Congestive Heart Failure and Cardiac Transplantation

Clinical, Pathology, Imaging and Molecular Profiles

Daniel J. Garry
Robert F. Wilson
Zeev Vlodaver
Editors

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ISBN 978-3-319-44575-5 ISBN 978-3-319-44577-9 (eBook)
DOI 10.1007/978-3-319-44577-9

Library of Congress Control Number: 2017935486

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

This book is dedicated to our wives:
Mary Grace Garry
Betsy Wilson
Dalia P. Vlodaver
For their encouragement, support, and inspiration

Preface

This book is a comprehensive overview of heart failure and the only curative therapy for this disease, heart transplantation. Since heart failure is so prevalent in our society and has such a profound impact in our healthcare system, we have targeted a diverse audience ranging from the student to the clinical trainee as well as the research investigator and the practicing clinical expert. As the title and table of contents outline, a unique feature of this book is its breadth. The intent is to produce a single book that comprehensively examines the field of heart failure and the therapeutic strategies, including cardiac transplantation, that would be of interest to the molecular biologist, the pathologist, the practicing clinician, the radiologist, and the surgeon.

Introductory chapters are provided as a platform for the depth of the subsequent chapters. Chapter 1, which presents an extensive historical perspective, provides a unique beginning to the book. Subsequent chapters in Part I explore the basic concepts in the physiology, molecular biology, pathology, and epidemiology of the normal and failing heart and also highlight emerging research discoveries that are having a significant impact on the field. Part II addresses the known causes of heart failure, such as right heart failure, valvular cardiomyopathy, molecular mechanisms of sarcomeric cardiomyopathies, and neuromuscular cardiomyopathy. These chapters serve as an outstanding resource for the practicing clinician and the research investigator. In Part III, the progression of heart failure is outlined, with chapters devoted to cardiorenal syndrome, neurohormonal activation, remodeling, and arrhythmias in cardiomyopathy. Advanced therapies for the heart failure patient are discussed in Part IV, including cardiac resynchronization, ventricular assist devices, and cellular strategies for structural and hemodynamic improvement of the failing heart. An area of intense interest is the field of regenerative medicine and Chap. 23 highlights the state-of-the-art research strategies and their potential clinical impact for this field. Part V addresses the field of cardiac transplantation. These chapters detail the rich history of surgical, immunobiological, and therapeutic discoveries that are the signature for this field and target the clinical management of the heart transplant recipient. Topics include the cardiac transplant procedure, the early and late management of the post-transplant patient, allograft rejection, heart-lung transplantation, and xenotransplantation.

A unique feature of this compendium is the authors' expertise and national and international reputations. Many of the authors direct research programs focused on heart failure and cardiac transplantation and these initiatives complement their outstanding clinical expertise in the field. They have further distinguished themselves as founders or leaders of institutes, cardiovascular programs, pulmonary hypertension programs, neuromuscular programs, physiology departments, robotic surgical and transplant programs, adult congenital heart programs, structural heart disease programs, regenerative medicine programs, and start-up cardiovascular companies. The expertise of the authors and the comprehensive nature of this book serve as an important resource both for the practicing clinician in her/his daily practice and for trainees and research investigators. Importantly, it is the editors' hope that this scholarly effort inspires the next generation to pursue innovations and discoveries that will bend the path of heart failure and cardiac transplantation and lead to cures for these diseases.

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Acknowledgements

The editors are grateful for all the efforts and insights provided by the authors of the respective chapters in this book. The research and clinical expertise of the authors is unparalleled and serve to distinguish this book.

The editors recognize the foundational impact of the innovative contributions to cardiovascular medicine that is reflected in our book by the following pioneers.

C. Walton Lillehei, MD, internationally renowned as the "Father of Open-Heart Surgery," was professor of surgery at the University of Minnesota under Dr. Owen Wangensteen. In 1952, Lillehei participated in the world's first successful open-heart surgical procedure using hypothermia, which was performed at the University of Minnesota. In 1954, he performed the world's first open-heart surgery using cross-circulation and these procedures provided the platform for use of the heart lung machine. In 1958, Dr. Lillehei was responsible for the implantation of the world's first small, portable, battery-powered pacemaker; he also developed and implanted the world's first prosthetic heart valve in 1966. Thousands of cardiac surgeons across the world were trained by Dr. Lillehei and his colleagues at the University of Minnesota and revolutionized the field of cardiovascular surgery. Dr. Garry pays special acknowledgement to the late Dr. Lillehei who together with his late spouse, Kaye Lillehei, established the Lillehei Heart Institute, which is led by Dr. Garry.

Jesse E. Edwards, MD, was a world-renowned pioneering cardiovascular pathologist. He was professor of pathology at the Mayo Clinic in Rochester, Minn., and at the University of Minnesota, Minneapolis. He taught many medical students, pathologists, cardiologists, cardiac surgeons, and visiting medical experts from around the world. Dr. Edwards housed an enormous collection of autopsied hearts at United Hospital, St. Paul, Minn., known as the Dr. Edwards' Cardiovascular Registry that became a principal resource for his illustrated reference books: *An Atlas of Acquired Diseases of the Heart and Great Vessels* (1961), and *Congenital Heart Disease* (1965). He also coauthored nearly 800 journal articles and 14 books. Dr. Vlodaver pays special acknowledgment to Dr. Edwards who was his teacher, mentor and "inspirational force in his medical life."

Howard B. Burchell, MD, cardiologist, professor of medicine at the Mayo Clinic in Rochester, and the inaugural chief of cardiology at the University of Minnesota. He was editor-in-chief of the journal *Circulation* from 1965 to 1970. Scholarship and education with a central theme of sound scientific evidence were hallmarks of Dr. Burchell's career. Drs. Garry and Wilson pay special acknowledgement to Dr. Burchell as they led the Cardiovascular Division at the University of Minnesota in the same spirit of innovation, discovery, and the delivery of outstanding cardiovascular care.

Jay N. Cohn, MD, Professor of Medicine at the University of Minnesota, discovered much of the basic physiology of heart failure and its relationship to afterload and vascular tone. Dr. Cohn created an integrative conceptual framework for understanding heart failure that shaped our understanding of the pathophysiology and guided a revolution in therapy. Today, he is widely recognized as the Father of Heart Failure as he founded the Heart Failure Society of America and served as the inaugural editor-in-chief for the *Journal of Cardiac Failure*. Dr. Cohn also served as the chief of cardiology for 22 years and established one of the world's leading heart failure programs in the world. Dr. Wilson pays special acknowledgement to Dr. Cohn who recruited him to the University of Minnesota and was supportive in his studies of sympathetic reinnervation after transplantation.

The editors wish to acknowledge all the trainees that they have worked with throughout their careers. It is our hope that the discoveries and discussions we shared together will serve as a platform to inspire you to further impact the field.

We acknowledge and thank Jane Hutchins-Peterson for her outstanding assistance and for handling the flow of material from the writers to the publisher.

We recognize with deep appreciation Barb Umberger for her dedication in the editing of the manuscript in the minutest detail to ensure the high quality of this project.

We acknowledge and thank Erik Munson and Cynthia DeKay for their assistance with the illustrations and artwork that appear in this book.

We extend our gratitude to Michael Griffin, Development Editor for Springer Publishing, for his outstanding efforts, support, and attention to the details needed for publication of this book.

We wish to acknowledge the support of Janet Foltin, Senior Editor of Clinical Medicine, at Springer, for her encouragement for this project and all her efforts to help bring the project to reality.

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History and Basic Mechanisms of Heart Failure

A Historical Overview of Cardiovascular Medicine and Heart Failure

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_1

1

Introduction

» For as long as we have been self-aware, we have been in awe of the fact that there is something so vital, so alive, within our bodies: a relentlessly active core with a will of its own. An animating essence that does not obey our commands the way our hands do, or our eyelids, or even our lungs. A link to the universal motion surrounding us, the tides and stars and winds, with their puzzling rhythms and unseen sources. Once this awareness dawned, it would have been impossible for us ever again to look at ourselves or the world the same way. S. and T. Amidon [1]

These lines from *The Sublime Engine* are a good place to begin any historical excursion into the heart's role in the history of medicine. They remind us that, from the earliest moments of self-awareness at the dawn of humanity, the heart has been a constant companion of motion within us. Whatever that may have meant for our early ancestors is anyone's conjecture, but we do know that it was on people's minds from the very outset of our human journey. While the study of the heart has a rich and dynamic history, it also provides a platform for research that would focus on the pathophysiology of the failing heart and the discovery of therapies that would impact the course of this disease. Here, we provide a historical overview of the studies of the heart and heart failure as a foundation for the emerging technologies that are described throughout the remainder of this textbook. As Sir Winston Churchill stated, "Those who fail to learn from history are doomed to repeat it."

A Brief History of the Heart and Cardiovascular System

Recent research into Ardèche cave dwellings in France from the Aurignacian and Late Magdalenian cultures of the Paleolithic Era (35,000–10,000 B.C.) has shown that, among the wall etchings and paintings of hunting parties and the hunted, of spirits that lurk in the forces of nature, a vocabulary of symbols may exist literally. Among these is a surprisingly unmistakable outline of a heart or cordiform shape [2]—an almost childlike rendition of a valentine (Fig. 1.1). Whatever this may reflect in symbolic value, it could reasonably signify the organ so often seen in a butchered catch, a horrifically injured hunter, or in any accident that rendered the heart bare and exposed to the unsparing milieu of prehistory.

Ancient Egyptians

As we move forward in time to the ancient Egyptians, we find a culture that fully embraced the heart not only medically and physiologically but psychologically as well. Although there is

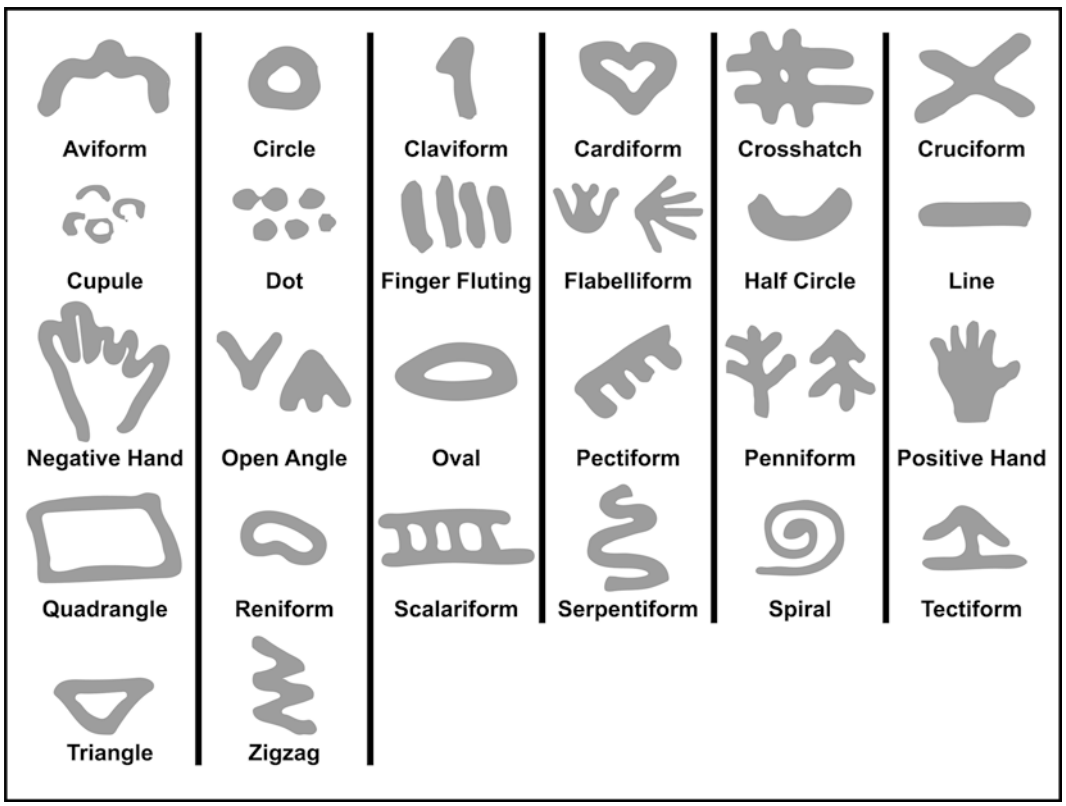

Fig. 1.1 Twenty-six signs all drawn in the same style but compiled from 146 prehistoric sites in France covering 25,000 years—from 35,000 to 10,000 B.C. These symbols may represent a written form of code transmitting information. While the cordiform symbol is heart-shaped, its symbolic meaning remains open to interpretation. *Source*: www.ancient-wisdom.co.uk/caveart.htm

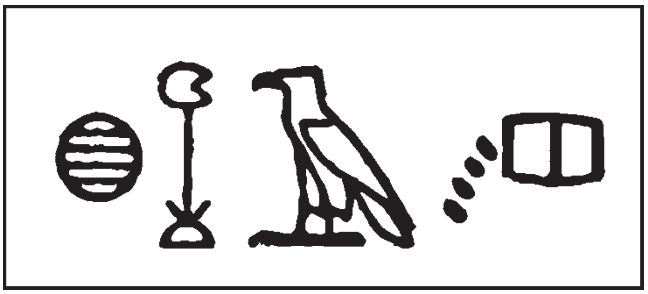

Fig. 1.2 The hieroglyphic characters from the Edwin Smith Papyrus, ca. 1700 B.C., portrays the "counting" or "measuring" of the pulse. The symbol on the *right* is a depiction of counting seeds or beads from a container. These characters represent the first account of tabulating the rate of the pulse and would later be replaced by water vessels in which incremental loss of water could be correlated with the pulse and a reference to time. *Source*: Brewer LA 3rd. Sphygmology through the centuries. Historical notes. Am J Surg. 1983;145(6):696–702

no defined structure of a circulatory system proper, the Edwin Smith Surgical Papyrus (c.1600 B.C.) does record its author's awareness that the status of the heart can be assessed by the pulse. It also records the first written observation of the heartbeat (Fig. 1.2). From the beginning, the papyrus' text suggests that: *The counting of anything with the fingers* [*is done*] *to recognize the way the heart goes. There are vessels in it leading to every part of the body. When a Sekhmet priest, any sinw doctor…puts his fingers to the head…to the two hands, to the place of the heart…it speaks…in every vessel, every part of the body* [3]. Furthermore, it was believed that all the "inner juices of the body" (e.g, blood, air, mucous, urine, semen, and feces) flowed through channels that extended from the heart and were distributed peripherally throughout the body in harmony and collected at the anus and recirculated [3]. Any disruption of the flow resulted in illness.

References to the anatomy and physiology of the heart are also evident in the Ebers Papyrus (circa 1550 B.C.). Aside from its biology, the papyrus described the heart as bearing the ponderous role as the center of emotion, memory, thought, will, and personality. As such, it was the final arbitrator in the afterlife by which one's integrity and eventual fate were determined. In this final judgment, unlike the other organs that were removed during mummification and placed in canopic jars to be buried with the body, the heart remained in the body. And according to the prescriptions of the Egyptian Book of the Dead, it was weighed in a balance against an ostrich feather, called the feather of Ma'at (Fig. 1.3). If found worthy, one would join the gods in the Fields of Peace. If the heart of the deceased weighed more than the feather—that is, more evil than good—the heart was immediately devoured by the chimeric demon Ammit. In effect, this condemned the bearer to dying a second death that signaled complete annihilation.

Egyptian medical knowledge of the heart would diffuse through time and eventually influence the early Greeks, including Praxagoras, the Cnidians, and the Sicilians in seeing the primacy of the heart, even as the seat of intelligence [4]. Nevertheless, much of Egypt's religion-based medicine was largely abandoned by the Greeks for a more rational approach to disease and medicine.

Ancient Greece

In Greece's Homeric period (1100–750 B.C.), aspects of cardiovascular anatomy were largely known in the traumatic context of battle wounds and lesions, including the well-known account in Homer's *Iliad* (760–710 B.C.) about the dying Alcathous and his still-pulsating heart: "… *while fighting Idomeneus stabbed at the middle of his chest with the spear, and broke the bronze armor about him which in time before had guarded his body from destruction. He cried out then, a great cry, broken, the spear in him, and fell, thunderously, and the spear in his heart was stuck fast but the heart was panting still and beating to shake the butt end of the spear*" [5].

Although later in the Archaic period, Hippocrates (460–355 B.C.) would hold a prestigious position within Greek medicine because of his compendium of medical practice which sought a rational basis for disease. Actual knowledge of the cardiovascular system within the Hippocratic Corpus was limited and, in many cases, erroneous, including its description of the heart as "a firm thick mass so richly supplied with fluid that it does not suffer harm or manifest pain [6]." Nevertheless, anatomical detail was not only useful but would historically help to define the organ with greater precision, including the heart's description as four-chambered. Other details included its unidirectional flow of blood through the aortic valve, the shape of the pulmonary valve, and the pericardial sac and fluid.

In the Classical Period (480–323 B.C.), Greek contribution to cardiology was modest, as reflected in the work of Diocles of Carystus (400 B.C.), who is attributed with distinguishing the aorta from vena cava, and Aristotle (384–322 B.C.), who took a cardiocentric position regarding the heart. He noted it as three-chambered and the seat of the soul. He also described the heart and great vessels as the source of all vessels.

Paraxagoras (ca. 340 B.C.) proposed a distinction between arteries and veins, with the former arising from the heart, transporting air, and the latter arising from the liver and transporting the blood. While Herophilus (335–280 B.C.) would further characterize and distinguish arteries and veins, noting that the arterial wall was thicker and pulsated, it was his colleague Erasistratus (304–250 B.C.) who championed the Greek contribution to cardiology with his observations on the nature of vessels, the valves of the heart, and his conceptualization of the vascular angioarchitecture.

Galen and Erasistratus

Most of what has been preserved about circulation theories comes by way of Galen. Judging from Galen's references to Erasistratus' works, Erasistratus was not far from an

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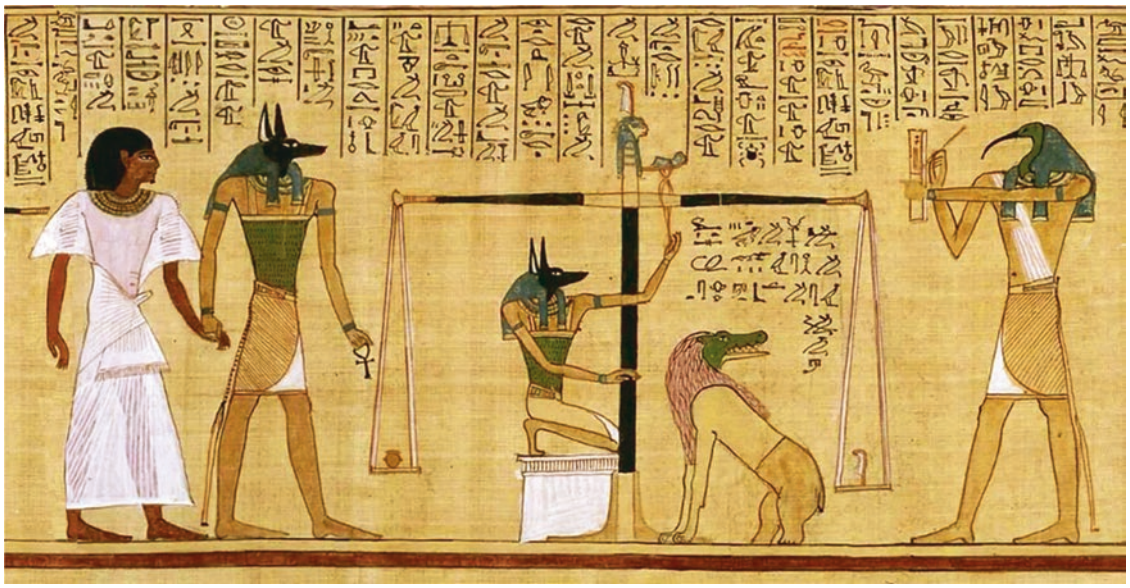

Fig. 1.3 A hieroglyphic and graphic representation of the ritual of the weighing of the heart from the Papyrus of Hunefer. Anubis, the jackal-headed god associated with mummification and the afterlife, takes Hunefer, dressed in white, by the hand to lead him to the ritual. Anubis is shown a second time checking the scale to assure its accuracy, while Ammit stands below the scale awaiting the results. The Ibis-headed god Thoth, the record-keeper and arbiter of godly disputes, stands on the right ready to record the outcome. Hunefer's heart is placed on one side of the balance and Ma'at's feather on the other. If the heart weighs less, reflecting the good life that Hunefer embraced while alive, he will join the gods in the Fields of Peace. If it weighs more, indicative of an evil life, the heart will be consumed by an anxious and hungry Ammit. This action condemns the lost to dying a second time, signaling complete annihilation. Fortunately, Hunefer's heart weighed less and will be presented to Osiris for admission into the afterlife and granted eternal life in Aaru

understanding of circulation—and, certainly, a more contiguous relationship between arteries and veins, both of which he believed arose from the heart: *The vein* (*pulmonary artery*) *arises from the part where the arteries*, *that are distributed to the whole body*, *have their origin*, *and penetrates to the sanguineous* [*or right*] *ventricle*; *and the artery* [*or pulmonary vein*] *arises from the part where the veins have their origin*, *and penetrates to the pneumatic* [*or left*] *ventricle of the heart* [7]. Furthermore, he held that arteries contained exclusively air and, when punctured, the air escaped. Blood seeped in from arteries to fill the space which was observed to spill from the cut vessel. Like Herophilus, Erasistratus believed that veins contained and transported blood only.

As Aird (2011) points out in his elegant analysis, the focus of the Greek school of cardiovascular thought was understanding how nourishment is disseminated to all parts of the body [8]. Erasistratus described an open-ended vascular system (Fig. 1.4a) where absorbed nutrients were converted in the liver into blood that flowed via the hepatic vein to the vena cava, and from there, to the rest of the body. A portion of the blood was directed to the right ventricle and, ultimately, to nourish the lungs. Conversely, he said the pulmonary veins take up air and transport it to the left ventricle and ultimately carry it to the tissues by arteries. Although flawed, such a system explained what he thought he observed in his dissections and would continue to influence cardiology until the time of Galen.

Galen (129–216 A.D.), whose name and theories alike would come to cement medical knowledge for thirteen centuries, was a Greek physician born in Pergamon. His seemingly unlimited knowledge of medical science likely was derived from his firsthand knowledge as court physician to several Roman emperors, surgeon to the gladiators, and avid dissector of numerous animal species including the Barbary ape and pigs. His cardiological work builds on a refinement of Greek physiology that relied heavily on the four bodily humors (blood, black and yellow bile, and phlegm). The underlying principle is that, although the heart is the source of innate heat that gives life and soul to the body, it must be cooled. In Aristotle's interpretation, cooling was the brain's task, while Galen held the novel idea that the lungs provided this activity. Galen provided an open-ended theory of the vascular system that expanded upon Erasistratus' scheme—providing an innovative way the blood flowing in both arteries and veins (Fig. 1.4b).

In Galen's scheme, the heart and arteries stood in parallel with the liver and veins, and the brain and nerves to form a tripartite system of governance. Each provided a functional component of the living system: brain and nerves brought sensation and thought, the heart and arteries replenished life-giving energy, and the liver and veins provided nutrition and growth. Each also generated a pneuma (πνεῦμα, an ancient Greek word for "breath") or spiritual substance that animated and nourished the body. He believed the heart

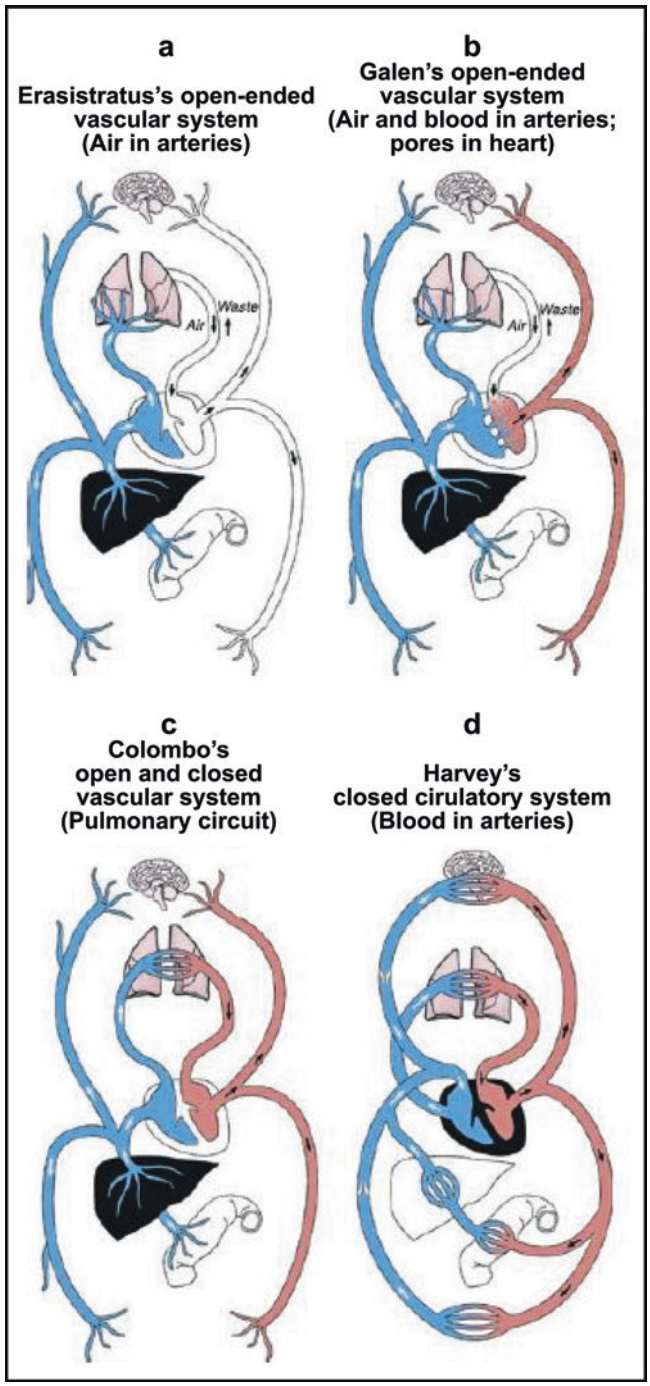

Fig. 1.4 A schematic of the circulatory system, comparing major advances in the conception of the cardiovascular system. (**a**) The work of Erasistratus illustrates his belief that the arterial and venous systems were separate. The venous system transported blood, while the arteries carried air. Food absorbed from the intestines was transported via the portal veins to the liver where the nutrients were transformed into blood that was delivered to the rest of the body via the vena cava. (**b**) Galen's scheme was designed around the arteries that carried blood—derived from venous blood that passed through pores of the interventricular septa. (**c**) Colombo's scheme provided for an accurate pulmonary circulation but maintained the Galenic distribution of most venous blood passing directly to the tissues of the body and only a portion to the right ventricle. (**d**) Harvey's system expanded the pulmonary route to include the entire body whereby all venous blood passes from the tissues and lungs to the right ventricle, and arterial

produced vital pneuma, the liver a natural pneuma, and the brain an animal pneuma.

The actual flow of blood via the Galenic system has not been without debate due to translation and the interpretation that comes with translation. Foibles also arise from Galen's own ambiguities which can be found in his descriptions. As Henri de Mondeville (1260–1320) would later note, "God did not exhaust all his creative power in making Galen [9]." That said, the following is a simple and generalized scheme of the Galenic system.

His scheme begins with the intake of food. Once digested, it is transported from the intestines to the liver via the portal vein (Fig. 1.5). In the liver, the nutrients were changed to blood which was suffused with natural pneuma that endowed it with the power of growth and nutrition—signaled by the dark red color of the newly formed blood. From the liver, the vitalized blood passed to several destinations. One portion flowed through the vena cava and downstream veins and throughout the body to bring the nutrient potential to muscles and organs. Some blood, however, diverted from the inferior vena cava to the right ventricle of the heart. Here, some flow continued to the lungs via pulmonary arteries (*arteria venialis*), while a portion of the flow filling the right ventricle passed through invisible pores located within the interventricular septum and into the left ventricle. Here, the blood mixed with air transported from the lung via *arteria venialis* and pulmonary vein by ebb and flow motion and infused with the vital spirit. The imbued blood, now bright red, was transported via pulsatile arteries to the rest of the body where it was consumed by the tissues and a portion of flow to the brain. The latter blood diverted to the brain was further vitalized by the animal pneuma, a rarefied pneuma that vitalized the brain and flowed peripherally via nerves to bring power to the muscles and perception via the senses.

Finally, as to pulsation, while Erasistratus saw the heart as a suction-and-force "bellows" that produced a passive distention of the artery due to the expulsive force of pneuma from the left ventricle during its contraction [10], Galen believed the pulse was generated by the active contraction and dilation of the muscular coats within the arterial wall. The stimulus arose in the heart and propagated down the wall [11]. Both were incorrect. For Erasistratus, the pulse arose from the action of the heart, but it was pneuma, not blood, that pulsed through the arteries. For Galen, it was blood that flowed through the arteries—but due to the pulse produced by the arterial wall.

Many clinicians today have asked why Galen, a scientist of discerning and incisive insight, failed to deduce the obvious role of the heart within a circulatory scheme. Many have

Fig. 1.4 (continued) blood passing from the lung is pumped to the rest of the body. Although no direct evidence existed in William Harvey's time for capillary beds to link the closed system, Marcello Malpighi later wrote of a porous transfer between the two. *Source*: Aird WC. Discovery of the cardiovascular system: from Galen to William Harvey. J Thromb Haemost. 2011;9(Suppl 1):118–29

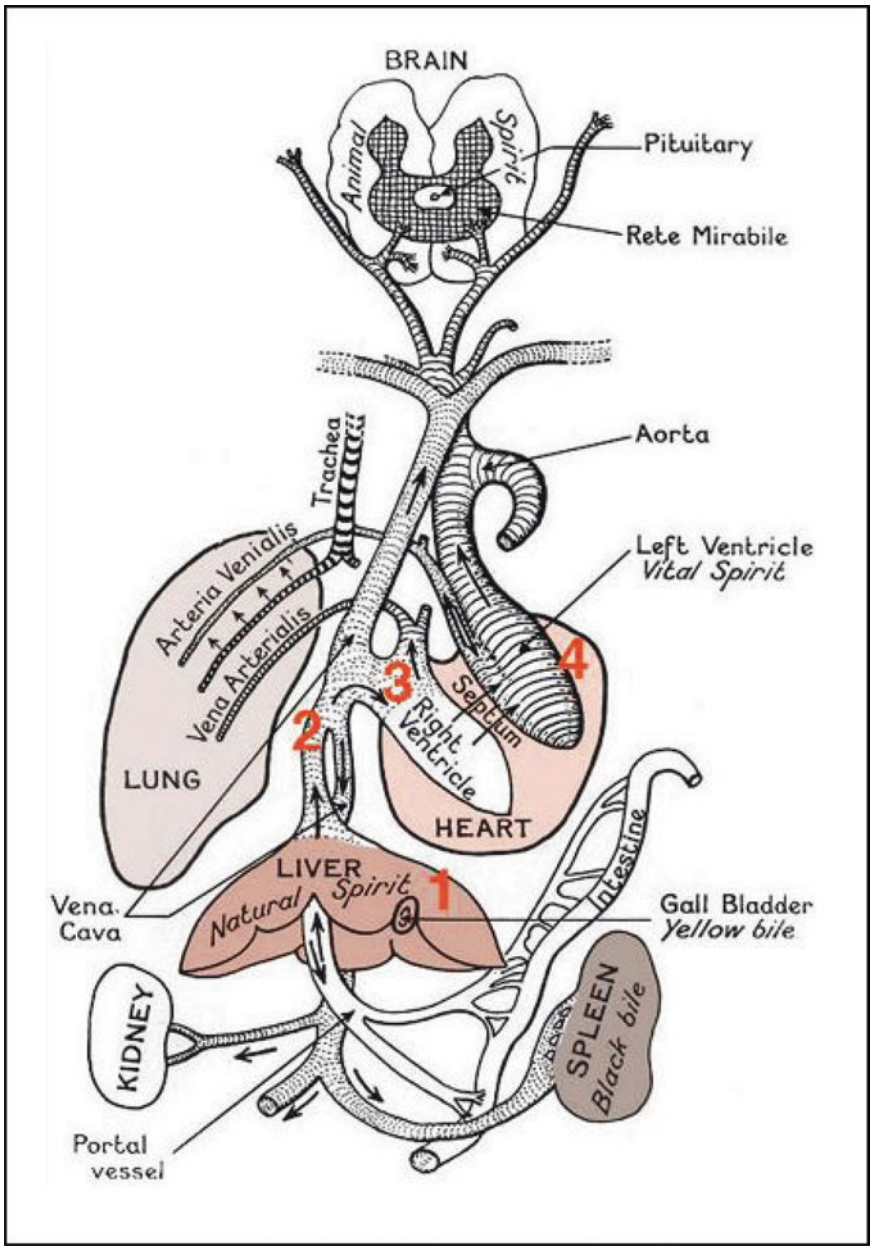

Fig. 1.5 A schematic representation of Galen's concept of circulation. Nutrients passing by way of the portal veins were carried to the liver (*1*) where, mixed with the natural pneuma, formed blood was distributed to the entire body by the vena cava (*2*) and a small portion to the right ventricle (*3*) by the ebb and flow motion from the liver. Some blood in the heart flows to the lungs to emit "sooty vapors," while some flows through pores of the interventricular septum where it is suffused with "vital spirits" from the pneuma and transported via the trachea. Blood flowing further into the brain was imbued with animal spirits before being distributed to the body via nerves considered to be hollow. *Source*: Singer C. A Short History of Anatomy and Physiology from the Greeks to Harvey. New York: Dover; 1957

also proposed answers to this puzzling question. An increasing number support the thesis that Galen became consumed and distracted by his ongoing dispute with the Stoics [12]. His agenda became a polemical dialectic to discredit the Stoics' concept of an indivisible soul while maintaining his own allegiance to the Platonic concept of the tripartite soul. The intensity of the debate allowed little option of moving beyond this defensive position. The Galenic system would become the predominant paradigm that would influence and guide medical practice and education down through the subsequent ages as it was further emulated and canonized during the Middle Ages.

The Galenic system would eventually be challenged in the thirteenth century by physicians of the Islamic world who had greater familiarity with the ancient Greeks. This included the Arab physician Ibn al-Nafis (1210–1288), who took clear exception to the existence of invisible pores within the interventricular septum that enabled blood passage from right to left ventricle and, furthermore, provided an accurate basis of pulmonary circulation. While the West continued to embrace and teach Galenic principles, new developments in the twelfth century would eventually lead to a reevaluation of Galen's all-pervasive influence.

Italy

Although it has been referred to as a "Civitas Hippocratica," the School of Salerno represented a fresh and integrated approach to medicine and medical education in an otherwise unresponsive era. Beginning the in the tenth century and arising in the context of Benedictine monasticism,

including Monte Cassino, it became the first medical school in the world and, subsequently, an outstanding secular institution. It returned to the earlier historical practice of animal dissection as one of its chief merits. As Castiglioni points out, "up to that time anatomy had been taught simply *sicut asserit Galenis* ('thus does Galen declare')" [13]. At Salerno's peak in the twelfth century, anatomic dissection, particularly of the pig, was systematically undertaken, and although still steeped in Galenic perspective, faculty members were beginning to embrace the importance of independent observation.

The first public dissection of the human body for medical instruction was performed by Mondino de Luzzi (1275–1326) at the University of Bologna in 1315. Dissection of the body was evident as well in the work of the great Italian Renaissance artists who were less confined by the ideas of Galen or even Aristotle or Hippocrates. They sought to examine firsthand what the visually impoverished medical texts of the period failed to relay. Human dissections, including those of da Vinci, provided the anatomic and mechanical basis that conferred dynamics of motion and function to the body in life. Leonardo da Vinci (1452–1519) has only recently been properly acknowledged for his impressive knowledge of the heart, both in terms of function and anatomical features.

Our temptation is to regard Leonardo exclusively as an artist or illustrator, but he was much more. He was a scientist at heart, driven by an inquisitive nature, open to novel ideas and explanations, and heavily dependent on firsthand observation and experimentation. From age 14, he apprenticed in art and art history in the workshop of Andrea del Verrocchio and at the age of 33 was appointed director of the Academy of Science and Art in Milan. For 17 years, da Vinci undertook numerous engineering and architectural projects for the Duke of Milan. He explored and studied the elements of city planning, military engineering, mathematics, hydrodynamics, and the physics of optics and motion.

The principles applied in these studies and projects were ultimately focused on his abiding interest in anatomy—dynamic anatomy—and recorded in his notebooks anatomical dissections which he had planned to publish. His anatomical works spanned two intervals: 1480–1497 and 1506–1509. Of his 5000 known pages of notes and illustrations largely on mechanics, 190 recorded the anatomy of autopsied human subjects and animals, of which 50 were devoted exclusively to the heart [14]. Aside from the amazingly detailed surface features of the heart (Figs. 1.6 and 1.7), Leonardo explored the inner aspects of the chambers and conduits, noting the architecture of the valves, papillary muscles—even the moderator band obvious in the ox heart and more difficult to distinguish in the human that he correctly identified as a muscular bridge stabilizing the right ventricle from over-distention. His drawings astutely record and analyze the physics of motion through the trileaflets of the aortic and pulmonary valves.

Aside from the intricacies of the heart itself, Leonardo regarded the heart as a muscle, not flesh, as stated by Galen. He clearly characterized for the first time the heart as four-chambered with atria distinct in configuration and function as they contracted to fill the ventricles. He also elegantly traced and defined the course of the coronary arteries as those that supplied the muscle of the heart itself and provided cogent demonstrations of the bronchial arteries (Fig. 1.8). Nevertheless, all this wealth of knowledge issued from the pen and drawings of da Vinci would never see the light of his age. With his death, his rich insights into the anatomy and function of the heart would be lost for almost 400 years.

During the century of Leonardo's death, several distinguished anatomists would prove essential to the continuing evolution of cardiology. Perhaps the most well known of these would be the Flemish anatomist Andreas Vesalius (1514–1564) who would publish his *De Humani Corporis Fabrica* and *Epitome* in 1543. This was a startling collection of dissected images of the human body illustrated by Jan van Calcar, his friend and pupil of the artist Titian, and unlike anything published to date. Despite the exquisite drawings, including those of the vascular system, his heart images remained modest and illustrated the interventricular pores of Galen (Fig. 1.9). On the other hand, the sentiment expressed in his text would indicate otherwise:

> The septum of the ventricles, composed of the thickest substance of the heart abounds on both sides with little pits impressed in it. Of these pits, none, so far as least as can be perceived by the senses, penetrate through from the right to the left ventricle, so we are driven to marvel at the handiwork of the Almighty, by means of which the blood sweats form the right to the left ventricle through passages which escape human vision. [15]

Whether the sarcasm was deliberate or unintentional, da Vinci simply had nothing else to substitute for Galen's explanation. Nevertheless, his instincts as a precise and careful scientist led him to conclude otherwise. In his second edition of the *Fabrica* (1555), he does assert no evidence for the pores. "*Not long ago I would not have dared to turn aside even a hair's breadth from Galen. But it seems to me that the septum of the heart is as thick, dense and compact as the rest of the heart. I do not see, therefore, how even the smallest particle can be transferred from the right to the left ventricle through the septum*" [15].

In addition to the work of Vesalius, others would provide strategic insights in moving forward the study of the heart. Michael Servetus (1511–1553), a Spanish physician, suggested evidence of a pulmonary circulation. While this was new to the West, it had been firmly articulated earlier by the Arab physician, Ibnal-Nafis, who clearly described the flow of blood from the right ventricle via the pulmonary artery to the lung and from the lung via the pulmonary veins to the heart and through the aorta to the rest of the body. Unlike Ibn al-Nafis' observations that were based on autopsies and human dissections [16, 17], the thesis proposed by Servetus was mainly based on his observations—primarily on the color of the blood and ventricular and pulmonary dimensions. Furthermore, his work was largely unknown because it

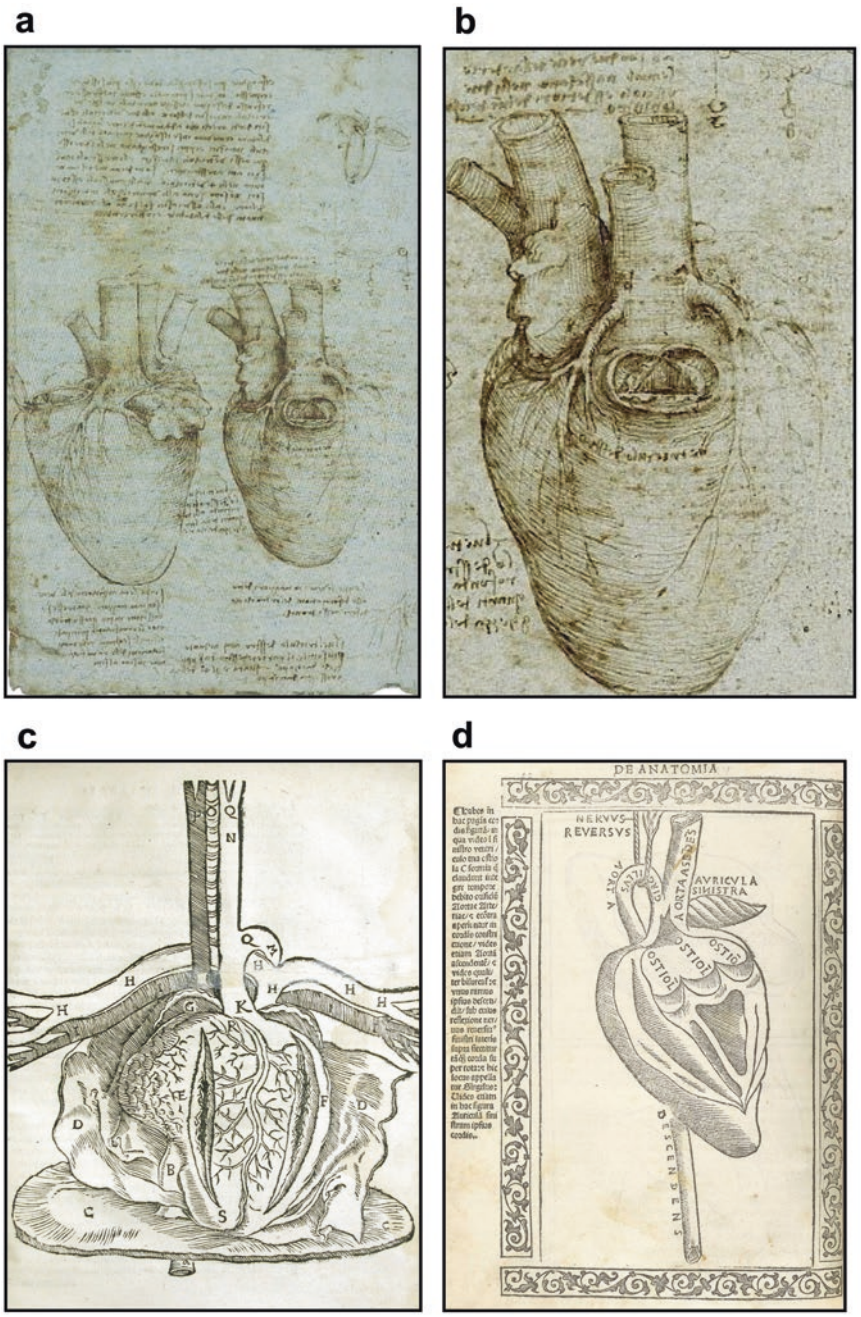

Fig. 1.6 A comparison of heart drawings by Leonardo da Vinci and contemporaries. (**a**) Leonardo's drawing of the ox heart, showing detailed images of the coronary arteries, the atria, as well as the great vessels. (**b**) An enlarged image showing the posterior facet of the base of the aorta with the pulmonary trunk cut away (1511–13). (**c**) The graphic representation of dissected hearts drawn by Mondino di Luzzi (1541) and (**d**) Berengario da Carpi (1523)

was found within his theological treatise, *Christianismi Restitutio*. He wrote it to clarify the origins of the Holy Spirit in the air-blood interface of the heart, "*Ab aere inducit Deus anima*" [From the air, it induces the soul].

Andrea Cesalpino (1519–1603), an Italian physician and contemporary, was interested in the dynamics of blood flow within the veins. For the most part, he understood that blood in veins flow in a single direction, and the distinctive differences between pulmonary artery and vein, and aorta and vena cava. He demonstrated in his *Quaestionum Peripateticum* (1593) the disposition of the blood above and below the point of a ligature placed on the arm. In showing the dilation below and the collapse above the ligature and, thus, a centripetal flow in the veins, he became the first to publish such experimental data and the first to have used the term circulation in print. His exact meaning of the term, however, is still debated. Some believe it referred exclusively to the cooling of blood in the heart [18] or that is was chemical (distillation) rather than physical in nature [19]. Others, taking a de novo translation and analysis of the original Latin text, concluded that "it is inescapable that this author, several decades before William Harvey, had a clear general understanding of the circulation of the blood [20]."

It would come as no surprise that the latter opinion could be true because Cesalpino was a student of the next major figure of this era. Realdo Colombo (1516–1559), a surgeon

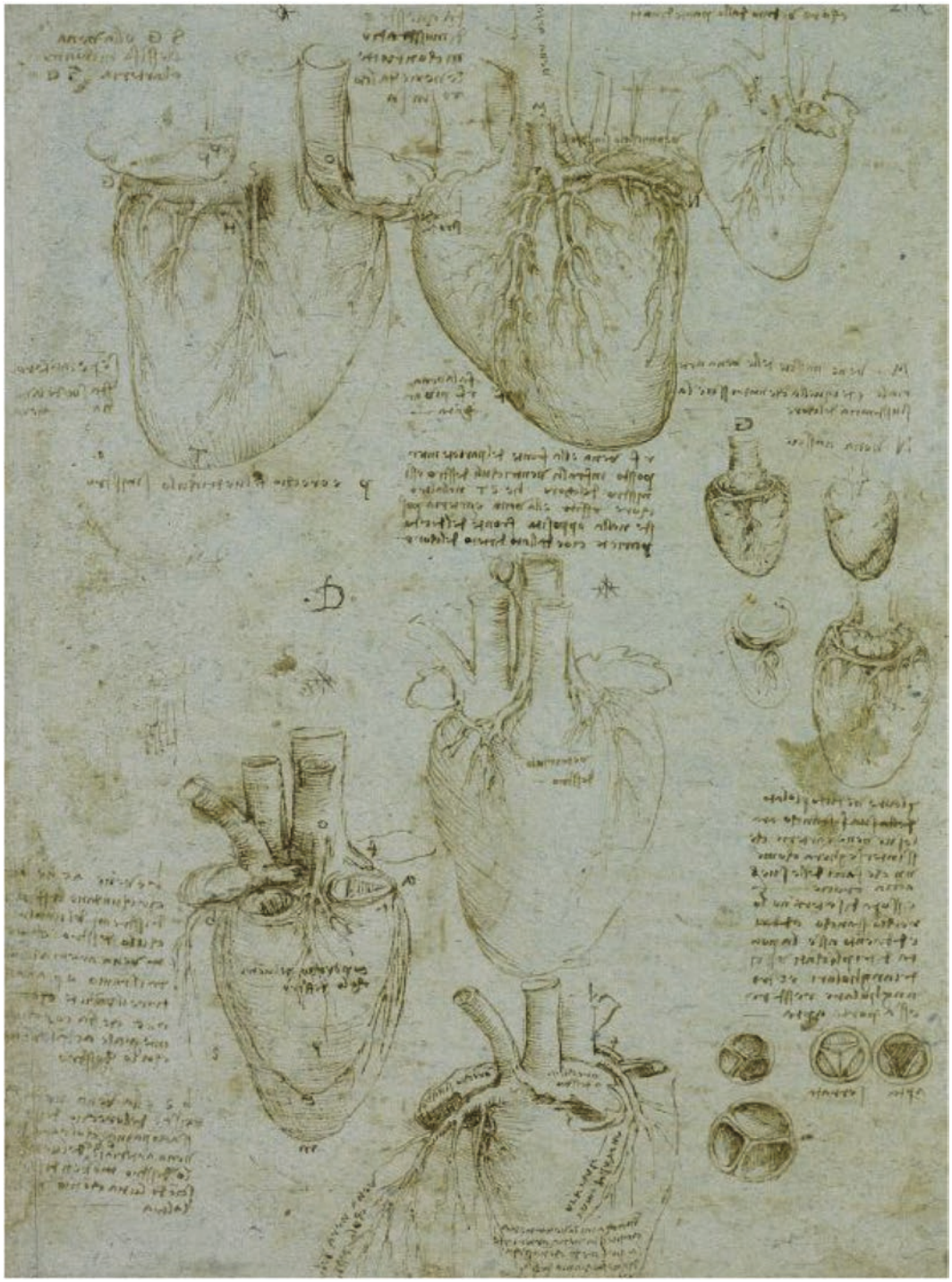

Fig. 1.7 Da Vinci's drawings of the human heart—both surface features and a study of the open and closed aortic valves—shown in the lower right margin of his notebook. Harvey asserted that the pulse was felt throughout the body and correlated with the heartbeat. As he stated, "And the same thing happens in the bodies of animals by means of the beating of the heart which generates a wave of blood through all the vessels, which continually dilate and contract. And dilatation occurs on the reception of superabundant blood, and diminution occurs on the departure of the superabundance of the blood received. This, the beating of the pulse, teaches us when we touch the aforesaid vessels with our fingers in any part of the living body"

and professor of anatomy, was a student and then colleague of Vesalius and, later, his successor at Padua. Later in Colombo's career, he would criticize Vesalius who, reacting strongly to the critique, ended their relationship [21]. Colombo would prove to be a sentinel, signaling that the full understanding of systemic circulation was at hand. Unlike his contemporaries, Colombo clearly presented his observations in a straightforward and scientific manner, which is

1

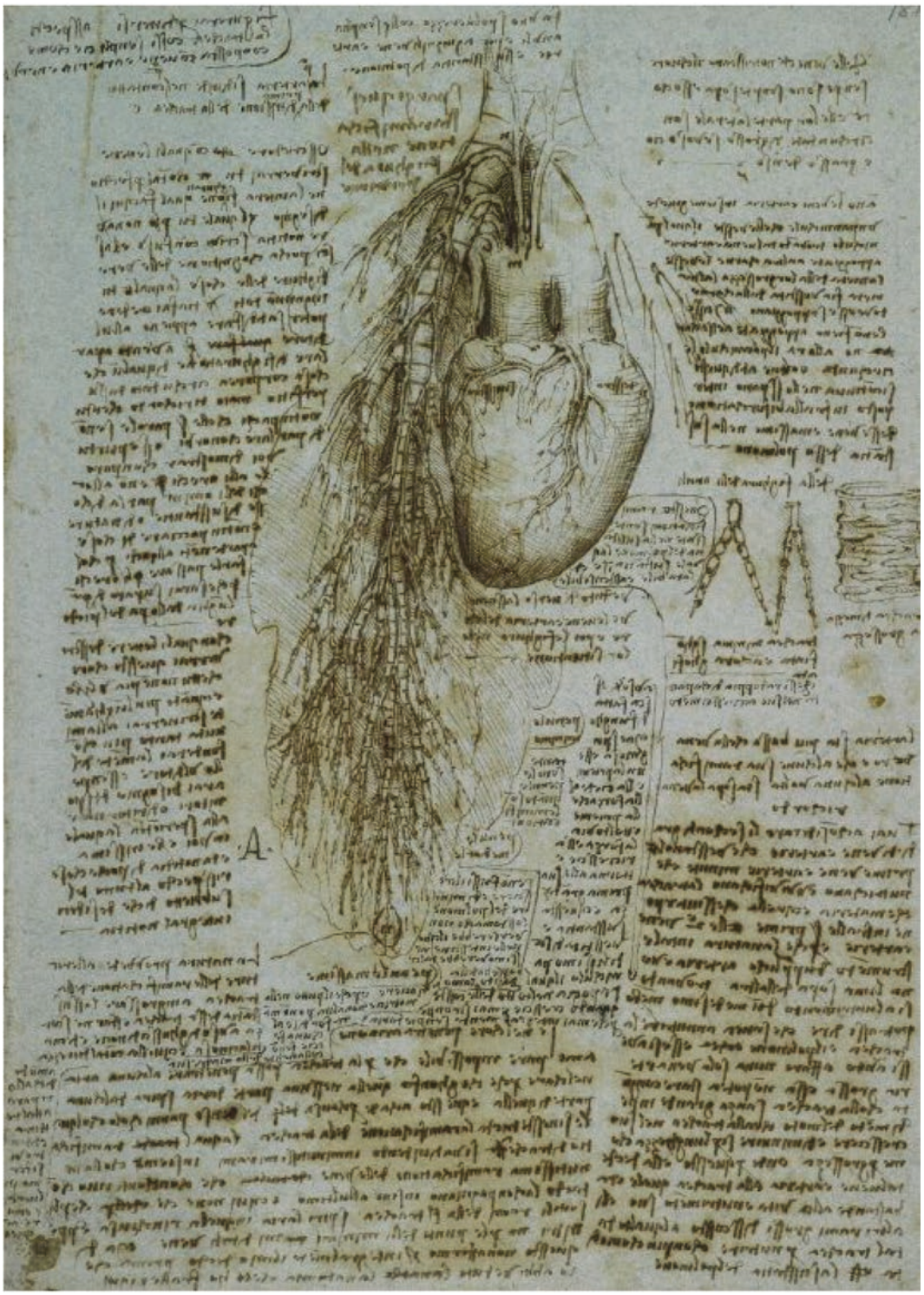

Fig. 1.8 Da Vinci's drawings of the bronchial arterial blood supply. Leonardo's views indicated an awareness of a perfusion of blood within the bodily organs for normal function. This included the size and the function of the organ

apparent in his *De Re Anatomica* (1559), published shortly after his death.

For example, much of Servetus' work, obfuscated by theological interests, was clearly articulated in Colombo's scheme of circulation, although he makes no mention of his name or work. Much of Colombo's scheme is Galenic, with veins arising from the liver, but no pores present in the interventricular septum. He dismisses the pulmonary vein as the conduit of air and fuliginous vapors and, given the true function of the cardiac valves, denies access of arterial blood retrogradely to the lungs:

» Between these ventricles there is a septum through which most everyone believes there opens a pathway for the blood from the right ventricle to the left, and that the

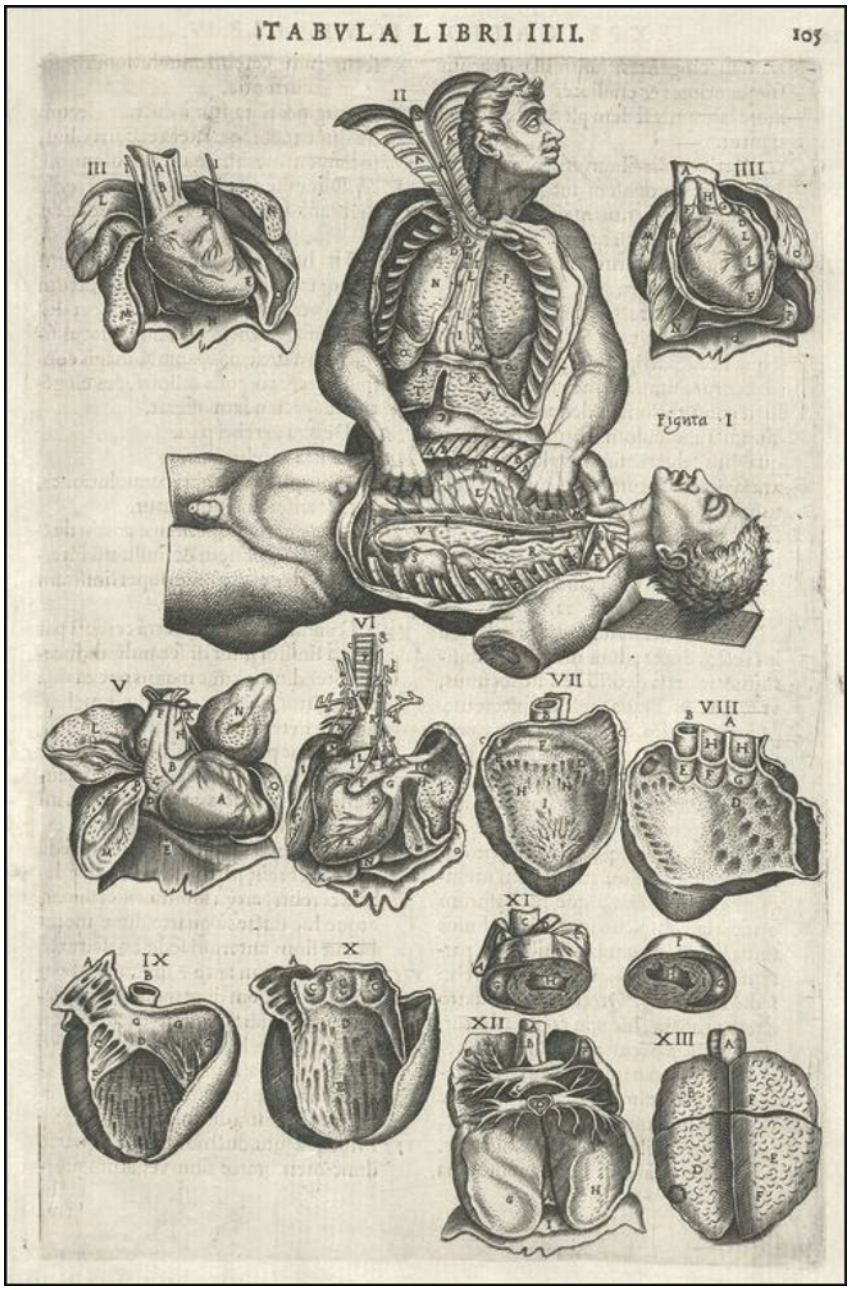

Fig. 1.9 The illustration of the heart dissected free of the chest and presented to show its various facets. In the first edition of *Fabrica*, the small pits were shown within the interventricular septum across which the blood passed from the right to left ventricle. This Galenic version of blood flow was omitted in this later edition (1566) of Andreas Vesalius' work

> blood is rendered this so that this may be done more easily for the generation of vital spirits. But they are in great error, for the blood is carried through the pulmonary artery to the lung and is there attenuated; then it is carried, along with air, through the pulmonary vein to the left ventricle of the heart. Hitherto no one has noticed or left in writing, and it especially should be observed by all [22].

Colombo's schema gave rise to both an open and closed system circulatory schema—open in the lungs but closed elsewhere in the body (Fig. 1.4c). Such a proposal clearly stood in contrast to but did not dismantle the Galenic system and was not unlike that proposed earlier by Ibn al-Nafis and Servetus. Colombo did not know of either man and arrived at his conclusions independently.

Colombo's successor at Padua was Girolamo Fabrizio (1537–1619), Italian anatomist and surgeon, also known as Fabricius. In addition to making remarkable discoveries, he taught a generation of notable anatomists and physicians including William Harvey, who succeeded Colombo at Padua. Fabricius was interested in circulation as well but focused his work on the valves present in walls of large veins. As shown in his *De venarum ostiolis* [On the Valves of the Veins], he proposed the hemodynamic feature of valves in facilitating the progressive flow of blood through a vessel and preventing retrogressive movement. Much of his work on the

tricuspid valves had already been described in da Vinci's work but went unknown to contemporaries.

All of these sixteenth-century physicians, anatomists, and professors contributed to a formative and fomenting period for cardiology. Their work led to the definitive moment when the undisputed center, the heart, would be ultimately understood as the source of motion that propelled the blood throughout a closed cardiovascular system. If we ask who discovered the pulmonary circulation, the reply would have to be all three: Ibn al-Nafis, Michael Servetus, and Realdo Colombo. Although followers have long favored their own candidate, the work of Meyerhof [23] and Temkin [24] in the 1940s spurred a general agreement that all three arrived at their conclusions independently, largely based on a comparison of their own commentaries. Later, Wilson [17] would concur due to all three sharing a common knowledge of Galenic physiology, but each using different evidence to support their observations and conclusions.

Many have suggested that Cesalpino discovered systemic circulation because of his comprehensive understanding of the circulation of blood based on careful empirical observations presented in his *Quaestionum peripateticarum* (1571) and *Quaestionum medicarum* (1593) [25]. He was the first to use the expression "circulatio sanguinis" in a hemodynamic sense. His physiological demonstrations with ligatures on the arm present in a compelling way as progenitors of Bauhin's iconic presentation of valves later used by Frabricus and still later by Harvey as the only illustration in his *De Motu* (Fig. 1.10).

But like many of his contemporaries, Cesalpino's work was a crucial footstep toward a definitive understanding of systemic circulation. That understanding would arrive very shortly with a work that struck literally at the very heart of the issue: *De Motu Cordis*. The very title, *On the Motion of the Heart*, cut to the chase. The heart was the source of the motion that systemically circulates the blood within a closed system.

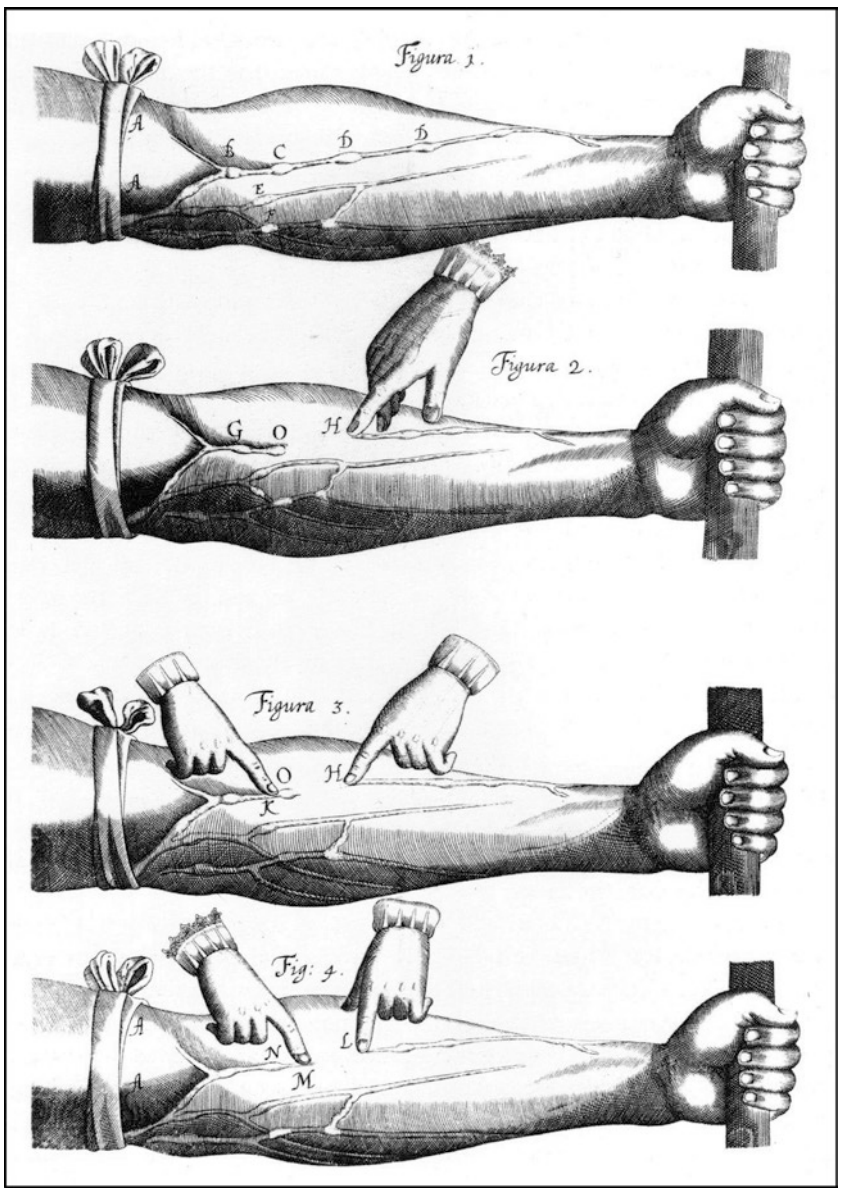

Fig. 1.10 The illustration used by Harvey in his *De Motu Cordis*, showing ligatures placed on the arm for the collection of blood. The original appeared in Bauhin's anatomical textbook (*Theatrum Anatomicum*, 1605) and later used by Fabricius. Before Harvey's use of the illustration, no one noted or addressed the obvious conflict. If the blood flowed centrifugally from the liver to the extremities, as it was held from the time of Galen, then the vein on the proximal side of the ligature should have showed swelling

William Harvey

Between 1597 and 1602, William Harvey (1578–1657) studied at and received his doctorate of medicine from the University of Padua. While a student there, he studied under Fabricus of Aquapendente. Fabricus would have a lasting influence on Harvey and, in particular, his appreciation of the venous valves. Harvey later intimated to Robert Boyle that this appreciation formed the basis of his interest in circulation [26].

After his return to England in 1602, Harvey was appointed Lumleian lecturer at the Royal College of Physicians. The gradual synthesis of his lecture notes and numerous experiments led him in his understanding of veins and blood flow. He may have initially shared his theory of circulation with his students between 1617 and 1619 when he most likely began to write. Experimental work including ligature experiments, jugular experiments, and heart dissections of deer and other animals to quantify flow-rate dynamics and intrinsic movement of heart muscle ensued for nearly another 10 years. Finally, the publication of his *Exercitatio Anatomica de Motu Cordis et Sanguinis Animalibus* in 1628, generally known simply as *De Motu Cordis*, made his theory of circulation known to all. Harvey began his work with a preface acknowledging his teacher Fabricus as "a venerable old man" and acknowledged his work, *De Respiratione* (1615).

Harvey maintained some of Colombo's ideas, including the assertion that the primary motion of the heart is contraction (systole), which propels blood into the arteries, which dilate (pulse) in response to the contraction of the heart and propulsion of blood. The pulse as demonstrated by Harvey was not blood being pulled into the heart but rather the blood being propelled by the heart into the arteries. Harvey had no role for interventricular septal pores since the blood of the right ventricle is propelled into the lungs by the pulmonary artery and from the left chamber into systemic circulation. Completing this circuit during diastole, blood flows from the great veins into the atria and ventricles. Unlike those who had gone before, Harvey believed the arteries transported nutrients throughout the body and, although undefined within the periphery of the tissues, blood passed from artery to vein, providing a circular basis of flow (◘ Fig. 1.4d) where the flow of venous blood is essentially centrifugal. Thus, the blood was not consumed by the tissues, as conjectured by the Galenists, nor by the liver, per generation de novo. The anatomical design of the veins with their valves is oriented toward the heart, with the heart as the source of the blood's movement, not the liver.

It has been suggested that this circular pattern came to Harvey because of his admiration of Aristotle who regarded circular motion as a symbol of perfection, perpetuity, and embodied qualities of preservation [8]. It was still remarkable that the definition of the circulatory system had so long eluded even the most skilled of physicians and the most astute of philosophers. Yet controversy arose as soon as *De motu cordis* was published. Harvey was not hailed as a hero but even as a scorned "circulator" (traveling quack) by his most vitriolic of opponents, Jean Riolan (1577–1657), who could not forgive Harvey's disrespect for Galen. Even more outspoken was Guy Patin (1601–1672) who stated that Harvey's theory was "paradoxical, useless, false, impossible, absurd, and harmful" [27]. Despite these and other vocal critics, Harvey had his supporters, including many eminent colleagues like Richard Lower (1621–1691) who, in his own work, demonstrated Harvey's system to be empirically sound. In addition to the negative reaction to his work, Harvey's troubles did not end in academic contention alone. He had served as court physician to King Charles I, who had kindly provided Harvey with deer from the royal parks for his experiments. Because he remained loyal to Charles even after his beheading in 1649, Harvey's residence was ransacked during the Cromwellian Civil War [Third English Civil War (1649–1651)], and many of his notes and papers were destroyed. Although Harvey died of a stroke in 1657, his legacy formed much of the basis for modern cardiology and its continuing evolution into modern times.

A History of Heart Failure

Heart failure was a recognized disease from ancient Greece, India, and Egypt, but mechanistic insights were limited until Harvey's description of the circulation, Rontgen's discovery of x-rays (1895), Einthoven's development of the electrocardiogram (1903), the discovery of echocardiography by Inge Edler (1953), the discovery of cardiac catheterization by Werner Forssmann (1929), and other medical interventions. These interventions initially used leeches for bloodletting (by the "barber-surgeons" of the day; ◘ Fig. 1.11) and later used Southey's tubes (established by Dr. Reginald S. Southey in 1877) to drain peripheral fluid from the patient with heart failure [28]. The practice of bloodletting continued up to the middle of the twentieth century when diuretics became available.

Diuretics

In addition to bloodletting, paracentesis was also used to remove fluid from the abdominal cavity. Dr. William Withering introduced the use of Digitalis purpurea in 1785, as outlined in his book, *An Account of the Foxglove*. Toward the end stage of the disease, patients were noted to be incapable of lying flat and were reclining in a semi-upright state. Heart failure patients were typically described as having dropsy (from the Greek word for water) which reflected the edematous state of the patient [28]. Various therapies were implemented including mercury (i.e., Mercupurin, Thiomerin, Mercuhydrin, Salyrgan), which served as a diuretic as outlined by Dr. John Blackall (1771–1860) in his book, *The Nature and Cure of Dropsies* [28]. During this time period, patients were primarily managed with bed rest, fluid restriction, and diuretic therapy.

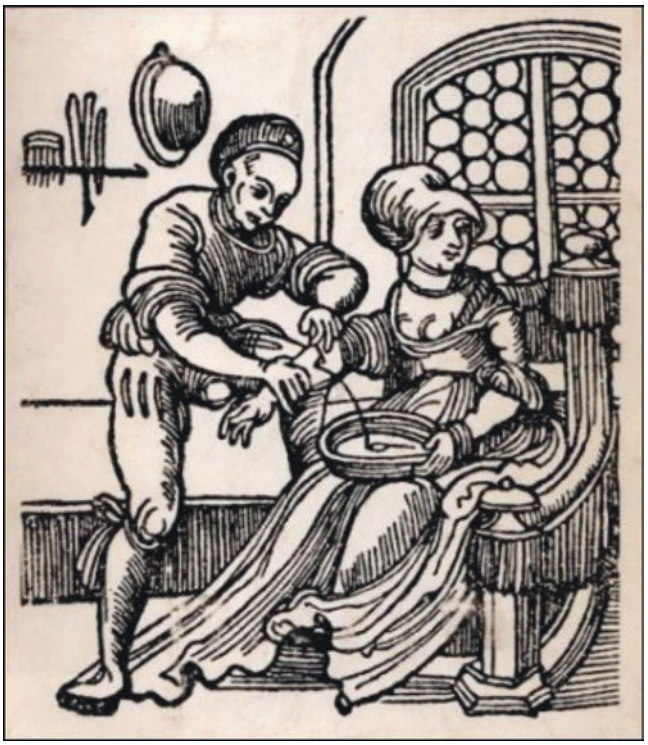

Fig. 1.11 The surgeon-barber provided health care for the community. The barber-surgeons performed a number of duties ranging from haircuts, beard trimming, teeth pulling, wound treatments, amputations, and bloodletting. Drawing emphasizes the bloodletting by the barber-surgeons. Barbers and surgeons remained part of the same trade guild until the mid-1700s

In a small study in 1957 of 15 patients with heart failure, a benefit was observed following sublingual nitroglycerin [28, 29]. Additional diuretics were discovered and used in the 1950s. (Karl Beyer led a team of scientists at Merck that synthesized chlorothiazide in the late 1950s.) The mechanisms of action for loop diuretics were examined in the 1960s and shown to impact those with heart failure.

Pump Failure

It was not until the mid-1980s before pump failure (systolic dysfunction) was recognized as a major contributor to heart failure. In response to systolic dysfunction, investigators realized the patient had a decrease in cardiac output, vasoconstriction, sodium and water retention, impedance, and increased peripheral resistance [29]. Vasodilator Heart Failure Trial (V-Heft) investigators led by Jay Cohn and colleagues introduced the benefit of vasodilator therapy, including hydralazine and nitrates [30].

In the early 1990s, research focused on the neurohormonal system and the renin-angiotensin-aldosterone system (RAAS) as many patients with heart failure had elevated peripheral catecholamines [29, 31, 32]. Collectively, numerous trials have established the predictive value of neurohormonal measurements (baseline and serial measurements) as reliable indicators for risk stratification in patients with heart failure [30, 33, 34]. Plasma brain natriuretic peptide (BNP), plasma renin activity (PRA), aldosterone, atrial natriuretic factor (ANF), and endothelin-1 are markers for morbidity and mortality in heart failure patients. Clinical trials (SOLVD, Studies of Left Ventricular Dysfunction; CONSENSUS, the Cooperative North Scandinavian Enalapril Survival Study) established the important role for angiotensin-converting enzyme inhibitors (ACE-I) in the reduction of morbidity and mortality in adults with dilated cardiomyopathy [33, 35, 36]. Angiotensin receptor blockers (ARBs) were shown to be similarly effective.

Drug Therapies

After Raymond Ahlquist discovered functionally distinct catecholamine receptors in the adult heart muscle in 1948 (termed alpha- and beta-adrenoceptors), intense effort focused on drug development. For example, a number of beta blockers were synthesized including pronethalol (1960), propranolol (1962), practolol (1964), and atenolol (1968) and shown to impact the treatment of angina and hypertension [37–44]. One of the first clinical studies using beta blocker therapy (i.e., practolol or alprenolol) was performed in the early 1970s and shown to improve heart function [43, 44].

In the 1980s, a number of laboratories, including those directed by Bristow and Lefkowitz, conducted biochemical studies and demonstrated perturbed signaling pathways following beta blockade in animal models and humans with heart failure compared to controls. Multicenter studies such as the MDC (Metoprolol in Dilated Cardiomyopathy), the US Carvedilol Heart Failure Study (led by Drs. Milton Packer, Michael Bristow, Jay Cohn, Wilson Colucci, and others), CAPRICORN (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction) trial, COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) trial, MERIT-HF (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure), and CIBIS II (Cardiac Insufficiency Bisoprolol Study II) demonstrated improved mortality and morbidity in patients with heart failure.

