the waiting list. This facilitates establishment of a perioperative game plan.

Social support is extremely important for visceral transplant patients. Poor social support is one of the risk factors for long-term poor prognosis [4].

Cardiac Evaluation

Cardiac evaluation is essential for successful operative and postoperative management. It goes without saying that obtaining patients' past-medical and family history and examining cardiac risk factors are important initial steps. We recommend electrocardiograms and echocardiograms as a standard procedure. Cardiac stress tests should be performed for patients who fall in the age group for high incidence of

coronary artery disease or for those with histories warranting further heart evaluation. In select cases, a left heart catheterization is required to assess the extent of coronary artery disease. A right heart catheterization is required to measure pulmonary artery pressure when pulmonary hypertension is identified in the echocardiogram. Pulmonary hypertension is sometimes confusing in the setting of end-stage renal disease. Since pulmonary hypertension could cause right heart failure when the vena cava is cross-clamped (or preload decreases) and during reperfusion, it is essential to note the presence of pulmonary hypertension prior to transplantation.

Respiratory Evaluation

Pulmonary status should be investigated for those with previous histories of lung disease or smoking using CT scan of the chest and pulmonary function test with arterial blood gas.

Gastrointestinal and Hepatobiliary Evaluation

Gastrointestinal (GI) anatomy is evaluated using radiologic studies such as CT scan, upper GI series, small bowel follow-through, barium (or Gastrografin) enema, and endoscopic studies (upper and lower endoscopy).

Mild liver dysfunction is very common in patients with intestinal failure. Hyperbilirubinemia alone may not necessary warrant liver replacement since cholestasis can be reversible. A critical part of the examination is to look for portal hypertension (thrombocytopenia, presence of varices in endoscopy, and collateral portal flows on CT scan). Liver biopsy for the patient with liver dysfunction is essential in order to determine the need for simultaneous replacement of the liver and small intestine, unless the patient has obvious cirrhosis by clinical and radiological examination. The presence of bridging fibrosis or cirrhosis is an indication for liver replacement, although isolated intestinal transplant alone can be performed in certain settings if no portal hypertension is seen. Adequate specialized management of TPN (reduction of the amount of lipid to less than 1 g/kg/day) can result in significant improvement of liver dysfunction, avoiding the need to replace the native liver. We prefer transjugular liver biopsy and measurement of portal pressure gradient rather than percutaneous liver biopsy.

In order to decide whether or not liver replacement is necessary and better plan surgery, we routinely perform conventional visceral angiograms and portograms unless there are contraindications [5]. This can be replaced by CT angiogram/venogram or MR angiogram/venogram in other programs.

Nutritional Evaluation

Nutritional assessment is an essential part of pretransplant evaluation. Measurements include height, weight, head circumference (especially in children), triceps skin-fold thickness, and mid-arm circumference. Grip tests and five-minute walking tests can be useful, especially for patients with liver disease (such as those in Group 2 and 3). Evaluation of growth is essential in children. Assessment of current TPN for appropriate calories, proteins, lipids, vitamins, and minerals is important, keeping in mind that overfeeding can be harmful for patients with liver disease. Cycling TPN, limiting the amount of lipid (to <1 g/kg/day), and maximizing enteral feeding are essential in the setting of TPN-related liver disease. Blood levels of vitamins A, D, and E, zinc, carnitine, selenium, copper, and manganese are also measured at evaluation.

Renal Evaluation

Renal dysfunction is commonly seen in the setting of intestinal failure because of multiple episodes of dehydration due to diarrhea, high output from ostomy, and line sepsis, which frequently accompany acute renal failure. It is important to educate patients to avoid nonsteroidal anti-inflammatory drugs prior to transplantation. Some patients need simultaneous kidney transplants. We have lowered the threshold to perform combined visceral and kidney transplantation, especially because the posttransplant intestine tends to be more sensitive to hypotension during dialysis.

Endocrine Evaluation

In our program, a cortisol stimulation test is used to assess adrenal gland function to assure an appropriate response to the intense surgical stress involved in transplantation [5]. Patients tend to have chronic steroid use or history of use. Therefore, our threshold to use postoperative hydrocortisone even after completing Solu-Medrol recycle is low.

DEXA (Dual-energy X-ray absorptiometry) scan is routinely performed in the pretransplant evaluation especially because osteoporosis is very common in the setting of intestinal failure. Appropriate treatment of osteoporosis is necessary prior to transplantation.

Hematology Evaluation

Hypercoagulable state work-up is mandatory in visceral transplantation. Thrombogenic events often cause intestinal ischemia, Budd-Chiari syndrome, or mesoportal thrombosis.

Vascular Access Evaluation

Patients with intestinal failure who need TPN are prone to difficulty maintaining adequate intravenous access due to frequent exchange of central venous catheters and

subsequent line infection and venous thrombosis. Therefore, it is fundamental to have information on the patient's upper and lower central venous system, which is also crucial information at the time of transplantation. We routinely perform venograms to study the upper and lower central venous system. Some programs may use Doppler sonogram or CT venogram instead. When patients have severe venous stricture or thrombosis, superior vena cava syndrome may be encountered. If it is found in the early stage, an experienced interventional radiologist may be able to open the vena cava or innominate vein. Some cases require transhepatic or lumbar vein catheterization for intravenous access. For patients requiring simultaneous replacement of the liver and small intestine, however, adequate central venous access above the diaphragm is imperative for volume resuscitation and transfusion of blood products during the anhepatic phase of the surgery.

It is extremely important to establish a game plan for venous access and discuss it with the anesthesia and interventional radiology teams prior to transplantation in the setting of difficult intravenous access [6].

Infectious Evaluation

Routine infectious disease work-up is performed similar to that done for liver or kidney transplantation. In addition, patients with intestinal failure have more frequent episodes of line infection. Sub-clinical line infection can be a serious problem for visceral transplantation. We routinely perform blood cultures once a week while waiting for transplant, although a false positive could be cumbersome. When a possible recipient arrives at the hospital, we need to make sure the patient does not have an active infection. In our program, we tend to avoid paracentesis, although spontaneous bacterial peritonitis is an important issue when a cirrhotic patient becomes sicker and/or develops GI bleeding. Patients with intestinal failure, especially dysmotility problems, frequently develop aspiration pneumonia, which may not be treated lightly, especially while the patient is on the transplant waiting list.

Immunologic Evaluation

An immunological evaluation is performed, with double confirmation of the patient's ABO group, human leukocyte antigen (HLA) typing, Panel Reactivity Antigen (PRA), and the presence of anti-HLA class I and II antibodies by Luminex® assay. When PRA is high, some programs advocate desensitization with intravenous immunoglobulin and plasmapheresis and/or rituximab/bortezomib, although this desensitization method is still controversial, even in the kidney transplant setting. In patients with documented high levels of anti-donor HLA antibodies, a virtual cross-match is performed at the time of the organ offer to guide the decision making process to accept that specific organ for the anti-HLA highly-sensitized recipient. The virtual cross-match is an attempt to reduce

the incidence of antibody-mediated rejection and later graft loss secondary to chronic rejection.

Anesthesia Evaluation and Preparation for Surgery

It is important for an attending transplant anesthesiologist to evaluate patients while on the waiting list. The anesthesiologist examines the patient, reviews the work up, and determines an anesthesia strategy. Central venous access and cardiovascular status and overall medical condition are taken in consideration. This will facilitate the pre-anesthesia evaluation when the patient is called for the organ offer.

In general, all visceral transplantations except isolated intestinal transplantation involve more extensive surgery than liver transplantation. It takes significantly longer due to the dissection of more raw surface areas on top of portal hypertension. It is imperative to prepare large amounts of blood product such as 10 units of packed red blood cells, 10 units of fresh frozen plasma, and 10 units of platelets, and coordinate with the blood bank for cases when the patient needs even more blood products.

Rapid sequence anesthesia induction should be used because clinical or subclinical delayed gastric emptying is common in these recipients. Intraoperative monitoring is similar to that used for liver transplantation.

We use the prophylactic antibiotics including vancomycin, aztreonam, metronidazole, and liposomal amphotericin B. We may pay attention to the re-dose timing, especially when we have large blood loss. In our program, preconditioning using lymphoid-depleting agents rATG (Thymoglobulin®, Genzyme, Cambridge, MA), or alemtuzumab (Campath-1H, ILEX, Cambridge, MA) [3] is started at induction of anesthesia, infused over four to 6 h, and completed before reperfusion of the allograft. Premedication with acetaminophen (650 mg orally), diphenhydramine (25 mg intravenously), and methylprednisolone (1 g intravenously) is necessary. A second dose of methylprednisolone (1 g intravenously) is given when the allograft is brought to the surgical field for implantation.

It cannot be emphasized enough that communication between surgeons and the anesthesia team is essential when venocaval clamping, aortic clamping, and reperfusion occurs. An attending anesthesiologist should be present in the operating room when surgeons reperfuse organs. Reperfusion syndrome could be more extensive due to the volume of organs when a multivisceral graft is used. Therefore, intraoperative serum potassium must be lower than 4 mEq/L [5].

A continuous infusion of intravenous tacrolimus (1 mg/24 h) is started after reperfusion of the allograft. After reperfusion, continuous infusion of prostaglandin E1 (PGE1, Asprostadil®) is started at the dose of 0.1–0.6 μg/kg/h to increase the blood flow to the intestinal allograft as an attempt to reduce ischemia-reperfusion injury, minimizing platelet adhesion to the vascular endothelium. Because PGE1 can cause

hypotension, this medication is not started until the patient's blood pressure is normal without the need for vasoactive agents.

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41. Anesthesia for Multivisceral Transplantation

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Introduction

Multivisceral transplantation has its roots in the "cluster of organs" concept developed by Dr. Starzl [1, 2]. According to this notion, intra-abdominal viscera resemble a cluster of grapes on a "grapevine," wherein each individual grape is removable without disturbing the integrity of the vine itself. Thus, as long as the nutrient central stem of the celiac axis, superior mesenteric artery, superior mesenteric vein, and portal vein are preserved, various organs can be removed from the cluster, thereby customizing the transplanted organ complex to the recipient's needs. Therefore, multiple combinations of transplanted organs—ranging from an isolated intestine to a large cluster containing the stomach, pancreas, duodenum, small and large intestine, liver, spleen, and kidneys—could be offered depending on the individual patient's needs.

Intestinal transplantation is an adaptation of this concept to patients with isolated intestinal failure. Development of concomitant liver failure (such as secondary to total parenteral nutrition) might necessitate addition of a hepatic graft (i.e., intestinal and

liver transplantation). Complications of severe portal hypertension, thrombosis of splanchnic arterial and/or portal circulation, and catastrophic pathology of the alimentary tract may require replacement of native dysfunctional units in the course of multivisceral transplantation. Profound disease of the alimentary tract such as locally aggressive nonmetastatic neoplasms, advanced gastrointestinal (GI) dysmotility disorders, severe trauma of the GI tract, multiple adhesions after prior surgery (especially if complicated by the development of enterocutaneous fistulas), or radiation enteritis affecting the pancreas and stomach may all require multivisceral transplantation [3, 4]. Concomitant chronic renal insufficiency and failure may require additional kidney transplantation, especially in the setting of frequent episodes of dehydration and the attendant renal toxicity of antimicrobial, antifungal, and immunosuppressive therapy.

Thus, intestinal transplant can be seen at the core of multivisceral transplantation. Inclusion of additional organ grafts usually reflects the individual patient's pathophysiologic needs to replace dysfunctional and affected organs.

Even though Drs. Lillehei and Starzl developed a successful surgical technique more than 50 years ago, intestinal transplantation achieved practical recognition only with the advent of modern immunosuppressive therapy, namely, tacrolimus, in 1989 [4–6]. Refractory graft rejection and sepsis that befuddled prior attempts at intestinal transplantation were attributed to strong intestinal expression of histocompatibility tissue antigens, and the presence of numerous resident leukocytes and microorganisms. Fortuitously, inclusion of additional organ grafts, such as the liver and spleen, appeared to confer more tolerance [6, 7], an important benefit of multivisceral transplantation. Further technical benefits of multivisceral transplantation include its orthotopic nature, maintenance of minute vascular networks, and the replacement of the native stomach and pancreaticoduodenal complex affected by adhesions and portal hypertension. Lower risks of technical complications, such as biliary leaks and vessel thrombosis, make multivisceral transplantation the procedure of choice for children with extensive pathology in some centers [6].

Intestinal allograft has been described as the Achilles heel of multivisceral transplant. [6] The pivotal importance of intestinal engraftment and prevention of allograft rejection lead to the introduction of novel immunosuppressive/immunomodulatory regimens. Perioperative partial depletion of recipient lymphoid cells with antibody induced immunosuppression with monoclonal IL-α_2 receptor blockers or polyclonal antilymphocyte agents was demonstrated to improve allograft tolerance, decrease the need for long-term post-transplant immunosuppression, moderate the frequency and severity of rejection and septic episodes, and contribute to improved patient and graft survival [4, 5].

With steady improvements of surgical and immunosuppression/immunomodulation techniques, multivisceral transplantation was increasingly viewed as a practical

therapeutic option, particularly in patients with extensive portomesenteric and splenic venous thrombosis [5–7]. Out of 1859 intestinal transplants reported to United Network of Organ Sharing (UNOS) until 2009, 37 % were intestine-only, 24 % included the intestine and liver, and 30 % included the intestine, liver, and pancreas. One-, 5-, and 10-year graft survival rates were 62, 45, and 36 %, respectively, for the intestine and liver, and 69, 48, and 33 %, respectively, for intestine, liver, and pancreas transplantation [8]. The longest survival of intestinal transplants was reported in recipients of combined intestinal and liver cadaveric transplants: 19 years in an adult and 18 years in a child.

Recipient age and transplantation in patients waiting at home as opposed to the hospital are associated with improved allograft and patient survival [4]. These factors probably reflect the recipients' functional status, and support the need for preemptive assessment in patients still tolerating parenteral nutrition. Additional factors contributing to longer allograft and patient survival include perioperative antibody induction immunosuppression with monoclonal IL-α_2 receptor blockers or polyclonal antilymphocyte agents (such as antithymocyte globulin), and surgical center experience (at least 10 cases). Center experience has proven to be extremely heterogeneous, reflecting the complexity of the integrated medical care required for these patients. Around the world, the vast majority (83 %) of intestinal and multivisceral transplants were performed by ten centers (out of 61 programs in 19 countries). More than three quarters of these were performed in the United States [4]. In the United Sates, out of a total of 43 programs, only 8 reported having performed 100 or more cases; the Miami Transplant Institute-Jackson Memorial Hospital, The Nebraska Medical Center, and the University of Pittsburgh Medical Center were reported as the most active United States centers, each performing more than 300 cases, and together contributing to half of all procedures worldwide [8].

Overview of the Surgical Aspects of Multivisceral Transplant

The intestine, liver, and pancreas with their intact donor circulation are retrieved simultaneously ("cluster of organs") from the same donor. The duodenum and parts of the stomach may be retained in continuity with the graft jejunum to avoid biliary reconstruction. Frequently, the enteric and celiac ganglia are preserved to lessen postoperative graft dysmotility. The colonic segment may be included en bloc with the intestine in some cases [5, 7]. The graft is infused with University of Wisconsin (UW) solution in situ and is immersed in UW solution for transport; that safely preserves the grafts for approximately 10 h [2]. If the recipient's liver, pancreas, or spleen are to be retained, these organs are removed from the "cluster" so that the liver could be used in another recipient (modified multivisceral transplant).

Intestinal graft availability is significantly constrained by its high sensitivity to

ischemia, particularly in brain-dead donors requiring vasoactive infusions, and by potential size mismatches between the donor and recipient [9]. Consequently, waiting times for patients in need of intestinal, intestinal-liver, or multivisceral transplants have been long. To alleviate the problem of size mismatch, reduced-size allografts may be used, particularly in children [5], or plastic surgery techniques may be needed to close the abdomen. Alternatively, part of the abdominal wall and intact inferior epigastric vessels may be harvested en bloc with the iliac vessels [7] to be used to close abdominal wall defects, especially in patients whose abdominal wall was damaged by multiple prior surgeries.

The recipient procedure is conceptually and broadly divided into two phases: abdominal exenteration (resection of native organs) and graft implantation [2, 7]. Similar to liver transplantation, the latter is further subdivided into anhepatic, reperfusion, and reconstruction periods. The selection of native organs to be removed, particularly the liver and kidneys, is based not only on the primary pathological process, but also on the extent of alimentary tract dysfunction due to portal hypertension, abdominal sepsis, adhesions, and the effects of nephrotoxic medications, parenteral nutrition and associated hypovolemia and episodes of septicemia.

Recipient surgery usually commences with lysis of multiple adhesion upon entry into abdominal cavity. During abdominal exenteration of affected intra- and retroperitoneal organs, the celiac axis and superior mesenteric artery are clamped and divided early to achieve dearterialization. This greatly facilitates mobilization and resection of the native viscera; sometimes the entire foregut, including distal stomach, duodenum, proximal jejunum, liver, and spleen are removed en bloc.

If the native liver is retained and a modified multivisceral transplant is planned, the hepatic artery and its branches are carefully dissected and preserved, allowing nutrient arterial hepatic flow during the time of portal venous flow interruption. The common bile duct and arterial supply (including the gastroduodenal and splenic arteries) are divided and all organs to be removed are dearterialized.

Hepatectomy during multivisceral transplant could be performed conventionally, (i.e., en bloc with the inferior vena cava [IVC]), or using the “piggy-back” technique (i.e., stripping the liver from the retrohepatic vena cava, leaving the IVC intact, and mitigating the hemodynamic consequences of caval flow interruption). In the “piggy-back” technique, partial IVC clamp occlusion allows systemic blood return. Veno-venous bypass can be used to facilitate venous blood return from mesenteric, portal, and systemic lower body basins to the axillary vein in patients who cannot tolerate the loss of portal and IVC venous return. The great majority of multivisceral transplantation in the United States is performed without veno-venous bypass [5–7, 9]. In intestinal-liver transplants , a porto-caval shunt may be performed to facilitate venous drainage of the retained native organs.

During the anhepatic stage , the vascular targets for graft revascularization are

prepared. Rearterialization of the composite graft is usually achieved from the recipient's infrarenal aorta to the donor's infrarenal aorta directly or by using an interposition graft. Venous drainage of the en bloc multivisceral transplantation is usually through the donor IVC or through a cuff of the hepatic vein to the host IVC. In a modified multivisceral transplant, venous drainage is created by anastomosis of the graft and host portal veins. Subsequently, the porto-caval shunt constructed earlier in the procedure may be taken down to facilitate blood flow to the liver graft. Thus, every effort is exerted to reconstruct graft vascular inflow, venous outflow, and exocrine drainage as close to normal as possible. However, the risks of porto-caval shunts disconnection and construction of porto-portal anastomoses may be substantial, and porto-caval shunts are frequently left in place without detriment to graft outcomes [5, 6, 9].

In preparation for reperfusion, the preservation solution is flushed out with sterile albumin and Lactated Ringer's solution from the composite graft, particularly the liver, in an attempt to lessen the severity of hemodynamic changes and risk of collapse. Reperfusion usually commences with unclamping of the suprahepatic IVC, infrahepatic IVC, and portal vein, and ends with an aortic conduit. That is the time of the most significant hemodynamic and metabolic changes, discussed in more detail further.

The reconstruction period after multivisceral transplantation may be extensive and prolonged; remaining adhesions are taken down, and targets for restoring intestinal and biliary continuity are chosen. Sites of proximal anastomosis may include the stomach (gastrostomy), duodenum, or proximal native jejunum; distal targets may include the colon with diverting ileostomy, or creation of a permanent ileostomy in patients without a colon. Following gallbladder removal, Roux-en-Y choledochojejunostomy may be required for biliary continuity in patients with intestinal and liver transplantation; if the duodenum was retained en bloc in a composite graft, no biliary anastomosis may be required.

Closing of the abdominal cavity may be difficult for many reasons, such as size mismatch, loss of abdominal domain, and abdominal and graft swelling. Therefore, consideration is frequently given to the use of smaller than recipient donors, smaller grafts, and plastic surgery techniques. Additionally, cadaveric grafting of the abdominal wall with intact inferior epigastric vessels has been used successfully to facilitate abdominal closure, particularly in recipients whose abdominal wall has been damaged by multiple prior surgeries, fistulas, or trauma [7].

Physiologic Challenges: Special Considerations in Multivisceral Transplantation

As it is evident from this brief description, the procedure may be prolonged, associated

with significant blood loss, metabolic abnormalities, temperature, fluid and electrolyte shifts, and coagulopathy. These challenges may be more difficult to overcome in malnourished and frequently dehydrated patients with significantly reduced physiologic reserves due to long-standing intestinal failure, complications of parenteral nutrition, and liver dysfunction. Prior episodes of central venous thrombosis with loss of central venous sites for cannulation, infections, abdominal sepsis, and renal insufficiency add to the complexity of perioperative care.

In the initial stage of surgery, in addition to the usual concerns related to multiple reentries into the abdominal cavity and lysis of adhesions, the exenteration of abdominal organs is itself associated with a rapid and progressive deterioration of systemic hemodynamics (cardiac preload and output), as well as derangements in oxygen, lactate, and glucose metabolism [10]. Therefore, hemodynamic and metabolic compromise due to blood loss and fluid shifts during the dissection and pre-anhepatic stage is frequently exaggerated by shock-like "centralization" of diminished cardiac preload and output associated with exenteration.