These studies ultimately led to the approval of carvedilol in 1997 for the treatment of heart failure. Continued mechanistic studies regarding adrenergic receptors in the heart and the impact of beta blockers have been detailed by a number of laboratories. Robert Lefkowitz received the Nobel Prize in 2012 for his contributions to the field. Collectively, these and many other studies have established that beta adrenergic receptor blockers such as carvedilol and long-acting metoprolol have been shown to promote reverse remodeling of the left ventricle (structural regression of the dilated failing heart), improve cardiac function, and decrease the risk of sudden cardiac death [33, 37–42].

Targeted Therapies

The notion of subpopulations of patients that might derive a greater benefit from selected therapies emerged from subgroup analysis of large clinical studies. Jay Cohn, Anne Taylor, and the A-HeFT (African-American Heart Failure Trial) investigators demonstrated the benefit of combining hydralazine and isosorbide dinitrate with standard heart failure therapy to increase survival of black patients with advanced heart failure [45].

Furthermore, Bert Pitt and colleagues demonstrated a survival benefit from the aldosterone blocking agent spironolactone on morbidity and mortality of patients with end-stage heart failure via the RALES study (Randomized Aldactone Evaluation Study) [46]. In addition, other mineralocorticoid receptor antagonists (e.g., eplerenone, in the EPHESUS, or the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) were also shown to have a survival benefit in patients with advanced heart failure and mild symptoms (using the New York Heart Association Functional Class II guidelines) [47].

Moreover, detectable cardiac troponin T (cTnT) levels in patients with heart failure have been shown to be predictive of adverse outcomes [48, 49]. Depressed left ventricular ejection fraction and evidence of left ventricular remodeling (increasing left ventricular internal diastolic dimension, LVIDd) have been shown to be strong predictors of morbidity and mortality risks in heart failure patients [30, 33]. In addition to these pharmacological therapies, device (defibrillator and/or cardiac resynchronization) therapies have been reported to further reduce heart failure mortality and are now conventional therapy for adult heart failure patients who have a reduced ejection fraction [50–52].

Risk models stratify adult heart failure patients. In 1928, the New York Heart Association established a classification of patients with heart disease to reflect their clinical status and prognosis. Since then, the classification has been revised several times but continues to describe a patient's functional capacity, from NYHA Class I to IV [53]. In addition to the New York Heart Association classification, the American College of Cardiology and the American Heart Association jointly prepared a set of guidelines in 2005, based on research and medical evidence to classify patients with heart failure (Class A–D). Furthermore, the Seattle Heart Failure Model is a commonly used multivariable risk model for heart failure [54]. This model incorporates age, gender, ischemic etiology, ejection fraction, systolic blood pressure, diuretic use, statin use, allopurinol use, hemoglobin, percent lymphocyte count, uric acid, sodium, cholesterol, and diuretic dose per kilogram as significant predictors of survival. This model has been validated in five cohorts of patients and provides an accurate estimate of 1-, 2-, and 3-year survival [55]. Collectively, these classification systems are an essential tool for the clinician and scientist alike in the classification of patients with heart failure.

In 1948, the National Heart Institute launched the Framingham Heart Study. The study examined a cohort of "normal" patients (5209) living in the town of Framingham, Mass., and the incidence of heart failure (since 1948). In addition to the original cohort, their descendants were added to the heart study in 1971. These longitudinal studies enhance our understanding of heart disease and heart failure and have provided a foundation for studies focused on heart failure prevention [56].

Summary

The history of the heart and cardiovascular medicine is dynamic and marked by tremendous innovations and discoveries that challenged existing philosophies and practices. This rich history of innovation also provided an important springboard for addressing the mechanisms of heart failure and the discovery of therapies. Bench science and clinical science have contributed to the pharmacotherapies and devices that have had a tremendous impact on the quality of life and have extended the life expectancy of adults living with heart failure.

The University of Minnesota has emerged as a leader in this field with its participation in the discovery of therapies such as the use of vasodilators, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, which improve the failing heart function and the survival of patients. The University of Minnesota team has further established the Heart Failure Society of America, *The Journal of Cardiac Failure*, and the Minnesota Living with Heart Failure Questionnaire [57]. The questionnaire monitors the quality of life of those with heart failure and heart failure prevention strategies and is widely used in clinical trial/study practice. These and many other advances over the past 150 years have redirected and improved the morbidity and mortality of those suffering from heart failure.

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Physiology of the Normal and Failing Heart

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_2

Introduction

The adult human heart is an architecturally assembled organ that is a muscularized pump. This organ beats more than two billion times in a lifetime and delivers more than 1900 gallons of blood to every organ in the body each day. The coordinated activity of the respective chambers, vessels, and valves allows for immediate responses to the constant physiological demands and for the maintenance of homeostasis. As such, the heart is a dynamic and highly responsive organ. These physiological responses allow for an efficiently regulated cardiovascular system. The adult heart is capable of numerous adaptations, known as cardiac remodeling, that occur following injury or infarct. These adaptations are transiently beneficial and then become pathological. In this chapter, we outline the physiological response of the normal adult human heart. We also highlight the numerous adaptations of the failing heart which occur in an attempt to preserve cardiac output. Importantly, the adult human heart is a constantly changing organ that adapts to signals and cues that allow for performance—an organ that, even today, cannot be fully replaced by an engineered heart.

The History of Cardiac Physiology

The term "cardiac" is derived from the Greek word "kardia," which means "related to the heart." The history of cardiovascular physiology is richly decorated with discoveries and innovations. These historical advances provide an important platform for understanding the impact and mechanisms of emerging therapies for heart failure. Perhaps one of the earliest cardiovascular physiologists was William Harvey, MD (April 1, 1578 to June 3, 1657). In 1628, Dr. Harvey published his classic work on blood circulation, entitled *De Motu Cordis* (On the Motion of the Heart and Blood) [1]. In this publication, Dr. Harvey outlined the movement of blood via a circuit, the coordinated ventricular contractions, and the analysis of the vasculature. These observations emphasized the importance of the heart as a contractile pump as opposed to the more ancient view that the heart served as the source of the body's heat (i.e., Galenic physiology). Dr. Harvey's power of observation and discovery served as the basis for additional studies of the heart and blood vessels, which led to a detailed examination of the heart's structure and function.

The importance of extracellular calcium in cardiac contraction had been appreciated since the classic studies in 1883 by Sydney Ringer, MD (1835–1910) (Ringer's Lactate Solution) [2]. As outlined in these studies, Dr. Ringer established the importance of calcium, potassium, and sodium ions for the heart's spontaneous contractile properties. In the ensuing years, Harold Reuter, MD, and N. Seitz, MD, discovered that a surface transport protein exchanged sodium for calcium in guinea pig atria [3]. Using an array of techniques, they found that the calcium sensitivity of the sarcomere and the regulation of calcium release from the sarcoplasmic reticulum could be studied in the absence of the sarcolemmal barrier. Interest in regulating calcium removal from the cytosol was heightened when phospholamban (a micropeptide), an inhibitor protein associated with the heart, was discovered by Kirchberber, Tada, Katz, and Inui [4, 5]. In 1920, Carl J. Wiggers, MD, was the first to describe the simultaneous electrical and mechanical events of the cardiac cycle [6]. Preceding this discovery (1870), Adolph E. Fick, MD (September 3, 1829 to August 21, 1901), identified the relationship among oxygen consumption, arteriovenous oxygen difference, and total flow through the lungs that provided the means for the calculation of cardiac output (Fick principle) [7]. In the 1940s, Cournand and colleagues used atrial sampling and Fick's principle to measure cardiac output in humans [8]. Otto Frank (June 21, 1865 to November 12, 1944) discovered that the maximum systolic pressure generated during isometric contraction was a function of the presystolic ventricular pressure (Frank–Starling law of the heart) [9]. In 1914, Ernest H. Starling (April 17, 1866 to May 2, 1927) showed that the ventricular stroke volume was a direct function of the end-diastolic volume (Frank–Starling law of the heart) [10]. In the mid-twentieth century, Stanley J. Sarnoff, MD (May 5, 1917 to May 25, 1990), demonstrated that stimulating the heart using inotropic agents could modulate the stroke work–preload relationship [11]. Similarly, Edmund H. Sonnenblick, MD (December 7, 1932 to September 22, 2007), used force–velocity relationships from isolated papillary muscle to quantify changes in contractility [12]. Dr. Sonnenblick showed that the maximum velocity of muscle shortening at zero afterload increased when positive inotropes such as norepinephrine were applied to the papillary muscle.

The interactions of the heart and blood vessels required to achieve cardiovascular homeostasis are complex and difficult to conceive and explore without the assistance of conceptual and mathematical models. In 1967, Arthur C. Guyton, MD (1919–2003), and Thomas D. Coleman, MD, proposed a model showing the integrated interactions of the heart, blood vessels, and kidney in the long-term regulation of arterial blood pressure [13]. The concept emphasized the kidney's role as the main determinant of arterial pressure over the long term. Later, intrinsic and extrinsic regulation of blood flow in different vascular beds, baroreceptor and chemoreceptor reflexes, and hormonal influences was added to the basic renal-body fluid loop to help predict cardiovascular responses to different perturbations.

Several developments in the late twentieth century led to a shift in focus toward the cellular and molecular basis of cardiovascular functions. First, techniques for isolating and culturing cardiac and vascular cells were perfected. Second, advances in our understanding of cell signaling pathways provided a conceptual foundation for investigations of cardiac and vascular cell responses to specific disturbances of their physical and chemical environments. Third, new developments in light microscopy enabled optical monitoring of a wide variety of physiological variables in living cells in space and time. Finally, the revolution in molecular biology provided the tools to probe the impact

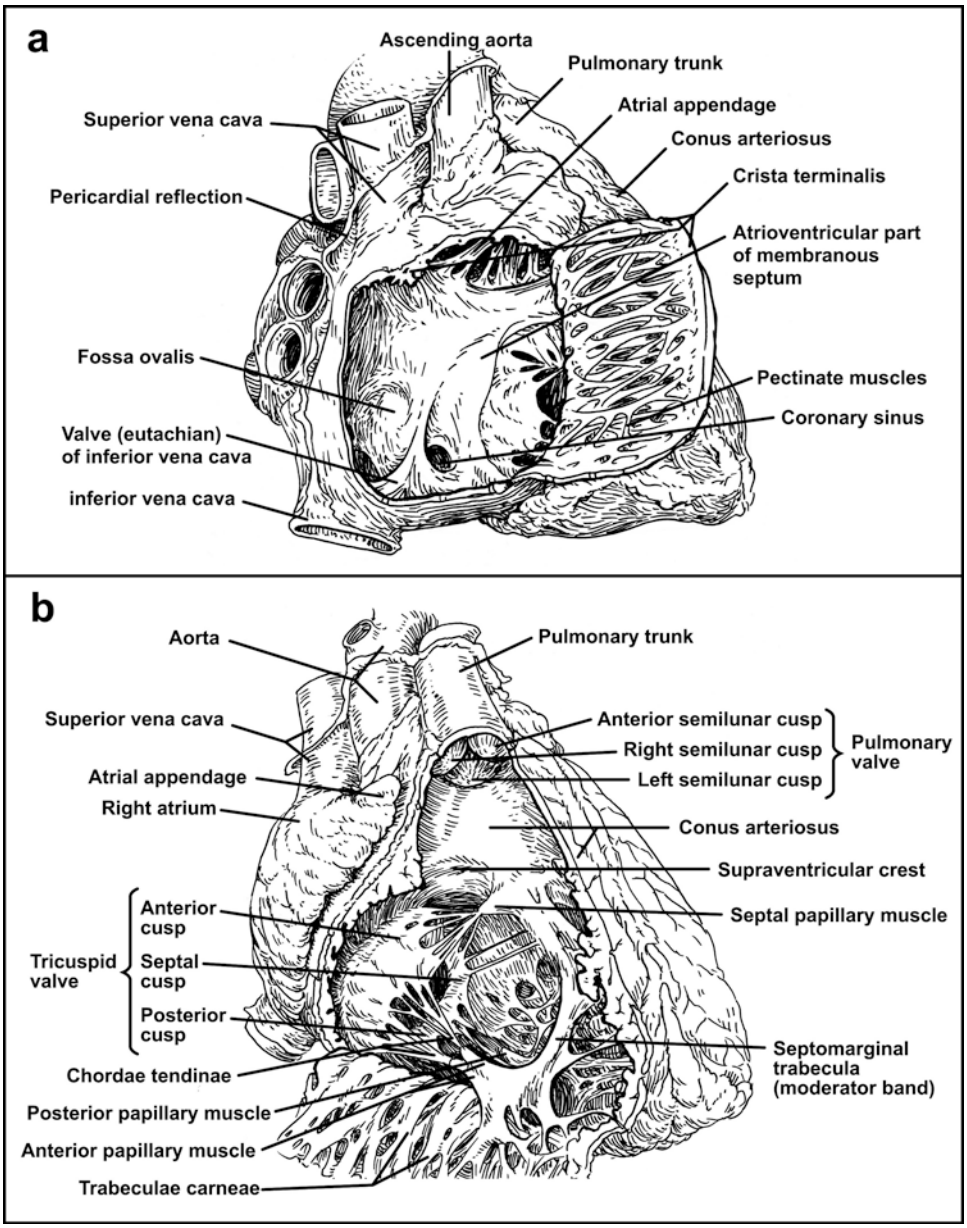

Fig. 2.1 The anatomical structures of the right side of the adult heart. (**a**) Schematic of the right atrium emphasizing the tricuspid valve, coronary sinus, and fossa ovalis. (**b**) Schematic of the right ventricle emphasizing the tricuspid valve, papillary muscles, thin ventricular wall, and outflow tract of the pulmonary artery

of gene overexpression, deletion, and modification on cultured cardiac and vascular cells and on the cardiovascular system of the intact animal. In recent decades, Eugene Braunwald, MD (b. 1929), a pioneer in the field of cardiovascular physiology, described studies in classic chapters of cardiovascular physiology, such as those addressing myocardial oxygen consumption, cardiovascular mechanics, and hemodynamics [14]. Dr. Braunwald illuminated our understanding of heart failure and revolutionized the management of postinfarction left ventricular remodeling.

Anatomical Structure of the Heart

Basic anatomical structure: The adult human heart is a four-chambered organ that weighs about 250–350 g. It is located within the mediastinum (T5–T8) and is closely associated with the adjacent lungs. The heart is enclosed in the pericardial sac, which serves to position the heart in the chest as well as to limit its expansion. The heart's contractile or pumping action is due to the coordinated activity of myocardial muscle cells (cardiomyocytes), which execute the cardiac contraction–relaxation cycle to generate blood flow and pressure [15]. The normal left ventricular shape of the heart is comparable to a prolate ellipsoid with an inferior apical region and a superior base. The average adult heart is about 12 cm in length from base to apex [16]. The valves are nearly coplanar and essentially lie in the plane of the base of the heart (Fig. 2.1). Above the base are the great vessels (i.e., the ascending aorta and the main pulmonary artery) as well as the left and right atria. The pulmonary veins (left atrium), superior vena cava (right atrium), and inferior vena cava (right atrium) empty into the respective atria (Figs. 2.1 and 2.2).

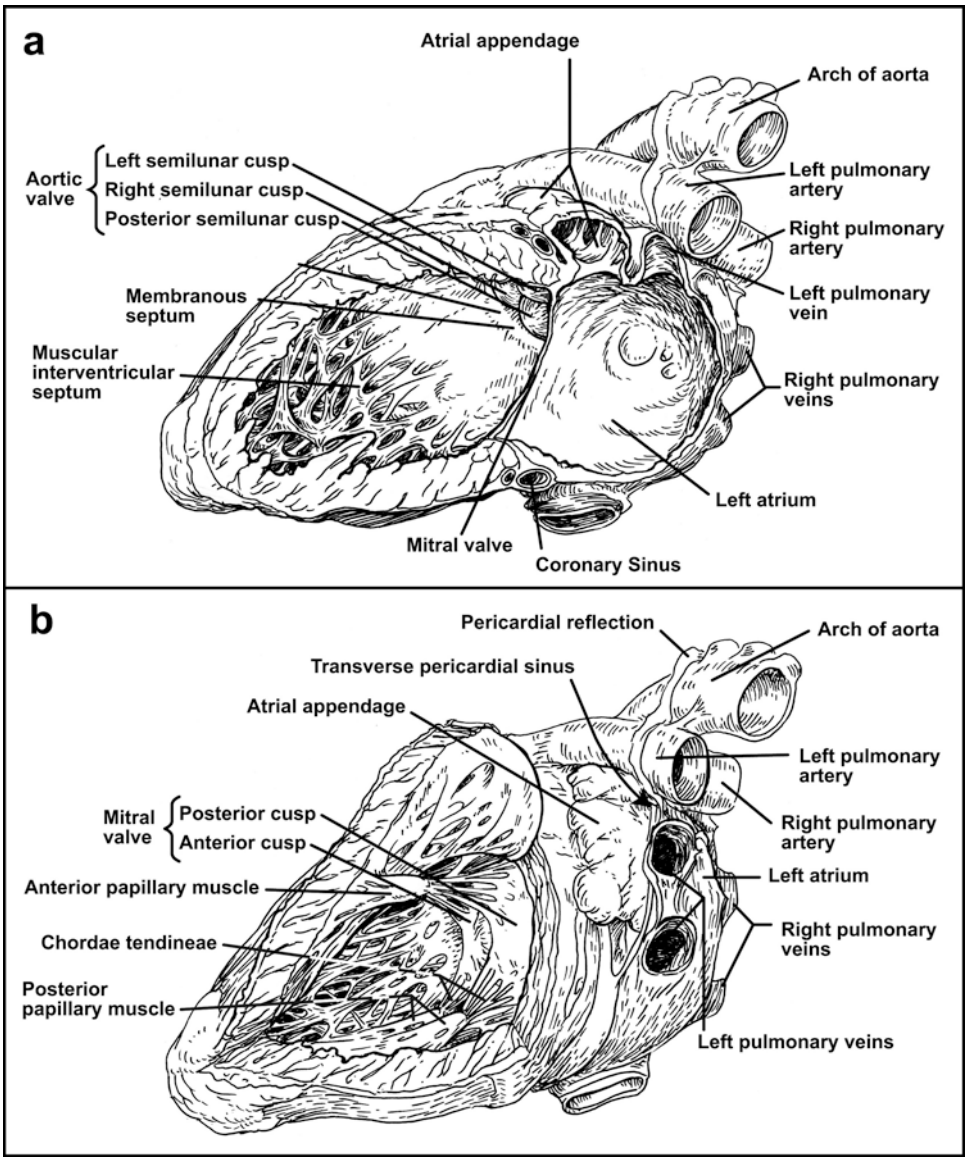

Fig. 2.2 The anatomical structures of the left side of the adult heart. (**a**) Schematic of the left atrium emphasizing the pulmonary veins and mitral valve. (**b**) Schematic of the left ventricle emphasizing the thick myocardial wall, septum, mitral valve, papillary muscles (anterior and posterior papillary muscles), and aortic valve

The right atrium wall is paper thin and translucent between the pectinate muscles. It is subdivided into two parts: a posterior smooth-walled region that accommodates the entry of the blood from the superior and inferior venae cavae and the thin-walled trabeculated portion that constitutes the original embryonic right atrium (Fig. 2.1a, b). A ridge of muscle called the crista terminalis separates the two regions of the atrium (Fig. 2.1b) [17]. It is most prominent superiorly and is adjacent to the orifice of the superior vena cava (SVC). The superior portion of the right atrium is the right auricle, which is not well demarcated and consists of pectinate muscles. The anterior border of the ostium of the inferior vena cava (IVC) has a fold of tissue that forms the IVC valve or Eustachian valve, which is often visualized using echocardiography in the "normal" heart, but varies in size and may be absent. The coronary sinus enters the right atrium just anterior of the Eustachian valve and is often accessed during electrophysiology studies performed in an electrophysiology laboratory (Fig. 2.1b) [18]. The interatrial septum forms the posteromedial wall of the right atrium. Although the interatrial septum is muscular, it has a shallow depression that forms the fossa ovalis. The area of the interatrial septum that is demarcated by the fossa ovalis, the right auricle, and the tricuspid valve is considered important in atrial pacing due to its proximity to the sinoatrial node. Furthermore, the fossa ovalis is often punctured during electrophysiology and interventional procedures to gain access to the left atrium (Fig. 2.1a).

The right ventricle (RV) is crescent or triangular in shape. A 3–5 mm-thick sheet of myocardial fibers forms the right ventricle. The RV has three segments: a posteroinferior inflow segment that contains the tricuspid valve, an anterosuperior outflow segment which is considered the origin of the pulmonary trunk, and the septum. Papillary muscle in the RV connects to the tricuspid value via chordae tendineae, trabeculae carneae, and muscular bands (Fig. 2.1b). One of the muscular bands (moderator band) is often seen on echocardiogram. The tricuspid valve is anchored with several papillary muscles

and their chordae tendineae (Fig. 2.1b). The pulmonary trunk arises superiorly from the RV and courses in a posterior–superior direction. The pulmonary trunk then bifurcates into the right and left pulmonary arteries (PAs).

The left ventricle (LV) is axisymmetric, truncated ellipsoid with almost 1 cm-thick muscular walls (Fig. 2.2a). This increased wall thickness is required in order to generate systemic pressures. In contrast, the left atrium (LA) is a thin, smooth-walled chamber that has four pulmonary veins entering from the right and left sides (Fig. 2.2a). The left atrial appendage (LAA) is variable in shape and size and is a continuation of the upper and anterior aspects of the LA. The LV septum is primarily muscular and consists of two layers: a thin layer on the RV and a thicker layer on the LV. The basilar portion of the ventricular septum is thinner and more fibrous and is referred to as the membranous septum.

The LAA contains small pectinate muscles and is considered the most common site for the development of thrombus, especially in patients with atrial fibrillation. The left ventricle (LV) has an average wall thickness of approximately three times that of the RV wall (Fig. 2.1a, b). The LV contains anterior and posterior papillary muscles, which connect to the mitral valve via the chordae tendineae and anchors the cusps to prevent prolapse or inversion (Fig. 2.2b).

Blood Supply of the Heart

The heart is a muscular organ and receives its blood supply from two main arteries: the left main coronary artery (LMA) and the right coronary artery (RCA) (Fig. 2.3a). The LM coronary artery originates from the left sinus of Valsalva and is short, 0.5–2 cm length and has a large diameter (3–4 mm). The LM coronary artery bifurcates into the left anterior descending (LAD) coronary artery and the left circumflex (LCx) artery (Fig. 2.3a, b) [19]. The LAD artery courses in the anterior interventricular groove and ascends a short distance following the posterior interventricular groove. The LAD artery has multiple branches including the septal branches, which supply the anterior two-thirds and apical portions of the septum, as well as a number of branches to the anteroapical portions of the left ventricle, including the anterior papillary muscle. The latter branches are called diagonals that vary in size and number. Usually, there are two or three diagonal vessels that are medium to large in size (1–2 mm diameter) (Fig. 2.3b). The second main branch from the LM coronary artery is the LCx coronary artery (Fig. 2.3b). It is usually smaller and courses in the left AV groove and branches into the obtuse marginal (OM1 and OM2) arteries to supply the upper lateral LV wall and the LA. The blood flow to the anterolateral papillary muscle in the LV is from the LAD (typically the diagonal branch) and the left circumflex (obtuse marginal artery) coronary arteries, and the blood flow to the posteromedial papillary muscle in the LV is from the posterior descending coronary artery (PDA), which is a branch of the RCA. This single source of blood supply contributes to posteromedial papillary muscle rupture and acute mitral regurgitation following right coronary artery occlusion [19, 20].

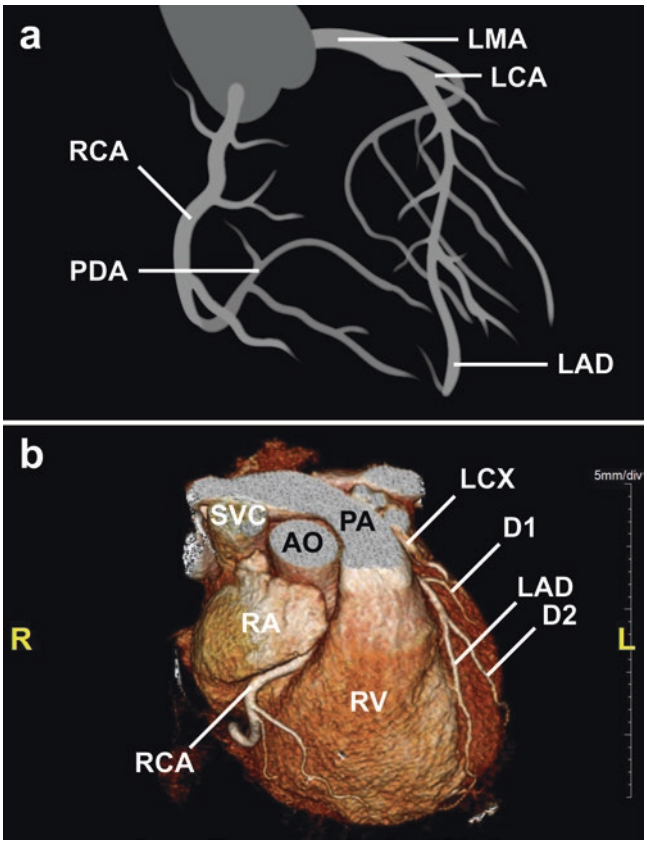

Fig. 2.3 The anatomy of the coronary vasculature in the adult heart. (**a**) Schematic demonstrating the coronary vasculature in the absence of the cellular components of the heart (*Ao* aorta, *LM* left main coronary artery, *LAD* left anterior descending coronary artery, *LCX* left circumflex coronary artery, *RCA* right coronary artery, *PDA* posterior descending coronary artery). (**b**) CT-angiography of the anterior aspect of the adult heart demonstrating the course of the RCA and LAD coronary vessels (*LAD* left anterior descending coronary artery, *D1* first diagonal coronary artery, *D2* second diagonal coronary artery, *LCX* left circumflex coronary artery, *LV* left ventricle, *PA* pulmonary artery, *AO* aorta, *RA* right atrium, *RCA* right coronary artery, *RV* right ventricle, *SVC* superior vena cava)

The right coronary artery (RCA) is the other main coronary artery that is responsible for the delivery of blood to the inferior wall of the heart (Fig. 2.3a). The RCA arises from the right coronary sinus of Valsalva of the aorta and courses in the right atrioventricular (AV) groove (Fig. 2.3b). The RCA branch, the posterior descending artery (PDA), courses in the posterior interventricular groove and supplies the posterior third of the interventricular septum [15].

Architectural Orientation of Cardiac Myofibers

The architecture of the heart is distinctive and functionally important. The myofibers are organized into laminated sheets that are approximately four cells thick. The ventricular

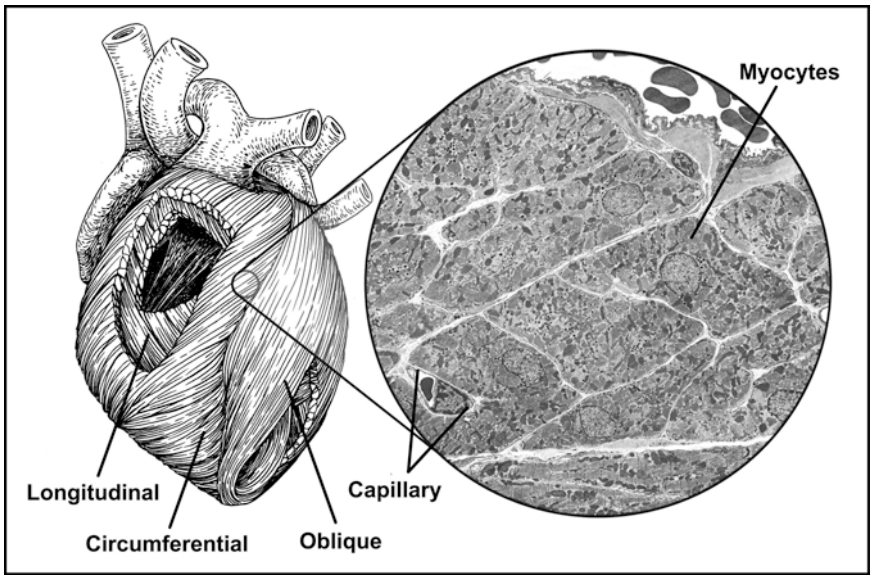

Fig. 2.4 Cellular and fiber orientations of the adult heart. Schematic of the adult heart demonstrating the oblique, circumferential, and longitudinal fiber orientations. Electron microscopic analysis of the cross section of the ventricular wall revealing mononuclear cardiomyocytes, myofibroblasts, endothelial cells, smooth muscle cells, and capillaries

myocardium is subdivided into three layers (superficial layer, middle layer, and deep layer) (Fig. 2.4) [15]. The superficial layer is composed of oblique fibers that form a sheet extending from the base and wrapping around the apex. These oblique fibers form a twin helix around the ventricle and cause a wringing effect (similar to wringing the water out of a towel) resulting in optimal ventricular filling and emptying. The middle layer consists of circumferential muscle bundles that are primarily located in the midwall at the base and closer to the epicardium [21]. The deep layer is composed of oblique, circumferential, and longitudinal fibers (Fig. 2.4). Collectively, the left ventricle has continuous fiber geometries with circumferential fibers associated with the upper septum and base and oblique fibers that extend from the midwall to the apex. This architecture of circumferential and oblique fibers results in increased efficiency of the pump (i.e., stress and strain) during the cardiac cycle.

Histological Organization of the Adult Human Heart

The myocardium comprises the vast majority of the heart's thickness (Fig. 2.4). It contains both myocytes and connective tissue (Fig. 2.4). Cardiac myocytes represent most of the myocardial mass and accounts for more than half the heart's weight [22]. About 70 % of the myocardium, however, is connective tissue that maintains the heart's strength and stiffness. Recently, flow cytometry studies in rodents suggested that the adult mouse heart contained 55 % myocytes and 45 % nonmyocytes, although investigators recognized the possibility of species differences regarding cellular composition. The nonmyocyte constituents include cells such as fibroblasts, myofibroblasts (smooth muscle-like fibroblasts), vascular smooth muscle, and endothelial cells (Fig. 2.4). Several types of myocytes are found in normal hearts, and they are classified based on their location in the atria and ventricles [22, 23]. Atrial myocytes are smaller than ventricular myocytes. Ventricular myocytes are long and narrow in shape. They are approximately 20 μm in diameter, 60–120 μm in length, and have a volume of 15,000–45,000 μm^3. Individual contractile myocytes in the atrium are elliptical in shape. The atrial myocytes are 5–6 μm in diameter, 20 μm in length, and have a volume of 500 μm^3 [24]. Compared to the ventricular myocytes, the atrial myocytes have bundles of atrial tissue separated by wide areas of collagen. Working myocytes are filled with cross-striated myofibers and mitochondria and usually contain a single centrally located nucleus (Figs. 2.4 and 2.5).

Atrial myocytes contain stores of active natriuretic peptide which functions as natriuretic factors and facilitates the dilation of vascular smooth muscle. The increasing stretch of the cardiac wall caused by vascular congestion with decompensated heart failure is a potent stimulus for the release of these peptides from the atria and ventricles. Cardiomyocytes contain a large number of myofilaments that are organized in a regular array of cross striations (Fig. 2.5). The cross striations of the myocardium reflect the organization of the contractile proteins into thick and thin filaments [22]. The sarcomere is defined as the area between the two Z lines and is considered the fundamental unit of striated muscle (Fig. 2.5).

As schematized in Fig. 2.5, the sarcomere contains the central A band and the two adjacent I bands. The sarcomere consists of the thick filaments composed largely of myosin that extend the length of the A band and contribute to the dark staining characteristics and its high birefringence. The thin filaments are composed of actin and the associated regulatory proteins—tropomyosin and troponin. Together, they form a complex that extends the length of the I bands and are characterized by the lightly stained striations and decreased birefringence. A broad dense M band is located in the center of each A band, while the I bands are bisected by Z lines (Fig. 2.5).

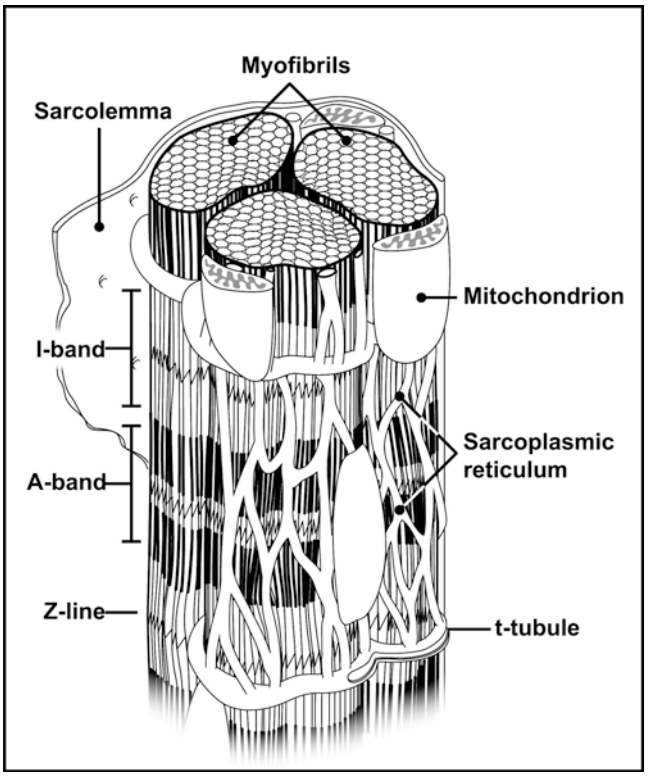

Fig. 2.5 Schematic of the organelles and cellular components associated with the cardiomyocyte. Note the overlying sarcolemma, ATP-producing mitochondria, sarcoplasmic reticulum, and t-tubule network. The sarcomere is defined by the Z lines and consists of myosin heavy chains (*thick filaments*) and actin chains (*thin filaments*). The A band consists of both the *thick* and *thin* filaments, whereas the I band consists of only the *thin* filaments

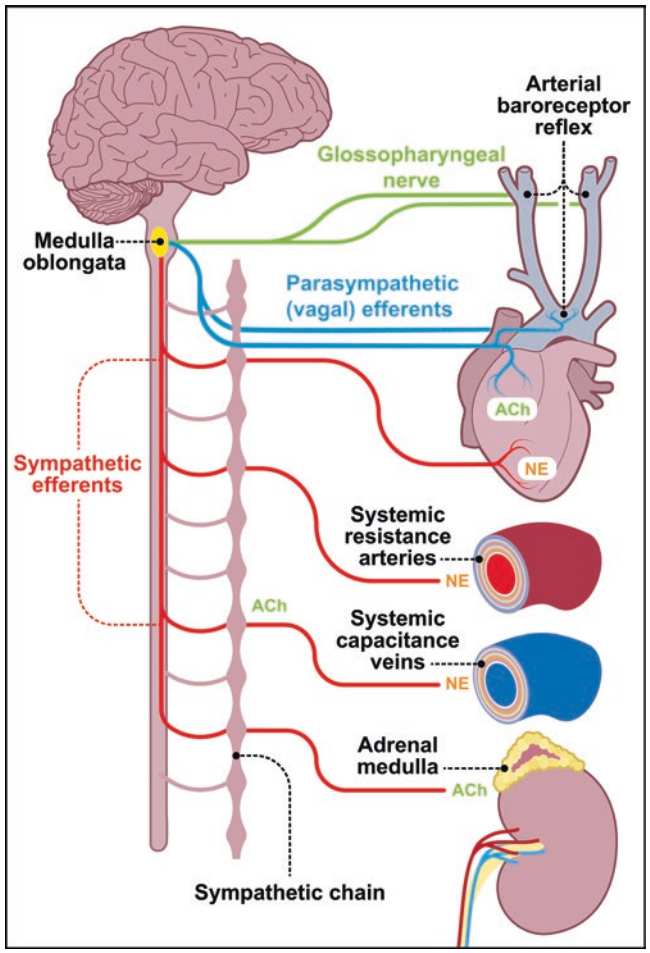

Fig. 2.6 Autonomic nervous system and the regulation of the cardiovascular system. Parasympathetic (Ach) and sympathetic (NE) innervation from the medulla oblongata to the cardiovascular target organs such as the arterial baroreceptor, atria, ventricles, vasculature, and adrenal glands, resulting in a coordinated response during rest or stress. Note the parasympathetic (*Ach* acetylcholine) and sympathetic (*NE* norepinephrine) neurotransmitters

Innervation of the Heart

The parasympathetic (cholinergic) and sympathetic (adrenergic) nerve fibers innervate the heart. The parasympathetic fibers arise from the cardiac components of the cranial neural crest cells and are propagated to the heart via the vagus nerve (Fig. 2.6). The vagus nerve is a mixed nerve that has both sensory and motor nerves. The right and the left vagal nerves course from the medulla to the heart via the carotid sheath and primarily innervate the sinoatrial (SA) and AV nodes.

The sympathetic nerve fibers arise from the medulla and course to the heart from the sympathetic ganglia (Fig. 2.6). The sensory nerves arise from the ectodermal placode of the nodose ganglion and are propagated via the vagus nerve. The nucleus ambiguus, the nucleus solitarius, and the dorsal motor nucleus in the medulla provide autonomic neuronal control for the cardiovascular system via the vagus nerve and the sympathetic ganglia. The nucleus solitarius receives sensory afferent input from chemoreceptors and baroreceptors and is a control center for the baroreflex (as well as exercise-induced reflexes such as the exercise pressor reflex and central command). The nucleus ambiguous and the dorsomedial nucleus (DMN) provide parasympathetic control for the parasympathetic control for the heart.

Sympathetic efferent nerves originate from the cervical and thoracic sympathetic ganglia and course with the blood vessels to innervate the atria and ventricles. The effects of the sympathetic nervous system are mediated by norepinephrine that binds to alpha-adrenoreceptors (to regulate vasoconstriction of the vasculature in response to dehydration) or beta-1 adrenoreceptors to increase chronotropy, lusitropy, inotropy, and conduction velocity. The parasympathetic system mediates its effects by the release of acetylcholine, which binds muscarinic receptors and regulates the SA and AV nodes (Fig. 2.6).

Collectively, the cardiovascular innervation and its global impact on the cardiac output are evident in a number of reflexes (i.e., vasovagal syncope, Bezold–Jarisch reflex, Valsalva maneuver, carotid sinus reflex, etc.). In the failing heart, decreased cardiac output promotes an increase in sympathetic activity resulting in remodeling and is associated with increased arrhythmias and sudden cardiac death. Heart failure symptoms and progression of disease are exacerbated

by a hyperadrenergic state. This increase in the sympathetic nervous system results in tachycardia, vasoconstriction, increased afterload, diaphoresis, oliguria, increased myocardial oxygen consumption, and progressive left ventricular remodeling. In short, norepinephrine becomes toxic to the myocardium. In patients with advanced heart failure who receive a cardiac transplant, the graft is denervated (i.e., vagus nerves are severed), and, typically, the heart rate is about 105 bpm.

The Role of Myoglobin

Tissue hemoglobins are found in diverse organisms including plants, mollusks, and mammals. These tissue hemoglobins include cytoglobin, neuroglobin, and myoglobin [4, 25]. In vertebrates, myoglobin is restricted to striated muscle (cardiomyocytes and oxidative skeletal myofibers) and is a monomeric cytoplasmic hemoprotein consisting of 154 amino acids [26, 27]. Myoglobin is named because of its functional and structural similarity to hemoglobin. Evolutionarily, myoglobin and hemoglobin arose from a common ancestral gene more than 500 million years ago [26, 28, 29]. In 1958, myoglobin was the first protein to be subjected to definitive structural analysis (Fig. 2.7a) [30]. Subsequently, a number of studies have established that the structure of myoglobin consists of a heme pocket, which is bracketed by histidine residues and has a backbone of eight alpha-helices (Fig. 2.7a). The flanking histidine residues stabilize the heme group and allow for the concentration of ligands (e.g., dioxygen, nitric oxide, carbon monoxide, etc.) to bind to the heme residue of myoglobin (Fig. 2.7a). In this fashion, myoglobin has been shown to have important roles as a facilitator of oxygen transport to mitochondria to maintain oxidative phosphorylation (and the generation of adenosine 5′-triphosphate, ATP) for myocardial contractility, as well as serve as a modulator of nitric oxide (NO) bioavailability and as a scavenger of reactive oxygen species [27, 31].

Previous studies using gene disruption technologies engineered a mouse model that lacked myoglobin (Fig. 2.7b) [32]. While many mutant embryos were nonviable, viable myoglobin null mice had preserved cardiac performance due to a number of adaptive mechanisms including an induction of the hypoxia-inducible molecular program, neovasculogenesis, and increased coronary flow [25, 33]. Collectively, the results of these genetic studies underscore the importance of myoglobin (and its role in oxygen transport and the generation of ATP), the redundancy of other tissue hemoglobins (in the absence of myoglobin), and the role of adaptive mechanisms to promote cardiac function, even in the absence of myoglobin [32].

Cardiac contraction and relaxation: The contractile proteins of the heart—actin and myosin—lie within the cardiomyocytes, which constitute about 75 % of the total volume of the myocardium (Fig. 2.5) [34]. The physical interactions between myosin and actin are activated by calcium and regulated by tropomyosin and troponins (Fig. 2.8) [22, 28].

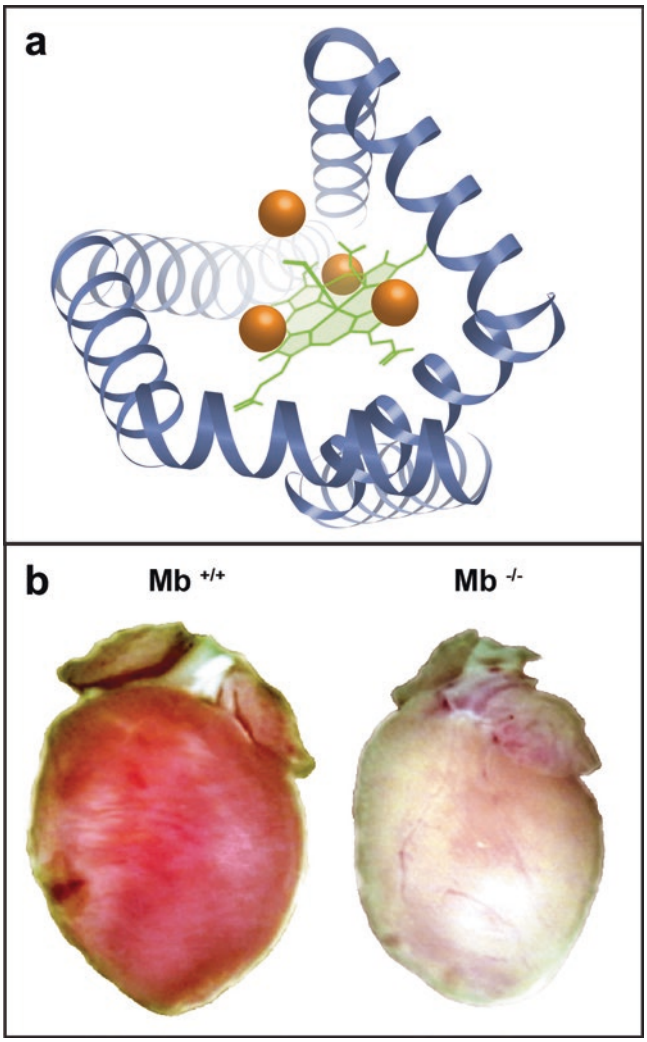

Fig. 2.7 Myoglobin is an essential hemoprotein for oxygen delivery to the cardiomyocyte. (**a**) Myoglobin was the first protein to have its structure defined. It contains a heme pocket stabilized by histidine residues that promotes the binding of dioxygen, nitric oxide, and carbon monoxide. (**b**) Using a gene disruption strategy, mice lacking myoglobin were engineered. The functional importance of myoglobin was evident as mice lacking myoglobin were viable only as a result of an increase in the hypoxia-inducible molecular program (Hif1), resulting in an increase in other tissue hemoglobins and myocardial vasculature

Troponins have several subtypes (C, I, and T) and are associated with actin thin filaments. The signaling process that initiates cardiac systole, called excitation–contraction (EC) coupling, begins when an action potential depolarizes the plasma membrane [35]. This EC coupling opens L-type voltage-dependent calcium channels during the action potential plateau and allows an influx of calcium to enter the cytosol from the extracellular fluid (Fig. 2.8) [22, 36]. This calcium influx triggers the opening of calcium-release channels in the sarcoplasmic reticulum (via the ryanodine receptor 2, RyR2) that releases a larger pool of this activator to the cytosol from stores within this intracellular membrane system (Fig. 2.8) [5, 37]. This increased cytosolic calcium concentration facilitates the binding of calcium to troponin C and the induction of contraction [38, 39]. Following

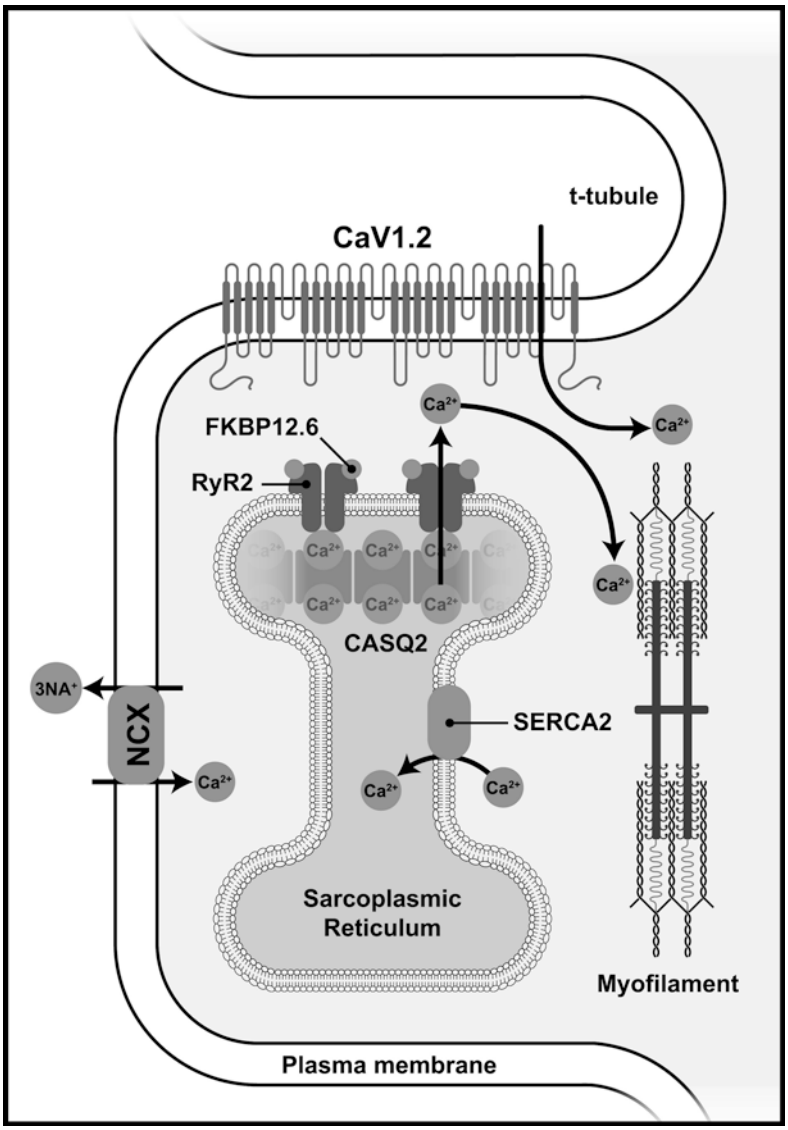

Fig. 2.8 Calcium signaling regulates myofilament contractility. Schematic highlighting the calcium influx into the cytosol of the cardiomyocyte, which promotes the release of calcium from the sarcoplasmic reticulum stores via the RYR2 channel. Calcium then binds to the myofilament unit and promotes contraction (systole). Calcium is then transported back into the SR via SERCA2 to promote diastole (*CaV1.2* voltage-dependent L-type alpha-1C subunit calcium channel, *FKBP12.6* FK506 binding protein 12.6 that interacts with RyR2, *RyR2* ryanodine receptor2, *SERCA2* sarcoplasmic endoplasmic reticulum calcium ATPase, *CASQ2* calsequestrin 2, *NCX* sodium/calcium exchanger, *NA* sodium, *Ca*, calcium)

contraction, the calcium is released from troponin C, and reuptake into the SR is facilitated by the SR calcium-ATPase 2a (SERCA2a) calcium pump (Fig. 2.8). The heart relaxes when calcium is transported out of the cytosol. A smaller amount of calcium is transported from the cytosol into the extracellular space by a plasma membrane calcium pump and sodium/calcium exchanger [22, 36]. The total time period required for cardiomyocyte depolarization, calcium-induced calcium release, contraction, relaxation, and recovery in the adult human heart is about 600 msec [38].

Regulation of cardiac contractile performance: Two mechanisms are traditionally viewed as essential for the regulation of the heart's contractile performance: the length-dependent regulation (the Frank–Starling law of the heart) and inotropic/lusitropic properties (Fig. 2.9).

End-diastolic volume: *the Frank–Starling mechanism*: The length-dependent regulation (Starling's law of the heart) is due to variations in end-diastolic volume that results in changes in sarcomere length and impacts the stroke volume of the heart (Fig. 2.9) [10]. This mechanism functions in matching the heart's output during systole to the return of blood during diastole [40]. Starling's law (or the Frank–Starling mechanism) showed that the greater the volume of the heart in diastole [(end-diastolic volume, EDV, which would increase the filling pressures; end-diastolic pressure, EDP)], the more forceful the contraction, which would increase the stroke volume (SV) [41]. Conversely, decreasing venous return is associated with decreased EDP and decreased SV (Fig. 2.9).

Regulation by inotropic properties: Changes in myocardial contractility are an important feature of cardiac muscle. Inotrope or myocardial contractility is the manifestation of all the factors that influence the interactions between contractile proteins with the exception of those that impact preload and afterload [13, 24]. Myocardial contractility occurs when the ability of the myocardium to do work is modified by factors other than altered fiber length (Starling's law). Myocardial

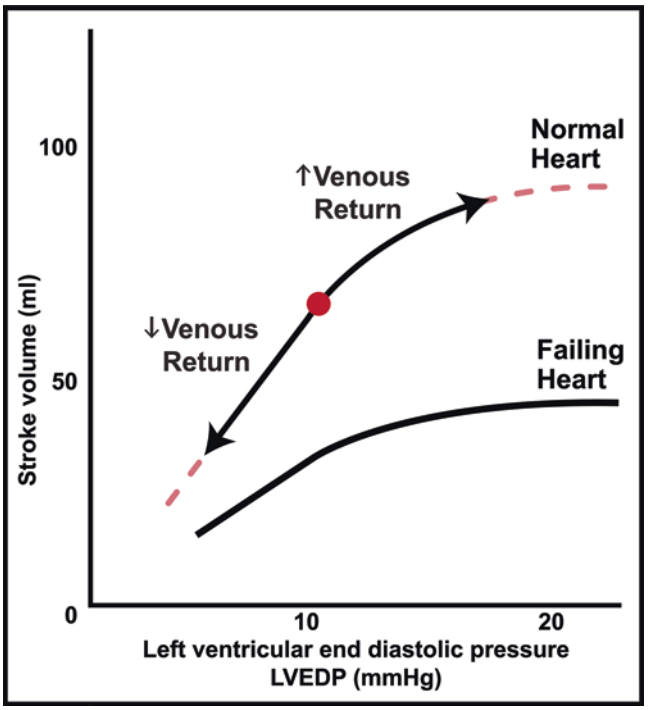

Fig. 2.9 Regulatory mechanisms that impact cardiac output. Frank–Starling curve demonstrating increased stroke volume in response to increased venous return to the heart resulting in increased cardiac output. Note the Frank–Starling curve in the failing heart with decreased stroke volume at any LVEDP

contractility is the heart's ejection and/or pressure development when the preload (venous return—EDV) and afterload (arterial pressure) are held constant. Most of the rapidly occurring changes in myocardial contractility are facilitated by variations in the amount of calcium delivered to the contractile proteins during excitation–contraction coupling [15, 21, 42].

Regulation by lusitropic (*relaxation*) *properties*: The clinical importance and quantification of the lusitropic property of the myocardium was not fully appreciated until echocardiography and nuclear techniques were developed. These techniques are able to measure the changes in the rate and the degree of ventricular filling and afford the opportunity to examine diastolic function in adult human patients [42, 43]. The heart relaxes when energy-dependent calcium pumps and exchangers lower cytosolic calcium concentration, which promotes the dissociation of calcium from troponin C. Relaxation is not simply the reversal of the processes involved in excitation–contraction coupling, because different mechanisms participate in calcium release and removal from the cytosol.

The cardiac cycle: The cardiac cycle is divided into systole and diastole (Fig. 2.10). These are further subdivided into four phases: isovolumetric contraction, ejection, isovolumetric relaxation, and filling (Fig. 2.10). The relationship between ventricular pressure and volume during the cardiac cycle can be illustrated by pressure–volume loops that will be discussed later in this chapter [6, 44].

The cardiac cycle consists of diastolic ventricular filling and augmentation by atrial systole to achieve the end-diastolic volume. During this period, the LV pressure increases until it exceeds that in the left atrium (normally 10–15 mmHg), which promotes the closure of the atrioventricular valves (i.e., the mitral and tricuspid valves) (Fig. 2.11). Following the closure of the AV valves, the LV and RV volume cannot change, and contraction must be isovolumetric (isovolumetric contraction) until the aortic (and pulmonary) valve(s) is forced open as the ventricular pressure exceeds that in the aorta and pulmonary artery (Figs. 2.10 and 2.11). Once the aortic (and pulmonary) valves are opened, blood is ejected from the ventricles into the major vessels, which is the phase of maximal ejection. The speed of ejection of blood is determined both by the pressure gradient across the aortic valve and by the elastic properties of the aorta, which undergoes systolic expansion (Fig. 2.12). Meanwhile, atrial pressure progressively increases during ventricular systole as blood continues to enter the atrium while the atrioventricular (AV) valves are closed. Once the ventricle reaches its end-systolic volume (ESV), there is a period of isovolumetric relaxation, which promotes the opening of the AV valves (mitral and tricuspid) and diastolic filling from the atrium into the ventricle to begin the next cycle (Figs. 2.10 and 2.11).

Throughout the diastolic ventricular filling period, the pressure gradient between the atrium and ventricle is minimal. This happens because a normal open mitral or tricuspid valve offers little resistance to flow; there is also significant passive filling of both the atrium and ventricle as blood returns from the systemic or pulmonary venous system. At a normal resting heart rate, diastole occupies about two-thirds of the cardiac cycle (Fig. 2.10). With increased heart rate, both systolic and diastolic intervals will shorten. Systole is defined by the interval between the first and second heart sounds lasting from the first heart sound to the point of closure of the aortic valve (Fig. 2.10). The remainder of the cardiac cycle is diastole.

The main difference between the left and right pumping systems is the pressure magnitude. In the normal heart, the pressures developed in the right heart are significantly lower than those on the left side, because resistance across the pulmonary vasculature is far less than the resistance to flow offered by the systemic vascular system. Normal pulmonary artery systolic and diastolic pressures typically do not exceed 30 mmHg and 15 mmHg respectively; maximal right atrial pressure is generally 8 mmHg (Fig. 2.10).

Pressure Versus Volume

Contractility is the inherent capacity of the myocardium to contract independently of the changes in the preload or afterload. Increased contractility means a greater rate of contraction, to reach a greater peak force. Frequently, increased contractility is associated with enhanced rates of relaxation, called the lusitropic effect (Fig. 2.11). An alternative term for contractility is inotropy. Contractility is an important regulator of the myocardial oxygen uptake. Factors that increase contractility include adrenergic stimulation, temperature, redox state, and pH.

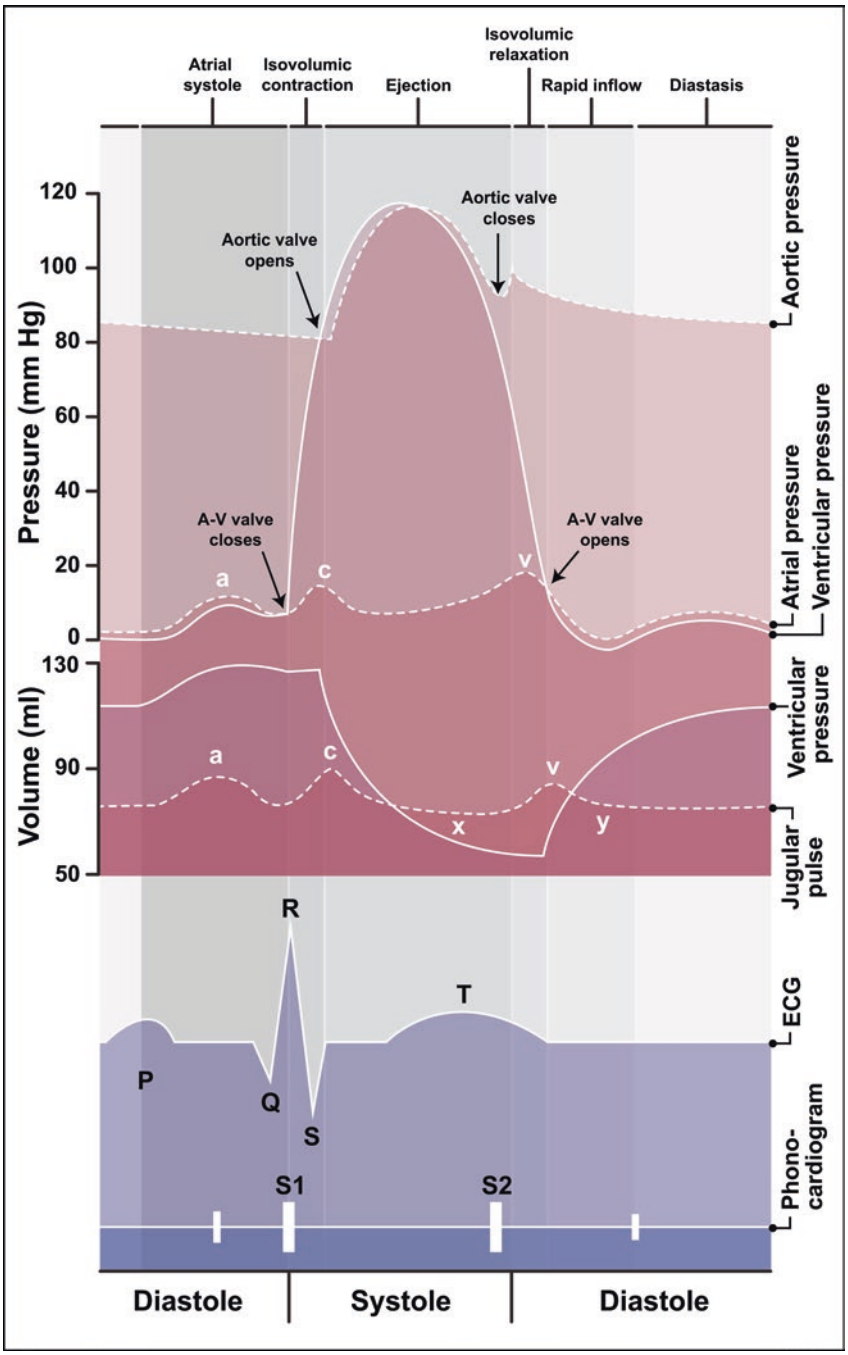

Fig. 2.10 Hemodynamic and physical exam signs associated with the cardiac cycle. Overlapping depiction highlighting the phases of the cardiac cycle; hemodynamics associated with the aorta, left ventricle, and atria; and electrocardiogram. (P wave represents atrial depolarization, QRS represents ventricular depolarization, and T wave represents repolarization.) Note S1 corresponds to the closure of the atrioventricular valves (tricuspid and mitral valves), and S2 corresponds to the closure of the semilunar valves (aortic and pulmonic valves). Individual hemodynamic tracings emphasize that the jugular venous pressure tracing reflects atrial contraction (*a*-wave), ventricular contraction, and bulging of the tricuspid valve into the right atrium during isovolumetric systole (*c*-wave), atrial venous filling (*v*-wave), atrial relaxation and downward movement of the tricuspid valve (*x*-descent), and the filling of the ventricle following the opening of the tricuspid valve (*y*-descent)

Pressure–Volume Relationships

Measurements using pressure–volume loops (PVLs) are traditionally used to assess the contractile behavior of the intact heart. The relationship between ventricular pressure and volume during the cardiac cycle has been described using pressure–volume loops. The relationship can be demonstrated by plotting LV pressure versus LV volume through one complete cardiac cycle (Fig. 2.11) [41, 45].

As illustrated in Fig. 2.11, the cycle starts with the opening of the mitral valve (A), which allows blood to flow from the atrium into the ventricle during the filling phase (A-B). Systole, then, is initiated at a point along the end-diastolic pressure–volume relationship (end diastole) located at the lower right corner of the loop (B), which is associated with the closure of the mitral valve. Once the mitral valve closes, the intraventricular pressure increases rapidly while both the mitral and aortic valves are closed. This phase represents isovolumetric contraction (IVC) (B-C). As soon as the aortic valve opens, the ventricle is exposed to the aortic pressure (C), and the ejection phase begins (C-D). Systole ends when the ventricular pressure and volume reach the end-systolic pressure–volume relationship, which describes the inotropic state of the ventricle at which the aortic valve closes (D). When the aortic valve closes (D), the blood is constrained within the ventricle; as a

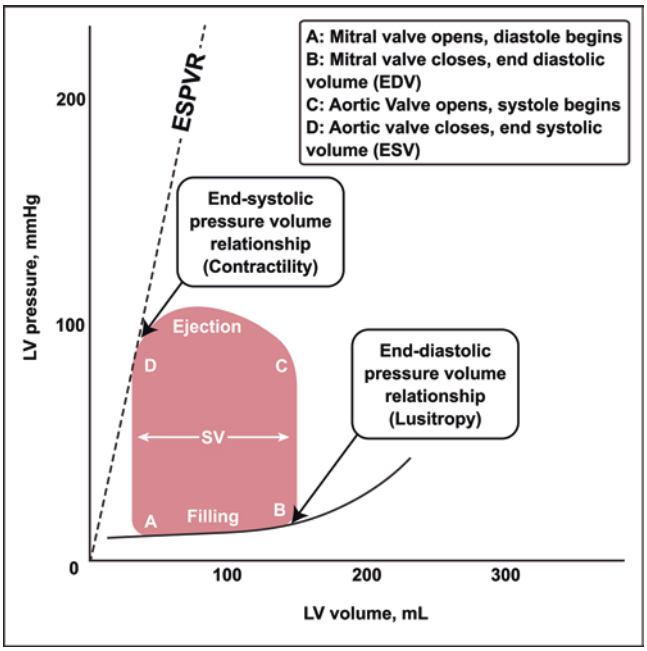

Fig. 2.11 Pressure–volume relationship of the adult heart. Note the pressure–volume relationship of the functional adult heart (*ESPVR* end-systolic pressure–volume relationship, *EDV* end-diastolic volume, *ESV* end-systolic volume, *SV* stroke volume, *LV* left ventricular)

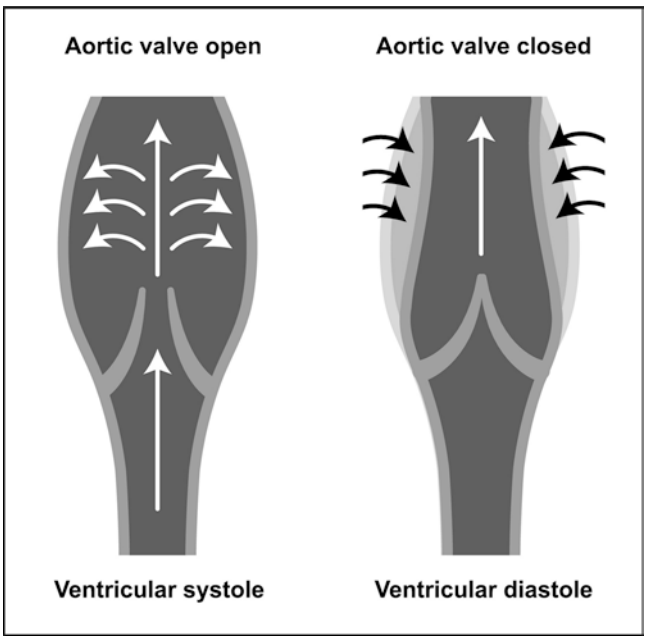

Fig. 2.12 The aorta is a compliant vessel. Schematic of the compliance of the aorta during systole and diastole. Note that this compliance decreases significantly with age and disease

result, relaxation begins. This phase is referred to as the isovolumetric relaxation (IVR) (D-A). When the LV pressure falls below that in the left atrium, the mitral valve opens (A) and blood flows from the atrium into the ventricle during the filling phase (A-B). Therefore, systole begins at (B) and ends at (D), while ejection begins at (C) and ends at (D). Similarly, diastole begins at (D) and ends at (B), while filling begins at (A) and ends at (B) (Fig. 2.11).

Factors Affecting Pressure–Volume Loops

The major determinants of the left ventricular pressure–volume relationship and cardiac output are cardiac preload (ventricular volume), myocardial contractility (inotropy), and afterload (Table 2.1) (Fig. 2.13). Unlike other striated muscles such as skeletal muscle, the myocardial PVL is constrained within two pressure–volume factors. The first factor is the end-systolic pressure–volume relationship, which is mainly determined by the inotropic property of the contracting myocardium. The second factor is the end-diastolic pressure–volume relationship, which is determined by the lusitropic property of the relaxed myocardium. Ventricular end-diastolic volume (EDV) is determined by the venous return, end-systolic volume and the lusitropic properties of the ventricle. Conversely, end-systolic volume is determined by EDV, aortic impedance, and contractility. These ventricular changes can be complex as preload, afterload, and inotropy are interdependent variables (Fig. 2.13a, b, d). The interdependency refers to the changing of one variable impact and changes the other variables as well.

Cardiac Preload

Cardiac preload is a semiquantitative composite assessment that is described as end-diastolic myocardial fiber tension, end-diastolic myocardial fiber length, ventricular end-diastolic volume, and ventricular end-diastolic filling pressure (Table 2.1) (Fig. 2.13a). Cardiac preload is an assessment of end-diastolic pressure—the ventricular pressure measured after atrial contraction just prior to the onset of systole [45, 46]. Left ventricular end-diastolic pressure (LVEDP) is often measured in the cardiac catheterization laboratory before coronary angiography to assess filling pressures. Noninvasive assessments of end-diastolic chamber volume are possible, but volume assessments rely on geometric assumptions that can be influenced by arrhythmias, changes in heart rate, localized wall motion abnormalities, and the chronic ventricular dilatation that occurs in many forms of heart failure. The passive pressure–volume relationship within a chamber, which is a reflection of the passive length–tension curve in isolated myocardium, is exponential rather than linear. This exponential property contributes to having the pressure as a surrogate for a preload-limited approach since the changes in chamber pressure to volume being greater at higher volumes compared to lower volumes. Furthermore, any myocardial and pericardial conditions (i.e., pathologies) will distort the relationship between pressure and volume. Increasing preload by giving intravenous fluids would increase preload volume, which eventually increases the end-diastolic pressures (Fig. 2.13a).

Furthermore, decreasing preload by administration of oral or intravenous diuretics would decrease the preload volume and eventually LVEDP (Fig. 2.13a). Patients with pericardial tamponade compromise the capacity of the RV to dilate to accommodate further volume, and, eventually, this inability to dilate results in decreased stroke volume (Fig. 2.13c).

Table 2.1 Factors affecting pressure–volume relationship

Preload	Increases	1. Greater circulating volume
		2. Exercise
		3. Bradycardia (increased ventricular filling time)
		4. Arterioventricular fistulae
		5. Increased ventricular compliance
		6. Heart failure with reduced ejection fraction (HFrEF)
		7. Increased afterload (by increasing end-systolic volume which leads to secondary increase in ventricular preload)
		(a) Increased aortic pressure
		(b) Aortic valve stenosis and insufficiency
		(c) Pulmonary valve stenosis and insufficiency
		(d) Pulmonary hypertension
	Decreases	1. Volume depletion (hemorrhage)
		2. Tachycardia (atrial tachycardia—decreased atrial filling time)
		3. Impaired atrial contraction
		4. Decreased venous return (gravity effect)
		5. Tricuspid or mitral valve stenosis
		6. Heart failure with preserved ejection fraction (HFpEF)
		7. Decreased afterload (enhances forward flow—ejection)
Afterload	Increases	1. Elevated systemic hypertension
		2. Aortic valve disease (stenosis and insufficiency)
		3. Increased vascular resistance
		4. Pulmonary hypertension
	Decreases	1. Decreased vascular resistance (septic shock)
		2. Low blood pressure
		3. Mitral regurgitation
Myocardium	Inotropy	• Increased
	Ability of the myocardium to eject	– Increased catecholamine level
		– Inotropic medication (dopamine)
		• Decreased
		– HFrEF
		– Parasympathetic stimulation
		– Beta-blockers
	Lusitropy	• Increased
	Ability of the myocardium to relax and fill	– Increased catecholamine level
		– Beta-adrenergic agonist
		• Decreased
		– Left ventricular hypertrophy (LVH)
		– HFpEF
		– Infiltrative heart disease (amyloidosis)

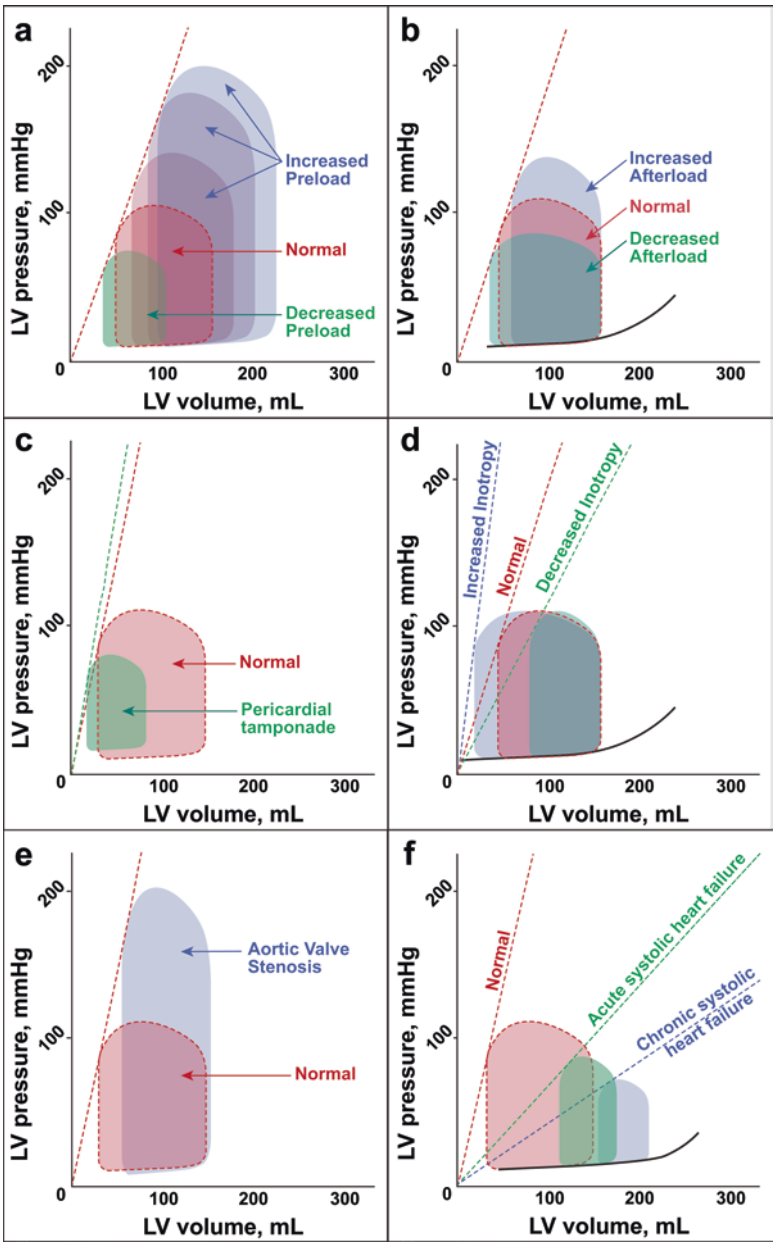

Fig. 2.13 Pressure–volume (PV) loops in the physiological and pathological states. (**a**) PV loops in normal, increased preload, and decreased preload states. (**b**) PV loops in response to increased and decreased afterload. (**c**) PV loops in the normal state and in the patient with decreased cardiac output due to pericardial tamponade. (**d**) PV loops with increased and decreased inotropy. (**e**) PV loops in the normal state and in the patient with severe aortic stenosis. (**f**) PV loops in normal, acute systolic heart failure and chronic heart failure

Overall, it should be emphasized that preload is a physiological factor that encompasses more than just a single value on a pressure tracing. Preload increases with increasing circulating volume, venoconstriction, exercise, arterioventricular fistulae, increased ventricular compliance, increased ventricular filling time, and systolic heart failure. Alternatively, preload decreases with volume depletion (dehydration), decreased venous return, impaired atrial contraction, tricuspid or mitral stenosis, and decreasing ventricular compliance (Fig. 2.13a).