The physiologic concerns during the anhepatic, reperfusion, and reconstruction phases are similar to those in liver transplantation [11], with the proviso that they are exaggerated by the poorer physiologic state of the recipients, larger fluid and electrolyte shifts, and by the increased complexity and duration of the procedure. Particularly worrisome is intestinal ischemia-reperfusion injury with severe graft edema, bacterial translocation, and hemodynamic shock due to production and release of multiple vasoactive and pro-inflammatory gut hormones [12, 13]. Cotemporaneous liver and intestinal reperfusion may lead to an increased severity of post-reperfusion syndrome.

The reconstruction period of the intestine and biliary complex is often longer than in liver transplantation alone, and may be associated with greater third-space losses and intestinal edema. This period may coincide with the phase of delayed ischemia-reperfusion reactions, such as neutrophil chemotaxis and late release of pro-inflammatory mediators. Indeed, pathological examination of intestinal grafts at the end of the transplantation suggests changes associated with ischemia-reperfusion injury [14]. Concomitant hypothermia, acidosis, and hypoxia may potentiate intestinal mucosal swelling, bacterial translocation, and systemic release of pro-inflammatory molecules , which all result in a systemic inflammatory response and sepsis-like clinical presentation. Conversely, rapidly improving hemodynamic, metabolic, and coagulation parameters during the reconstruction period may indicate graft well-being and recovery [14, 15].

Anesthetic Considerations in Multivisceral Transplantation

The described pathophysiologic considerations underpin the anesthetic plan and preparations required for the perioperative care of patients undergoing multivisceral

transplantation. The procedure will tax the severely diminished physiologic reserves of these patients. The ability of the patient's cardiac and pulmonary systems to respond to severe perioperative stress and to maintain oxygen delivery and tissue oxygenation in face of a highly variable cardiac preload and afterload, hemoglobin concentration, and pulmonary resistance is paramount for survival. In addition to "anesthetizing" the patient, the anesthesiologist assumes the role of critical care specialist in a highly volatile intraoperative milieu. Assuring the safe conduct of anesthetic care, intraoperative life support, and critical care are complimentary priorities of the anesthesia team caring for patients undergoing multivisceral transplantation.

Patients presenting for multivisceral transplantation are typically critically ill, and frequently at the point of exhaustion of all available therapeutic options. Dehydration, central compartment contraction, ascites, pleural effusions and anasarca, hepatic dysfunction, portal hypertension and concomitant renal insufficiency all profoundly affect the pharmacodynamics and pharmacokinetics of perioperatively administered medications [16, 17]. Intestinal insufficiency impairs the absorption of oral medications. Hepatic dysfunction due to paucity and diminished activity of hepatocytes reduced liver flow, and porto-caval shunting markedly decreases hepatic clearance, while impaired secretion of bile acids, bilirubin, and organic anions impair biliary excretion of medications. Low serum concentrations and qualitative changes in albumin and α_1-acid glycoproteins (due to malnutrition and impaired synthesis) lead to reduced plasma protein binding of circulating medications. An increased serum bilirubin concentration may further impair plasma protein binding of circulating medications. The presence of ascites in the context of low protein binding results in a large volume of distribution. Similarly, a low muscle mass and reduced metabolism of creatine to creatinine may render calculated creatinine clearance rates inaccurate, and lead to an under-appreciation of renal insufficiency and to a significant overestimation of glomerular filtration rate [18] and renal elimination of intravenously administered medications, such as antibiotics. Overall, some of the most important effects reported include decreased therapeutic efficacy of loop diuretics, and significantly increased patient sensitivity to the central effects of analgesics, opioids, anxiolytics, and sedatives.

Nonpharmacodynamic epiphenomena may influence the patient's clinical responsiveness to medications as well. For example, the presence of encephalopathy significantly potentiates the central nervous system effects of opioids and sedatives, presumably due to accumulation of endogenous nonbenzodiazepine $GABA_A$ receptor ligands. Diminished response to β-antagonists may be directly related to the degree of liver dysfunction and hyperdynamic pattern of circulation in patients with liver cirrhosis [16]. Additionally, variable hepatopetal blood flow during the initial dissection, coupled with blood loss, transfusions, large intraoperative fluid shifts, absence of hepatic metabolism during the anhepatic stage, and uncertain graft recovery during

reconstruction, all compound the complexity of multivisceral transplantation pharmacokinetics.

The effects of immunosuppressive medications on perioperatively administered medications have not been studied adequately, and most reports are largely limited to cyclosporine-A [19]. Overall, these appear to be poorly understood and have modest clinical effects.

Patient Selection and Pretransplant Evaluation

Prospective multivisceral transplantation recipients are usually very ill, receive high level of multidisciplinary support, and, therefore, usually present to the attention of an anesthesiologist having been fully worked up. The majority will have been treated for severe intestinal insufficiency with total parenteral nutrition (TPN) , and demonstrate either failure, or complications, of TPN therapy. For example, the loss of combined gastrointestinal, pancreatic, and biliary secretions may exceed intravenous infusion rates tolerated by the cardiopulmonary system, leading to frequent episodes of severe dehydration despite TPN and intravenous fluid supplementation. TPN-induced progressive liver dysfunction, thrombosis of two or more major central veins ("vanishing veins"), frequent episodes of line-induced systemic sepsis, and even a single episode of line-related fungemia, septic shock, or acute respiratory distress syndrome mandate multivisceral transplantation [20, 21]. Overall, patients requiring long-term TPN support suffer from 20 % 4 years mortality [22], a powerful argument for earlier consideration and referral for multivisceral transplantation. Additionally, multivisceral transplantation is offered to patients with terminal conditions not amenable for other medical therapies, such as slow-growing tumors of the upper abdomen involving the vasculature of the mesenteric root, liver metastasis without peritoneal and extraabdominal spread, portomesenteric thrombosis of various etiologies, abdominal catastrophes or a "frozen abdomen" [23].

Absolute contraindications to multivisceral transplantation include severe, life-limiting conditions such as metastatic cancer, ongoing or recurring infections resistant to treatment, or acquired immunodeficiency syndrome (AIDS) (based on criteria established by the Centers for Disease Control and Prevention: CD4 count of less than 200 cells/mm, presence of Kaposi's sarcoma or other neoplasm, and opportunistic infections, including aspergillosis, tuberculosis, coccidioidomycosis, and resistant fungal infections). Comorbidities rendering a patient "inoperable" or at "unacceptably high risk", inability to accept and tolerate potential complications from immunosuppressive regimens, and noncompliance preclude surgery as well [20, 21].

Preoperative evaluation of prospective patients includes a thorough examination of the cardiac and pulmonary systems, based on the current recommendations for major vascular and aortic (noncardiac) abdominal surgery [24–26].

Specific to the preoperative examination of patients presenting for multivisceral transplantation is venous access determination using duplex ultrasonography [27] or venography [28]. The majority of these patients may have demonstrated stenosis or obstruction of one or more central venous sites, and some may even require intraoperative arterial, intraosseous or surgical access to the IVC or hepatic veins. This is particularly true in patients exhibiting a hypercoagulable state and in those with IVC filters [28].

Perioperative Management

Similar to liver transplantation, preparation for multivisceral transplantation includes vasoactive medications, monitoring, and auxiliary equipment to ensure the hemodynamic and metabolic stability of the recipient and favorable milieu for graft reperfusion and recovery [29–31]. Wide temperature fluctuations , large fluid and electrolyte shifts, coagulopathy, blood loss, prolonged exposure of the abdominal cavity, the hemodynamic consequences of exenteration, vascular clamping, graft ischemia, reperfusion, and subsequent post-reperfusion syndrome, as well as recovery from ischemia-reperfusion injury during the reconstruction period mandate careful monitoring and ability to intervene rapidly and effectively.

Airway management commences with the realization of the high probability of prolonged postoperative ventilator support in an immunocompromised and malnourished patient at risk for ventilator-associated pneumonia. Additionally, the emergent nature of these procedures may necessitate “rapid-sequence” induction of general anesthesia and tracheal intubation. Choosing an endotracheal tube with subglottic secretion drainage (such as Mallinckrodt™ TaperGuard™ Evac Endotracheal Tube) may allow suctioning of subglottic secretions (intermittently or continuously) to lessen the risk of microaspiration and ventilator-associated pneumonia. Alternatively, silver-impregnated endotracheal tubes may be effective in suppressing microbial biofilm formation and endotracheal tube colonization with pathogens associated with ventilator-associated pneumonia [32]. Implementation of pulmonary protective ventilation strategies, such as maintaining tidal volumes of 6–8 ml/kg, application of mild positive end-expiratory pressures of 6–8 cm H_2O, and frequent recruitment maneuvers has been associated with significantly decreased pulmonary complications and improved patient outcomes [33]. However, performance of recruitment of maneuvers as defined in IMPROVE trial (continuous positive airway pressure of 30 cm of H_2O for 30 s repeated every 30 min) in hemodynamically unstable patients may lead to episodes of hypotension, and should be performed very cautiously.

Beat-to-beat blood pressure monitoring and frequent arterial blood gas analysis require direct arterial cannulation; for the sake of redundancy, two sites are frequently chosen. Adequate central venous access is essential for blood and fluid transfusion and

for intravascular volume monitoring; it should allow rapid volume delivery even when housing a pulmonary artery catheter. Cardiac performance, global flow indicators, and static indices of cardiac preload, such as central venous, pulmonary artery, and pulmonary artery occlusion pressures are continuously assessed using S_VO_2-enabled pulmonary artery catheters [34–36].

A number of less invasive alternatives to cardiac output monitoring based on arterial pulse contour analysis could be considered for intraoperative use [37]. However, during periods of hemodynamic instability, varying vasoactive support, and wide and acute changes in vascular tone, these devices may require frequent recalibrations and render cardiac output readings inaccurate and unreliable [37–41]. On the other hand, the ability of these devices to estimate pulse pressure and stroke volume variations with positive pressure ventilation could offer a distinct advantage in determining fluid responsiveness in the course of resuscitation. However, using the response to fluid loading as goal-directed therapy may be result in more aggressive volume loading, higher positive fluid balance, and longer ventilator support [42].

Echocardiographic assessment of global flow, using either transesophageal echocardiography (TEE) or esophageal Doppler, also allows for goal-directed fluid management [37, 43] and continuous monitoring of global flow indices (such as stroke volume). Additionally, TEE offers a continuous assessment of cardiac preload and myocardial performance (left and right ventricular ejection fractions). However, intraoperative TEE may be limited by operator-specific and institutional concerns (expense and need for training, expertise, and experience), patient-specific factors (tissue fragility, esophageal varices, and coagulopathy), and procedure-specific considerations (use of parts of the stomach in multivisceral transplantation).

The adequacy of peripheral perfusion traditionally was assessed using blood lactate and base excess determinations. In multivisceral transplantation, as is in liver transplant, intermittent blood lactate measurements may not be suitable for goal-directed resuscitation, since hyperlactatemia may indicate diminished hepatic lactate clearance rather than tissue hypoxia [40, 44]. Alternatively, tissue oxygen delivery and utilization could be continuously assessed with near-infrared spectroscopy of skeletal muscles (S_tO_2) or fronto-parietal brain parenchyma (regional cerebral oximetry). While definitive data is lacking, anecdotal evidence suggests a utility of near-infrared spectroscopy in goal-directed transfusion and resuscitation [45].

Prevention of hypothermia in face of prolonged abdominal cavity exposure, large fluid shifts and requirements [36] call for extensive monitoring and body surface and fluid warming. We consider the use of forced-air surface heating (such as full-access underbody and upper-body Bair-Hugger®, Arizant Healthcare, Inc, Eden Prairie, MN) and fluid warming in all cases. The choice of particular devices used for rapid fluid warming and administration is largely institution-specific. In our experience, high-flow

Ranger (3M™ Ranger™ Blood and Fluid Warming System, Arizant Healthcare Inc, Eden Prairie, MN) and Belmont fluid management system (FMS 2000, Belmont Instrument Corp., Billerica, MA) have been very effective and allowed a wide range of infusion rates [46, 47]. Core temperature monitoring is performed from several sites, usually from the pulmonary artery and urinary bladder [48], keeping in mind their respective limitations, such as exposure of the pulmonary circulation to cold graft effluent during reperfusion, and the degree of exposure of the urinary bladder to ambient temperatures during prolonged major abdominal surgery. Coagulopathy may increase the risk of bleeding during placement of the nasopharyngeal probe, and esophageal temperature probes may interfere with placement of the TEE transducer and reduce image quality.

Intraoperative point-of-care viscoelastic devices [49] have largely replaced traditional laboratory-based coagulation testing in the perioperative management of patients undergoing multivisceral transplantation. They provide real-time surveillance of various hemostatic processes and suggest effective therapeutic interventions [50]. In addition, they may alert to the extent of ischemia-reperfusion injury and delayed graft recovery [14, 51], and afford additional insight into the graft's metabolic activity [52]. However, the absence of standardization of various viscoelastic devices prevents complete data interchangeability [53], an important consideration when the decision to treat is based partly on the monitoring device in use [54].

The conduct of anesthesia is a central and integral part of perioperative care, and is planned and executed to integrate seamlessly with the postoperative critical care. To this end, compliance with the current recommendations for facilitation of transfer of care to ICU team, including protocols for pre-transport report to intensive care unit (ICU), patient transfer procedures and ICU admission, assessment, initial interventions and detailed report is paramount [55]. Development of standardized hand-out protocols for ICU report may improve safety of critically ill patients during the transfer of care from anesthesiologists to critical care specialists [56].

Conclusions

Advances in surgical techniques, increased understanding of immunologic reactions, and improvements in immunosuppressive regimens, anesthestic, perioperative critical care, and postoperative surveillance have allowed multivisceral transplantation to emerge as an effective, lifesaving option for patients running out of other therapeutic modalities. The perioperative care of these severely ill patients requires intense multidisciplinary collaboration, particularly within the triangle of surgeons, anesthesiologists, and intensivists. Despite all the progress made, much research remains to be done, especially in the area of patient outcomes, before the procedure could be offered outside few select, highly specialized, tertiary referral centers.

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42. Multivisceral Transplantation: Intraoperative Vascular Access Strategy

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Introduction

Patients who have short gut syndrome are unable to adequately absorb water and nutrients. Total parenteral nutrition (TPN) may maintain survival for a period of weeks to years, but the quality of life is often poor. Recurrent bloodstream infections [1], vascular thrombosis, and liver failure are life threatening complications. Multivisceral transplantation is a complex operation that has been used to replace nonfunctioning intestine and liver with graft organs [2]. Indications include: short gut syndrome due to infarction, multiple bowel resections or trauma; pseudo-obstruction; familial polyposis; and vascular failure of the portal or hepatic veins that prevent successful isolated liver transplantation. The graft may include liver along with intestine, stomach, and other organs. Substantial institutional commitment is needed for this to be successful; careful management is required well into the postoperative period. Immunosuppression to avoid organ rejection must be balanced against the need to prevent infection while the graft is continuously exposed to gastrointestinal contents.

Vascular access is needed for administration of medications, monitoring of hemodynamic parameters, sampling of venous and arterial blood, and replacement of

fluids and blood. Third space fluid loss may be extensive and blood loss can be massive. Vascular clamping to permit native organ removal and graft placement may sequester intravascular volume; maintaining adequate preload under these circumstances may require rapid addition of volume to the nonsequestered vascular beds. Establishing adequate and perhaps redundant vascular access needs to be accomplished with deliberate speed; transplant operations are always emergencies when graft organs become available. Preoperative planning including a strategy for vascular access will improve the likelihood of a successful outcome [3].

Stages of the Operation

The stages of multivisceral transplantation are: preoperative evaluation, induction of anesthesia, establishment of vascular access and other monitors, laparotomy with removal of nonfunctioning native organs, placement of the graft, reperfusion, reestablishment of bowel continuity, and abdominal closure. Recovery is often prolonged and may include return to the operating room for additional surgery. Because the native small bowel is missing or removed during surgery, portal venous flow does not require veno-venous bypass as used in isolated liver transplants [4].

Preoperative Assessment

Candidates are often cachectic and have multiple comorbidities. They are frequently colonized with antibiotic resistant organisms that are therapeutic challenges if they gain entry to the systemic circulation through vascular access devices. While many patients undergoing isolated liver transplantation are hypo-coagulable, patients undergoing multivisceral transplantation are often hyper-coagulable [5]. TPN is usually administered through central venous lines. The administered fluids are excellent growth media; line infection and thrombosis is common [6]. Progressive loss of veins that can be accessed conveniently increases the urgency for transplantation and also makes it more difficult.

Meticulous sterile technique during placement and dressing of vascular lines cannot be overemphasized. Lines should be secured to prevent both inadvertent line removal and the advancement of exposed (and potentially contaminated) sections of long catheters into the circulation. All but small bore catheters intended for early removal should be sutured. Multivisceral transplant patients have fragile skin due to malnutrition and the use of steroids and other drugs. If skin adhesives are used skin tears may result.

A venogram of the major veins including jugular, subclavian, femoral, and iliac veins can identify which vessels are open [7]. Sonograms, computed tomography (CT), or magnetic resonance (MRI) studies may be alternatives [8]. Due to the underlying medical problems and the many phlebotomies, peripheral veins are usually exhausted by

the time that transplantation is a consideration.

When central veins are blocked, blood return occurs through collateral channels. A system of well-developed collaterals may accommodate moderate additional flow but may not support massive transfusion. Bilateral occlusion of the jugular and subclavian veins can result in a *superior vena cava syndrome equivalent* with swelling of the face and upper extremities. Dilated veins on the chest wall may be noted; these superficial veins form anastomoses with abdominal veins permitting blood to return to the heart via the inferior vena cava or azygous system. This is referred to as a *reverse caput medusa*. Cannulation of these superficial veins is possible but they are usually distended, tortuous, and accommodate additional flow poorly; venipuncture sites may bleed profusely. Infused fluids may result in localized vascular congestion without restoring cardiac preload.

Anesthetic Induction and Monitoring

Anesthetic challenges include induction of anesthesia, adequate monitoring, and the ongoing delivery of appropriate fluids and medications to maintain hemodynamic stability both during surgery and into the recovery period.

Most patients should be considered to have “full stomachs” even if most of the small bowel has already been removed. Retained gastric and oral secretions, poor motility, and the emergent timing are all factors to consider; usually a rapid sequence induction of anesthesia is utilized if any reliable IV can be established. Other alternatives for anesthesia induction include intramuscular ketamine and succinylcholine for rapid sequence induction or alternatively, awake intubation under local anesthesia with inhalation induction after intubation. Intra-nasal administration of midazolam may help and if the risk of aspiration is felt to be low, inhalation induction by mask can be considered.

Following induction, monitors and definitive vascular access should be established. EKG, temperature, pulse oximetry, neuromuscular blockade monitors, and measurements of exhaled gases can follow standard anesthetic practice recognizing that adhesive electrodes are subject to dislodgement if they are near the surgical field. Blood pressure can be measured by cuff during induction, but direct measurement by percutaneous arterial line(s) permits continuous measurement. Arterial lines can be placed in the radial, ulnar, brachial, axillary, femoral, and *dorsalis pedis* arteries. As in liver transplantation, femoral arterial lines [9] usually give more reliable pressures than do radial lines after reperfusion. Femoral arterial lines may become temporarily unusable when the aorta is clamped to create an arterial anastomosis with the graft. A second arterial line in the upper extremities provides pressure monitoring during this period and permits pressure monitoring to be uninterrupted during sampling of arterial blood.

Continuous attention to the volume status is needed. Recurrent episodes of hypovolemia need to be minimized. A patient may recover from a single episode of hypovolemic or anemic stress [10], however, transplant operations are lengthy and each subsequent episode results in progressively poorer recovery. Volume overload results in tissue and pulmonary congestion. Edematous organs function poorly, are more difficult to implant, and in extreme cases may prevent abdominal closure. To maintain optimal preload, it is important to have a way to measure volume status [11, 12] and adequate means to replace fluid losses as they are occurring. Based on the venogram, patients can be categorized into three groups: patients who have patent veins both above and below the diaphragm; patients with blockages of veins equivalent to superior vena cava syndrome; patients with blockages equivalent to superior vena cava syndrome and also occlusions of the iliac system.

Vascular Access Strategies

Group One: Routine Vascular Access

Patients in the first group can undergo monitoring of preload with CVP and PA catheters inserted in the routine fashion. Skin preparation with antiseptics reduces the risk contamination. Likelihood of contamination is affected by site of insertion, how long the catheter remains in place, and any break in sterile technique in inserting or maintaining the catheter. During multivisceral transplantation, jugular veins are usually preferred over using the subclavian due to the risk of pneumothorax or arterial puncture. While pneumothorax can be treated with a chest tube, inadvertent puncture of the subclavian artery is more difficult to apply hemostasis.

If superficial veins are available conventional placement of IV catheters can be used. Catheter-over-needle devices are inserted through the skin into veins distended by use of a tourniquet, or alternatively into named veins using anatomic landmarks or ultrasound guidance [13]. The flow through a catheter is related to the viscosity of the fluid administered, the diameter of the catheter and the pressure gradient between the infusion device [14] and the intravascular space but may be difficult to predict [15]. Flow rate is inversely related to the length of the narrowest part of the catheter. Increasing the pressure of the infusion system can increase flow rate but carries risk of inadvertently infusing air and of injuring the vein. Instilling fluid under high pressure into a venous system that has outflow obstruction can lead to venous distension and regional edema formation. When high intravenous flow rates are needed a larger bore IV placed in a nonobstructed vein is usually preferred. Intravenous catheters come in a variety of lengths and diameters based on wire gauge. Catheter size is limited by the size of the vein. A large catheter can be challenging to place; it is often better to place a smaller catheter and then, using a guide wire and dilator, exchange it for one of a larger

size. Care must be taken to avoid losing the guide wire into the circulation [16]. If this should happen, the lost wire can often be removed by interventional radiology using a snare. Lost wires must be removed. Lost wires can become infected and can migrate within the vascular space. If ignored, they can become locked into position by fibrous tissue; then surgical removal is required.

The effectiveness of intravenous therapy requires that the catheter tip ends in the lumen of a vein that can accommodate the flow into the central circulation. Proper placement of an IV can be confirmed by aspirating blood or transducing a pressure waveform. Antecubital and saphenous veins sometimes will not have blood return even when properly placed due to valves. Other maneuvers to confirm that the catheter is located inside the vein lumen include: observation of flow rate with and without a proximal tourniquet; response to instillation of a test dose of vasoactive agent (similar to the test dose used during epidural placement); and observation of turbulent return to the right heart (by TEE) when fluid is instilled through the line. Padding and warming devices used during surgery may interfere with observation of the vascular access site but they should be checked periodically.

The ability to aspirate blood from the catheter, while not always possible, helps to confirm that the end of the catheter is inside the vein lumen. Intravenous catheters may be described as “infiltrated” [17], if fluids instilled in them fail to reach the central circulation. Injection may be painful if the patient is awake, flow rate is usually less than expected, and edema, erythema or pallor of the catheter site often develop as more fluid is infused. The end of the intravenous catheter may be located outside the vein in the surrounding tissues; medications instilled will not have the systemic effects expected and may have exaggerated local effects (sloughing of tissue). If the vein is patent but the infusion rate exceeds the flow capacity of the venous system, the vein becomes distended. If the catheter is relatively short, distension of the vein wall at the site of puncture (where the catheter enters the vein) will become larger than the catheter and fluid will leak into surrounding tissue even though the catheter tip is intraluminal and the vein connects to the central circulation. It is possible in this case to sometimes see blood return when the catheter is aspirated; nonetheless, rapid instillation of fluid is uncomfortable, local swelling can occur, and medication effects are unreliable. The catheter tip may be located inside the vein but the vein may be proximally obstructed. Medications instilled through such a catheter may reach the central circulation with a delay. The flow capacity is dependent on the collateral flow around the venous obstruction. Vein rupture and local swelling are potential problems.

If swelling is confined by tissue planes that limit volume expansion, tissue pressure increases and perfusion decreases. This is referred to as a compartment syndrome ; fasciotomy may be needed to prevent tissue ischemia.

Group Two: Lower-Body Vascular Access

Patients in the second group may have lines placed in the femoral veins; these are prone to infection and may become nonfunctional if the inferior vena cava is clamped during surgical manipulations or postoperatively if bleeding into the peritoneal space leads to abdominal compartment syndrome [18]. Measurement of CVP from below the diaphragm can be useful, but PA catheters should probably be avoided because they cross the surgical field. Preload assessment will rely more heavily on other monitors including TEE, pulse pressure variation, and response to fluid administration.

Group Three: Alternative Vascular Access

Patients in the third group are challenging and require creative management and coordination of the surgical and anesthesia teams. These patients often have extensive adhesions from multiple prior operations. Surgical entry of the abdomen may be difficult, bloody, and tedious. A plan to replace blood lost in the process of opening the abdomen may include a combination of procedures by interventional radiology along with intraosseous, intra-arterial, and surgically created vascular access. Some of these options, while potentially life-saving, are unconventional and can have specific hazards. The plan should include alternatives if the initial options fail.

Interventional Radiology

Consultation with interventional radiology can be invaluable. In addition to diagnostic venography, procedures by interventional radiology include re-cannulation of thrombosed veins and dilatation of stenotic but not completely occluded veins. Procedures usually have to be scheduled in advance. Time requirements make this prohibitive once graft organs are available. The maximal flow rate of catheters placed in this way may also be less than required intra-operatively during massive blood loss.

Intraosseous Catheters

Intraosseous access catheters [19] can be placed in tibia, humerus, sternum, or ilium. Virtually all medications used in standard CPR can be administered via intraosseous catheters. Meticulous sterile technique is important to avoid bone infection (osteomyelitis). Flow rates through intraosseous catheters may be inadequate for massive fluid and blood replacement. As patients age, the peripheral marrow spaces are replaced with fat. Flow rates may be diminished compared to more central sites (sternum and pelvis) and the possibility of embolizing fat into the circulation should be considered before infusing fluid under great pressure. Infusions through intraosseous catheters are sometimes painful on initial injection. If a single bone is repeatedly accessed, fluids may leak from the marrow space through previous punctures. Relative contraindications for intraosseous access include *osteogenesis imperfecta,*

osteoporosis, and bone tumors.

Arterial Lines for Fluid Delivery

Despite loss of accessible veins from phlebotomies and the consequences of TPN, the arteries are usually well preserved. Arterial lines are commonly used during anesthesia to monitor blood pressure and permit sampling of blood gasses. Replacement of volume through an arterial line is possible [20] and some medications are approved for administration via this route including contrast media, some chemotherapeutic agents and the fluids used to flush the line. Many more medications have been inadvertently administered by this route without complication; however some medications that can be safely given intravenously *cannot* be given through arterial lines without serious risk of arterial thrombosis and ischemia. Extreme care to avoid arterial infusion of clot, air bubbles, or other inappropriate material should be made. Arterial transfusion should be considered only when other options are unavailable and the procedure should if possible, be carried out under protocol with specific informed consent [21]. This usually requires not only planning but institutional approval, extensive patient disclosure, and preparation of special equipment.

Blood replacement transfused through an arterial line requires a pressured pump [22] with high quality filter; administering blood products using gravity-fed intravenous equipment, augmented by manual pumping to overcome the pressure difference between veins and arteries, may result in the unintended infusion of particles or air bubbles. The elevated pressure needed to move significant volume into the arterial tree may carry infused particles to distal sites remote from the artery accessed. If arterial administration of large volumes is needed, larger arterial cannulas may have to be inserted. It is important to be sure that these do not compromise arterial flow to the tissue beds distal to the arterial line. A pulse oximeter can be placed distally to demonstrate ongoing pulsatile flow to the extremity involved. Insertion and removal of these lines must be done with care to avoid artery injury and bleeding. Vascular surgical consultation should be readily obtainable both when planning and when carrying out transfusion through artery lines. If there is evidence of inadequate blood flow distal to an arterial line, line removal at the earliest practical time may be limb-saving. Forced air warming devices should be turned off if they cover an extremity that lacks perfusion to avoid thermal injury prior to restoring flow.

Surgically Created Vascular Access

Arterial and intraosseous catheters are not designed for long term use and will have to be removed during the early postoperative period. Patients who have undergone multivisceral transplantation usually have ongoing needs for parenteral medications (vasoactive agents, antibiotics, immune-suppressants) and nutritional support until the

graft becomes fully functional. Planning should include arrangements for medication delivery in the postoperative period. Surgically created venous access can usually be secured after the abdomen is open using veins that cannot be accessed percutaneously. Ovarian, mesenteric and other tributaries of the inferior vena cava can provide a route for administration of the antibiotics, fluids, and other medications needed in the recovery period. Special provisions are needed to safely permit removal of these lines when these are no longer needed. One strategy that has worked is to place a tunneled catheter through the abdominal wall and into the target vein; an elastic band placed over the vein before the catheter is inserted secures the end of the vein to the catheter and also may auto-ligate the vein when the catheter is removed. Preparations are needed for surgical intervention if auto-ligation fails.

Anesthesia for multivisceral transplantation requires careful preoperative plannig for adequate vascular access. Atypical access approaches may need to be considered.

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43. Postoperative Management for Visceral (Intestine, Intestine/Liver, and Multivisceral) Transplantation

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Introduction

Patients who require intestine-containing grafts can be categorized into the following three groups:

1. Patients who need an isolated intestinal transplant a modified multi-visceral transplant including stomach, duodenum, pancreas, small intestine for gut failure (Group 1).

2. Patients who need both an intestine and liver transplant for intestinal failure with total parenteral nutrition (TPN) and liver disease (Group 2).

3. Patients with liver cirrhosis/complete mesoportal thrombosis who need either an intestine/liver or a full multivisceral transplant (Group 3).

Group 1 patients are TPN-dependent and tend to become chronically dehydrated. Renal dysfunction is not uncommon. Sometimes they need a simultaneous kidney transplant. Isolated intestinal transplantation is a relatively less intensive procedure since there is no portal hypertension. A patient can be extubated either on the day of surgery or postoperative day one.

Group 2 consists of the Group 1 population with liver disease. They are much sicker than Group 1. Patients who have short gut syndrome with TPN-associated liver disease may not present signs of portal hypertension until the liver becomes more cirrhotic than the livers of regular cirrhosis patients, as portal flow is decreased due to short gut syndrome. They may lose a large amount of blood due to relatively larger raw surface area with portal hypertension in the operating room. Therefore, intraoperative and postoperative fluid management can be difficult. More intensive postoperative management is necessary than for liver transplantation.

Group 3 is essentially the same as patients who undergo (isolated) liver transplantation. Liver/intestine or full multivisceral transplantation is needed because of difficulty securing inflow (portal vein flow) to the liver. Postoperative management of this group is similar to management of liver transplant patients, although the intestine needs special care.

Neurologic Management

Sixty-eight percent of visceral transplant patients may have neurological complications such as headache, encephalopathy, seizures, neuromuscular disorders, opportunistic central nervous system infections, and ischemic strokes [1]. Tacrolimus (Prograf) especially can cause neurological toxicity such as tremor, headache, mental status change, seizure, and PRES (Posterior Reversible Encephalopathy Syndrome). Since many visceral transplant patients receive numerous kinds of medications, at least in the beginning, interaction between medication and their toxicities and metabolites can be frequent causes of neurological symptoms. Simplifying medications is advised if feasible.

Infection has to be ruled out when a patient develops unclear neurological problems. Sepsis, cytomegalovirus, herpes viruses, tuberculosis, *Cryptococcus*, and fungal infections need to be investigated.

Psychiatric Management

Patients often have pretransplantation psychiatric conditions (depression and anxiety disorders) partly because they tend to have long-standing chronic illnesses with frequent hospital stays and surgeries. Chronic use of pain medications is one of the most difficult problems to deal with, presenting a big challenge after transplantation in terms of pain control. Therefore, it is important for a pain management team and psychiatrist to see a patient with these issues before transplantation. Tacrolimus and steroid use also can cause neurotoxicity, which can manifest as psychosis.

Cardiac Management

Group 2 and 3 patients are treated like liver transplant patients. The Swan-Ganz catheter is useful in the operating room and soon after transplantation for these groups.

In the operating room, fluid management and coagulation management are essential in these patients, especially those in Groups 2 and 3. Proper fluid resuscitation with 5 % albumin or blood products should be obtained before starting infusion of vasoactive medications. If a vasopressor is necessary in the operating room, starting with a small dose of norepinephrine of 0.05 mcg/kg/min and titrating to a minimum necessary dose is preferred.

In the postoperative period, we prefer to start a continuous infusion of Prostaglandin E1 (alprostadil, Prostin VR® Pediatric, Pfizer) at small doses of 0.2 mcg/kg/h titrated to a maximum dose of 0.6 mcg/kg/h when hemodynamic stability is achieved. The dose is titrated up if the blood pressure tolerates it. The vasodilator and anti-platelet aggregation properties of alprostadil aim to protect the microvasculature of the recently reperfused intestine [2].

Hypertension is common after transplantation. Tacrolimus can cause renal vasoconstriction and corticosteroid administration may lead to fluid retention, both of which can cause high blood pressure. Calcium channel blockers decrease the arterial vasoconstriction caused by tacrolimus. Amlodipine has less of an effect on tacrolimus concentrations than on nondihydropyridine calcium channel blockers such as verapamil. Other medications such as beta-blockers, clonidine, and angiotensin-converting enzyme (ACE) inhibitors can be added if Amlodipine alone is not enough to control blood pressure. It is important to avoid hypotension due to excessive treatment, since transplanted intestine seems more sensitive to hypotension.

Respiratory Management

Group 1 (isolated intestine) recipients have better overall reserves and normally are able to be extubated on the same day of the transplant or on the first postoperative day. If the patient cannot be weaned from the ventilator soon after transplant, early tracheostomy should be considered. In the postoperative period, the importance of

avoiding aspiration pneumonia should be emphasized, since it is very common in intestinal transplant patients.

Gastrointestinal/Hepatobiliary Management

Liver management in Group 2 and 3 patients is similar to that of post liver transplantation patients. Liver enzyme and lactate trends and patient mental status are good indicators with which to evaluate liver functions. In general, liver enzymes trend down after transplantation. Doppler ultrasound is necessary for any uncertainty of liver functions, but we do not use it routinely.

In Groups 2 and 3, 16 % of patients have pancreaticobiliary problems, which include ampullary stenosis, bile duct stones, bile duck leak, necrotizing pancreatitis, edematous pancreatitis, and pancreatic duct fistula [3]. Pancreatitis can be encountered due to ischemic perfusion injury and can be managed with a nonoperative approach (NPO and octreotide, etc.). However operative interventions are sometimes necessary if pancreatic fistula is suspected. When ischemic reperfusion injury such as swelling of pancreas or hemorrhage in the pancreatic parenchyma, is seen during the operation, an octreotide drip is used. Biliary complication may occur in patients receiving modified multivisceral grafts containing stomach, duodenum, pancreas, and small intestine due to lack of blood supply from gastroduodenal artery and duct to duct biliary anastomosis. Sphincter dysfunction can be treated by sphictorotomy [3].

In all groups after visceral transplantation, gastrointestinal management is managed in the same way. TPN can start as soon as hemodynamic status is stabilized. In our protocol, surveillance ileoscopy and enteric biopsy is performed twice a week until 4 weeks posttransplant, then once a week until 3 months posttransplant. We routinely place jejunostomy tubes for postoperative tube feeding. As soon as gastrointestinal function is restored, tube feeding can start. TPN can stop when tube feeding meets the fluid and nutritional goals.

Nutritional Management

Short- and long-term nutritional goals for patients after intestinal transplantation are as follows [4]:

1. Autonomy from parenteral nutrition.

2. Discontinuation of intravenous replacement fluids.

3. Eventual removal of the central venous catheter.

4. Transition to oral feedings and discontinuation of tube feedings.

5. Appropriate long-term growth, especially in children.

Once fluid and electrolyte status have stabilized, parenteral nutrition (PN) is initiated 24–48 h after transplant and adjusted according to electrolyte and fluid status. Continuous tube feedings are initiated when there is evidence of bowel function with ileostomy output, usually 5–7 days after transplant. A low-fat, low-osmolarity, elemental formula is preferred for the first 4–6 weeks after transplantation. Tube feedings are initiated at 5 ml/h and increased by 5 or 10 ml/h daily based on ileostomy output, electrolytes, and clinical status. Recently, we sometimes even proceed with diet rather than tube feeding at our center. Pancreatic enzyme can be given since fat malabsorption is common after intestinal transplant. It is not uncommon for patients to have poor gastric motility in the months after transplant. Prokinetic agents such as Reglan or erythromycin can be used to assist gastric emptying, although it should be noted that erythromycin interacts with tacrolimus. Jejunal tube feedings are often required for a few weeks or months, with transition to gastric feedings when gastric motility improves. Percutaneously placed gastric or gastrojejunal feeding tubes are appropriate for this patient population because of the long duration of tube feedings after transplantation. Ideally, stool output should be <30 ml/kg/day after transplantation. Stomal outputs >50 ml/kg/day are considered excessive, and antidiarrheal agents or dietary fiber may be initiated to increase intestinal transit time [4]. Depending on fluid status, if stool output is in excess of 30–50 ml/kg/day, fluid loss from stool should be replaced with an IV solution such as 0.45 % saline to maintain hydration. Bicarbonate and other electrolytes such as magnesium are often added based on serum electrolyte values. Most often, patients are placed on a dilute enteral formula to provide adequate enteral hydration because of high fluid loss from the ileostomy. Formulas are normally diluted to between one-half and three-fourths strength with free water, depending on fluid requirements. Patients may need up to 150 ml/kg/day of enteral fluid to maintain hydration and discontinue intravenous replacement fluids.

However, if there is a history of milk or soy protein intolerance, or stool output increases with the transition, an elemental formula with appropriate fat content will be used for an extended period of time. PN is discontinued when 100 % of nutritional needs are met enterally. An age-appropriate multivitamin is started when TPN is discontinued. For patients who desire to eat a significant amount of food after transplantation, a low-lactose and low-fat diet is followed for the first 4–6 weeks after transplantation. A diet low in concentrated sweets is continued indefinitely to avoid osmotic diarrhea.

Renal Management

Patients tend to have baseline kidney problems due to frequent dehydration; therefore, it is important to ensure that patients have adequate hydration prior to transplantation. Patients after multivisceral or liver/intestinal transplantation tend to have more bleeding than post-liver transplant patients. They have more blood transfusions during transplantation. Therefore, postoperative fluid management plays a very important role in the intensive care unit (ICU). Diuresis is spared to the postoperative period after postoperative day 2 or 3. A Swan-Ganz catheter guides fluid management in the ICU. Patients tend to keep fluids in the third space; therefore, diuretic use concomitant with 25 % albumin is frequently used. We believe that albumin use plays a role in that setting. If the patient needs dialysis, continuous venous-venous hemodialysis is preferred over conventional hemodialysis in the ICU setting in order to prevent ischemia to the graft due to hypotension.

Electrolyte abnormalities may be caused by absorption problems or nephrotoxicity, or may be drug induced. Tacrolimus has been shown to cause hyperkalemia and hypomagnesemia. Potassium intake must be monitored closely, and excess potassium in parenteral and enteral nutrition should be avoided. Potassium-sparing diuretics and other medications causing hyperkalemia, including ACE inhibitors, should be used with caution. Oral magnesium may lead to increased ostomy output; therefore, magnesium replacement in the TPN or through intravenous boluses should be tried first.

Endocrine Management

Steroid use in the perioperative period and surgical stress can elevate serum glucose. Perioperative glucose control is achieved by insulin injection on a sliding scale and/or insulin adjustment in TPN.

We use Solu-Medrol for induction (1 g before Campath is given, and 1 g before graft is reperfused). Tapering doses of steroid (“recycle”) is used only for immunologically high-risk patients. If a patient does not need corticosteroid recycling, we perform a cortisol stimulation test at postoperative day 5 to assess adrenal function. If the test shows adrenal insufficiency, 50 mg of hydrocortisone sodium succinate can be starts intravenously every 8 h.

Osteoporosis is very significant problem in the long-term [5, 6], perhaps due to long-term TPN use prior to transplantation and that lack of vitamin D and calcium intake precipitate osteoporosis. It may start prior to transplantation. Therefore, it is important to start treatment even before transplantation. In addition, it is essential to keep serum levels of vitamin D, calcium, parathyroid hormone, and testosterone on track after transplantation. Dual-Energy X-ray Absorptiometry (DEXA) scan is conducted yearly to assess for osteoporosis. In addition to calcium and vitamin D administration,

zoledronic acid (Reclast) is used yearly for severe osteoporosis.

Hematologic Management

Sometimes transfusion of a massive amount of blood is necessary during surgery because of the large raw surface area in the operative field and portal hypertension. A cell savor can be used as long as the operative field is clean. Ionized calcium levels needs to be checked frequently with adequate supplementation of calcium gluconate during transplantation.

Controlling coagulopathy is another challenge in the operating room. It is not ideal to correct coagulopathy too much or too less. Overcorrection of coagulopathy could lead to thrombosis of the graft either in a micro or macro fashion. Therefore, thromboelastography (TEG) is very useful to assess coagulopathy in the operating room. We prefer use of cryoprecipitate to fresh frozen plasma in the postoperative period in case the patient needs coagulation factors because cryoprecipitate has more coagulation factors per volume [2].

Infectious Management

The most common morbidity and mortality is due to infectious complications. Therefore, surveillance and appropriate use of antibiotics/anti-fungal medication are extremely important. Perioperative antibiotics and anti-fungal medications are used between 10 and 14 days due to the nature of intestinal transplant operation. However, overuse of antibiotics could cause multidrug-resistant organisms, which may eventually be a significant morbidity factor if infection arises. Like most transplant infectious complications, initial infectious complications are due to surgical complications especially within 3 months after transplantation. Leakage from intestinal anastomoses, intra-abdominal abscesses, and perforation of intestine are seen. It is imperative to have a low threshold to take the patient to the operating room to inspect the abdomen and treat the cause of infection, even if the computed tomography scan did not reveal an intra-abdominal abscess or surgical concerns. Pneumonia, indwelling-line infection, and urinary tract infection need to be ruled out when the patient has signs of infection. In the immediate postoperative period, our threshold to replace indwelling-catheters as well as weekly surveillance blood cultures is low. In the freshly transplanted period, cultures from intra-abdominal Jackson-Pratt (JP) drains may play some role [7]. However, they are hard to interpret due to colonization in these JP drains, especially if the specimen is not obtained within a few postoperative days.