Afterload

Afterload is the force against which the heart has to pump blood into the aorta and the pulmonary artery through the aortic and pulmonic valves, respectively. Afterload is considered the stress encountered by LV myofibers as they contract against the end-diastolic volume (Table 2.1) (Fig. 2.13b). The relationship between the ventricle and its afterload is key to the concept of ventriculo-arterial coupling and can be illustrated by pressure–volume loops. During the LV ejection phase of the cardiac cycle, as ventricular volume decreases, the potential for the ventricle to develop pressure also declines. The lowest volume achieved is the end-systolic volume, at which point the stroke volume has been ejected. The aortic valve subsequently closes and the diastolic phase begins. The rise in aortic pressure, all else being equal, will correlate with a decreased stroke volume and a lower aortic pressure with an increased stroke volume and ejection fraction (EF). EF is calculated as follows: $[(EDV - ESV)/EDV] \times 100 = EF\ (\%)$, where EDV is end-diastolic volume and ESV is end-systolic volume. Therefore, increases in the

afterload (ESV) will cause a decrease in stroke volume and EF (Fig. 2.13b). For example, in an individual with aortic valvular stenosis or uncontrolled elevated blood pressures, as the afterload is increased, and if the preload (end-diastolic volume) and contractility of the ventricle (inotrope) are held constant, this will result in a smaller stroke volume and an increase in end-systolic volume, shifting the curve upward (Fig. 2.13).

Stroke volume is reduced as increased afterload reduces the velocity of muscle fiber shortening and the velocity by which the blood is ejected. The reduced stroke volume at the same end-diastolic volume reduces the ejection fraction. Over time, compensatory mechanisms such as ventricular wall hypertrophy will attenuate the high wall stress and improve the ventricle's ability to overcome the high afterload and increase the stroke volume, thus causing the loop to increase in width. Similarly, in patients with severe aortic valve stenosis, left ventricular emptying is impaired because of high outflow resistance caused by a reduction in the valve orifice area when it opens. This high outflow resistance results in an increase in the pressure gradient across the aortic valve during ejection, such that the peak systolic pressure within the ventricle is greatly increased (Fig. 2.13d). In contrast, a reduction in afterload (i.e., controlled blood pressure, vasodilators) allows the LV to eject blood with less resistance, resulting in an augmentation of the stroke volume and decreased end-systolic volume. This reduction in afterload shifts the pressure–volume loop into a compressed and wider configuration (Fig. 2.13b). With less blood remaining in the ventricle after the ejection phase, the ventricle will fill to a lower end-diastolic volume with the reduction of afterload. Despite this mild reduction in preload (end-diastolic volume), stroke volume shows a net increase because the reduction in end-diastolic volume is less than the reduction in end-systolic volume. Following the above equation, this will also cause a net increase in the ejection fraction.

Ventricular Contractility

Ventricular contractility represents the systolic function of the ventricles. Increasing contractility increases the velocity of fiber shortening at any given preload and afterload. This response enables the ventricle to increase the rate of pressure development and ejection velocity, which leads to an increase in stroke volume and ejection fraction and a decrease in end-systolic volume. In the PV loop diagrams, increased inotropy increases the slope, which permits the ventricle to generate more pressure at a given LV volume (Fig. 2.13d). Decreasing inotropy has the opposite effect—resulting in increased end-systolic volume and decreased stroke volume and ejection fraction (Fig. 2.13d). In patients with severe systolic heart failure, there is increased end-diastolic pressure and end-diastolic volume (Fig. 2.13e). Afterload reduction is considered a mainstay therapy in such situations. Intravenous or oral afterload reduction therapy is determined based on the clinical stability of the patient and cardiac output at the time of presentation.

Ventricular Compliance

Pressure–volume loops highlight the nonlinear pressure and volume relationship during diastolic filling. The instantaneous slope of the curve in the filling phase (i.e., change in pressure/change in volume) represents diastolic stiffness. This parameter is termed "elastance"; the ventricle is analogous to a spring with a stiffness that increases during contraction and decreases during relaxation. Elastance can be calculated at any point during the ventricle's diastole by calculating the gradient of the curve. Beyond a volume of approximately 140 mL (the exact volume will depend on individual heart dimensions), the chamber becomes progressively more difficult to fill, requiring a greater pressure increase to effect volume changes than earlier in diastole. A thicker, stiffer ventricle, for example, in an individual with left ventricular hypertrophy, will show a steeper gradient in the diastolic curve and, hence, a greater elastance.

Left Ventricular Remodeling and the Law of Laplace

In the initial stages of failure, the heart becomes less sensitive to preload and more sensitive to afterload. The ventricular myocardial wall tension contributes to the afterload. The law of Laplace states that the wall tension is equal to the radius of the ventricular chamber multiplied by the pressure and divided by the wall thickness $[T=(P\times r)/h]$ (Fig. 2.14). Furthermore, ventricular dilation results in increased tension associated with each myofibril, and increased wall thickness (i.e., myocardial hypertrophy) reduces afterload by distributing tension among more myofibrils. As a consequence, wall tension is greatest in the endocardial surface and is more vulnerable to reductions in coronary blood flow. While ventricular dilation initially is favorable (in order to maintain stroke volume), it brings decreased efficiency, high wall tension, and increased afterload, resulting in increased energy expenditure and deterioration of energy-starved cardiomyocytes, leading to progressive heart failure (Fig. 2.14).

Increasing ventricular dilation ultimately leads to valvular insufficiency, programmed cell death, and further impairment of myocardial performance. As remodeling progresses, the cellular constituents change, resulting in an increase in the non-cardiomyocyte components (including myofibroblasts, inflammatory cells, adipocytes, extracellular matrix, etc.). Therefore, effective therapies for heart failure are directed toward reverse remodeling strategies, including the use of beta-adrenergic receptor blockers, anti-fibrotic agents, and angiotensin-converting enzyme inhibitors.

Summary

In conclusion, the adult heart functions in a coordinated fashion that is highly responsive to increased stress and demand with increased cardiac output. The architectural

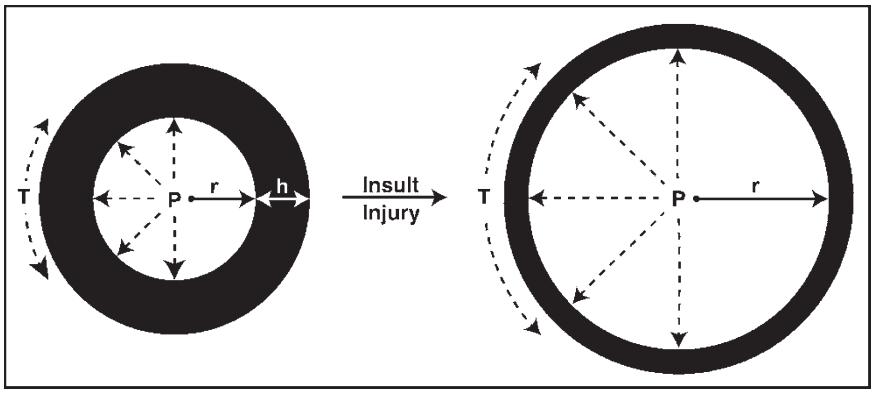

Fig. 2.14 Law of Laplace and cardiomyopathy. End-stage heart failure results in ventricular remodeling and chamber dilation. Based on the law of Laplace [$T=(P\times r)/h$], wall tension increases due to increased chamber dilation resulting in increased energy expenditure and progressive heart failure (*T* wall tension, *P* ventricular pressure, *r* radius of the chamber, *h* wall thickness)

organization of the heart consists of cardiomyocytes, endothelial cells, smooth muscle cells, fibroblasts, extracellular matrix, and neuronal components that collectively produce a functional syncytium. In response to a severe injury, the heart adapts in an attempt to maintain cardiac output by remodeling, which over time becomes detrimental due to a hyperadrenergic state, increased energy expenditure, increased program cell death, and progressive dilation—ultimately leading to end-stage heart failure. An enhanced understanding of the pathophysiology of the normal and failing heart allows for early implementation of conventional and emerging therapies that promote reverse remodeling of the failing heart.

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Molecular Biology of the Normal and Failing Heart

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_3

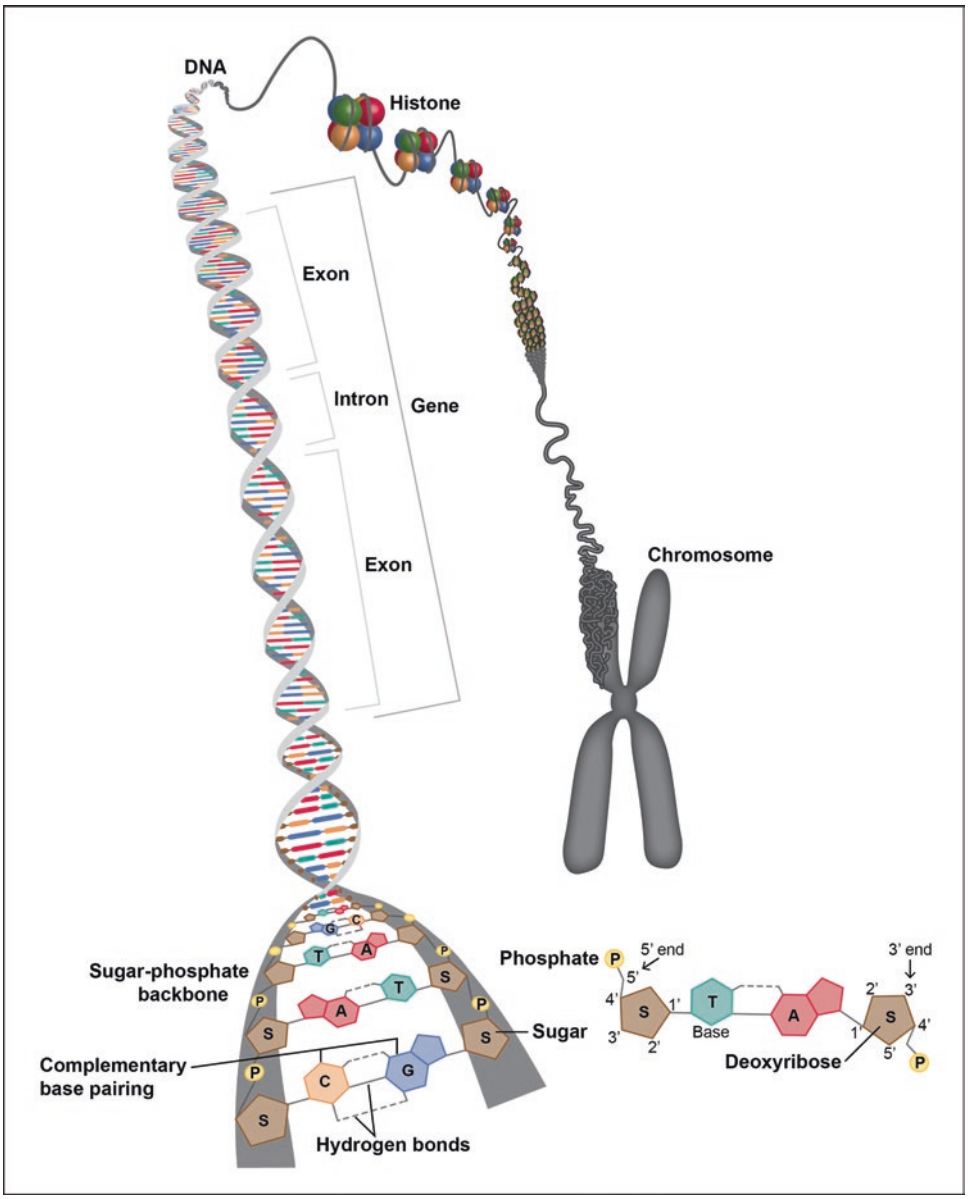

Fig. 3.1 The molecular structure of DNA from nucleotide to chromosome. DNA at the molecular level is composed of nucleotides, which consist of a nitrogenous base (adenosine, cytosine, guanine, and thymine), a deoxyribose sugar, and a phosphate group. The nucleotides form complementary base pairs via hydrogen bonding. The base pairs form the double-stranded helical structure of DNA with a sugar-phosphate backbone. Segments of DNA form genes that encode for proteins and have coding segments called exons and noncoding segments called introns. The DNA is wrapped around histone proteins and further packaged into chromatin. The DNA containing chromatin is then further packaged into chromosomes

Fundamentally, DNA stores genetic information, and its structure is critically important in its function of replicating and transmitting genetic information [2]. DNA is composed of nucleotides which include a monosaccharide deoxyribose sugar, a phosphate group, and a nitrogen-containing base: guanine (G), adenine (A), thymine (T), or cytosine (C). The nucleotides form a single strand of DNA via covalent bonds that connect to the 5′ carbon of one deoxyribose sugar and to the 3′ carbon phosphate group of the next, creating a sugar-phosphate backbone with unidirectionality. The single strand of DNA serves as a template for the complementary strand, with hydrogen bonds forming between nucleotides—with A always binding to T and C always binding with G. These two strands of DNA run antiparallel (5′–3′ of one strand and 3′–5′ of the other strand) and are twisted around one another to form a double helix (Fig. 3.1).

This double-helix structure of DNA is important in storing and replicating biological information, given that the

DNA backbone is resistant to cleavage and the double strands of DNA each store the same biological data. In total, 3.2 billion bases of DNA provide a blueprint for the synthesis of all proteins in the human body.

3

Promoters, Enhancers, and Repressors

The DNA structure enables it to serve as a template for storing biological data. Transcription is the first step in gene expression, where ribonucleic acid (RNA) is synthesized via RNA polymerase using the DNA template (Fig. 3.2). For initiation of transcription, an RNA polymerase (RNAP II) binds to the double-stranded DNA in the promoter region. Promoter sequences are regions of DNA that define where the initiation of transcription by RNA polymerase begins. Promoter sequences are located at the 5′ end of the transcription initiation site, and they define the direction of transcription and which strand of DNA is transcribed.

RNA polymerase and transcription factors form a transcription complex and bind to the promoter sequence. The complex unwinds the DNA and allows the RNA polymerase to transcribe a single strand of DNA to RNA [3–5]. Similar to DNA, RNA is composed of nucleotide bases, but RNA polymerase substitutes uracil (U) in RNA for thymine (T) moieties found in DNA. The RNA strand is transcribed in a 3′–5′ direction until it reaches a sequence in the DNA known as the termination sequence that enables the RNA polymerase to detach from the DNA.

The regulation of transcription is critically important as it temporally controls the initiation of transcription and the amount of RNA generated. Transcription of a gene can be regulated by transcription factors that can enhance or repress the gene expression. Enhancers are sites in the DNA helix where activators bind to enhance the interaction between RNA polymerase and a promoter. Enhancers increase the attraction of RNA polymerase for the promoter and/or change the structure of DNA to increase the expression of a gene. Repressors bind to the operator region, a sequence of DNA close to or overlapping the promoter region. The repressor acts to impede the RNA polymerase binding or the progress of transcription, which results in decreased or silenced gene expression. Enhancing or repressing gene expression is crucial to the maintenance of health; variations and abnormalities contribute to individual differences in gene expression and disease, respectively.

Introns and Exons

The initial transcription of DNA to RNA produces an unedited RNA molecule known as pre-RNA. Within the pre-RNA are sequences that code for proteins known as exons and noncoding sequences known as introns. Mature messenger RNA (mRNA) is produced from pre-RNA by splicing, which is the process of removing the noncoding intron sequences. The spliceosome is a complex of proteins and small RNA molecules which excise introns and join together adjacent exon sequences. While introns were previously thought to be useless (or "junk") sequences, ongoing research has revealed that introns harbor noncoding RNAs, which may have an important role in gene expression and allow for alternative splicing.

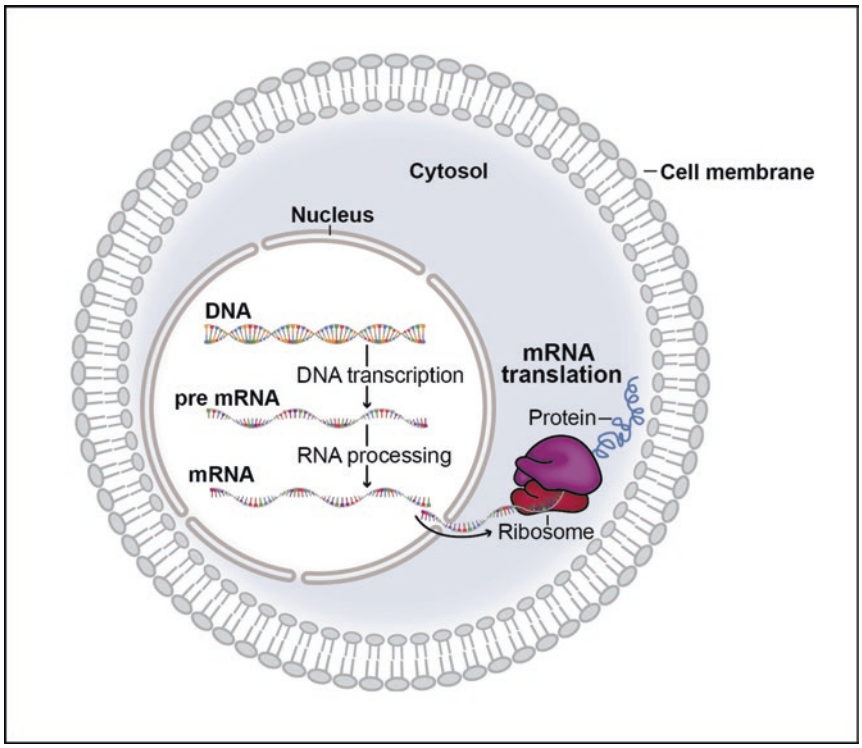

Fig. 3.2 Representation of the central dogma of biology. DNA is located within the nucleus of the cell and transcribed into pre-messenger RNA. The pre-messenger RNA is further processed into mature messenger RNA and, subsequently, is exported out of the nucleus into the cytosol. The messenger RNA is then translated into protein via the ribosome

Together, the spliced exons represent protein-coding messenger RNA. There are untranslated regions (UTRs)—sequences of mRNA that precede the start codon for protein translation and sequences that follow the stop codon that are not translated into protein. These regions are known as the five prime UTR (5′ UTR) and three prime UTR (3′ UTR) sequences, respectively.

UTR sequences are present in mature mRNA and promote mRNA stability. The mature mRNA also has a 5′ cap composed of a specifically altered guanine nucleotide and, at the 3′ end, a chain of adenine nucleotides known as the poly(A) tail. These additional modifications to the mature mRNA enable attachment of the ribosome for protein translation, transport of mRNA, and prevention of mRNA degradation. Subsequently, the mature mRNA is transported out of the nucleus and is translated to protein by ribosomes. The mRNA has protein information encoded by RNA sequences that are read by ribosomes in a grouping of nucleotide triplets termed codons. Each codon represents a specific amino acid and the specific sequence of amino acids is determined by the mRNA sequence.

MicroRNA-Mediated Gene Regulation

While molecular biology primarily focused on protein-encoding genes, recent discoveries of microRNAs (miRNAs) and noncoding RNAs have indicated that these sequences play important roles in the regulation of gene expression [6]. MicroRNAs are a recently identified class of short, noncoding RNAs that impact the regulation of gene expression at the posttranscriptional level. MicroRNAs are embedded within the introns of the pre-mRNA and frequently have similar expression profiles as the mRNA. MicroRNA genes are transcribed by RNA polymerase II as a large pri-microRNA with a hairpin loop (Fig. 3.3).

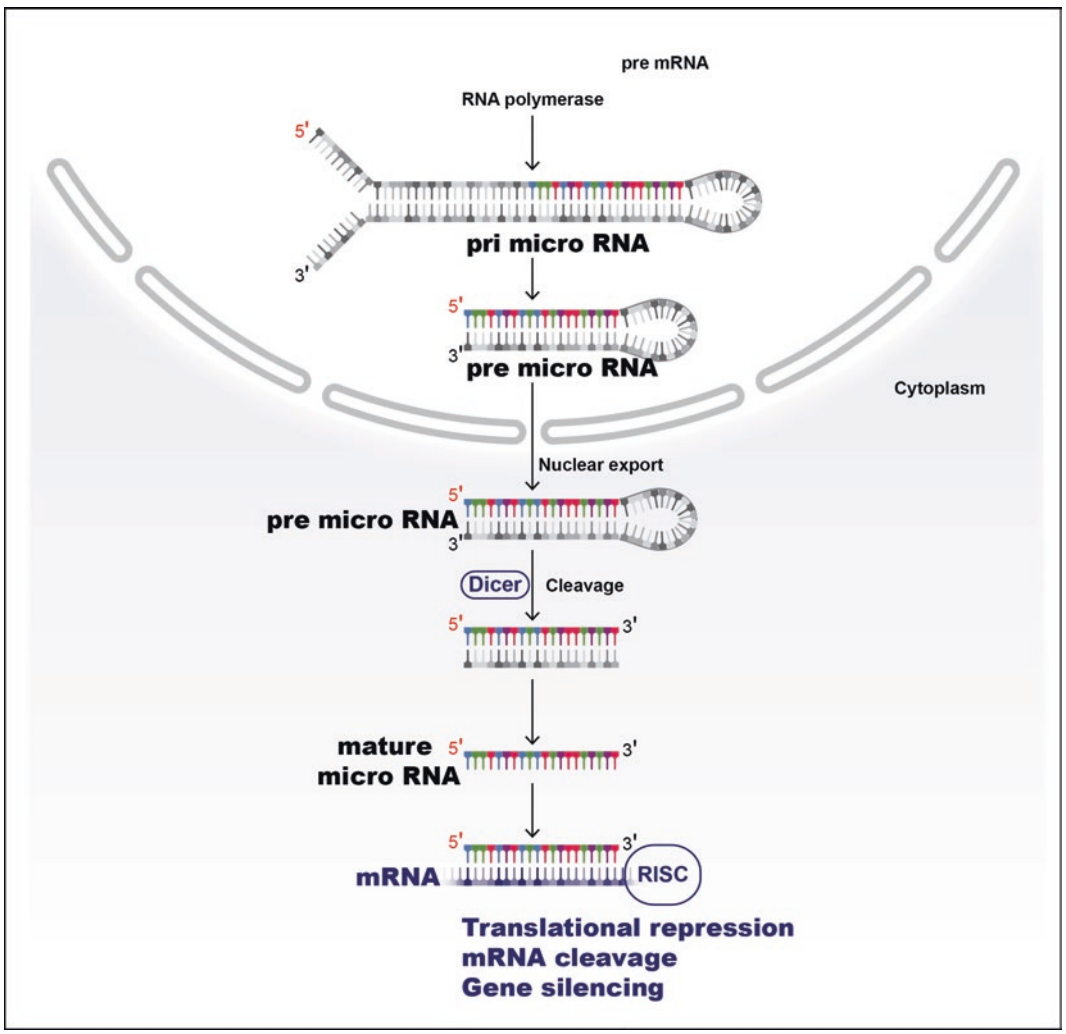

Fig. 3.3 MicroRNA biogenesis. The production of mature microRNA begins with production of the primary (pri)-microRNA transcript via RNA polymerase. The pri-microRNA is further processed to a short hairpin structure called pre-microRNA by the Drosha nuclease. The pre-microRNA is exported from the nucleus to the cytoplasm. In the cytoplasm, the pre-microRNA complexes with the RNase dicer, which cleaves the microRNA to its 21–23 nucleotide mature length. The functional single strand of mature microRNA interacts with the RNA-induced silencing complex (RISC) to guide mRNA cleavage, translational repression, and gene silencing

The pri-microRNA is further processed by an RNase III enzyme known as Drosha, which creates a smaller ~70 nucleotide precursor-microRNA (pre-microRNA). The pre-microRNA is transported to the cytoplasm where it interacts with dicer, another RNase II enzyme, which cleaves the hairpin to form a single-strand, mature microRNA of 21–25 nucleotides. Mature microRNA is incorporated into the RNA-induced silencing complex (RISC). MicroRNAs bind to the 3′ UTR of the target mRNA and form heteroduplexes with the target sequences.

The binding of the microRNA is mediated by the seed sequence, which is a 2- to 8-nucleotide sequence of the miRNA that recognizes the mRNA target and promotes binding [7]. The RISC mediates gene silencing via microRNA base pairing with complementary sequences in mRNA.Therefore, the mRNA can be silenced by either cleavage of mRNA, destabilization of mRNA, or less efficient translation to proteins.

The role of microRNAs in the heart has received intense interest and is hypothesized to play an important role in cardiovascular development or in response to stressful stimuli. Deletion of the microRNA processing *Dicer* gene in mice resulted in severe heart failure and premature death [8]. Similarly, inhibition of the microRNA miR-1, the most abundant microRNA in the heart, led to perturbed cardiac development [9].

Recent studies have also identified specific microRNAs that mediate changes in transcript expression in cardiovascular disease states. In a seminal study regarding microRNAs and cardiovascular disease, a group of stress-induced microRNAs were identified to be up- or downregulated in response to transverse aortic banding in a mouse model of cardiac hypertrophy [10]. These investigators also overexpressed microRNA miR-195, which was upregulated in hypertrophy, and were able to induce a heart failure state in animal models. MicroRNA profiling has also been conducted in various heart failure states and significant microRNA expression changes have been noted. Ikeda et al. have analyzed microRNAs in human left ventricular samples from patients with ischemic cardiomyopathy, dilated cardiomyopathy, and aortic stenosis [11]. These investigators detected 87 microRNAs that were differentially expressed, including the upregulation of the prohypertrophic miR-214 and the downregulation of the anti-hypertrophic miR-71–76 in dilated cardiomyopathy and aortic stenosis.

In another study of failing human left ventricular myocardium, investigators demonstrated an upregulation of microRNAs that reactivate the fetal gene program [12]. Thum et al. also demonstrated that the majority of microRNAs that are differentially expressed in the failing human heart are similar to those expressed in fetal cardiac tissue, further suggesting a role for microRNAs in the reactivation of the fetal gene program during ventricular remodeling [13]. Further studies focused on microRNA expression, and regulation may enhance our understanding about the identification of microRNA targets and their impact on prognosis and treatment of cardiovascular disease.

Epigenetic Regulation

While gene regulation can be impacted by a number of genetic factors at the transcriptional and translational level, epigenetic regulation involves heritable changes in gene expression without alterations in the DNA sequence that occurs in response to a stimulus. Two major mechanisms of epigenetic regulation involve chromatin remodeling and DNA methylation. Chromatin is a complex of DNA wound around histone proteins. It is the chromatin that forms chromosomes.

First, histones can be posttranslationally modified through methylation and acetylation. The modified histones assume a different configuration and impact the means by which DNA wraps around the histones. Therefore, DNA may be more or less available for transcription, and this epigenetic modification alters the expression of the resultant gene. Second, epigenetic regulation can occur through the methylation of DNA at cytosine bases by DNA methyltransferases. The DNA methyltransferases convert cytosine to 5-methylcytosine. Methylated DNA serves as a docking site for methyl-binding proteins that oligomerize through DNA to recruit chromatin-remodeling complexes. This results in chromatin being less available for transcription, leading to a reduction in gene expression.

Epigenetic inheritance is a mechanism that allows for stable propagation of gene activity states from one generation of cells to the next. It is associated with the differentiation of immature cells in disease states. For example, somatic cells may have an epigenetic mark that restricts expression of genes involved in self-renewal or pluripotency, thus resulting in the terminal differentiation of the cell. These epigenetic mechanisms were apparent in the cloning of the sheep, Dolly (1996) [14]. Here, the nucleus from a differentiated cell was delivered into an enucleated unfertilized oocyte to clone a sheep.

While geneticists were ultimately successful in the cloning of a sheep, the process of somatic cell nuclear transfer (SCNT; also referred to as cloning) was very inefficient. The research investigators identified that, while the nucleus of the differentiated cell contained the DNA necessary to engineer an entire sheep, it was not easy to revert a fully differentiated nucleus into a pluripotent state. This strategy demonstrated the importance of epigenetic regulation in cell differentiation, which resulted in heritable changes that restricted gene expression patterns and defined cell identify.

While these epigenetic marks are stable, the recent discovery of human-induced pluripotent stem cells establishes the capacity of adult somatic cells (i.e., skin cells from an adult) to revert or reprogram the epigenome of the cell to a more pluripotent state when it is exposed to a cocktail of transcription factors [15–17]. Additionally, Ieda et al. showed that cardiac developmental transcription factors could be used to directly reprogram dermal fibroblasts into differentiated cardiac-like cells, which resulted in an epigenetic shift of cardiac genes [18].

While the epigenome may be able to be reprogrammed to allow for a more pluripotent state, somatic cells may have

epigenetic memory, which results in a preference for differentiation to their original cell lineage. Sanchez-Freire et al. derived human-induced pluripotent stem cells from both skin fibroblasts and cardiac progenitor cells and demonstrated that human-induced pluripotent stem cells derived from cardiac progenitor cells differentiated more efficiently into cardiomyocytes [19]. Also, the dermal fibroblast-derived human inducible pluripotent stem cells had increased methylation of the *Nkx2-5* gene, which is a critical factor in cardiac development.

Epigenetics may also play an important role in cardiovascular disease development, especially the heart failure state. Movassagh et al. identified three genes having a role in angiogenesis, which were differentially methylated in human heart failure regardless of etiology [20]. Kaneda et al. also identified differential histone modifications associated with human heart failure that impacted significant cardiac signaling pathways [21]. Further understanding of epigenetic regulation in cardiovascular disease may provide important mechanistic insights into environmental stimuli, the development of disease states, and may serve as candidates for novel therapies.

Genomic Approaches to Cardiovascular Disease and Heart Failure

Molecular medicine began with the identification of the structure of DNA in 1953. Nearly 50 years later, in 2001, the sequence analysis of the entire human DNA truly heralded the genomics era. A genomics approach to studying cardiovascular disease requires screening all the genes and gene variants associated with a particular disease state across the human genome. New sequencing technologies have accelerated this approach by making genome sequencing feasible, representing an important advance in further elucidating cardiovascular diseases.

The Human Genome Project began in 1990 as an international collaboration with the monumental goal of decoding the entire human genome, the sum of the genetic material of a human being. The human genome is encoded on 46 chromosomes (23 pairs) consisting of 3.2 billion base pairs of DNA. Molecular biologists and scientists working for the Human Genome Project sequenced the 3.2 billion base pairs in the human genome. Not only did they identify the sequence but also the location of the sequences of DNA on each chromosome and the linkage maps to evaluate genes.

In 2001, Human Genome Project biologists and scientists published a working draft of the human genome [22], and, in 2003, the full human genome was sequenced. The project identified the approximately 20,500 genes in the human genome, which were fewer than the initial prediction of 50,000–100,000 genes. Additionally, the Human Genome Project has spurred identification of specific genes that lead to disease states and pharmacologic therapies specific to genetic mutations. For example, PCSK9 was identified as a gene and a mutation resulted in an autosomal dominant variant of familial hypercholesterolemia [23]. This discovery was made shortly after the human genome was sequenced. Novel pharmacotherapies have been developed to inhibit PCSK9 and have been tested in several clinical trials [24–26].

Not only has the Human Genome Project resulted in identification of disease-causing genes, but emerging technologies have increased the efficiency of genome sequencing. While the initial human genome took more than 10 years to sequence, at a cost of several billion dollars, today, sequencing an individual's genome can be completed in several days at a cost of less than $8000. Decoding the human genome has proven to be a major advance in genomics, but the real challenge resides in understanding how the sequences of DNA impact human health and disease.

Exome Sequence Analysis

The exome constitutes the protein-coding fraction of the genome—about 1 % of the total human genome. While it represents a relatively small subset of the entire genome, the exome is predicted to harbor up to 85 % of disease-associated mutations [27]. Whole-exome sequence analysis requires the selection of the exome portion of the genome and subsequent high-throughput DNA sequencing. Therefore, whole-exome sequence analysis represents a realistic and cost-effective technique to identify genetic variations that cause genetic and common diseases. Whole-exome sequence analysis has been used to identify novel mutations for patients with familial cardiomyopathy who tested negative on routine genetic testing [28, 29]. Importantly, exome sequence analysis does not include the analysis of introns.

GWAS and SNP Analysis

A genome-wide association study (GWAS) evaluates a large number of genetic variants to identify associations between specific genetic variants and complex human diseases. The study requires screening a large number of patients affected by a specific disease state, such as non-ischemic cardiomyopathy, and searching for alleles that are more frequently found in affected patients than in healthy individuals. Typically, GWAS focuses on identifying allelic variants known as single nucleotide polymorphisms (SNPs). GWAS relies on data from the Human Genome Project, International HapMap Project, and SNP Consortium, which have identified millions of SNPs [30].

Large genome-wide association studies have identified a significant amount of alleles associated with cardiovascular disease, largely focused on coronary artery disease [31]. Relatively fewer studies have focused on heart failure, but several loci associated with heart failure have been identified. Among these, variations in the *BAG3* and *HSPB7* genes were

found to be associated with dilated cardiomyopathies [32]. Larson et al. performed a GWAS to investigate their association of heart failure in the Framingham Heart Study and identified an SNP, rs939398, which maps to the ryanodine receptor gene and is associated with heart failure [33]. Genome-wide association studies, while useful, have a number of limitations including the need for large sample sizes and the lack of identification of causative genes responsible for disease.

Molecular Signaling in the Normal and Failing Heart

Genetics play a significant role in human cardiovascular disease; however, intracellular signaling pathways play a central role in regulating cardiac function. Adaptations in the signaling pathways in response to stressors can be adaptive, but can also lead to disease states. An enhanced understanding of the normal signaling pathways and the alterations in the pathways that lead to cardiac remodeling and heart failure at the cellular level is critical to elucidating molecular mechanisms and the development of new therapies.

Beta-Adrenergic Signaling

β-adrenergic receptors are members of the G-protein-coupled receptor (GPCR) superfamily and serve as a link between the cardiovascular and sympathetic nervous system. β-adrenergic receptors regulate cardiac contractility, heart rate, and automaticity.

Two major subclasses of β-adrenergic receptors (β1 and β2) exist in the heart, of which the β1-receptor is predominant in the normal, unperturbed adult heart. Stimulation of the β-adrenergic receptors by catecholamines, such as norepinephrine or epinephrine, results in the activation of the stimulatory G-protein (Gs) and adenylate cyclase (AC) signaling pathway, which results in increased cyclic AMP (cAMP) (Fig. 3.4a) [34].

The primary target for cAMP is protein kinase A (PKA). PKA phosphorylates' key downstream targets include voltage-gated calcium channels, sarco-/endoplasmic reticulum (SR) calcium transport ATPase (SERCA), troponin I, ryanodine receptors, and phospholamban. Phosphorylation of these proteins leads to increased cardiac inotropy and chronotropy through the increase of calcium influx via the voltage-gated calcium channel, increased calcium reuptake into the sarcoplasmic reticulum via SERCA, and the modulation of cardiac sarcomeric calcium sensitivity via troponin (Fig. 3.4a).

In the failing heart, circulating catecholamines increase in response to increased sympathetic activity. Initially, heightened sympathetic activity is adaptive in boosting cardiac output through increased inotropy and chronotropy. But chronic catecholamine activation can lead to a loss of contractility. In the failing human heart, β1-adrenergic receptors are selectively downregulated and desensitized in an attempt to protect the heart from deleterious signaling due to chronic catecholamine stimulation. Both β1- and β2-adrenergic receptors become uncoupled from the signaling pathways secondary to β1-downregulation, but also, more specifically, due to desensitization via phosphorylation of β-adrenergic receptors by specific kinases, such as GRK family kinases.

A family of inhibitory proteins, β-arrestins, also bind to phosphorylated proteins and prevent activation of G-proteins. This leads to sequestration of β-receptors, internalization, and eventual lysosomal degradation (Fig. 3.4b). The consequence of β-adrenergic downregulation and desensitization is that, for a given level of adrenergic stimulation, less cAMP is produced. This, in turn, leads to decreased activation of PKA, causing decreased downstream effectors.

β-adrenergic receptor blockers are now a standard treatment in heart failure. Multiple trials have shown a significant mortality benefit from β-blockers in heart failure patients (US Carvedilol Heart Failure Study, MERIT-HF, etc.) [52–54]. β-adrenergic blockers can lead to prevention of chronic β-adrenergic stimulation and result in both upregulation of β-adrenergic receptors and resensitization of the receptor.

Calcineurin and CaMK Signaling Pathways

Calcium is a major second messenger in cardiac signaling and has the ability to activate multiple signaling cascades, including the calcineurin and calcium/calmodulin-dependent kinase (CaMK) pathways. Calcineurin, a serine/threonine phosphatase, is activated by binding to calcium-bound calmodulin (Fig. 3.5). It results in dephosphorylation of nuclear factor of activated T cells (NFAT), enabling NFAT to translocate into the nucleus.

Activation of NFAT leads to activation of the myocardial hypertrophy gene pathways via association with a number of transcription factors, including GATA4 and MEF2C. Calcineurin has been implicated in physiological and pathological cardiac hypertrophy and shown to be upregulated in heart failure where it promotes hypertrophy and apoptosis.

CaMK is a family of regulatory enzymes that phosphorylate a number of proteins that modulate cardiac contractility and hypertrophy. CaMKs are autophosphorylated in the presence of increased intracellular calcium. CaMKII is the predominant cardiac isoform, which modulates hypertrophy, contractility, and cell survival via activation of the transcription factor MEF2C results in the activation of the fetal gene program and cardiac hypertrophy. CaMKII is noted to be increased at the transcriptional level, protein level, and during enzymatic activity in the heart failure state [35]. Similar to the impact of calcineurin signaling in heart failure, CaMKII activation can lead to apoptosis and cell death.

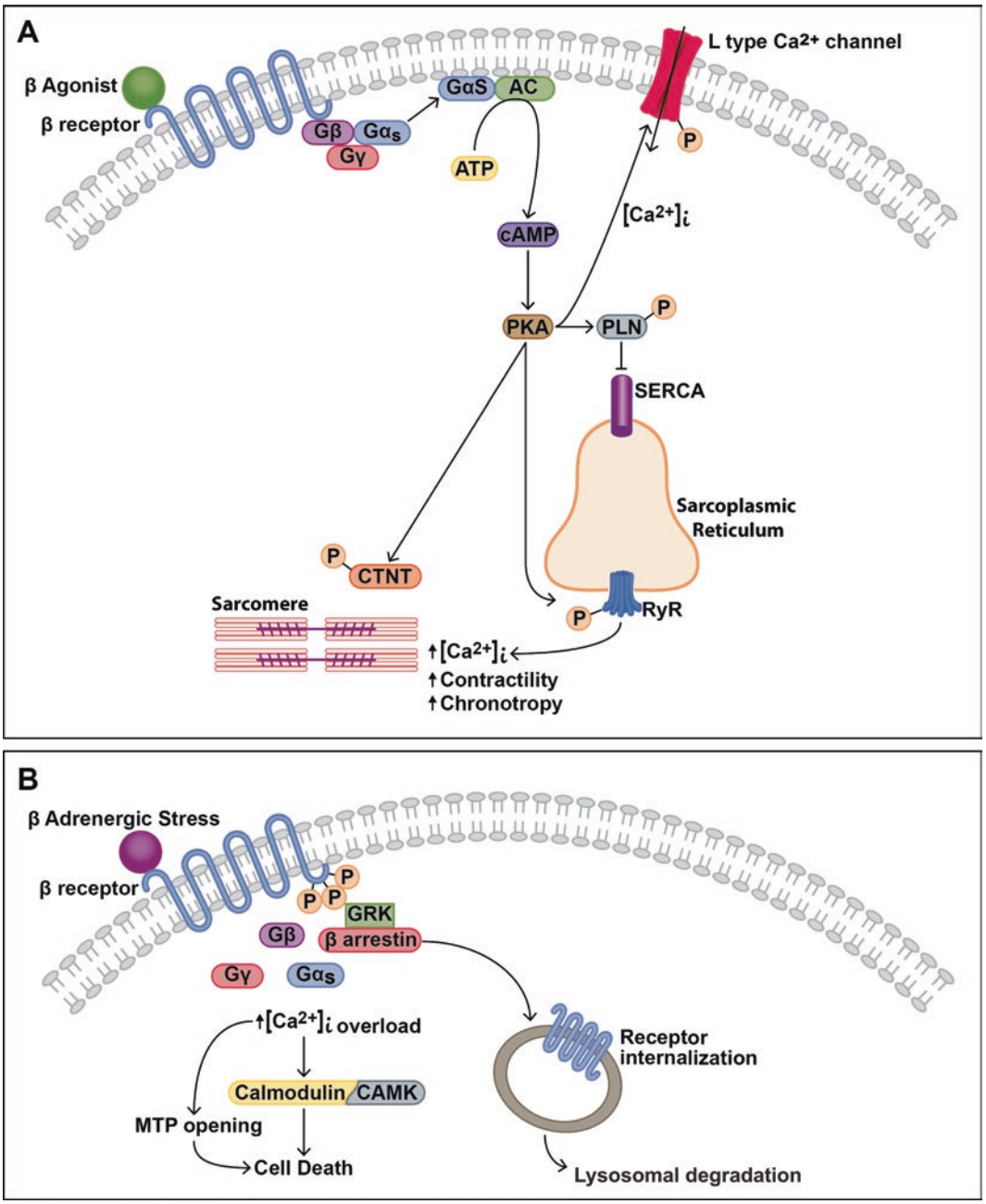

Fig. 3.4 β-adrenergic signaling pathway. (**a**) β-agonist catecholamines bind to the β_1 receptor at the cell membrane. This activates $G_{\alpha s}$, which disassociates from Gβ and Gγ, and associates with adenyl cyclase (AC). This leads to the generation of cyclic AMP (cAMP), which in turn activates protein kinase A (PKA). PKA phosphorylates several effector proteins including phospholamban, ryanodine receptor (RYR), voltage-gated L-type calcium channel, and cardiac troponin T (cTNT). These changes lead to increased intracellular calcium, which translates to increased contractility and chronotropy. (**b**) Chronic β-adrenergic stimulation in heart failure. Chronic β-adrenergic stimulation of cardiomyocytes results in GRK-mediated phosphorylation of the β-adrenergic receptor as well as recruitment of β-arrestin. The inhibitory β-arrestin binding to the β-adrenergic receptor leads to sequestration of the receptor, internalization, and eventual lysosomal degradation. Additionally, chronic β-adrenergic stimulation leads to increased intracellular calcium concentrations, which in turn stimulates the calmodulin-CaMKII pathway. Ultimately, this leads to mitochondrial transition pore opening and eventual cell death

MAPK Signaling Pathways

The mitogen-activated protein kinase (MAPK) cascade consists of a series of successively activated protein kinases (Fig. 3.6). The three major MAPK branches include the extracellular signal regulated kinases (ERKs), c-Jun N-terminal kinases (JNKs), and p38 MAPKs. Mitogenic stimuli and stresses lead to activation of the MAPK signaling cascade via activated G-protein-coupled receptors (GPRCs). The activated Gαq protein activates small G-proteins such as Ras directly via the released Gβγ-subunits, which are activated by growth factors such as EGF, FGF, IGF-1, and TGFβ.

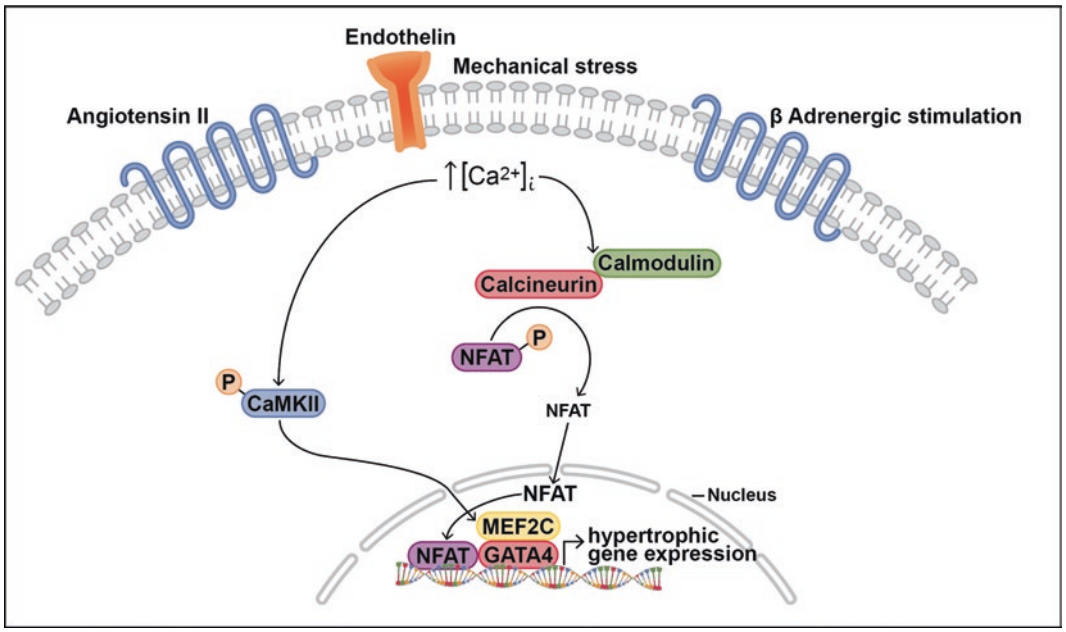

Fig. 3.5 Calcineurin and CaMK signaling pathway. Extracellular stimuli that increase intracellular calcium levels result in saturation of calmodulin. Calmodulin binds calcineurin, which leads to activation of calcineurin. Calcineurin dephosphorylates the transcription factor NFAT, which can then translocate into the nucleus. Nuclear NFAT leads to hypertrophic gene expression. Similarly, an increase in intracellular calcium levels also leads to activation of CaMK. CaMKII phosphorylates histone deacetylases, which leads to subsequent derepression of hypertrophic gene expression

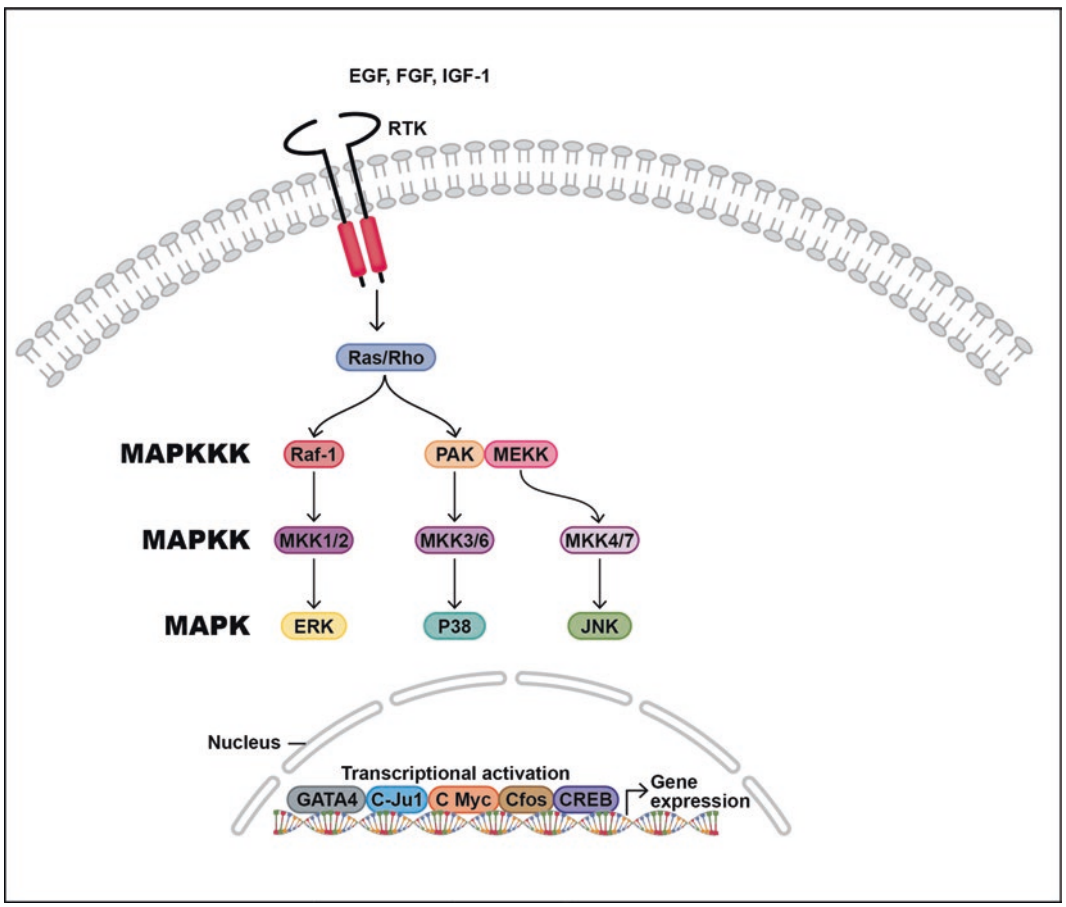

Fig. 3.6 Mitogen-activated protein kinase (MAPK) signaling pathway. The receptor tyrosine kinase (RTK) is activated by the binding of ligands such as fibroblast growth factor, insulin-like growth factor-1, and epidermal growth factor. The activated RTK leads to activation of the GTPase proteins such as Ras and Rho. The activated GTPases stimulate the MAPK signaling cascade. The MAPK cascade is organized into three tiers including MAPKkinase kinase kinase (MAPKKKs) which then activate MAPKinase kinases (MAPKKs) and subsequently activate MAPKinases, which include ERK, p38, and JNK. The activated MAPK can translocate into the nucleus and lead to transcriptional activation of genes including GATA4, C-Jun1, C-myc, C-fos, and CREB

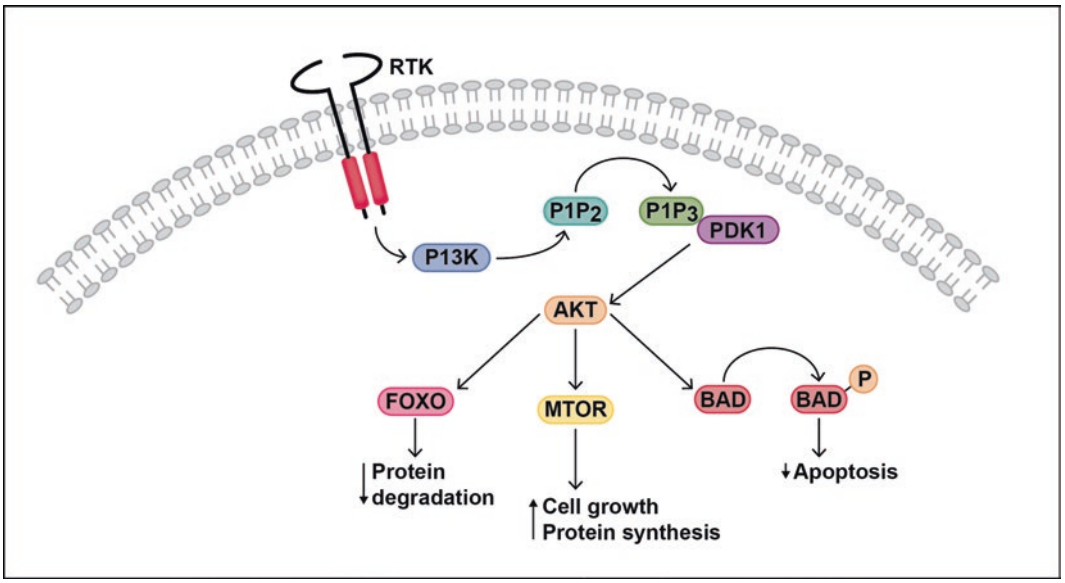

Fig. 3.7 Phosphoinositide 3-kinases (PI3K)-Akt pathway. PI3K can be activated through the binding of various extracellular stimuli that activate receptor tyrosine kinases (RTKs), which then activate PI3K. The activated PI3K forms the second messenger phosphatidylinositol (3,4,5) trisphosphate (PIP_3) by binding and phosphorylating PIP_2 at the cell membrane. PIP_3 in association with PDK1 leads to activation of Akt. Akt, which is a serine/threonine kinase, can phosphorylate many downstream targets, including those involved in apoptosis, cardiac survival, and protein translation. Akt can activate the mammalian target of rapamycin (mTOR), which leads to increased protein synthesis of cytoskeleton and sarcomeric proteins at the ribosomal level to promote cardiomyocyte hypertrophy. Akt can also suppress protein degradation by downregulation of the FoxO (*forkhead*/winged helix) transcription factor family, which leads to decreased protein degradation by the ubiquitin-proteosome system. Akt also has antiapoptotic effects through the phosphorylation of Bad (a proapoptotic protein) and prevention of apoptosis by caspases

The initial MAPK pathway leads to activation of MAPK kinase kinase (MAPKKK), resulting in sequential activation of MAPKK and then effector MAPK kinases (ERK), c-Jun N-terminal kinases (JNKs), and p38. The activated MAPKs are able to phosphorylate transcription factors that have the ability to regulate cardiac gene expression, including hypertrophy and cell survival.

In heart failure, the role of MAPK pathways in the progression of disease is complex due to the intersection and overlap of pathways. However, MAPK pathway activation is known to occur in heart failure, and the p38 and JNK pathways are hypothesized to contribute to pathological remodeling in heart failure [36].

PI3K/Akt Signaling Pathways

Phosphoinositide 3 kinase (PI3K) and protein kinase B (PKB), which is also known as Akt, are key signaling pathways in cardiac growth and cell survival. PI3K can be activated through various stimuli including insulin, insulin-like growth factor-1, cardiotrophin, β-adrenergic agonists, ischemia, and pressure overload (Fig. 3.7). The activated PI3K forms the second messenger phosphatidylinositol [3,4,5] trisphosphate (PIP_3) by binding and phosphorylating PIP_2 at the cell membrane.

PIP_3 in association with PDK1 leads to activation of Akt. Akt, which is a serine/threonine kinase, can phosphorylate a number of downstream targets, including those involved in apoptosis, cardiac survival, and protein translation. Akt can activate the mammalian target of rapamycin (mTOR), which leads to increased protein synthesis of cytoskeleton and sarcomeric proteins at the ribosomal level to promote cardiomyocyte hypertrophy. Akt can also suppress protein degradation by downregulation of the FoxO (*forkhead*/winged helix) transcription factor family, which leads to decreased protein degradation by the ubiquitin-proteasome system. Akt also has antiapoptotic effects through the phosphorylation of Bad (a proapoptotic protein) and prevention of apoptosis by caspases. Given the complexity of the PI3K/Akt pathway, its specific role in heart failure is transient and is dependent on pathological versus adaptive hypertrophy and specific activation or repression of downstream effectors.

G-Protein-Coupled Pathways

Guanosine nucleotide-binding proteins or G-proteins are a family of proteins that transduces extracellular stimuli and functions as molecular switches. The proteins play a critical role in cardiac homeostasis. G-protein-coupled receptors (GPCRs) are located at the cell membrane and consist of seven transmembrane-spanning domains.

GPCRs are activated by various ligands including epinephrine and hormones. G-proteins are bound to the intra-

cellular portion of the GPCR and consist of three subunits: Gα, Gβ, and Gγ. In the unstimulated state, Gα is bound to GDP. When the GPCR is stimulated by a signaling ligand, it promotes a conformational change in the GPCR and activation of the G-protein complex. The Gα subunit becomes bound with GTP in its active state and dissociates from the Gβγ-protein subunits. Activation of the G-protein can lead to production of second messengers including cAMP, diacylglycerol (DAG), and inositol 1,4,5 trisphosphate (IP3) via interaction with adenylyl cyclase and phospholipase C, respectively. Subsequently, the second messengers can interact and modulate a number of downstream signaling pathways. The G-protein becomes inactivated through GTPase which hydrolyses GTP to GDP.

Four major G-protein families are based on the α subunits: Gs, Gi, Gq/11, and Gα12/13. The Gs class activates adenylyl cyclase and can modulate increases in cardiac contractility. The Gi class is comprised of inhibitory G-proteins that decrease agonist-stimulated cAMP. Gq subunits activate phospholipase C, leading to production of IP3 and DAG, which promotes release of calcium from the sarcoplasmic reticulum. It also activates calcineurin and CaMK signaling pathways. Gα12/13 signals via small G-protein Rho and regulates cellular growth and cytoskeletal changes.

GPCRs can be desensitized via persistent agonist stimulation and have a critical role in signaling to attenuate stimulus response. Three regulatory proteins are involved in GPCR desensitization, including protein kinases A and C, G-protein-coupled kinases (GRKs), and arrestins. Activated PKA and PKC participate in a feedback regulation loop where they phosphorylate the GPRC and uncouple it from the G-protein. GRKs phosphorylate the receptor in an agonist-dependent manner. Subsequently, arrestins displace the receptor from the GPRC, resulting in receptor downregulation and receptor internalization.

Adrenergic receptors and angiotensin receptors are major GPCRs that have a functional role in heart failure and are current targets of standard heart failure therapy. The β-adrenergic receptor downregulation in heart failure occurs via GPCR modulation. GPCR pathways also interact with a number of other cardiac signaling pathways to produce the cellular responses seen in heart failure.

TGF-β-Signaling Pathway

The transforming growth factor β (TGF-β)-signaling pathway is critically important in cardiac signaling and governs inflammation, extracellular matrix deposition, cell proliferation, differentiation, and growth. TGF-β binds to TGF-β type II receptor, a serine/threonine receptor kinase, and phosphorylates the TGF-β type I receptor, leading to a hetero-tetrameric complex with the TGF-β. The activated complex phosphorylates the cytoplasmic signaling molecules, Smad2 and Smad3 (Fig. 3.8). Smad2/3 partners with Smad4 and translocates into the nucleus. The activated Smad complex binds a variety

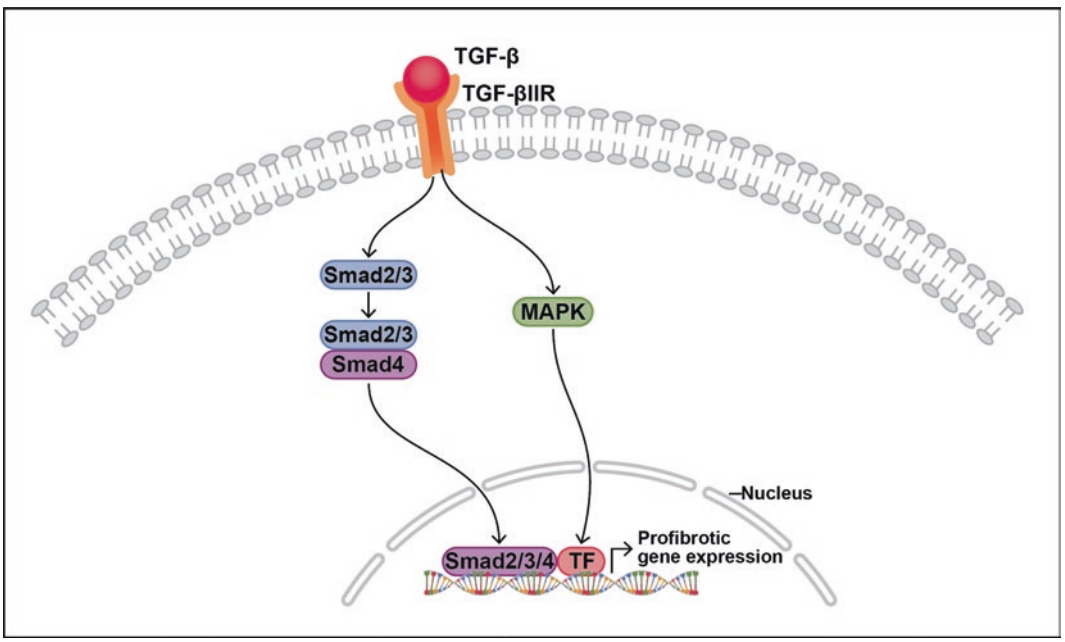

Fig. 3.8 TGF beta pathway. TGF-β binds to TGF-β type II receptor, a serine/threonine receptor kinase and phosphorylates the TGF-β type I receptor, leading to hetero-tetrameric complex with the TGF-β. The activated complex phosphorylates the cytoplasmic signaling molecules, Smad2 and Smad3. The Smad2 and 3 partners with Smad4 and translocates into the nucleus. The activated Smad complex binds a variety of transcription factors that promote profibrotic gene expression. TGF-β can also affect Smad-independent pathways including Erk, JNK, and p38 MAPK pathways

of transcription factors. TGF-β can also affect Smad-independent pathways including Erk, JNK, and p38 MAPK.

TGF-β has known profibrotic and hypertrophic effects and is released in response to various stresses. TGF-β is known to be elevated in patients with heart failure and induces the expression of extracellular matrix components by cardiac fibroblasts. Ultimately, this leads to cardiac fibrosis, remodeling, and progression of heart failure.

Cell Cycle Regulation

The cell cycle is a highly regulated process that enables cellular division and replication. The cell cycle is divided into three periods: interphase, a relatively long period where the cell prepares for cell division; the mitotic phase, where cell division occurs; and cytokinesis (or the completion of cell division). Regulation of the cell cycle plays an important role in cellular health and development of disease states.

The cell cycle consists of four phases: S, M, G1, and G2. The two most critical are the S phase, during which time chromosomes replicate, and the M phase, or mitosis phase, when the chromosomes separate and the cell divides into two daughter cells containing the full complement of hereditary material (Fig. 3.9).

The S and M phases are separated by the gap phases, G1 and G2. G1 represents the gap phase after mitosis, during which time the cell prepares for DNA replication in response to cellular growth signals. The G2 phase occurs after chromosomal replication in the S phase and allows preparation for mitosis. Mitosis is a relatively short phase characterized by condensed chromatin, which forms the visible mitotic spindle apparatus. Once the mitotic spindle is formed, the microtubule-based spindle promotes the segregation of the duplicated chromosomes and cell division into two daughter cells.

Cyclins and CDKs

Regulation of the cell cycle is governed by the cyclin-dependent kinases (CDKs), which are serine/threonine protein kinases, and the cyclins, which are regulatory subunits. The CDK-cyclin complexes regulate the four phases of the cell cycle. The G1 phase is mediated by cyclin D-CDK4 and cyclin D-CDK6 complexes, which are produced in response to growth factors. The cyclin D-CKD complexes phosphorylate and partially inactivate retinoblastoma tumor suppressor protein (Rb) and induce expression of cyclin E. Cyclin E complexes with CDK2, and further inactivates Rb, which pushes the cell from the G1 to the S phase.

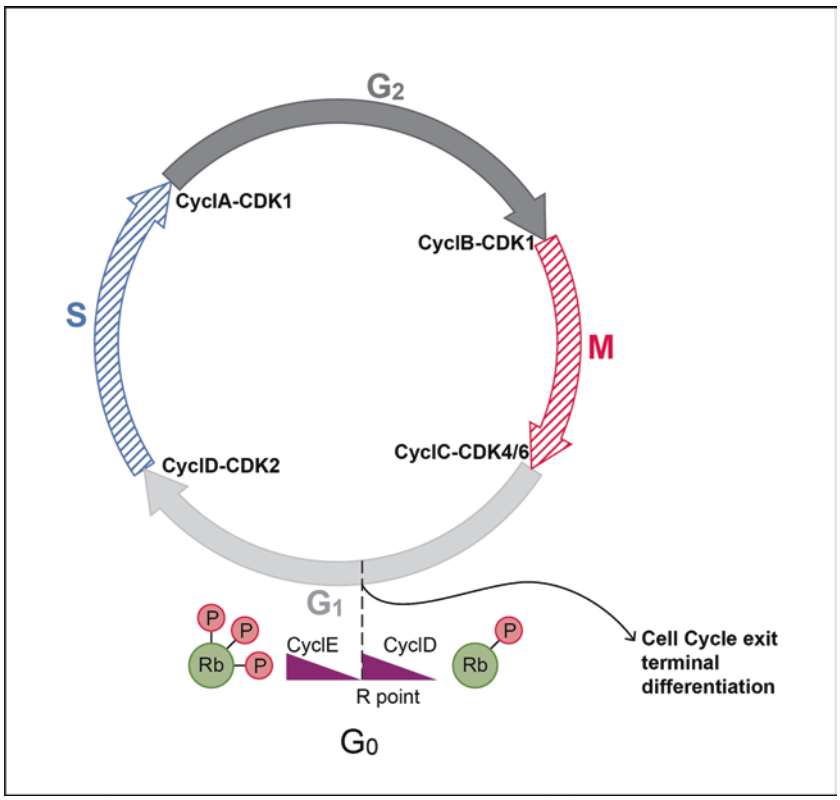

Fig. 3.9 The cell cycle. The phases of the cell cycle include G_1, S, G_2, and M, which each has unique cyclin-CDK complexes that mediate the transition from one phase to the next. The cyclin D (CycID) CDK 4/6 complex promotes inactivation of the retinoblastoma tumor suppressor protein (Rb). Rb inactivation leads to activation of cyclin E-CKD2 which promotes transition from G1 to S phase, which corresponds to DNA replication. Cyclin A-CKD1 promotes transition to the G2 phase and cyclin B-CKD1 promotes transition to the mitosis or M phase. The restriction (R) point is where cells can exit the cell cycle. Exiting of the cell cycle leads to terminal differentiation of cells, such as cardiomyocytes

Cyclin A-CDK1/2 complexes are activated during the later stages of DNA replication to promote progression through the S phase. They phosphorylate the pre-replication complexes to prevent the formation of new complexes. This ensures that the cell's genome is replicated only once.

Cyclin B-CDK1 triggers the transition from the G2 phase into mitosis and stimulates proteins involved in the mitotic spindle assembly, as well as the breakdown of the nuclear membrane. During mitosis, the anaphase-promoting complex (APC), a ubiquitin ligase, is activated. The APC targets cyclins for destruction, ensuring cell division can proceed. Inhibitors of the cyclin-CDK complex are known as the cyclin-dependent kinase inhibitors (CKIs). CKIs are expressed in the G1 phase to inhibit cyclin-CDK activation, which prevents progression through the G1 checkpoint. The CKIs are another regulatory mechanism to prevent cells with DNA defects from being propagated; they are known as tumor suppressor proteins.

Surveillance mechanisms known as checkpoints also serve to monitor and control cell cycle progression to ensure the correct order of events. The G1/S and G2/M checkpoints are designed to ensure that damaged or incompletely synthesized DNA is not passed to the daughter cell. The G1/S phase transition is the rate-limiting step in the cell cycle and is known as the restriction point. Terminally differentiated cells typically stop the cell cycle at this point and enter the resting or Go phase.

Cell Cycle Reentry

In humans, cardiomyocyte proliferation is critical during embryonic development, but shortly after birth, cardiomyocytes lose their ability to proliferate and heart growth becomes dependent on hypertrophy. As terminally differentiated cells, cardiomyocytes were thought to not reenter the cell cycle. However, there is evidence that adult cardiomyocytes continue to divide in vivo.

Bergmann et al. evaluated ^{14}C in cardiomyocytes in cardiac samples of patients who were alive during aboveground nuclear bomb testing (1952–1963). These nuclear tests led to the release (or pulse) of ^{14}C, which was incorporated into plants and animals and subsequently the diet of humans. In this fashion, the ^{14}C was incorporated into the DNA and served as an "indication of the cell's birth date."

Rigorous analysis revealed that about 1 % cardiomyocyte turnover took place by the human age of 20, which decreased to 0.3 % after the age of 75 [37]. While endogenous cardiomyocyte regeneration occurs at low levels and is unlikely to compensate for cell death due to myocardial infarction, stimulation of cardiomyocytes to reenter the cell cycle may allow for increased cardiac regeneration.

While the mechanisms of cardiac regeneration through cardiomyocyte proliferation are not yet known, intense investigation has identified several factors that may regulate the cell cycle of cardiomyocytes. Recently, Meis1 was identified as a transcription factor that regulates the cardiomyocyte cell cycle. Deleting Meis1 in adult mouse cardiomyocytes promoted cell cycle reentry and proliferation [38]. Similarly, microRNAs, including microRNA-590 and microRNA-199a, have also been shown to promote adult cardiomyocyte proliferation [39]. Further investigation into the mechanisms of cardiomyocyte cell cycle reentry will provide a platform for new therapies aimed at the promotion of cardiomyocyte renewal after cardiac injury.

Mechanisms of Cell Death

In response to injury, a series of molecular, cellular, and physiologic changes occur that lead to a heart failure state marked by chamber dilation and a decrease in systolic function. Ultimately, cardiomyocytes are lost through apoptosis, necrosis, or autophagy [40, 41].

Necrosis

Necrosis is a form of cell death that occurs in response to cell injury such as ischemia or toxins. It results in unregulated, irreversible autolysis, or digestion of cellular components, leading to cell death. Morphologically, there is loss of plasma membrane integrity and cellular edema. Significant adenosine triphosphate (ATP) also is depleted due to mitochondrial dysfunction. Ultimately, these processes lead to the loss of cellular homeostasis and cell death.

The release of cellular components into the interstitial space also results in inflammatory response. Necrosis is commonly seen in response to ischemia due to myocardial infarction, but cardiomyocyte necrosis has also been shown to contribute to heart failure [42].

Apoptosis

In contrast to necrosis, apoptosis is a programmed cell death pathway that is highly regulated. Morphologically, apoptotic cells appear shrunken due to cytoplasmic shrinkage and demonstrate plasma membrane blebbing, nuclear condensation, and fragmentation of the nucleus and cytoplasm in membrane-enclosed apoptotic bodies [42] (Fig. 3.10). The apoptotic bodies are phagocytosed by macrophages and, therefore, lack an inflammatory response seen in necrosis.

The trigger to initiate apoptosis can occur within the cell, such as oxidative stress, DNA damage, misfolded proteins, or through external stressors. Once apoptosis is triggered, it is mediated by the extrinsic and intrinsic pathways, with the ultimate goal of activating caspases (Fig. 3.11). Caspases

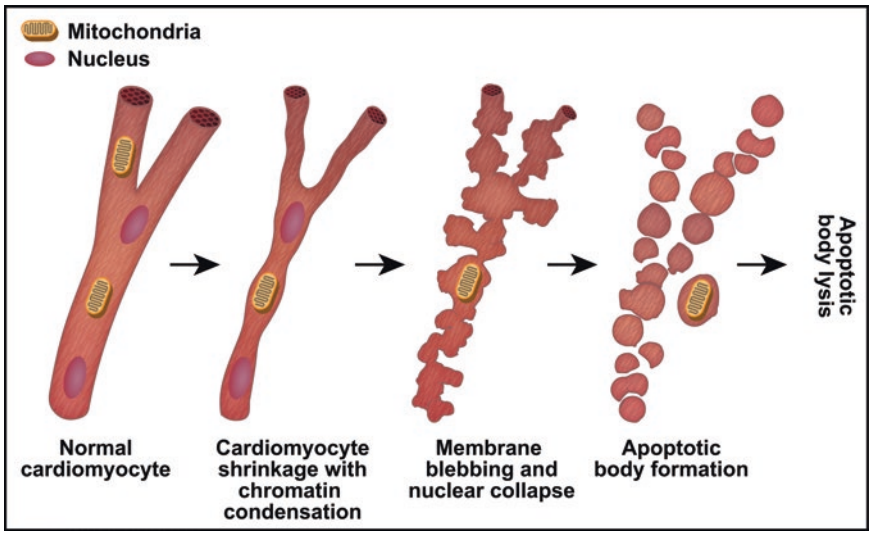

Fig. 3.10 Apoptosis results in programmed cell death. Apoptosis can be triggered by intrinsic or extrinsic stimuli and results in the shrinkage of the cytoplasm and condensation of chromatin. Subsequently, there is plasma membrane blebbing and loss of the nucleus. Ultimately, the cytoplasm and nucleus are fragmented and enclosed in apoptotic bodies, which are later phagocytosed by macrophages to avoid an inflammatory response

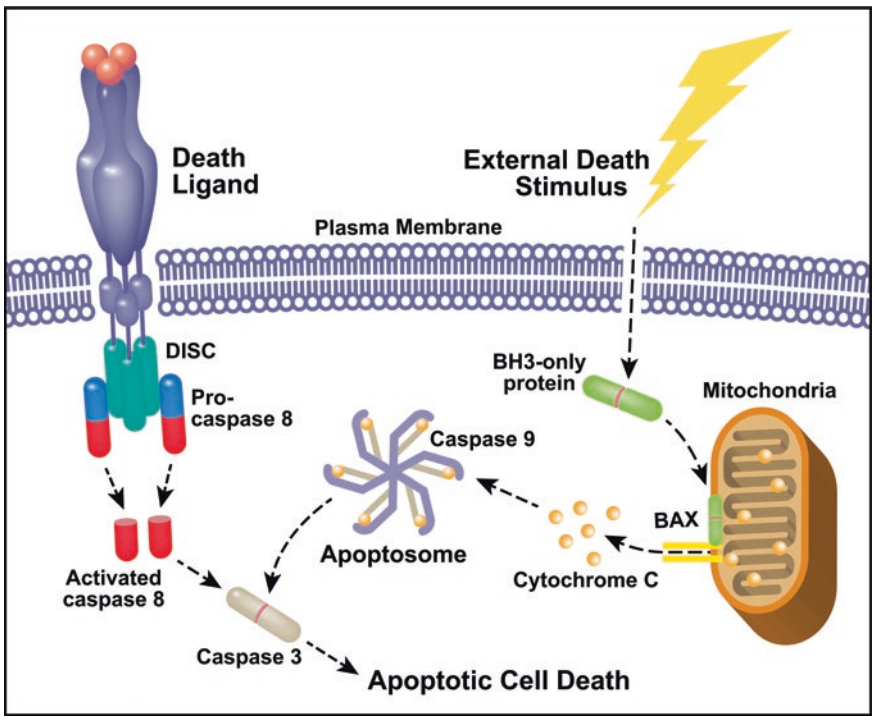

Fig. 3.11 The apoptosis pathway is highly regulated. Apoptosis can be triggered via death ligands binding death receptors and results in recruitment of the multi-protein death-inducing signaling complex (DISC). In the DISC, Pro-caspase 8 is activated through dimerization and, subsequently, activates downstream caspases such as caspase 3. External death stimuli can also trigger caspase cleavage of the Bid molecule (Bcl-2 homology domain interacting domain death agonist), which translocates to the mitochondria. Apoptotic proteins such as Bid, Bax, and Bcl-2 localize to the mitochondria and result in mitochondrial release of cytochrome C and other adaptogens into the cytoplasm. Downstream caspases and apoptogens form an apoptosome, which also triggers caspase-3-mediated apoptotic cell death

are a class of proteases that are typically synthesized in their inactive form as procaspases.