Aspiration pneumonia is a leading concern throughout the course of intestinal transplantation. When a lung nodule is identified, aspergillosis, nocardia, tuberculosis, and malignancy are concerns. Bronchoscopy/bronchoalveolar lavage (and possibly

navigated bronchoscopic biopsy) is needed to make a proper diagnosis.

Cytomegalovirus (CMV) is a real problem in intestinal transplantation since CMV enteritis still can occur even in the era of ganciclovir/valganciclovir. CMV/Epstein-Barr virus polymerase chain reaction is conducted weekly soon after transplant. Ganciclovir or valganciclovir prophylaxis is continued until 6 months after transplant unless a CMV-negative donor to CMV-negative recipient transplant occurs.

Bactrim is used for lifetime *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*) pneumonia prophylaxis after intestinal transplantation.

When ostomy output increases or the patient develops diarrhea, infectious enteritis due to *Clostridium difficile*, adenovirus, rotavirus [8], and infection need to be ruled out in addition to rejection.

Immunosuppression Therapy

At UPMC, we use the lymphoid-depleting agents alemtuzumab (Campath-1H, ILEX, Cambridge, MA) for adults or antithymocyte globulin (Thymoglobulin; Sangstat Medical Corp, Fremont, CA) for children [5]. We use tacrolimus (Prograf, FK 506, Astellas Pharma US, Inc., Deerfield, IL) monotherapy with avoidance, when possible, of maintenance steroid therapy as a posttransplant immunosuppression strategy. Posttransplant outcomes with this "pre-conditioning" regimen are superior to those with conventional immunosuppressive regimens [5]. Campath can be waived for patients with liver-containing grafts if they have a high Model for End-Stage Liver Disease score or severe portal hypertension. Campath can cause coagulopathy and can be a real problem when operating in the field of severe portal hypertension with coagulopathy.

An intravenous dose of tacrolimus is started after reperfusion in the operating room to achieve a 12-h trough level of 10–15 ng/ml by the third postoperative day. The same level is aimed for in the first three postoperative months, after which levels of 5–10 ng/ml are sought [2]. A variable course of methylprednisolone , or more commonly hydrocortisone , is added in patients with positive T/B cell cross-match and those who develop serum sickness syndrome, adrenal insufficiency, allograft rejection, and graft-versus-host disease.

Highly immunologically sensitized patients may need to use an anti-B cell/plasma cell medication such as the proteasome-inhibitor bortezomib (Velcade®, Millenium Pharmaceuticals, Cambridge, MA).

Sirolimus (Rapamune, Wyeth-Ayerst Laboratories, Philadelphia, PA), derived from the fungus *Streptomyces hygroscopics*, is a target of rapamycin (TOR) inhibitor , that is used in some centers as maintenance therapy in addition to corticosteroids and allows use of a reduced dose of tacrolimus, particularly in patients with renal dysfunction. When possible, concurrent use of other nephrotoxic agents should be avoided.

Even with higher levels of immunosuppression, rejection is still common in

intestinal transplant recipients. Historically, 70–90 % of recipients experienced at least one rejection episode. With the use of various forms of antibody-induction, the incidence of rejection has decreased to less than 25–30 % [9, 10]. Mild rejection episodes are initially treated with a 2–3 day intravenous methylprednisolone bolus of 10–20 mg/kg per day. If a rejection episode does not respond to corticosteroids or moderate to severe rejection, antibody therapy consisting of antithymocyte globulin (Thymoglobulin; Sangstat Medical Corp, Fremont, CA) is warranted.

Currently, it is our practice to carry out protocol surveillance intestinal biopsies at day 5–7, followed by biweekly biopsies until week 4, and weekly until week 8–12; then monthly or every other month after 3 months. We do perform annual intestinal biopsies with donor-specific antibody checks. Indications for biopsies other than the screening biopsy are often nonspecific and include unexplained fever, change in stoma output or appearance, and gastrointestinal bleeding. It seems that the gross appearance of the mucosa does not always correlate with histologic appearance. Endoscopy with biopsy remains the gold standard for diagnosis of rejection in intestinal allografts. Acute rejection of an intestinal allograft is characterized by a varying combination of findings and an increase in crypt cell apoptosis. Although crypt cell apoptosis is not a specific or absolute finding, it represents a distinctive feature of acute cellular rejection even when other changes are minimal. Chronic rejection is characterized by vasculopathy with intimal thickening affecting the medium-sized vessels; unfortunately, mucosal changes in the presence of chronic rejection are nonspecific or may even be absent, making diagnosis very difficult.

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Part IX
Composite Tissue Graft Transplantation

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44. Reconstructive Transplantation: Evolution, Experience, Ethics, and Emerging Concepts

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History and Evolution

Study the past if you wish to define the future
Confucius, Chinese philosopher and reformer (551 BC–479 BC) [1].

Mythology and Antiquity

The association of gods, phantasmic creatures, or saints with healing powers is widespread in mythology and religion spanning multiple civilizations [2].

Earliest evidence from the Egyptian civilization, represent divinities as human–animal hybrids in ancient art and sculptures. Some examples of such xenomorphic creatures include Anubis (the god of embalming with the head of a jackal), Thot (the god of scriptures with the head of an Ibis), Hathor (the goddess of fertility with the head of a cow), Horus (King of all Pharaohs with the head of a hawk), and others such as the

Phoenix (with the head of a lion), Khnum (with the head of a lamb), and Sobek (with the head of a crocodile) [3].

During the Mesopotamian era (circa 720 BC), winged bulls with bearded human heads (the *Lamassu*) guarded the palace of Sargon II of Assyria in Khorsabad (current day Dur-Sharrukin in northern Iraq near Mosul) [4, 5].

In Greek mythology, most of the Pantheonic figures were also human–animal hybrids. In his book, Symposium, Plato wrote: "According to Greek mythology, humans were originally created with four arms, four legs and a head with two faces. Fearing their power, Zeus split them into two separate parts, condemning them to spend their lives in search of their other halves" [6, 7]. Some are well known, such as the Sphinx (half human–half lion) and Centaur (half human–half horse) while others include the Typhon and Echidna, the Gorgons: Stheno, Euryale, and Medusa. Many of these creatures were snake- or dragon-headed humanoids whose stare could turn a person to stone. Then there was the Cerberus and Hydra—the dog- and serpent-headed monsters, similar to the Gorgons, regrew their heads after being cut off.

If these monsters remind us of the earliest concepts of tissue regeneration , the true icon in mythology, which has come to represent modern transplantation, is the Chimera (a mythical creature combining a lion, goat, and snake) [8, 9]. The Chimera is the imaginative or implausible mythic creature that has been used to describe the coexistence of disparate parts; either tissues or cells in solid organ transplantation and immune tolerance (chimerism) [10].

Similar to other lore, Hindu mythology has numerous examples of Gods and xenomorphic divinities that represent concepts of tissue grafting. Foremost among these examples are the legends of Ganesh (the elephant-headed God of new beginnings created by Shiva) (Fig. 44.1) and that of lord Narasimha (Sanskrit: Nara (man); siṁha (lion), who is an avatar of the Hindu god Vishnu (Great Protector). Narasimha is described in Hindu mythology, epics, and iconography as having a human-like torso and lower body, with a lion-like face and four to eight upper limbs with claws [11, 12] (Fig. 44.2).

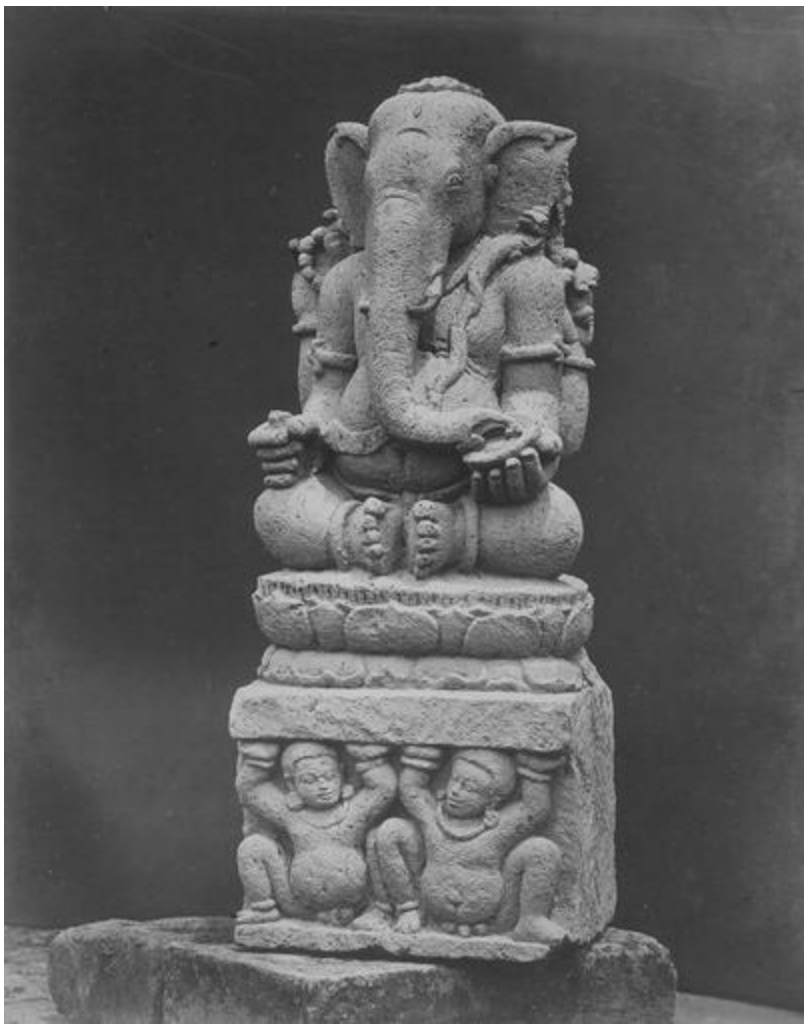

Fig. 44.1 Ganesha, the elephant-headed Hindu god of new beginnings (eighteenth century, Temple Relic) Credit—British Museum, Public Domain

Fig. 44.2 Narasimha, the lion-headed fourth avatar of Vishnu killing the demon Hiranyakashipu on his lap, as Prahlada watches at the left. Credit—eighteenth century, British Museum, Public Domain

The Edwin Smith Papyrus is the oldest known record of the use of local flaps in reconstruction of tissue defects (circa 3000 BC). In 600 BC, the Indian surgeon Sushruta described the earliest forehead flap for nasal reconstruction, the principles of which are still in use today [13]. There are many examples of twin saints with divine healing powers throughout mythology (Ashvins of Rig Veda and the Greco-Roman Dioscuri). Similar accounts exist for the Middle Ages (the Christian patron saints, Cosmas and Damian) [14, 15].

The Middle Ages and Renaissance

Cosmos and Damian, the patron saints attributed to have performed the first extremity transplantation were twin brothers who lived in Egaea, in Cilicia (current day Turkey) in the third century [16].They were known to possess acclaimed powers of healing, which lead to suspicions of mysticism and their death due to persecution in 283AD. Per legend, these martyr saints are credited to have grafted a leg from a deceased Ethiopian

in a patient (deacon Justinian) who suffered an amputation of a cancerous limb. This work of Cosmas and Damian is depicted in artistic works by Matteo di Paccino (1350–75); J. Huguet (1415–92), or Fra Angelico (c.1438) (Fig. 44.3) [17, 18].

Fig. 44.3 Saints Cosmas and Damian performing a miraculous cure by transplantation of a leg. c. 1495 (by artist Master of Los Balbases) Credit—Church of Saints Cosmas and Damian, Burgos, Northern Spain. Featured in a book Legenda Aurea by Jacobus de Voragine, c. 1275

The Recent Era

Throughout history, the desire to restore and replace diseased or damaged body parts has been ingrained in human ethos and psyche. However all claims of success with ancient transplantation remained rooted in misleading myth, legend and folklore, or in the realms of philosophical or science fiction for ages [19]. It was not until the mid-twentieth century that the mysteries of immune rejection of grafts were first unraveled, ushering the "fictional-reality" of solid organ or reconstructive transplantation, which was more than a literary oxymoron [20].

The modern era of RT begins with the injuries sustained in World War II that spawned the seminal immunologic work of Medawar, Billingham, and Brent in skin grafts. Scores of Allied sailors and pilots suffering with devastating burn injuries were admitted to the Plastic Surgery unit in Glasgow, Scotland for treatment. It was here that biologist Peter Medawar was investigating the immunogenicity of skin with his colleagues Billingham and Brent. He joined plastic surgeon, Thomas Gibson who performed the first skin allografts in these Allied soldiers. Medawar's groundbreaking research earned him the Nobel Prize for Medicine in 1960 and later, Knighthood [21].

In 1954, Joseph E. Murray, who was a plastic surgeon, along with his colleagues John P. Merrill and Harwell J. Harrison performed the first kidney isograft between identical twins [22–25].Shortly after, in 1957, Earle Peacock, also a plastic surgeon, transplanted en bloc a digital flexor tendon mechanism. Peacock called this a "composite tissue allograft" (now termed as vascularized composite allograft) [26, 27]. In 1959, Murray and team went on to perform the first successful kidney allograft [28]. Although Murray used total body irradiation for his first transplant, he pioneered in association with Roy Calne, the clinical use in renal transplants of azathioprine (Imuran), a drug discovered by Hitchings and Elion [29, 30]. Murray became the only plastic surgeon in history to receive the Nobel Prize.

Over the next 50 years, successful solid organ transplantation was spurred by advancements in pharmacologic immunosuppression. In 1964, almost a decade after Murray's and Peacock's first attempts with organ and composite grafts, Roberto Gilbert Elizalde a young general surgeon in Guayaqil, Ecuador attempted the first unilateral hand transplantation in a sailor that underwent bilateral amputations (Fig. 44.4) [31, 32]. Although Gilbert used the same immunosuppression as that of Murray and Calne (azathioprine and prednisone), the graft failed at 3 weeks, necessitating amputation due to irreversible rejection [33].

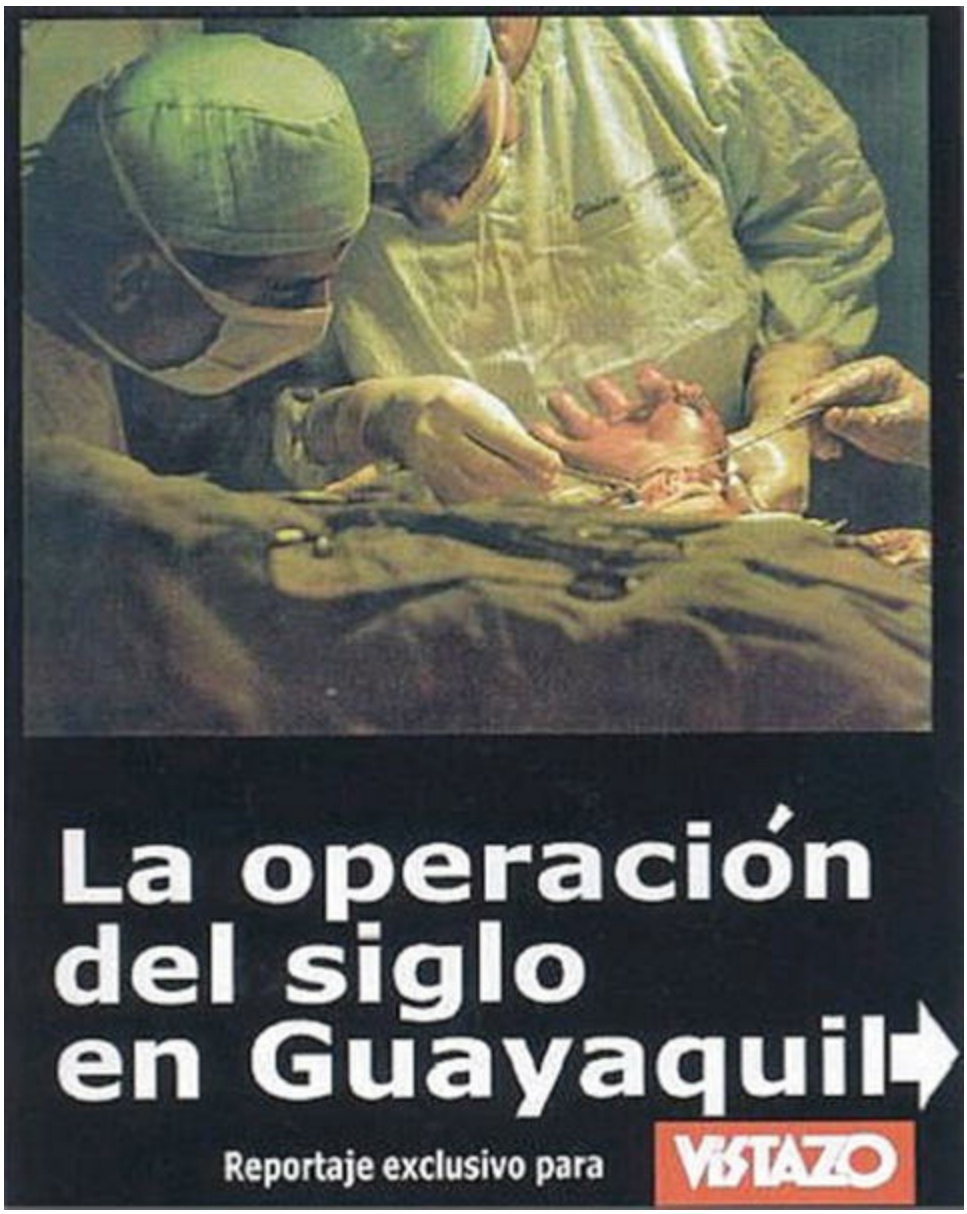

Fig. 44.4 The first hand transplantation in modern human history. Dr. Roberto Gilbert and Dr. Gabriel Panchana performing a hand transplant in a sailor, Julio Luna in Guayaquil, Equador in February 1964. Credit—Vistazo Magazine, Ecuador

The discovery and clinical approval of novel and more effective immunosuppressive drugs such as cyclosporine (CsA) in 1980s improved the success of solid organ transplantation but was toxic in limb transplant studies in non human primates [34, 35]. These results reinforced scientific dogma that skin was an insurmountable antigenic barrier to conventional immunosuppression, hampering research progress.

It was drugs such as tacrolimus and mycophenolic acid mofetil discovered in the 1990s [36], that enabled reproducible survival of skin bearing limb transplants in small animals (rodents) and large animals (pigs) [37]. It was also not until the early 1990s

when skin grafts placed synchronously in renal transplant patients successfully survived with routine immunosuppression [38, 39]. These developments and insights were watershed moments that overturned prevailing dogma about skin antigenicity in reconstructive transplants, spawning the groundbreaking field of vascularized composite allotransplantation (VCA) [40].

The first skin bearing upper extremity allotransplants under modern combination immunosuppression (tacrolimus, mycophenolate mofetil and prednisone) were performed in the late 1990s. Jean-Michel Dubernard and team performed the world's first unilateral hand transplant in September 1998 in Lyon, France [41] followed by the first hand transplant in the USA by Warren Breidenbach and team in January 1999 in Louisville, Kentucky [42]. Ever since, the field of RT has expanded and rapidly emerged to become one of the most promising, challenging, and controversial fields of solid organ transplantation [43].

This chapter reviews the world experience, ethical considerations, and emerging prospects in this exciting field.

World Experience

Reconstructive Transplantation: State of the Art

Unlike routine solid organ transplantation (SOT), RT involves transplantation of composites of multiple tissue types that may include skin, muscle, tendon, vessel, nerve, bone, cartilage, lymph nodes, and bone marrow [44]. Since these grafts are derived from either deceased (or in some cases living donors), and since they are "primarily vascularized," the Organ Procurement and Transplantation Network (OPTN) has recently enacted policy changes to designate these VCAs as "solid organs" for the purposes of donation and transplantation [45].

The reconstructive ladder is the cornerstone of soft tissue reconstruction with treatment principles that are tiered from the simplest to the most complex [46]. Transfer of vascularized tissues across sites in the body has been the most complex step in the reconstructive ladder. Advancements in microsurgery over the past 50 years have enabled the transfer of functional units of muscle and nerve as well as allowed expansion and prefabrication of flaps prior to transfer [47]. The advent of RT and progress in transplant immunology has allowed VCA to replace free tissue transfer and overcome its inherent limitations in reconstructive surgery by eliminating donor site morbidity secondary to use of autologous tissues for major tissue loss [48].

Undoubtedly, VCAs when successful have the potential to restore the appearance, anatomy, and function of debilitating or devastating civilian or combat injuries, not conducive to conventional reconstruction. Successful RT procedures can also avoid the need for multiple revisions or achieve superior functional and/or aesthetic outcomes,

without the high costs of multiple surgeries/hospitalizations seen in conventional reconstruction [49, 50].

RT is now the new realm of solid organ transplantation. Despite such promising initial results, growth of this groundbreaking field has been slow, primarily due to concerns for risks of lifelong, high-dose, multidrug immunosuppression. Unique from solid organs, RT allow visual monitoring, directed biopsies and enable timely, site-specific therapeutic interventions, which may help sustain rejection-free RT survival, while minimizing/eliminating the risks of chronic systemic immunosuppression [51].

Unlike SOT, RT offers unique opportunities for graft access (targeted therapies) and monitoring (clinicopathologic correlation of rejection). Yet current "state of the art" RT management is with chronic systemic or adjunctive topical immunosuppression with morbidity, risks, and complications (including deaths) that have been reported in RT recipients of VCA [52].

Emerging Insights

Devauchelle and team in Amiens, France performed the first facial VCA in 2005, 5 years after the first upper extremity transplantations. The recipient had tissue loss due to a dog bite involving the mid face (lips, nose, central cheeks) [53–56]. This patient and the first Louisville patient respectively remain the recipients of the longest surviving face transplant (11 years) and upper extremity transplant (16 years) in the world [57, 58].

Over the past 15 years, more than 100 upper extremity transplants and over 30 craniofacial transplants have been performed across multiple centers around the world. Patient/allograft survival and immunologic/functional outcomes have been mixed, ranging from poor to suboptimal to encouraging across different VCAs. A summary of outcomes with upper extremity in the USA is shown in Fig. 44.5 and around the world in Figs. 44.6, 44.7, and 44.8 (Tables 44.1 and 44.2). The world outcomes with craniofacial transplantation are shown in Fig. 44.9 (Table 44.3).

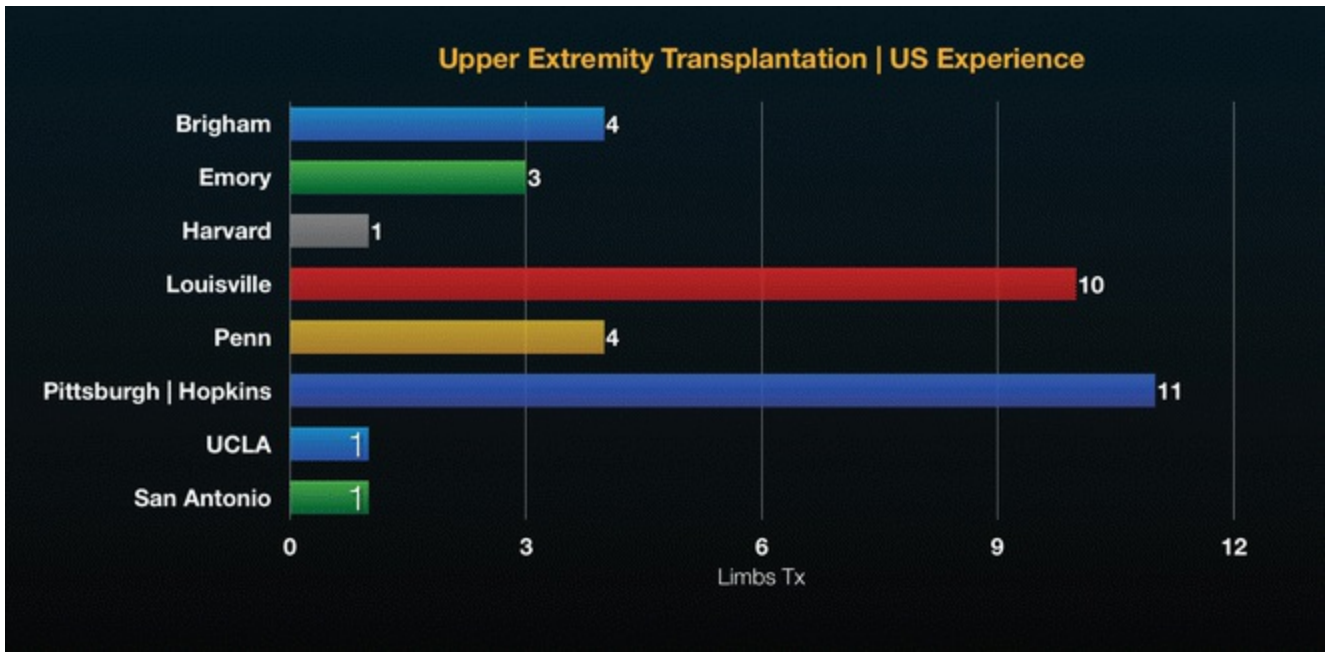

Fig. 44.5 Total number of upper extremity allotransplantations (unilateral and bilateral) performed in the USA

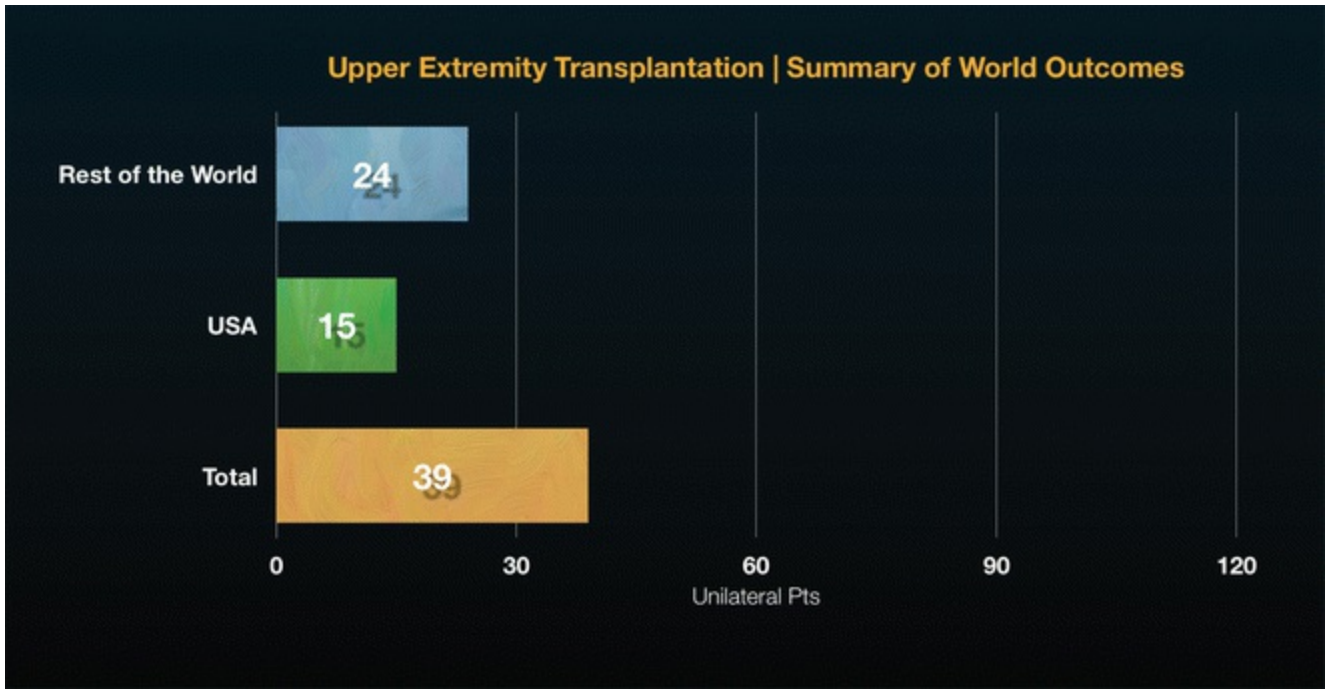

Fig. 44.6 Total number of upper extremity allotransplantations (unilateral) performed in the world

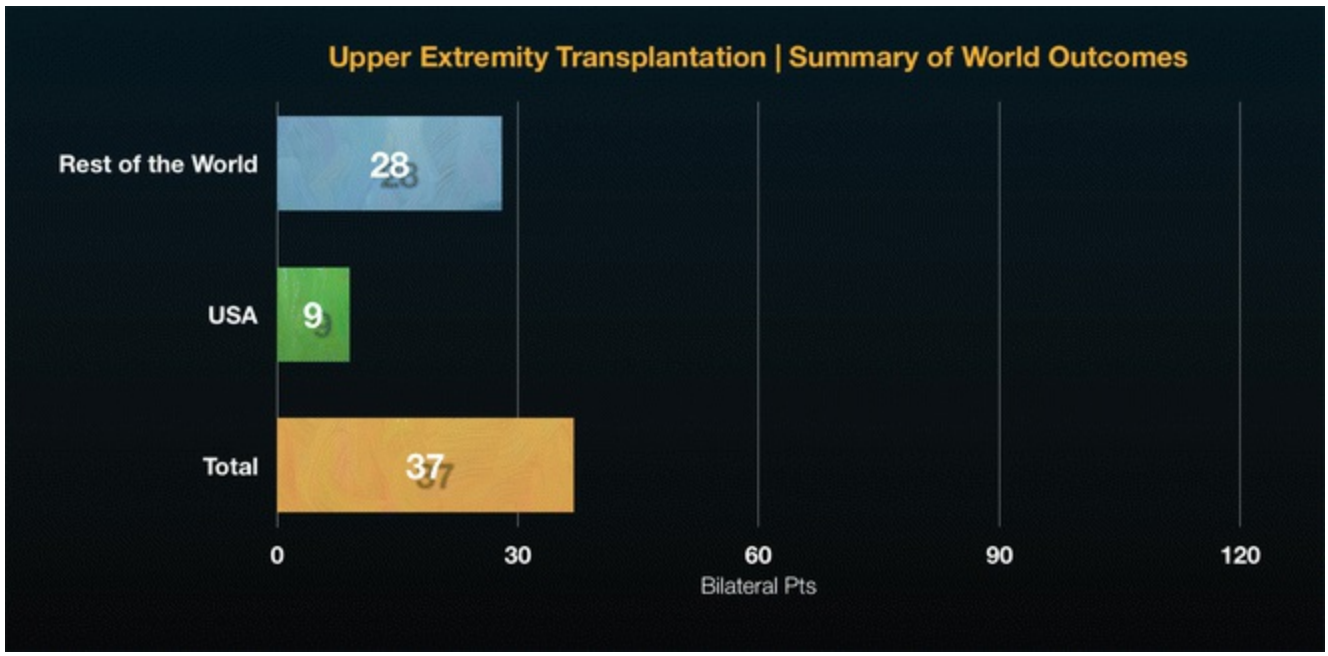

Fig. 44.7 Total number of upper extremity allotransplantations (bilateral) performed in the world

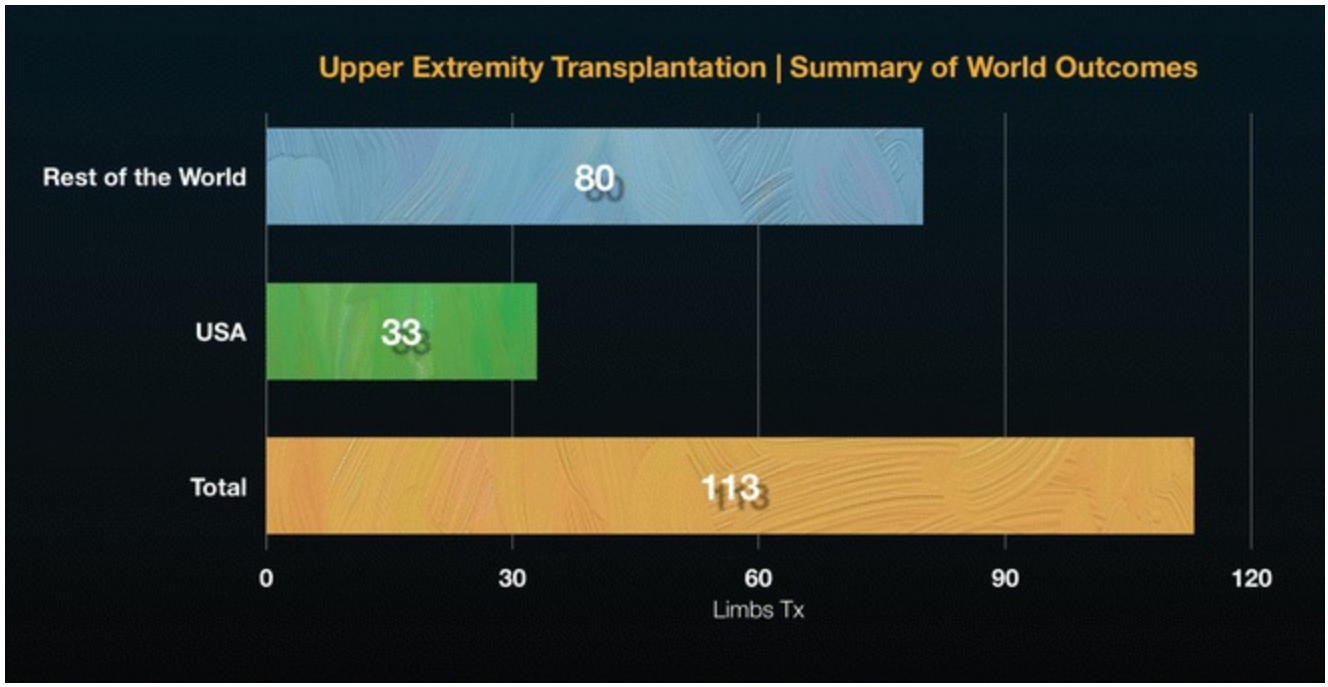

Fig. 44.8 World experience with uppe r extremity allotransplantations (unilateral and bilateral) performed in the world

Table 44.1 Outcomes in upper extremity transplantation : world experience

Country	Center	Total number of UE transplants	Number of graft losses	Mortalities	Reported in lay media	Reported in peer literature
Australia	Melbourne	1				
Austria	Innsbruck	9				
Belgium	Brussels	1				

China	Six centers	15	7		No	Yes (partially)
France	Lyon	11	1		Yes	Yes
	Paris	2	2	1	Yes	Yes
Germany	Munich	2				
India	Kochi	4				
Iran	Tehran	1	1		No	No
Italy	Milan	3				
	Monza	2				
Malaysia	Selayang	1 (twin–twin)				
Mexico	Mexico City	4	2	1	Yes	Yes
Poland	Wroclaw	7	1			No
Spain	Madrid	2				
	Valencia	6				
Turkey	Ankara	2	2	1	Yes	Yes
	Antalya	8	2	1	Yes	No
UK	Leeds	1				
Total world		82	18	4		

Table 44.2 Outcomes in upper extremity transplantation : US experience

Center	Total number of UE transplants	Number of graft losses	Mortalities	Reported in lay media	Reported in peer literature
Brigham and Women's Hosp	4	2		No	No
Emory	3	2		No	No
U. Pittsburgh/Johns Hopkins	12	2		No	No
MGH	1				
U. Louisville	9	2	1	Yes	No
UCLA	1	1		No	No
U. Pennsylvania	4				
Wilford Hall (SAMMC)	1				
Total	35	9	1		

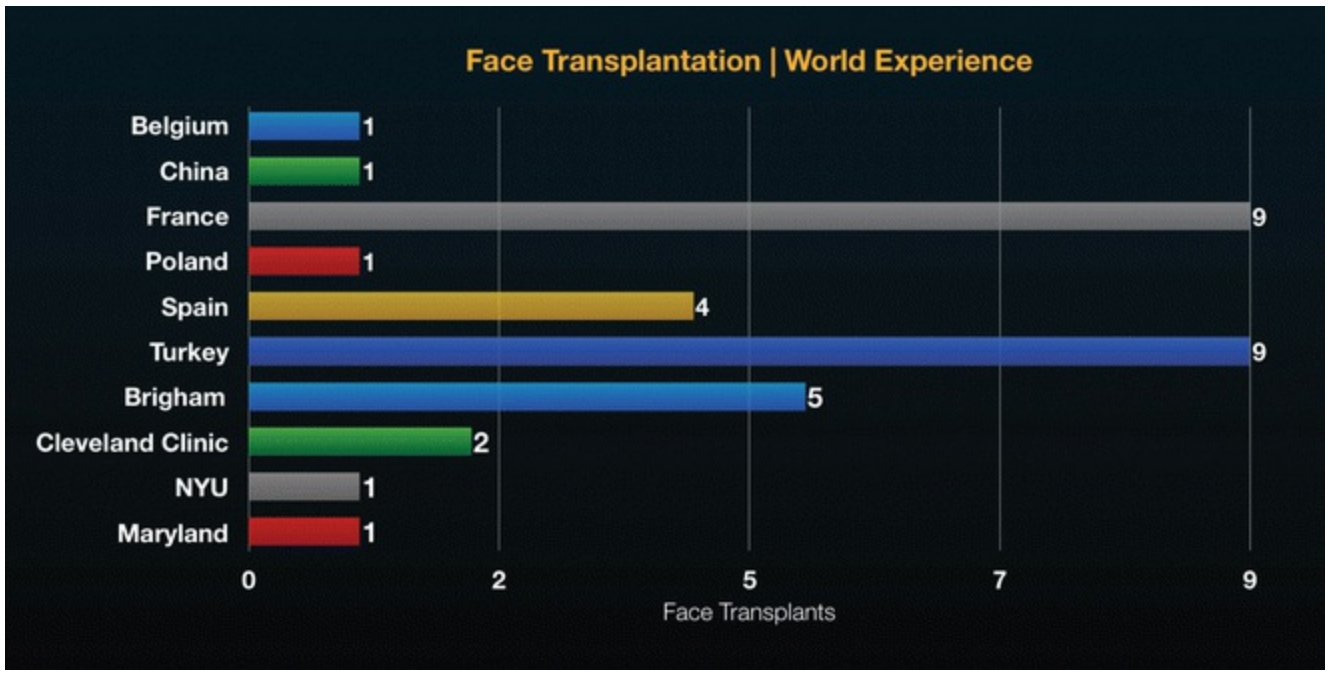

Fig. 44.9 World experience with craniofacial allotransplantations (partial, total face, scalp, ear, and other craniofacial components) performed in the world

Table 44.3 Outcomes in craniofacial transplantation : world and US experience

Center	Total number of CF transplants	Number of graft losses	Mortalities	Reported in lay media	Reported in peer literature
Brigham and Women's Hosp	5				
Cleveland Clinic	2				
NYU	1				
U. Maryland	1				
Poland	2				
Spain	4	1	1	Yes	Yes
Turkey	9	2	2	No	No
France	9	1	1	Yes	Yes
Belgium	1				
China	1	1	1	Yes	No
Total	35	5	5		

The experience with clinical RT over the past 15 years has providing insights into the multifaceted aspects of these innovative procedures. We have learned that (1) RT is not life saving but, when successful, these procedures can enhance quality of life; (2) RT recipients are otherwise healthy without accompanying diseases but need lifelong immunosuppressive treatments that result in a range of life-shortening, quality of life limiting or even life threatening morbidity; (3) acute rejection can be monitored visually

(not in all instances) which allows for timely local graft or systemic intervention; (4) topical therapies of skin potentially allow reduction or supplementation of systemic therapy; and (5) risk–benefits in RT can vary between different VCAs and thus such consideration for RT patients must be individualized for each VCA and for each defect include a comprehensive risk–benefit analysis including a robust exit strategy [59, 60].

Although the most common RT procedures are upper extremity and craniofacial VCAs, to date, close to 200 VCA procedures, including but not limited to, extremity, craniofacial, genitourinary, tracheal, or abdominal tissues have been performed at active clinical RT centers spanning the globe across most continents.

Other Types of VCA

With the advent of RT and rapid expansion of the field around the world since the 1990s, a host of other types of VCA have been performed by centers including but not limited to laryngotracheal, bone and joint, abdominal wall, uterine, penile, tongue, ear, scalp, and lower extremity transplantations. Pediatric and combination VCAs (face and upper extremity or upper and lower extremity transplants) have also been performed.

Abdominal Wall Transplantation

The first abdominal wall VCA was performed by Tzakis and colleagues in 2003 in recipients of intestinal or multivisceral transplants with loss of abdominal domain [61].These VCAs were unique as the patients were already on immunosuppression for SOT. Since then 38 full-thickness vascularized abdominal wall transplants, six partial-thickness vascularized, and 17 partial-thickness nonvascularized rectus fascia grafts have been reported worldwide [62]. Despite failures in some patients, these grafts have been used to facilitate primary, tension free closure of abdominal wall in SOT patients with visceral coverage and reduced complications [63, 64]. Taken together, despite mixed success, the numbers of abdominal wall transplantations exceeds that of craniofacial VCA.

Laryngotracheal Transplantation

Kluyskens and Ringoir performed the first laryngeal transplant in 1969 for reconstruction after tumor extirpation [65, 66]. However, the tumor recurred leading to death at 8 months and the graft was lost to rejection when immunosuppression was withdrawn. Following this early attempt, Strome and colleagues performed the first successful laryngotracheal VCA (including thyroid and parathyroid glands) in 1998 in Cleveland prior to the first upper extremity transplantation in Louisville [67, 68]. The patient who suffered from laryngeal trauma recovered swallowing and phonation with excellent quality of life outcomes until this graft was lost to chronic rejection 14 years

later [69]. Following this, Tintinago et al. from Medellin, Colombia performed over 18 laryngotracheal VCA, including the first esophageal VCA [70–72]. Majority of patients were weaned from tracheostomies. There is a report of two graft losses, but this experience remains mostly unpublished with long-term outcomes unknown.

Knee Joint and Femur Transplantation

Hofmann and colleagues performed the first series of knee joint and femur VCAs in Munich between 1996 and 2006 [73]. These include six human vascularized allogeneic knee transplantations and three femoral diaphyseal transplants for long segmental bone defects [74]. All of these grafts were successful in the short term but were lost within the first 56 months due to reasons including infections, non-adherence to medications and chronic graft rejection [75, 76].