The two types of caspases are upstream [2, 8–10] and downstream [3, 6, 7]. Upstream caspases become activated through dimerization in the death-inducing signaling complex (DISC) [43]. Upstream caspases activate downstream caspases through proteolytic cleavage. The downstream activated caspases cleave cellular structural and regulatory proteins. The extrinsic apoptotic pathway relays signals from external death ligands, such as tumor necrosis factor α or the Fas ligand. When the ligand binds the corresponding receptor, it initiates formation of the multi-protein DISC through recruitment of Fas-associated death domain (FADD) and upstream caspases. Upstream caspases dimerize in the DISC and subsequently activate downstream caspases. The extrinsic pathway is connected to the intrinsic pathway through the Bid molecule (Bcl-2 homology domain interacting domain death agonist). Bid is cleaved by caspase-8 and translocates to the mitochondria, activating the intrinsic pathway. The intrinsic pathway is activated by extracellular and intracellular death stimuli that are transduced to the mitochondria and endoplasmic reticulum via apoptotic

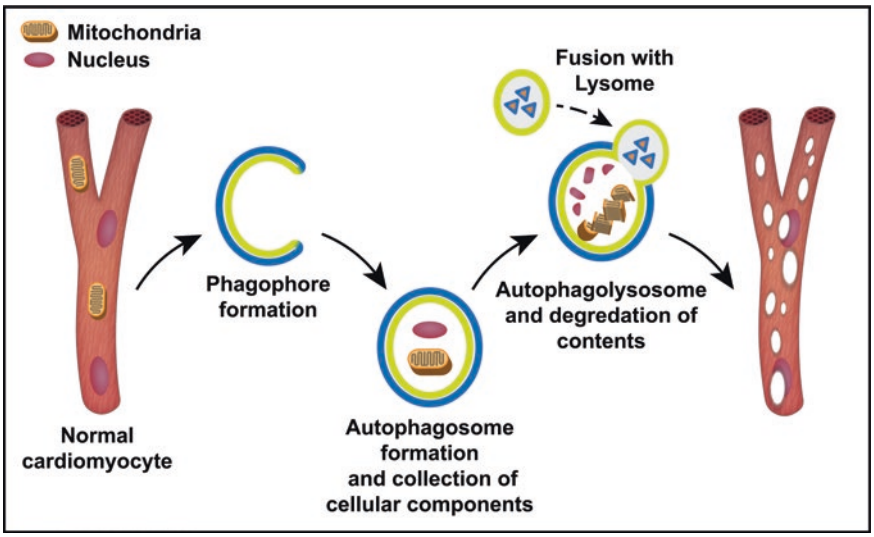

Fig. 3.12 Autophagy is a method of intracellular component recycling and cell death. Autophagy can be triggered by a number of stressors including starvation. Autophagy is initiated by the formation of a double membrane structure known as the phagophore. Organelles and cellular components targeted for autophagy are collected in the autophagosome. Subsequently, the autophagosome fuses with a lysosome, forming the autophagolysosome. The cellular components are lysed and degraded in the autophagolysosome

proteins, Bcl-2, Bid, and BAX. These proteins result in the mitochondria releasing cytochrome C into the cytosol. Cytochrome C and other mitochondrial adaptogens trigger the formation of the apoptosome, a multi-protein complex. In the apoptosome, caspase 9 is activated and cleaves other downstream caspases to result in apoptosis of the cell.

Apoptosis has an important functional role in the development and regulation of cellular and organ function, and, thus, alterations in apoptosis can result in disease states. In heart failure, cardiomyocyte apoptosis is increased in comparison to normal hearts [44]. In advanced heart failure, cytokines such as tumor necrosis factor α are increased, and these proapoptotic cytokines can drive apoptosis, leading to subsequent adverse remodeling [45].

Autophagy

Autophagy is a method of intracellular component recycling through which cellular components are transported in vesicles to the lysosome or autophagosome for degradation (Fig. 3.12) [46]. This process allows for catabolism and releases the fatty acids, amino acids, and protein back to the cell to be used for energy in times of stress or starvation. Autophagy is initiated by formation of the autophagosome through Beclin-1, vacuolar protein sorting 34, and UVRAG (UV radiation resistance-associated gene).

While autophagy overall is a survival mechanism for cells, it has been associated with cell death. It remains unclear whether autophagy is the cause of cell death or whether it occurs to prevent cellular demise. In failing human hearts, an increase in autophagosomes has been noted [40]. However, autophagy is difficult to study due to the lack of specific markers. Therefore, the role of autophagy in the pathophysiology of heart failure remains unclear.

Molecular Response to Stress

The heart can respond to various stress stimuli, such as increased volume or pressure, in a number of ways that can either be adaptive or maladaptive. A number of signaling pathways and resultant molecular and physiologic changes occur during the stress response to maintain cardiovascular homeostasis.

Immediate Early Gene Response

The heart responds to increases in workload and strain through cell hypertrophy and eventual change in function. While these changes can take months to years to occur, immediate early gene responses take place within minutes. These immediate early gene responses are caused by rapid and transient transcriptional regulation due to extracellular stresses. Ligands bind extracellular receptors and activate protein kinase C, MAP Kinase, and PI3K pathways, and these signals are rapidly transduced. The initial group of genes activated during stress are c-fos, c-jun, Egr-1, and c-myc [47, 48]. The immediate early gene response leads to a cascade of gene expression that regulates cellular growth and survival and is critical to cellular stress response.

Re-expression of the Fetal Gene Program

A group of genes are expressed in the fetal heart during cardiac development, but not postnatally. However, these proteins are re-expressed in response to mechanical and other stress stimuli.

The fetal gene program includes atrial natriuretic protein (ANP), brain natriuretic protein (BNP), β-myosin heavy chain, skeletal α-actin, and others. The fetal gene program

response is mediated through the immediate early gene response that results in increased transcription of the fetal gene program. The re-expression of fetal sarcomeric proteins is adaptive, initially, to promote hypertrophy in response to hemodynamic stresses. It can also result in remodeling observed in advanced heart failure.

BNP, a fetal gene product, is used as a biomarker of heart failure; increased serum levels are observed in patients with heart failure. Additionally, the fetal gene program also promotes a switch from fatty acid to glucose metabolism via expression of glycolytic enzymes. Glucose is a less efficient energy source for the heart, but the oxidation of glucose requires less oxygen. Therefore, in a failing heart, this metabolic switch can be a protective mechanism.

Heat Shock Proteins/Chaperones

Cells' heat shock response is a pro-survival mechanism that was initially described during the exposure of cells to a mild heat stress. But the response can be elicited by a number of stress stimuli including oxidative and heavy metal toxins [49]. These stresses largely induce protein denaturation and aggregation of unfolded or misfolded proteins. The cellular response to counter these effects is to reduce protein translation and induce transcription factors known as heat shock factor 1 (HSF1).

In their inactive state, HSFs are monomeric and interact with heat shock protein 90 (Hsp90) and chaperone proteins. However, in response to stress, unfolded proteins compete with HSF1 for binding with Hsp90, and thus, HSF1 is released from the complex. HSF1 forms a homotrimer, the active state, which can translocate from the cytoplasm to the nucleus. The HSF1 complex then interacts with DNA to bind to the promoter of heat shock proteins and induces their expression.

Inducible heat shock proteins act as molecular chaperones to refold proteins and prevent protein aggregation [50]. They also promote cell survival by the prevention of apoptosis through a number of mechanisms. Heat shock proteins can block the release of proapoptotic signals such as the release of cytochrome C from the mitochondria. They also bind inactive caspase-3 and prevent activation [51]. Heat shock proteins have an important functional role in the stress response and impact a number of molecular mechanisms that promote cell survival.

Conclusions

The sequencing of the human genome has enhanced our understanding of the molecular pathways that govern physiological and pathological cardiovascular responses to stress. These pathways will provide an important foundation for emerging therapies aimed at promoting reverse remodeling of heart failure and preventing the progression to advanced disease.

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Pathology of Ischemic Heart Disease

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_4

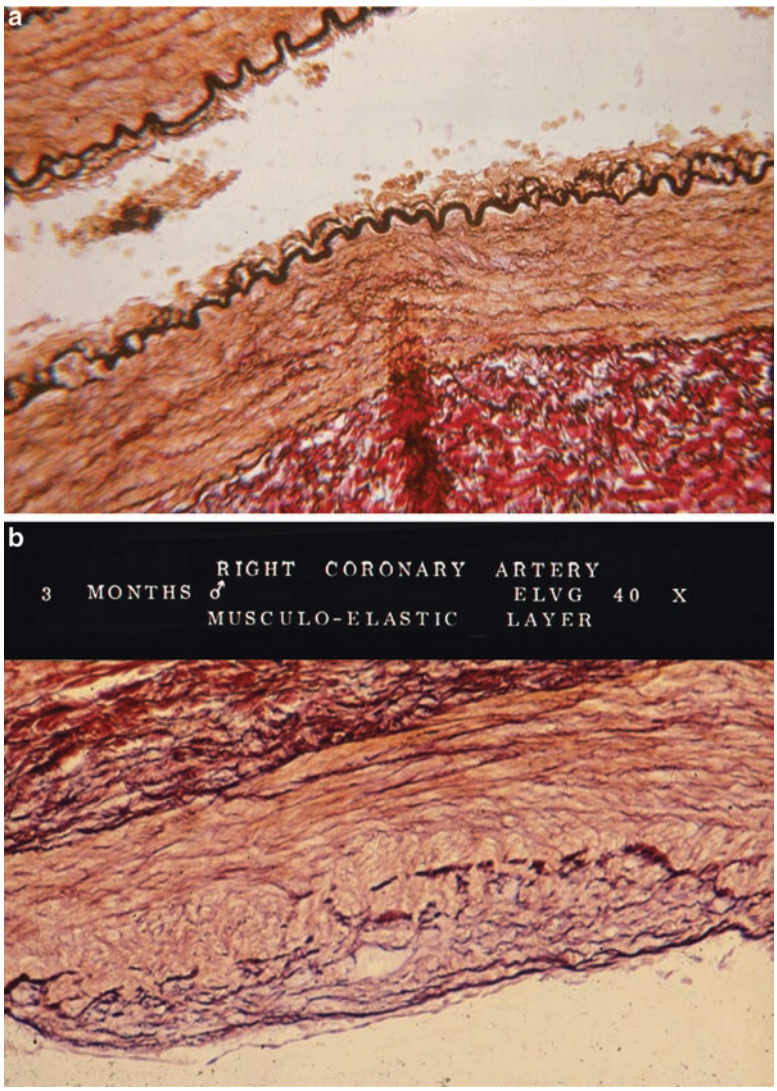
Ischemic heart disease is a broad term encompassing several closely related syndromes caused by myocardial ischemia, an imbalance between cardiac blood supply perfusion and myocardial oxygen and nutritional requirements.

Ischemic heart disease in its various forms remains the leading cause of mortality in the United States and other developed nations, accounting for seven million deaths worldwide each year. These deaths are most commonly caused by thrombotic occlusion of a high-risk coronary plaque, resulting in myocardial infarction or cardiac death.

Coronary Atherosclerosis

The normal coronary artery in infants is characterized by a muscular media with fibers oriented in a circular manner. The intima, which is composed of delicate connective tissue with a thin layer of endothelial cells, is separated from the media by an internal elastic membrane, while the external membrane separates the media from the collagenous adventitia (◘ Fig. 4.1a A).

A normal variation, which may be observed even in the young, includes an extra layer between the intima and



◘ **Fig. 4.1** (**a**) **Panel A**. From a newborn infant 4 days old. The intima is the indistinct layer lying upon the internal elastic membrane (I). Elastic fibers are distributed irregularly in media (M). The adventitia (A) is thick and collagenous. Elastic tissue stain ×170. **Panel B**. From a 3-month-old infant. Image shows focal thickening of the wall by formation of the musculoelastic layer. Elastic tissue stain ×40. (**b**) Coronary arteries in male infants from three ethnic groups. **Panel A**. There are differences in the intensity and quantity of the structural findings between the sexes and among various ethnic groups in early life. **Panel B**. Mean values of measurements of the intima and musculoelastic layer in coronary arteries in males of three ethnic groups (Adapted from Vlodaver Z, Kahn HA, and Neufeld HN. The coronary arteries in early life. Circulation. 1969; 39:541 [1]) Elastic tissue stain ×40

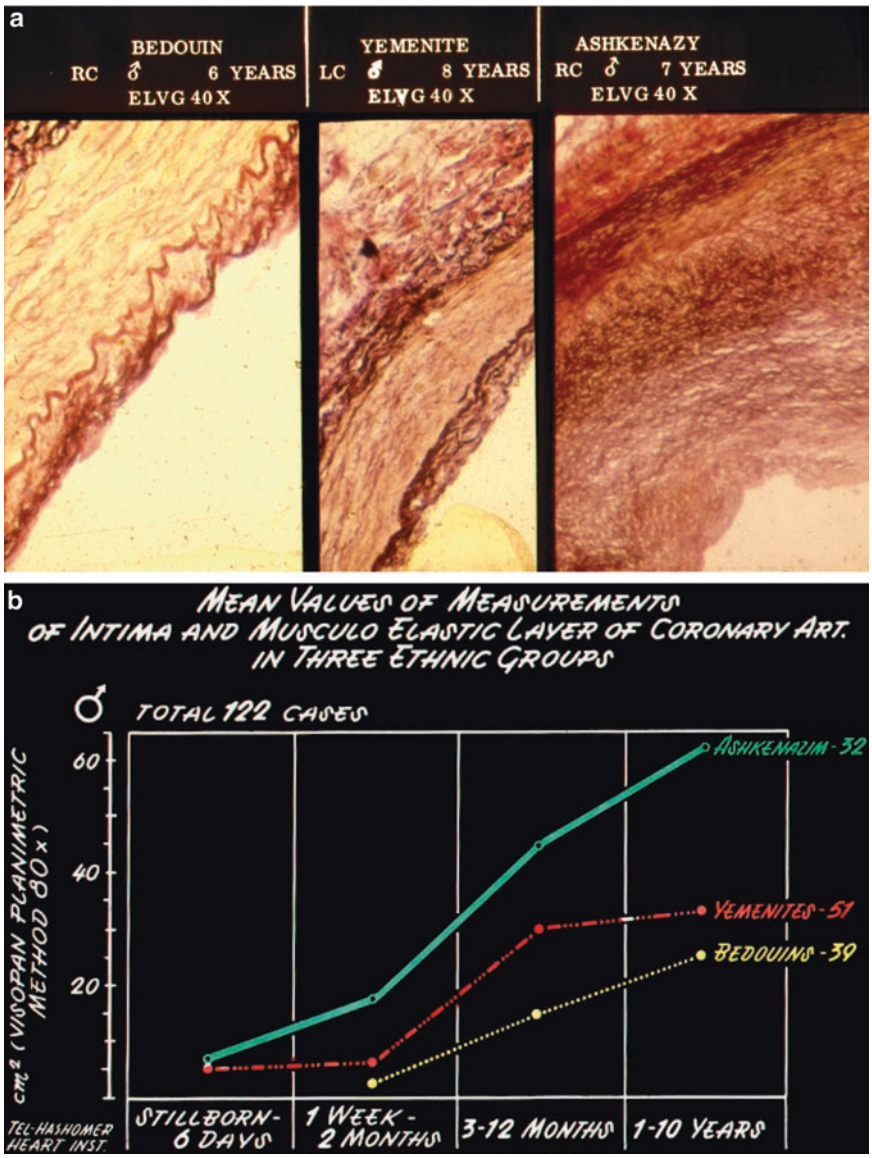


Fig. 4.1 (continued)

media. This is a musculoelastic layer, characterized by a focal aggregation of smooth muscle and connective tissue (Fig. 4.1a B).

Coronary Vascular Changes in Childhood

Intimal Thickening

The earliest vascular change described microscopically is intimal thickening, which consists of layers of smooth muscle-like cells and an extracellular matrix. Segments of the media related to the musculoelastic layer may show thinning.

Thickening of the intima in childhood may relate to later development of coronary artery disease.

In 1969, we described the histological changes in the coronary arteries in full-term fetuses, infants, and children of 211 consecutive necropsy specimens from Ashkenazy, Yemenite, and Bedouin groups [1]. We found differences in early life in the intensity and quantity of the structural findings between the sexes and among various ethnic groups (Fig. 4.1b A and B).

These differences between sexes and ethnic groups in children up to 10 years old were consistent with the known differences in the prevalence of coronary atherosclerosis, coronary heart disease, and myocardial infarction in the corresponding adult population.

Intimal Fatty Streak

Intimal fatty streaks are lesions primarily composed of abundant macrophage foam cells interspersed with smooth muscle cells. Although this entity is referenced as the earliest of atherosclerotic lesions, in most cases its development is a reversible process with no progressive tendency. Many

studies describe the complete regression of the intimal fatty streak [2, 3].

In 2000, based on morphologic characterizations, Virmani proposed a modified American Heart Association (AHA) Consensus Classification of coronary atherosclerotic lesions with emphasis on the relationship between atheromatous progression and acute coronary syndromes, grouping the lesions without and with thrombosis [4].

Atherosclerotic Lesions Without Thrombosis

Pathologic Intimal Thickening

The earliest of progressive lesions is called pathologic intimal thickening. These lesions are mainly composed of layers of smooth muscle cells aggregated near the lumen with an underlying lipid pool existing as a relatively acellular area rich in hyaluronan and proteoglycans.

Fibrous Cap Atheromas

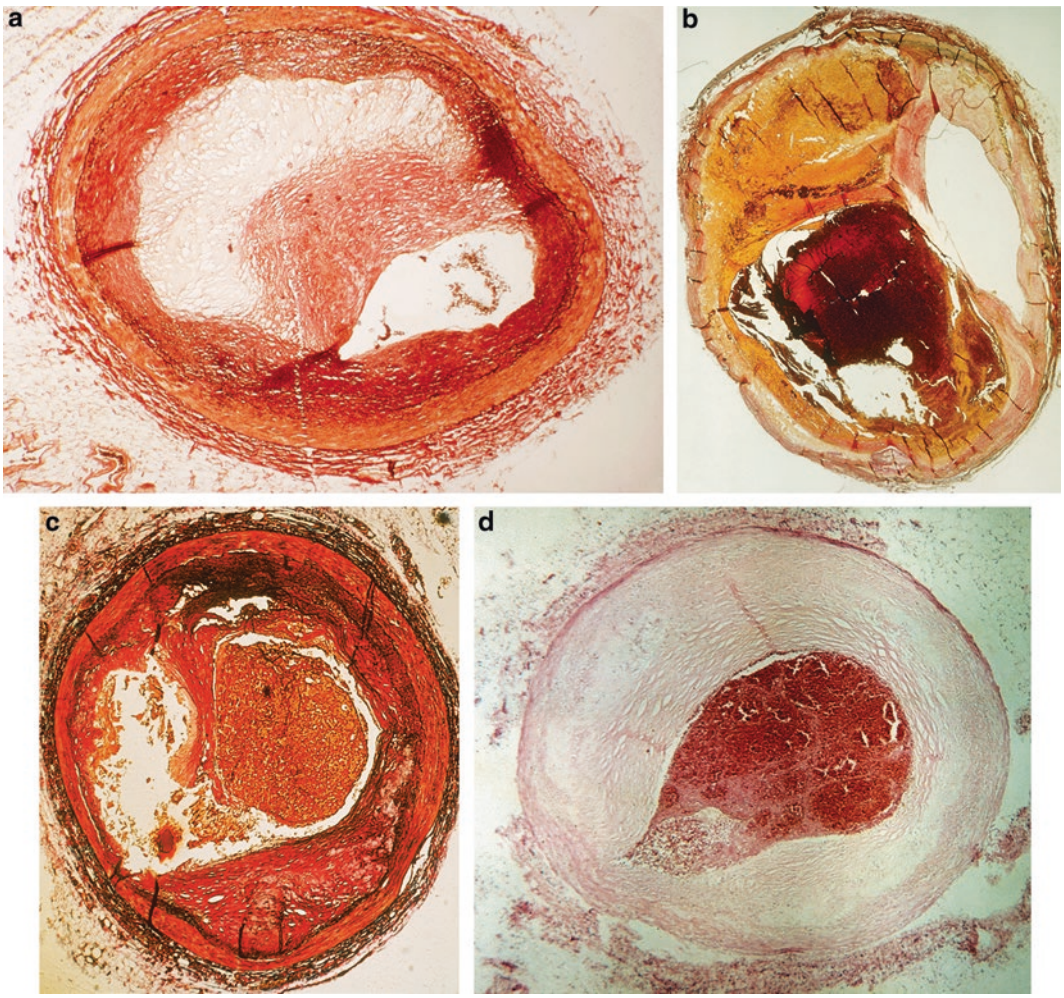
Fibrous cap atheromas are characterized by an acellular necrotic core which is contained by an overlying layer of fibrous tissue forming a distinct entity referred to as the "fibrous cap" (◘ Fig. 4.2a). It is distinguished from lipid pool lesions of pathologic intimal thickening and represents a further progressive stage of atherosclerotic disease [5].

In the early stages, a focal macrophage infiltrates into areas of lipid pools, and, in later stage of necrosis, a loss of matrix occurs with resultant extensive cellular debris. The fibrous cap is critical to maintaining the integrity of the lesion and is subject to thinning prior to the onset of rupture.

Thin-Cap Fibroatheroma

Thin-cap fibroatheromas (TCFAs) are lesions that exhibit large necrotic cores with overlying thin, intact fibrous caps infiltrated by macrophages (◘ Fig. 4.2b).

Thin-cap fibroatheromas, traditionally referred to as vulnerable plaques, morphologically resemble ruptured plaque,



◘ **Fig. 4.2** (**a**) Fibrous cap atheroma characterized by an acellular necrotic core which is contained by an overlying layer of fibrous tissue. This forms a distinct entity referred to as the "fibrous cap." (**b**) Thin-cap fibroatheroma with hemorrhage in atheroma exhibits large necrotic cores with overlying thin, intact fibrous caps infiltrated by macrophages. (**c**) Plaque rupture. Disruption of the fibroatheroma cap, and a luminal thrombus communicates with the underlying necrotic core. (**d**). Plaque erosion. The plaque structure is similar to the plaque in cases with rupture, but with no communication of the thrombus with the necrotic core

although they are discriminated by the lack of a luminal thrombus and disrupted fibrous cap. Typically, few or no smooth muscle cells are present within a fibrous cap.

Vulnerable plaque is a term that represents "the susceptibility of a plaque to rupture." Studies of autopsies of patients who had died of cardiac causes show that the most common underlying plaque morphology was a ruptured thin-cap fibroatheroma with superimposed thrombosis [6].

This pathophysiological background spurred interest in identifying such vulnerable plaques in stable patients. The ultimate goal is preventing plaque rupture, thereby averting myocardial infarction and sudden death [7].

Narula et al. [8] compared stable plaques, thin-cap fibroatheromas, and ruptured caps in sudden death victims. They found that fibrous cap thickness was the best discriminator of plaque type, measuring <54 μm in ruptured plaques, 54–84 μm in most TCFAs, and >84 μm in stable plaques. In this pathologic study, the authors also observed that the incidence of myocardial infarctions tended to emerge from previously obstructed lesions, the TCFA exhibited >50 % stenosis, and majority of ruptured plaques showed >75 % stenosis.

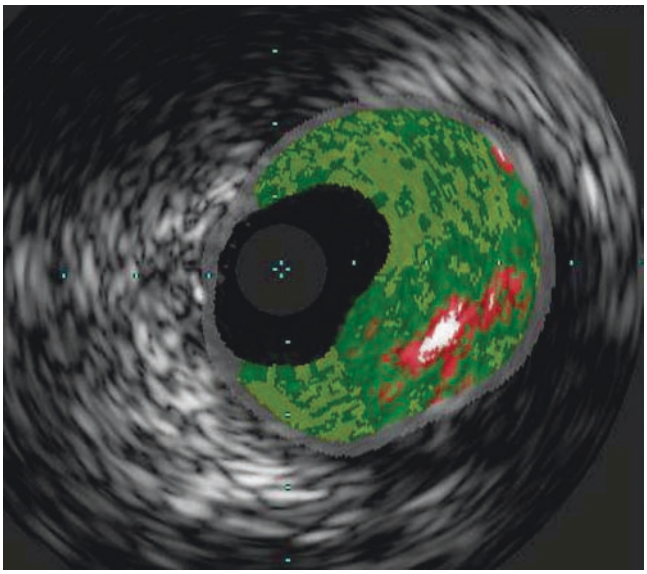


Fig. 4.3 Intravascular ultrasound of a coronary segment with large atherosclerotic plaque. Using "virtual histology" analysis of the plaque composition, the plaque is composed of fibrofatty tissue (*green*) and necrotic core (*red*). The white areas represent calcification

Atherosclerotic Lesions Associated with Acute Thrombosis

Plaque Rupture

With plaque rupture, *we see* disruption of the fibroatheroma cap and the luminal thrombus communicating with the underlying necrotic core (Fig. 4.2c).

The fibrous cap consists mainly of type I collagen with varying degrees of macrophages and lymphocytes and very few, if any, alpha-actin-positive smooth muscle cells. The luminal thrombus often is platelet-rich near the actual rupture site, giving a white appearance (white thrombus). In contrast, near the rupture site and at sites of propagation, the luminal thrombus is composed of layers of fibrin and red blood cells (red thrombus) seen at the proximal and distal ends of the thrombus.

Rupture of an atherosclerotic plaque had been uniformly accepted as the primary causative event in sudden coronary death. Although the underlying mechanisms of plaque rupture are poorly understood, several critical processes including matrix degradation by matrix metalloproteinases (MMPs), high shear stress regions, stress branch points, macrophage death, and microcalcification and iron accumulation within the fibrous cap are thought to play a role [9].

Plaque Erosion

Several studies of patients who died due to acute myocardial infarction (AMI) or sudden death described superficial erosion of plaque as an important substrate for coronary thrombosis, usually nonocclusive.

This plaque structure is similar to the plaque in cases with rupture, but there is no communication of the thrombus with the necrotic core (Fig. 4.2d).

Serial sectioning confirms that, with plaque erosion, the thrombus is confined to the luminal plaque surface with an absence of fissures or communication with an underlying necrotic core. The term "erosion" is used because the luminal surface beneath the thrombus lacks endothelial cells [10].

Intimal Calcification

The extent of coronary artery calcification correlates with plaque burden. Calcified nodules might disrupt the fibrous cap, leading to thrombosis [6]. Recurrent plaque rupture and hemorrhage with subsequent healing might result in the development of obstructive fibrocalcified lesions and are frequently found in patients with stable angina and sudden coronary death.

Intravascular ultrasound (IVUS) has played an important role in understanding the pathology and treatment of atherosclerosis in humans. Several grayscale IVUS features have been associated with either clinical instability or a high risk for cardiovascular events in patients with coronary artery disease who undergo percutaneous coronary intervention (Fig. 4.3) [11].

Stem Cells and Atherosclerosis

A variety of mechanisms contributes to the development and progression of atherosclerosis, including genetic and immunologic mechanisms, hemodynamic effects, and risk factors both known and unknown. However, a principal initiator of atherosclerosis appears to be the development of endothelial dysfunction following arterial injury.

Circulating stem cells and progenitor cells derived from the bone marrow and vasculature play critical roles in vascu-

lar repair and homeostasis and may serve to counteract the development of atherosclerosis following vessel injury [12].

Since the initial observation that circulating human $CD34^+/KDR^+$ mononuclear cells assume an endothelial phenotype in culture and incorporate into newly formed vasculature in the ischemic hind limb, a new paradigm for postnatal vasculogenesis was discovered [13]. Multiple studies have confirmed the importance of these putative endothelial progenitor cells (EPCs) and other bone marrow-derived cells in promoting vascular health. This is supported, in part, by the relationship in many studies between the number of circulating EPCs and the development of atherosclerosis [14].

Paradoxically, stem cells and progenitor cells may also contribute to the progression of atherosclerosis. The development of transgenic animals that develop atherosclerosis—for example, apolipoprotein E knockout ($ApoE^{-/-}$) mice—or express markers on bone marrow-derived cells, green fluorescent protein (GFP), has provided new insight into how vascular and bone marrow-derived stem cells and progenitor cells are involved in the biology of atherosclerosis.

Recent investigation has shown that bone marrow-derived EPCs and smooth muscle progenitor cells (SPCs) may play important roles in the biology of atherosclerosis and plaque rupture. EPCs may increase vascularization of the plaque, which may increase the likelihood of plaque rupture [14], while SPCs may increase plaque stability [15]. These seemingly contradictory roles of stem and progenitor cells in atherosclerosis are the subject of ongoing investigation.

Acute Myocardial Infarction

Coronary syndromes that cause a relatively rapid onset or increase of symptoms or ischemia are termed acute coronary syndromes (ACSs). An ACS is a continuum of unstable coronary syndromes that stretches from "unstable angina" to acute ST segment elevation myocardial infarction (STEMI).

Acute myocardial infarction (MI) occurs when there are severe reductions in coronary blood flow and myocardial delivery for more than 20 min. The infarct begins in the subendocardium (inner or mid wall of the heart) and is confined in the first 30 min to 2 h. If the artery thrombosis is transient or does not cause complete coronary artery occlusion, an infarct to the subendocardium infarction develops, also described as non-Q or non-ST segment elevation myocardial infarction (NSTEMI). If the coronary artery occlusion is sustained for longer periods, the myocardial necrosis progresses toward the epicardium in the next 2–3 h, and a "Q wave" or STEMI transmural infarction develops.

The role of coronary artery thrombosis in causing MI was debated until studies by DeWood and colleagues in 1980 demonstrated by coronary arteriography that coronary thrombosis is virtually always the cause of acute Q wave or STEMI [16]. Ninety percent or more of STEMIs have prolonged occlusive coronary artery thrombosis in the infarct-related coronary artery [17].

Only about 30 % of patients with NSTEMI have an occlusive thrombus in the infarct-related artery. In most patients with NSTEMI, transient coronary artery occlusion is initiated by platelet aggregation and associated vasoconstriction is present. Distal embolization, the cause for the rise in biomarkers, is frequently present with NSTEMI.

Local accumulation of endothelium causes marked vasoconstriction. Serotonin, adenosine diphosphate, thrombin, and endothelin are mitogens, and they likely contribute to subsequent local fibroproliferation with increases in the neointima, with further narrowing of the lumen of the endothelium-injured coronary artery. Reduction in fibrinolytic capability at sites of vascular endothelium injury is associated with decreases in vascular tissue concentration of protacyclin, tissue plasminogen-activating factor, and nitric oxide. This contributes to coronary artery thrombosis, vasoconstriction, and fibroproliferation at these sites [18].

The process of NSTEMI and STEMI begins with coronary endothelium injury, usually atherosclerotic plaque ulceration or fissuring. The degree of coronary artery stenosis where plaque ulceration or fissuring occurs may be mild or severe. About half of the coronary stenosis where plaque fissuring or ulceration occurs are sites of less than 50 % normal luminal diameter [19].

Fissuring and ulceration of the plaque often occur in the asymmetric portion or "shoulder region" with a thin fibrous cap that is lipid laden. Inflammation at the sites of these fibrous plaques with adjacent lipid cores best predicts the vulnerable atherosclerotic plaque and one likely to fissure or ulcerate [20].

Inflammation is characterized in the unstable plaque by the accumulation of monocyte-derived macrophages, activated T cells, and mast cells. Most likely, proteases released from the infiltrating mononuclear cells contribute to thinning of the fibrous cap through their degradation of collagen and subsequent atherosclerotic plaque fissuring and ulceration [20].

Pathologic Features

Myocardial infarcts less than 12 h old usually are not grossly apparent. However, infarcts more than 3 h old can be visualized by exposing myocardium to vital stains, such as triphenyltetrazolium chloride, a substrate for lactate dehydrogenase. Because ischemic necrosis causes the enzyme to leak out of damaged cells, the infarcted area is unstained (pale), while old scars appear white and glistening.

At about 12 h postinfarct, the involved myocardium may grossly reveal a bluish hue. Histologically, the involved myocardial fibers may be somewhat more eosinophilic than fibers in the uninvolved areas of the ventricle.

By 24 h, the bluish hue gives way to a slightly tan shade. Histologically, there may be some clumping of the cytoplasm of the myocardial fibers. The capillaries tend to be dilated, and early interstitial exudation of leukocytes, predominantly neutrophils, takes place, and the fibers appear more eosinophilic (Fig. 4.4a).

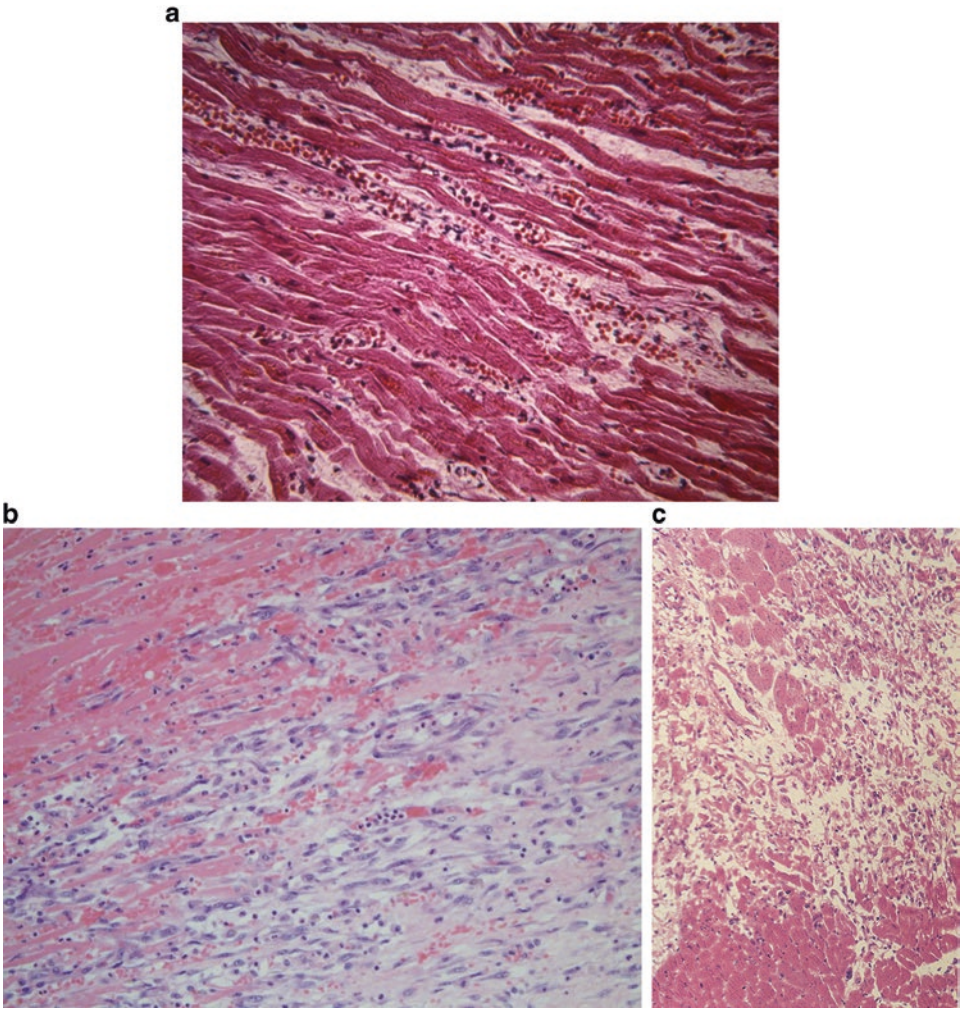


Fig. 4.4 (**a**) By 24 h, there is clumping of the cytoplasm of the myocardial fibers, the capillaries tend to be dilated, and early interstitial exudation of leukocytes, predominantly neutrophils. H and E ×162. (**b**) At day 5, one may identify removal of necrotic muscle fibers, a process that continues for weeks until all or most of the necrotic fibers are removed. As the leukocyte infiltration begins at the periphery of the infarction, so does the removal of necrotic fibers. Courtesy from Dr. Juan Manivel and Mr. Dykoski Ricchard. Dept. Pathology. V.A. Hospital Minneapolis, MN. (**c**) In the third week following infarction, the stage of scar formation begins as a change in color of the depressed red band at the periphery of the infarction and the appearance of a ground- glass, gray hue. Histologically, it is represented by activity of fibroblasts and the formation of collagen fibers

Between 24 and 48 h, a yellow discoloration of the infarcted and non-infarcted areas is easily delineated. The gross feature corresponds to the established leukocytic infiltration into the infarction with a concentration at the periphery of the infarction.

At 2 and 3 days, the nuclei of the myocardial fibers tend to become indistinct and the cross-striations become coarse but do not disappear.

At day 5, one may identify removal of necrotic muscle fibers, a process which continues for weeks until all or most of the necrotic fibers are removed. As the leukocyte infiltration begins at the periphery of the infarction, so does the removal of necrotic fibers (Fig. 4.4b).

In the second week, the picture of removal of myocardial fibers is characterized grossly by a band of reddish-purple between the yellow infarcted muscle and the normal muscle. Histologically, at this stage, there is fragmentation of muscle fibers and interstitial infiltration of macrophages and lymphocytes, while the stroma, composed of capillaries and supporting connective tissue, remains.

An irregular zone appears between the necrotic muscle of the infarction and the viable muscle. The zone is characterized by alteration between small masses of viable but ischemic muscle and small areas of infarction. This "junctional zone" may be termed "the twilight zone." It may be responsible for the clinical complication of electrical failure after the acute episode and perhaps for the segmental and T wave changes characteristic of acute myocardial infarction.

In the third week following infarction, the stage of scar formation begins as a change in color of the depressed red band at the periphery of the infarction, now appearing as gray-hued ground glass. Histologically, it is represented by activity of fibroblasts and the formation of collagen fibers (Fig. 4.4c).

By week 4, in most cases, the necrotic muscle is removed and its place is taken by scar tissue formed by the new connective tissue and the preexisting stroma. At the site, the cardiac wall is thinned, and the endocardium overlying the infarction increases in thickness (fibroelastosis).

Clinical Manifestations

The clinical diagnosis of myocardial infarction is generally justified on the basis of prolonged pain (1–2 h of severe ante-

rior chest pain), but documentation requires QRS (Q wave) abnormalities shown on an electrocardiogram (ECG) as well as ST segment T changes and a rise in serum biomarkers that are released by the injured myocardium. While myocardial infarction may be without symptoms recognized by the patient (silent) or associated with typical symptoms, the majority of patients seek help because of unremitting chest distress with a few displaying perspiration, some dyspnea, and anxiety.

Deaths from ventricular arrhythmias are common in the first few hours if the patient is unattended.

Characteristically, patients experience mild fever and leukocytosis for 3–4 days, and a pericardial rub can be heard in many patients with STEMI.

Myocardial (pump) failure; rupture of the free wall, septum, or papillary muscle; and aneurysm formation are dreaded complications.

Postinfarction pericarditis is generally benign, but the severity of the distress and temperature elevation may be surprising, and cardiac tamponade can occur.

Complications of Acute Myocardial Infarction

Complications of acute myocardial infarction include mechanical ("pump failure"), arrhythmia, thromboembolism from the heart, and pericarditis.

A major arrhythmia may result in a sudden circulatory collapse. Mechanical failure usually means acute heart failure due to inadequate ventricular function and may be present with signs of acute pulmonary edema or shock, either alone or together.

Ventricular arrhythmia is a common complication of acute myocardial infarction, occurring in most patients experiencing an MI. It is related to formation of reentry circuits at the confluence of the necrotic and viable myocardium. Premature ventricular contractions (PVCs) occur in about 90 % of patients. The incidence of ventricular fibrillation is about 2–4 %.

The significance of ventricular fibrillation in myocardial infarction has been reevaluated in the context of the interaction between severe systolic dysfunction and the potential for sudden cardiac death. Although implantable defibrillators have reduced mortality in patients with an ejection fraction less than 30 %, regardless of the presence of ventricular dysrhythmia, their placement in the first month after MI has not proven beneficial. That results, in part, because many patients given prompt reperfusion have a significant recovery of LV function in that time period [21]. These patients also have a lower risk of serious dysrhythmias later on.

Supraventricular arrhythmias (mainly atrial fibrillation) occur in fewer than 10 % of patients with acute myocardial infarction. These patients tend to have more severe ventricular dysfunction and, potentially, a worse outcome.

Bradyarrhythmias, including atrioventricular (AV) block and sinus bradycardia, occur most frequently with inferior myocardial infarction. Complete AV block occurs in about 20 % of patients with right ventricular infarction. These episodes of heart block are usually associated with a narrow QRS complex; the site of conduction block is in the AV node. Infranodal conduction disturbances with wide, complex ventricular escape rhythms occur most often in large anterior myocardial infarction and portend a very poor prognosis.

Mechanical Complications

Mechanical complications of acute myocardial infarction include left ventricular failure and cardiogenic shock, cardiac rupture, and mitral insufficiency.

Left Ventricular Failure

The degree of LV pump failure is generally related to the size of the perfusion field distal to the thrombotic coronary occlusion. Infarction of more than 40 % of the LV muscle mass usually results in cardiogenic shock and death. Prior infarction, mitral insufficiency, an acquired left-to-right shunt (usually from an infarct-related rupture of the ventricular septum) [VSD], or a large aneurysm potentiates the effects of acute infarction on overall pump function, dramatically increasing the risk of death.

Other conditions not immediately related to the myocardial infarction, such as chronic pulmonary disease, non-infarct-related valvular heart disease, left ventricular hypertrophy, and hypertension, further increase the risk of heart failure and shock. Before reperfusion therapy was available, large infarcts often resulted in death due to low cardiac output or intractable arrhythmia. While these patients are still very ill, prompt reperfusion and temporary circulatory support can sometimes allow the muscle time to recover function and sustain life.

In instances where extensive myocardial infarction is responsible for LV failure, the infarction may be both acute and, in part, healed. When the infarction is only acute, LV failure usually means that the infarction is transmural and involves an extensive portion of the LV (◘ Fig. 4.5a–d).

Less commonly, the LV failure results from extensive, acute subendocardial infarction (circumferential infarction). When lesser amounts of acute myocardial infarction are present, LV failure may result from the acute infarction damage plus extensive damage from an old myocardial infarction. Preexisting diastolic noncompliance, much more common in women and patients with hypertension, doubles the risk of heart failure after MI. Conversely, patients with small, more distal infarctions may have discrete regional wall motion abnormalities with preserved overall LV function because of compensatory hyperkinesis of unaffected segments.

Congestive heart failure (CHF) occurs in about 15–25 % of patients who experience MI and is associated with an in-hospital mortality rate of 15–40 %. In their 2002 report based on the Second National Registry of Myocardial Infarction

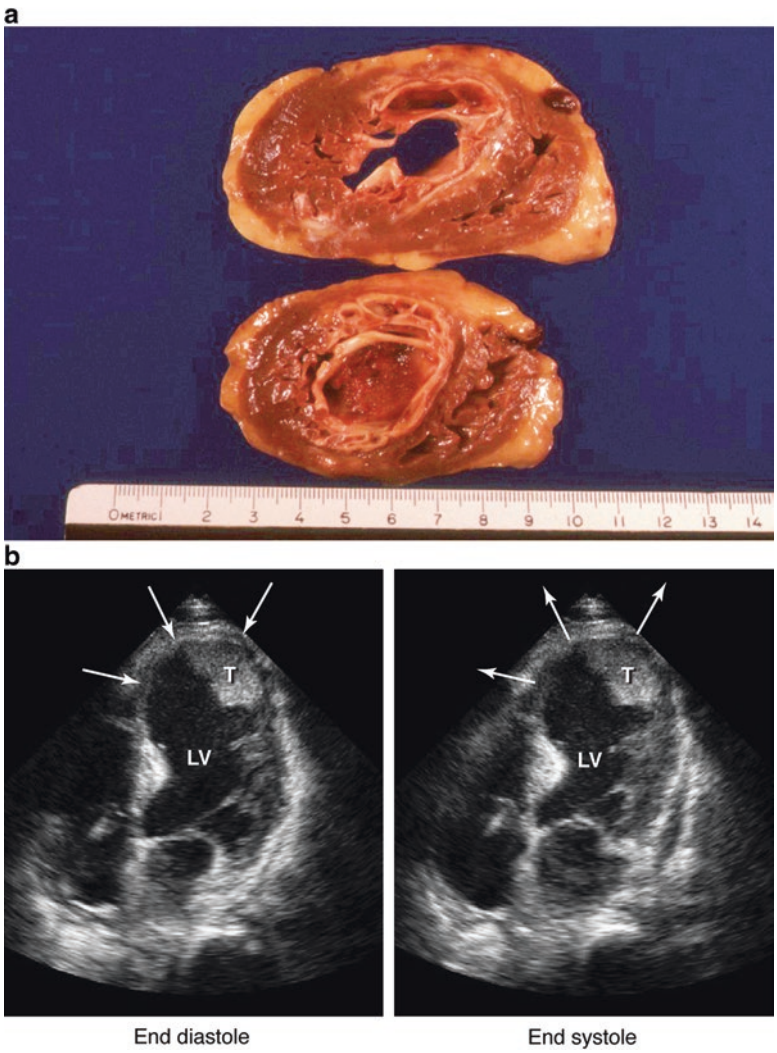


Fig. 4.5 (**a**) Cross-sections of the ventricular portion of the heart. There is transmural acute myocardial infarction involving the anteroseptal area. (**b**) Echocardiogram in (**Panel A**) end diastole and (**Panel B**) end systole from a patient with STEMI demonstrating extensive anteroapical infarction with aneurysm (*arrows*), poor ejection fraction, and apical thrombus (T). (**c**) **Panel A.** T2-weighted scan shows bright segments of LV myocardium representing edema from an acute injury in the LAD distribution (*thin arrows*). **Panel B.** This scan demonstrates increased gadolinium uptake or delayed enhancement (*arrows*) in the left anterior descending (LAD) coronary artery distribution. The delayed enhancement is present in more than 50 % of myocardial wall thickness representing a transmural myocardial infarction (*arrows*). (**d**) **Panel A.** Cardiac magnetic resonance imaging (MRI) was performed 3 days after an occlusion of the left anterior descending artery. This scan shows the LV early after gadolinium. Microvascular obstruction or early hypoenhancement is present (*thin arrows*) from a lack of capillary filling. A large apical thrombus is also seen (*fat arrow*). **Panel B.** End-diastolic FFSP cineangiogram image of a patient following an acute anterior MI. The *small arrow* shows slow flow with an LV apical thrombus (*Fat arrow*)

(NRMI-2), Wu et al. analyzed the outcomes for patients with ST elevation MI with CHF (Killip classes II and III), and they found that 19 % had CHF on admission [22].

Patients presenting with CHF were older and more often female and had a longer time to hospital presentation and a higher prevalence of anterior/septal AMI, diabetes, and hypertension. They also had longer lengths of stay and a greater risk for in-hospital death. Patients with CHF were less likely to receive aspirin, heparin, oral beta-blockers, fibrinolytics, or primary angioplasty and more likely to receive angiotensin-converting enzyme (ACE) inhibitors. Congestive heart failure on admission was one of the strongest predictors of in-hospital death.

Left Ventricular Failure and Cardiogenic Shock

Cardiogenic shock is defined as a state of inadequate tissue perfusion resulting from severe impairment of ventricular pump function in the presence of adequate intravascular volume. It is the leading cause of death for patients with acute myocardial infarction.

Despite advances in the treatment of myocardial infarction, the incidence of cardiogenic shock has remained at 7–10 % during the last 25 years. In a prospective study of 293,633 patients with ST elevation myocardial infarction (STEMI), Babaev et al. found that 8.6 % experienced cardiogenic shock [23].

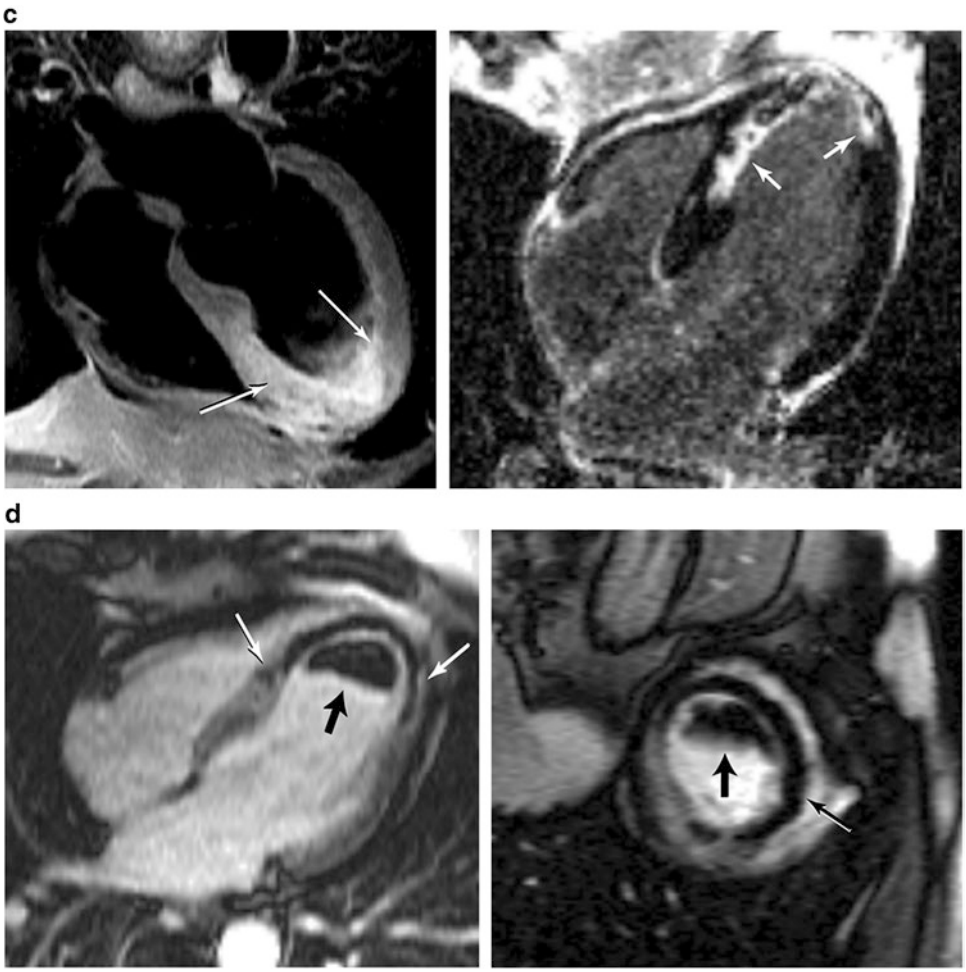


Fig. 4.5 (continued)

Hospital mortality for patients experiencing cardiogenic shock was about 90 % in the 1970s. It has improved over the years, but in-hospital mortality is still estimated to be about 50 % [22]. For persons older than 75 years, the mortality rate is higher. The short-term survival rate has increased in recent years—at the same time that use of coronary reperfusion and temporary circulatory support strategies has increased.

The vast majority of patients with cardiogenic shock have LV failure; in about 12 % of cases, cardiogenic shock is related to other infarct-related mechanical causes, including acute mitral insufficiency, ventricular septal rupture, and ventricular free wall rupture.

Risk factors for developing cardiogenic shock include STEMI, older age, anterior myocardial infarction location, hypertension, diabetes mellitus, multivessel coronary artery disease, prior MI, and prior CHF. All of these risk factors are correlated with either a large perfusion field distal to the thrombosed coronary lesion or to reduced diastolic compliance of the ventricle.

Most patients develop cardiogenic shock because of extensive myocardial ischemia or necrosis. This directly impairs myocardial contractility, resulting in diminished stroke volume and arterial pressure. On a mechanical level, a marked decrease in contractility, reduced ejection fraction and cardiac output, and, ultimately, ventricular failure result in systemic hypotension and/or pulmonary edema.

Varying pathological stages of infarction confirm the stuttering and progressive nature of myocardial necrosis. A combination of new and old infarctions consistently involves at least 40 % of the myocardium.

A systemic inflammatory response mechanism has been implicated in the pathophysiology of cardiogenic shock. Elevated levels of white blood cells, interleukins, and C-reactive proteins are often seen in large infarcts. Inflammatory nitric oxide synthase (iNOS) is also released in high levels and induces nitric oxide (NO) production, which may uncouple calcium metabolism in the myocardium, resulting in stunned myocardium. Additionally, iNOS leads to the expression of interleukins, which may themselves cause hypotension.

Elevated sympathetic neural tone and elevated circulating catecholamines increase systemic vascular resistance, cause pulmonary vein constriction, and may reduce blood flow to non-infarct-related coronary perfusion fields. The result can be a limitation of hyperemic blood flow to the remaining muscle, exhibiting compensatory hyperkinesis to

make up for the loss of function in the infarct zone. All of these factors and the diminished coronary artery perfusion from hypotension trigger a vicious cycle of further myocardial ischemia and necrosis, resulting in even lower blood pressure, lactic acidosis, multiple organ failure, and, ultimately, death.

Patients in cardiogenic shock generally will have a sustained blood pressure less than 90 mmHg (or 30 mmHg below baseline mean arterial pressure) for at least 30 min or the need for vasopressors to maintain the systolic blood pressure above 90 mmHg or a mean atrioventricular opening (AO) pressure >65 mmHg [24].

These patients may have a cardiac index less than 2.2 L/min/m^2 not related to hypovolemia (pulmonary artery wedge pressure less than 12 mmHg), arrhythmia, hypoxemia, acidosis, or atrioventricular block. Outcomes significantly improve only when rapid revascularization can be achieved. The Shock Trial Registry demonstrated that overall mortality when rapid revascularization occurs is 38 %. When rapid revascularization is not attempted, the mortality rate approaches 70 % [25].

Patients in cardiogenic shock generally have severe orthopnea, dyspnea, and oliguria and may have altered mental status, as well as multisystem organ failure from hypoperfusion. Additionally, an S3 gallop, pulmonary rales, and elevated jugular venous pressure are common findings on physical examination.

Patients with cardiogenic shock caused by acute myocardial infarction generally have extensive electrocardiographic changes demonstrating a large infarct, diffuse ischemia, or multiple prior infarcts. Chest radiography likely reveals pulmonary edema. Laboratory tests may demonstrate lactic acidosis, renal failure, and arterial hypoxemia.

Two-dimensional echocardiography and pulsed-wave and color Doppler imaging provide a comprehensive assessment of the anatomic and hemodynamic status at the bedside. They also help identify other mechanical complications of myocardial infarction that may contribute to cardiogenic shock.

In a small fraction of patients, hypovolemia (e.g., from vomiting or lack of oral intake) in the setting of acute MI, can cause hypotension. When the intravascular volume status is unclear, clinicians should assess pulmonary artery wedge pressure for patients in cardiogenic shock. This may help distinguish between primary LV failure and other mechanical causes of cardiogenic shock.

Cardiac Rupture

Rupture of the Free Wall

Rupture of the free wall of the left ventricle is found in less than 1 % of living patients with an acute myocardial infarction [26].

Myocardial rupture was a frequent cause of death in those patients dying in the acute or early phases after their first myocardial infarction [27].

The profile of a patient with rupture of the heart following infarction has certain characteristics, typically: (1) age 70 or older; (2) female gender; (3) pre-existent hypertension with little or no ventricular hypertrophy; (4) STEMI; (5) myocardial rupture that may occur from 1 day to 3 weeks after infarction (vs. most ruptures, which occur 3–5 days after infarction); (6) rupture site devoid of scars, although scars from previous infarctions may be present in other areas; (7) the rupture occurs in the periphery of the infarction near the non-infarcted muscle; and (8) poor collateral vessels.

An additional potential risk—and one that is controversial—is thrombolytic therapy. Honan et al. studied the relationship between the risk of cardiac rupture and the timing of thrombolytic therapy for acute MI [28].

Thrombolytic therapy early after MI improves survival and decreases the risk of cardiac rupture. Late administration of thrombolytic therapy also appears to improve survival but may increase the risk of cardiac rupture. The risk of myocardial rupture was significantly decreased by successful angioplasty in all age groups studied. In a retrospective study review of 2209 patients with acute MI treated with percutaneous coronary intervention (PCI), the risk of cardiac rupture was 0.7 % when successful reperfusion was achieved within 12 h, 0.9 % when reperfusion occurred within 12–24 h, and 3.8 % after failed reperfusion [29].

Prompt reperfusion with PCI appears to have reduced the incidence of rupture.

Specific types of rupture of the heart include rupture of the ventricular septum, of a papillary muscle, and of the free wall of the LV. When the free wall of the LV ruptures, the lesion represents a laceration of the wall's endocardium with secondary extravasation of blood through the free wall and into the pericardial sac (◘ Fig. 4.6a). Typically, rupture of the free wall of the LV is associated with hemopericardium, pericardial tamponade, and cardiogenic shock, but cases of incomplete rupture or rupture without hemopericardium have been reported. Many autopsy specimens show abundant epicardial fat, which has been postulated to contain the tear and prevent hemopericardium. As to sites of infarction which underlie rupture of the free wall, [30] found equal distribution of cardiac rupture of the anterior, lateral, and posterior walls of the LV.

The high incidence of rupture through the lateral wall of the LV compared to a relatively low incidence of isolated transmural infarction in this area is of interest. It suggests that the zone of the LV between the papillary muscles, when infarcted, is more susceptible to the forces leading to rupture than is the case with other sites of myocardial infarction.

Early diagnosis of myocardial rupture is crucial if lifesaving therapy is to be applied. Recent chest pain with further ST segment elevation, bradycardia, syncope, hypotension, and cardiogenic shock in the setting of an acute or recent myocardial infarction should alert clinicians to the possibility of this complication, particularly in patients with an extensive transmural (Q wave) infarction. Transthoracic or transesophageal echocardiography affords a rapid, potentially

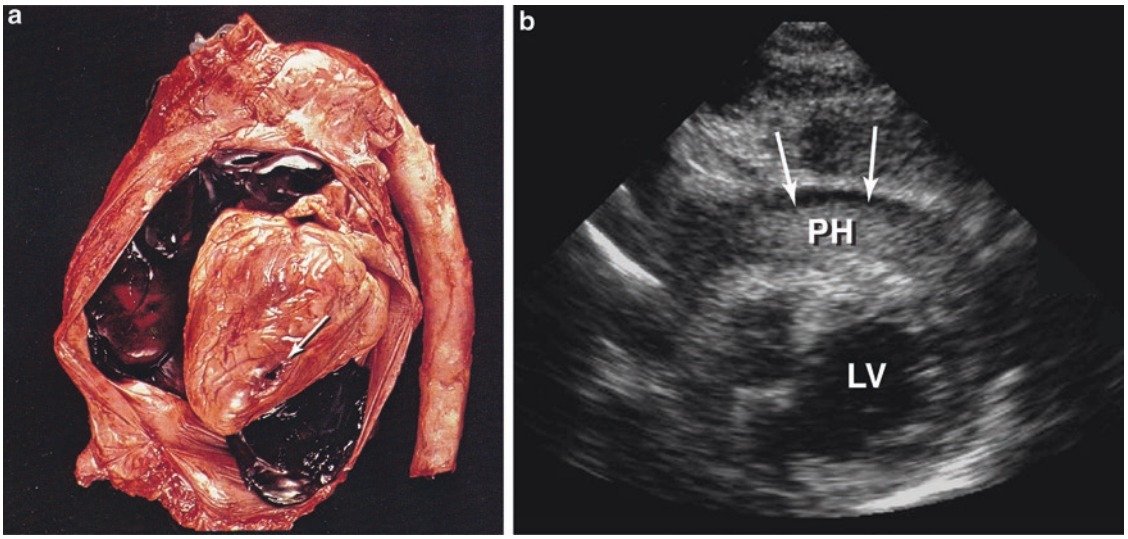


Fig. 4.6 (**a**) Exterior of the heart viewed from the front. There is a perforation (*arrow*) in the anterior wall of the left ventricle (LV) with cardiac tamponade complicating an acute myocardial infarction. (**b**) Echocardiogram in a case with rupture of the free wall of the LV, complicating STEMI, showing a large pericardial hematoma (PH) and small pericardial effusion

definitive diagnostic tool (Fig. 4.6b). Pericardial fluid can be visualized, overall LV function assessed, the area of infarction localized, and the presence of false or true aneurysm revealed. Definitive treatment is surgical, with infarctectomy, if possible, to repair the rupture. Coronary bypass may or may not be necessary. Before surgery, hemodynamic monitoring and stabilization with appropriate fluids, vasopressors, and inotropic agents should be promptly initiated. Pericardiocentesis can provide temporary relief of hemodynamic compromise. Intra-aortic balloon counterpulsation has been used for emergency stabilization, but its role is controversial.

Rupture of the Free Wall of the LV with Formation of "False Aneurysm"

In exceptional instances of rupture of the free wall of the LV complicating acute myocardial infarction, the leak is restricted. The pericardial hematoma is contained and the patient survives. With time, the periphery of the hematoma becomes organized to form the wall of a false aneurysm. The latter maintains communication with the cavity of the LV (Fig. 4.7a). A false aneurysm may mimic a classic LV aneurysm clinically and usually shows a relatively narrow communication with the cavity of the LV. This feature contrasts with that of a true aneurysm, in which, characteristically, a wide communication is present between the aneurysm and the LV cavity.

The tendency for a false aneurysm to rupture contrasts with the very low tendency for a true ventricular aneurysm to rupture. False aneurysms may be associated with pericardial effusion. Some patients may have recurrent tachyarrhythmia, systemic embolization, and heart failure. Patients may have systolic, diastolic, or to-and-fro murmurs related to the blood flow across the narrow neck of the false aneurysm.

A chest radiograph may show cardiomegaly, with an abnormal bulge on the cardiac border. There may be persistent ST segment elevation on the ECG. A diagnosis of false aneurysm can be confirmed by echocardiography, MRI (Fig. 4.7b), or computed tomography angiography (Fig. 4.7c, d).

Spontaneous rupture can occur without warning in about 45 % of patients with false LV aneurysms, even when small. Therefore, surgical intervention is recommended for all patients, regardless of symptoms or the size of the aneurysm, to prevent sudden death [31].

Rupture of the Ventricular Septum

Ventricular septal rupture in acute myocardial infarction is a well-recognized mechanical complication associated with a very high mortality. The use of thrombolytic agents seems to have reduced the incidence from 1 to 2 % to 0.2 %. Most septal ruptures now occur in patients who present very late (>24 h) after infarction. Septal rupture typically occurs 3–5 days after onset of symptoms. Overall mortality at 30 days is 73.8 % [32].

Patients selected for surgical repair of a ventricular septal defect (VSD) had better outcomes than patients treated medically. Patients treated medically have a 30-day mortality of about 97 %, compared with about 47 % for patients treated surgically. Advanced age, anterior infarction, and female sex are risk factors for infarct-related VSD.

Two types of rupture are recognized: simple rupture, with direct, through-and-through defects, and complex ruptures, associated with serpiginous dissection tracts remote from the primary site of tear of the ventricular septum (Fig. 4.8a). Ruptures that involve the inferobasal portion of the septum are more likely to be complex than ruptures in other locations [33].

Early in the disease process, patients with a septum rupture may appear relatively asymptomatic, followed by a rapid

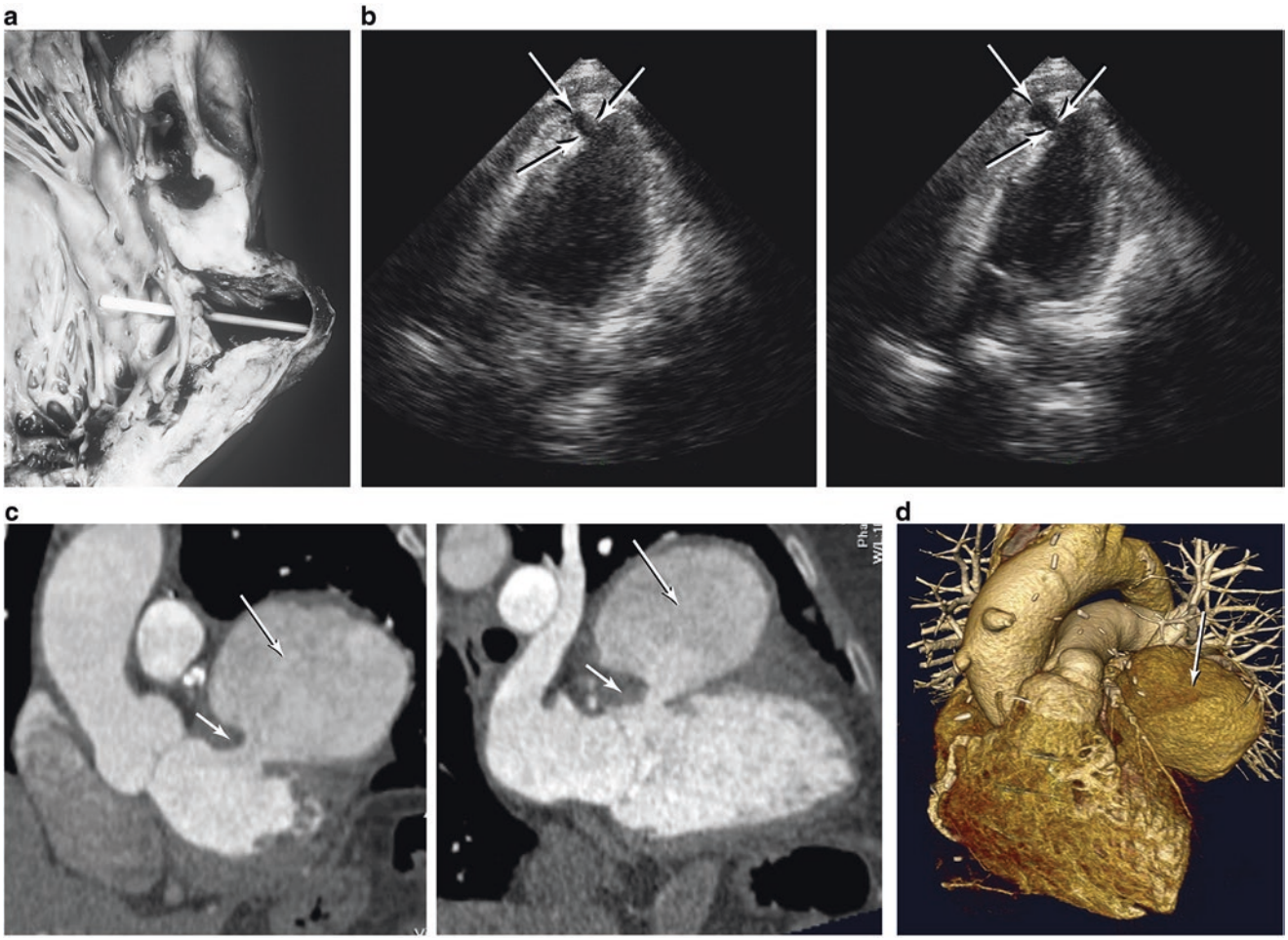


Fig. 4.7 (**a**) Section through the lateral wall of the LV showing an upper non-ruptured aneurysm and the lower aneurysm, containing a probe. (**b**) Echocardiogram shows a small pseudoaneurysm of the LV (*arrows*) following an acute anteroapical infarction. **Panel A**. Diastole. **Panel B**. Systole. (**c**) A 2D multi-planar reformatting (MPR) technique with a coronary computed tomography angiogram (CCTA) is shown for a patient with a recent diagonal branch occlusion. The LV site of perforation in the basilar anterolateral wall (*short arrow*) with a pseudoaneurysm (*long arrow*) is shown. **Panel A**. Diastole. **Panel B**. Systole. (**d**) A volume-rendered technique of a cardiac CT angiogram shows an LV pseudoaneurysm mass (*arrow*) that occurred following the acute closure of an intermediate artery. The mass is contained as a result of mediastinal scarring in this patient with a prior coronary artery bypass graft (CABG)

recurrence of angina, hypotension, shock, or pulmonary edema. Rupture of the ventricular septum is often accompanied by a new, loud, pansystolic border and a systolic thrill at the left lower sternal border. The ECG often shows a new conduction defect (LBBB; Mobitz type II block or complete heart block).

Transthoracic and transesophageal echocardiography with color Doppler are the best methods for diagnosing rupture of the ventricular septum (Fig. 4.8b). Echocardiography can define LV and RV function, important determinants of mortality, as well as the size of the defect and degree of left-to-right shunt by assessing flow through the pulmonic and aortic valves.

Features of a ruptured interventricular septum complicating acute myocardial infarction can be clearly defined with cardiac magnetic resonance imaging (CMRI), as shown in Fig. 4.8c. Early surgical closure is the treatment of choice because it is associated with a lower mortality rate than conservative treatment [34, 35].

Mortality is higher when repairing an inferior myocardial infarction (70 %) compared to anterior infarction (30 %) because of increased technical difficulty and the frequent need for mitral valve repair when septum rupture is associated with mitral regurgitation. A high surgical mortality rate is associated with cardiogenic shock and multisystem failure.

Early surgery improves survival, but long-term outcome depends on residual shunting and left ventricular function. Sutures may tear early from an acutely infarcted area. Residual shunting because of patch dehiscence is common, despite an apparent successful closure, and may require reoperation.

Alternative treatment with transcatheter closure of residual VSDs has been reported successful in select cases. The method is most successful in VSDs that are less serpiginous and located away from the mitral apparatus.

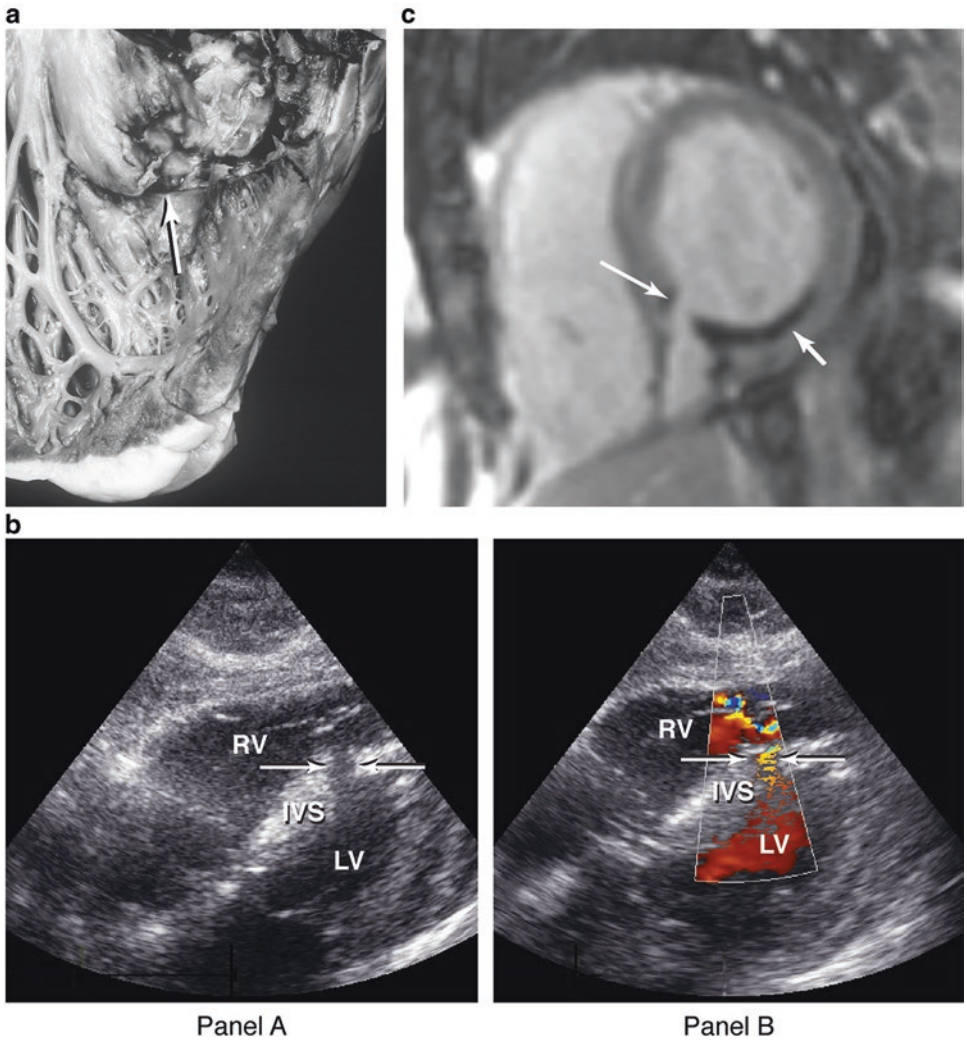


Fig. 4.8 (**a**) Inferior wall of the LV. Note the zone of discoloration and the beginning of a tract (*arrow*), representing the LV aspect of a rupture of the ventricular septum. (**b**) **Panel A**. Echocardiogram in a case of a rupture of the interventricular septum, complicating a myocardial infarction, is identified by dropout of the septum (*arrows*). In **Panel B**, color Doppler shows a regurgitant jet across the septum (*arrows*). (**c**) A cardiac MRI early after gadolinium following an acute RCA occlusion shows an inferoseptal defect (*long arrow*). A basilar inferolateral segment with subendocardial microvascular obstruction (early hypoenhancement) (*short arrow*) helps to confirm the recent nature of the infarction

Mitral Insufficiency

Mitral insufficiency following acute MI can occur as a result of a number of mechanisms, including mitral valve annular dilation secondary to LV dilatation, papillary muscle dysfunction with associated ischemic regional wall abnormality in close proximity to the insertion of the posterior papillary muscle, or partial or total rupture of papillary muscle and chordae.

Mild-to-moderate-degree mitral regurgitation is not uncommon following acute MI. It is mostly transient and asymptomatic, resulting from hypokinesis of the papillary muscle or surrounding myocardium or dilation of the LV cavity. Mitral insufficiency caused by papillary muscle rupture, however, is a life-threatening complication of acute myocardial infarction.

Rupture of the papillary muscle is associated with severe (3+ or 4+) mitral regurgitation, pulmonary edema, and cardiogenic shock, and prompt intervention is required for survival. Papillary muscle rupture occurs in 5% of all fatal myocardial infarctions [32, 35].

Rupture of a Papillary Muscle

The classic situation involves rupture of the entire posteromedial papillary muscle. Rupture of the anterolateral papillary muscle is unusual. In either case, the flail papillary muscle has looped through the interchordal space (Fig. 4.9a).

Approximately two-thirds of ruptures involve the posterior papillary muscle and nearly all ruptures occur within 7 days of the infarct. In cases of papillary muscle rupture, patients become short of breath and rapidly develop pulmonary edema and hypotension.

Most patients with mitral insufficiency have a loud, apical, holosystolic murmur that radiates to the left axilla. Many develop cardiogenic shock, characterized by systemic hypotension, oliguria, acidosis, and poor peripheral pulse and perfusion. Frequently, patients with ruptured papillary muscle have ECG evidence of an inferior acute infarction. Chest X-rays nearly always show signs of pulmonary congestion, interstitial pulmonary edema, and pulmonary venous engorgement. The heart may or may not be enlarged.

Transthoracic echocardiography (TTE) confirms wall motion abnormalities, assesses the degree of mitral regurgi-

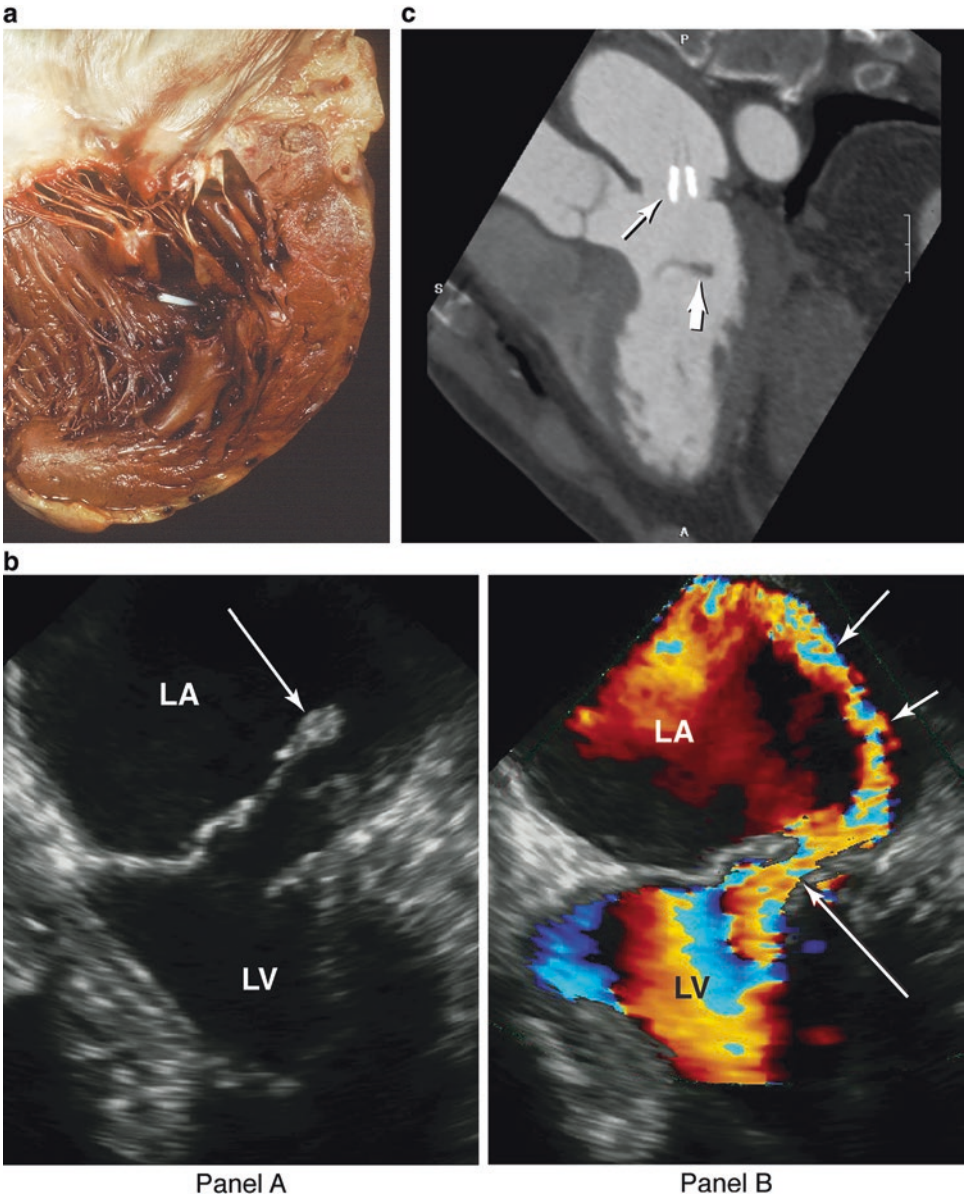


Fig. 4.9 (**a**) Rupture of the entire posteromedial papillary muscle (*near probe*), complicating an acute myocardial infarction. (**b**) **Panel A.** Transesophageal echocardiogram in a case with rupture of the papillary muscle of the mitral valve (*arrow*). **Panel B.** From the same case, color Doppler shows an eccentric jet of severe mitral regurgitation (*arrows*). (**c**) The patient had a cardiac CT angiogram following hospitalization for an acute inferolateral MI, complicated by severe mitral insufficiency. A mechanical mitral prosthesis is present (*thin arrow*) and a portion of a ruptured papillary muscle remains (*thick arrow*)

tation, and often demonstrates flail mitral leaflets. Transesophageal echocardiography (TEE) is the diagnostic imaging tool of choice and is more definitive for evaluating the degree of mitral regurgitation and the status of the posterior papillary muscle. Color flow velocity mapping documents the presence of mitral regurgitation and semiquantitative evaluation of its severity (Fig. 4.9b).

In Fig. 4.9c, cardiac computed tomography angiography (CCTA) illustrates the rupture of papillary muscle. Prompt surgery is the best choice for survival for most patients with acute, severe mitral regurgitation postinfarction [36].

A few highly screened patients without papillary muscle rupture early in their presentation have been treated by emergency percutaneous transluminal coronary angioplasty (PTCA) in an attempt to reduce the size of the infarct and, thereby, reduce mitral regurgitation [36].

Thrombus in the Chambers

The incidence of left ventricular thrombus formation after ST elevation myocardial infarction (STEMI) appears to have dropped from about 20–5 % with more aggressive use of antithrombotic strategies. When a mural thrombus does develop within 48–72 h of a STEMI, the prognosis is poor because of complications of a large infarction such as shock, reinfarction, rupture, and ventricular arrhythmia rather than emboli from the LV thrombus. Factors that predispose to thromboembolic events in patients with HF include low cardiac output, relative stasis of blood in the cardiac chambers, very impaired myocardial performance, regional wall motion abnormalities, and concomitant atrial fibrillation. Myocardial thrombi are most commonly seen in the LV apex.

Figure 4.10a shows an echocardiogram from a patient with a history of extensive anteroseptal infarction and LV

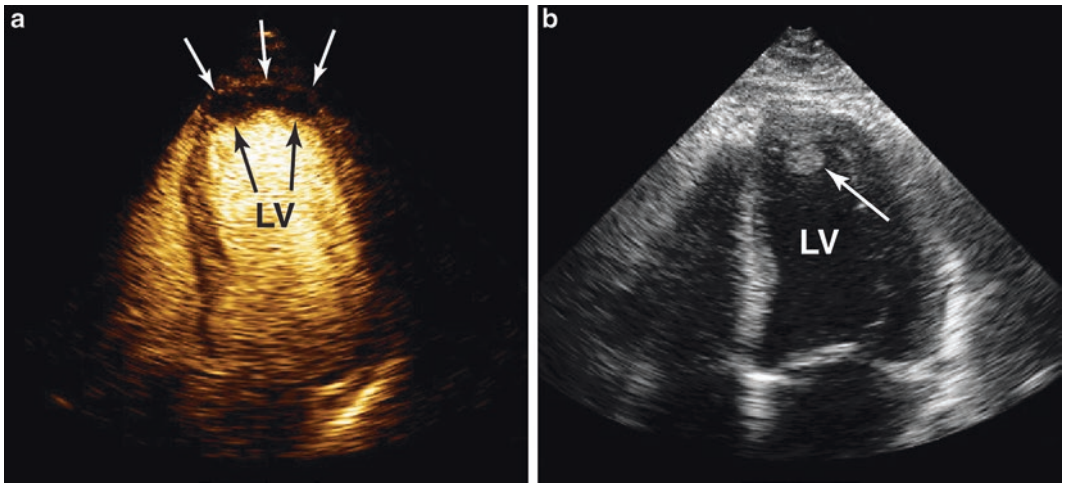


Fig. 4.10 (**a**) **Panel A**. Echocardiogram with a flat left ventricular mural thrombus (*arrows*). **Panel B**. Left ventricular thrombus (*arrow*) protruding into the left ventricular cavity

apical thrombus. Figure 4.5d shown previously is a magnetic resonance imaging (MRI) scan from a patient with STEMI and LV apical thrombus.

An estimated 10 % of mural thrombi result in systemic embolization. Heart failure is believed to be a hypercoagulable state, with impaired endothelial function in the heart's chambers and peripheral vasculature. It is clear that patients with HF and atrial fibrillation benefit from therapy with warfarin, but the role of anticoagulation with antiplatelet drugs and/or warfarin for patients with HF and normal sinus rhythm (NSR) remains understudied.

Although left ventricular thrombus is well known to form acutely on the endocardial surface of the heart in patients with acute myocardial infarction, about 20–40 % undergo spontaneous resolution without anticoagulant therapy in the first year, and another 42–88 % resolve with anticoagulant therapy. Persistence of LV thrombus is more common when anticoagulant therapy is not used [37].

Thromboembolic events occurred at a rate of about 1.7 % per year in patients entering the relatively recent sudden cardiac death in heart failure trial (SCD-HeFT) [38].

Older, retrospective natural history studies reported an annual incidence of thromboembolic events in patients with HF at 2.7–3.5 % per year. To this day, it is not certain that patients with HF who are in normal sinus rhythm clearly benefit from anticoagulation with either aspirin, warfarin, or clopidogrel. Randomized clinical trials such as the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial demonstrated relatively few thromboembolic events. They were also slow to enroll patients and have generally not provided clear and convincing evidence to justify warfarin, aspirin, or clopidogrel use on a routine basis for patients with HF and impaired LV function who are in NSR.

The use of aspirin for these patients remains controversial. Current clinical practice guidelines recommend antiplatelet therapy for patients with HF and CAD. However, patients randomized to aspirin in WATCH had a higher hospitalization rate for HF. Nevertheless, the study does not have the power to refute or recommend its routine use. Aspirin may be beneficial in patients who have HF with recent myocardial infarction or multiple vascular risk factors [39].

Right Ventricular Infarction

Right ventricular infarction is almost invariably caused by thrombotic occlusion of the right coronary (RC) artery proximal to the RV branches in the setting of inferior wall infarction. Hemodynamically significant RV dysfunction occurs in only 10 % of patients with inferior or inferoposterior wall infarction. Despite the younger age, lower rate of anterior myocardial infarction, and higher prevalence of single-vessel disease of the RV compared with LV shock patients, mortality is unexpectedly high and similar to patients with LV shock [40].

Most acute "RV infarctions" are initially diagnosed by right-sided ST elevations (typically, lead V4R). Interestingly, they generally do not progress to myocardial necrosis and subsequent scar formation. This accounts for the far lower percentage of autopsy-reported RV infarcts than clinically suspected infarcts. The latter group includes many patients with a stunned or hibernating RV free wall, which recovers more readily than a similarly injured LV wall. This more rapid recovery occurs in part because of the rich collateral perfusion of the right ventricular free wall and septum from the left coronary (LC) artery and the relatively greater penetration from the blood cavity by the Thebesian veins [41].

About one-third to one-half of patients with acute inferior LV infarction and accompanying RV infarction will show the effects of LV volume underload. The hemodynamic effect may include elevated jugular venous pressure and a noncompliant pattern of the right atrial pulse waveform similar to that of constrictive pericarditis. Reduced RV contractility may lead to a serious deficit in LV preload with a

resultant drop in cardiac output and consequent hypotension that will require vigorous fluid administration. Cases with occlusion of the proximal segment of the RC can compromise the blood supply of the sinus node and AV node, producing sinus bradycardia, atrial infarction, AV block, or atrial fibrillation. The triad of hypotension, jugular venous distension with clear lungs, and absence of dyspnea has high specificity but low sensitivity for RV infarction.

A rare but clinically important complication is right-to-left shunting secondary to increased pressures in the RA and RV and opening of the foramen ovale, resulting in systemic hypoxemia unresponsive to supplemental oxygen.

Echocardiography is the diagnostic study of choice for RV infarction. It demonstrates inferior wall motion abnormalities in conjunction with dilated RV and hypokinetic RV walls.

Hemodynamic monitoring with a pulmonary artery catheter reveals high right atrial pressure with low pulmonary capillary wedge pressure (PCWP), unless severe LV dysfunction is also present. Cardiac output is often depressed.

Left Ventricular Failure and Healed Myocardial Infarction

The term "ischemic cardiomyopathy" is now commonly used to describe patients with HF and concomitant coronary artery disease or a history of myocardial infarction.

Heart failure due to an ischemic etiology is known to be independently associated with a poorer long-term outlook than for patients with HF from other causes [42, 43]. The patient with true ischemic HF typically has severe coronary artery disease (CAD) involving a single large area of the LV or substantial scar involving several distributions of blood flow (Fig. 4.11a). Patients manifest a dilated LV chamber with impaired systolic performance. Signs and symptoms of HF and Q waves are present on the EKG, which shows a marked dilated LV with defined areas of akinesis and thinning of the wall (Fig. 4.11b). In most cases, one or more myocardial infarctions are documented, and an epicardial scar is visible by MRI (Fig. 4.11c). An estimated 50 % of HF incidence in the general population is due to CAD, and CAD is the under-

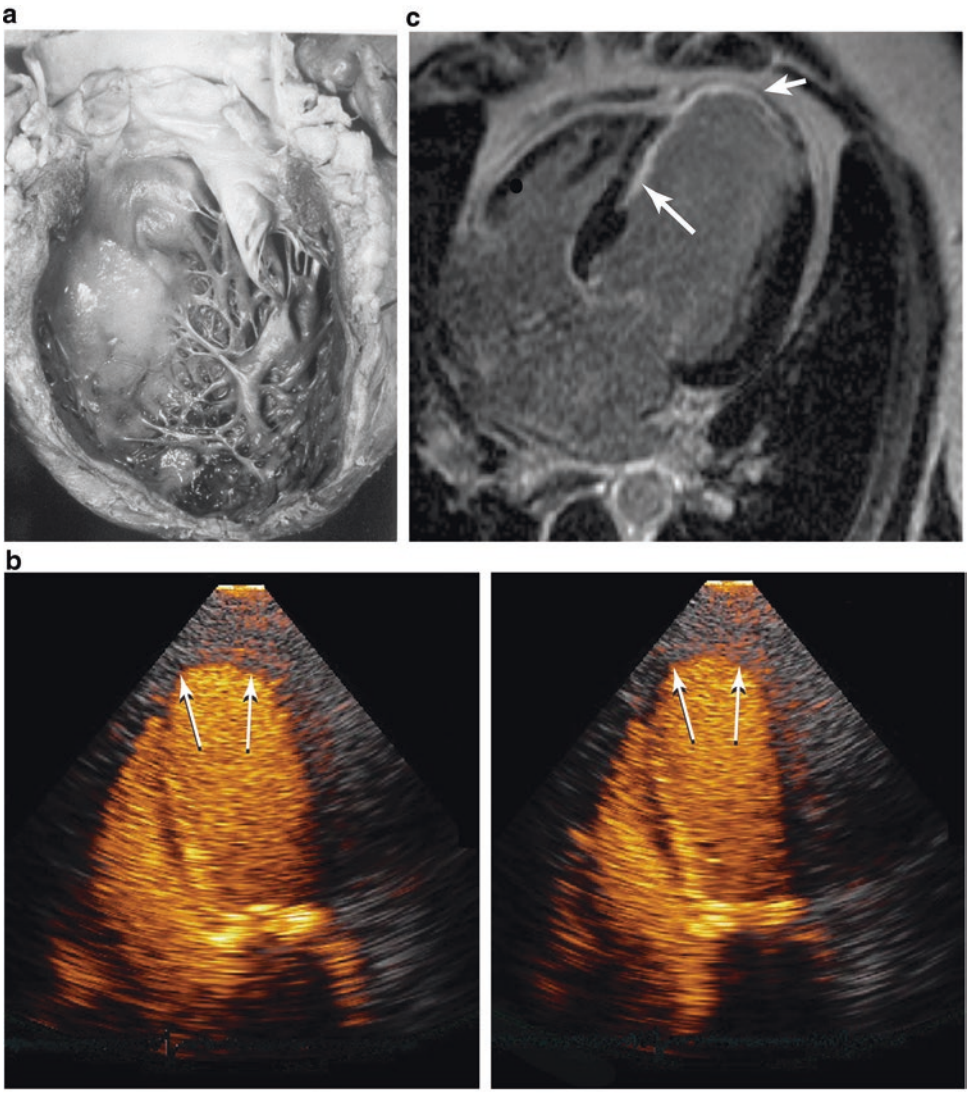


Fig. 4.11 (**a**) Inferior wall of LV. Scarring of the thinned anterior wall and bulging of the ventricular septum toward the RV. Mural thrombus at the apex. (**b**) Echocardiogram in end diastole (**Panel A**) and end systole (**Panel B**) in a case with previous anterior myocardial infarction, with left ventricular dilatation and wall thickening. (**c**) Scan shows delayed enhancement (*thin arrow*) in 50 % of the apical septum. The true apex is thinned and the wall has 100 % delayed enhancement signifying a chronic scar (*thick arrow*)

lying etiology of HF in nearly 70 % of patients, at least in the Western world [44].

Classic congestive heart failure is characterized by a reduction in systolic performance which leads to increased filling pressures and shortness of breath and, in the later stages, is accompanied by a low cardiac output, fatigue, and edema. The primary feature is progressive remodeling of the heart so that it assumes a more spherical, globular shape. The LV internal dimension increases in size, and the LV ejection fraction is reduced. Essentially, the heart does not empty its contents with sufficient force and power. The afterload increases commensurate with the increase in LV radius and wall tension, and the preload rises commensurate with the increase in filling pressures. For any given increase in sarcomere length, there is little or no further development of contractile force (reduced Starling effect) [45]. The combination of perverse loading conditions and reduced contractile strength is responsible for impaired systolic function.

In chronic ischemic HF or ischemic cardiomyopathy, contractile tissue is partially replaced by noncontractile, dense scar tissue. Acute myocardial ischemia may be superimposed on chronic ischemic HF and can lead to further reductions in contractile muscle strength. Chronic myocardial under perfusion of the heart can lead to a condition known as "hibernating myocardium." In this state, the metabolism of the myocardium is reduced to a lower level of activity, presumably in an adaptive attempt to conserve energy, resulting in a less forceful contraction [46].

Hibernating myocardium is a potentially reversible condition and serves as part of the basis for revascularization therapy. The condition can be diagnosed by a combination of coronary arteriography and positron emission tomography, which has emerged as an important step in the identification of chronically ischemic but viable myocardium.

Patients who develop systolic HF in the setting of a healed myocardial infarction have an annual mortality of 8–20 % per year, depending on New York Heart Association (NYHA) class, duration of symptoms, age, severity of LV dysfunction, and comorbidities. Sudden unexpected death occurs in 30–50 % of these patients, depending on how one defines sudden death. The sudden death rate has probably been reduced by the widespread use of implantable cardioverter defibrillators (ICDs), cardiac resynchronization therapy (CRT), and improved medical therapy over the past few decades. Still, the relative importance of an acute coronary event as a trigger for sudden death in patients with ischemic cardiomyopathy is high, as acute coronary findings are frequent in these patients at autopsy, even though they are not usually clinically diagnosed [47].

Recurrent myocardial infarction is likely a frequent cause of terminal HF in patients with chronic CAD.

Acute systolic HF syndromes occur in patients with CAD and healed myocardial infarction and may take many forms. These syndromes are defined as a rapid or gradual change in signs and symptoms in patients with chronic HF or new-onset HF that requires urgent therapy. Such episodes may present as acute coronary syndromes, often with some element of mitral regurgitation, and usually require investigation that includes coronary arteriography [47].

Left Ventricular Aneurysm

The term "LV aneurysm" or "true aneurysm" implies a discrete, dyskinetic area of the LV wall with a wide "neck" that is observed months or years after a STEMI. It is most commonly seen after a large anterior myocardial infarction. It should be differentiated from the far more common dyskinetic or akinetic areas of the left ventricle that occur early after STEMI and that may resolve or improve over time. Poorly contracting areas of the LV that are frequently seen early after STEMI are referred to as regional wall motion abnormalities and not LV aneurysms.

The wall of a true aneurysm is "old," thinned out, and composed of a combination of fibrous tissue, necrotic muscle, and, occasionally, some viable myocardium.

In Fig. 4.12a, true LV aneurysms vary in size but can be up to 8 cm in diameter. After many years, they may become somewhat calcified. Figure 4.12b, echocardiogram, and Fig. 4.12c, MRI, show features of LV aneurysm.

Unlike false aneurysms, true aneurysms rarely rupture. This is especially the case when they are quite old. One feature of true LV aneurysms is that they are usually subserved by a totally occluded coronary artery and have no collaterals or are very poorly collateralized.

Although true LV aneurysms are relatively inert, they can be a source of lethal ventricular arrhythmias. When death occurs, it can be sudden. Such aneurysms can also be a source of mural thrombus and systemic embolization.

Some physicians favor long-term anticoagulation with warfarin in these patients. Surgical aneurysmectomy is rarely performed today, unless contractile performance in the remaining ventricle is relatively preserved, and the patient has refractory angina, heart failure, arrhythmias, or systemic embolization.

Mitral Insufficiency

Mitral insufficiency stems from a structural problem involving the mitral valve; this can include the subvalvular apparatus, the annulus, the valve leaflets' chordae tendinae, papillary muscles, and left ventricular wall [48].

While there are many causes of mitral insufficiency, it is a well-known complication of acute myocardial infarction (AMI).

Mitral regurgitation as a consequence of AMI can be chronic and lead to progressive LV remodeling and chronic congestive HF. What happens more commonly, especially following a large STEMI, is that LV remodeling occurs as a response to the acute myocardial injury [41], the LV changes shape (becomes more spheroid) and dilates, the papillary muscles are displaced to some extent, and mitral regurgitation

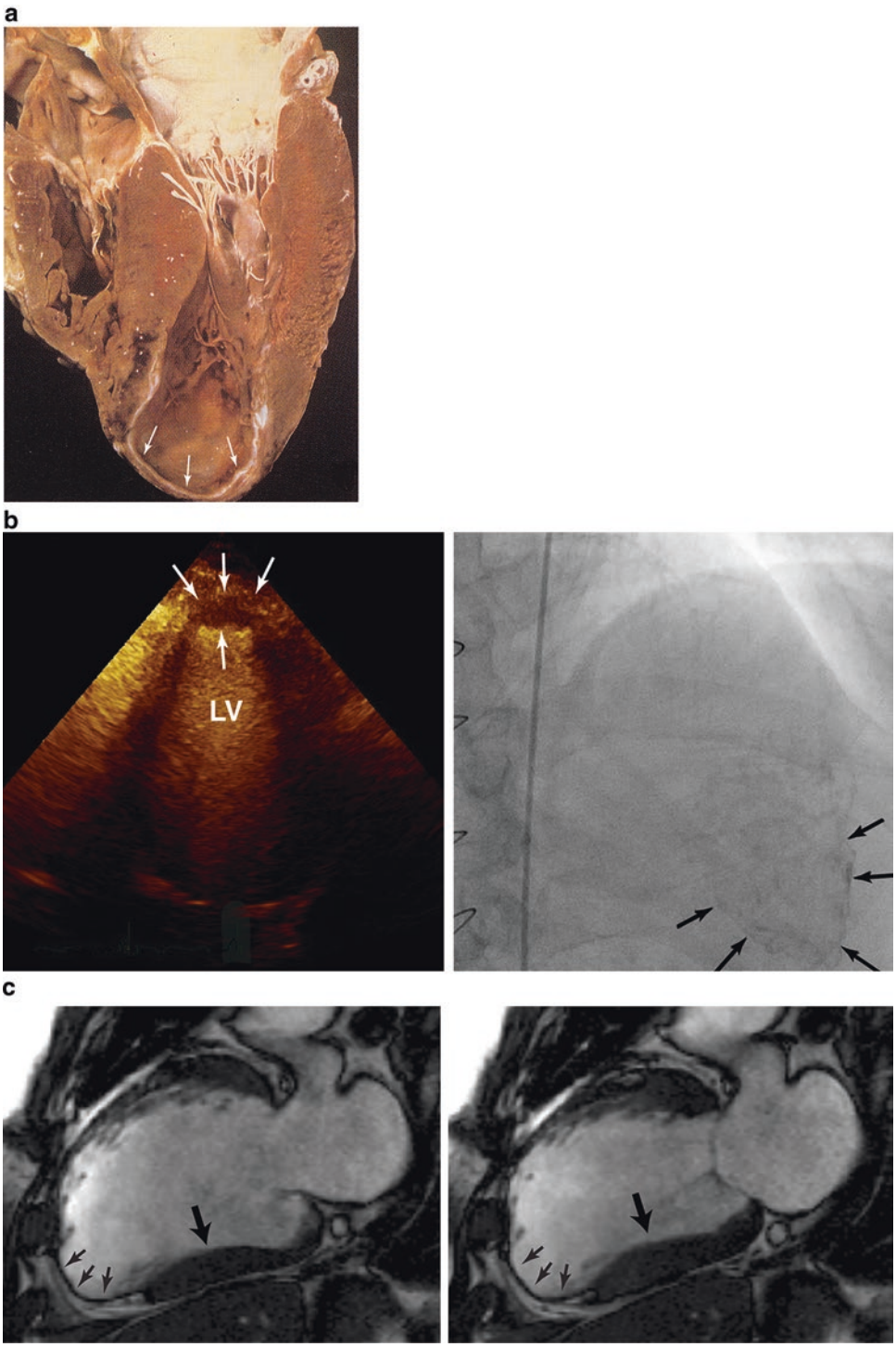


Fig. 4.12 (**a**) True LV aneurysm (*arrows*). Courtesy from Dr. Juan Manivel and Mr Dikoski Richard. Dept Pathology. V.A. Hospital, Minneapolis MN. (**b**) **Panel A**. Echocardiogram from a case with a previous healed myocardial infarction and LV aneurysm. **Panel B**. Chest film in RAO projection with LV aneurysm and calcified wall. (*arrows*). (**c**) **Panel A**. End-diastolic cineangiographic image on MRI shows wall thinning in the LAD distribution with no apparent myocardium present (*small arrows*). Normal myocardial thickness is present in the basilar inferior wall (*thick arrow*). **Panel B**. From the same patient cineangiographic image in end systole

more gradually ensues. Such cases are referred to as "functional" mitral insufficiency to distinguish them from mitral insufficiency as a consequence of structural abnormality of the mitral leaflets themselves, as might occur in mitral valve prolapse. So-called functional mitral insufficiency can become quite severe and can cause signs and symptoms of HF, requiring coronary artery bypass grafting (CABG) and repair or replacement of the mitral valve.

Postmortem study reveals a large LV with area of thinning of the wall affecting the papillary muscles (Fig. 4.13a).

Echocardiography often indicates papillary muscle dyssynchrony, widened vena contracta, mitral valve tenting, alteration of the mitral regurgitation color flow jet area to the left atrial area ratio, displacement of mitral leaflet coaptation, and often an eccentric mitral regurgitant jet. Echocardiographic features of "functional" mitral regurgitation from a patient with a history of previous inferior myocardial infarction and chronic heart failure is illustrated in Fig. 4.13b.

With mitral insufficiency, the LV internal chamber dimension is usually increased and the LV ejection fraction

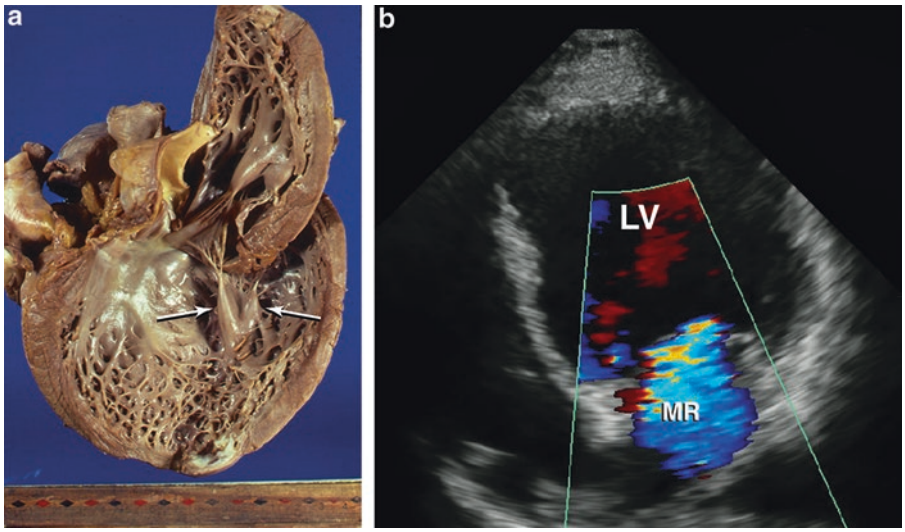


Fig. 4.13 (**a**) Large LV with area of thinning of the wall affecting the papillary muscles (*arrows*). (**b**) Apical four-chamber echocardiogram and color flow imaging in a case with previous healed myocardial infarction shows LV dilatation, apical akinesis, and severe mitral regurgitation (MR)

may be diminished. The left atrium may be enlarged if the mitral insufficiency has been chronic.

Preoperative LV viability studies are needed to plan surgical intervention, as the surgery can be high risk and some patients do not derive obvious benefit.

Whether mitral insufficiency is due to a dilated mitral annulus or distortion of LV, geometry is a matter of some controversy, as is the architecture of the subvalvular apparatus. Although both mechanisms may be operative, it is likely that LV geometric distortion and ischemia/infarction of the LV wall and the subvalvular apparatus are primarily responsible for the functional mitral insufficiency that occurs in patients with healed myocardial infarction and ischemic cardiomyopathy. Some element of mitral annular dilation may be present in patients with extremely dilated left ventricles, but for the most part, this probably plays a minor role in the genesis of functional ischemic mitral insufficiency.

Another myth is that surgically correcting the mitral insufficiency will mitigate the low-pressure circuit into the left atrium, thus causing an acute afterload stress on the heart and acute left HF following surgery. Although this can probably occur when there is little or no contractile reserve, more often than not, the wall stress (afterload) is actually *reduced* following correction of severe mitral insufficiency. As progressive LV remodeling is abrogated, the LV actually becomes smaller, and the wall stress diminishes gradually over time. Evidence from observational studies suggests that surgical intervention is beneficial [49].

Depressed LV function is an independent predictor of poor outcomes but is not a contraindication to mitral valve repair. In fact, earlier surgery seems to be creeping into our consideration of surgical treatment for this condition. It is unclear whether asymptomatic patients with severe mitral insufficiency who demonstrate no LV dysfunction or dilatation, atrial fibrillation, or pulmonary hypertension should undergo early surgery. In recent years, improved preoperative viability testing, better anesthesia, intraoperative transesophageal echocardiography, better control of rapid perioperative atrial fibrillation, and the ability to repair the mitral valve have led, in most cases, to improved survival for patients undergoing mitral valve surgery for functional ischemic mitral insufficiency.

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The Pathology of Cardiomyopathies

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_5

In 1972, Goodwin and Oakley defined cardiomyopathies as myocardial diseases of unknown origin and proposed three morphological types: dilated (DCM), hypertrophic (HCM), and restrictive or obliterative (RCM) [1]. In 1980, the World Health Organization (WHO) and the International Society and Federation of Cardiology (ISFC) introduced the term, specific heart muscle disease, where the cause of myocardial dysfunction was known [2]. This expanded the definition of cardiomyopathies by adding the functional component. Thus, the definition was expanded to diseases of myocardium with myocardial dysfunction.

This definition was used until 2006 when the American Heart Association (AHA) proposed a genetic-based classification [3]. It redefined cardiomyopathy as a heterogeneous group of diseases of myocardium associated with mechanical and/or electrical dysfunction, which usually (but not invariably) exhibit inappropriate ventricular hypertrophy of dilation, due to a variety of causes that frequently are genetic. With this modification, some cardiomyopathies could no longer be classified as idiopathic or heart muscle disease of unknown cause. Their cause has been discovered. In the AHA definition, primary cardiomyopathy referred to sole or predominant cardiac involvement. It did not mean diseases of myocardium associated with myocardial dysfunction as in the WHO/ISFC classification. The term secondary cardiomyopathy was used when dysfunction was part of a systemic process, excluding coronary, hypertensive, valvular, or congenital heart disease.

In 2008, the European Society of Cardiology developed a classification, which included two aspects: a morpho-functional phenotype and an etiologic description [4]. Cardiomyopathy was defined as a myocardial disorder in which the heart muscle is structurally and functionally abnormal. The phenotypes, which are used in day-to-day clinical practice, are: dilated, hypertrophic, restrictive, arrhythmogenic right ventricular cardiomyopathy, and unclassified variety. The accompanying etiologic classification is either familial genetic or nonfamilial nongenetic. The cardiomyopathy was defined as familial when present in more than one member of the family. A genetic cardiomyopathy is sporadic when the causative mutation is de novo—occurring for the first time in a single-family member.

In this chapter we adapt the AHA classification. There are two groups of cardiomyopathies: primary and secondary. These will be discussed separately. Primary cardiomyopathy is discussed in this chapter. This condition is predominantly confined to the myocardium and may include genetic, nongenetic, or acquired diseases.

Genetic

Hypertrophic Cardiomyopathy

The condition hypertrophic cardiomyopathy has been extensively studied. Details of its pathologic and physiologic features have been studied by many investigators [5, 6]. HCM is a complex cardiac condition characterized by variable degrees of left ventricular (LV) hypertrophy. It is not associated with defined causes of LV hypertrophy, such as systemic hypertension, but with mutations in sarcomeric protein genes. It is a common genetic heart disease, occurring as an autosomal dominant condition [7]. The prevalence is reported to be 1:500 individuals in the general population, which yields an estimate of over one million in Europe alone.

The hypertrophy may be either asymmetrical, involving primarily the ventricular septum, or symmetrical, involving both the septum and the free wall. The right ventricle may be involved as well. HCM may obstruct the left ventricular outflow tract. The obstructive form historically has been called hypertrophic obstructive cardiomyopathy (HOCM) and idiopathic subaortic stenosis (IHSS), reflecting the obstruction of the subaortic area by the hypertrophied ventricular septum (Fig. 5.1a). Systolic movement of the anterior leaflet of the mitral valve toward the ventricular septum contributes to the obstruction in many patients. In some of these patients, mitral regurgitation occurs as well, often from coexistent abnormalities of the mitral valve itself. These include mitral valve prolapse and insertion of the papillary muscle directly into the valve leaflets (absent chordae) cusps. The area of the ventricular septum where the mitral valve repeatedly strikes develops a fibrous plaque, often referred to as "SAM" (systolic anterior motion) lesion (Fig. 5.1b). Histologically, there is disarray of myocardial fibers from the normal linear orientation. The fibers run in various directions (Fig. 5.1c). The myocardial cells are significantly hypertrophied, and there is often increased interstitial fibrosis, which affects ventricular compliance and, ultimately, leads to decreased systolic and diastolic function.

Microvascular ischemia and myocardial fibrosis may be present, and intramyocardial arteries are often dysplastic.

Hemodynamically, patients with asymmetrical HCM often exhibit dynamic LV outflow obstruction either at rest or with physiological provocation. Mitral valvular regurgitation related to systolic anterior motion of the anterior leaflet of the mitral valve also may contribute to the outflow tract obstruction. With the onset of ventricular systole, there is normally rapid early ejection of blood into the aorta; then, as the anterior leaflet of the mitral valve contacts the ventricular septum, a marked reduction in outflow takes place until late systole. The degree of obstruction is affected by changes in myocardial contractility, afterload, and preload. An increase in contractility as from inotropic agents, a decrease in preload as from a Valsalva maneuver, or a decrease in afterload from standing increases the gradient between the left ventricle and aorta. The opposite effects in each of these changes results in a decreased gradient.

In both forms of the condition, in addition to the development of systolic dysfunction, the left ventricle becomes stiffer because of myocardial hypertrophy and fibrosis. Ventricular relaxation becomes limited. Adverse effects of systolic and diastolic dysfunction result.

The LV outflow obstruction may cause dyspnea, chest pain, and presyncope. Heart failure is uncommon, except in

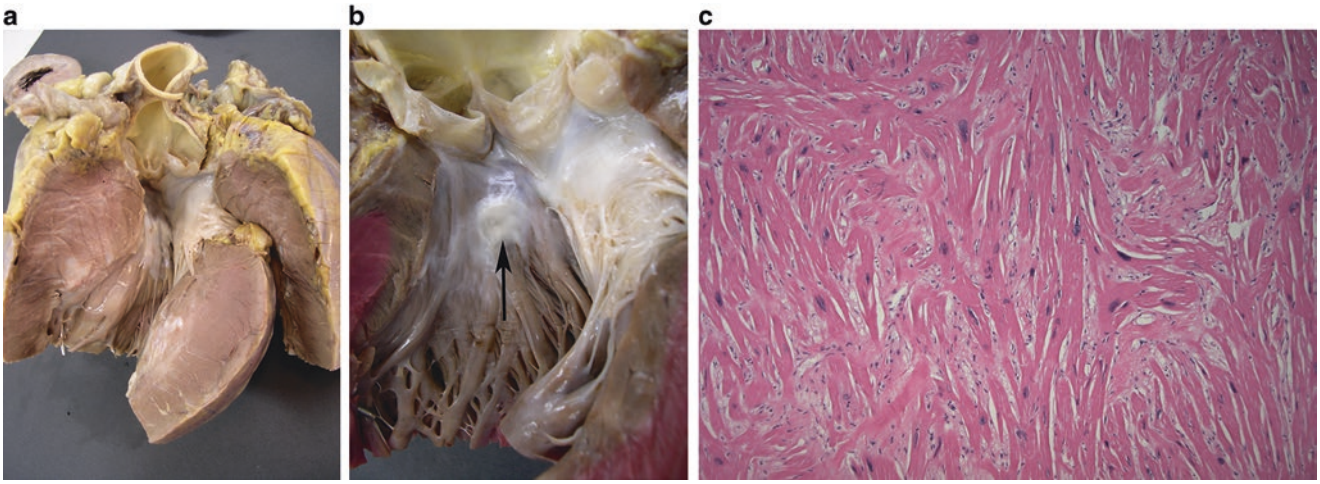

Fig. 5.1 (**a**). Hypertrophic cardiomyopathy. Left ventricular outflow tract view showing marked left ventricular hypertrophy, outflow tract obstruction, and systolic anterior motion lesion. (**b**) Closer view of systolic anterior motion lesion (*arrow*) in left ventricular outflow tract. (**c**) Myocyte disarray, hallmark histologic feature of hypertrophic cardiomyopathy (H&E; 40×)

the subgroup of patients who develop end-stage disease, which manifests itself as extensive myocardial fibrosis, often with markedly dysplastic intramyocardial arteries. Sudden death may be the initial presentation of the disease and represents the target of preventive efforts.

On physical examination, the arterial pulses are sharp from the rapid ejection during the first part of systole. The apex may be displaced leftward and a left ventricular heave palpated. The first and second heart sounds are normal, but the third and fourth heart sounds are present in about half of patients. A systolic ejection murmur is present in most patients, its loudness increases with maneuvers, which accentuate contractility or reduce pre- or afterload (standing, straining on a Valsalva maneuver, nitroglycerine).

Echocardiography enables assessment of the degree and location of ventricular hypertrophy, the degree of obstruction, and its significance. Systolic and diastolic function can be assessed (Fig. 5.2a, b). Mitral regurgitation can be recognized and its severity analyzed. If the ratio of the ventricular septum to free wall exceeds 1.2:1, the diagnosis of HCM is strongly suspected. Also, absolute measurements of the free wall and septum can be made and compared to normal.

Although echocardiography is an excellent technique for assessing patients with HCM, it is occasionally limited by poor acoustical windows, incomplete visualization of the left ventricular wall, and inaccurate evaluation of the left ventricular mass. MRI has the ability to evaluate wall thickness and the distribution of involvement better than echocardiography, especially in the anterolateral wall of the LV (Fig. 5.2c).

In the differential diagnosis, glycogen storage diseases must be considered. Although uncommon, their clinical features and prognosis differ from classic hypertrophic cardiomyopathy. Mutations have been found in LAMP2 and PRKAG2 genes in patients with ventricular hypertrophy. In the LAMP2 variant, myocardial cells have prominent cytoplasm, many vacuoles, and pleomorphic nuclei (Fig. 5.3). Patients present with symptoms similar to hypertrophic cardiomyopathy, but usually at a younger age, and the prognosis is poor. Patients have concentric hypertrophy and pre-excitation electrocardiographically. In the PRKAG2, variant shows ventricular hypertrophy and prolonged survival. Progressive conduction system involvement may require placement of a pacemaker and control of arrhythmias.

Arrhythmogenic Ventricular Cardiomyopathy

Historically, this condition has been called dysplasia, but this is inaccurate, and the term has largely been eliminated [8]. This is a common genetically determined myocardial disorder, which may involve primarily the right ventricle, primarily the left ventricle, or both. It is characterized by fibrofatty replacement of the right ventricular (RV) or left ventricular (LV) myocardium. In the early disease stage, structural changes may be absent or subtle. The changes are initially confined to a localized region of a ventricle. In the right ventricle, the area may be in the inflow tract, outflow tract, or apex. In the left ventricle, the findings are within the subepicardial myocardium (Fig. 5.4a).

Patients are often asymptomatic in the early disease stages but are at risk of sudden death, particularly with exercise. In the electrical phase, individuals present with symptomatic arrhythmias and morphological RV abnormalities, recognized by imaging of the heart (Fig. 5.4b). Later still, with more diffuse involvement, biventricular heart failure develops, resembling dilated cardiomyopathy.

Arrhythmogenic cardiomyopathy (AC) is familial with autosomal dominant inheritance. There are recessive forms, however, including Naxos disease and Carvajal syndrome.

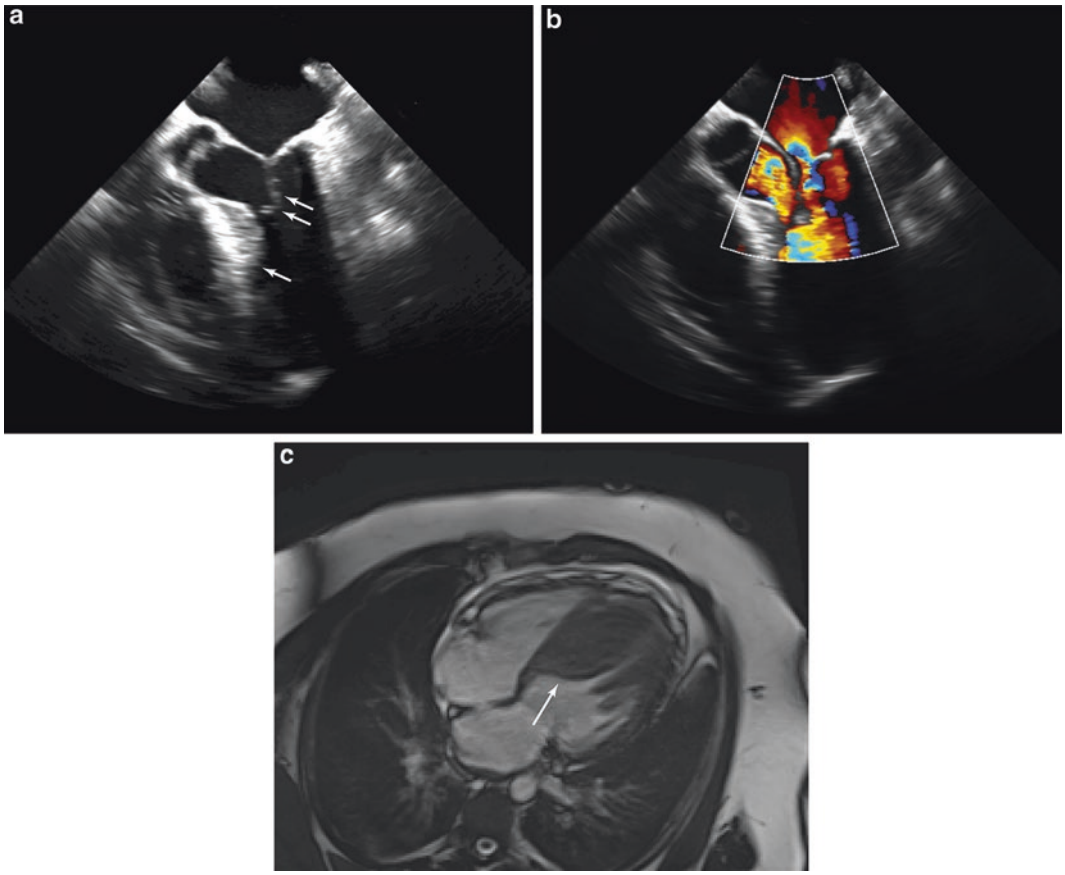

Fig. 5.2 (**a**) Hypertrophic cardiomyopathy. Transesophageal echocardiogram. Four-chamber view. Markedly thickened interventricular septum (IVS) (arrow). The anterior leaflet of mitral valve displaced toward the IVS (SAM) narrows the LV outflow tract (arrows). (**b**) Color Doppler shows posteriorly directed jet of mitral regurgitation. (**c**) Cardiac MRI. Axial view. Marked thickness of IVS (*arrow*). In contrast, thickness of posterior wall (PWLV) is normal

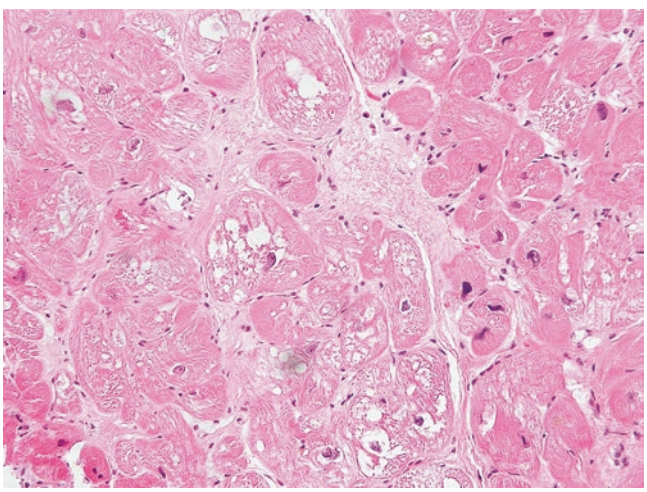

Fig. 5.3 Markedly hypertrophic myocytes with numerous cytoplasmic vacuoles, characteristic of glycogen storage disease, which may mimic hypertrophic cardiomyopathy clinically (H&E; 40×)

Left Dominant Arrhythmogenic Cardiomyopathy (LDAC)

As the study of ARVC progressed, it became evident that the spectrum was broader than originally thought. Recently, forms of predominant involvement of the left ventricle have been reported [9]. These patients tend to have inverted T waves in the lateral and inferior EKG leads and ventricular arrhythmias of left ventricular origin. The frequency and severity of arrhythmias are greater than the extent of left ventricular dysfunction. There is an enlargement of the left ventricle with reduced systolic function. Dyskinesis may coexist. Pathologically, this form of the condition is characterized by subepicardial fibrofatty replacement of the myocardium and compact myocardium of the septum. These changes are often circumferential but may be confined to the free walls only. The posterior wall is the most frequently involved wall. Myocyte degeneration is present in myocytes entrapped within the areas of fibrosis, and foci of myocarditis are often present (Fig. 5.5).

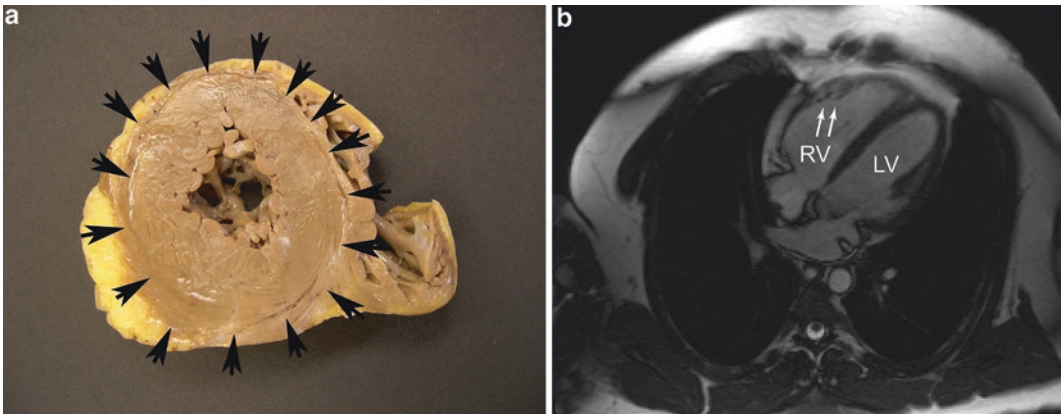

Fig. 5.4 (**a**) Arrhythmogenic cardiomyopathy/ventricular cross-sectional slice containing circumferential subepicardial fibrofatty replacement of the left ventricular free walls and compact myocardium of the septum, characteristic gross finding of arrhythmogenic cardiomyopathy, left ventricular dominant form (*arrows* point to subepicardial and septal fibrofatty replacement). (**b**) Arrhythmogenic cardiomyopathy. Cardiac MRI. Axial views. Right ventricular (RV) enlargement. Fatty replacement (*arrows*) of cardiac muscle in RV wall

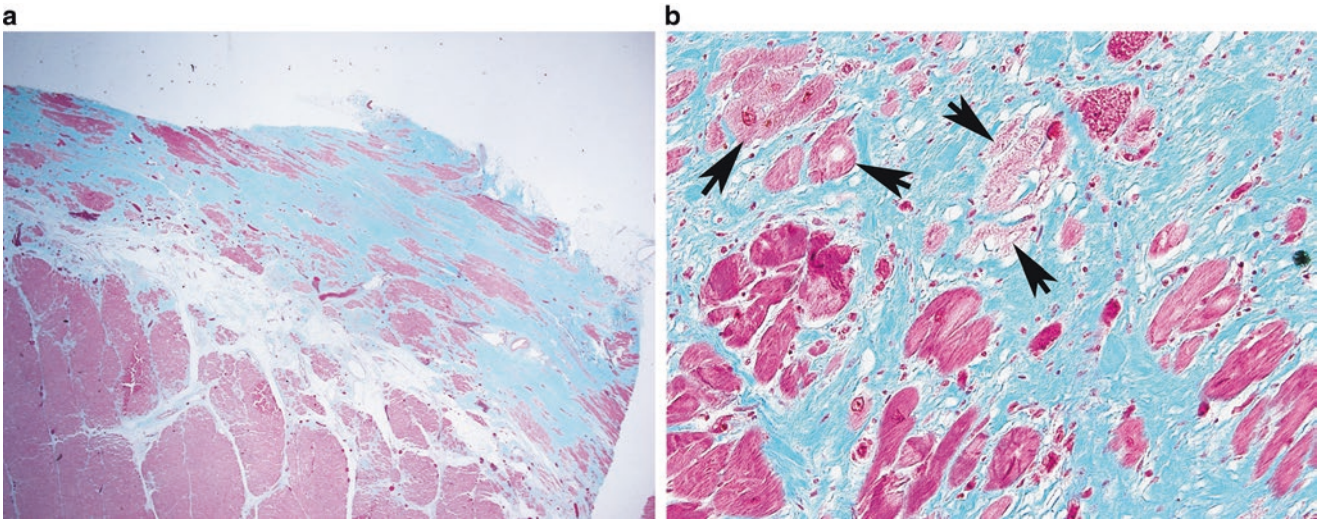

Fig. 5.5 (**a**) Fibrofatty replacement of the subepicardial myocardium of the free wall of the left ventricle in a band-like distribution, hallmark histologic finding of arrhythmogenic cardiomyopathy, left ventricular dominant form (Masson's trichrome; 1.25×). (**b**) Photomicrograph demonstrating degeneration of entrapped myocytes within the areas of fibrofatty replacement (at *arrows*), a histologic requirement of arrhythmogenic cardiomyopathy (Mason trichrome; 40×)

LV Noncompaction (LVNC)

LVNC, previously termed "spongy myocardium," is a rare cardiomyopathy that can be diagnosed at any age. It probably results from arrest of the compaction process during development. During cardiac development, the myocardium is trabeculated and gradually becomes denser and compacted. If this process does not occur, a spongiform cardiomyopathy results.

LVNC is characterized by a thin, compacted subepicardial layer and an extensive noncompacted subendocardial layer. The subendocardium has prominent trabeculations and deep recesses that communicate with the cavity of the LV, particularly at the apex and mid-portion of the ventricle (Fig. 5.6a, b). It does not communicate with the coronary circulation. The compacted section may be thinned. A ratio of noncompacted to compacted myocardium of 2:1 at the end of systole has been considered a criterion for diagnosis. The trabeculae have the same appearance as the noncompacted myocardium and move synchronously with ventricular contraction. A second form characterized by hypertrabeculation also is recognized.

Since it was relatively recently described, we do not know the exact occurrence of LVNC, but it may be present in 1:500 individuals. It may be isolated or coexist with cardiac abnormalities. The proportion coexisting with other abnormalities of the heart may be exaggerated, since it is identified by echocardiography or other imaging techniques which many

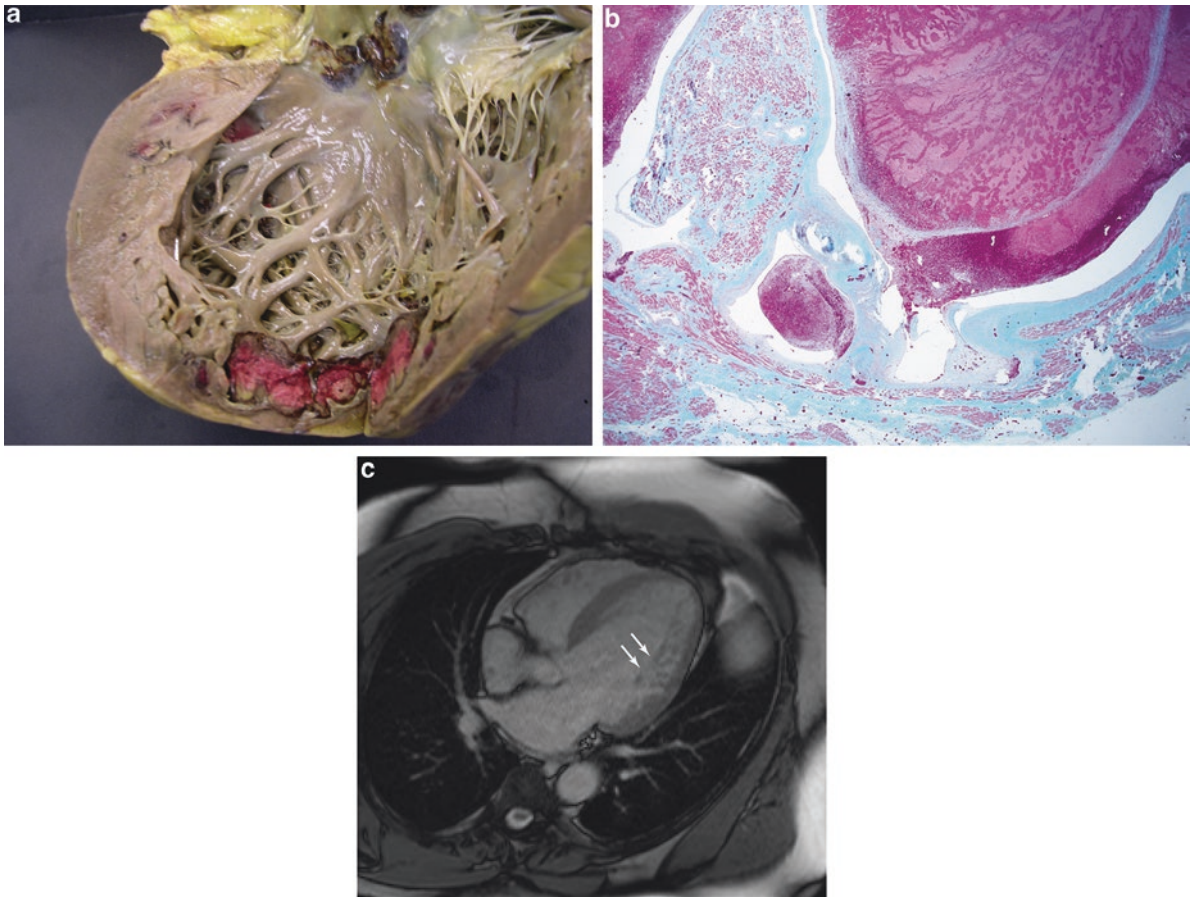

Fig. 5.6 (**a**) Noncompaction. Left ventricular apex with poorly formed compact myocardium, large trabeculae, and apical mural thrombus. (**b**) Photomicrograph from (**a**) demonstrating the large trabeculae and intratrabecular recesses with mural thrombus. There is marked myocardial fibrosis (Mason trichrome; 1.25×). (**c**) Left ventricular noncompaction. Cardiac MRI. Axial view. Noncompacted areas (*arrows*) show prominent trabeculation and deep intertrabecular recesses

cardiac patients undergo. The prevalence lies between 0.014 and 1.3 % in the general population as observed on echocardiographic examinations.

Symptoms of LVNC vary. Many patients are asymptomatic. Symptomatic patients can have congestive heart failure, life-threatening ventricular arrhythmias, and embolic events [10]. There may be both systolic and diastolic dysfunction contributing to the failure. In children, Wolff-Parkinson-White syndrome and ventricular tachycardia occur more commonly, while atrial fibrillation and ventricular arrhythmias are found in adults. Embolization is secondary to mural thrombi in the trabeculations, ventricular dysfunction, or atrial fibrillation. Sudden death is uncommon in this disease.

Both familial and nonfamilial forms have been reported [4]. In familial forms, inheritance may be autosomal dominant, X-linked, or mitochondrial. A number of genes may be associated with LVNC. Family members of a patient with this condition should be screened to identify individuals who may be asymptomatic. The increased incidence of neuromuscular diseases in patients with LVNC suggests careful clinical evaluation of the muscular and neurological systems.

In making this diagnosis, it is critical to have images of the cardiac apex. These are obtained best by magnetic resonance imaging (Fig. 5.6c).

Molecular Cardiomyopathies

Ion Channelopathies

Ion channelopathies are probably more common than HCM. They are inherited disorders causing arrhythmias [11]. They are associated with mutations of the genes encoding ionic channel proteins, which modulate cell membrane transit of sodium, potassium, and calcium ions. Several specific conditions have been identified which can be identified by their electrocardiographic features. They are associated with cardiac dysrhythmias, syncope, and sudden death. They may be transmitted in autosomal dominant or recessive patterns; however, autosomal dominant is more common.

The most common of these is the long QT syndrome in which the QT interval is prolonged. It is associated with a

polymorphic ventricular tachycardia and a considerable risk of syncope and sudden death. Many mutations are associated with this condition. It can coexist with deafness and is termed the Jervell and Lange-Nielsen syndrome [12], or, without deafness, called Romano-Ward syndrome [13]. The former is an autosomal recessive trait and the latter an autosomal dominant trait. Several individual genes controlling primarily potassium channels have been identified and, if found, these are useful in making the diagnosis.

Another channelopathy is the Brugada syndrome [14]. It has a characteristic electrocardiographic pattern showing complete right bundle branch block and ST segment elevation in the anterior precordial leads. It is associated with sudden death. The Brugada syndrome is found in Southeastern Asian men and, in that culture, has been given various names associated with beliefs about the causation.

In the Short QT syndrome [15], the QT interval is less than 330 msec. The T waves are tall and peaked as in hyperkalemia. Ventricular tachycardia or fibrillation can lead to sudden death.

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

CPVT is a rare arrhythmogenic disorder with two defined genetic patterns, one being autosomal dominant and the other autosomal recessive. The mutation involves calcium channels or proteins related to calcium channels.

Patients have no structural cardiac anomaly and a normal electrocardiogram. Patients manifest bidirectional and polymorphic ventricular tachycardia induced by exercise or other adrenergic stress. Often the symptoms present by age 20 years as a fainting spell which may be associated with a seizure. This may be considered as a primary neurologic condition, so the diagnosis of CPVT is delayed. Holter monitoring or exercise stress tests show monomorphic or polymorphic premature ventricular beats or bidirectional or polymorphic VT. Atrial premature beats, atrial tachycardia, and atrial fibrillation commonly coexist [16]. A careful family history revealing exercise-induced syncope or sudden death is very helpful in pursuing a diagnosis of CPVT.

Mixed (Genetic and Nongenetic)

Dilated Cardiomyopathy

Dilated cardiomyopathy is a condition of reduced ventricular function that is unrelated to causes such as myocardial infarction or systemic hypertension. The coronary arteries are not significantly narrowed by atherosclerosis. The heterogeneous group of conditions that causes DCM is characterized by marked LV dilatation with mild hypertrophy of the ventricular wall (Fig. 5.7a). While both ventricles may be involved, it is mainly the LV function that is affected with reduced contractility, leading to progressive congestive heart failure. With the dilatation, mitral regurgitation develops as the papillary muscles are displaced outward. A secondary complication is the development of mural thrombi in the cardiac apex or atria if atrial fibrillation develops. Systemic or pulmonary embolization is a complication of these thrombi.

Histologically, the findings range considerably. In most instances, varying degrees of fibrosis and myocardial degeneration are observed. Foci of myocytolysis may be present. Diffuse interstitial fibrosis may be found. Lymphocytes may be present in interstitial areas and found in perivascular locations. The nonspecific nature of the histologic changes precludes making a diagnosis of dilated cardiomyopathy on the basis of biopsy alone.

The patient presents with symptoms and signs of progressive reduction in systolic function of the left ventricle. Initially, there is fatigue on exertion which progresses to reduced exercise tolerance. As the LVED pressure becomes elevated, dyspnea and orthopnea develop. These symptoms may be associated with rales and signs of right heart failure with hepatomegaly and neck vein distension. With dilatation of the atria, atrial fibrillation occurs. Conduction abnormalities may result from myocardial fibrosis.

The diagnosis is made by echocardiography, which shows abnormalities before the patient has symptoms of the DCM. The findings are diffuse and show enlarged, poorly contracting ventricles (Fig. 5.7b). Ventricular dimensions are increased, and the ejection fraction is reduced. On echo Doppler, evidence of atrioventricular regurgitation from the ventricular dilatation may be found (Fig. 5.7c). Coronary arteriograms in these patients will reveal normal features (Fig. 5.7d, e). Thrombi may be identified in the cardiac apex or atria.

DCM occurs most often in the third and fourth decades of life but can occur at any age, including infancy. Dilated cardiomyopathy is largely irreversible. It is a common cause of heart failure and the most frequent cause of heart transplantation (Elliot et al., [4]).

This form of cardiomyopathy occurs from a variety of origins. About one-third are reported as familial [17]. The predominant mode of inheritance is autosomal dominant, as an X-linked autosomal recessive trait has been identified. Mitochondrial inheritance occurs less frequently. Peripartum cardiomyopathy, alcoholic cardiomyopathy, and chemotherapy-related cardiomyopathy are three distinct clinical situations where it occurs, but they lack specific histologic features. Dilated cardiomyopathy with or without lymphocytic infiltrates has been described in some patients with immune deficiency syndrome. Many types of infectious disease, particularly viral, but also bacterial and fungal, also can involve the heart and may result in dilated cardiomyopathy. In addition, patients with various muscular dystrophies develop DCM as their skeletal muscle disease progresses. The symptoms may be muted by the patient's reduced ability to exercise because of the skeletal myopathy.

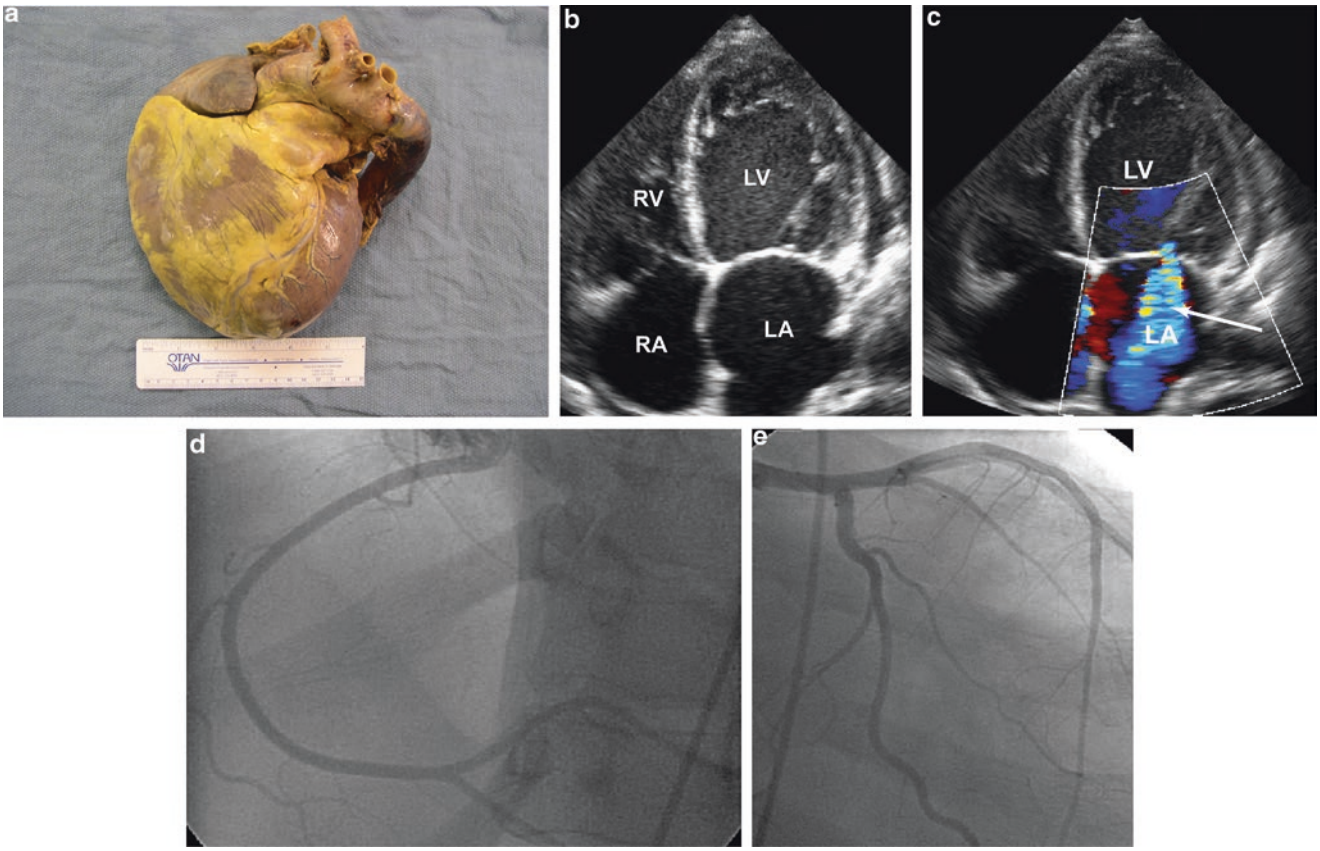

Fig. 5.7 (**a**) Dilated cardiomyopathy with marked four-chamber enlargement and globular shape of the heart. (**b**) Dilated cardiomyopathy. Echocardiogram. Apical four-chamber view. Diffuse dilatation left ventricle (LV), left atrium (LA), and right atrium (RA). (**c**) Color Doppler from (**b**) demonstrates moderate to severe mitral regurgitation (arrow). (**d**) Normal left coronary arteriogram from patient in (**b**). (**e**) Right coronary arteriograms from same patient in (**b**); normal features are present

Primary Restrictive Nonhypertrophied Cardiomyopathy

Primary restrictive nonhypertrophied cardiomyopathy is the least common type of cardiomyopathy. It is associated with biatrial enlargement, a normal- or small-sized LV and RV, and normal atrioventricular valves and ventricular wall thickness [18]. The histologic appearance is often normal, but may show hypertrophied myocytes and interstitial fibrosis. Some cases result from autosomal dominant inheritance, but most appear sporadic.

The functional effect is limited ventricular filling. It appears as if the compliance of this chamber is reduced, so filling is impaired. Systolic function is normal or near normal. With reduced ventricular compliance, the pressure in the corresponding atrium is elevated. The left atrium enlarges, often significantly. Pulmonary venous pressure increases, leading to pulmonary edema. Pulmonary hypertension is associated because of reflex pulmonary vasoconstriction. With the elevated pressures in the right ventricle and atrium, systemic venous pressure increases as well.

The patient's primary symptoms and signs are those of pulmonary venous obstruction and right heart failure. Respiratory symptoms are prominent with dyspnea, fatigue, and reduced exercise tolerance. Sudden death may occur [19]. No murmur is present on physical examination, but the pulmonary component of the second heart sound is accentuated. Gallop rhythm may be found. The liver is enlarged and the jugular venous pulses increased.

Echocardiograms show greatly increased atrial size in the presence of normal atrioventricular valves. Ventricular sizes are normal, but ventricular function may decrease with time. Ventricular diastolic function is decreased as indicated by an elevated E/A ratio and measurement of atrial-pulmonary vein reversal parameters.

Acquired

Myocarditis (Inflammatory Cardiomyopathy)

Myocarditis is an inflammatory disease of the myocardium with cardiac dysfunction. It is most commonly of viral origin. At least half of patients recover, perhaps a quarter of patients progress to cardiac failure, and an

Table 5.1 Causes of myocarditis

Infectious agents
1. Viral: group B coxsackievirus, influence A and B virus, adenovirus, parvovirus B19, HIV, cytomegalic virus, enterovirus, hepatitis C virus, Epstein-Barr virus
2. Bacterial: diphtheria, mycoplasma pneumonia, meningococcal, psittacosis, streptococcus staphylococcus, tick-borne bacterium
3. Rickettsia: typhus, Rocky Mountain spotted fever, fungal (*Aspergillus fumigatus*)
4. Parasitic (*Trypanosoma cruzi* in Chagas disease, *Toxoplasma gondii*)
5. Fungi: *Candida*, *Aspergillus*, *Histoplasma*
Toxins and drugs
Cocaine, interleukin, as well cases with giant cell myocarditis and endocardial fibroelastosis
Other diseases
These include lupus, connective tissue disorders, and rare inflammatory conditions, such as Wegener's granulomatosis

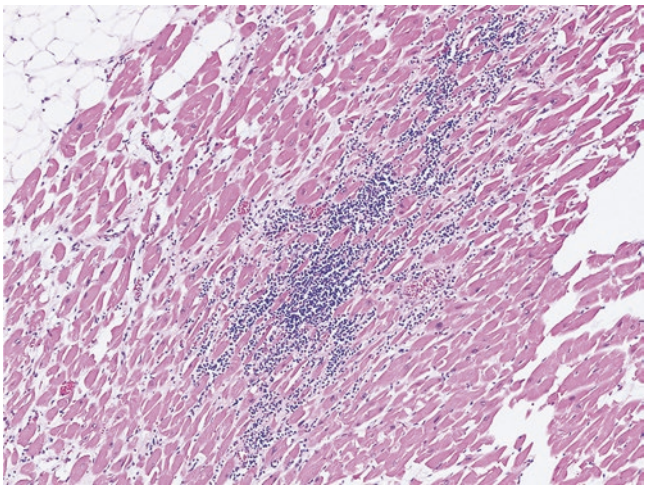

Fig. 5.8 Prominent lymphocytic infiltrate with definite myocyte injury, classic histologic findings in lymphocytic myocarditis (H&E; 10×)

unknown percentage die suddenly. The gross appearance of the heart is often unremarkable, even in the presence of diffuse histologic changes. It may be diffusely dilated in acute myocarditis. The natural history of myocarditis is frequently characterized by the evolution to a dilated cardiomyopathy.

Clinical features vary considerably from being asymptomatic to unexplained congestive heart failure. In patients with myocardial involvement by an infectious disease, the only manifestation is isolated ST segment changes. Other patients may have a period of tachycardia and easy fatigability, which gradually resolves. With more severe cardiac involvement, congestive cardiac failure develops rapidly and presents a major problem in management. LV dilatation and/or segmental wall motion abnormalities are observed on an echocardiogram. Another serious clinical issue relates to the conduction system. A variety of arrhythmias and conduction abnormalities develop which can be associated with syncope and, occasionally, sudden death. Usually, the electrocardiographic changes are temporary and resolve with time. LV dilatation and/or segmental wall motion abnormalities are observed on an echocardiogram.

Life-threatening arrhythmias may occur in both the acute and healed stages of the disease. The wide spectrum of clinical forms ranging from subclinical to severe depends on various factors, such as the infectious agents, genetics, age, and gender of the patient and underlying immunocompetence.

Different infectious agents and a variety of toxins and drugs have been implicated as causes of myocarditis [20] (Table 5.1). Toxins such as anthracyclines and cocaine can diffusely damage myocardium and result in the histologic features of myocarditis. Viral myocarditis can trigger an autoimmune reaction that causes damage to the myocardium and skeletal muscles.

Early and definitive diagnosis of myocarditis still depends on detection of inflammatory infiltrates in endomyocardial biopsy specimens (Fig. 5.8). Immunohistochemistry has not been useful in identifying cell populations or the causative agent.

Stress (Takotsubo) Cardiomyopathy

Stress or "takotsubo" cardiomyopathy has been described as a stress-induced cardiomyopathy or as an apical ballooning syndrome. It is an acquired condition that disproportionately affects women [21]. It occurs abruptly after a profound psychological stress, an acute medical illness, or major neurologic event and results in myocardial injury. Patients usually present with chest pain and electrocardiographic abnormalities of ST segment elevation as with an acute myocardial infarction. About a quarter of patients have mild to moderate congestive cardiac failure on presentation. Sudden death is uncommon but may occur. Moderate troponin elevation is found. Echocardiographic and other left ventricular imaging techniques show preserved basilar function but akinesis or hypokinesis of the cardiac apex.