Tongue, Ear, and Scalp Transplantation

In 2003, Ewers and colleagues performed the first total tongue VCA in Vienna, Austria in a recipient following carcinoma resection [77]. Following a short period of success, the patient succumbed to tumor recurrence. In 2004, Hui and team transplanted both ears bridged by cephalocervical scalp skin in a recipients following extirpation of melanoma [78]. Again, the patient succumbed to tumor recurrence. More recently, in 2015, a team from MD Anderson Cancer Center performed a combined partial calvarial and scalp transplant in a SOT recipient suffering from a wound defect secondary to tumor removal from the scalp. Long-term outcomes remain to be seen.

Penile Transplantation

Hu et al. performed the first penis allotransplantation in Guangzhou, China in 2006, in a patient suffering from traumatic penile amputation [79]. After a short course of success with normal urination, the transplant was electively removed at 2 weeks due to psychosocial rejection experienced by the recipient and his spouse [80]. More recently, in 2014, a team lead by Andre van der Merve from South Africa performed a penis transplant in a recipient suffering from complicated circumcision [81]. A year later, this patient is reported to have ejaculatory and erectile sexual function, although it is unclear if erogenous sensation has recovered. Two programs have recently received OPTN approval to perform penile transplants in the USA.

Uterus Transplantation

The earliest attempt at uterine transplantation was in Saudi Arabia by Fageeh et al. in 2000 [82]. The graft failed at 99 days due to ischemic uterine torsion. This attempt was followed by another transplant in Antalya, Turkey, in 2013, lead by Ozkan et al.

[83–85]. Both these early attempts were based on deceased donors. Despite survival of the transplant, pregnancy was not accomplished in this recipient. In 2014, Brannstrom and colleagues achieved the first successful pregnancy in uterine transplantation in a recipient with absolute uterine infertility (AUI) . This team performed a total of 9 deceased donor uterine transplants with four live births [86, 87].

Uterus transplantation may be the first available treatment for AUI, which is caused by absence of the uterus or the presence of a nonfunctional uterus. Similar to abdominal wall transplants, where the patient is usually on immunosuppression for the SOT, uterine transplants benefit from reduced immunosuppressive drug exposure (coverage only needed during gestation) [88–91].

Lower Extremity and Simultaneous Combination Reconstructive Transplantation

Four cases of lower extremity VCA have been reported (two bilateral and two unilateral) [92]. In 2006, Zuker and colleagues performed the first unilateral lower limb VCA in ischiopagus conjoined twin infants [93]. Given that this was a twin–twin VCA, postoperative immunosuppression was not needed. Over a 6-year period, the patient recovered motor and sensory function to allow ambulation with assistance [93].

In 2010, Cavadas and colleagues performed the first bilateral above knee lower extremity VCA in a 21-year-old recipient in Valencia, Spain [94, 95]. At 1 year, there was recovery of knee flexion and extension with some ankle function. In 2012, Ozkan and colleagues performed a simultaneous bilateral upper limb VCA in combination with a unilateral lower extremity VCA in Antalya, Turkey. Both the Spanish and Antalya patients succumbed after transplant, one to post transplant lymphoma and the other to post transplant end organ failure secondary to disseminated aspergillosis. In the same year, Nasir and coworkers performed a bilateral lower extremity VCA in combination with upper extremity VCA in Ankara, Turkey. The patient died perioperatively due to surgical complications [96].

Other *simultaneous complex* transplants have been reported across the world involving combination face and upper extremity or upper and lower extremity VCA (bilateral or unilateral) [97]. Three of four of these reported tandem transplants have died due to operative or perioperative complications that include overwhelming sepsis or shock [98, 99]. One patient survived but had to undergo removal of both upper extremities only to preserve a face transplant. Uniformly, quadruple VCA and triple VCA have been associated with very high failure. There are risks of the large antigenic burden, overwhelming ischemia–reperfusion injury, large volume resuscitation requirements, extended anesthesia times among a host of surgical and technical challenges [100].

Pediatric VCA

In July 2015, the world's first bilateral pediatric hand transplant was performed by Levin and team in an 8 year old boy at University of Pennsylvania. The recipient was a SOT patient and thus already under immunosuppression [101, 102].

Ethical Considerations

Ethics of Equipoise, Autonomy, Informed Consent, and Risk–Benefit Balance

Although much has been learned in hand and face transplantation, equipoise continues to be important for VCA procedures gaining recent attention (lower extremity, penis, uterus) [103]. In all attempts, old or new, the prospect of unintentional and unanticipated harm must be balanced or preferably exceeded by the potential known or anticipated. Such "equipoise" is the reasonable yet deliberate educated judgment of VCA teams initiating new programs in the uncertainty of research setting and must be accomplished prior to ethically proceeding with larger clinical trials [104].

All VCA teams must recognize the individual variability of subjects in prior life experiences, level of education and processing of information, conceptual and theoretical capacities, and subjective weight or trade-off given to estimations of benefits and risks. Any or all of these factors may affect decision making by patients [105]. "Autonomy" is the concept that addresses the respect for the subject as detailed in the Belmont Report and is defined as "at a minimum, self-rule that is free from both controlling interference by others and from limitations, such as inadequate understanding, that prevent meaningful choice" [106].

The overarching crux of ethical debate in VCA is a risk–benefit analysis, which surrounds a surgical procedure with lifetime medical consequences but with a primary goal of non-life-prolonging outcomes [107]. A distinctive aspect of VCA is the need for lifetime immunosuppression, with its attendant risks of infection, malignancy, and other medication side effects, the assessment of which, unlike in SOT is difficult in VCA recipients who are otherwise healthy. Similarly, functional status can be measured, but sensory improvements are more difficult to evaluate objectively in patients with VCA. Thus the surgical, medical, psychological, and social risks of the procedure must be weighed against the potential improved quality of life with a possibly better functioning, more "normal" VCA. Because the risks and benefits and functional outcomes are not comparable across VCA or even within similar VCA, it is critical to base the informed consent on known facts.

Inherent to every IRB mandated VCA program is a thorough, supervised informed consent process. Ideally, every informed consent is an ongoing process, comprehensive

in inclusion of known and relevant benefits and risks, alternate options as well as potential unanticipated harms providing a thoughtful balance of relevant objective and subjective information to patients in an easily comprehensible template of non-technical verbiage. Given the complexity and relative novelty of VCA procedures, investigators may be deemed to have an actual or perceived conflict of interest in providing informed consent in complicated and groundbreaking research, as they are required to be objective patient advisers on risk-to-benefit analyses as well as a researchers striving at pioneering achievements [108].

Ethics of Utility and Exit Strategy

Utility is a determination of a subject's decision/preference to undergo RT for his/her disability/deformity to achieve the maximum expected overall health benefit [109]. Of the approaches for measuring or quantifying preferences, time-trade-off (TTO) and standard gamble (SG) arguments are widely used [110–112]. In TTO, recipients choose between remaining in a state of ill health for a period of time, or being restored to perfect health and having a shorter life expectancy. No RT procedure, with its lifelong immunosuppressive burden is expected to restore a subject suffering from an unreconstructable defect to "perfect health." In fact, it is realistic to expect that most RT procedures will reduce life expectancy even in the healthiest of subjects [113].

It is the ethical and scientific responsibility of the provider to ensure that each RT procedure offered to a potential eligible subject is thoroughly evaluated for appropriate exit strategies in the event of catastrophic failure. The first step in this process is to elicit the preferences from the subject seeking RT via an exhaustive informed consent process that must be clear and sensitive to the potential benefits and risks of the procedure while offering unbiased advice on alternate options. There may exist a frame of reference bias in investigators based on the psychological proclivity to highlight the relative "promise" of benefits in favor of realistically underscoring the "threat" of risks. The meaning and consequences of failure, partial success, and complete success must be clearly described, in terms of the nature, magnitude, duration, and likelihood of any anticipated effects, as well as the posttransplant regimen and the anticipated length of follow-up.

Ethics of Innovative VCA

Pediatric VCA

We have learned about social and ethical issues in adult VCA recipients over the past decade, but issues unique to children are yet to be identified [114]. Pediatric VCA warrants the utmost ethical safeguards in patient selection as well as planning and preparation to ensure the highest chance of success [115].

Overarching issues relate to patient autonomy and vulnerability (informed/proxy consent, cognitive preparedness), personal identity (body integrity/body image perception), risk–benefit equipoise (immunosuppressive risks versus improved quality of life), and non-adherence to medications or rehabilitation after transplant. These need to be thoroughly examined to mitigate harm to patient. Ensuring the optimal environment of caregiver and social support conducive to compliance with postoperative recommendations, in addition to formulation of a comprehensive exit strategy inclusive of behavioral counseling and therapy in the event of transplant failure are of paramount importance. Adaptation and neurointegration after congenital loss are unknown. Critical emphasis must be on continuous assessment of psychosocial, compliance and emotional issues as the child evolves into adulthood, all of which can impact transplant outcomes [116].

Genitourinary and Penile Transplants

It is critical and an ethical prerogative for providers to carefully balance indications, risks, benefits of transplant versus conventional reconstruction [117]. Conventional reconstructive techniques have proven to be able to achieve high functional and aesthetic standards in genitourinary injury. It is thus key for teams to assess expectations and motivations of patients with penile injury seeking transplant (whether it is body image restoration, fertility or sexual function) and match them with unknown and known risks of the procedure (including the use of a penile prosthesis for erection in case of functional failure, which increases the risk of rejection due to mechanical irritation).

Uterine, Ovarian, and Testicular Transplants

Ethicists and experts argue against indications beyond AUI that VCA teams have proposed for uterine VCA in lieu of alternative options such as gestational surrogacy. These also include the inclusion of living donors. There is extensive ethical and cultural debate about these VCA given the unknown risks, benefits, and short/long-term impact on living donors, recipients, and offspring [118–121].

Transplantation of ovaries and testicles presents new possibilities for patients with a variety of fertility conditions, including some conditions that are untreatable with current options [122]. The types of patients that might benefit from such VCA over other types of fertility options will depend greatly on the type of RT, whether a donor is necessary, the individual's preferences, the benefits and burdens of current alternative options, and how well RTs develop into safe, ethical, cost-effective, and efficacious treatments when compared with existing options.

There must be open investigation and ethical debate of all the above aspects as well as a constant reevaluation of exit strategies in a field as young and as dynamic as VCA. It is the ethical responsibility of VCA providers to not endanger patients with the sure

specter of death (in the event of graft failure) under the premise of short-term "health utility" outcomes that are not totally free from morbidity of lifelong antirejection medications. It is especially critical to avoid giving rise to therapeutic misconception, whereby providers overstate potential benefits of a particular RT to vulnerable subjects and create unduly high expectations of benefit without a real assessment of an exit that may be indeed be fatal to the patient.

Emerging Prospects

The history of modern SOT and VCA began five decades ago with the pioneering work of two plastic surgeons, Murray and Peacock [13]. Despite recent progress in VCA, and graft survival that is superior to the SOT experience, clinical failures (many remain unpublished and unpublicized) have resulted from existing limitations including but not limited to adverse effects of chronic high dose immunosuppression regimens, chronic rejection or uncontrolled acute rejection due to medication nonadherence (which may be underreported in VCA) or other etiologies. Importantly, unlike SOT, suboptimal nerve regeneration in VCA can result in limited or loss of functional outcomes in many patients.

Evolving innovative strategies in VCA attempt to improve the risk-to-benefit equipoise of these procedures by making them safer, functionally effective, and ethical reconstructive options. Just like developments in SOT, pharmacologic immunosuppression and transplant immunology helped lay the foundation for VCA. Now disruptive advances in regenerative medicine, tissue engineering, nanotechnology, computational biology, predictive analytics, or other multidisciplinary or cross-disciplinary fields disparate from RT are helping push VCA toward new frontiers [123]. Some of these strategies include immunomodulation (stem cell therapies, immunobiologics) [124], neuroregeneration (neurobiologics) and targeted therapeutic, graft specific treatment, monitoring or diagnostic strategies in VCA (local immunosuppression with sustained release drug platforms, gene therapy, immunosurveillance, noninvasive molecular/multimodality imaging of rejection, ex vivo preservation techniques for ischemia mitigation and prevention of reperfusion injury, immunocloaking, and immunoevasion in donor grafts) [52].

RT has witnessed a tumultuous yet transformative evolution and stands to surpass SOT in its life-changing and life-giving impact and scope for treating the disfigured and disabled recipient suffering from unreconstructable tissue loss. More RT procedures continue to be performed across the world. Recently two unilateral hand transplantations were performed (Duke University and U. Toronto) and one bilateral hand transplant was performed in Kochi, India Rapid progress in the fields of regenerative medicine, tissue engineering, molecular imaging, nanotechnology, drug delivery, and biomaterials could fuel further progress in VCA, improving safety and

outcomes while expanding clinical applications. The success of immunomodulation or tolerance protocols could change the future of reconstructive surgery by bringing VCA procedures into the mainstream of clinical practice and standard of care.

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45. Reconstructive Transplantation: Program, Patient, Protocol, Policy, and Payer Considerations

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Introduction

In devastating tissue loss due to trauma, tumor removal or congenital defects, despite the best reconstructive efforts, functional and esthetic outcomes are limited to poor, morbidity and costs high, and recovery is long [1]. Reconstructive transplantation (RT) is the emerging specialty in solid organ transplantation (SOT) that involves the transplantation of composite grafts to restore and recreate the appearance, anatomy, and function in disabling or disfiguring indications [2].

The ideal goals of RT are similar to reconstructive surgery—that is to replace and restore missing tissue as functional "whole" subunits—goals that can be achieved by

vascularized composite allotransplantation (VCA). VCA can achieve near perfect restoration of tissue defects with improved functional and esthetic outcomes and avoidance of multiple surgeries and donor site morbidity [3].

During the past decade, more than 50 VCA programs have been established around the world, performing more than 150 VCA procedures including over 100 upper extremity and 30 facial transplants with encouraging outcomes [4]. The technical, immunologic, and functional feasibility of VCA as an alternative restorative option has been established in indications such as hand or face RT.

If we consider overall graft *survival* outcomes alone in RT, results to date have been superior compared to the early outcomes with solid organs. However, the clinical potential of these procedures has remained untapped due to the known and unknown lifelong hazards of immunosuppressive drugs. Much remains desired in improving the safety, efficacy, and applicability of these promising reconstructive modalities [5].

This chapter overviews the programmatic, patient, provider, payer, and policy-related considerations in VCA with special emphasis and critical appraisal of key aspects.

VCA Programs: Requirements, Challenges, and Goals

Latest data (as of December 25, 2015) indicate that there are 53 VCA programs located at 24 RT centers (including civilian transplant programs and military or Veteran's Affairs (VA) hospital affiliated institutions) across the Nation. All these programs have been approved by the Organ Procurement and Transplantation Network (OPTN) for VCA. Figure 45.1 shows the programs in the USA and across the world performing RT [6].

Fig. 45.1 World programs actively performing or approved for reconstructive transplantation

In the USA, the majority of programs (44/53) are approved for upper extremity, head & neck, or abdominal wall VCA. A minority (9/53) of the programs are approved for genitourinary (GU) VCA (may include penile, ovarian, testicular), penile (only), uterine, and lower extremity VCA. The total list of body parts (Table 45.1) that are expected to fulfill the nine criteria that define VCA as solid organs are proposed by the OPTN Final Rule (Table 45.2) [7].

Table 45.1 Approved list of body parts classifiable as VCA per UNOS VCA Committee designation

Upper limb (including, but not limited to, any group of body parts from the upper limb, or radial forearm flap)
Head and neck (including, but not limited to, face including underlying skeleton and muscle, scalp, larynx, trachea, thyroid, or parathyroid gland)
Abdominal wall (including, but not limited to, symphysis pubis and other vascularized pelvic elements)
Genitourinary organs (including, but not limited to, uterus, internal/external male and female genitalia, or urinary bladder)
Lower limb (including, but not limited to, pelvic structures that are attached to the lower limb and transplanted intact, gluteal region, vascularized bone transfers from the lower extremity, anterior lateral thigh flaps, or toe transfers)
Adrenal gland
Spleen
Musculoskeletal composite graft segment (including, but not limited to, latissimus dorsi, spine axis, or any other vascularized muscle, bone, nerve, or skin flap)

Table 45.2 OPTN and UNOS definitions of vascularized composite allografts

Primarily vascularized grafts [1]
Contain multiple tissue types [2]
Recovered from a human donor as an anatomical/structural unit [3]
Transplanted into a human recipient as an anatomical/structural unit [4]
For homologous use (the replacement or supplementation of a recipient organ with that performing the same basic function in recipient as in donor [5]
Minimally manipulated (i.e. processing that does not alter the original relevant characteristics of the organ relating to the organ's utility for reconstruction, repair, or replacement) [6]
Not combined with another article such as a device [7]
Susceptible to ischemia and, therefore, only stored temporarily and not cryopreserved [8]
Susceptible to allograft rejection, generally requiring immunosuppression that may increase infectious disease risk to the recipient [9]

There are 58 organ procurement organizations (OPOs) that work across 11 geographic regions to help organ procurement and allocation. The largest numbers of VCA programs are in Regions 2 and 11. Every region has at least one designated VCA program. Programs in Region 1, 2, 3, 4, 5, 7, 9, 10, 11 have performed at least one VCA. Programs in Region 6 and 8 are yet to perform a clinical VCA. No program has yet performed a GU, penile, or uterine transplant [8].

Five-year survival rates of VCA (esp. face and upper extremity) are superior to solid organs. Solid organ programs rigorously report SOT outcome data (graft survival and loss) to the Scientific Registry of Transplant Recipients (SRTR). However, currently there are no comparable requirements or actual reporting of VCA data by providers/teams to a central patient registry database. This will change with United Network of Organ Sharing (UNOS) requirements on future transplants but there is no policy for retrospective reporting of data collected over 15 years by teams. The nine active VCA programs in the USA do not openly or proactively share outcomes data with each other. There are no agreed program standards on patient selection or true indications in VCA as well as for data monitoring and analyses.

Clinical RT requires a multidisciplinary team of providers with extensive experience in issues faced by patients with complex trauma. Depending on the type of VCA, this team should thus represent specialties that include hand, plastic, orthopedic, head and neck, urology, ob-gyn, and transplant surgeons, internal medicine, physical therapy, psychiatry, pharmacy, and anesthesia. In addition, the transplant coordinator, social workers, caregivers, and patient advocates play an important role [9].

The key prerequisites for the planning and establishment of a successful clinical VCA program are detailed under program requirements, challenges and goals in Table 45.3. Every team must carefully ensure the pre-approval, personnel, procedures, preoperative, perioperative, and postoperative protocols and procedures, required

infrastructure, resources, psychosocial, pharmacologic, and physical therapies involved in patient selection, management and procurement aspects that are critical components of a VCA program. Teams must also include media and public relations, regulatory and fiscal considerations, and ethical concerns in program planning, preparation, and establishment [10].

Table 45.3 VCA program requirements , challenges, and goals

Program requirements	Program challenges	Program goals
Institutional and organizational support	Reimbursement of care by private or federal payers	Collaboration with other VCA teams
Regulatory review and approval [3]	Maintaining the right public perception of VCA	Sharing of data and outcomes with other VCA programs
Adequate infrastructure and resources in transplant services	Creating positive awareness and education in the patient and public	Validation of safety, efficacy, and feasibility of protocols
Multidisciplinary team expertise	Access to patients and donors	Maximize patient benefit and optimize outcomes of VCA
Defined protocols, procedures, and criteria for patient selection	Establishing program standards in screening and selection of patients	Impact standard of clinical practice
Study compliance and oversight management [7]	Obtaining consensus of other programs on monitoring and outcomes measures	Inform health policy
Fiscal or cost analysis of UNOS approved VCA with funding assurance by institution or third parties	Barriers to referral of patients by providers	Provide high-quality clinical evidence and objective cost analysis
Organ procurement organization support and collaboration	Compliance with evolving policy	Timely and transparent disclosure of patient outcomes (including complications) to peers and public and publication of program data in scientific literature

The programmatic, procedural, patient, and protocol-related aspects are well detailed in the literature for individual VCA including upper extremity, craniofacial, and other types of RT [11–16].

As RT has moved from experimental to investigational to innovative therapy and now in some select programs to standard of care (SOC) there is an imminent need for prompt, rational, effective, objective, rigorous, and deliberate evaluation of existing and novel therapeutic indications for VCA. This is because VCA has unique recipient and donor considerations unlike SOT and also currently costs are currently non-reimbursable for these innovative procedures.

Programs must work together and with UNOS to increase the generalizability of results by pooling or comparison among centers that individually lack necessary sample

size or power. The benefits of UNOS and OPTN oversight (Table 45.4) in VCA include access to a larger number of participants from different geographic, ethnic, and etiopathologic groups. Most importantly reporting VCA outcomes to UNOS and SRTR affords the best means of increasing the quality of evidence for clinical decision making, approval, and adoption of a given therapeutic option, provide objective cost analysis, and inform health policy.

Table 45.4 Impact of OPTN and UNOS oversight of vascularized composite allografts

Establish program standards for screening | selection | monitoring | outcomes (data collection, reporting, and analysis)
Validate safety, efficacy, and feasibility of protocols
Maximize benefits and optimize outcomes
Increase awareness of VCA as a treatment option
Educate public, peers, and patient advocacy groups
Support quality of life as justification for transplant
Streamline donor access and allocation
Impact standards of clinical practice, inform health policy and gain federal regulatory approval

Patients and Providers: Roles and Responsibilities

Emerging outcomes from several VCA programs confirm that patient-centered aspects including understanding of risks and benefits, decision-making, motivation, and matched expectations regarding the transplant, dissatisfaction with functional outcomes, poor commitment/compliance with study regimens (e.g., nonadherence [NA] to immunosuppressive or lack of engagement with rehabilitation regimens), maladaptation with the transplants and coping with graft failure are all key challenges to VCA recipients. Regardless of the efficacy of the immunosuppressive or immunomodulatory protocol, without patient adherence to medication [17], commitment to physical therapy, and provider recommendations, no VCA will be successful in the long term.