The name takotsubo refers to the characteristic image of the apex, which resembles a Japanese fishing pot designed to capture octopus. The apex has a narrow neck and a fat, round body. Wall motion abnormality and significant reduction of global LV function are evident (Fig. 5.9).

Many patients have an excellent prognosis with full recovery of LV function, but the long-term consequences are

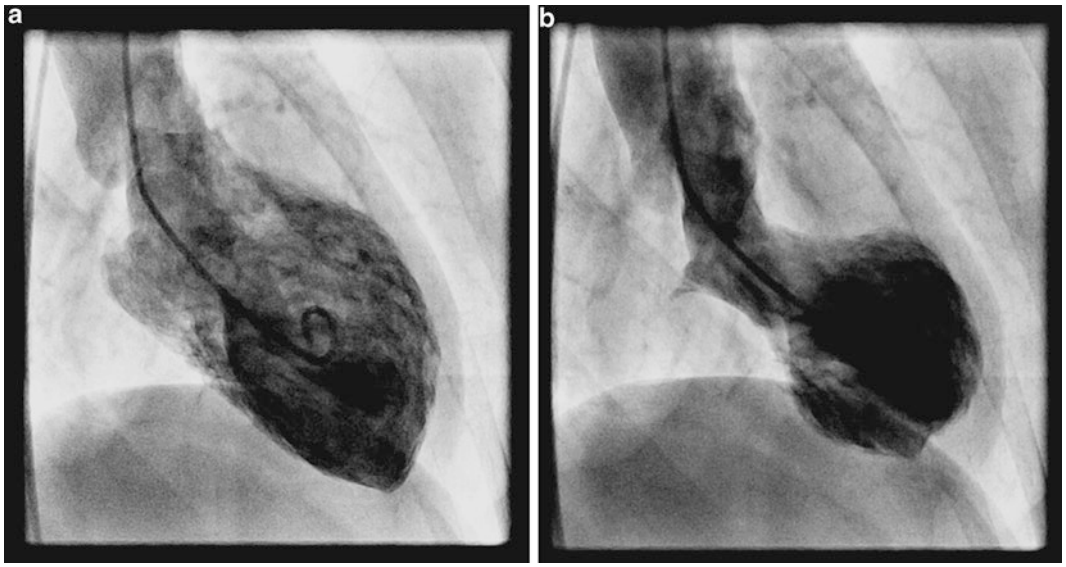

Fig. 5.9 Stress cardiomyopathy. Left ventriculogram. RAO view in 30° projection. (**a**) Diastole. (**b**) Systole. Large anterior wall motion abnormality

unknown. In those with congestive cardiac failure, there may be significant myocardial fibrosis. Mechanisms for the injury to the myocardium include effects of excess catecholamines, coronary spasm, and microvascular dysfunction induced by the extreme distress. The most widely accepted mechanism is excess plasma catecholamines, increased epinephrine release from the adrenal medulla, and increased sympathetic tone. Multiple focal areas of myocardial ischemia are often found scattered throughout the myocardium. Evidence of cell injury and death may be present.

Peripartum (Postpartum) Cardiomyopathy

Peripartum cardiomyopathy occurs late in pregnancy or in the first 5 months following delivery. The woman develops symptoms of cardiac failure, and echocardiographic findings show increased LV size and decreased systolic function.

The pathophysiology is unclear. One consideration is a disturbed oxidative stress, which cleaves prolactin into a potent antiangiogenic, proapoptotic, and proinflammatory substance [22]. This theory could lead to discovery of disease-specific biomarkers and novel targets for therapy.

The development of peripartum cardiomyopathy appears to begin with an unknown trigger that initiates an inflammatory process. This process leads to myocardial injury and development of cardiomyopathy. This form of cardiomyopathy occurs most frequently in obese, multiparous women 30 years old or older and in women with preeclampsia. About half of the women recover within 6 months; others may have progressive clinical deterioration leading to heart failure or death or require transplantation.

Amyloid Cardiomyopathy

Amyloid cardiomyopathy is a primary cardiomyopathy as part of a systemic disease or rarely with isolated cardiac involvement. It is a restrictive disease and affects diastolic function. It may be present only in the heart or as one of a number of organs affected by amyloid. It exists as several forms: primary cryptogenic, with multiple myeloma, with non-Hodgkin lymphoma, as a reaction to a chronic disease, or in a senile form. Identifying an underlying disease is useful in directing management. Amyloid is one of the most common causes of cardiomyopathy found on cardiac biopsy.

Amyloidosis results from abnormal protein metabolism so that abnormal amyloid is deposited within the interstitium and blood vessel walls (Fig. 5.10). The principal cardiac change is an increase in wall thickness, be it ventricular septum, free walls, or papillary muscles. As in restrictive physiology, atrial enlargement is present. Deposits may be found on the endocardial surface or in the conducting system. The cardiac involvement produces angina, heart failure, and arrhythmias.

There may be evidence of other organ involvement, such as enlarged lymph nodes, tongue, and liver.

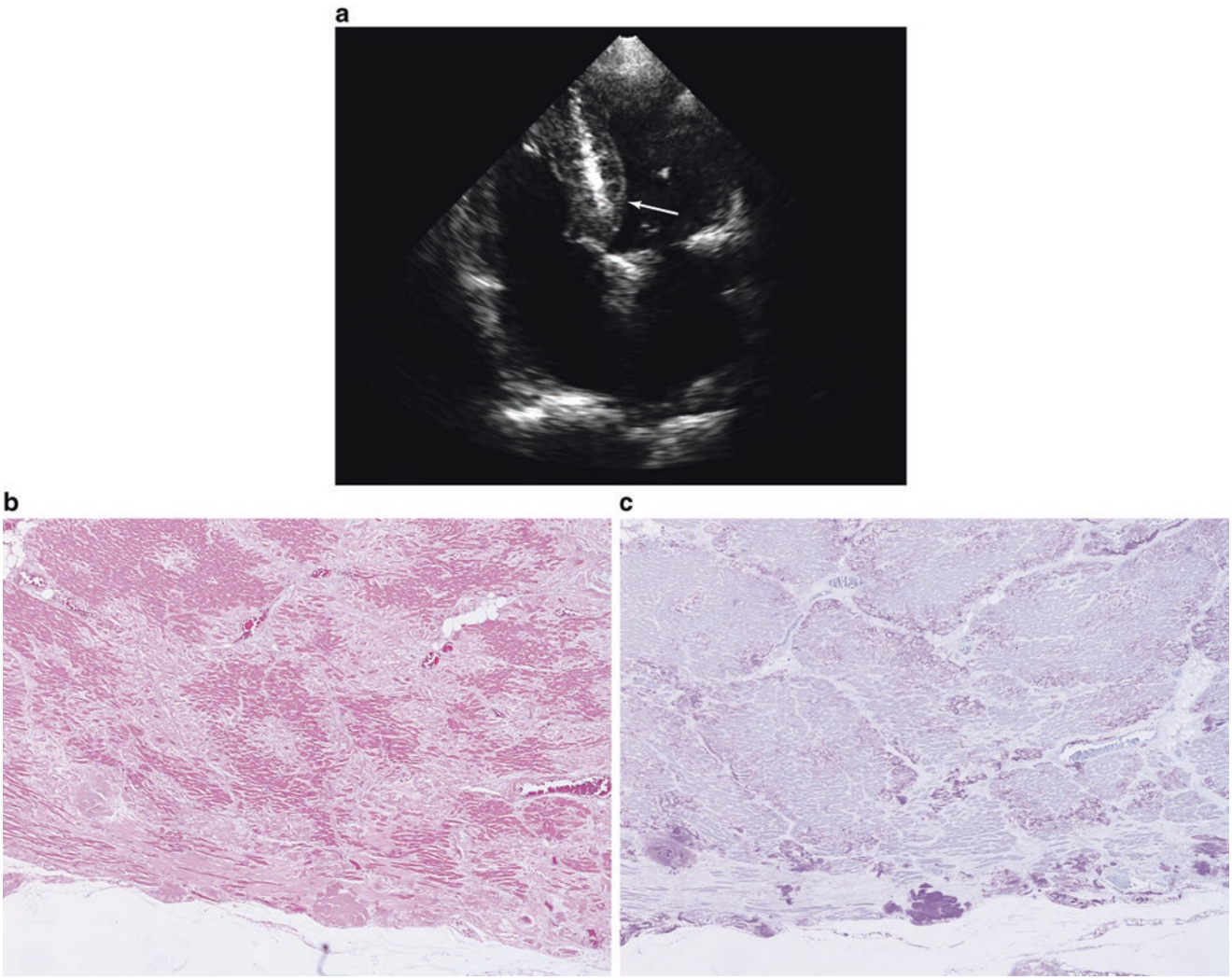

Fig. 5.10 Cardiac amyloidosis. (**a**) Echocardiogram. Apical four-chamber view. Thickening of the interventricular septum (arrow) with "granular" appearance. (**b**) Pale-staining eosinophilic material within the interstitium is amyloid (H&E; 1.25×). (**c**) Crystal violet stain highlights the amyloid material, which stains dark purple (1.25×)

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Epidemiology of Heart Failure

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_6

Introduction

Heart failure (HF) is described as an "emerging epidemic" or "the cardiovascular epidemic of the twenty-first Century" [1, 2]. Currently, it is estimated that 5.7 million Americans over 20 years have heart failure, a number anticipated to grow to over eight million by 2030 [3]. According to the National Heart, Lung, and Blood Institute (NHLBI), there are 870,000 new cases of heart failure per year [1]. The worldwide total is projected to be 78 million in 2030 [4]. While heart failure is a disease associated with aging, there are also significant racial, ethnic, and gender differences [3].

Heart failure is a clinical syndrome involving cardiac function, skeletal muscle, renal function, and neurohumoral dysfunction. Its presentation can be in acute and/or chronic states. There are many underlying causes in the clinical syndrome of heart failure, but outcomes are poor with an estimated 50 % mortality by 5 years, worse than many cancers [5].

The epidemiology of heart failure is well studied but obtaining accurate, high-quality data faces many difficulties. The clinical diagnosis of the HF syndrome is challenging alone, but new diagnostic technologies are emerging. The underlying causes of HF are changing with the widespread treatment of risk factors such as hypertension and coronary heart disease. The advent of new technologies for treatment, as described in other chapters in this book, presents a moving target for the understanding of HF trends.

Definitions

Heart failure is not a disease in the traditional sense. It is a clinical syndrome that results from structural and functional disorders impairing the heart's ability to adequately perfuse the body [6]. Clinical history is manifested by fatigue, dyspnea, reduce exercise tolerance, and fluid retention. On physical examination, it is manifest by increased jugular venous pressure (JVP), pulmonary rales, S3 gallop, peripheral edema, and hepatomegaly. Laboratory testing may include chest X-ray, echocardiogram, and biochemical markers. The etiology of heart failure is also complex and includes ischemic heart disease, hypertension, cardiomyopathy, rheumatic heart disease, infectious diseases, congenital heart disease, arrhythmias, and many other disorders which affect the endocardium, myocardium, pericardium, heart valves and the great vessels [7]. The clinical diagnosis is based on history, physical exam, and laboratory values as accessed by the diagnosing clinician. Clinical judgment is important and opinion varies. There is no gold standard diagnostic tool [8].

The diagnosis of HF is further complicated by staging systems and functional classifications. The New York Heart Association (NYHA) functional classification is based on physical activity capacity ranging from no limitations to symptoms of heart failure at rest in an I–IV system [7]. This is widely used to classify the severity of the disease. The American College of Cardiology/American Heart Association system also includes symptoms but focuses on a continuum from heart failure risk factors to refractory HF requiring specialized interventions in an A–D scale [7]. Attempts to standardize the diagnosis of HF based on medical record data are frequently in conflict with expert cardiology panels where sensitivity and specificity are modest [8].

Further complicating the diagnosis of heart failure is the presence of numerous etiologies. These include ischemic heart disease, hypertension, cardiomyopathy, rheumatic heart disease, infectious diseases, congenital heart disease, arrhythmias, and many others. Many of these diseases also affect additional organs leading to complexity in making the diagnosis. There are also numerous risk factors for heart failure including age, sex, ethnicity, socioeconomic status, lifestyle factors, weight, smoking, diabetes, sedentary lifestyle, increased alcohol, diet, and others [3, 7, 9, 10].

These many factors present challenges for epidemiologists attempting to describe the epidemic in terms of incidence, prevalence, and mortality. Counting cases with the lack of a gold standard; comparing functional changes with treatment, underdiagnosis, missing data in charts; and evolving disease patterns in the population are challenging. This is particularly true when comparing different studies and attempting to chart trends in the disease and its outcomes [11].

An example of the challenges faced is found in the trends in in- and outpatient diagnoses of heart failure. Much of the literature is based on inpatient diagnoses, but in the last several decades, at least half and sometimes more of the diagnosis are made in the outpatient setting. Patients diagnosed in the outpatient setting have a modestly improved 5-year survival. This might be due to early diagnoses and/or better treatment. The inclusion of outpatient diagnoses in the studies leads to a perception of an increasing number of cases (incidence) and better outcomes [12].

Incidence

Incidence is defined as the first diagnosis of HF. Evaluation depends on cohort studies starting with healthy people and long-term follow-up to detect cases or administrative data sets with long-term historical inpatient and outpatient data.

Incidence is estimated at 2–5 per thousand person years with men having higher incidence than women. There are 500,000–870,000 new cases of HF per year in the United States [3, 10]. Lifetime risk is 20–30 % [3]. The Framingham Heart Study estimates 10 per thousand person years in those above 65 with increased rates in men compared to women and rising rates with age shown in Fig. 6.1. Incidence data are dependent on the age, sex, and race of the population. The ARIC cohort found the highest incidence in Black men and Black women with lower incidence in White men and White women (Fig. 6.2) [3]. The Cardiovascular Health Study found an incidence of 19.3 per thousand person years in those greater or equal to age 65 [10]. The MESA study found

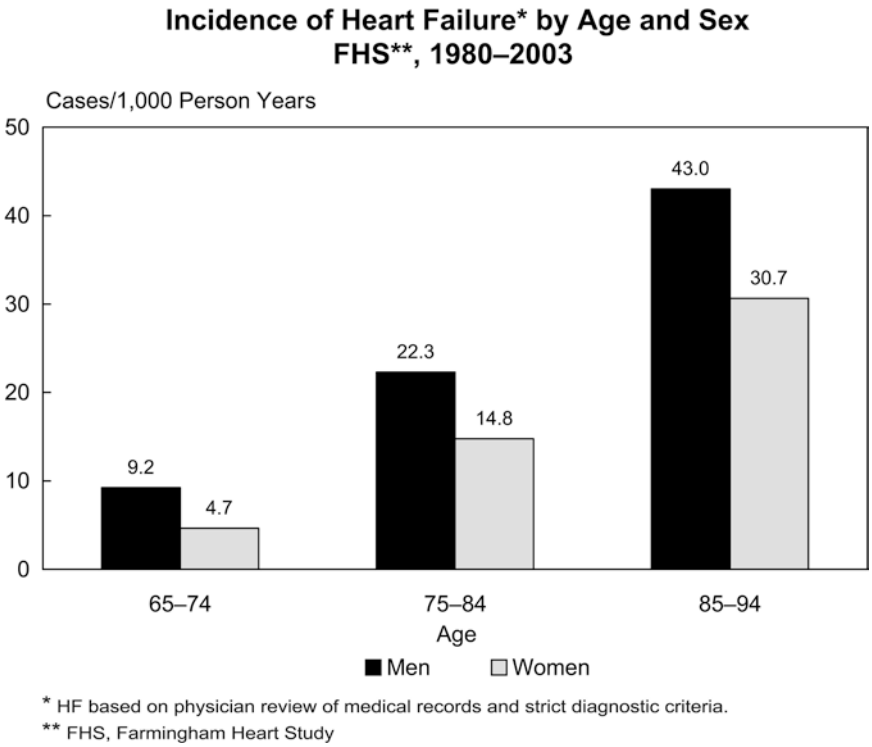


Fig. 6.1 The incidence of heart failure in men and women approximately doubles with each 10-year increase from ages 65–74 to 85–94; however, it triples for women between ages 65–74 and 75–84. *Source*: National Heart, Lung, and Blood Institute. Incidence and Prevalence: 2006 Chart Book on Cardiovascular and Lung Diseases. Bethesda, MD: National Institutes of Health; 2006

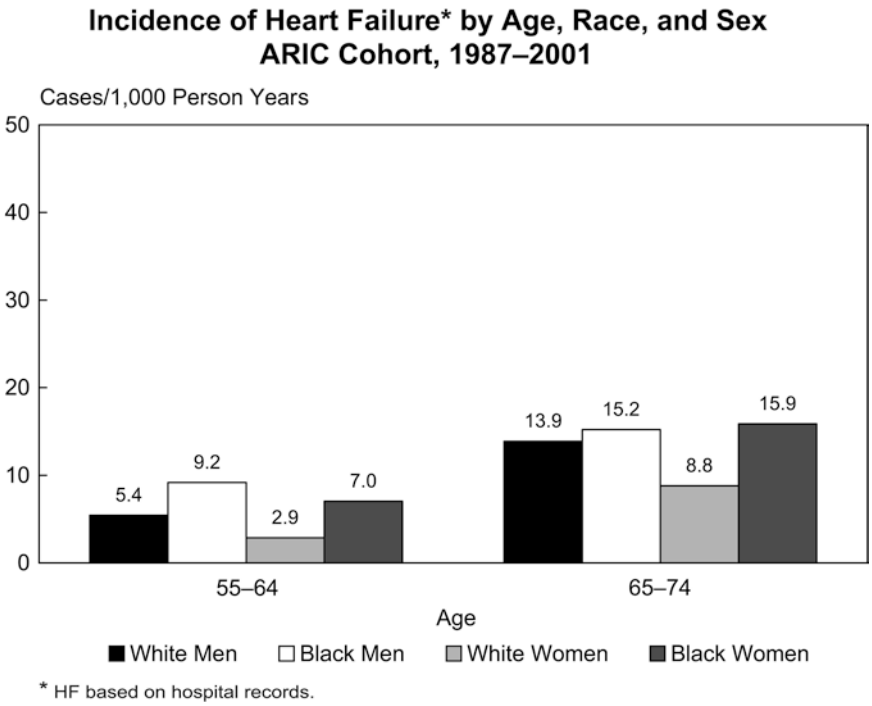


Fig. 6.2 For ages 55–64 and 65–74, the incidence of heart failure is higher in Black women than in White women. *Source*: National Heart, Lung, and Blood Institute. Incidence and Prevalence: 2006 Chart Book on Cardiovascular and Lung Diseases. Bethesda, MD: National Institutes of Health; 2006

the highest incidence in African-American men followed by Hispanic then White. Chinese had the lowest incidence [13].

It is clear that early in the heart failure epidemic, the diagnosis and incidence were increasing [1]. However, analysis of later trends differs. In Olmsted County, incidence is stable or falling slightly [7]. In a study of the Kaiser Health System from 2000 to 2005, rates were stable combining both in- and outpatient diagnoses [14]. A study of Medicare records from 1994 to 2003 found a small decline of 32 per thousand to 29 per thousand person years in those 65 years or older (Fig. 6.3) [15]. These trends included both in- and outpatient diagnoses. Declines occurred equally among different age groups [15].

Incidence data, in addition to dependency on site, source, and quality of diagnoses, is also a reflection of other factors. These include increased survival from acute myocardial

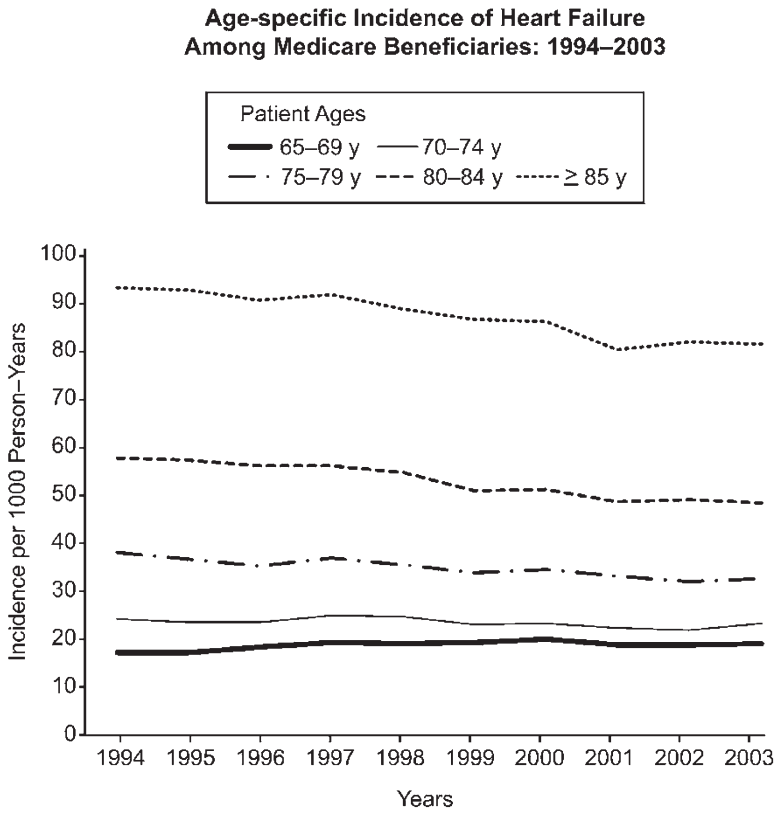


Fig. 6.3 Age-specific incidence of heart failure among Medicare beneficiaries from January 1, 1994, through December 31, 2003. From 1994 through 2003, the incidence of heart failure increased slightly among the youngest Medicare beneficiaries and declined among older beneficiaries [15]

infarction. Damaged myocardium and reduced ejection fraction is the result of an infarction leading to diminished pumping capacity. Increasingly sensitive diagnostic instruments and better clinician awareness of the diagnosis lead to earlier case finding and appropriate classification. Improved treatment and control of hypertension, lipids, and smoking should lead to decreasing heart failure rates through less atherosclerosis or other mechanisms. These factors in combination influence the ongoing trends.

Prevalence

It is estimated that 5.7 million Americans currently have heart failure according to the National Health and Nutrition Examination Survey (NHANES) [3]. This is projected to reach 8 million individuals by 2030. It is similarly estimated that 78 million individuals worldwide will have heart failure in 2030 [4]. Most estimates suggest the prevalence in the United States is 2–3 % of the general adult population [10, 16]. However, there are widely varying estimates in different reports. These differences are a function of the age sampled, the case definition, and the site (in- or outpatient) of case finding.

According to NHANES in 2009–2012, heart failure is a disease associated with aging. In the youngest adult age group (20–39 years), under 1 % are afflicted, while for those 80 years and above, over 10 % report the condition (Fig. 6.4). Heart failure prevalence also affects men differently than women (Fig. 6.5). As shown in Fig. 6.5, Blacks have significantly higher rates than Whites and men higher rates than women.

It is also clear that prevalence rose during the past decades. Curtis et al. using Medicare data (65 years and above) found prevalence of 90 per thousand person years in 1994 which rose to 121 per thousand person years in 2003 [15]. Data from the Kaiser Health Plan found the prevalence rising in their population for both men and women with men having a higher rate than women. Their rates range from 1.01 to 2.12 % of their patient population [14].

The study of a French population found a prevalence of 0.9 % for those aged 55–64 rising to 17.4 % prevalence in those 85 years and above [16]. A more recent study of Medicare on the prevalence of 13 % as shown in Table 6.1, in a 5 % sample of Medicare records, prevalence is steadily rising [15].

There are a number of factors thought to be acting in increasing prevalence in the setting of flat or declining incidence. Better recovery from acute myocardial infarction is cited as one [3], but there is also improved survival from sudden death episodes, better methods of treatment, and a better recognition of the disease [3]. All of these factors improve survival; however, part of the increased prevalence may be a function of a so-called "lead time bias" where more sensitive diagnostic measures lead to a discovery of earlier cases which have a longer life post diagnoses.

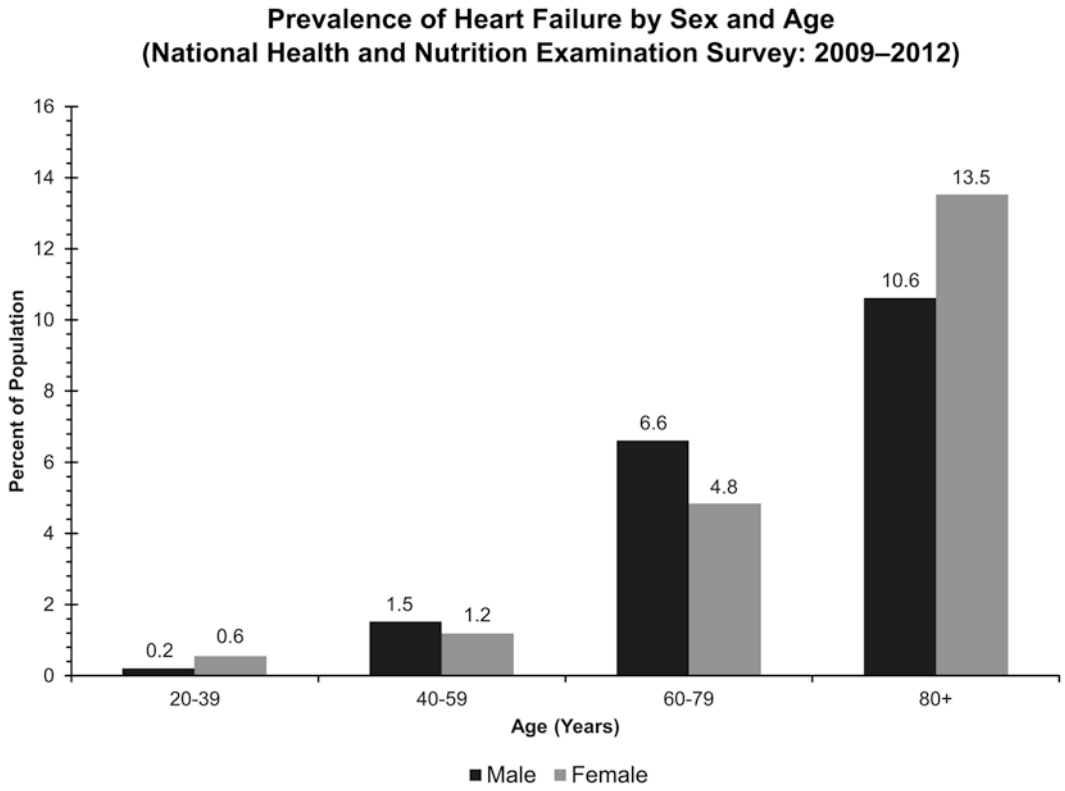
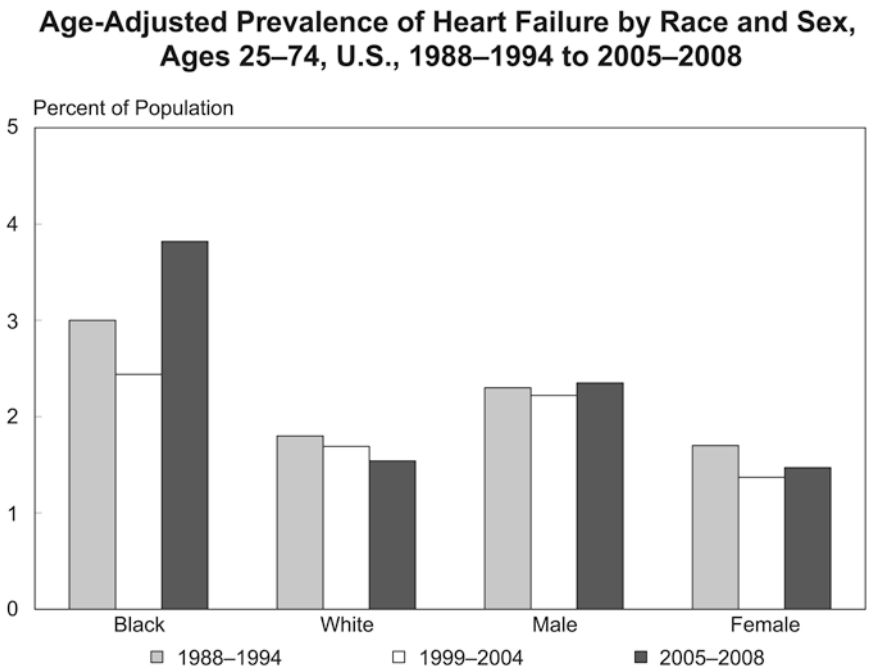


Fig. 6.4 Prevalence of heart failure by sex and age between 2009 and 2012. National Health and Nutrition Examination Survey: 2009–2012. *Source*: National Center for Health Statistics and National Heart, Lung and Blood Institute [3]

Fig. 6.5 From 1988–1994 to 2005–2008, the prevalence of HF increased in Blacks (except the decrease in 1999–2004) and decreased slightly in Whites; it remained stable in males but decreased slightly in females [18]



Mortality

Heart failure is a deadly disease. Death is frequently associated with other illnesses, but in many cases heart failure is the underlying cause. The analysis of data from Scotland finds that heart failure has a higher mortality rate than the four leading causes of cancer combined [17]. The 2008 death certificate data found 88/100,000 population mentions of heart failure with 17/100,000 population as the underlying cause of death [18]. Data from Olmsted County found 60 % 5-year

Table 6.1 Prevalence of heart failure in the Medicare 5 % sample by sex and year[a]

Year	Female	Male	Total
1994	86,450 (86.3)	53,390 (95.4)	139,840 (89.9)
1995	94,726 (94.0)	58,456 (103.7)	153,182 (97.9)
1996	101,024 (100.4)	62,520 (110.4)	163,544 (104.4)
1997	105,932 (105.6)	66,309 (117.1)	172,241 (110.3)
1998	109,381 (109.7)	68,942 (122.6)	178,323 (114.9)
1999	111,230 (112.4)	70,465 (125.6)	181,695 (117.8)
2000	113,068 (114.4)	72,133 (127.9)	185,201 (119.9)
2001	114,593 (114.4)	74,177 (128.3)	188,770 (120.1)
2002	116,732 (114.6)	76,376 (128.2)	193,108 (120.2)
2003	118,485 (115.1)	78,709 (129.2)	197,194 (121.0)

[a]Data are given as number (rate). Rates shown are per 1000 eligible Medicare beneficiaries
$P < 0.01$ for females, males, and the overall group for all years [15]

mortality after diagnosis [19]. Similar data are observed in other industrialized countries including the Netherlands, Australia, Scotland, and Canada [19–22]. Heart failure is frequently associated with sudden death and increases with increasing NYHA severity classification [23].

Heart failure rates as underlying cause of death by race are shown in Fig. 6.6. Blacks have the highest rate followed by Whites, American Indians, Hispanics, and Asians. Men have higher rates of heart failure as the underlying cause than women. Heart failure death is strongly associated with age as shown in Fig. 6.7. Heart failure diagnosed in an inpatient admission has a significantly worse prognosis than heart failure diagnosed as an outpatient [24]. However, the prognosis in both is poor at 5 years. There is 90 % mortality at 10 years [5].

The trends for heart failure mortality have improved. This begins within hospital mortality where a 10.9 % rate in 1980–1984 fell to 6.5 % in 2000–2004 [25]. However, 30-day mortality improvement after hospitalization was less dramatic with 12.8 % mortality in 1993 and a 10.7 % mortality in 2006. Clearly, more patients were dying at home [26]. Overall, Medicare data in all adults 65 and older hospitalized found an 8.5 % mortality in 1993 and 4.3 % in 2006 [26]. Similar trends were observed elsewhere including Australia where 1-year mortality fell from 22 % in 1990–1993 to 17 % in 2002–2005 [20]. Similar declines were noted in Sweden and Scotland [22, 27].

Heart failure is a deadly disease with few living beyond 10 years after diagnosis. Improved acute care has reduced in-hospital mortality. Prolonged care has also reduced mortality. The combination has resulted in increased prevalence in heart failure under the care of health systems.

Heart Failure: Preserved and Reduced Ejection Fraction

With the widespread availability of imaging to measure ejection fraction, it became apparent that many patients with signs and symptoms of heart failure did not have reduced ejection fraction associated with pump failure. This was initially termed diastolic heart failure in the clinical presentation and was associated with an ejection fraction above 45 % [19]. The pathologic findings associated with preserved ejection fraction are concentric remodeling of the left ventricle and left ventricular hypertrophy [28]. In recent years, considerable work has occurred to better define heart failure with preserved ejection fraction (HFpEF) in comparison to those patients with reduced ejection fraction (HFrEF). Depending on the inclusion criteria, it is estimated that 13–74 % of all heart failure is HFpEF [10, 29]. When ascertaining prevalence, definitions become an important issue. Various authoritative sources have suggested anywhere from an ejection fraction of less than 35 % to less than 45 % defines HFrEF [7].

There has been considerable increase in our understanding of HFpEF. Those with this condition are more likely to be older women. They have a history of hypertension, diabetes, atrial fibrillation, sleep apnea, renal disease, and pulmonary disease [30]. They are less likely to have a history of coronary heart disease [31].

While outcomes for HFpEF are somewhat better than HFrEF, they both carry substantial morbidity and mortality. Individuals with HFpEF are more likely to die of noncardiovascular disease than those with reduced ejection fraction [31].

The improvement in outcomes observed in heart failure is attributable mainly to reduction in death rate from HFrEF. HFpEF continues to have a poor outcome, and efforts to improve survival and treatment have lagged [10].

Heart Failure Hospitalizations

Most epidemiologic data comes from hospitalized patients. Despite the increasing awareness of outpatient diagnoses forming at least half of heart failure incidence, the availability of hospital and insurance records and discharge codes makes this a commonly used resource. As shown in Fig. 6.8, hospitalizations for heart failure rose steadily from 1980 among those age 45–64 and 65 and older. In the older group, heart failure peaked in 1998 and then fluctuated through 2009. The absolute number of discharges for heart failure was similar in 2010 (1,023,800) compared to 2000 (1,008,000) despite the fact that the population aged significantly during that time [3]. Some argue that the "epidemic" seen in the earlier years is a function of increasing hospitalization and survival not increased incidence [32]. Noteworthy is that in-hospital case-fatality rates for heart failure have been steadily falling [25]. As shown in Fig. 6.9, this trend is consistent for both younger (45–64 years) and older (≥65 years) patients [3]. While inpa-

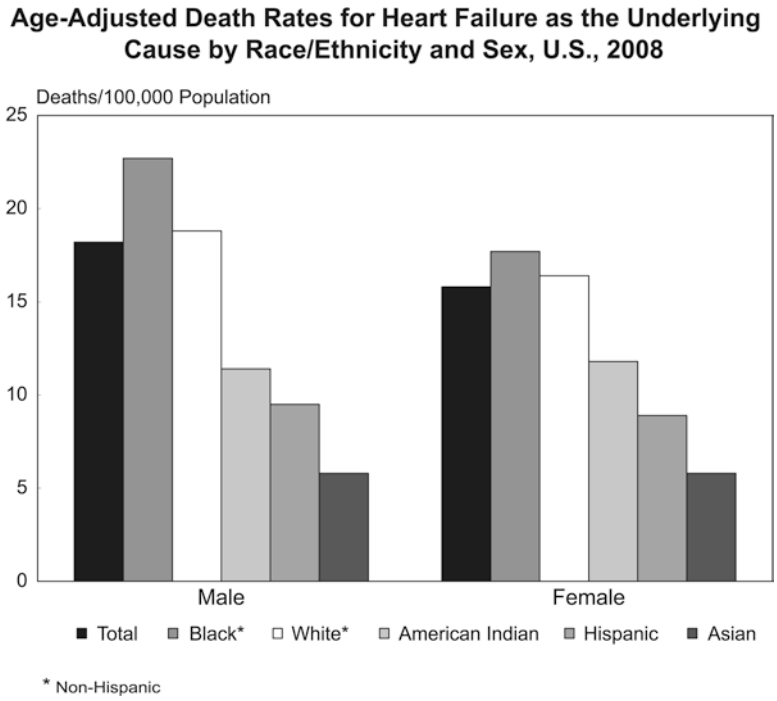


Fig. 6.6 In 2008, death rates for HF as the underlying cause were slightly higher in males than in females. Within sex groups, death rates were highest in non-Hispanic Blacks and non-Hispanic Whites and lowest in Asians [18]

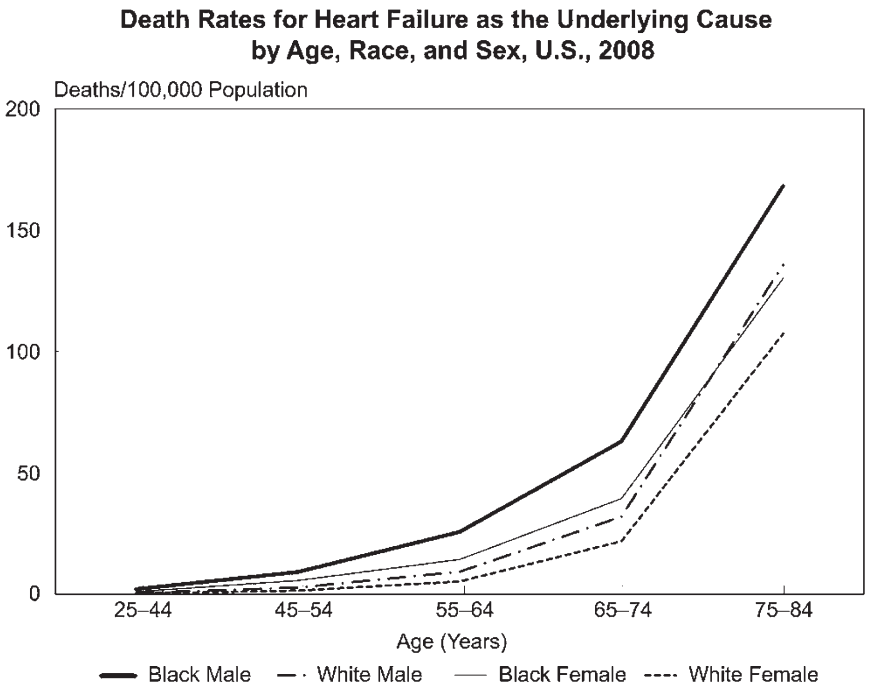


Fig. 6.7 In 2008, HF mortality as the underlying cause increased with age. Within sex groups, rates were higher in Blacks than in Whites; and within racial groups, rates were higher in males than in females [18]

tient mortality is improving, one result is increased readmissions. A study in Toronto, Canada, found that annual readmission for cardiovascular disease was 967 per thousand person years among those with ischemic heart failure [33]. For those with nonischemic heart failure, the rate was 621 per thousand person years. So while most hospitalized patients survive the episode, they are highly likely to be rehospitalized with 25 % returning to the hospital in 30 days [7].

In the United States, the advent of diagnostic related groups (DRG) or payments for diagnoses has led to increasing use of classifications for illnesses resulting in higher insurance payments [15]. HF is among the higher reimbursement DRGs. This has led to financial penalties for hospitals where patients return for hospitalization within a 1-month time. This financial disincentive may result in a decline in heart failure admissions.

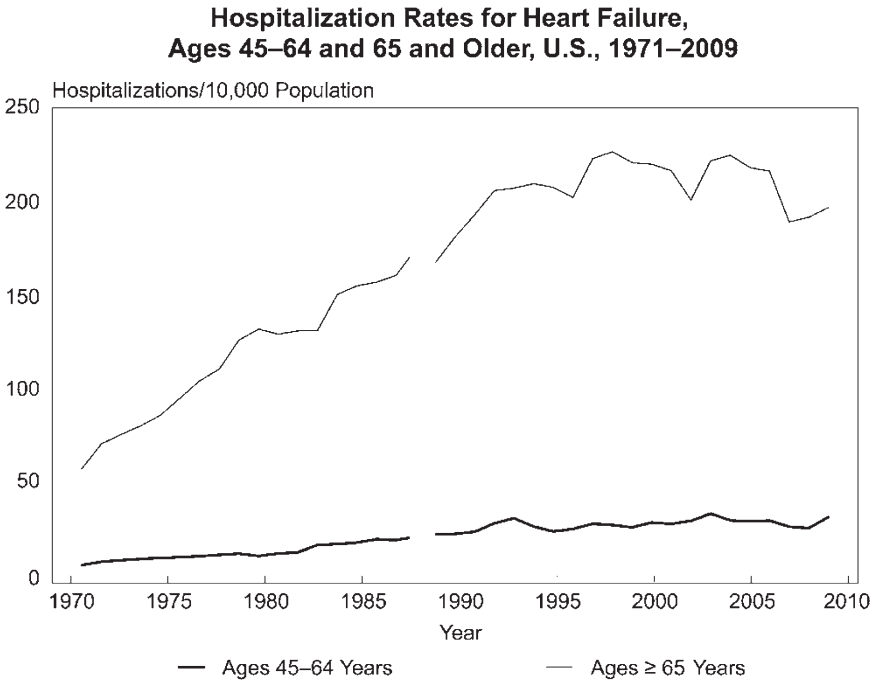


Fig. 6.8 From 1971 to 1993, hospitalization rates for HF increased in those aged 45–64 years and then remained stable through 2009. For those aged 65 years and older, rates peaked in 1998 and then fluctuated through 2009 [18]

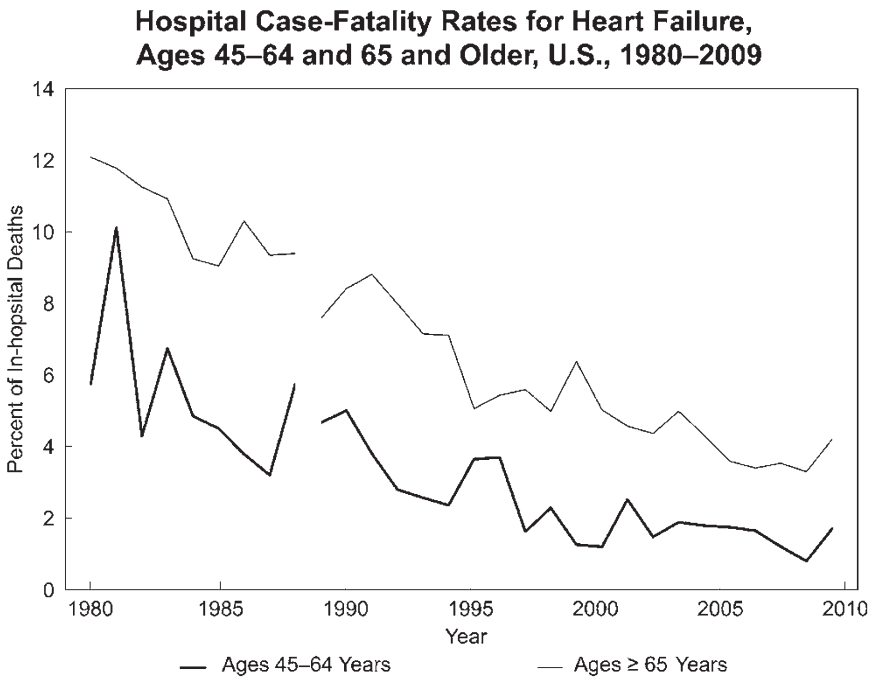


Fig. 6.9 From 1980 to 2009, hospital case-fatality rates for HF were rather erratic for those aged 45–64 years and those aged 65 years and older; overall however, the rates declined appreciably for both groups during the period [18]

International Trends

Heart failure is a worldwide problem. It is estimated that 23 million people were affected in 2011 [10], but HF is projected to increase as lifespan is extended and coronary heart disease becomes more common in many countries [15]. It is estimated that in 2030, there will be 78 million cases worldwide [4].

The etiologies of heart failure vary by region of the world. While ischemic heart disease is responsible for the majority of heart failure in Europe and North America, it constitutes a smaller portion in East Asia and Latin America [34]. In sub-Saharan Africa, ischemic heart disease is estimated to underlie only 10 % of heart failure [34]. However, cardiomyopathies, rheumatic heart disease, congenital heart disease, hypertension, and endomyocardial fibrosis account for a significant proportion of the clinical disease [3]. Rheumatic heart disease is still an important issue in Southeast Asia, and Chagas disease is an important factor in heart disease in South America [6].

Table 6.2 Underlying conditions associated with heart failure

• Arrhythmias
• Congenital heart disease
• Coronary heart disease
• Diabetes
• Genetic disorders
• Heart valve diseases
• Hypertension
• Infections (bacterial, viral, parasitic)
• Radiation therapy
• Toxic (chemotherapy)
• Unknown

Disease Associations

The syndrome of heart failure is associated with many diseases. Table 6.2 lists some of these conditions. Among the most common is coronary heart disease with its resulting damage to the myocardium [9]. Hypertension is also strongly related to heart failure and is more commonly found in HFpEF. Other causes include heart valve diseases, such as rheumatic disease, which, while less common in industrialized countries, is widely observed in much of the rest of the world. Recent growth areas in heart failure are conditions associated with the treatment of cancer. The effective treatment of many juvenile cancers with chemotherapy and radiation results in heart disease among middle-age survivors [35]. This is most probably due to cardiotoxic chemotherapies such as anthracyclines or chest radiation. Diabetes is also increasing. The Framingham Heart Study found that diabetes increased the likelihood of heart failure by two times in men and five times in women [36].

Risk Factors

There are a number of risk factors associated with the occurrence of heart failure. Some may be in the causal chain, others merely associated. Lifestyle factors such as weight, smoking, sedentary lifestyle, alcohol abstinence, reduced breakfast cereal consumption, and reduced fruits and vegetable consumption are all associated with an increased likelihood of heart failure [3]. These may be associated with low socioeconomic status, also predictive of heart failure [9]. Unmodifiable risk factors such as age, sex, and ethnicity are all predictive.

Disease states known to be associated with heart failure include heart valve disorders, sleep apnea, diabetes, hypertension, and renal and pulmonary diseases [8, 14]. It is of interest that statistical adjustment for blood pressure and diabetes eliminated Black/White ratio differences in one study suggesting that the racial differences are secondary to these factors [13].

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Etiology of Heart Failure

Acute Heart Failure

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_7

Introduction

Heart failure is a major cause of cardiovascular mortality in the United States. It often develops as a consequence of maladaptive cardiac remodeling in response to severe stress, toxin exposure, or injury. The prevalence of heart failure in the United States includes more than six million individuals (2 % of the US population), resulting in the demise of about 100,000 patients each year [1]. Furthermore, heart failure has had a tremendous economic toll on the US healthcare budget, accounting for more than $30 billion of the $320 billion spent on cardiovascular-related disorders [1, 2]. The majority of this expenditure is directly related to the hospitalization of patients with acute decompensated heart failure (ADHF).

Although heart failure is a chronic medical condition that can be caused by a number of insults, most heart failure patients will develop at least one episode of ADHF requiring either an emergency room (ER) visit and/or hospitalization. About 670,000 ER visits in the United States are secondary to ADHF, accounting for 20 % of the total heart failure-specific ambulatory care visits [3]. Ultimately, 80 % of these ER visits result in hospitalization for ADHF [3]. Thus, the magnitude and impact of ADHF on not only US healthcare expenditures but, more importantly, on the lives of the individual heart failure patients are enormous.

Over the past decade, the heart failure medical community has gained valuable insights from both the Acute Decompensated Heart Failure National Registry (ADHERE) and the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registries regarding the initial presentation, epidemiology, and management of ADHF [4–10]. These registries have demonstrated that the underlying etiology of the ADHF is nearly equally divided between patients with heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF). Since the assessment and management of HFpEF patients is discussed in other chapters of this textbook, this chapter focuses on the epidemiology, pathophysiology, diagnostic assessment, and clinical management of HFrEF patients presenting to the hospital with ADHF.

Heart Failure Classification

The spectrum of patients hospitalized with acute heart failure is broad, ranging from mild congestion to cardiogenic shock. Management strategies are tailored to meet the degree of hemodynamic compromise, with more aggressive regimens reserved for patients with advanced disease. To guide clinicians in managing acute heart failure, patients are typically assigned a "Stevenson Hemodynamic Profile" based on their initial clinical presentation [11]. These profiles describe the degree of compromise (Fig. 7.1) based on physical examination. Importantly, these clinical profiles appear to correlate with invasive hemodynamics, with Profile B and C individuals having a higher pulmonary capillary wedge pressure than patients with Profile A, while Profile C patients tend to have a lower cardiac output/index than Profiles A and B. In addition, patients with Profile C (wet-cold) have a lower 1-year survival than Profile B patients. Therefore, it is important to accurately assign patients into the correct hemodynamic profile on presentation, with treatment regimens appropriately tailored to the degree of hemodynamic compromise.

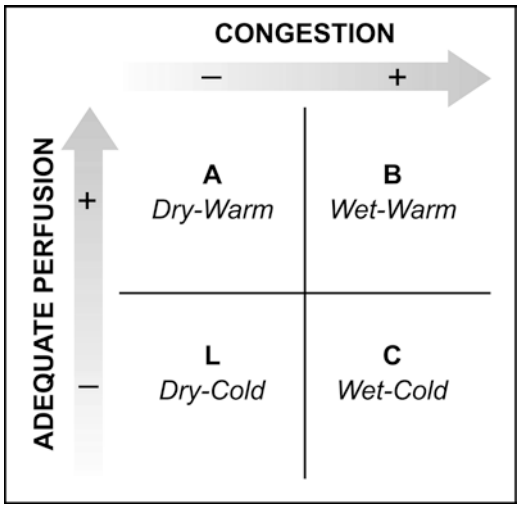


Fig. 7.1 The use of the Stevenson Hemodynamic Profile as a guide for acute heart failure management. Congestion is determined by the presence of orthopnea, jugular venous distension, rales, hepatojugular reflex, ascites, peripheral edema, a leftward radiation of the pulmonic heart sound, and/or a square-wave blood pressure response to the Valsalva maneuver. Inadequate perfusion is determined by the presence of a narrow pulse pressure, pulsus alternans, symptomatic hypotension, cool extremities, and/or impaired mentation (modified from Nohria et al. J Am Coll Cardiol. 2003;41(10):1797–804)

Biomarkers and Heart Failure

Acute decompensated heart failure contributes to a significant proportion of hospital admissions and is associated with high morbidity and mortality rates [2, 7–10]. A variety of biomarkers related to heart failure have emerged to provide not only more precise diagnosis but have also been correlated to response to therapy and, more importantly, to prognosis. Circulating natriuretic peptides and cardiac troponins have emerged as the leading biomarkers in the field of heart failure. Measuring their levels is now part of the standard of care in the assessment and management of a patient who presents to a medical facility with signs and symptoms of ADHF [12–15].

Biomarkers and Heart Failure: Natriuretic Peptides

Cardiac myocytes release natriuretic peptides in response to wall stress, typically in the setting of chamber dilation resulting from volume overload or myocardial injury [16, 17]. These hormones activate cyclic guanosine monophosphate-dependent signaling cascades. Through this pathway, these

"counterregulatory hormones" exert a number of actions that counteract the hemodynamic aberrations commonly observed in heart failure.

Three predominant natriuretic peptides circulate in the bloodstream and have been well characterized (Table 7.1).

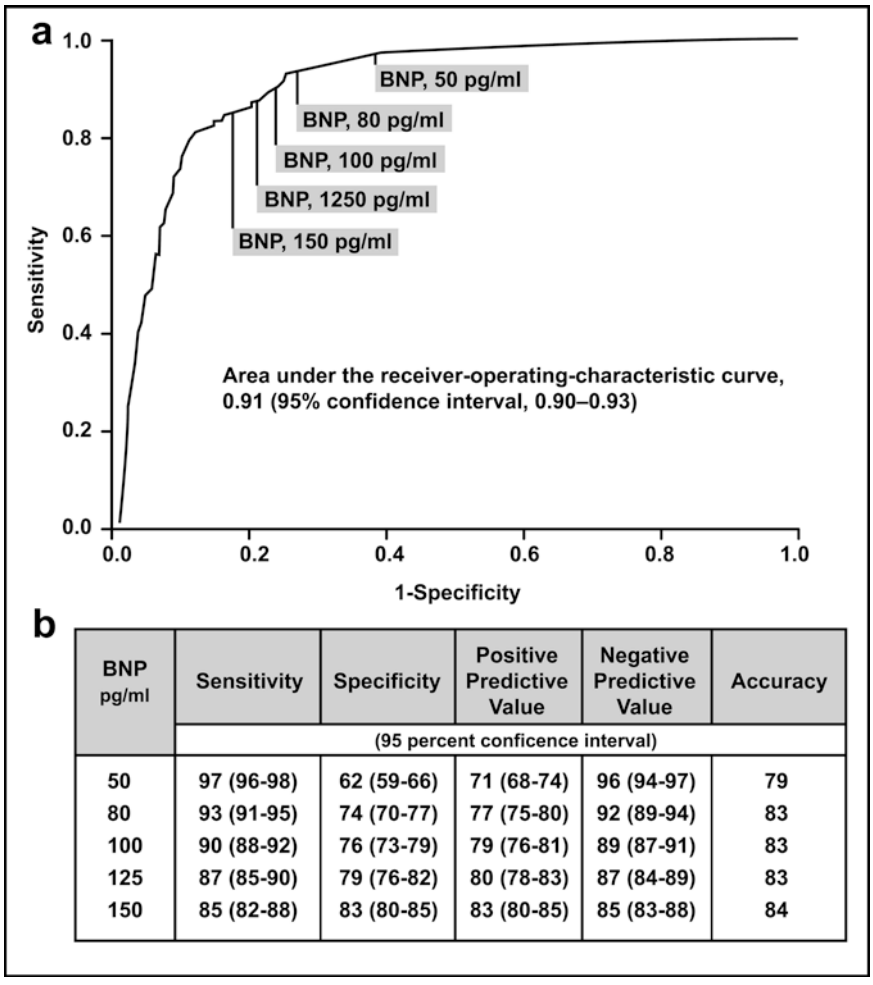
Table 7.1 Natriuretic peptides in heart failure

Natriuretic peptide	Stimulus	Actions
A-type (ANP)	Atrial distension	Vasodilation, natriuresis, attenuation of RAAS, promote renal blood flow
B-type (BNP)	Ventricle distension	Vasodilation, natriuresis, attenuation of RAAS, promote renal blood flow
C-type (CNP)	Vascular endothelium	Vasodilation, natriuresis, attenuation of RAAS, antiproliferation of vascular smooth muscle

RAAS renal-angiotensin-aldosterone system

Natriuretic peptides, specifically the B-type natriuretic peptide (BNP) and amino-terminal counterpart (NT-proBNP), are useful for establishing the diagnosis of acute heart failure and distinguishing heart failure from other noncardiac causes of dyspnea [18]. BNP and NT-proBNP levels are well correlated and either assay can be utilized in this setting. Generally, as the BNP threshold level is increased, the sensitivity for heart failure declines, but specificity rises (Fig. 7.2) [18]. As demonstrated in the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) trial, natriuretic peptides are most helpful when used in conjunction with and to support medical decision-making [19], particularly when the cause of dyspnea is not evident. However, it is important to note that elevated plasma levels may result from a variety of conditions, including acute coronary syndromes, valvular heart disease, myocarditis, pericarditis, atrial fibrillation, and/or cardiac surgery [1].

Natriuretic peptides also have important prognostic implications, as higher BNP levels indicate an increased risk of mortality [20–25]. Furthermore, changes in BNP over time are associated with corresponding changes in the risk of death [21]—and while natriuretic peptide levels generally improve with the treatment of heart failure [21, 26–28], it is unclear whether "guided therapy" leads to improved outcomes.



b

BNP pg/ml	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
	(95 percent conficence interval)				
50	97 (96-98)	62 (59-66)	71 (68-74)	96 (94-97)	79
80	93 (91-95)	74 (70-77)	77 (75-80)	92 (89-94)	83
100	90 (88-92)	76 (73-79)	79 (76-81)	89 (87-91)	83
125	87 (85-90)	79 (76-82)	80 (78-83)	87 (84-89)	83
150	85 (82-88)	83 (80-85)	83 (80-85)	85 (83-88)	84

Fig. 7.2 The role of B-type natriuretic peptide (BNP) in assessing the etiology of dyspnea. (**a**) Receiver operating characteristic curve for various cutoff levels of BNP in differentiating between dyspnea due to congestive heart failure and dyspnea due to other causes. (**b**) Table outlining the sensitivity, specificity, predictive values, and accuracy of BNP levels. Note that the figure was adapted from reference #18

Trials examining such a strategy have generally been limited by sample size and power; however, in two meta-analyses, therapy guided by natriuretic peptide levels led to reductions in all-cause mortality [29, 30]. Prospective, randomized controlled studies are ongoing to determine whether outcomes are improved by titrating heart failure medications to achieve a target NT-proBNP level [31]. The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) 2013 guidelines on heart failure management therefore provide a class IA recommendation for the inclusion of natriuretic peptide levels to establish the diagnosis of heart failure as the cause for dyspnea in the acute care setting, but a class IIB recommendation for the use of these hormones to guide therapy after the diagnosis of heart failure has been made [32]. It is important to note that natriuretic peptides are dependent on renal clearance; thus, BNP and/or NT-proBNP levels may be elevated in the setting of acute kidney injury. In addition, an inverse correlation exists between natriuretic peptide levels and body mass index. Therefore, obese individuals may have falsely low levels of BNP and/or NT-proBNP.

Biomarkers and Heart Failure: Cardiac Troponins

Cardiac troponin levels have previously been shown to correlate with impaired hemodynamics and BNP levels in patients with HF [33]. This finding implies that in the setting of HF, there is ongoing injury and destruction of cardiomyocytes that contributes to the decline in clinical status [34]. Similar to natriuretic peptide levels, elevated troponin levels are associated with worse outcomes [33–40]. The ACCF/AHA 2013 guidelines on heart failure management therefore provide a class IA recommendation for including cardiac troponins for risk stratification of patients hospitalized with acute heart failure [32].

Myocardial Infarction and Acute Decompensated Heart Failure

Myocardial infarction is common and is associated with tremendous morbidity and mortality. Each year, more than 700,000 Americans have a myocardial infarction, of which 500,000 of these patients experience their first heart attack [2]. About 25–40 % of these myocardial infarctions are ST-segment elevation myocardial infarctions (STEMIs) [2]. These STEMI injuries result in complete occlusion of the coronary vessel and cause a transmural infarct in the absence of an intervention. While healthcare education and primary percutaneous interventional revascularization strategies have decreased the number of transmural infarctions, acute pump failure due to proximal left anterior descending (LAD) artery occlusion requires urgent attention. These patients typically present with tachycardia, hypotension, pulmonary edema, and end-organ dysfunction (elevated hepatic transaminases, renal dysfunction, etc.). This low-output state or cardiogenic shock (cardiac index less than 2 l/min/m^2) still requires percutaneous revascularization and, in the absence of aortic insufficiency or peripheral vascular disease, support with a short-term mechanical circulatory support device [e.g., Impella (2.5 or 5.0), intra-aortic balloon pump (IABP), or TandemHeart]. In addition to the mechanical support provided by a temporary ventricular assist device, supplemental oxygen and low-molecular-weight heparin can be used with or without intravenous nitroglycerin. The goal is to promote cardiac perfusion and decrease afterload to ultimately promote cardiac output. Patients with myocardial infarction and Killip class IV (cardiogenic shock) (Table 7.2) have a mortality rate of about 25 % and require intervention, ICU monitoring, and nursing support [25–41].

Table 7.2 Killip classification in patients following ischemic cardiac insult

Killip Classification	
Killip class I	Signs of heart failure
Killip class II	Rales and diffuse wheezing over the lung fields, and/or an S_3
Killip class III	Acute pulmonary edema
Killip class IV	Cardiogenic shock

Structural Complications and Acute Heart Failure

Following the patient's immediate stabilization, it is important to monitor for structural complications. The profile of patients at higher risk for structural complications following myocardial infarction (MI) includes female gender, first ischemic event, low body mass index, and advanced age [2]. Typically, ventricular (septal or free wall) rupture occurs about 2–8 days following the transmural infarct and is associated temporally with extracellular remodeling of the infarct [46–49]. The mortality for patients with these structural perforations is extremely high and requires immediate surgical intervention. Typically, an ischemic myocardial rupture following an acute myocardial infarction involves the left ventricular or right ventricular free walls, ventricular septum, or left ventricular papillary muscle (in decreasing order of frequency) [46–49]. Rupture may cause pericardial tamponade, formation of a pseudoaneurysm, acute mitral regurgitation, or shunt (ventricular septal defect resulting in a left-to-right shunt) (Fig. 7.3). The diagnosis usually is established using transthoracic echocardiography. Physical exam findings include a holosystolic murmur with or without a thrill (typically associated with a ventricular septal rupture) appreciated at the left sternal border, and hypotension.

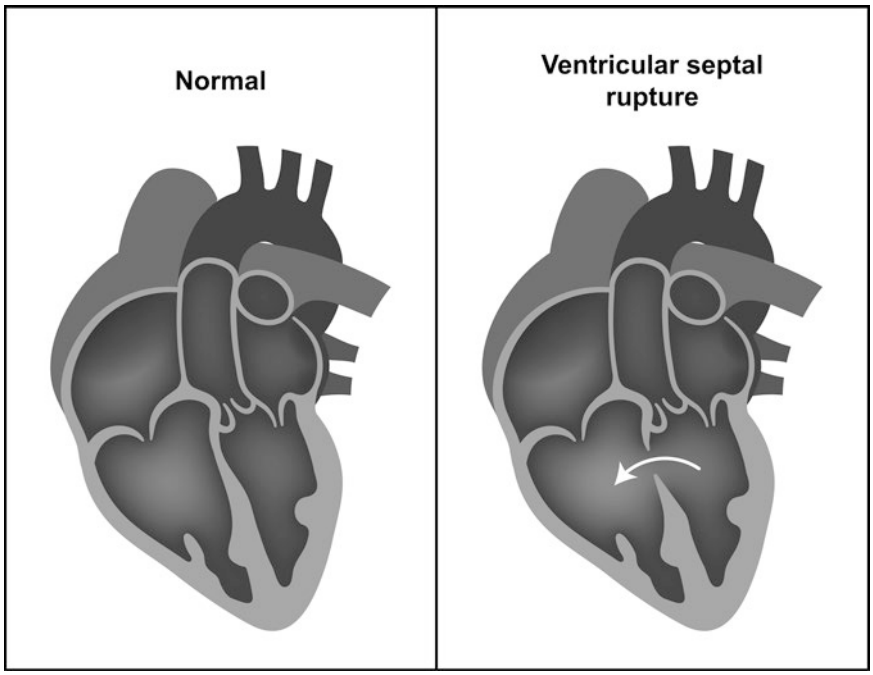


Fig. 7.3 Ventricular septal rupture following a myocardial infarction results in acute heart failure. Schematic highlighting ventricular septal rupture following a myocardial infarction and subsequent left-to-right shunt

Inferior wall myocardial infarctions involving the posterior descending coronary artery are also associated with structural complications. These complications are due to the single-vessel (typically the right coronary artery) blood supply to the posterormedial papillary muscle for the mitral valve. Rupture of the posterormedial papillary muscle results in acute and severe mitral regurgitation. The acute rupture of the posterormedial papillary muscle results in hypotension (decreased cardiac output), pulmonary congestion (resulting in hypoxia), a holosystolic murmur appreciated at the apex and radiating to the axilla, and tachycardia. This complication requires immediate intervention with parenteral agents such as sodium nitroprusside (SNP) to decrease afterload, decrease the regurgitant fraction, and increase forward flow (increase cardiac output) with diuretic therapy, and surgical consultation for mitral valve replacement. Acute rupture of the posterormedial papillary muscle with severe mitral regurgitation, pulmonary edema, and hypotension is a surgical emergency. While SNP and IABP support may improve cardiac output, surgical intervention is required for improved morbidity and survival following ischemic rupture of the posterormedial papillary muscle and acute heart failure.

Myocarditis

Myocarditis is another cardiovascular disease state resulting in ADHF and characterized by inflammation and damage to the heart muscle. Myocarditis is believed to be a relatively common cause of sudden cardiac death in the young; about 10 % of sudden cardiac deaths are due to myocarditis [50–52]. The causes of myocarditis include autoimmune diseases, viral infections (Coxsackie B, hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or human parvovirus B19), nonviral infections (*Borrelia burgdorferi*, *Aspergillus*, *Haemophilus influenzae*, *gonococcus*, *Corynebacterium diphtheriae*, etc.), toxins (alcohol, cocaine, etc.), and adverse reactions to medications (anthracyclines, antipsychotics, digoxin, dobutamine, cephalosporins, etc.) [50, 52, 53]. Typically, patients complain of flu-like symptoms (fever, chills, myalgias, night sweats, malaise, etc.), chest pain, and symptoms consistent with congestive heart failure (i.e., shortness of breath, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, etc.). Patients will often have an elevated erythrocyte sedimentation rate, C-reactive protein, complete blood count, serum cardiac troponin levels, and electrocardiogram (ECG) findings. These ECG findings may consist of ST-segment elevation, T-wave inversion, ST-segment depressions, or Q waves that extend beyond a single coronary artery distribution. An endocardial biopsy (revealing an eosinophilic infiltrate, myocardial edema, inflammation, cardiomyocyte necrosis, etc.) remains the gold standard for the diagnosis (Fig. 7.4), but the increasing use of cardiac magnetic resonance imaging has also been useful (Fig. 7.5) [52]. Other specific causes of myocarditis include sarcoidosis, eosinophilic myocarditis, or giant cell myocarditis [50, 52, 54–56]. Giant cell myocarditis is relatively rare but typically is rapidly progressive and lethal. Diagnosis of giant cell myocarditis is based on the presence of multinucleated giant cells and a T-lymphocytic cellular infiltration on biopsy (Fig. 7.6). As outlined in the Multicenter

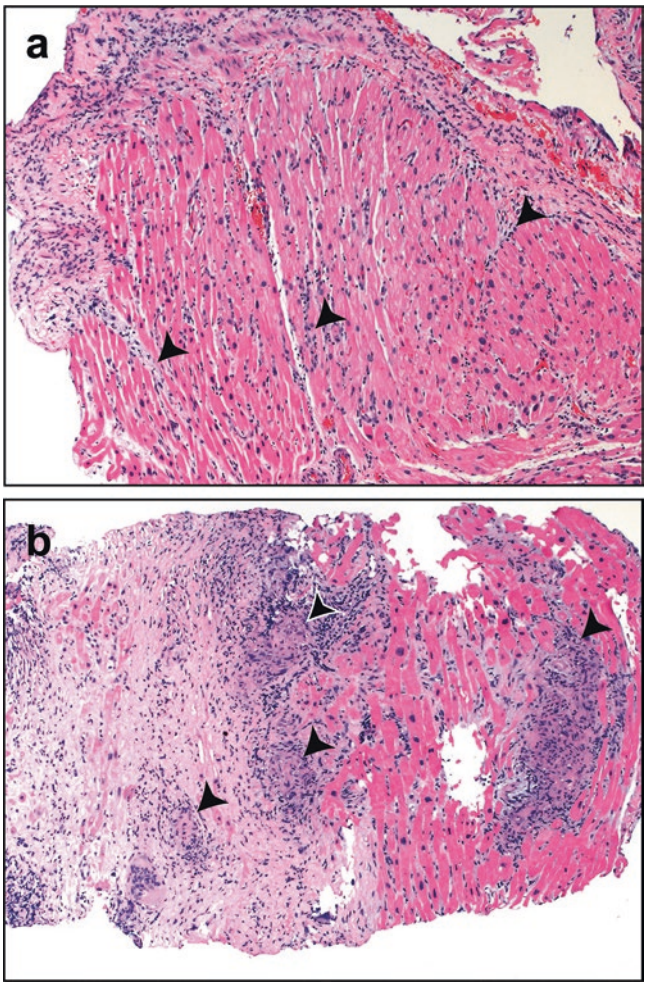


Fig. 7.4 Endomyocardial biopsy is the gold standard for the diagnosis of myocarditis. (**a**) An endocardial biopsy in a patient with lymphocytic myocarditis shows myocardial edema, lymphocytic infiltration (*arrowheads*), and cardiomyocyte necrosis. (**b**) An endocardial biopsy from a patient with cardiac sarcoid. Note the noncaseating epithelioid-cell granulomas (*arrowheads*) that may convert into hyaline connective tissue

Giant Cell Myocarditis Study Group, acute heart failure is the typical presenting symptom in more than 75 % of the patients [54].

Medical Management of Acute Heart Failure

The ACCF/AHA 2013 guidelines on heart failure management recommend that goal-directed medical therapy be continued for all patients requiring hospitalization for acute heart failure in the absence of hemodynamic instability [1]. However, all maintenance heart failure medications should be reviewed carefully on hospital admission to determine whether it is appropriate to continue, adjust, or temporarily withhold heart failure medications based on an individual's hemodynamic profile.

The ACCF/AHA 2013 guidelines on heart failure recommend that beta blockers should generally be continued during the hospitalization for acute heart failure if it is reasonable and safe for the patient [1]. This recommendation is based on data derived from large studies evaluating patients hospitalized with acute heart failure, which demonstrated improved survival among individuals whose beta blockers were continued during hospitalizations for acute heart failure [57, 58]. For example, the ESCAPE trial showed that continuation of beta blockers throughout hospitalization was associated with a reduction in the rate of rehospitalization or death within a 6-month period following discharge [57]. Similarly, the *Carvedilol Or Metoprolol European Trial* (COMET) showed that 1- and 2-year mortality rates were higher in patients whose beta blockers were discontinued [58]. It is important to emphasize that the higher mortality rate among individuals for whom beta blockers were stopped is related, in part, to the severity of their underlying disease, and there are a number of scenarios in which beta blockers should be discontinued [58]. For example, beta blockers should be withheld on patients who present with a "wet-cold" profile (Fig. 7.1; Stevenson Hemodynamic Profile C), with evidence of congestion, and with a low-output state (inadequate perfusion) until they are stabilized [1].

Similarly, angiotensin-converting enzyme (ACE) inhibitors and aldosterone receptor antagonists (ARBs) should be continued during hospitalizations for acute heart failure, as long as it is reasonable to do so [1]. ACE inhibitors may be advantageous in this setting, by reducing afterload and systemic vascular resistance and by promoting natriuresis [58]. Patients with significant rises in creatinine (representing a decrease in glomerular filtration rate, GFR) should have temporary reductions in the dosage of ACE inhibitors/ARBs or have the drugs held altogether until the renal function normalizes.

Diuretics are a class I indication for patients admitted with heart failure who have evidence of volume overload (e.g., Stevenson Hemodynamic Profile B or C) [1]. Generally, the dose administered should be equal to or greater than the patient's chronic daily oral dose, and the diuretic should be administered as an intravenous formulation. In the Diuretic Optimization Strategies Evaluation (DOSE) trial, there was no difference in symptoms or change in renal function when diuretics were administered as either a bolus or continuous infusion [60]. Thus, the method of intravenous administration is generally based on clinician experience/preference. For patients who have congestion refractory to loop diuretics, clinicians may elect to either increase the dose of intravenous loop diuretics or add a thiazide diuretic to promote natriuresis [1]. When attempts for diuresis are unsuccessful, ultrafiltration may be considered as an adjunctive therapy. However, outcomes on ultrafiltration in this context are mixed. In one study of 200 patients admitted with acute heart failure and congestion, ultrafiltration led to greater weight and fluid loss than intravenous diuretics, as well as a reduction in 90-day rehospitalizations [61]. However, in a

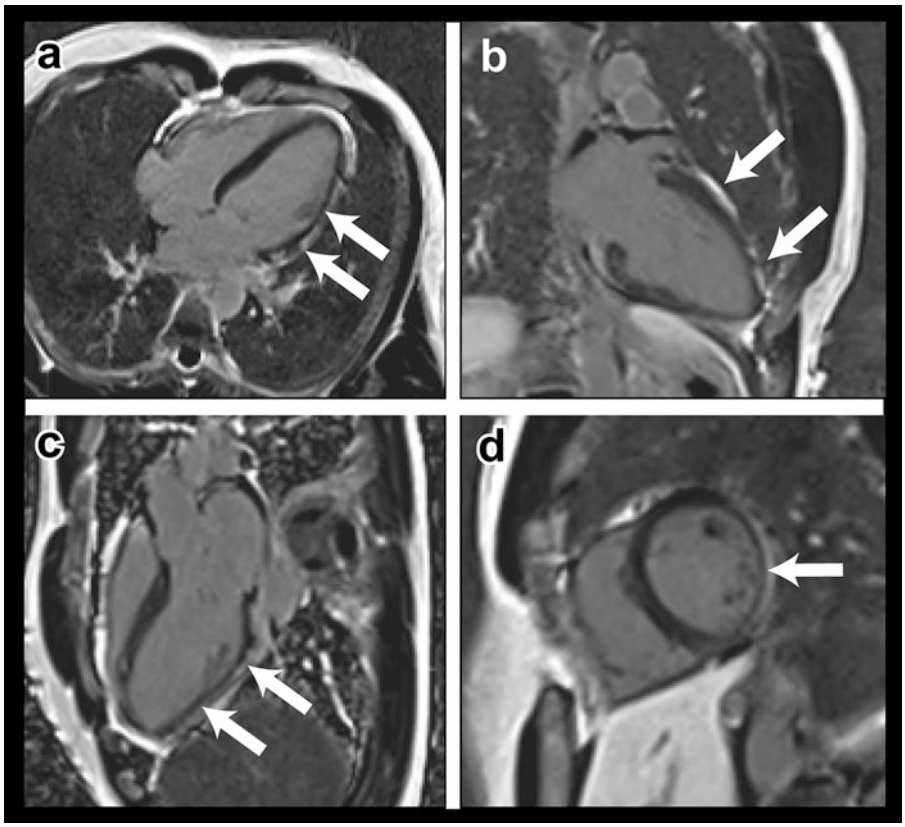


Fig. 7.5 Cardiac magnetic resonance (CMR) imaging and gadolinium enhancement is useful for the diagnosis of myocarditis. CMR of a patient with acute viral myocarditis demonstrating epicardial hyperenhancement (*white arrows*) in the anterior and lateral walls. Panel **a** is the four-chamber view, Panel **b** is the two-chamber view, Panel **c** is the three-chamber view, and Panel **d** is the short-axis view

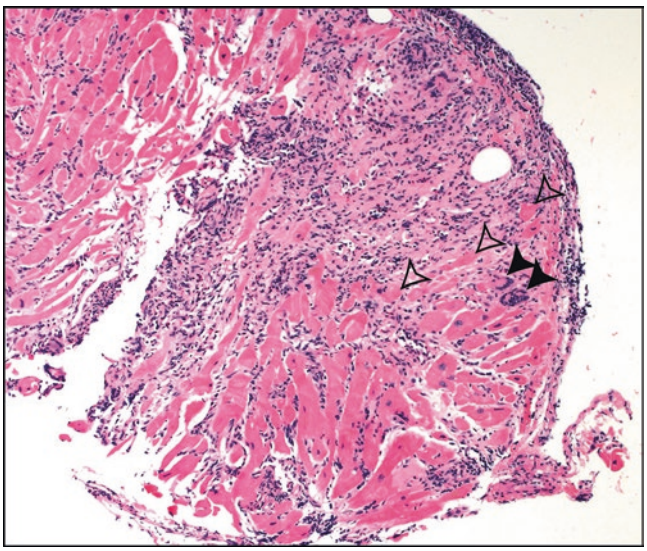


Fig. 7.6 Endomyocardial biopsy is essential for the diagnosis of giant cell myocarditis. Endomyocardial biopsy specimen from a patient with giant cell myocarditis. Note the extensive infiltrate of lymphocytes, macrophages, and giant cells (*solid arrowheads*) with cardiomyocyte necrosis (*open arrowheads*)

similarly sized cohort of patients with acute decompensated heart failure and congestion, pharmacologic therapy (intravenous diuretics) more effectively reduced creatinine levels than ultrafiltration [62]. Furthermore, ultrafiltration use was associated with a higher rate of adverse events, including worsening renal failure, bleeding complications, and catheter-related complications [62].

Attempts at diuresis are frequently impaired by hyponatremia. In states of hypervolemic hyponatremia, arginine vasopressin antagonists may be considered to allow for continued diuresis. Vasopressin antagonists have been shown to improve serum sodium levels in this patient population [63]; however, there is no survival benefit associated with their usage [64].

Regarding the management of acute myocarditis, therapy usually consists of providing supportive care, which includes conventional heart failure medications such as vasodilators, ACE inhibitors, diuretics, parenteral inotropic medications (i.e., milrinone or dobutamine), and/or insertion of a short-term mechanical circulatory support device for decompensated acute heart failure. The use of inotropic agents and/or mechanical support requires intensive care unit monitoring due to the hemodynamic instability of the patient, the need for one-on-one nursing care, potential complications related to the mechanical device, and the pro-arrhythmic effects of inotropic agents. The use of immunosuppressive agents (i.e., prednisone, cyclosporine, or azathioprine) has been shown to have no survival benefits in patients randomized to immunosuppression vs. conventional supportive therapies (Myocarditis Treatment Trial) [65–67]. Furthermore, the Intervention in Myocarditis and Acute Cardiomyopathy study (a double-blind randomized study of 62 patients with myocarditis) did not show a survival benefit or improvement in cardiac function with the use of intravenous immune globulin [67].

Table 7.3 Types of short-term mechanical circulatory support devices for optimization of cardiac output in patients with refractory heart failure

Device	Level of support	Duration of support	Adverse events
IABP	0.5–1.0 L/min [71–73]	7–14 days	Thrombocytopenia: 50 % [74]
			Fever: 36 % [74]
			Sepsis: 15.7 % [81]
			Limb ischemia: 4.3 % [81]
			Thromboembolism: 1 % [74]
Impella 2.5	1.0–2.5 L/min [71]	6 h–7 days [75]	Aortic insufficiency
			Tamponade
			Thromboembolism
Impella 5.0	5.0 L/min	6 h–7 days [75]	
TandemHeart	3.5–4.0 L/min [75]	6 h–14 days [75]	Tamponade
			Bleeding
			Limb ischemia
			Residual ASD

ASD atrial septal defect, *IABP* intra-aortic balloon pump

Advanced Therapies for Acute Decompensated Heart Failure

Several therapeutic strategies exist for management of patients with advanced heart failure. Inotropes (typically either milrinone or dobutamine) are employed early in the treatment course for patients with evidence of congestion and inadequate end-organ perfusion [7, 68, 69]. However, patients with decompensated heart failure will often require a more aggressive treatment strategy, and, in such cases, mechanical circulatory support is employed either in the form of short-term or durable (permanent) left ventricular assist devices (LVADs). Orthotopic heart transplantation (OHT) may also be considered for patients with refractory disease.

Short-Term Mechanical Circulatory Support for Decompensated Heart Failure

Several types of devices are available to provide additional circulatory support for patients with heart failure refractory to medical management (Table 7.3). Decisions regarding which device(s) to use depend on clinician experience/preference and the level of support needed [70–74]. Generally, these devices can be incorporated as a "bridging strategy" to support decompensated patients, while the failing left ventricle recovers, or while patients are awaiting definitive treatment in the form of either LVAD or OHT [75, 76].

While these devices have the advantage of optimizing cardiac output, they are not without risks. Major risks linked to these devices include vascular complications associated with device insertion, thrombocytopenia, limb ischemia, infection, and thromboembolic phenomena. Generally, IABPs are associated with a high rate of thrombocytopenia and fever, whereas the TandemHeart is associated with a higher risk of bleeding [77].

Despite the widespread use of these devices (more than 70,000 IABPs are inserted annually in the United States [78]), outcomes are mixed. IABP does not improve outcomes when used as a prophylactic strategy prior to revascularization in high-risk patients suffering from acute myocardial infarction (AMI) [79], or in AMI patients suffering from cardiogenic shock [80]. The Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) investigators reported a 30-day mortality of nearly 40 % among AMI patients with cardiogenic shock [80]. Further, when compared with IABP, the use of the Impella 2.5 led to similar rates of major adverse cardiac events at 30 days (35.1 % for Impella 2.5 vs. 40.1 % for IABP, $P = 0.227$) [81].

Long-Term Treatment Strategies for Decompensated Heart Failure

OHT has long been considered the only curative therapy for patients with advanced heart failure. However, over the past several decades, advancements in LVAD technology have led to widespread implementation of these devices for patients with advanced or end-stage heart failure as either a bridge-to-transplantation (BTT) or destination therapy (DT) for individuals ineligible for transplant (Table 7.4). To determine eligibility for OHT or LVAD, patients with ACC/AHA Stage D heart failure are further categorized into "INTERMACS profiles" based on the severity of the disease (Table 7.5).

Table 7.4 Contraindications to orthotopic heart transplantation

Age greater than 70 years
Obesity: body mass index > 35 kg/m^2
Uncontrolled diabetes mellitus
Pulmonary hypertension with TPG > 15 mmHg or PVR > 6 Wood units
Cancer history < 5 years
Recent tobacco use
History of medication noncompliance
Lack of social/financial support

PVR pulmonary vascular resistance, *TPG* transpulmonary gradient

Patients with current-generation LVADs (HeartMate II or HeartWare) have a much greater survival rates than individuals with older pumps that are no longer in use. For example, according to the sixth annual INTERMACS report, the 1-year survival rate was ~80 % with current-generation LVADs; older devices no longer in use had an associated 1-year survival rate of ~50 % [82, 83]. In contrast, the 1- and 3-year survival rates for OHT are ~90 % and 80 %, respectively [84].

Conclusions

The human heart is an elegant contractile pump that beats more than two billion times in a lifetime and delivers more than 1900 gal of blood each day to peripheral organs. In response to a severe stress such as an ischemic insult, mechanical perturbations, toxins, viral illnesses, and environmental stimuli, the heart is compromised and fails acutely. This initial stress and the resulting acute heart failure episode may further result in sudden cardiac death or hemodynamic collapse. Parenteral afterload reducing agents, inotope agents, or surgical therapies may be urgently required. Furthermore, the increasing use of devices and orthotopic heart transplantation has provided more definitive therapies for irreversible acute decompensated heart failure. Efforts are being directed toward increased education for bystanders in response to sudden cardiac death and cardiac reperfusion strategies following ischemic causes of sudden cardiac death. In addition, future efforts will include educational programs to encourage patients to seek medical care earlier in their illness and the rapid transport of patients to quaternary medical institutions, which have access to conventional and advanced heart failure therapies.

Table 7.5 INTERMACS profiles

Profile	Shorthand name	Time to mortality	Indication for advanced therapies
INTERMACS 1	"Crash and burn"	Hours	Yes
INTERMACS 2	"Sliding fast" on inotropes	Days	Yes
INTERMACS 3	"Stable" on inotropes	Few weeks	Yes
INTERMACS 4	"Resting symptoms"	Months	If peak VO2 ≤ 12
INTERMACS 5	"Housebound"		If peak VO2 ≤ 12
INTERMACS 6	"Walking wounded"		
INTERMACS 7	Advanced NYHA III HF		

INTERMACS Interagency Registry for Mechanically Assisted Circulatory Support, *VO2* peak oxygen uptake

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Ischemic Cardiomyopathy

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_8

Incidence and Prognosis

Ischemic cardiomyopathy is the most common cause of systolic heart failure, accounting for about 60 % of cases worldwide [1, 2]. It also is associated with a significantly higher mortality rate than non-ischemic cardiomyopathy (Fig. 8.1) [3–5]. An individual patient's long-term prognosis is related primarily to his or her left ventricular ejection fraction (LVEF), the extent of coronary artery disease (as reflected by the extent of inducible ischemia), and prior myocardial infarction (MI). Other parameters that reflect the extent of congestive heart failure secondarily adversely affect prognosis. These include moderate to severe mitral valve regurgitation, atrial fibrillation, pulmonary hypertension, secondary right heart failure, and elevated biomarkers of heart failure, such as circulating catecholamines, and B-type natriuretic peptide.

The diagnosis of ischemic cardiomyopathy is straightforward in patients with extensive prior myocardial infarction (particularly involving the large perfusion field of the left anterior descending artery) and stenosis of all three coronary arteries or the left main coronary. However, it can be difficult to differentiate ischemic from non-ischemic etiologies in many patients because of the ubiquitous nature of coronary atherosclerosis in older patients [5]. Heart failure in patients with limited coronary disease (e.g., single-vessel disease) should prompt a search for other causes of cardiomyopathy. In addition, patients can have more than one etiology of heart failure, particularly synergistic combinations such as combined valvular disease and coronary artery disease.

Mechanisms of Ischemic Cardiomyopathy

Normal Control of the Myocardial Blood Flow

Myocardial blood flow at rest is about 0.8 ml/g muscle/min and can rise to about 2.5–3.0 mL/g/min with increased myocardial oxygen demand [6]. Blood flow is autoregulated normally by dilation and constriction of the coronary arterial

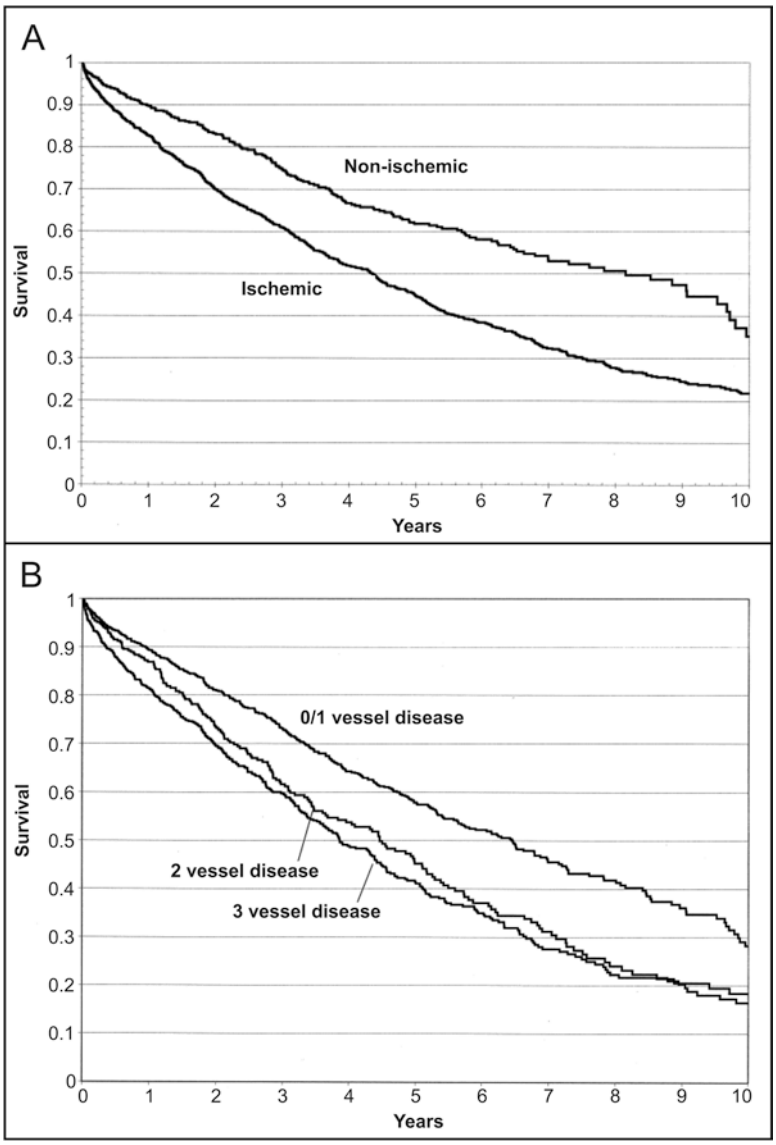

Fig. 8.1 Survival of patients with ischemic cardiomyopathy compared to those with a non-ischemic etiology. *Left panel*: Patients with ischemic cardiomyopathy have a higher mortality risk than do those with non-ischemic cardiomyopathy. *Right panel*: The mortality risk increases with more widespread coronary artery disease. *Source*: Duke Database, Felker et al. J Am Coll Cardiol. 2002;39(2):210–8 [3]

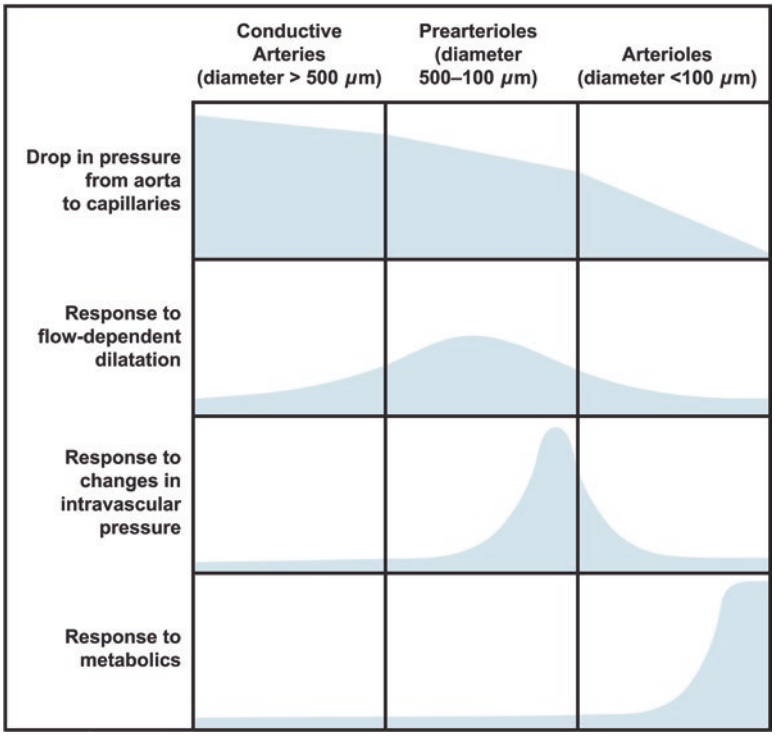

Fig. 8.2 A schematic of the coronary circulation. The large epicardial coronary arteries are conduits to the microcirculation and provide little resistance. The vessels close to the capillary bed dilate and constrict in response to metabolic needs of the cardiomyocyte to match oxygen demand and delivery. The larger microcirculation dilates primarily through endothelial mechanisms

tree [7]. The delivery of oxygen is tightly coupled to the cardiomyocyte needs. Increased demand caused by increases in myocardial workload lead to coronary dilation and increased conductance of blood (and oxygen). Similarly, reductions in blood oxygen-carrying capacity (usually due to anemia) lead to reduction of coronary resistance to increase coronary blood flow and maintain oxygen delivery.

The coronary tree can be divided arbitrarily into four zones. The large arteries that can be seen on an angiogram or with the naked eye are more than 400 μm in diameter (Fig. 8.2). These arteries are often referred to as conduit arteries because they normally provide very little resistance to blood flow. For example, the blood pressure in the left anterior descending artery when it reaches the cardiac apex is about 95 % of the blood pressure in the left main coronary.

The large conduit arteries divide into the proximal microcirculation (vessels 200–400 μm in diameter). The smooth muscle of these vessels actively constricts and dilates in response to luminal blood flow velocity, autonomic tone, and circulating vasoactive compounds such as catecholamines, vasopressin, and serotonin.

The distal microcirculation (vessels with a thin, smooth muscle media and luminal endothelial layer) extends from the proximal microcirculation to the capillary level. These very small arteries are bathed in the extracellular fluid of cardiomyocytes. They respond by dilating and constricting to mediators of oxygen need (such as pH and adenosine) produced by the cardiomyocytes. This response links demand with oxygen delivery.

The tone and caliber of arteries from the coronary ostium to the microcirculation (i.e., vessels 200 μm diameter or larger) are modulated by endothelial production of dilators (primarily nitric oxide, NO). In their native state, the coronary arteries are prone to constrict were it not for the continual generation of NO by the enzyme NO synthase within the endothelial cell (eNOS). With increases in myocardial metabolic oxygen requirements—such as increase in heart rate, blood pressure, or preload—the microcirculation closest to the myocyte (microcirculation of 50–200 μm) dilates to increase blood flow.

In most mammals, including humans, the artery seeks to maintain a flow velocity of 12–17 cm/s. When the distal microcirculation dilates, the velocity of flow increases in the upstream coronary, stimulating shear stress receptors on the luminal side of the endothelial cell. This causes the endothelium to release more NO. The NO permeates the underlying vascular smooth muscle, leading to an "ascending wave" of coronary dilation.

This combination of distal microcirculation dilation in response to the myocyte need and the ascending dilation caused by NO release reduces coronary resistance and increases myocardial blood flow. In this way, the blood flow to the myocardium is closely paired to the metabolic requirements. This coupling of blood flow to myocardial metabolic need enables the cardiomyocyte to rapidly increase contractility and shortening.

Coronary Atherosclerosis

The most common cause of IschCM is atherosclerosis of the large coronary arteries. About six million people in the USA suffer from heart failure related to coronary atherosclerosis, making it a leading cause of death and disability.

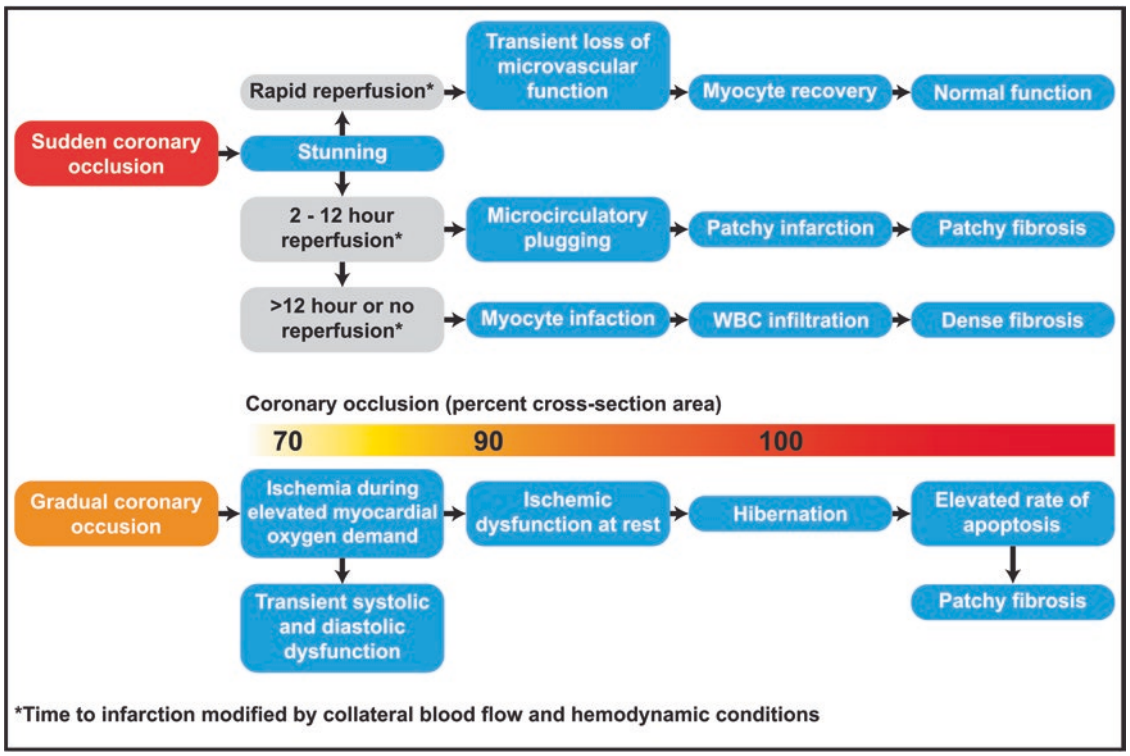

Fig. 8.3 Effects of coronary occlusion on the myocardium, as a function of the rate and severity of occlusion

Mechanisms of Atherosclerosis-Related Ischemic Cardiomyopathy

Atherosclerosis causes myocardial dysfunction through several mechanisms. In its most advanced state, thrombotic closure of an epicardial conduit artery leads to downstream myocardial infarction and replacement of functioning cardiomyocytes with noncontracting fibrous tissue (Fig. 8.3). Just short of infarction, gradual closure of the coronary arteries, usually accompanied by ingrowth of collateral vessels from neighboring coronary branches, leads to chronic cardiomyocyte ischemia. The chronic ischemia results in a noncontracting myocyte that eventually enters a hibernating state [8]. This results in impaired systolic function and impaired diastolic relaxation. Finally, atherosclerosis-associated abnormal vasomotion and constriction of the coronary arteries can lead to both transient loss of cardiomyocyte function and loss of myocytes in the subendocardium.

Atherosclerosis is usually preceded by reduced endothelial control of vascular tone. Since arteries are prone to constrict in the absence of tonic NO production by the endothelium, these arteries are prone to inappropriate constriction at both the micro- and conduit vessel levels. For example, transient sympathetic stimulation that might cause an increase in contractility and blood flow can lead to microvascular constriction [see the heading below, "Stress-Induced Ischemic Cardiomyopathy"] in the face of increased oxygen demand due to the elevated contractile state. This can result in transient myocardial ischemia and dysfunction but usually does not lead to chronic heart failure or loss of pump function.

As atherosclerotic deposits develop within the coronary arteries, the usual initial response to increased coronary wall thickness is for the artery to grow externally (i.e., increase its outer diameter) while preserving the lumen caliber. This "positive remodeling" described by Glagov et al. continues until the wall thickness is increased by about 40 % [9]. Thereafter, the lumen of the artery slowly diminishes in caliber, usually in an eccentric manner. As the conduit coronary lumen narrows, blood flow to the downstream cardiac muscle is maintained by dilation of the microcirculation. Typically, this downstream microvascular dilation is engaged when the cross-sectional area of the large coronary lumen is about 70 % reduced, compared to the original lumen caliber [10].

With this downstream autoregulation, blood flow at rest is preserved. When myocardial oxygen requirements increase, however, capacity for further dilation is limited. This results in demand-induced ischemia. Typical demands that result in ischemia are exercise and elevated heart rate. Although elevated blood pressure also invokes more oxygen demand, it is accompanied by increased driving pressure for coronary flow through the stenotic lesion, which mitigates the effects of the stenosis.

As the arterial lumen narrows further, blood flow at rest diminishes because the downstream microcirculation is fully dilated and cannot further compensate for the upstream obstruction to flow. This occurs when 90 % of the arterial

lumen cross-sectional area is obstructed. On the arteriogram, these lesions appear to cause subtotal occlusion of the epicardial artery, and the distal flow of contrast media is slow.

The effects of an upstream stenosis on myocardial blood flow can be mitigated by collateral blood vessel connections between the coronary branches. Small collateral arteries that usually connect the microcirculatory branches exist in most human hearts to a variable degree. The branches are most prominent in the subendocardium but can be found throughout the circulation [11]. In non-ischemic coronary beds, the available collateral blood flow is low: around 0.2–0.4 mL/g/min [12]. Repetitive ischemia can lead to the growth in diameter of collateral blood vessels such that, in some patients, collateral blood supply can nearly reach the level of the original flow from the epicardial artery [13]. Diabetics and patients with microcirculatory disorders appear to have less collateral blood flow [14].

Collateral blood flow can increase rapidly. Typically, hibernating myocardial segments, where the initial coronary occlusion did not result in infarction, have markedly better collateral blood flow. After sudden coronary occlusion, 48 % of patients have angiographically visible collateral support of the occluded coronary risk area at 6 h, whereas by 1–30 days, 92 % had angiographically visible collateral blood flow to the infarct risk area [15].

Physiology of Acute Myocardial Infarction and Relation of Ventricular Function

Most myocardial infarctions are due to a relatively sudden occlusion of an epicardial coronary artery at a site of atherosclerotic plaque rupture. The muscle zone fed by that artery is referred to as the "area at risk." The larger the risk area, the larger the infarction, and the worse the outcome. Increases in the infarct volume bring a stepwise increase in long-term mortality. Infarction of more than 40 % of the left ventricular mass is generally not survivable [16].

Assessing the impact of therapies on myocardial infarction center on risk area measurements: Effective therapies change the ratio between the area at risk and the area of infarction. Cardiac magnetic resonance imaging (CMRI) with T2 weighting enables measurement of the edema that occurs in the area at risk after a prolonged ischemic episode. Delayed gadolinium (Gd) imaging, where the Gd contrast agent clears slowly from injured myocytes (early infarction) and fibrotic areas (late infarction), allows measurement of the infarct area. Using the two methods, an infarct-to-risk area ratio can be obtained.

Mechanisms of Infarction and Preconditioning

When atherosclerotic plaques rupture, the luminal platelets are activated by the collagen and other clot promoters in the plaque, such as tissue factor. This leads to intraluminal thrombosis, which can be highly variable. Patients with enhanced platelet function (such as those with inflammatory diseases or cigarette smokers) develop greater clot volume than others. Pieces of the intraluminal thrombus often break off and embolize downstream, leading to microinfarctions throughout the thickness of the downstream muscle. Activated platelets generate potent vasoconstrictors, such as thromboxane A2 and serotonin, leading to transmural ischemia from microvascular constriction downstream and spasm in the epicardial artery. Moreover, the thrombus in the artery is dynamic. Plasmin gradually dissolves the fibrinogen holding the platelets together, leading to thrombus resorption. Additional platelet activation leads to more clot deposition. As a result, arteries often open and close actively.

All of these factors lead to recurrent bouts of myocardial ischemia.

The ischemic episodes can result in ischemic preconditioning. In clinical studies, ischemic preconditioning can occur quite rapidly. For example, a 1-min coronary occlusion with an angioplasty balloon causes brief preconditioning to subsequent coronary occlusion. The time to ischemic changes showing on an electrocardiogram (ECG) lengthens with each subsequent balloon occlusion. Similarly, patients with prior intermittent angina before infarction have a better outcome and smaller infarction for the area at risk, presumably aided by preconditioning.

When an epicardial coronary artery becomes occluded suddenly, the ischemia is most profound in the subendocardial layers. Infarction occurs first in these layers and proceeds out to the mid- and subepicardial layers with prolonged occlusion. The periphery of the risk area is usually better supplied with nearby collateral blood flow from the surrounding unobstructed arteries. If, however, the surrounding arteries are also occluded or severely narrowed, the availability of collateral blood flow will be diminished, leading to a more extensive and dense infarction in the area at risk.

Left Ventricular Remodeling

Advanced IschCM leads to remodeling of the left ventricle. The muscle in infarcted areas has reduced or no contraction, leaving the remainder of the myocardium to sustain stroke volume. As a result of reflexive changes and increased filling pressures, the surrounding non-infarcted muscle becomes hypercontractile. Reduced pump capacity activates the sympathetic nervous system (both neural and through release of catecholamines from the adrenal glands). The prolonged increased load on the remaining muscle can lead to hypertrophy. In many cases, however, the blood supply of the surrounding muscle is also impaired. The increased load on the non-infarcted muscle can lead to chronic ischemia and worsening of the heart failure through deterioration of the contraction of the surviving viable muscle.

Over time, the left ventricle dilates, changing from a prolate ellipsoid to a spherical chamber. This increases the wall stress needed to develop a given intraventricular pressure, further increasing the workload of the remaining myocytes. Unlike many non-ischemic cardiomyopathies, IschCM is usually associated with segmental, nonhomogeneous loss of LV contraction. This further reduces ventricular efficiency by creating "hinge points" between contracting and noncontracting segments [17].

Regional loss of contraction can particularly affect mitral valve function. Akinesis in the areas supporting the papillary muscles leads to mitral regurgitation due to impaired systolic mitral closure. Like all dilated cardiomyopathies, dilation of the ventricle leads to an enlargement of the mitral annulus and reduced tethering of the mitral leaflets (the ventricle enlarges more than the mitral chordae lengthen), leading to mitral insufficiency. The degree of mitral regurgitation (MR) is affected substantially by changes in LV volume and geometry—and it can be quite dynamic.

Eventually, the downward spiral of left ventricular dilation, sympathetic overdrive, secondary left atrial dilation (often inciting atrial fibrillation), pulmonary congestion leading the pulmonary hypertension and right ventricular failure, and fluid retention from inadequate renal perfusion results in death.

Imaging in Ischemic Cardiomyopathy

Imaging can give important information about ventricular and valvular function, myocardial blood flow, changes in tissue histology, and, more recently, cardiomyocyte biochemistry. Much of this is discussed in Chaps. 5, 12, and 14. In general, the prognosis of ischemic cardiomyopathy is a function of the volume of infarcted muscle, expressed as a percentage of the myocardium; the volume of hibernating muscle; and the volume of muscle that becomes ischemic under stress conditions. Each of these parameters can be imaged using a variety of methods.

Assessment of Ischemia, Hibernation, and Infarction

Detection of Inducible Ischemia

The prognosis of all patients with coronary artery disease is related to the presence and volume of myocardial ischemia that can be induced under a stress condition. Whether ischemia is detected by ischemic electrocardiographic changes during stress (ST segment depression), loss of contraction on echocardiographic stress imaging, or a focal reduction in ventricular perfusion (nuclear imaging), the greater the volume of ischemic muscle and the less stress required for induction of ischemia, the worse the prognosis [18]. Not surprisingly, most studies show that the presence and extent of inducible ischemia also predicts, in part, the prognosis of patients with IschCM [19, 20].

Assessment of Fibrosis and Viability

A simple but insensitive and somewhat nonspecific method for detecting myocardial scar is the presence of Q waves on the electrocardiogram [21]. Initial determination of the volume and location of infarction-related fibrosis is derived from X-ray contrast ventriculography or standard echocardiography. Akinetic areas are assumed to be fibrotic, particularly if wall thinning or loss of trabeculation could be detected.

Identifying myocardial hibernation, however, makes clear that simple assessments of contractile state do not accurately reflect the underlying viability or presence of cardiomyocytes (as opposed to scar). Moreover, the area and transmural depth of fibrosis after myocardial infarction varies widely after myocardial infarction. The presence of collateral blood flow to the area at risk, the occurrence and timing of reperfusion of the infarct-related artery, and ischemic preconditioning prior to coronary occlusion all impact the extent of the infarction and subsequent fibrosis. Hence, some areas might be densely infarcted, whereas others have patchy or only a subendocardial-layer scar.

The extent of myocardial focal scar can be assessed indirectly by nuclear (201-Tl and 99-Tc agents) imaging, where the absence of tracer uptake (on immediate and late imaging) implies the presence of scar. The spatial resolution of these methods, however, limits their utility for precise quantitative assessment [22]. Positron emission tomography (PET) imaging [see below] improves spatial resolution but still has limitations for precise transmural volumetric assessment.

The most accurate method for assessing the volume and distribution of myocardial fibrosis is MR imaging after gadolinium-based contrast agent infusion. Gd agents wash out slowly from fibrotic tissue and can be imaged after the initial perfusion scan is obtained. Survival is tightly linked to the fraction of the ventricle that contains scar tissue; the greater the volume of scar, the greater the mortality risk (◘ Fig. 8.4).

Myocardial viability can be assessed indirectly by the muscle response to stimulus intended to evoke enhanced contraction, or it can be inferred from noncontractile myocardium that is not fibrotic.

Horn et al. identified a subset of patients with reduced ventricular function who had improved contraction during epinephrine infusion (a so-called epinephrine ventriculogram) [23]. In addition, it was observed that the contraction after a premature ventricular contraction (PVC)—with its compensatory pause and heighted inotropic state—is enhanced. This enhanced contraction with potentiation could be imaged easily during left ventricular angiography. Increased contraction in an akinetic or hypokinetic zone was predictive of improved function after revascularization [24, 25]. This led Diamond et al. to coin the term hibernation to describe the phenomenon [26].

Noninvasive approaches to assessing viability in noncontractile zones have centered on perfusion imaging. Initially, ^{201}thallium agents or ^{99}technetium agents are initially taken up by cardiomyocytes in proportion to blood flow. Ischemic muscle appears as a perfusion defect on single photon emission imaging. Over time, however, these agents are concentrated by the cardiomyocytes—and concentrated by myocytes even in the presence of ischemia. Repeat imaging after a 4- to 24-h interval allows the ischemic muscle to concentrate ^{210}Tl. Scar does not concentrate ^{201}Tl. If a perfusion defect on the

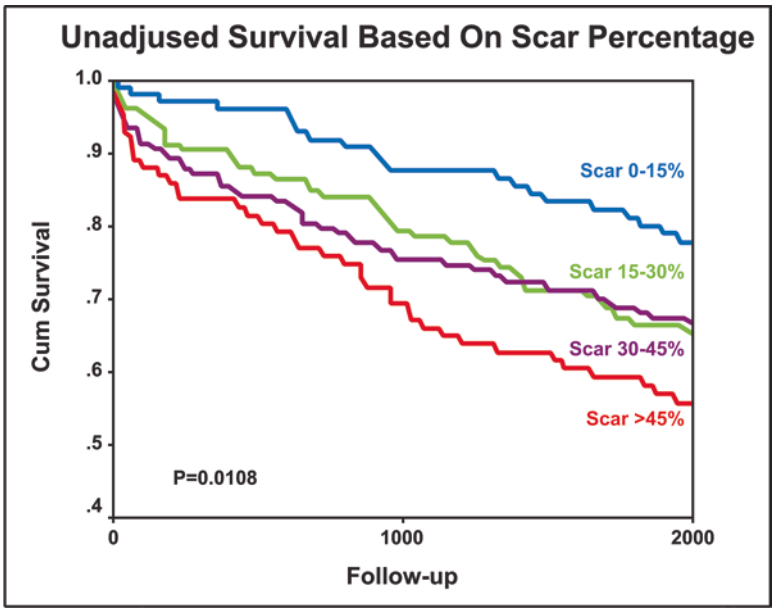

Fig. 8.4 Survival of patients with ischemic cardiomyopathy as a function of the amount of scar tissue (expressed as a percentage of the left ventricular mass) measured using late Gd enhancement on MR imaging. *Source*: Kwon et al. Circulation. 2012;126(11 Suppl 1):S3–S8 [55]

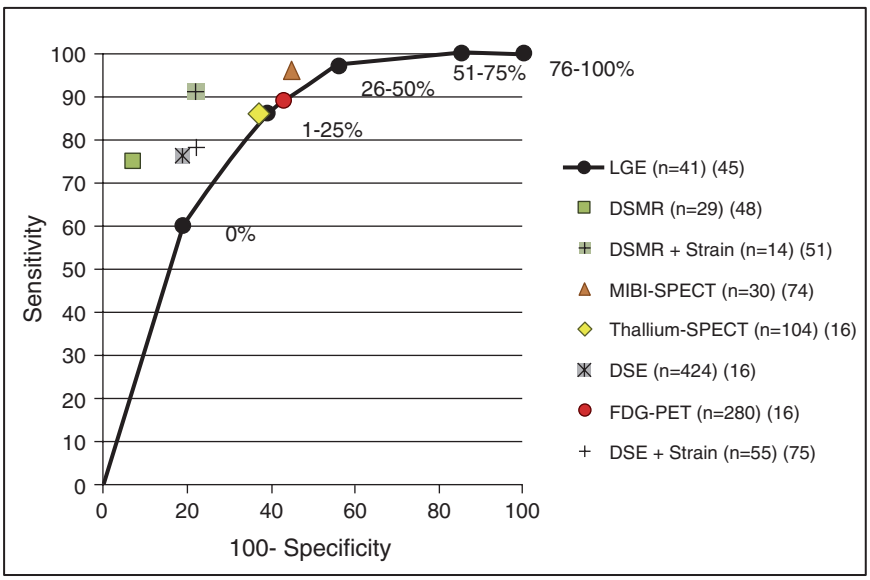

Fig. 8.5 Receiver operating curve showing the diagnostic accuracy of different techniques to assess myocardial viability. DSE = dobutamine stress echocardiography; DSMR = dobutamine stress magnetic resonance; FDG = fluorodeoxyglucose; LGE = late gadolinium enhancement; MIBI = methoxyisobutylisonitrile. *Source*: Schuster et al. J Am Coll Cardiol. 2012;59(4):359–70 [29]

initial scan fills in on late imaging, the area can be assessed as viable but ischemic. Occasionally, a second dose of radiotracer is given to intensify late enhancement of the ischemic zone.

Nuclear imaging was improved by adding PET agents that enabled more accurate assessment of myocardial perfusion, better spatial resolution, and, also, direct assessment of myocardial metabolism. Imaging with ^{82}Rb, ^{14}N ammonia, or ^{15}O water enabled progressively better measurements of myocardial blood flow with better spatial resolution than the older ^{201}Tl- or ^{99}Tc-based compounds. Assessment of glucose metabolism using fluorodeoxyglucose (^{18}FDG) permitted imaging of cardiac muscle that has switched from fatty acid (oxidative) metabolism to glucose as an energy source (anaerobic metabolism). *Areas with reduced blood flow and preserved anaerobic metabolism indicate ischemic but viable myocardium*.

Subsequently, the response to catecholamine stimulation, usually by intravenous dobutamine, during echocardiographic imaging was developed as a test of contractile reserve [27]. The normal response to dobutamine infusion is a stepwise improvement in contraction and ventricular ejection fraction. Ischemic but viable noncontracting muscle typically has a two-phase response. Initially, the contraction improves. As the stimulant dose is increased, however, the segment again become dysfunctional. Nonviable myocardium either has no significant contractile response or becomes dyskinetic.

Although these indirect methods of assessing viability have some accuracy in detecting muscle that will improve function with revascularization, they are only modestly accurate [28, 29] (Fig. 8.5). MR imaging allows much better special resolution of perfusion by the flow of imaging Gd-based contrast agents within the myocardium. Gd agents are taken up slowly and released slowly from the extracellular space of

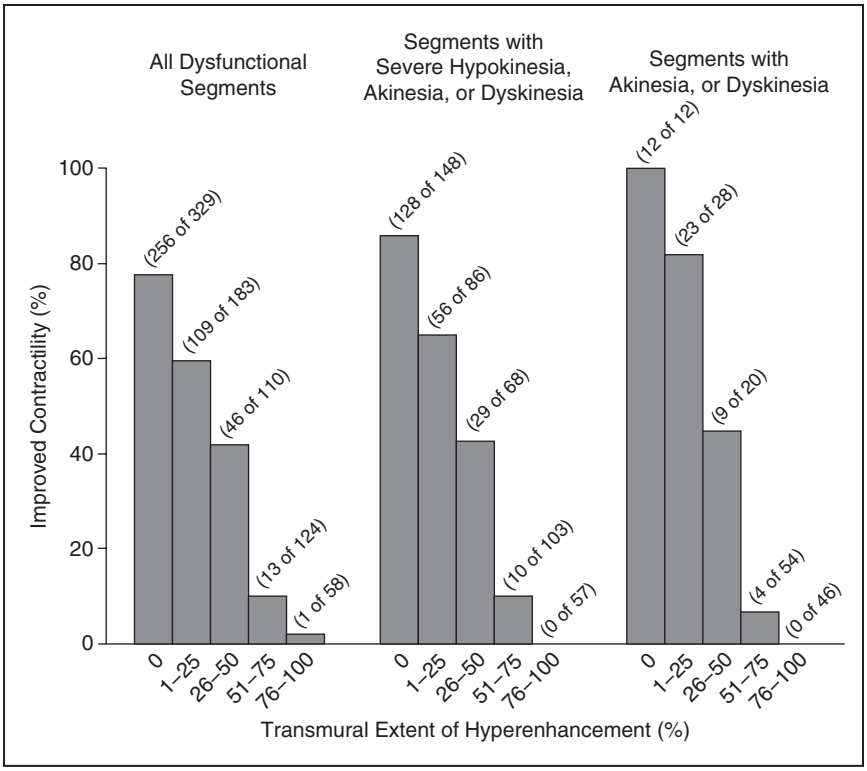

Fig. 8.6 Relation between the transmural extent of hyper-enhancement before revascularization and the likelihood of increased contractility after revascularization. *Source*: Kim et al. N Engl J Med. 2000;343(20):1445–53 [30]

fibrous tissue, allowing excellent spatial identification of scar. Areas with reduced perfusion and the absence of scar are, in theory, viable. In one study, severely hypokinetic or akinetic myocardium without scar (i.e., no hyper-enhancement with Gd agents) had 86 % and 100 % incidence, respectively, of improved contraction after revascularization [30].

Viable but akinetic myocardium is quite common in patients with ischemic cardiomyopathy, but the volume of hibernating muscle varies considerably. One major advantage of MR imaging is that the transmural distribution of blood flow and fibrotic tissue can be assessed quantitatively. Most infarctions are not transmural. The thickness of the infarction has a great impact on the ability of the myocardial segment to return to meaningful function after revascularization. Segments with less than 25 % wall thickness scar usually improve in function significantly. Those with >50 % scar usually remain akinetic [30] (Fig. 8.6).

Using MR to assess viability can be enhanced by administering dobutamine to determine if wall motion improves in an akinetic section—in a manner similar to dobutamine stress echocardiography. The advantage of MR imaging is that it is three-dimensional and offers greater spatial resolution. In addition, the use of strain imaging may improve the assessment of viability [31].

Patients with viable, under-perfused muscle treated with medical therapy alone tend to have a worse prognosis than those with segments that are either dead or alive, and well perfused [32–34]. Prognosis is related in part to the volume of hibernating muscle [35].

Complications of Ischemic Cardiomyopathy

Infarction-Related Aneurysm

A full thickness scar can develop in densely infarcted areas, leading to aneurysm formation and bulging of the LV chamber during systole (Fig. 8.7). This reduces LV efficiency and provides an area of blood stasis that often leads to thrombus formation [36]. The efficacy of anticoagulation therapy is unclear. In one recent report, warfarin anticoagulation did not appear to be effective [37]. In addition, the rim of the aneurysm can be the substrate for recurrent ventricular tachycardia and sudden death. Most aneurysms are in the perfusion field of the mid or distal left anterior descending artery, although they can occur anywhere in the ventricle. Aneurysms located near the papillary muscles' mitral apparatus can cause mitral regurgitation.

Patients with a large, discrete, dyskinetic aneurysm and heart failure symptoms or thrombus in the aneurysm may benefit from surgical aneurysmectomy to improve ventricular efficiency and reduce the likelihood of thromboembolism. In addition, ventricular arrhythmia that cannot be controlled with ablative therapies can be treated with aneurysm resection.

Percutaneous placement of the Parachute device, which occupies the aneurysmal cavity, may also be effective in reducing symptoms from a discrete apical aneurysm [38]. Thrombus within the aneurysm is a contraindication.

Embolism

Although all cardiomyopathies have a higher risk of cardioembolic events (primarily stroke), ischemic cardiomyopathy has a particularly elevated risk for several reasons. First, the presence of dyskinetic myocardium can lead to blood flow stasis and clot formation. Second, ischemic heart disease is often a disease of coronary thrombosis. Many patients with ischemic cardiomyopathy have a greater propensity to clot.

Prior to the intense anticoagulation that is now part of the treatment for acute myocardial infarction, cardioembolism was common, afflicting nearly 1 in 20 patients with acute MI. Most of these emboli originated in an akinetic or dyskinetic infarct area of the LV cavity (Fig. 8.8). In addition, large infarctions cause atrial fibrillation, which in turn can lead to thrombosis of the left atrial appendage. Of importance, patients presenting with myocardial infarction are usually "prothrombotic"—with enhanced platelet function and low antithrombin levels.

In chronic ischemic cardiomyopathy, areas of blood flow stasis can be seen on Doppler echocardiography in the ventricle, especially in a-dyskinetic segments. These patients have a higher risk of embolic events and may benefit from systemic anticoagulation, but there is little experimental data to guide treatment of patient.

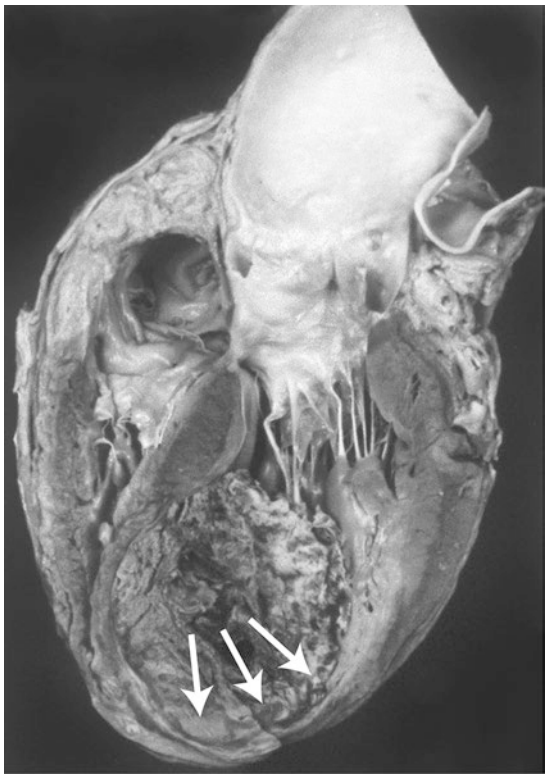

Fig. 8.7 An apical left ventricular aneurysm (*arrows*) due to a prior myocardial infarction in the left anterior descending territory is shown from a postmortem examination

Mitral Regurgitation

Mitral regurgitation in the setting of ischemic cardiomyopathy is associated with more debilitating symptoms and a much poorer outcome. Although MR itself amplifies the degree of congestive heart failure symptoms from ischemic cardiomyopathy, it also tends to accompany more advanced cardiomyopathy, where the LV cavity size is more dilated. Hence, the independent role of MR in prognosis is less certain, particularly where the MR is only a moderate volume that would normally be tolerated in a patient with mild LV dysfunction.

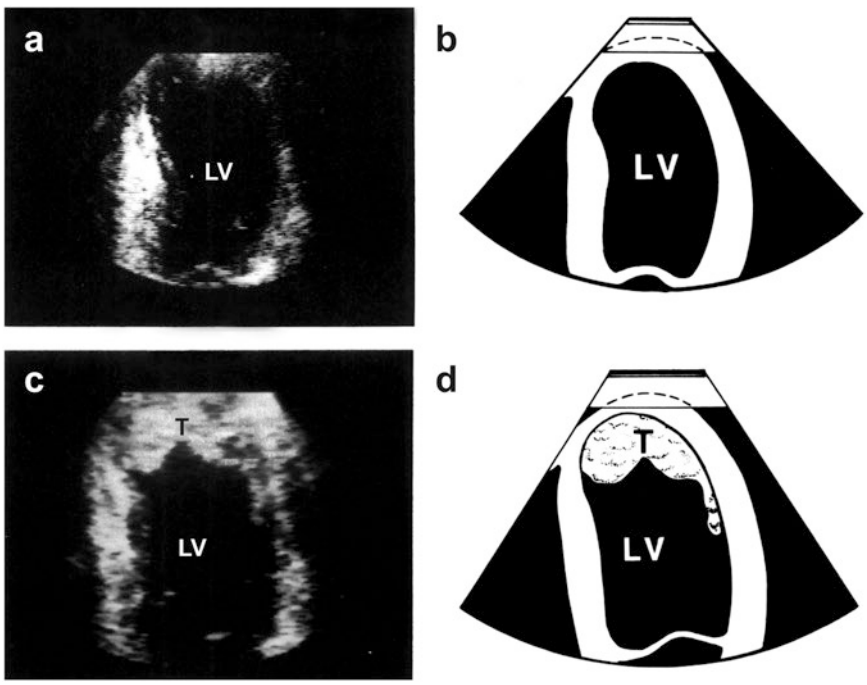

Fig. 8.8 Panel **a**: An echocardiogram still frame of a patient 7 days after an anterior wall myocardial infarction showing no thrombus in the left ventricle. Panel **b**: A diagram describing the echocardiogram in Panel **a**. Panel **c**: An echocardiogram of the same patient 11 days after infarction showing an anterior wall mural thrombus (T) related to dyskinesis of the muscle. Panel **d**: A diagram describing the echocardiogram in Panel **c**. From Asinger et al. [45]

Medical treatment, especially with beta receptor antagonists, can lead to reduction in MR through reverse remodeling of the dilated ventricle and improved LV synergy. Similarly, a more synchronized contraction through dual-chamber pacing (cardiac rhythm therapy or cardiac resynchronization therapy) can improve mitral tethering and reduce the volume of the LV cavity.

Surgical treatment of MR associated with ischemic cardiomyopathy consists of mitral repair with an annuloplasty ring, mitral valve replacement, and percutaneous placement of a clip to connect the two mitral leaflets in the middle (the Alfieri stitch) [39]. The open surgical approaches usually occur at the time of coronary bypass revascularization, making it difficult to assess the relative role of the mitral procedure on the outcome.

In patients with severe MR, treatment of the valve is important. Both repair and replacement, usually in conjunction with bypass revascularization, lead to remarkable reductions in LV volumes and congestive heart failure symptoms. In one trial, mitral valve replacement was more durable over time than was repair [40]. For patients with moderate MR, the data are less clear. Mitral repair with an annuloplasty ring to reduce the mitral annular circumference and reduce further annular dilation was effective in early trials of moderate MR-complicated ischemic cardiomyopathy but not at all effective in a recent randomized trial [41, 42]. Ventricular dimensions and symptoms were similar at 1 year in those with and without mitral repair. Almost one-third of patients undergoing repair, however, develop recurrent, significant MR [43]. The long-term effects are less clear.

Medical Therapy for Ischemic Cardiomyopathy

Medical treatment for ischemic cardiomyopathy is similar to that for all congestive heart failure with the exception that additional treatment is needed to prevent further myocardial ischemia and infarction. In particular, beta adrenergic receptor blockade has the dual role of reducing ischemia and blocking the adverse cardiomyocyte effects of excessive catecholamine drive. Additionally, treatment with HMG-CoA reductase inhibitors ("statin"-type drugs) and antiplatelet agents (primarily aspirin) to reduce the likelihood of subsequent infarction is important to long-term prognosis.

Anticoagulation with warfarin, or factor 2A or 10A inhibitors, can reduce the incidence of stroke in patients with atrial fibrillation or ventricular aneurysm. The benefit to patients with large akinetic segments is less clear. Asinger et al. demonstrated that 46 % of patients with a large anterior infarction had intracavitary thrombus that could be imaged on echocardiography. For this reason, some physicians recommend anticoagulation to reduce the incidence of stroke during the first 6 months after a large anterior infarct with an associated large akinetic or dyskinetic zone [44]. Anticoagulation is often complicated by stent placement during the infarction. Stent placement that requires intense antiplatelet treatment can make further anticoagulation more dangerous. It is unclear whether prolonged anticoagulation is helpful in these patients or in those with intraventricular blood flow stasis (so-called smoke) on Doppler echocardiographic imaging [45].

Cardiac Rhythm Therapy

Because sudden death is more prevalent in patients with an ischemic cardiomyopathy, they may benefit from an implantable cardiac defibrillator (ICD). Current data suggest that patients with a left ventricular ejection fraction less than 35 % have reduced mortality with ICD therapy [2, 46]. The role of ICD therapy soon after infarction is more controversial. The preponderance of data suggests that, in many patients, ventricular function improves in the first month after an infarction and that ICD therapy is ineffective in these patients. Selected patients with very large, dense infarctions may benefit from the protection of a defibrillator vest (e.g., LifeVest from ZOLL Medical Corporation) until an implantable device can be placed, especially if they have ventricular ectopy on monitoring.

Dilation of the left ventricle, fibrosis involving the conduction system, and focal dyssynergy from infarction or hibernating tissue impair ventricular efficiency. Dual-chamber pacing (most often right ventricular pacing and left ventricular pacing via the coronary sinus) can be effective in improving that synergy of contraction. Patients with a left ventricular ejection fraction less than 30 % and widening of the QRS interval on the ECG (especially if it displays a left bundle branch block pattern) benefit from dual-chamber pacing, often referred to as cardiac rhythm therapy. Symptoms and left ventricular ejection fraction generally improve following dual-chamber pacing and cardiac dilation regresses. Patients with dyssynergic contraction on imaging and moderate ventricular systolic function also may benefit, even though their ventricular dysfunction is not severe [47]. In one study, placement of pacing leads near areas of fibrosis diminished the impact of dual-chamber pacing [48].

Surgical Therapy for Ischemic Cardiomyopathy

Role of Revascularization

It seems logical that revascularization of ischemic but viable myocardium would improve ventricular function and outcome. The clinical trials, however, have been confusing and suggest that only a portion of patients benefit. In part, this may reflect the competing immediate risk of surgical revascularization and the ongoing but lower-level risk of the ischemic cardiomyopathy. Moreover, volume and homoge-

neity of hibernating muscle may affect the impact of revascularization [49]. For example, patients with a small amount of hibernating muscle (i.e., <10 % of the LV mass) might derive little benefit, whereas those with large hibernating segments might derive substantial benefit. Unfortunately, most of the data supporting a "dose–response" relationship of revascularization of hibernating myocardium is anecdotal or from small and unblinded studies. One meta-analysis, however, showed a remarkable reduction in late mortality for patients with hibernating myocardium who underwent surgical revascularization compared to medical therapy alone [32].

The initial trials of coronary bypass surgery showed that patients with 2- or 3-vessel coronary disease and moderately reduced left ventricular function (ejection fraction 30–50 %) benefited significantly from surgery, both in terms of longer survival and reduced ischemic symptoms [50, 51]. These trials, however, generally failed to show an important overall improvement in ventricular function and heart failure. Moreover, patients with severe ischemic cardiomyopathy and congestive heart failure were excluded because of the high risk of surgery.

Subsequent trials have focused on the benefit of revascularization in relation to the mass of scar, ventricular function and dimensions, and the presence of viable but nonfunctioning myocardium identified with imaging [52–55]. The recent Surgical Treatment for Ischemic Heart Failure (STICH) trial randomized 1212 patients with an ischemic cardiomyopathy and an LVEF <35 % to bypass surgery plus medical therapy or medical therapy alone (Fig. 8.9). At 6-year follow-up,

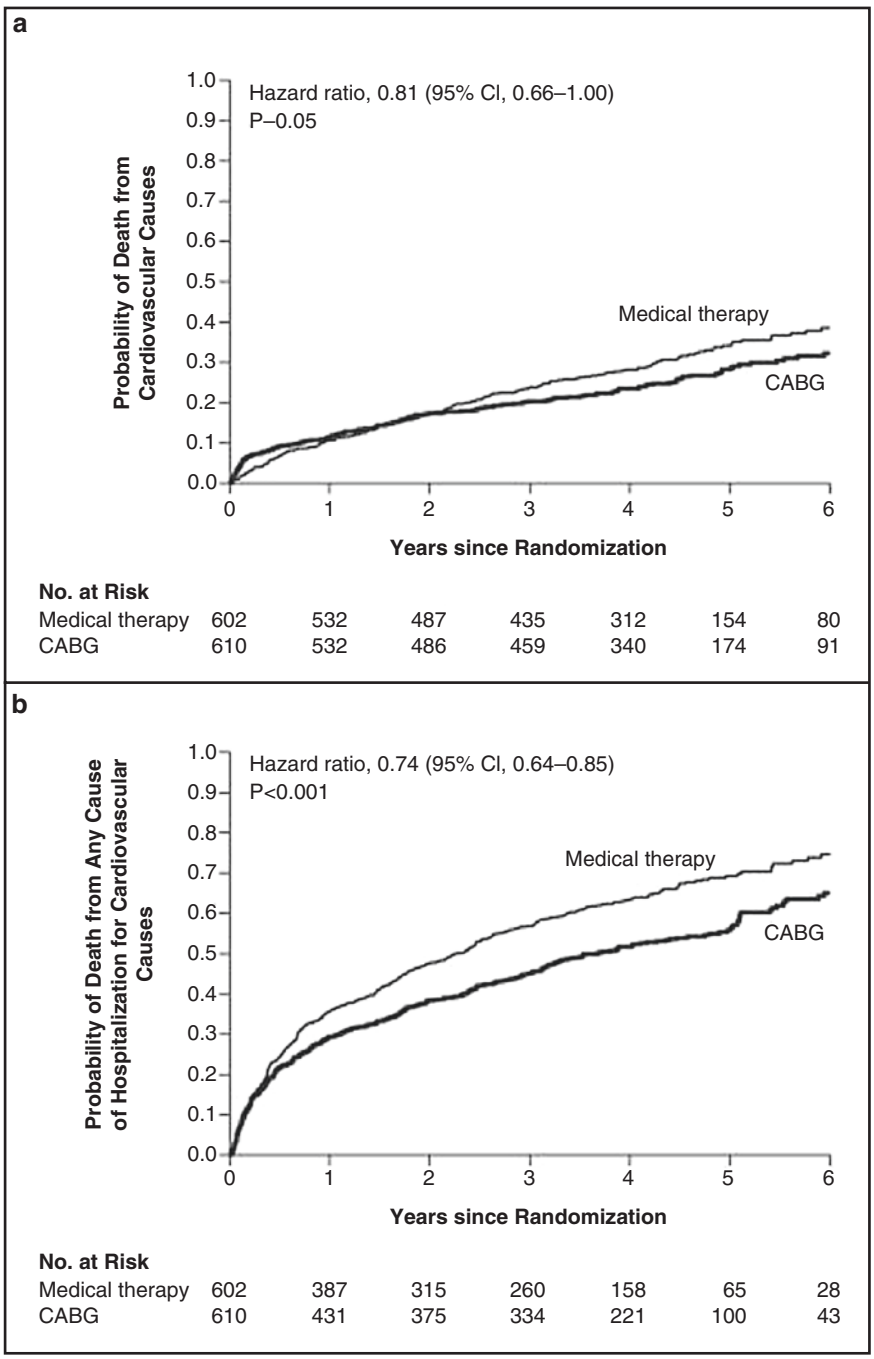

Fig. 8.9 Long-term mortality in patients enrolled in the STICH trial with severe ischemic cardiomyopathy and treated with coronary bypass surgery or medical therapy alone, analyzed by actual treatment (rather than the randomization-assigned treatment). Patients undergoing revascularization had a lower risk of mortality over the 6-year follow-up period. *Source*: Panza et al. J Am Coll Cardiol. 2014;64(6):553–61 [56]

those undergoing bypass had lower mortality and fewer symptoms. Patients with lower left ventricular ejection fraction, more ventricular dilation (greater end-systolic volume index), and more extensive coronary obstruction had the most benefit from bypass surgery (as compared to medical therapy alone) [56]. Taken as a whole, the current clinical data suggest that patients with a severe ischemic cardiomyopathy and unrevascularized ischemic or hibernating myocardium benefit significantly from coronary bypass surgery, provided that adequate revascularization can be technically accomplished.

In a subgroup analysis, the presence of viable ischemic myocardium was not related to improved survival from bypass surgery. However, the methods of assessing viability varied between sites, and the mass of viable muscle—an important predictor of revascularization response—was not quantitated. Importantly, those with viable myocardium had better survival, regardless of their treatment arm [57].

The role of percutaneous revascularization is not well studied, in part because many patients with ischemic cardiomyopathy do not have coronary anatomy amenable to angioplasty. Advanced multivessel disease, marked diffuse or calcific atherosclerosis, and chronic total coronary occlusion—all markers of angioplasty failure—are more common in patients with ischemic cardiomyopathy. There are anecdotal reports of markedly improved LV function and symptoms following multivessel percutaneous coronary intervention (PCI), particularly when the coronary occlusion is recent and easier to reopen by stenting.

LV Volume Reduction Surgery

Reductions in left ventricular cavity size by reverse remodeling (usually from treatment) lead to reduced MR. It is possible to reduce the LV cavity volume by excising a portion of the LV—reducing the cavity volume and the wall stress needed to develop a given blood pressure. Left ventricular volume reduction surgery (LVVRS) can range from excision of a discrete apical aneurysm to the Battista operation, where a wedge of ventricle—at least some of it viable—is removed [58]. The role of LVVRS in treating ischemic cardiomyopathy is not clearly defined, but most evidence suggests that it is marginally effective in most patients. In a small nonrandomized patient series, ventricular reduction surgery was reported to, in fact, reduce ventricular size and improve ejection fraction and heart failure symptoms [59, 60]. When patients were randomized to bypass surgery with ventricular reduction or bypass alone in the STICH trial, the results were less clear. Compared to those undergoing coronary bypass alone, patients undergoing reduction surgery had similar long-term outcomes regarding symptoms and repeat hospitalization, although ventricular volumes were reduced [61]. Interestingly, however, patients with less severe baseline ventricular dilation appeared to benefit most.

Stress-Induced Ischemic Cardiomyopathy

A large sympathetic discharge can lead to transient systolic dysfunction and infarction of the left ventricle. The condition has a number of names, but the two most commonly applied are stress-induced cardiomyopathy and takotsubo cardiomyopathy [62, 63]. Common precipitating causes are sudden fright, stroke, seizure, or other physiologic condition associated with massive sympathetic discharge, such as postoperative hemorrhage. Typically, patients present with chest pain and usually have significant ST-T wave changes on their electrocardiogram. Some patients also exhibit ST elevation in the anterior leads. Markers of cardiac injury (e.g., troponin isoforms, creatine kinase MB) are usually mild to modestly elevated. Imaging shows a characteristic ventricular hypocontractile pattern. The reduction in contraction mirrors the distribution of the sympathetic nerves within the left ventricle; the anterior wall and apex are most severely affected. The exact mechanism has not been elucidated but is presumed to be related to intense coronary constriction, likely at the microcirculatory level where the resistance vessels are well innervated by sympathetic fibers and the vessels are sensitive to circulating catecholamines [64].

The syndrome occurs primarily in female adults (96 % in one series) [65]. The age distribution is wide, from the 30s to the 90s, with the average patient in his or her 60s. No reliable predisposing factors have been reported.

Cardiac MR imaging shows a variety of contraction patterns, but most patients have involvement of the apex as well as other areas of myocardium—most often the anterior wall. Of note, about 1 in 5 patients also have hypokinesia of the right ventricle. The average ejection fraction was 32 % (range, 15–55 %) in one series. Ventricular function normalized within 3–51 days in three-fourths of patients and in all but 5 % within 3 months.

Although many patients rapidly recover, the syndrome is not always benign. The sudden ischemic loss of ventricular function can lead to cardiovascular shock, serious ischemic arrhythmia, intraventricular thrombus, and in 1–2 %, death. Mortality in the first 2 years after presentation is elevated over the age-adjusted average. Recurrences happen in 2–6 % of patients [66].

A similar syndrome can be seen after iatrogenic administration of large doses of catecholamines or endogenous release of catecholamines from a pheochromocytoma, which can lead to generalized transient ventricular dysfunction and patchy necrosis [67].

Almost all patients recover ventricular function within 1–14 days, although a minority are left with some persistent dysfunction. Recurrent episodes are not common, but limited information suggests that individuals with one episode of stress cardiomyopathy are somewhat more likely to have another compared to the general population.

Pathologic examination usually shows a pathognomonic "contraction band" necrosis pattern that characterized myocytes' death due to catecholamine excess.

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Valvular Cardiomyopathy

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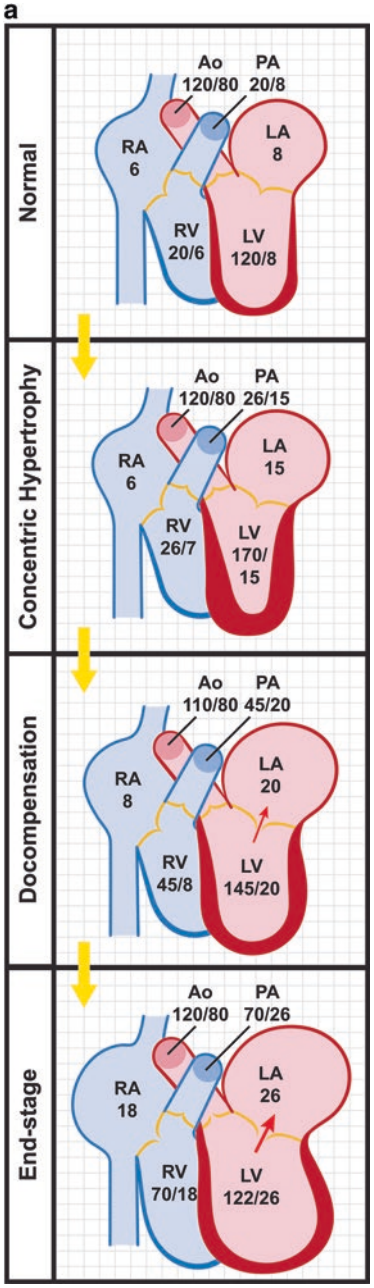
D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_9

Heart valve dysfunction is a common primary cause of heart failure; it is also a common complication of cardiomyopathies from other causes. For discussion purposes, heart valve disease in heart failure can be divided into primary and secondary valve disease. Primary valve disease results from structural abnormalities of heart valves due to a variety of inherited or acquired illnesses. Secondary (or functional) valvular disease results primarily from myopathic changes in cardiac structures that lead to dysfunction of a relatively normal valve, mainly causing mitral and tricuspid valve insufficiency. Valvular dysfunction reduces cardiac efficiency and accelerates the course of cardiomyopathy, whatever the cause. This chapter reviews the more common valvular conditions associated with congestive heart failure.

Valve Disease Leading to Heart Failure

Valvular abnormalities induce two types of cardiac responses. Stenotic lesions of the aortic and pulmonic valves lead to pressure overload-mediated incitement of concentric ventricular hypertrophy. Volume overload from valvular insufficiency leads to ventricular dilation and longitudinal, eccentric hypertrophy (Fig. 9.1).

a



b

	Normal	Concentric Hypertrophy	Decompensation	End-stage
Cardiac output	Normal	Normal	Reduced	Very reduced
LV ejection fraction (%)	55-65	>65	35-55	<35
Aortic valve gradient (mmHg)	Trivial	>40	30-70	<30 to 40
Aortic valve area (cm^3)	2.5-3.5	≤1.0	<0.8	<0.6
Pulmonary artery pressure	Normal	Normal to mild elevation	Elevated	Very elevated
Right heart failure	-	-	- to +	+++
LV fibrosis	-	+	++	+++

Fig. 9.1 Panel **a**: Morphological changes in the left ventricle in response to aortic valve stenosis. The initial response of concentric hypertrophy and heart failure with preserved ejection fraction gives way to a dilated cardiomyopathy, pulmonary hypertension, and reduced cardiac output. Panel **b**: Typical changes associated with the progressive aortic valve stenosis

The Aortic Valve

The normal aortic valve has three thin cusps that reflect from and are supported by the sinus of Valsalva. During systole, the valve is opened by the blood being ejected from the ventricle to the aorta, creating an orifice that has an effective cross-sectional area of 2.5–3.5 cm^2 and trivial pressure gradient between the ventricle and aorta. During diastole, the cusps are pushed shut by the pressure gradient between the aorta and ventricle. When the cusps coapt together, the back-pressure load of the aortic blood causes the cusps to pull the sinus of Valsalva inward and the cusp tissue to stretch. Hence, a normal aortic valve is dynamic and that movement aids valve sealing in diastole.

Aortic Valve Stenosis

One to two percent of the population have a congenitally abnormal valve, the most common of which is a failure of the cusps to separate in fetal life. This leads to a bicuspid valve with one large (fused) cusp and one small (normal) cusp [1]. Bicuspid valves have turbulent blood flow during systole, leading to thickening and fibrosis and retraction of the valve tissue over time. Males are affected twice as often as females.

Patients with bicuspid valves typically present with severe aortic valve stenosis in their teens to 60s. As the valve orifice becomes fibrotic, it calcifies, adding further to the valve rigidity and obstruction of ventricular outflow. Progressive stenosis leads to a pressure gradient across the valve during systolic blood ejection. The restricted blood flow jet through a stenotic valve stimulates dilation of the aorta just above the sinus of Valsalva, presumably related to the high-velocity jet stimulating aortic growth.

The second major cause of aortic stenosis is a poorly understood degenerative process in which the valve tissue becomes fibrotic and calcified. Both atherosclerosis and inflammatory processes have been suggested as the inciting causes, but at present there is no convincing evidence for any etiology. The degenerative process is slow. The average reduction in effective orifice area (EOA) is 0.1 cm^2/year. Most patients with severe aortic stenosis from a degenerative valve present in their 60s and beyond.

The third common cause, particularly in developing countries, is rheumatic heart disease, where a valvulitis leads to late fibrosis and calcification of the valve. Rheumatic disease of the aortic valve is usually accompanied by thickening of the mitral valve; the absence of mitral thickening makes a rheumatic etiology unlikely. Like bicuspid valvular disease, degenerative and rheumatic aortic valve disease leads to aortic dilation and a high-velocity jet across the valve, although the jet is usually seen with less intensity in bicuspid valves.

The increased pressure load on the ventricle imposed by valve restriction initiates a concentric hypertrophic process. Sarcomeres proliferate in parallel to each other, causing cardiomyocytes to grow in diameter and increasing the thickness of the ventricular wall. In later stages, the fibrous connective tissue between myocytes also proliferates. The hypertrophy causes the ventricular cavity to shrink in volume and the muscle to become less compliant. Longitudinal shortening of the ventricle all but disappears as the fibers rearrange their orientation, reducing the efficiency of cardiac contraction.

The hypertrophy and valvular obstruction initially cause heart failure with preserved ejection fraction. Stroke volume is diminished by the small left ventricle (LV) chamber size and reduced diastolic left ventricle filling due to reduced left ventricle compliance. High systolic intraventricular pressure creates increased pressure load on the mitral valve, potentiating functional mitral regurgitation. Higher diastolic left ventricle filling pressure leads to left atrial dilation and, eventually, to pulmonary hypertension and right heart failure. The elevated atrial pressure causes dilation of the mitral annulus, which in turn causes or augments the degree of mitral insufficiency.

This syndrome of hypertrophy-related diastolic abnormalities occurs most often in older women, many of whom have markedly reduced cardiac output in the face of normal left ventricle ejection fraction. In advanced stages, cardiac output declines, reducing renal perfusion and leading to fluid retention and congestive heart failure [2].

A contributing cause of elevated diastolic ventricular pressure is a combination of valve restriction and insufficiency. The same processes that cause stiffening of the valve cause tissue retraction and poor coaptation of the cusps. The resulting diastolic leak through the valve increases diastolic filling pressure and, in some patients, may be a major cause of symptoms.

As the pressure overload continues and the valve restriction becomes more severe, the ventricle may dilate, and systolic function, as measured by ejection fraction, declines. This often leads to functional mitral regurgitation, reduced cardiac output, atrial fibrillation from left atrial distension, and a spiral to severe heart failure and death.

Symptoms

The cardinal symptoms of aortic stenosis are chest pain, dyspnea, and syncope. Hypertrophy and high pressure-induced workload lead to myocardial subendocardial ischemia, reduced diastolic relaxation, and chest pain. The epicardial arteries feeding the muscle send penetrating branches through the thickened muscle. These branches are compressed, reducing availability of subendocardial blood flow. In addition, although the muscle mass increases significantly, the number of vascular channels does not, reducing the ratio of vascular cross-sectional area to muscle mass. Hypertrophy and subendocardial ischemia lead to dyspnea on exertion.

Of note, while many believe that syncope in patients with aortic stenosis results from vasodilation in the face of inadequate cardiac output, it usually results from reflexive dilation of the peripheral circulation in response to excessive intraventricular pressure [3]. This explains in part why it often

occurs just after exercise and often disappears as the ventricle dilates and fails—and no longer generates very high pressures.

Diagnosis

The degree of valvular stenosis is usually defined by the mean systolic pressure gradient across the valve or the effective orifice area. Gradients from 10 to 40 mmHg imply moderate stenosis. Gradients over 40 mmHg imply severe stenosis. The problem with using pressure gradient as the measure of valve stenosis is that it is dependent on stroke volume. Patients with reduced stroke volume, whether from loss of left ventricle chamber dimension from concentric hypertrophy or from reduced systolic contraction, have a reduced systolic pressure gradient for a given level of stenosis. This can lead to some confusion about the severity of the stenosis because patients with severe aortic valve obstruction can have a low-pressure gradient due to a low stroke volume.

Effective orifice area, an engineering calculation to estimate the orifice of a rounded-edge pipe obstruction, theoretically reflects the degree of obstruction, independent of stroke volume. When the EOA falls below about 0.8 cm^2/m^2, a pressure gradient develops across the valve and the ventricle begins the hypertrophic process. As the valve disease progresses, the hypertrophy intensifies. The hypertrophy reduces ventricular compliance, leading to mild diastolic heart failure. Most patients report mild reduced exercise capacity during this phase. As the EOA falls below 1.0 cm^2, symptoms of chest pain, syncope, and congestive heart failure develop. When the EOA falls below 0.5 cm^2, the risk of sudden death increases and survival is markedly reduced.