We need to improve methods, tools, and guidelines for psychosocial screening to understand how eligible VCA subjects transition into the role of RT recipients and assimilate information about the lifelong burdens of transplant including risks of immunosuppression and of surgery (e.g., death in the event of catastrophic graft failure or systemic life threatening complications), commitments to the physician recommendations, and financial and caregiver stresses. Chemical dependency or dissatisfaction with transplant outcomes can all mar such a transition. Currently, no teams actively measure NA in VCA. Arguably, prevalence of NA in VCA may thus be under-detected/reported. Postoperative assessment of patient behavior combined with selected clinical metrics can help better estimate NA, ensuring timely and specific intervention with graft-sparing measures that improve overall outcomes. Development

of consensus guidelines for NA in VCA will allow larger RT trials for superior validation of surrogate metrics.

With patient-centered models of medical care growing in popularity and clinical attention increasingly focused on the spiritual, emotional, and sociocultural factors affecting patient decision-making it is timely to implement qualitative, data-driven research methods in the clinical understanding of RT/VCA protocols and outcomes. This is especially important given the small numbers/cohorts of patients undergoing these procedures. It is key for future studies to look at RT/VCA outcomes and adherence challenges from the viewpoint of the people they affect most: patients and their families.

It is important to highlight that "barriers" in existing VCA patients could help enhance outcomes in future VCA recipients, most notably the high number of wounded service members, by improving patient selection and institution of proactive/preventative psychosocial, caregiver, and other supportive measures in select patients.

The VCA surgeon (provider) must not consider a defect/deformity as "treatable" just because VCA is "technically feasible" but rather thoroughly balance this against failed or nonavailable conventional reconstructions, nontransplant alternatives (e.g., prostheses), psychosocial benefits versus known/unknown complications of life long immunosuppression/chronic rejection, or salvage/exit strategies (death in a face transplant patient versus amputation in a hand transplant patient). However, a review of the literature of RT procedures reveals a scenario where providers have performed VCA in recipients with co-existing morbidities such as HIV, HCV, associated active infection or malignancy under the premise of advancing the field with seminal procedures [18, 19].

These decisions become extremely difficult given the varying complexity of face and hand VCA, especially highly risky combination VCA (face and hands or hands and feet). As more complex VCA become technically facile, VCA surgeons are boldly embarking on "bigger" "more extensive" "riskier" procedures (especially craniofacial transplants). VCA teams may feel pressure to enroll patients to be the "first" to perform a procedure, compromising on thoroughness and due diligence in screening/indications. All of these issues threaten the field. Just as every graft success of a life changing VCA is a step ahead in for fostering peer scientific, payer reimbursement support or positive public reinforcement for VCA, every graft failure is a step back.

The lay/mass media could sensationalize such cases leading to the risk of the public believing VCA surgeons are not driven by ethical principles of beneficence, justice and most importantly primum-non-nocere (do no harm) [20]. Providers thus bear the burden of pushing the boundaries of the field of RT while cautiously balancing public perception of these advances. Lay media and peer literature reports cover new VCA procedures being performed; however there are no media reports or peer literature reports on VCA failures. Providers also bear the burden of public and peer transparency

and accountability with both successes as well as failures—or else there is a threat of losing public trust/support for these procedures.

Protocols in VCA: Balancing Immunologic and Functional Goals

Overall, intermediate and long-term graft and patient outcomes have been encouraging for extremity and facial VCA with improved quality of life. The prospect of allograft dependency on chronic, lifelong drug immunosuppression, with the risk of infectious, metabolic, or neoplastic complications remains a significant hurdle for clinical advancement of VCA [21]. Thus, development of safe and effective protocols consistent with immunosuppression-free graft survival is an immediate priority in non-life-saving transplants such as VCA. The seminal work of Owen, Medawar, Burnet, and Billingham in the 1940s, laid the foundations for the concepts of immunological tolerance, which is the state of immunologic unresponsiveness of a recipient towards a fully mismatched donor in the absence of immunosuppression [22].

Seventy years since, these findings have galvanized efforts to achieve tolerance in the clinic both in solid organs as well as VCA, although this has proved to be a formidable task. These strategies operate by inducing peripheral or central tolerance to the allograft, but little is known as to their efficacy when confronted with the human immune system: preexisting memory T cells and "heterologous immunity" in antigen-sensitized recipients (a state not seen with immunologically naïve rodents or other lab animals), or infections and early activation of innate immune response and the related inflammation-induced cytokine milieu that pose significant barriers to tolerance induction [23–25]. The goal of achieving clinical tolerance "up front" is thus enormously challenging, given the genetic heterogeneity of donor-recipient combinations and prior priming of the immune system to environmental antigens, which cross-react with those of the donor organ. Furthermore, continuing improvements with immunosuppressive drugs that produce good medium-term outcomes make it difficult to introduce new "tolerance" protocols that may bear unknown long-term risks including loss of the transplanted organ [25].

The emerging compromise has been to aim at harnessing immunomodulatory (not tolerance per se) mechanisms in RT recipients as a means of minimizing the dose and number of drugs administered [26, 27].

Over the past five decades, more than 50 different methods of tolerance induction have succeeded in small or large animal models including to some extent in nonhuman primates [28]. Some proof of principle has been established for experimental cellular therapies (mesenchymal, dendritic, or regulatory cells) in both SOT and VCA [26, 29, 30]. While there are clinical reports of whole bone marrow infusion after hand and face

transplants, there are no reported clinical attempts incorporating other isolated or enriched cell types in VCA [27, 31]. Multiple studies in the preclinical VCA literature reinforce the promise and potential for cell therapies in prolonging allograft survival and other aspects (promoting nerve regeneration, protecting from ischemia reperfusion injury) that could improve overall graft outcomes after VCA. Many questions do persist, such as the mechanisms underlying tolerance or graft acceptance, optimizing the conditioning regimen in the context of induction immunosuppression, the dosing, timing, route and frequency of cell administration and the use of combinations of cells to improve synergistic, complementary, or additive efficacy after VCA [32–35].

Despite the promise of cell-based strategies , tolerance protocols have not widely (routinely) replaced immunosuppression in SOT or RT. The reason for this is straightforward. Many of the tolerance protocols are too risky for clinical application. In other protocols, the risks remain unknown. Therapies designed to reprogram the immune system toward better self-regulation will require biomarkers for monitoring rejection, tolerance, and undesired toxicity, but there are no reliable biomarkers in VCA or solid organs for that matter. Research must be invested in surrogate measures of graft functional and immunologic health, such as in research into 3D functional microtissues, organoids, or in silico computational modeling of cytokine or gene expression profiling to complement clinical trials in RT, especially given the small patient numbers undergoing these procedures [36].

The momentum for harnessing tolerance processes seems unstoppable. But, we must not overlook the fact that, we really do not know how far we can go on the route to reprogramming the immune system. At some point, we will need to take stock and decide whether the patient's interests can best be served by maintaining them on a safe dose of drugs, or whether we aim for complete tolerance with the possibility that some stochastic event may disturb that process and so jeopardize the transplanted organ. Identifying the most successful of immunomodulatory strategies and then translating them to larger animals to test their suitability for the patients is the next step. This demands persistence and meticulous investigation to confirm the robustness and longevity as well as safety of the tolerance inducing regimens. If we are successful in doing this, then we may still arrive at our chosen destination, although it may seem very distant with tolerance induction therapies aimed at systemically conditioning RT recipients.

Perhaps the compromise will be that of aiming for tolerance by weaning patients off their *multidrug* to *minimal drug* regimens facilitated by targeting immunosuppression delivery to the graft and not to the recipient with its end organ toxicity. If successful, graft targeted immunomodulation/suppression holds the promise of systemic minimization of immunosuppressive treatment and offers the prospect of eventually weaning transplant recipients off their drugs [37, 38].

Although the predominant focus of most ongoing research in VCA is to develop novel immunomodulatory or tolerogenic therapies to minimize or eliminate life-long

immunosuppression in VCA, the life long burden of immunosuppression is not the only hurdle to VCA. Neuroregeneration remains the other major, yet relatively understudied barrier in VCA. Functional outcomes after clinical VCA such as upper extremity or face transplantations have been acceptable in some patients, but in many cases, motor and even more so sensory function, have remained unsatisfactory. Slow or sub-optimal nerve regeneration or delayed muscle re-innervation (or denervation), could all predispose to poor recovery. Such inadequate or ineffective nerve regeneration can result in loss of graft function, which equates to graft "failure" even in an immunologically viable graft. This is a feature unique to VCA in contrast to solid organs. Hence, for broader feasibility of VCA, it is imperative that we explore strategies that facilitate rapid and effective nerve regeneration as well as timely distal target reinnervation [39].

Evolving VCA Policy: Scope, Intent, and Limitations

Recent policy changes enacted by the Organ Procurement and Transplantation Network (OPTN) and United Network for Organ Sharing (UNOS) designate VCA as "solid organs" for the purposes of donation and transplantation. However, specific authorization for VCA donation (e.g., hand, face, abdominal wall, penis, and uterus) is required, and is requested separately from donation for all "traditional" organs. This policy was developed to protect "life saving" SOT from being negatively impacted by the request for VCA donation [8].

The OPTN policy includes no requirement that potential donors be made aware that VCA are considered organs that can be gifted for transplantation just like solid organs, but it does require specific consent to VCA donation. Because most registered donors are unaware (or rather not made aware) that their faces, hands, uteri or penises, and other "body parts" that are defined as VCA by OPTN (Table 45.1) can be donated, consent will obviously fall to next of kin or families. Central to the ethical debate is whether such policy undermines the core premise of an educated altruistic donor-designation towards VCA by withholding information that VCA can be donated like solid organs [40].

Experts also argue that by treating the consent process for VCA differently than for other organs, such a policy may undermine public education efforts towards recognizing donor designation as a legally binding decision. Paramount to these goals is protecting public trust in VCA, which could be compromised by developing policies or practices in a void without truly gauging public sentiment, accurately garnering public interests and priorities or correcting erroneous perceptions and biases towards VCA [6].

The policy status quo is a state-centered approach through state registries, largely tied to drivers licenses but uncoordinated across the states. Until recently no centralized collection of donation preferences was in existence and data points collected vary

greatly by registry. Thus the aspects concerning the public include but are not limited to improving awareness, interest, and willingness to participate in or be recipients of VCA donation [41].

Without directed outreach and education to prospective donors and next of kin on benefits of VCA donation, access of patients to innovative VCA therapies may be hampered.

It has also been argued by many including UNOS that there is no immediate cause for concern or need to address donor shortage in RT/VCA as the number of VCA procedures have been few and suitable donors have been identified by OPOs through separate authorization from donor families or next of kin.

It is also important to note that evolving UNOS policies regarding deceased and living-related (e.g. uterine) VCA are currently being developed without addressing or understanding true public sentiment regarding VCA. The practice of seeking "public comment" via the UNOS website within a given time window are not optimal and do not encompass the attitudes and responses of the donor population at large. If VCA policy is developed without truly considering or respecting public opinion, it could threaten public trust in VCA.

Similarly, if immunosuppression minimization, immunomodulation, or tolerance strategies become a reality, VCA numbers could expand exponentially where availability of donor VCA could be mismatched with clinical need without active efforts to understand public attitudes or overcome barriers to donation. The consequences of not identifying and employing these strategies on a large scale could be significant both for the field of VCA as well as for organ donation in general.

VCA policy must also be in step with advancements in the field of RT and the integration and interfacing of innovation in regenerative medicine (e.g., cell therapies), tissue engineering (e.g., biomimetic/biodegradable scaffolds), and biomaterials/drug delivery (e.g., graft embedded technologies or graft manipulations). Current UNOS definitions of a VCA may not encompass future developments in the field.

Payer Barriers: Reimbursement Pathways to Progress

Over the past two decades VCA has evolved as a multidisciplinary specialty with unique risk—benefit considerations compared to SOT. Although public funding has been instrumental for clinical VCA procedures across various centers, this funding has only partially covered these expensive procedures needing lifelong care support. The vast majority of VCA have been covered with intramural/institutional funds, making these programs/procedures not viable/sustainable entities [42–44].

Donor access barriers, patient selection issues, and immunosuppressive risks aside, if there is one major barrier to expansion of RT or availability of VCA procedures, it is lack of insurance reimbursement. Reimbursement strategies in VCA must include a

thorough review by providers of existing insurance contracts, to identify precedents that could be applicable to VCA.

One path to reimbursement is qualification of a particular VCA as SOC. Experimental surgical procedures go through three stages, experimental, SOC and acceptance by regulatory stakeholders. The public, and health care professionals are the treatment stakeholders, that determine if a given VCA is SOC. The insurers and regulators are the regulator stakeholders, who can accept the procedure as SOC but not define it.

Most VCA continue to be defined as experimental research (or investigational or innovative therapy) in some centers while being accepted as SOC in others. Such definitions have broad implications on policy, payment, and practice. There are six signs indicating treatment stakeholders are advocating for a given VCA as SOC. The six signs indicating SOC are: (1) A majority of the medical community accepts the procedure as medically necessary, or a majority of the medical profession in the field of RT, (2) Ethical committees and scholarly papers deem the procedure ethical, (3) A series of institutions carried out the procedure under IRB review with a record of successes, (4) A majority of the medical community, or an area accepts a particular VCA as SOC, (5) Scholarly work demonstrates beneficial outcome measurements, and (6) Indications that there is public desire for the surgical procedures [45].

There are five signs by regulator stakeholders that they agree with the SOC definition, and find it cost effective, and appropriate for regulation. Strong positive findings in the above areas are sufficient to indicate that a surgical procedure is SOC. But to achieve wide spread acceptance and payment the following regulatory stakeholder acceptance is desirable. The five signs of this acceptance are: (1) Payment acceptance by private insurers, (2) Payment acceptance by the federal government, (3) Positive outcomes and cost utility studies, (4) High utility values of a given VCA (5) Appropriate Incremental Cost-Utility Ratio (ICUR). Payers need to be presented with the ICUR calculation, quality adjusted life years (QALY) and disability adjusted life years (DALY) to support coverage justifications. ICUR = [Cost VCA − Cost alternate (SOC) option]/[QALY VCA − QALY alternate (SOC) option].

A few VCA teams have been successful in obtaining partial or total coverage for hand or face VCA in select patients through payer approvals for local/single patient coverage decisions. Other teams are evaluating the possibility of Medicare coverage for components of RT care, workmen's compensation and self-pay patients.

Coverage refers to the terms and conditions under which Medicare and private payers will (or will not) provide payment for VCA procedures. Coverage is the first, and unquestionably the most important, component of the reimbursement process. The evidence must support the procedure's effectiveness in substantially improving HRQOLs over existing technologies (e.g., prosthetics). Most evidence in VCA is from observational and comparative studies and not from randomized clinical trials given the

small numbers of these transplants performed under IRB oversight.

It is important to comprehensively understand payer for their expectations, concerns, and needs related to issues of VCA reimbursement, explore options for VCA coverage with evidence development, single patient approvals, and local coverage determinations. In this regard, teams must begin to work with representatives from federal (Centers for Medicare and Medicaid Services [CMS], Veterans Health Care [VHA], Tricare Management Agency [TMA]) as well as private payers (United Health Care, Anthem, Humana, Aetna, Wellpoint, Cigna, Highmark, Kaiser, Centene, HealthNet, Wellcare, Molina, Magellan, etc.). Costs/charge ratios between VCA programs that have paid for these procedures may be compared to claims data from programs that have obtained coverage from private/federal payers. This could allow payers to assess if the utility of these VCA procedures and the actuarial analysis of cost to benefit justify their "medical benefit" or "added value" as compared to "SOC" or approved alternative options for the indication. Understanding payer attitudes, perceptions, and biases regarding opportunities and challenges for reimbursement in VCA may be instrumental to improving wider availability of these procedures.

Devastating extremity, craniofacial and genitourinary trauma is often associated with unreconstructable injuries leading to lifelong disabling, psychosocial consequences. It is unlikely that any other populations stand to gain as much from life changing advances in RT/VCA.

Key scientific focus in RT has remained on advances in transplant immunomodulation and tolerance as well as peripheral neuroregeneration to minimize risks and improve functional outcomes. However, directing future areas of VCA research to address programmatic, patient, provider, payer and policy-relevant factors, and effective targeting of barriers emanating from large and small populations including the public, prospective, and existing patients, referring and practicing providers, and cost-utility analysis for payer approval and reimbursement is key to drive the momentum and critical progress of this promising field.

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46. Anesthesia for Composite Tissue Allografts

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Keywords Composite tissue allografts – Upper extremity transplantation – Face transplantation – Transplantation anesthesiology

Composite tissue allografts (CTA) transplants, unlike other solid tissue transplants involve multiple tissues including skin, muscle, tendons, blood vessels, nerves, lymph nodes, bone, and bone marrow. Each of these tissues has distinct immunogenicity posing more complex considerations regarding immunologic and graft survival and are discussed elsewhere. CTA have been performed for upper extremities, vascularized joints, craniofacial tissue, larynx, trachea, and abdominal wall. The purpose of this chapter is to discuss anesthetic management for these highly complex procedures.

Special concerns for operative anesthetic management of these patients need to focus on vascular access, fluid management, intraoperative monitoring, and the potential use of regional anesthesia strategies. The most experience exists with upper extremity and face transplants worldwide. Regional techniques are important with respect to upper extremity transplantations, and the discussion of this topic will be limited to this area.

For centers that embark in this new and exciting field, the anesthesiologists must learn from the few centers that have managed these patients and thus avoid pitfalls from prior experiences. What may not be appreciated initially, and cannot be over-emphasized, is the need for adequate vascular access and monitoring to deal with continued fluid shifts, blood loss, the potential coagulopathy, and metabolic derangements.

For procedures involving upper extremity and transplantation, continuous bleeding from dissected tissues can be an underappreciated problem. Constant oozing from exposed tissue beds may occur for hours. This blood loss is difficult to measure as the blood is not suctioned easily and loss on the surgical field. Greater than 30 units of PRBC transfused for upper extremity and similar volumes for face transplants have been reported. As a result of this problem and third spacing fluid loss, adequate vascular access is essential.

The Pittsburgh Upper Extremity Transplant Anesthesiology Protocol (PUETAP) was developed at the University of Pittsburgh Medical Center by the division of Transplantation Anesthesiology (Fig. 46.1) [1]. It will be referred to here and is currently the management of choice for these patients. As mentioned above, similar problems with blood loss and fluid management exist with face transplantation procedures and this protocol may be modified to deal with these patients [2]. In face transplantation procedures the airways is normally already secured via tracheostomy. Internal jugular access will not be possible, so large bore intravenous access must be obtained from the upper extremity and femoral vessels.

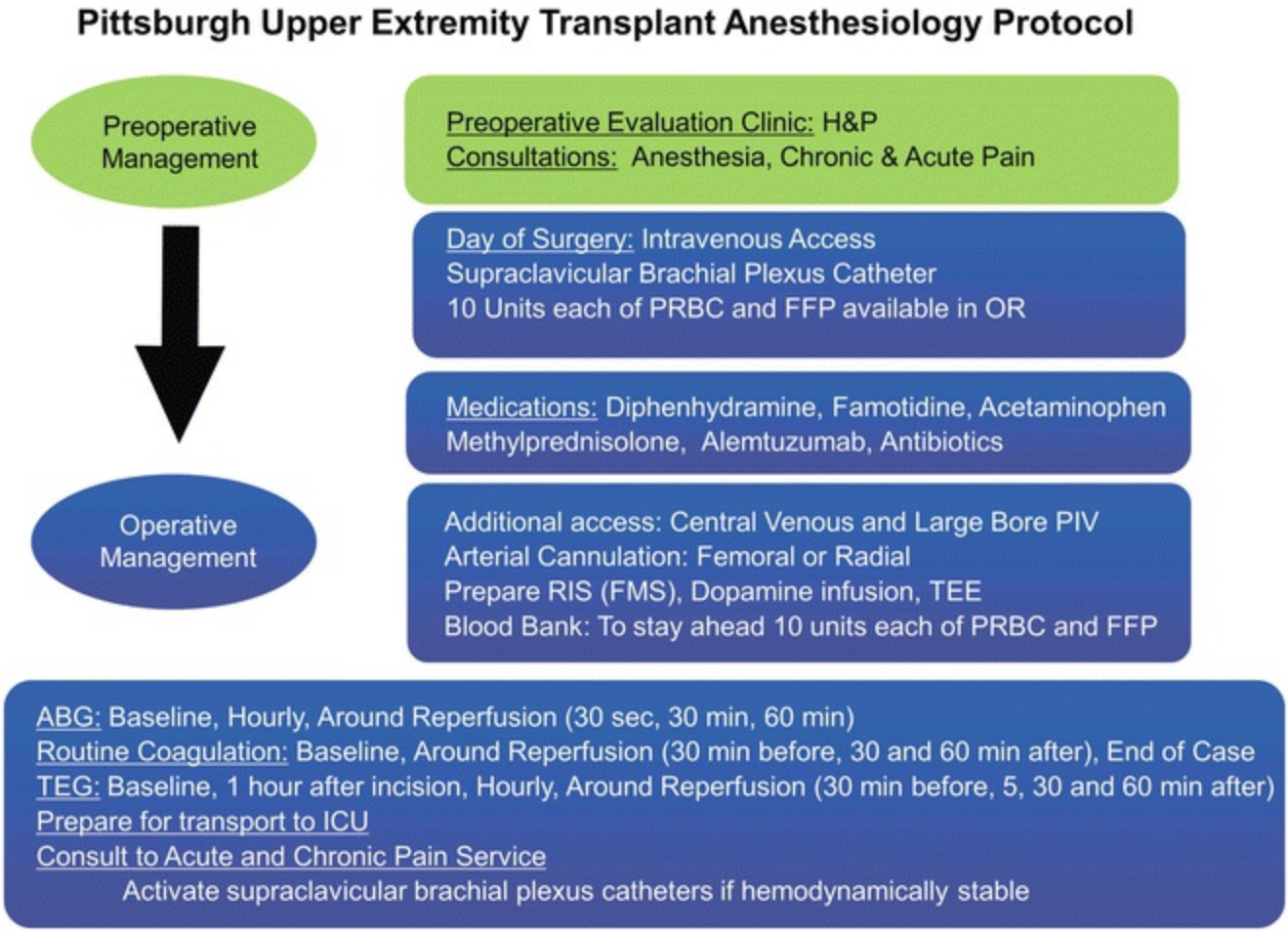

Fig. 46.1 Pittsburgh upper extremity transplant anesthesiology protocol

The PUETAP recommends intravenous (internal jugular) access via a large bore (Cordis or Shiley) catheter. Central venous pressure (CVP) monitoring is via a single lumen infusion catheter (SLIC) inserted through the introducer for unilateral hand/extremity transplant (UHT). An additional 14-gauge IV catheter is recommended in the nonoperative arm for UHT. Bilateral hand transplant (BHT) has limited upper extremity IV access requiring an additional 7-French double lumen or equivalent central venous internal jugular catheter. A 20-gauge radial artery catheter in the nonoperative arm for UHT and an 18-gauge femoral artery catheter for BHT are recommended. Monitoring of coagulation with ROTEM or TEG is essential. A rapid infusion system (RIS) such as the fluid management system (FMS) is also indispensible. Transesophageal echocardiolgraphy (TEE) should be available if required.

The blood bank must be prepared to provide the operating room with 10 units of RBC, 10 units of FFP and 10 units of PLT at the beginning of the procedure and maintain these same volumes of products in the blood bank immediately available to the OR at all times.

The PUETAP follows the trauma resuscitation protocol of 1 unit packed red blood cells (PRBC) : 1 unit fresh frozen plasma (FFP) : 250 cc normal saline (NS). This ratio achieves a hematocrit of 26–28 % in the RIS reservoir. A fluid warmer is used for the infusion of cold solutions. An increase in ambient room temperature, use of forced air warmers, and extensive surgical draping help maintain body temperature throughout the procedure. Alpha agonists should be avoided as they may affect graft perfusion. Dopamine is instituted when hypotension is not adequately corrected by infusion of IV fluids or blood products, such as vasodilation in response to donor extremity reperfusion. Low dose dopamine maintains regional blood flow by increasing cardiac contractility through beta-1 agonist effects and sustains renal perfusion via dopaminergic receptors.

Laboratory services must be able to process hourly or more frequently stat labs. The PUETAP protocol recommends monitoring of arterial blood gases (ABG), sodium, potassium, calcium, glucose, lactate, hemoglobin, and serum osmolality during surgery in all patients. ABGs are documented at baseline and hourly. Additionally, after reperfusion of the transplant, 30-s, 30-min, and 60-min ABGs are determined along with the above laboratory values. These times points are defined to help assess peak potassium concentrations as well as other immediate metabolic and physiologic changes associated with reperfusion.

Routine coagulation panels including a prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), platelets, and fibrinogen are performed at baseline, 30 min prior to reperfusion, and 30 and 60 min after reperfusion. A final coagulation panel is performed at completion of transplantation. A thromboelastogram (TEG) is also monitored at regular intervals; at baseline, 60 min after incision, and then hourly until surgical completion. Additional

TEGs are evaluated 30 min before reperfusion, 5, 30, and 60 min after reperfusion. The three TEGs studied after reperfusion (5-, 30-, and 60-min) should include natural (N), amicar (A), and protamine (P) channels to exclude coagulopathy related to possible fibrinolysis or heparin from the donor graft. Though a completed TEG takes up to 30 min for completion, important information, such as R-time, angle, and MA, can be obtained much sooner by seeing the progressive readout on TEG monitors in the operating room. Calcium chloride or gluconate is used to correct for decreases in ionized calcium noted on ABG and/or after large volume blood transfusion. Base deficits >7 or pH <7.2 must be corrected with sodium bicarbonate.

Regarding regional anesthesia strategies for upper extremity transplantation the PUETAP recommends ultrasound guided preoperative placement of supraclavicular brachial plexus nerve blocks unilaterally or bilaterally depending on the surgical site. Supraclavicular access is a useful route for brachial plexus blockade and securing indwelling catheters. A single bolus of a short acting local anesthetic is used during catheter placement to confirm function of the block. However, it is not activated for postoperative analgesia and vasodilatation by continuous infusion until completion of the transplant. This approach avoids the potential contribution of upper extremity vasodilation that may in theory contribute to brisk bleeding and hypotension during the procedure. After the initial bolus has worn off, an opioid general anesthetic helps patient tolerance of the tourniquet. Postoperative analgesia, provided by regional anesthetics, also helps diminish stress responses secondary to pain, such as pain during early physical therapy.

Other concerns are the use of immunosuppressant drugs required as with all transplants. Individual protocols have been established at each transplant center. Side effects of these agents may include hypotension, coagulopathy, pulmonary edema, and allergic (anaphylactic) reactions. Depending on the immunosuppressant protocol , premedications needed to be available include diphenhydramine, famotidine, acetaminophen, and methyprednisolone. Upper extremity and face transplantation are technically and logistically complicated procedure that can last upwards of 15–20 h. The overriding goals are to ensure effective anesthesia and analgesia, reduce vasopressor use and vasospasm, avoid hypotension, improve oxygenation, and optimize graft function.

The success of the PUETAP required the anesthesiologists to become true perioperative physicians. Given the complexity of these cases, it is recommended that transplant anesthesiologists meet with every listed recipient prior to surgery to clarify the anesthetic procedure and plan, as well as allay any patient concerns for this major surgery. The patient must also have the option to meet with a member of the Acute Interventional Perioperative Pain Service to discuss the use of regional anesthesia and expectations for pain control immediately following the procedure. Chronic pain specialists should be consulted postoperatively to ensure adequate pain control during

the prolonged recovery.

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47. Postoperative Management of Composite Tissue Graft Transplantation

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Keywords Composite tissue allotransplantation (CTA) – Postoperative management – Ventilator-associated pneumonia – Venous thromboembolism – Stress ulcer – Immunosuppression – Antibiotics

Introduction

Composite Tissue Allotransplantation (CTA) involves transplantation of body structures such as the limbs, larynx, abdominal wall, tendons, and face. In this chapter, we will discuss general and specific postoperative management of patients following CTA.

General Measures

The following general preventative measures should be implemented:

Elevation of the Head of the Bed

A particular concern in the intensive care unit is ventilator-associated pneumonia (VAP) , defined as pneumonia that develops more than 48 after initiation of mechanical ventilation. Several preventative strategies have been examined to reduce the risk of VAP, including oropharyngeal decontamination, probiotics, silver coated endotracheal

tubes, closed circuit suction tubes, and patient positioning. Elevation of the head of the bed is easy to implement without additional cost or adverse effects. The Center for Disease Control recommends that ventilated patients should ideally be placed in the semi-recumbent position with the head of the bed elevated at an inclination of 30–45°. Several randomized control trials have demonstrated that maintaining patients in the semi-recumbent position decreases the incidence of VAP.

Venous Thromboembolism (VTE) Prophylaxis

Development of venous thromboembolism is believed to evolve from abnormalities in endothelial injury, venous stasis, and hypercoaguability. Non-pharmacologic methods against VTE are available, though pharmacologic methods are preferred. Graduated compression stockings aim to prevent the pooling of blood in the lower extremities and prevent the development of venous clots. When appropriately used, compression stockings have been shown to decrease the rate of deep vein thrombosis. Pneumatic compression stockings applied to the lower extremities similarly operate by intermittently inflating and squeezing blood through the venous system to reduce the risk of venous stasis. Unfractionated heparin is most commonly used for prophylaxis against VTE. Both unfractionated heparin (UFH) and low molecular weight heparins (LMWH) have been shown to decrease the incidence of clinically detected VTE compared to placebo. Standard VTE prophylaxis, using compression stockings and pneumatic compression devices, should be used in all patients. Additionally, UFH can be used carefully in those without recent bleeding and without significant coagulopathy.

Stress Ulcer Prophylaxis

Stress related mucosal injury occurs in ICU patients within the first few days of ICU admission. The most important risk factors for the development of gastrointestinal bleeding are coagulopathy and need for mechanical ventilation. Other risk factors include history of gastrointestinal bleeding, hypotension, and multi-organ system dysfunction. Most of these risk factors are common in prior to and in the immediate postoperative period after transplant. Early trials of acid suppression used antacids, sucralfates, and H2 blockers and reported benefit in decreasing the incidence of both clinically significant and life-threatening gastrointestinal bleeding. Proton pump inhibitors (PPIs) are now commonly used as prophylactic measures against gastrointestinal bleeding. PPIs are more potent than H2 blockers in increasing gastric pH in critically ill patients; however, no study has shown improved efficacy with PPI to prevent gastrointestinal bleeding. Long-term PPI has been associated with increased risk of community acquired pneumonia, as well as healthcare associated pneumonia, and Clostridium Difficile infection.

Specific Measures

Postoperative Intensive Care of the Face Transplant Patient

Face transplantation is a complex and long surgery that is associated with significant perioperative challenges, and multiple postoperative complications. Face-grafting techniques require a well-defined organization of all the teams involved. Patients typically spend several days in the ICU.

Airway Management

Patients usually have a tracheostomy tube (size will be variable) in place. Many centers avoid the use of circumferential tracheostomy neck ties that normally fasten the tracheostomy tube. If these ties are used, tight application may lead to neck swelling and potentially venous outflow obstruction of the facial graft.

Postoperative severe graft edema is expected in most patients and head elevation at 30–45° will promote venous drainage and prevent VAP [1]. Extra care must be taken to avoid airway loss because that complication has devastating consequences.

Sedation

The goal is to have all patients liberated from the mechanical ventilator within the first 24 h after surgery. Combinations of sedatives and narcotics are usually required. Great care should be taken to avoid over sedation. Sedation interruption should be implemented for patients who require ventilation longer than 24 h.

Ventilation

Patients are ventilated with positive pressure volume controlled mode with FiO2 to keep paO2 levels between 100 and 150 mmHg [1]. Pulse oxymetry is helpful to wean or titrate FiO2; however, arterial blood gases are generally required to guide manage acid base balance. The Risk of developing Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) is high partly due to high operative transfusion requirement.

Hemodynamics

The goal is to have normal hemodynamics and avoid extreme swings (high or low) in blood pressure and heart rate as much as possible.

Hypothermia, hypovolemia, and pain can cause vasoconstriction, which in turn may compromise the free flaps. Normothermia, mean arterial pressure (MAP) of 65 mmHg, urine output up to 0.5–1 ml/kg/h should be the goal. Graft perfusion monitoring is performed by Doppler velocities of the external carotid artery but continuous Doppler probes may be used.

Hypotension and shock can be hypovolemic, hemorrhagic, or vasodilatory and the management should be implemented accordingly. There is no evidence to suggest using one vasopressor or inotrope is better than another so local protocols in managing shock should be utilized.

Volume Status

Graft edema is expected because of the long operation, long ischemia time, and disrupted lymphatic drainage. Elevation of the head 30–45° and relatively negative fluid balance can used to reduce face edema. Use of small does of diuretics may be used if deemed necessary by the team.

Massive Transfusion

Large blood losses are expected intraoperatively due to high vascularity of the face and prolonged procedure time as a result of complex anastomoses during the preparation and grafting phase. Maintaining Hct > 27, Plt > 50K, INR < 1.5 and Fibrinogen > 100 are common clinical practice targets [2].

Prophylaxis

Venous thromboembolism (VTE) prophylaxis with low-molecular-weight or unfractionated heparin are implemented as long as there is no evidence of bleeding. H2 blockers or proton pump inhibitors are frequently used for stress ulcers prophylaxis.

Enteral Feeding

Most patients have a gastrostomy or jejunostomy tube and Enteral feeding should be started in all patients usually on the first postoperative day. High protein formulas are used to help ensure adequate healing (25–30 kcal/kg/day and 1.5–2.0 g of protein/kg/day), and water needs at 25–30 ml/kg/day. In our institution, IMPACT 1.5 has been the formula of choice in free flap patients. Periodic speech-and-swallow evaluations are performed after the first 24 h to assess safe oral feeding.

Vascular Access

Femoral venous lines are placed for the perioperative use but should be discontinued as soon as possible. If indwelling catheters are needed for longer duration, peripherally inserted central catheters (PICC) may be considered.

Infections and Antibiotics

Patients generally receive perioperative broad spectrum antibiotic prophylaxis and the

choice depends on the local institution microbiological resistance pattern. Early infections if it occurs are mostly bacterial. The risk of infection mandates early removal of all invasive lines and subsequent frequent screening. The most severe infections occur during times of over-immunosuppression, such as the induction phase or management of acute rejection. Cytomegalovirus (CMV), Epstein Barr virus (EBV), and cutaneous herpes simplex infections have been reported [1]. CMV can trigger rejection that can be challenging to control; therefore, ganciclovir must be administered based on donor and recipient data. *Candida albicans* infection has also been reported. Prophylaxis with Ganciclovir as well as antifungals like fluconazole and Bactrim for pneumocystis should be considered. Infectious disease specialists should be involved in tailoring antibiotics to the results of surveillance cultures from both the donor and the recipient [3].

Immunosuppression

Proper levels of immunosuppression should minimize the risks of opportunistic infectious complications. A sentinel skin graft is placed sometimes in the left infra-mammary area to monitor rejection episodes [1]. Acute rejection has been reported as early as 4 days postgrafting. Induction immunosuppression is achieved with anti-thymocyte globulin as well as steroid taper. Maintenance immunosuppression involves a regime of tacrolimus, mycophenolate mofetil, and prednisone, and must be closely followed up for the duration of the patient's or allograft's life. Over-immunosuppression leads to undesirable side effects, such as infections, while under-immunosuppression leads to rejection of the allograft. Blood levels of immunosuppression medications need to be monitored, especially calcineurin inhibitors which are associated with significant nephrotoxicity, and dosages must be adjusted constantly to prevent deleterious side effects, while maintaining drug efficacy.

Rehabilitation

Social workers provide postoperative support on an as needed basis. They typically meet with the patient every 1–2 days during the acute postoperative period. The team's psychiatrist meets daily with the FT recipient during his/her perioperative hospitalization. After discharge, the psychiatrist meets weekly with the recipient, or on an as needed basis. Rehabilitation is crucial to the attainment of maximum motor recovery during the postoperative period. The rehabilitation protocol is created and adjusted for each patient and must be started as early as possible. The initial focus is on mobility and airway clearance, and soon after, therapeutic exercise.

Upper Limb Transplant

Airway Management

There is no special airway management described for patients with upper limb transplant. Risk of ARDS from massive transfusion and postoperative infections are possible. Patients are sedated and ventilated until they are hemodynamically stable and there is no acute concern about the graft function. Usually they are extubated in the first 24 h after surgery.

Hemodynamics

Central venous catheter is usually placed in the internal jugular vein to be used not only for access but also to obtain central venous pressure (CVP) and mixed oxygen saturation (SVO2). An additional 14-gauge IV catheter is recommended in the nonoperative arm for a unilateral hand transplant. Hemodynamic monitoring by a 20-gauge radial artery cannula in the nonoperative arm or an 18-gauge femoral artery cannula for bilateral hand transplant recipients is undertaken.

Similar to face transplant, vasoconstriction caused by hypothermia, hypovolemia, and pain could have a negative impact on the free flap [4]. Circulatory monitoring should be continued in the ICU to maintain mean Arterial pressure between 60 and 65 mmHg. Alpha- agonists should be avoided as they may affect graft perfusion. Dopamine is instituted when hypotension is not adequately corrected by infusion of IV fluids or blood products, such as vasodilation in response to donor extremity reperfusion. Flap/replantation assessment includes capillary refill and pulse check every hour as well as hourly monitoring via the implanted Doppler and two pulse oximeters. In unilateral transplants, it is crucial to compare the waveforms and oxygen saturations between the new graft and the non-transplant contralateral control limb [4, 5]. In bilateral transplants, this becomes a more challenging exercise and even subtle changes should be documented and reported. The transplanted limb is elevated, warm air blankets cover the limb, and the room is kept warm at 75 °F to prevent vasoconstriction.. Pain management includes continuous nerve block(s), acetominophine, and intravenous narcotics as needed.

Transfusion Requirements

Similar to face transplant, large volume of blood product transfusion may be necessary. The Pittsburgh protocol follows the trauma resuscitation protocol of 1 unit packed red blood cells (PRBC): 1 unit fresh frozen plasma (FFP): 250 cc normal saline [6]. This ratio achieves a hematocrit of 26–28 % [7]. Other parameters are similar to the face transplant management.

Volume Status

Close monitoring of volume status by trends in central venous pressure and hourly urine output is essential. Graft edema in the postoperative phase is managed conservatively by elevation and compressive bandaging. If venous stasis or lymphedema is suspected clinically, appropriate investigations (venograms or lymphangiograms) are performed to exclude these conditions. Limb volumetry is performed during the early therapy phase to identify and monitor subtle volume change [4]. Risk of acute kidney injury is high due to a combination of events including the lengthy surgery, the release of endogenous nephrotoxins from muscles and tissues, and the initiation of immunosuppressive drugs.

Prophylaxis

Deep vein thrombosis prophylaxis with low molecular weight heparin and stress ulcer with proton pump inhibitors is continued.

Immunosuppression

Immunosuppression is induced by a specific medication regimen. Postoperative immunosuppressions have included induction with antithymocyte globulin in some patients and basiliximab in others. Maintenance immunosuppression can be achieved by any of the following:

– Tacrolimus, mycophenolate, and corticosteroids.

– Tacrolimus and steroids.

– Rapamycin and mycophenolate.

– Rapamycin with topical steroid and tacrolimus.

Patient survival is 100 %. The first hand transplant recipient lost his graft due to rejection from noncompliance. Five other patients lost their grafts due to inability to continue immunosuppression [8, 9].

Skin and muscle biopsies are performed per institutional protocol to assess for evidence of acute rejection such as endpoint edema, erythema, and necrosis. Acute rejection was seen in some patients, most of them between 7 and 14 weeks posttransplantation. All the episodes were reversed with the use of intravenous steroids/lymphocyte depleting agents, alemtuzumab [10] or ATG/basiliximab and/or topical tacrolimus/corticosteroid.

Immunosuppression

The University of Pittsburgh Medical Center (UPMC) developed and implemented a new protocol based on the hypothesis that immunomodulation with donor bone marrow cell-based therapies would reduce long-term immunosuppression requirements [4, 6, 8].

There are three components to the “Pittsburgh Protocol”: induction therapy with Alemtuzumab (30 mg), tacrolimus monotherapy (0.2 mg/kg/day) at 12 h with an initial target trough level of 10–12 ng/ml, and whole bone marrow cells infused on day 14.

The protocol is efficacious and well tolerated, and episodes of acute rejection are low-grade and infrequent. Functional, immunologic, and graft survival outcomes continue to be assessed during long-term follow-up.

Infection

All patients receive prophylactic antibiotics, antifungals, and antivirals similar to patients with face transplant. Risk of postoperative pneumonia, CMV, and other infections like cutaneous mycosis and ulnar osteitis due to *Staphylococcus aureus* have been reported and need to be managed aggressively. Graft failure can occur due to postoperative infections.

Other Complications

Early postoperative complications include vascular thrombosis, limb loss, bleeding, and deep venous thrombosis (DVT). Re-exploration of the anastomosis may be necessary. Hip osteonecrosis has also been reported in long-term follow-up due to steroid use. Potential complications of prolonged immunosuppression as well as increased risk of malignancy, nephrotoxicity, neurotoxicity, gastrointestinal toxicity, hypertension, and diabetes, which are all related to the immunosuppressive medication. No graft versus host disease, no chronic rejection, and no malignancies or life-threatening conditions due to hand transplantation were reported. Hand graft survival rates have been higher than other forms of solid organ transplants [11]. Management of graft failure involves amputation followed by use of prosthesis or another transplant.

Rehabilitation

Postoperatively, electrical muscle stimulation may improve tendon gliding; therefore, encore electrodes should be placed along the median and ulnar nerves (above the transplant), along with a transcutaneous electrical nerve stimulator [8]. The patient should receive physical and occupational therapy daily for at least the first postoperative week.

Involvement of physical therapists and rehabilitation consultants is aimed to achieve optimal outcomes. The postoperative psychotherapy should be enhanced or reduced in accordance with the patient's history of compliance with health care needs, as determined by the social worker and psychiatrist preoperatively.

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