The calculation of EOA requires measurement of the mean systolic pressure gradient and the stroke volume. These can be easily measured invasively in the cardiac catheterization laboratory, but precise measurements are increasingly less reliable in low cardiac output states. Similarly, echocardiographic estimates of cardiac output from the continuity equation and valve pressure gradient by Doppler methods are less reliable in conditions of low cardiac output and ventricular dilation. This leads to diagnostic uncertainty in patients with a relatively low transvalvular gradient but typical symptoms of aortic stenosis, particularly if there are other causes for heart failure (such as prior myocardial infarction).

Another parameter to assess the degree of aortic valve obstruction is the concept of valve impedance (Z) [4]. As in an electrical circuit, valve resistance is completely independent of blood flow. The concept is appealing because it characterizes the "load" on the ventricle during contraction. Unfortunately, this parameter is not often used in clinical practice or research reports.

Efforts to refine the contribution of aortic stenosis to the myopathic process have centered on assessments of valve gradient and EOA with inotropic stimulation. The most common test is a dobutamine infusion stress echo, where a low dose of dobutamine is infused intravenously as the valve gradient and cardiac output are measured [5]. Patients with viable myocardium and severe aortic stenosis have an increased stroke volume and valve gradient and a reduction in measured EOA. Those with a primarily myopathic process have no change in cardiac output or a rise in output but no change in EOA (Fig. 9.2).

Medical Therapy of Aortic Stenosis

In general, medical therapy is used to palliate the symptoms of aortic stenosis but it has no effect on disease progression. Although counterintuitive and previously thought to be harmful, many patients both tolerate and improve with the use of nitrates and vasodilators. Many older patients with severe aortic stenosis have both a high transaortic valve pressure gradient and a high systolic blood pressure beyond the stenotic valve (due to reduced vascular compliance). The ventricle "feels" the total resistance to blood flow ejection, both valvular and postvalvular.

Reduction of systolic blood pressure can improve symptoms. The caveat is that some patients with severe aortic stenosis and limited cardiac output reserve can develop syncope if exposed to excessive vasodilation, particularly if they are volume depleted (such as upon awakening or from excessive diuretic therapy). Careful and judicious dosing of vasodilators is important.

In patients with severe aortic stenosis, reduced left ventricle systolic function, and severe congestive heart failure, cautious use of nitroprusside (in an intensive care unit setting) can increase cardiac output and alleviate congestion. In these patients, reduced systemic vascular resistance is compensated for by a rise in cardiac output.

Atrial fibrillation is a common "tipping point" for patients with severe aortic stenosis. Patients with new onset of congestive heart failure due to aortic stenosis can often see improvement from cardioversion. Atrial fibrillation tends to recur, however, and cardioversion should be seen as a temporary solution before valve surgery.

Surgical Aortic Valve Replacement

The definitive treatment for severe aortic valve stenosis is valve replacement. Prosthetic heart valves increase the EOA from less than 1.0 cm^2 to about 1.5–2.5 cm^2, depending on the valve type and size. Aortic valve replacement (AVR) usually leads to a remarkable improvement in symptoms and regression of much of the acquired ventricular adaptations. Hypertrophy regresses, ejection fraction improves, and functional mitral regurgitation lessens [6–8]. For patients with aortic stenosis, maximal regression of hypertrophy and improvement in left ventricle function take an average of 2 years. The ventricular fibrosis that occurs over time in patients with severe aortic stenosis and heart failure is associated with persistent left ventricle dysfunction after AVR [9]. Patients with more severe preoperative left ventricle systolic dysfunction or an aortic valve gradient <40 mm Hg (often indicating low stroke volume and more advanced disease) have a less complete recovery of left ventricle dimensions and symptoms [10]. Although markedly improved, mortality is still more than that of age-matched controls.

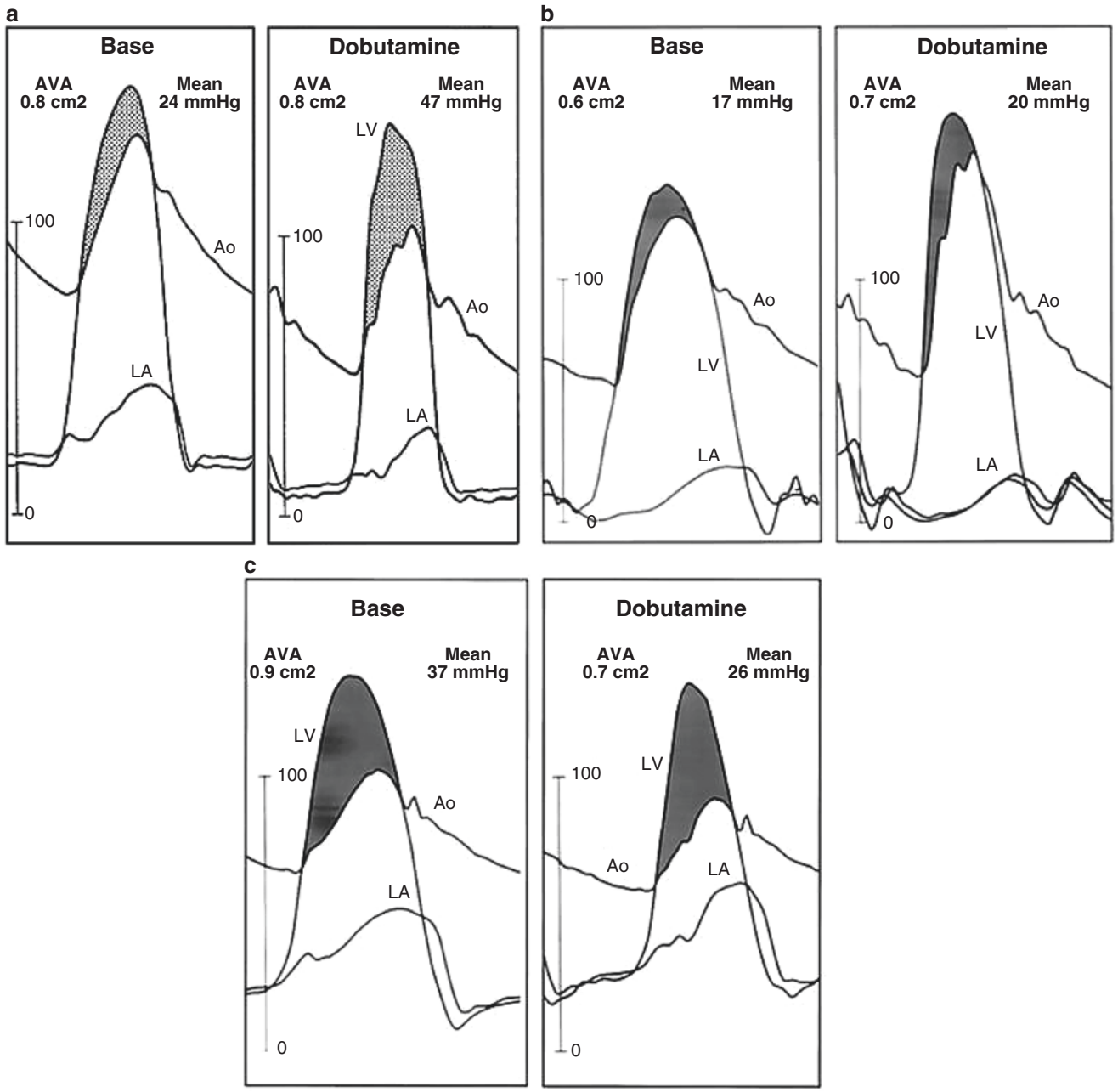


Fig. 9.2 Dobutamine infusion stress test to assess myocardial viability and the relative degree of aortic stenosis and ventricular failure in patients with "low-gradient" aortic stenosis. Panel **a**: Normal response to dobutamine (increase in cardiac output and aortic valve gradient). Panel **b**: Low-gradient mild aortic stenosis with small increase in valve gradient during dobutamine infusion. Panel **c**: No change in valve gradient, a reduction in cardiac output, and hypotension during dobutamine infusion in a patient with very severe aortic stenosis. This is an example of low cardiac output, low valve gradient, and severe, advanced, aortic valve stenosis. *Source*: Nishimura et al. Circulation. 2002;106(7):809–13

Of importance, the use of a small prosthetic valve (e.g., 21 mm or less), such that the postoperative valve area is less than 0.85 cm^2/m^2, often fails to eliminate the heart failure symptoms of aortic stenosis because the patient is still left with moderate to severe stenosis. This "patient-prosthesis mismatch" is associated with higher rates of death. In some smaller patients with severe calcification of the aortic valve base, aortic root transsection and revision may be needed to place an adequately sized valve and avoid late heart failure symptoms.

Transcatheter Aortic Valve Replacement

The recent development of transcatheter aortic valves has provided an opportunity to improve aortic valve orifice size using a biologic tissue valve mounted on a stent rather than a bulky sewing ring (which reduces orifice size). Initial results in higher-risk older patients (most with degenerative stenosis) suggest that these newer valves have favorable flow characteristics (average EOA 1.7 cm^2) and a more laminar flow to the ascending aorta. Early clinical studies show faster

regression of hypertrophy and return of systolic function in patients treated with a transcatheter compared to a surgical prosthesis.

Aortic Valve Regurgitation

Because the aortic valve is suspended from the sinus of Valsalva, aortic regurgitation can be caused by structural abnormalities of the aorta and sinus of Valsalva. The most common causes of acute aortic regurgitation are infective endocarditis, a type A dissection of the aorta, and a ruptured aortic valve with cusp prolapse (usually related to preexisting valve malformation such as a bicuspid or fenestrated valve, or blunt trauma) [11, 12]. Chronic aortic valve, regurgitation results from conditions leading to dilation of the aorta or fibrosis and retraction of the valve cusps. Conditions such as Marfan syndrome, ankylosing spondylitis, prolonged hypertension, and aortitis (e.g., syphilis, giant cell arteritis, Takayasu arteritis) lead to chronic, progressive dilation of the aortic "annulus," lack of cusp coaptation, and, occasionally, diastolic prolapse of an aortic cusp. Valvulitis from radiation, rheumatic fever, autoimmune conditions, and certain drugs (e.g., fenfluramine/phentermine) cause valve fibrosis and, eventually, loss of mechanical valve structure and coaptation.

Aortic regurgitation (also referred to as insufficiency) results in a backflow of blood into the left ventricle during diastole. That causes a rapid increase in diastolic left ventricle pressure. When severe, premature closure of the mitral valve can occur (functional mitral stenosis) or even diastolic mitral regurgitation (i.e., reverse flow through the mitral valve in diastole).

Acute aortic regurgitation is poorly tolerated. Left ventricular diastolic, left atrial, pulmonary venous, and, eventually, pulmonary artery and right ventricular systolic pressures rise quickly. Patients develop rapid onset of heart failure, leading to pulmonary edema. The thin right ventricle (RV) is unprepared for the elevated pulmonary resistance, eventually leading to dilation and failure of the RV, and low cardiac output.

Aortic regurgitation that progresses more slowly leads to adaptive changes in the left ventricle and aorta (Fig. 9.3). The regurgitant volume load that is shuttled between the aorta and ventricle with each cardiac cycle leads to dilation of both structures. The ventricle dilates and develops eccentric hypertrophy. With eccentric hypertrophy, cardiomyocytes lengthen much more than they increase in diameter.

Dilation of the ventricle greatly reduces myocardial efficiency. The wall stress that must be generated to produce a given intraventricular pressure rises directly with the radius of the ventricular cavity (the law of Laplace). In addition, the shape of the ventricle changes from a prolated ellipse to an almost spherical shape, which also reduces the mechanical advantage of contraction.

As the ventricle dilates, ventricular wall thickness remains relatively constant (usually less than 1.1 cm), but the left ventricle mass increases dramatically. Patients with advanced aortic regurgitation typically have the largest left ventricle mass of any cardiac condition, much larger than that induced by aortic stenosis where wall thickness increases but the left ventricle is much less dilated. As time progresses, a proliferation of fibrous connective tissue develops between the myocytes, causing the ventricular mass to become more fibrotic [13] (Fig. 9.4).

To accommodate the regurgitant volume, the aorta also dilates markedly in patients with aortic regurgitation. Intrinsic aortic disease can augment the degree of dilation for a given regurgitant volume load, as can the presence of concomitant valvular stenosis, where the high-velocity jet ejected across the valve during systole creates high shear stresses on the aortic wall, causing aortic growth.

Assessment of Aortic Regurgitation

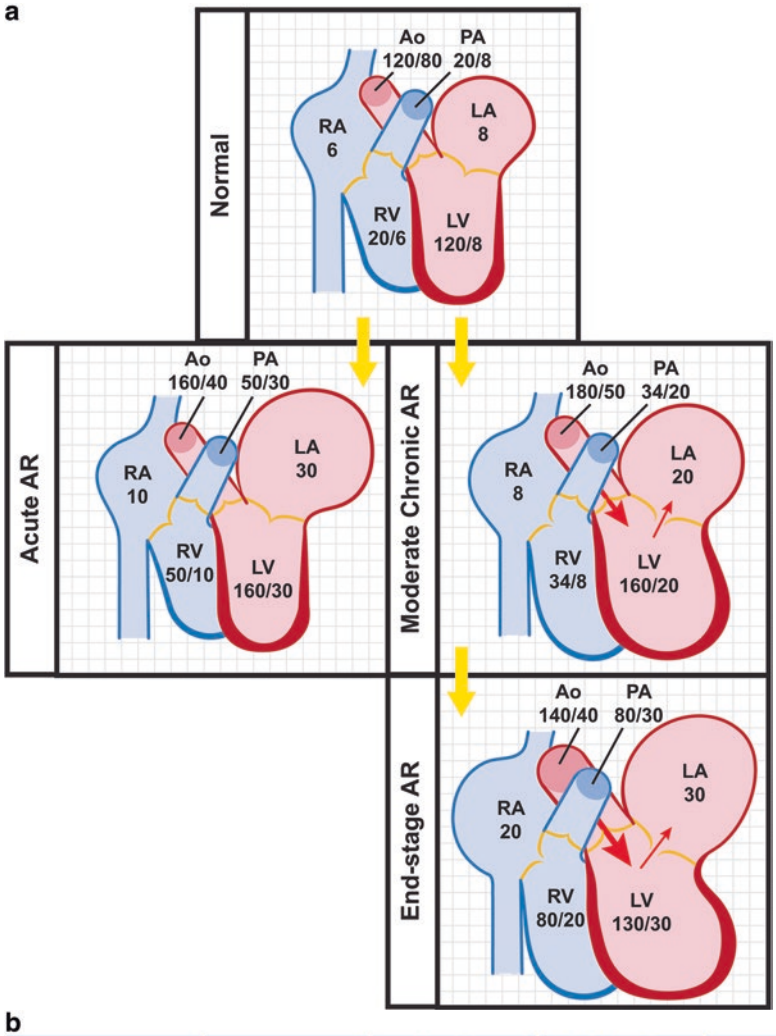
Evaluation of aortic regurgitation involves measurement of the amount of the blood regurgitating through the valve and the impact on the left ventricle and other cardiac structures. The initial method for assessing regurgitation was physical examination. A decrescendo diastolic murmur can be heard best at the left sternal border and over the precordium. The magnitude of regurgitation parallels the intensity and duration of the murmur, although in very severe, acute aortic regurgitation, the murmur may stop in mid-diastole due to equilibration of aortic and left ventricle pressure. In chronic aortic regurgitation, the left ventricle is markedly dilated, and the ventricular contraction palpated on the left chest wall is laterally displaced and very broad. In most patients with heart failure, a third heart sound is prominent and a mid-diastolic rumble of partial mitral inflow restriction is heard. The pulse pressure is usually quite wide due to the ejection of a large stroke volume into the aorta (high systolic pressure) and subsequent backflow into the left ventricle (low diastolic pressure).

The second method for assessing aortic regurgitation is injection of X-ray contrast media into the ascending aorta (an aortogram). Regurgitation is classified as 1+ to 4+ using the system described by Amplatz [14].

The extent of aortic regurgitation is most commonly assessed with Doppler echocardiography. While the extent and location of regurgitation can be visualized on color Doppler examination, certain parameters are useful in quantitating the magnitude of regurgitation (Table 9.1). Echocardiography enables quantifying the degree of regurgitation and visualizing the impact of aortic regurgitation on cardiac size and function, as well as pulmonary artery pressure.

The degree and chronicity of regurgitation can be inferred from the structural changes to the heart. Acute regurgitation results in little change to ventricular volumes, but marked changes in function. These include premature closure of the mitral valve (and a corresponding Austin Flint diastolic murmur) and elevated pulmonary artery pressure. Chronic aortic regurgitation leads to the dilation and loss of systolic contraction described above. Acute or rapidly worsening aortic regurgitation and structural changes should prompt early surgical correction.

a



b

	Normal	Acute AR	Moderate Chronic AR	End-stage AR
Cardiac output	Normal	Normal	Normal	Reduced - very reduced
LV ejection fraction (%)	55-65	Normal	35-70	35-55
LV size	Normal	↑	↑↑-↑↑↑	↑↑↑↑
Aortic size	Normal	Normal	↑↑	↑↑↑-↑↑↑↑
Pulmonary artery pressure	Normal	Elevated	Normal to mild elevation	Elevated - very elevated
Right heart failure	-	- to ++	- to +	+ - ++
LV fibrosis	-	-	++	+++

Fig. 9.3 Panel **a**: Morphological changes in the left ventricle in response to aortic valve regurgitation. The chronic volume overload induces eccentric hypertrophy, a change in ventricular shape from elliptical to spheroid. Panel **b**: Typical changes associated with progressive aortic valve regurgitation. Untreated, the muscle begins to fibrose, leading to permanent ventricular dysfunction

Medical Therapy of Aortic Regurgitation

Reduction of aortic pressure and afterload lessens the amount of regurgitation. Afterload reduction with nitroprusside can lead to a marked and rapid temporary improvement in acute aortic regurgitation, but is not practical for chronic treatment.

Angiotensin-converting enzyme (ACE) inhibitors, hydralazine, and other agents that reduce systemic vascular

resistance can provide symptomatic relief in some patients with chronic aortic regurgitation [15]. Treatment with ACE inhibitors does not reduce the progression of ventricular dilation in patients with mild to moderate aortic regurgitation. Overall, medical therapy with afterload reduction for chronic aortic regurgitation has proven disappointing [16, 17]. For symptomatic patients, vasodilator therapy is generally relegated to a stabilizing role prior to valve replacement.

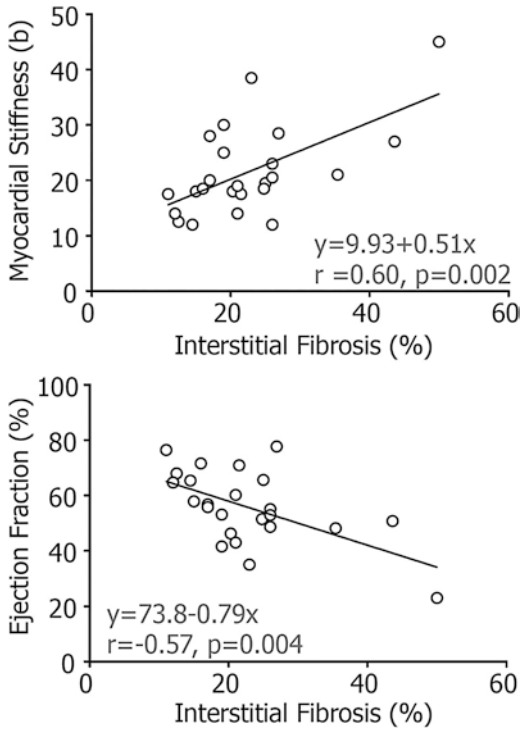


Fig. 9.4 The relationship between ventricular fibrosis and recovery of ventricular function in patients with severe aortic valve regurgitation after valve replacement. *Source*: Villari et al. Circulation. 2009;120(23): 2386–92. Residual myocardial stiffness (*upper panel*) increases and ejection fraction falls with the fibrotic content of the ventricle

Beta-receptor antagonists can be used to prevent the decline in systolic ventricular function that occurs later in the disease and may improve survival [18].

Surgical Treatment

The primary surgical therapy is replacement of the aortic valve with a prosthetic valve. For most patients with aortic regurgitation, the aorta is also dilated, and surgery may involve replacing the dilated aortic root using a composite graft and reimplanting the coronary arteries. Some patients may benefit from a reconstruction of the valve and root [19], which has the potential advantage of a more durable result [20].

After valve replacement, the left ventricle slowly falls in size and transforms back toward a prolated ellipse [21]. Systolic contraction improves, but usually does not return to normal. Cardiomyocyte hypertrophy nearly normalizes but the fibrosis that characterizes advanced regurgitation does not recede. The result is persistent reduction of ventricular compliance due to reduced ventricular elasticity. The improvement in systolic function after valve replacement is inversely proportional to the degree of fibrosis at the time of valve replacement.

The lack of full ventricular recovery after aortic valve replacement for regurgitation has led many experts to recommend early valve replacement to avoid irreversible changes to ventricular structure. In most patients, valve replacement is indicated when the ventricle dilates significantly, or the ejection fraction falls. An end-systolic dimension >50 mm and a left ventricular ejection fraction <50 % are commonly accepted triggers for valve surgery. In patients without symptoms and/or with preserved left ventricular systolic pressure, marked dilation (end-diastolic dimension >65 mm) may also trigger surgical intervention.

Transcatheter valve replacement can be accomplished in some patients with pure aortic regurgitation and might be appropriate for a fraction of patients. One valve is approved for deployment in regurgitant aortic valves (JenaValve). This

Table 9.1 Parameters of chronic aortic regurgitation

	Mild AR	Moderate AR	Severe AR	Advanced AR
LV ejection fraction	Normal	Normal-↓	↓-↓↓	↓↓-↓↓↓
LV size	Normal-↑	↑-↑↑	↑↑↑-↑↑↑↑	↑↑↑↑
LA size	Normal	↑-↑↑	↑↑-↑↑↑	↑↑-↑↑↑
Cardiac output	Normal	Normal	Normal to ↓	↓-↓↓
PA pressure	Normal	Normal-↑	↑-↑↑	↑↑
Angiographic grade	1+	2–3+	3–4+	3–4+
Regurgitant volume (mL)	<20	20–60	>60	>60
Regurgitant fraction (%)	<15	15–50	>50	>50
Effective regurgitant orifice (cm^2)	<0.2	<0.4	>0.4	>0.4

LV left ventricle, *LA* left atrium, *PA* pulmonary artery, *AR* aortic valve regurgitation

valve uses retention clips that prevent migration of the valve to the ventricle. The inability to treat the associated aortic dilation, the large size of the prosthetic valves required, and the inability to debride infected valves limits it applicability to present transcatheter approaches.

The Mitral Valve

The two mitral valve leaflets are normally supported by the mitral annulus at their bases and by chordae tendineae along the leaflet coaptation edges [22, 23]. The chordae are attached to one of two papillary muscles. The papillary muscles arise from the anterolateral and posterolateral ventricular myocardium, about two-thirds of the way down from the ventricular base to its apex.

During ventricular contraction, the rising pressure in the ventricle pushes the mitral leaflets toward the low-pressure atrium like a parachute. The mitral annulus contracts somewhat. The chordae tighten as the leaflet edges move toward the atrium and the attached papillary muscles and their underlying myocardium contract. This interaction limits mitral travel beyond the leaflet coaptation point (i.e., prevents valve prolapse) and improves ventricular contraction by giving the ventricle a tether to pull on to shorten. Hence, not only do the chordae tether the mitral leaflets, they also tether the ventricle and improve ventricular function. This interaction between the annulus, chordae, and ventricle improves mitral valve closure and left ventricular systolic performance. Preservation of the chordae apparatus during surgical replacement of the mitral valve results in better long-term ventricular function after surgery.

The normal mitral valve has a significant amount of redundant tissue—about twice that of the mitral cross-sectional area. In addition, the fibrous annulus supporting the base provides considerable structural support, as opposed to the aortic valve, which has no true annulus. This is needed because the mitral orifice is roughly two times that of the aortic cross-sectional area. In cattle, where the mitral annulus is even larger, mature cows actually ossify a portion of the annulus to bone, presumably to provide adequate support to the large valve circumference.

Functional Mitral Regurgitation

Functional mitral regurgitation refers to abnormal mitral valve function, predominantly regurgitation, due to changes in the structures surrounding and supporting the mitral valve [24]. Many cardiomyopathies caused by intrinsic cardiomyocyte disease (such as viral, inflammatory, or some genetic cardiomyopathies) and the more prevalent ischemic cardiomyopathies eventually lead to ventricular dilation and fibrosis.

As the left ventricle dilates, the papillary muscles attached to the dilating ventricle move out and away from the mitral leaflets (Fig. 9.5). During systole, the chordae tether the leaflets open and restrict complete closure. In addition, ventricular dilation usually changes the shape of the ventricle from a prolate ellipse to a more spherical chamber. This changes both the attachment angle of the chordae and the shape of the mitral annulus. The more oblique tethering angle of the chordae increases stress and pulls against coaptation. The dilation of the mitral annulus, moving from a "D" shape to a more circular one, withdraws the leaflets away from the coaptation point, further limiting coaptation and complete systolic closure. This global dilation typically results in a central regurgitant jet.

Symmetrical mitral annular dilation by itself can be well tolerated with little mitral regurgitation in the absence of regional wall motion abnormalities or papillary muscle/chordae lengthening [25]. Asymmetrical annular dilation, however, can increase functional mitral regurgitation due to diminished annular systolic contraction [26]. In cardiomyopathies where there are regional differences of dysfunction and dilation, specific loss of coaptation can occur, even in the absence of marked global ventricular dilation. For example, an apically and posteriorly displaced posterior papillary muscle will typically tent open the posteromedial portion of the posterior mitral leaflet, leading to focal regurgitation [27]. Anterior myocardial infarction preferentially leads to dilation of the septal length of the annulus, leading to reduced coaptation [28].

Adaptations to Ventricular Dilation

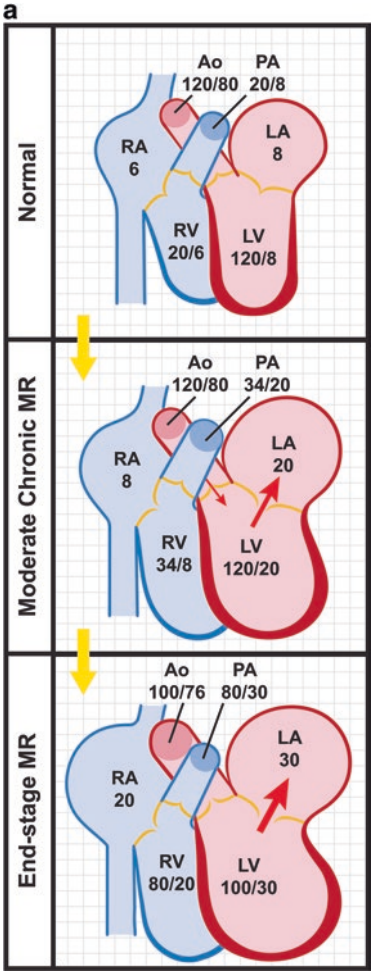
In a subset of patients, ventricular dilation is accompanied by lengthening of the mitral chordae and enlargement of the mitral leaflets [29, 30]. This may explain some of the heterogeneity among patients in response to ventricular dilation. Of note, however, leaflet growth and redundancy can be associated with leaflet fibrosis due to greater stress on and excessive fluttering of the leaflets. It is not uncommon to see thickening of the mitral leaflets associated with dilated cardiomyopathy [31].

Primary Mitral Regurgitation

Mitral regurgitation resulting from structural abnormalities in the valve itself is less common than functional mitral regurgitation. Like functional mitral regurgitation, these valvular diseases can lead to marked mitral regurgitation, causing a volume overload of the ventricle, longitudinal eccentric hypertrophy, marked atrial dilation, and congestive heart failure. Unlike functional mitral regurgitation due to ischemic cardiomyopathy, however, the ventricle does not develop regional contraction abnormalities, and systolic function declines later in the course of the disease because the underlying muscle is normal.

The most common causes of acute mitral regurgitation are abnormalities in chordal rupture (often associated with a myxomatous valve disease or a congenital abnormality in

a



b

	Normal	Moderate MR	Severe MR
Cardiac output	Normal	Normal	Reduced-Very reduced
LV ejection fraction (%)	55-65	35-70	<30
LV size	Normal	↑↑ - ↑↑↑↑	↑↑↑↑
Left atrial size	Normal	↑↑	↑↑↑ - ↑↑↑↑
Pulmonary artery pressure	Normal	Mild-moderate elevation	Elevated-Very elevated
Right heart failure	-	- to +	+ - +++

Fig. 9.5 Panel **a**: Morphological changes induced by chronic mitral regurgitation. The volume load shuttling between the vertical and atrium leads to eccentric ventricular dilation, a spherical change in ventricular shape, atrial dilation, pulmonary hypertension, right ventricular failure and dilation, and tricuspid regurgitation. Panel **b**: Typical changes associated with progressive mitral regurgitation

connective tissue), endocarditis, papillary muscle rupture due to infarction, acute valvulitis (e.g., rheumatic fever), and acute, fulminant cardiomyopathy with secondary functional mitral regurgitation.

In developed countries, prolapse of a myxomatous mitral leaflet is the dominant cause of primary mitral regurgitation. Other tissue abnormalities such as those seen in Marfan syndrome and Ehlers-Danlos syndrome cause hyperelasticity of the valve and chordal structures. These changes in elasticity cause increased stress on the valve and eventual tensile failure.

Globally, rheumatic fever is the most common source of mitral regurgitation. The acute valvulitis results in a fibrotic valve and chordal apparatus that retracts and shortens, leading slowly to regurgitation from incomplete coaptation of the leaflets. Radiation treatment can cause a valvulitis that eventually results in valve deformation and insufficient coaptation. Similarly, the aftermath of infective endocarditis also can leave the patient with tears in the valve leaflet, fibrosis, and retraction of the leaflet, discontinuity or fibrosis of the chordal structures, and weakness or discontinuity of the annular support structure.

Course and Symptoms

Primary mitral regurgitation from chordal rupture can present with acute fulminant heart failure. As with acute aortic valve regurgitation, the normal-sized ventricle is overwhelmed by the volume load, leading to markedly elevated diastolic ventricular left atrial and pulmonary venous pressures. This usually causes pulmonary edema with acute respiratory insufficiency. In severe cases, pulmonary artery pressure elevates and the right ventricle can exhibit acute failure.

Chronic mitral regurgitation presents as a gradual loss of exercise tolerance and dyspnea on exertion. The left atrium and ventricle undergo dilation as the regurgitant volume is shuttled between the ventricle and atrium with every contraction. The time frame and degree of dilation are related to the amount of regurgitation. Regurgitation is often quantified by echocardiographic and Doppler imaging. An "effective

Table 9.2 Parameters of chronic primary mitral regurgitation

	Mild MR	Moderate MR	Severe MR	Advanced
LV ejection fraction	Normal	↑	Normal-↓↓[a]	↓↓↓
LV size	Normal	↑-↑↑	↑↑-↑↑↑	↑↑↑
LA size	Normal	↑-↑↑	↑↑↑	↑↑↑
Cardiac output	Normal	Normal	Normal to ↓	↓-↓↓
PA pressure	Normal	Normal	↑	↑↑
Angiographic grade	1+	2–3+	3–4+	3–4+
Regurgitant volume (mL)	<20	20–60	>60	>60
Regurgitant fraction (%)	<15	15–50	>50	>50
Effective regurgitant orifice (cm^2)	<0.2	<0.4	>0.4	>0.4
Central MR jet: LA area (%)	<20	20–40	>40	>40

LV left ventricle, *LA* left atrium, *PA* pulmonary artery, *MR* mitral regurgitation
[a]Dependent on the duration of MR. LV function is reduced with time
Adapted from Nishimura et al. J Am Coll Cardiol. 2014;63:43–129

Table 9.3 Parameters of chronic functional mitral regurgitation

	Mild MR	Moderate MR	Severe MR	Advanced
LV ejection fraction	↓-↓↓	↓-↓↓↓	↓↓-↓↓↓	↓↓-↓↓↓
LV size	Normal	↑-↑↑	↑↑-↑↑↑	↑↑↑-↑↑↑↑
LA size	Normal	↑-↑↑	↑↑↑	↑↑↑-↑↑↑↑
Cardiac output	Normal	Normal	Normal to ↓	↓-↓↓↓
PA pressure	Normal	Normal-↑	↑-↑↑	↑↑-↑↑↑
Angiographic grade	1+	2–3+	3–4+	3–4+
Regurgitant volume (mL)	<20	20–30	>30	>40
Regurgitant fraction (%)	<15	15–50	>50	>50
Effective regurgitant orifice (cm^2)	<0.1	0.1–0.2	>0.2	>0.2

LV left ventricle, *LA* left atrium, *PA* pulmonary artery, *MR* mitral regurgitation
Adapted from Nishimura et al. J Am Coll Cardiol. 2014;63:43–129

regurgitant orifice" (ERO) and regurgitant volume are often used to characterize the degree of regurgitant flow. Of importance, these parameters are dependent on the blood pressure and heart rate at the time they are measured. Tables 9.2 and 9.3 show these parameters in various degrees of regurgitation.

Ventricular contraction often appears "supernormal" early in the disease because the left atrium acts as a low-pressure "pop-off" valve, lowering the ventricular afterload. In patients with severe mitral regurgitation, the ventricular ejection fraction rises by about 10 % (absolute) for a given level of systolic ventricular performance, causing overestimation of the ejection fraction after the valve is repaired. Over time, and similar to patients with aortic valve regurgitation, the ventricle hypertrophies and eventually fibroses, leading to irreversible reductions in diastolic compliance and, eventually, systolic contraction.

Medical Therapy

Medical therapy with vasodilators, nitrates, and diuretics can improve (for a time) left ventricular volume and result in a lower regurgitant orifice area. As in patients with aortic regurgitation, the acute effects of afterload reduction with nitroprusside are often impressive. Treatment can reduce the amount of regurgitation by lowering the blood pressure and also by reducing left ventricular size through its venodilating actions, which essentially sequester a portion of the blood

volume into the venous system. A reduction in ventricular size can lead to better coaptation of the mitral leaflets.

Chronic vasodilator therapy using ACE inhibitors has been less effective. In the absence of marked hypertension, symptomatic improvement is modest and there is no improvement in surgery-free survival. A combination of nitrates (to venodilate) and hydralazine (to afterload reduce) can also be used and may have more effects. Hydralazine inhibits nitrate tolerance.

More important can be the management of intravascular volume. Lower intravascular volume reduces the size of the left ventricle, promoting valve closure. Diuretics and avoidance of a diet high in sodium salt intake can improve symptoms.

Beta-adrenergic receptor blockers can have significant effects on functional mitral regurgitation. In addition to improving contractility, they reduce hypertrophy and improve left ventricle remodeling [32]. This reduces chordal tethering and can reduce mitral annular circumference. Beta-receptor antagonists appear to improve survival [33]. Atrial fibrillation is a common cause of a sudden deterioration of patients with mitral regurgitation (or almost any of the valvular cardiomyopathies). Restoration of sinus rhythm can significantly improve congestive symptoms, but sinus rhythm is often difficult to maintain due to the marked left atrial dilation that accompanies mitral regurgitation.

Cardiac Rhythm Therapy (CRT)

Reduction of ventricular size and dyssynchrony are primary goals of treatment, short of mitral valve repair or replacement. In about half of patients, CRT can improve functional mitral regurgitation through a reduction in ventricular dyssynchrony and in left ventricle volumes, as well as improved left ventricle contraction [34]. The effect is often seen as early as 1 week after CRT implantation [27]. The site of lead implantation can be important. Implantation at or near a left ventricle scar renders the therapy less effective or ineffective [35, 36].

Surgical Treatment

Functional Mitral Regurgitation

Surgical therapy for functional mitral regurgitation is complicated by the reduced ventricular function of patients with functional mitral regurgitation and the ongoing, progressive nature of the ventricular disease that led to the functional mitral regurgitation. The three methods of surgical repair are placement of a restrictive ring to reduce annular dilation, repair of the valve to improve coaptation, and replacement of the valve entirely with a rigid prosthetic valve. Many of the studies of surgical valve therapy are limited by the addition of concomitant treatments, such as coronary artery bypass, a maze procedure for atrial fibrillation, or tricuspid valve repair.

The most common method is placement of a rigid annuloplasty ring (usually in patients with ischemic cardiomyopathy at the time of bypass surgery), usually aiming for a mitral coaptation length of about 8 mm. The durability of mitral repair with a ring alone ranges from 85 to 50 % in different studies, likely in part related to patient selection and the rate of progression of ventricular dysfunction after surgery (influenced, e.g., by the completeness of revascularization) [37, 38]. In one randomized trial of patients with ischemic cardiomyopathy and moderate mitral regurgitation, 60 % of patients with bypass surgery alone had moderate or severe mitral regurgitation at 5-year follow-up compared to none of the group that also received a ring [39]. Moreover, the annuloplasty group had better functional capacity and lower pulmonary artery pressure—26 mmHg compared to 38 mmHg in the bypass surgery alone group.

Repair of the mitral valve itself for functional mitral regurgitation is accomplished by leaflet extension techniques (edge-to-edge repair, pericardial extension) and chordal modification where needed. An annuloplasty ring is almost always placed at the same time.

In patients with secondary mitral regurgitation, repair can increase operative mortality and recurrence of mitral regurgitation can be common. Most studies show no mortality benefit. It is worthwhile noting, however, that functional mitral regurgitation represents a constellation of interacting functional and anatomical mechanisms, along with many comorbid conditions. Individual patients might derive significant benefit if the surgery addresses the underlying causes of the functional mitral regurgitation. For example, in the Randomized Ischemic Mitral Evaluation (RIME) Trial of patients with severe functional mitral regurgitation due to an ischemic cardiomyopathy, patients randomized to bypass surgery plus repair had a 4 % incidence of recurrent mitral regurgitation that was moderate or severe (compared to 50 % in the bypass surgery only group), smaller ventricular dimensions, and improved functional scores [40].

Primary Mitral Regurgitation

Patients with severe primary mitral regurgitation should undergo surgical repair of the valve, regardless of symptoms [41]. Asymptomatic patients and patients with symptoms and moderate mitral regurgitation should undergo repair when the ventricle dilates significantly (left ventricular end-systolic dimension >40 mm) or when the systolic contraction falls (ejection fraction <60 %). In general, repair is always preferred to replacement because the functional outcome and durability are superior.

A number of repair techniques have been described, including leaflet resection or plication, chordal replacement or repair, and placement of an annuloplasty ring.

Failure to repair or replace the mitral valve in patients with severe mitral regurgitation leads to a reduction of systolic function and irreversible fibrosis of the ventricle. When the left ventricular ejection fraction falls below 30 %, operative risk increases dramatically because the dysfunctional ventricle may not be able to handle the increased afterload imposed by a competent mitral valve (where the low-pressure "pop-off" into the left atrium is sealed and the ventricle contracts against aortic pressure).

Percutaneous Repair of Mitral Regurgitation

Percutaneous mitral valve repair using the MitraClip device has been used recently to attach the mitral leaflets together with a clip and thereby improve coaptation. The procedure is derived from the open surgical "Alfieri stitch" developed decades ago and now is adapted to a transcatheter approach that uses a clip rather than a suture to connect the leaflets [42]. The procedure has been successful in markedly reducing mitral regurgitation [43]. Mitral regurgitation was reduced to Grade 1–2 in 8 % of patients, ventricular volumes fell, and at 12-month follow-up, 82 % of patients were functioning at New York Heart Association (NYHA) Functional Classification of Class 1 or 2 [44]. Left ventricular ejection fraction was unchanged. Initial studies indicate that the clip is effective in both primary and secondary mitral regurgitation. Patients with renal dysfunction may have poorer outcomes [45].

Tricuspid Valve

The structure of the tricuspid valve is similar to the mitral valve except that the tricuspid valve has three unequally sized leaflets and the chordal structure is somewhat different. Each of the three papillary muscles attaches to one leaflet, whereas each papillary muscle of the mitral valve attaches to chordae connected to both leaflets. The tricuspid papillary muscles are attached to the anterior free wall of the RV, the septum, and the diaphragmatic inferior wall. Distortion or akinesis of these zones can lead to tethering and lack of coaptation of individual leaflets. Like the mitral valve, tricuspid annular dilation can also cause loss of coaptation and regurgitation. Finally, the tricuspid valve is a "low-pressure valve" adapted for the lower pressures of right ventricular contraction. A rise in RV pressure leads to regurgitation.

Functional Tricuspid Regurgitation (TR)

Functional tricuspid regurgitation is most commonly caused by left heart failure, especially when combined with mitral regurgitation [46, 47]. Almost half of patients with severe chronic mitral regurgitation have functional TR [48]. Functional TR accounts for almost 90 % of all significant TR seen on imaging studies. Functional tricuspid regurgitation is more common in patients with ischemic cardiomyopathy than in those with other causes of congestive heart failure.

Like functional mitral regurgitation, functional tricuspid regurgitation is characterized by annulus dilation and deformation, right ventricular enlargement, and papillary muscle displacement with leaflet tethering [49]. Although right atrial and annular dilation precedes right ventricular dilation, RV dilation and papillary muscle tethering are a requirement of moderate to severe functional TR.

Functional tricuspid regurgitation is associated with fewer symptoms than functional mitral regurgitation. The most common symptoms are peripheral edema and a nonspecific lack of energy, related in the most part to reduced cardiac output. Mild functional TR carries a benign prognosis, but moderate to severe functional TR is a predictor of mortality in patients with left ventricular dysfunction, even in the absence of significant symptoms [47, 50].

Treatment of Functional TR

Functional TR is difficult to treat. The best treatment is to improve the underlying left heart disease. The mainstay of medical therapy is diuresis, which can reduce edema but also can lead to a low cardiac output syndrome and renal failure. As with functional mitral regurgitation, surgical therapy centers on reducing the tricuspid annular size with a rigid annuloplasty ring, leaflet extension, and valve replacement. Early treatment with transcatheter valves is promising [51, 52].

Mixed Valve Disease

Many patients with valvular heart disease have dysfunction of more than one valve. Certain etiologies affect more than one valve. For example, myxomatous disease often affects both the mitral and tricuspid valves, and rheumatic fever can affect all of the valves. In addition, changes in ventricular size or shape can induce dysfunction in other valves. Aortic regurgitation commonly causes marked ventricular dilation that leads to mitral insufficiency. Left heart failure caused by left heart valve disease often leads to pulmonary congestion, pulmonary hypertension, and right ventricular dilation. The tricuspid valve is a "low-pressure" valve, and the elevated right ventricular systolic pressure that accompanies pulmonary hypertension causes tricuspid insufficiency. Additionally, one investigator found that cardiomyopathic hearts also have structural changes in the valvular extracellular matrix with disruption of the collagen and elastic fiber network [53]. Mixed valve disease reduces survival and complicates treatment.

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Molecular Mechanism of Sarcomeric Cardiomyopathies

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_10

Sarcomere Function

The sarcomere is the fundamental unit of force production in the cardiac myocyte [5]. It is made up of two major interdigitating filaments: the thin filament and the thick filament. The thin filament is made up of actin, tropomyosin (Tm), and the heterotrimeric troponin (Tn) complex including troponin I (TnI), troponin T (TnT), and troponin C (TnC). The thick filament is anchored by the giant protein titin (TTN), with myosin and myosin-binding protein C (MyBP-C) decorating its surface (Fig. 10.1).

Contractility begins with an action potential, activating the voltage-gated L-type Ca^{2+} channel to allow a small amount of Ca^{2+} through the sarcolemma and initiating Ca^{2+}-induced Ca^{2+} release from the sarcoplasmic reticulum through activation of the ryanodine receptor [6]. This floods the cytosol with Ca^{2+} where it can bind to the thin filament protein TnC. TnC binding of Ca^{2+} induces a slight opening of TnC's hydrophobic pocket, allowing TnI to bind to this region [7]. TnI binding to TnC pulls TnI's inhibitory region away from actin, enabling Tm to slide on actin, which reveals strong binding sites on actin for myosin [8]. Myosin then strongly binds actin and, in an ATP-dependent manner, produces force. Relaxation initiates through the release of Ca^{2+} from TnC and subsequent TnI disassociation from TnC and association with Tm/actin, which inhibits myosin strong binding to actin and contraction (Fig. 10.1). Through this process, multiple protein-protein interactions and movements dictate the overall Ca^{2+} affinity of TnC and force production, referred to as Ca^{2+} sensitivity [9, 10].

Ca^{2+} sensitivity of the sarcomere operates in a physiological range defined by normal alterations such as sarcomere length (SL) and posttranslational modifications. On a beat-to-beat basis, SL stretch increases Ca^{2+} sensitivity, described by the Frank-Starling mechanism, to increase pump function [11]. Phosphorylation of cTnI through a protein kinase A-dependent mechanism decreases Ca^{2+} sensitivity of the sarcomere [12]. Maintaining Ca^{2+} sensitivity within a physiologic range is critical to normal heart pump function, and alterations in Ca^{2+} sensitivity outside the normal operating zone can lead to disease. Myofilament Ca^{2+} sensitivity is significantly altered in multiple disease states. Myocardial infarction decreases Ca^{2+} sensitivity through an acidosis-based mechanism [13]. Recently, advanced heart failure has been associated with increased Ca^{2+} sensitivity, possibly due to decreased cTnI phosphorylation [14]. Mutations within sarcomeric proteins can result in either increased or decreased Ca^{2+} sensitivity. Either one can lead to disease [15].

Clinical Overview

Sarcomeric cardiomyopathies are defined by a causal mutation in a gene that encodes for a cardiac sarcomeric protein giving rise to a diseased heart [4]. Criteria for a causal mutation usually include: cosegregation with the disease phenotype in

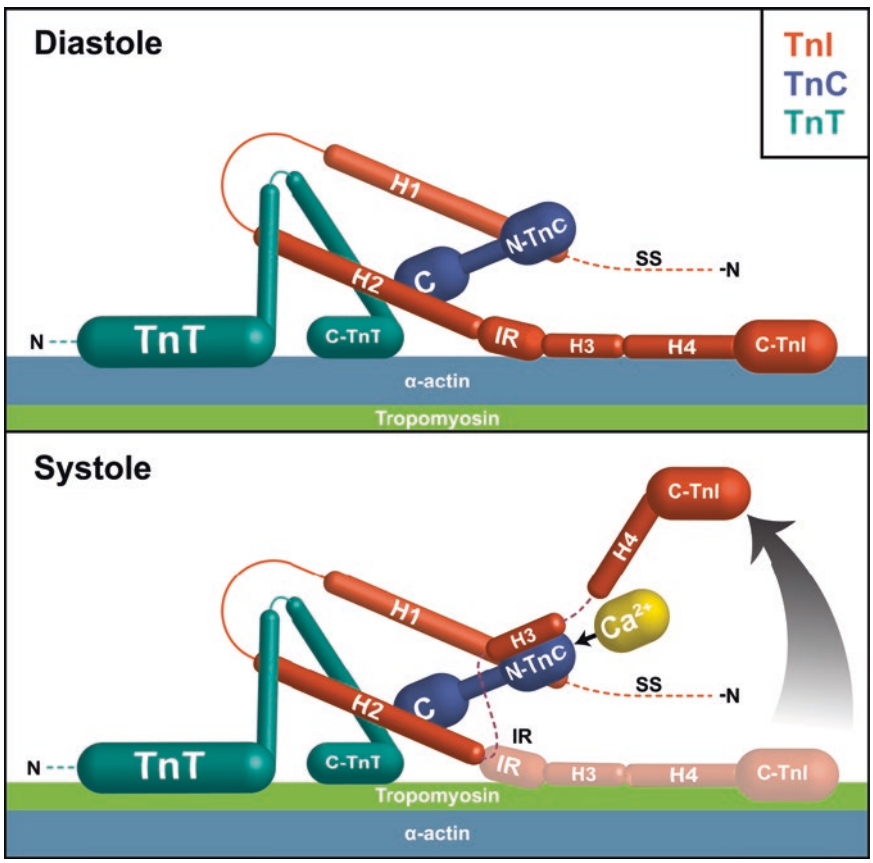

Fig. 10.1 Schematic representation of troponin function during diastole and systole. cTnI (*orange*), cTnC (*blue*), and cTnT (*cyan*) form the troponin complex. In diastole the cTnI inhibitory region (IR), helix 4, and the C-terminal domain (C-TnI) interact with actin to inhibit strong binding sites for myosin on actin. In systole as Ca^{2+} levels rise, cTnC N-terminal lobe (N-TnC) interacts with Ca^{2+} which in turn allows cTnI helix 3 (H3) to interact with cTnC. This transition causes cTnI IR and the C-TnI domains to move away from actin allowing tropomyosin to slide on actin revealing myosin strong binding sites

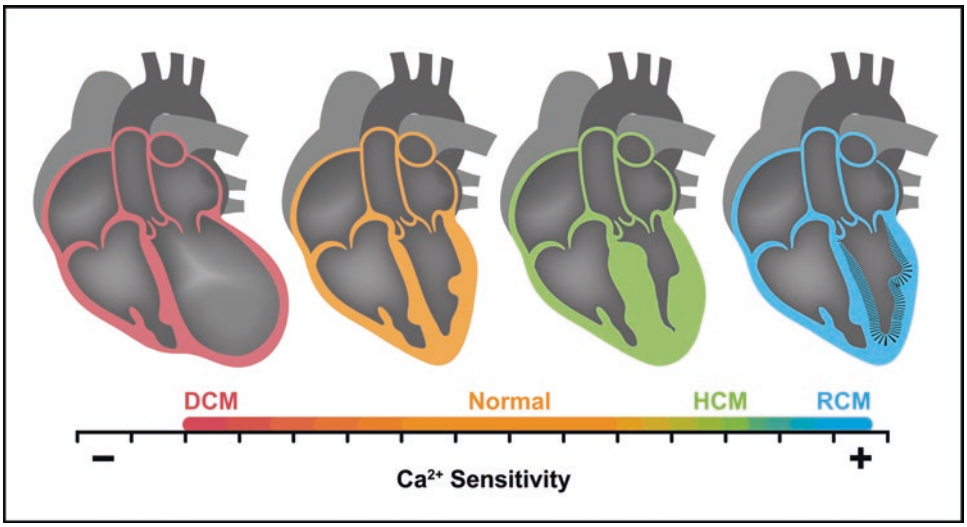

Fig. 10.2 Common morphological features of sarcomeric cardiomyopathies in relation to myofilament Ca^{2+} sensitivity. DCM (*pink*) hearts have thin left ventricular walls and a dilated left ventricular chamber. HCM hearts show increased thickness of the septal wall and left ventricular free wall. RCM hearts show no hypertrophy but have decreased left ventricular end-diastolic dimensions due to "stiff" walls. Ruler of Ca^{2+} sensitivity depicting the common molecular phenotype of DCM has decreased Ca^{2+} sensitivity, while HCM and RCM commonly have increased Ca^{2+} sensitivity

a familial manner, prior evidence of pathogenicity, not present in a control population, occurs as an evolutionary conserved residue in a critical portion of the protein and/or major protein structure/function phenotypes in basic science experiments [16]. Genetic mutations in sarcomeric genes have been identified as causative in three different clinically classified cardiomyopathies: (1) dilated cardiomyopathy (DCM), (2) hypertrophic cardiomyopathy (HCM), and (3) restrictive cardiomyopathy (RCM) (Fig. 10.2) [8, 17, 18].

DCM is clinically characterized by left ventricular dilation and poor systolic function with a high propensity for heart failure, death, or transplant. HCM, on the other hand, is clinically characterized by left ventricular hypertrophy, normal or enhanced systolic function, and impaired left ventricular relaxation. RCM is characterized by, restrictive left ventricle filling and major diastolic dysfunction leading to heart failure and potential transplant at a young age. All three have an autosomal-dominant inheritance pattern with ~50 % of offspring affected with variable penetrance and expressivity, leading to heterogeneous disease presentation and progression, even within the same family [16, 19–23].

Multiple explanations can account for the heterogeneous presentation including gene dosage, location of the mutation, age-related protein quality control, posttranslational modifications, modifier genes and other environmental factors [4]. Adding to the complexity of these diseases is that multiple mutations have been identified in some individuals, leading to increased severity of disease in some cases [24]. With the increase in genetic testing of family cohorts, more patients are identified with a causative sarcomeric mutation while not exhibiting the phenotypic morphological changes that clinically define these diseases. These patients are referred to as genotype positive-phenotype negative [4, 16, 25, 26]. Although they do not present with the normal diagnosis phenotype (i.e., morphological features), they present with subtle, altered systolic function (DCM) or impaired relaxation and abnormal ECGs (HCM) [3, 4, 26–28]. This implicates the intrinsic functional alteration on the sarcomere by the mutant protein as a determinant of whether a dilated or hypertrophic phenotype presents. As such, a deeper understanding of the mutation's structure/function relationship in the context of the sarcomere is needed to know how to treat these patients prior to presentation of the morphological disease phenotype.

Sarcomere Mutations

DCM

Sarcomere mutations make up an estimated 40 % of genetic DCM with other cytoskeletal, sarcolemmal, metabolic, and nuclear envelope proteins making up the rest [22, 29]. Dominant mutations in actin (ACTC1), myosin-binding protein C (MYBPC3), β-myosin heavy chain (MYH7), α-myosin heavy chain (MYH6), troponin I (TNNI3), troponin C (TNNC1), troponin T (TNNT2), α-tropomyosin (TPM1), and titin (TTN), all can lead to DCM (Fig. 10.3) [29]. Titin truncations make up ~25 % of genetic DCM while the remaining sarcomeric mutations are single missense mutations or small insertions/deletions [22, 29]. Titin functions as a molecular ruler, regulating sarcomere length, and it provides elasticity and passive force to the sarcomere [30, 31]. Little direct research has been conducted on the TTN truncating mutations which cause DCM, but they are hypothesized to alter sarcomere assembly, interactions, and signaling. As such, this chapter's analysis of molecular mechanisms of sarcomeric DCM will not include these truncations.

Many but not all sarcomeric mutations that cause DCM result in decreased Ca^{2+} sensitivity of the myofilament. Thin filament reconstitution assays showed that multiple DCM mutations decrease the Ca^{2+} affinity of cTnC with increased Ca^{2+} dissociation rates and decreased Ca^{2+} association rates [32, 33]. Assays using the entire myofilament showed multiple DCM mutations alter the Ca^{2+} sensitivity of force and ATPase activity [32, 34, 35]. Although these assays do not

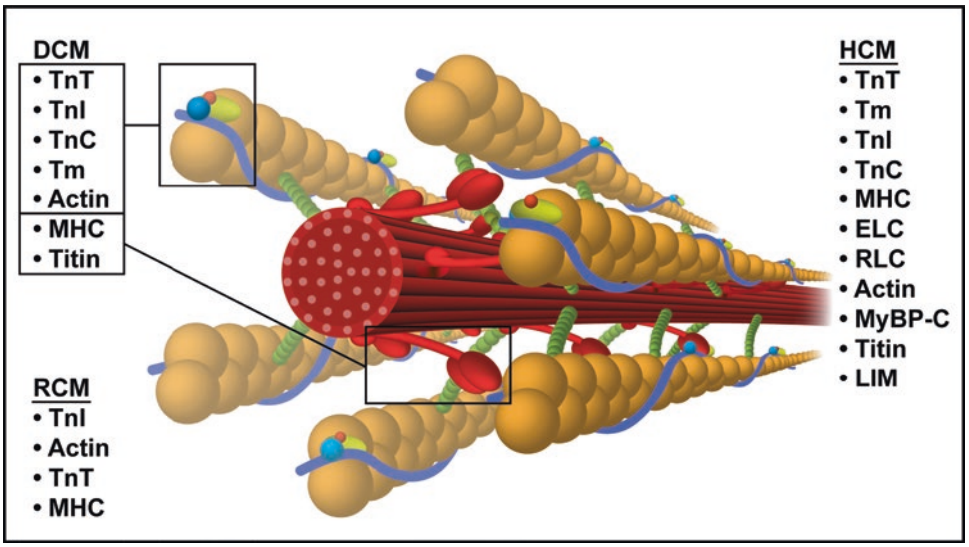

Fig. 10.3 Cardiomyopathy mutations: Multiple genetic loci converge on the sarcomere. Schematic representation of the sarcomere with *boxes* highlighting the thin filament and thick filament proteins. Listed are the sarcomeric proteins that have been implicated as disease causing in the three sarcomeric cardiomyopathies: DCM, HCM, and RCM. Actin, *beige*; Tm, *blue*; TnT, *yellow*; TnC, *light red*; TnI, *cyan*; Titin, *maroon*; MHC, *red*; MyBP-C, *green*. Adapted from source [88]: Davis J, Westfall MV, Townsend D, Blankinship M, Herron TJ, Guerrero-Serna G, Wang W, Devaney E, Metzger JM. Designing heart performance by gene transfer. Physiol Rev. 2008;88(4):1567–651

recapitulate all aspects of cardiac myocyte function, they do reveal the most basic biophysical role of the mutations, with the only variable being the mutation itself.

Moving to more complex systems, cTnC mutations were transduced into adult cardiac myocytes. Both permeabilized and membrane-intact cellular function revealed decreased Ca^{2+} sensitivity of force development, decreased contractile amplitude, and faster relaxation [36]. These cellular phenotypes all indicate altered sarcomere function with an inability to activate contractility within the normal physiologic range. Knock-in and transgenic mouse models of cTnT, myosin, and Tm DCM mutations revealed similar phenotypes to human patients with left ventricular dilation, systolic dysfunction, and decreased Ca^{2+} sensitivity of force development in isolated myofibers [27, 37–40]. These studies have built a model of sarcomeric DCM as a Ca^{2+} desensitized myofilament, leading to decreased contractility, decreased systolic function, and pathologic remodeling.

HCM

With a prevalence of 1 in 500 people, hypertrophic cardiomyopathy is the most common inherited cardiomyopathy. Clinically, it is defined by asymmetric left ventricular hypertrophy and diastolic dysfunction, with a high propensity for arrhythmias and sudden cardiac death. HCM is the leading cause of sudden cardiac death in the young and in athletes [4, 19]. The first gene mutation implicated in this disease was found in MYH7 [1], [2]. Since that time, more than 1400 mutations in 11 genes have been identified as causative for HCM [16]. An estimated 60 % of HCM is caused by sarcomeric gene mutations, with MHY7 and MyBP-C3 accounting for up to 80 % of those, while TNNT2, TNNI3, and TPM1 make up about 10 % [41]. Excluding MyBP-C3 mutations, which often result in truncated proteins and haploinsufficiency, the vast majority of mutations are missense or small insertion/deletions [3]. The mutant proteins act as poison peptides through incorporation into the sarcomere to dominantly alter sarcomere function.

Early in vitro motility assays, in combination with Ca^{2+} sensitivity of force development, identified an increase in Ca^{2+} sensitivity and force development as the primary common biophysical phenotype for most HCM mutations [27, 42, 43]. Ca^{2+} affinity assays showed increased Ca^{2+} affinity with decreased dissociation rates for many HCM mutations, suggesting that altered Ca^{2+} binding by cTnC is the end effector of sarcomere function [33]. Studies using membrane-intact adult cardiac myocytes transduced with mutant TNNI3 or TPM1 genes showed increased contractility, slower relaxation, and altered Ca^{2+} cycling [36, 44, 45]. Further work with knock-in or transgenic mouse models with MYH7/MYH6, MYBPC3, TNNC1, or TNNT2 mutations revealed in vivo hypertrophy, diastolic dysfunction, Ca^{2+} cycling abnormalities, arrhythmias, and metabolic inefficiency [42, 46–55]. All of these phenotypes recapitulate the human disease, making these preclinical models appropriate to study the molecular mechanisms of disease.

From a structural perspective, each mutation affects the sarcomere in a unique way, making the location of the mutation an important factor in determining the impact on sarco-

mere function. Most mutations alter protein-protein interactions that are crucial for activating/inactivating contractility. For example, the majority of mutations in TNNI3 are all located in critical regions of the protein that interact with actin, cTnC, or Tm [8]. In the end, the common denominator of these mutations is to alter cTnC's affinity for Ca^{2+}, which in turn determines the time of cross-bridge cycling and the rate of relaxation. This is the basis for increased force generation and diastolic dysfunction seen in animal models and human mutation carriers.

The increased Ca^{2+} affinity of the sarcomere also results in secondary effects, such as increased arrhythmias and decreased energy efficiency, which are common phenotypes in HCM patients [11, 49, 56]. Through the use of a cTnT mutant transgenic mouse and small-molecule Ca^{2+} sensitizers, it was determined that Ca^{2+} sensitization leads to increased arrhythmogenesis [57]. Further research determined that the Ca^{2+} buffering by the sarcomere and focal energy deprivation lead to increased arrhythmogenesis in independent but parallel mechanisms [58, 59]. Through the use of a small-molecule Ca^{2+} sensitizer in normal wild-type hearts, these studies directly link Ca^{2+} sensitization to decreased energy efficiency and increased arrhythmias. In addition, with the use of a small-molecule Ca^{2+} desensitizer in an HCM model, the increase in arrhythmic potential could be abrogated [59]. These studies highlight how Ca^{2+} sensitivity can lead to many of the common clinical phenotypes associated with HCM patients.

RCM

Restrictive cardiomyopathy is a rare but devastating inherited disease of the sarcomere. RCM presents with restrictive LV filling and major diastolic dysfunction, leading to heart failure and transplant or death at a young age. To date, RCM-linked mutations have been found in TNNI3, MYH7, TNNT2, and ACTC [60, 61]. Several reports provide evidence for overlap between HCM and RCM, both clinically and genetically. At least two separate mutations in TNNI3 have been associated with HCM and RCM. D190G was associated with a mix of HCM and RCM in a 12-member family [62]. R145W was associated with RCM and HCM in two separate families, and R145G and R145Q have been linked to HCM, making codon 145 a hotspot for HCM and RCM mutations [62, 63]. These clinical findings suggest that, in addition to the location of the mutation, the amino acid that replaces the endogenous amino acid is critical to the end phenotype and that environmental, epigenetic, and modifier genes can alter the phenotypic presentation.

As with the other sarcomeric cardiomyopathies, RCM mutations alter the Ca^{2+} sensitivity of the sarcomere. Similarly to HCM, RCM mutations lead to increased Ca^{2+} sensitivity but to a much larger extent. In vitro experiments using myofilaments with reconstituted mutant proteins showed increased Ca^{2+} sensitivity of ATPase and force development [64]. Further research showed increased Ca^{2+} affinity of cTnC with a cTnI mutation, suggesting a similar molecular signature with HCM [65]. In addition, many of the TNNI3 mutations alter the ability of cTnI to fully inhibit myosin binding to actin, resulting in increased diastolic tone and slower relaxation [64]. Several studies compared HCM and RCM mutations. In vitro Ca^{2+} sensitivity of force and ATPase assays differentiated the RCM-linked mutation R145W cTnI compared to the HCM-linked mutation R145G [66, 67]. The RCM mutation had a greater increase in Ca^{2+} sensitivity of force and ATPase and increased maximal force development compared to the HCM mutation at the same codon. Acute genetic engineering of adult cardiac myocytes was used to compare three HCM mutations to three RCM mutations in cTnI [45]. Membrane-intact sarcomere dynamics and Ca^{2+} transient analysis showed normal contractile amplitude, slow relaxation times, and increased Ca^{2+} decay rates for all mutations, with the RCM mutations altering these parameters to a greater extent. Further work showed that most RCM mutations and some HCM mutations alter the resting sarcomere length, indicating increased diastolic tone [45, 68, 69]. Transgenic mice expressing R193H cTnI show higher end-diastolic pressures and a progressive diastolic dysfunction with age [69, 70]. These in vivo phenotypes could be explained by the increased Ca^{2+}-independent diastolic tone that could result in restrictive filling of the LV.

Genotype-Phenotype

Although morphological features have historically categorized sarcomeric cardiomyopathies into DCM, HCM, and RCM, the molecular boundaries separating these phenotypes are complex and difficult to compartmentalize. As indicated above, these three morphologically distinct phenotypes share similar genes and a similar molecular end effector (sarcomere Ca^{2+} affinity). All three are predominately inherited as an autosomal-dominant mutation that results in a poison peptide capable of altering sarcomere function through incorporation into the sarcomere. Heterogeneous presentation of disease can be explained, in part, through the location of the mutation, which can result in differing levels of Ca^{2+} sensitization/desensitization as discussed above. With a similar molecular mechanism based on multiple preclinical models from reconstituted thin filaments up to genetically engineered rabbit myocytes, the current clinical definition of these diseases needs to be examined. Preclinical evidence points to morphological features of sarcomeric cardiomyopathies as a late-stage phenotype, with abnormalities in Ca^{2+} sensitivity occurring much earlier.

With advances in genetic testing, more family members of patients with sarcomeric cardiomyopathies are being identified as carriers before any morphological phenotype is present [16]. As the genotype positive-phenotype negative

population expands, new clinical markers are needed to track disease progression and early treatment efficacy before morphological changes manifest. These markers should be informed by the basic science that has defined multiple intrinsic properties of these mutations in terms of physiologic measures. Although myofilament Ca^{2+} sensitivity cannot be measured in a noninvasive way, alternate markers of diastolic and systolic function, in addition to noninvasive P^{31} magnetic resonance spectroscopy (MRS) to monitor energetic alterations, may enhance our ability to monitor early-stage functional changes in patients.

Experimental Therapeutics

Current therapies in the clinical setting primarily treat symptoms of sarcomeric cardiomyopathies and do not alter the fundamental genetic basis of disease. Increasing identification of genotype-positive individuals without morphological evidence of disease poses both opportunities and challenges for physicians caring for these patients. The potential to treat patients early and prevent or delay the onset of clinical symptoms is a major advantage of genetic testing. A number of early therapeutic targets have been identified, including changes in myofilament Ca^{2+} sensitivity, metabolism, vascular function, and ion channel function [3]. However, many sarcomeric cardiomyopathy mutations can result in phenotypically different outcomes, with different ages of onset and different severities. In some cases, carriers never develop clinical disease [42]. Modifier genes, epigenetic changes, and environmental factors can all lead to a heterogeneous clinical presentation even among members of the same family [71].

These factors, in addition to the lack of early disease markers, make evaluating treatment efficacy before the onset of fulminant disease difficult. Making treatment decisions before the presence of a clinical phenotype is very challenging for patients and families. Yet a growing body of research seeks to target subclinical manifestations of sarcomeric cardiomyopathies. As knowledge of genotype-phenotype transition and early disease markers increases, early treatment of sarcomeric cardiomyopathies will become an increasingly viable option for patients [4].

Normalizing Ca^{2+} sensitivity has been investigated as one early intervention that may potentially alter the course of sarcomeric cardiomyopathy development. In a proof-of-principal experiment, dual gene transfer of a Ca^{2+} sensitized cTnI mutant with a Ca^{2+} desensitized cTnC mutant in adult cardiac myocytes resulted in functional effects that were normalized toward controls compared to either mutant alone [36]. This suggests that normalizing Ca^{2+} hypersensitivity with a desensitizer may have therapeutic benefit. Drug screens have led to identification of a number of potential compounds, most of which are still in the preclinical stages of research. These include molecules that directly modulate the function of myosin or the troponin complex, or the phosphorylation of these proteins [72]. One of these compounds, the cardiac myosin activator omecamtiv mecarbil, has been evaluated in clinical trials for systolic heart failure [73]. Recently, it was tested in a preclinical model of DCM with a tropomyosin E54K mutation and resulted in increased myofilament Ca^{2+} sensitivity [74]. Another Ca^{2+} sensitizer, propyl gallate [75], was found to decrease remodeling and increase survival in a DCM mouse model with knock-in of cTnC-ΔK210 [37], suggesting an important mechanistic role of myofilament Ca^{2+} sensitivity in sarcomeric cardiomyopathies' disease pathology. One challenge to overcome with Ca^{2+} sensitizer and desensitizer therapy as a treatment for preclinical disease is overcompensation. Today, titration of these treatments is difficult due to the lack of clinical markers to assess myocardial Ca^{2+} sensitivity.

Targeting ion channels is another therapeutic strategy for sarcomeric cardiomyopathies. Increased intracellular Ca^{2+} can result from myofilament Ca^{2+} sensitization, which can lead to CAMKII upregulation and activation of phosphorylated ion channels, manifesting as electrophysiological abnormalities [3]. The Ca^{2+} channel blocker diltiazem prevented hypertrophy, fibrosis, and hemodynamic abnormalities in a preclinical model of HCM [76]. Diltiazem has also been tested in a pilot clinical study to determine whether it can delay the onset of a phenotype in genotype-positive, phenotype-negative patients. Patients were of ages 5–39 and treated for 1–3 years. The drug was well tolerated, and there were minor improvements in left ventricular end-diastolic dimension. Data stratification revealed that patients with MYBPC3 mutations responded more favorably to treatment than patients with MYH7 mutations [77]. This study is most notable for its long-term treatment aiming to prevent a disease phenotype that was not present at baseline.

Vascular abnormalities and metabolic inefficiency are often present early in sarcomeric cardiomyopathies and, therefore, may also be therapeutic targets that could change disease outcome [3]. Perhexiline, originally used as an antianginal agent, has been tested in a clinical trial of HCM patients. Perhexiline changes myocardial substrate utilization, decreasing lipid oxidation and increasing glucose oxidation, which results in decreased oxygen consumption [78]. In HCM patients, perhexiline normalized diastolic filling during exercise and increased the PCr/ATP ratio and peak VO_2 [79]. Future studies should test long-term outcomes of perhexiline treatment in sarcomeric cardiomyopathies and whether it can delay the onset of hypertrophy in subclinical disease.

An increasing amount of preclinical research on sarcomeric cardiomyopathies focuses on gene therapeutic strategies. Gene therapy has the advantage of correcting the primary cause of the disease, rather than treating functional abnormalities resulting from the mutated gene. Gene therapeutic strategies thus far have focused on increasing the amount of the non-mutated protein contained in the sarcomere. This has been accomplished by

either decreasing expression of the mutant allele or increasing expression of the non-mutated protein. The overarching goal of gene therapy in the context of sarcomeric cardiomyopathies is to change the natural history of the disease, reducing its severity or preventing the onset of the disease phenotype [3].

To date, messenger ribonucleic acid (mRNA) trans-splicing [80], exon skipping [81], and gene replacement [53] have all been studied as potential therapies for knock-in mice with a mutant form of MYBPC3. The G > A transition in MYBPC3 exon 6 in this model leads to the presence of multiple disease-causing mRNA variants and decreased total cMyBP-C protein expression and incorporation into the sarcomere. All three strategies served to increase expression of wild-type cMyBP-C transcript or a naturally occurring functional variant. However, only delivery of full-length WT-cMyBP-C resulted in sufficient protein expression and sarcomeric incorporation to improve functional outcomes in mice up to 34 weeks of age [53]. In this study, cMyBP-C was delivered via AAV9 to 1-day-old neonatal mice. The treatment dose dependently increased mRNA and protein expression and decreased expression of disease-causing variants. This coincided with a significant decrease in left ventricular hypertrophy and some improvement in echocardiographic and hemodynamic measures [53]. Increasing expression of the non-mutated protein, as was done in these studies, is ideal for haploinsufficient mutations or in cases where the diseased allele is not preferentially incorporated into the sarcomere, allowing the wild-type protein to outcompete the mutated protein for limited positions within the sarcomere.

In another mouse model of sarcomeric cardiomyopathy expressing the R403Q mutation of myosin heavy chain (MHC), a gene-silencing approach was attempted [82]. RNA interference (RNAi) was delivered via AAV9 to silence the mutant allele. Although transcript expression of MHC-R403Q was decreased by less than one-third with RNAi treatment, this was sufficient to prevent hypertrophy, fibrosis, and prolongation of the QRS interval. RNAi in this context did not reverse hypertrophy nor was it able to prevent its development as the mice aged to 11 months [82]. One limitation of treatment with RNAi against a diseased allele is the need to develop and optimize an RNAi sequence for each patient. On the other hand, this strategy offers promise for those with haploinsufficient sarcomeric cardiomyopathy mutations and a high penetrance of the diseased allele.

Although these preclinical studies show the potential for gene therapeutics in the treatment of human sarcomeric cardiomyopathy, much work remains to develop effective gene delivery systems. Long-term expression of the transgene, efficient gene transfer, and avoidance of a host-immune response are factors that must be optimized [83]. The preclinical studies described above all employed adeno-associated virus serotype 9 (AAV9). The safety of AAV1 has been demonstrated in an early-phase clinical trial of SERCA2a gene delivery in heart failure patients [84].

Viral gene delivery is not without challenges, however. For example, 38–72 % of healthy humans were found to be seropositive for antibodies specific for AAV1, 2, 5, 6, 8, and 9 [85], precluding them from treatment via AAV gene delivery. The clinical applicability of gene therapeutics for sarcomeric cardiomyopathies will therefore depend on increasing the proportion of the population eligible to receive this type of treatment.

A new technology that works to correct the genomic DNA directly is the CRISPR/Cas9 system [86]. Cas9 is a nuclease that can be targeted to a precise location in the genome, which then initiates a DNA double-strand break. After this occurs, an exogenous template can facilitate homology-directed repair to correct the mutated gene. In theory, this could cure sarcomeric cardiomyopathies because the disease-causing mutation is no longer in the genome. This technology was recently demonstrated in vivo in mdx mice. CRISPR/Cas9 was delivered to mdx zygotes that were implanted into a pseudopregnant female [87]. Genome correction ranged from 2 to 100 % and mice with corrected dystrophin expression had decreased serum CK and increased grip strength [87]. Currently, this technology cannot be used in humans, but the development of methods to deliver CRISPR/Cas9 components to the appropriate cells in vivo may pave the way for technological advances in the future.

Conclusion

Understanding the genetic basis of sarcomeric cardiomyopathies opened the door for novel insights into disease mechanisms. Historically, these diseases were clinically defined by morphologic changes. Currently, with the ample data on disease mechanisms pointing to sarcomere function as the primary, common insult, the clinical definition of sarcomeric cardiomyopathies needs to be reexamined. New diagnostic and prognostic markers need to be instituted and followed to better understand the early stages of disease. This could lead to novel therapeutics that alter sarcomere function and prevent disease progression (Fig. 10.4).

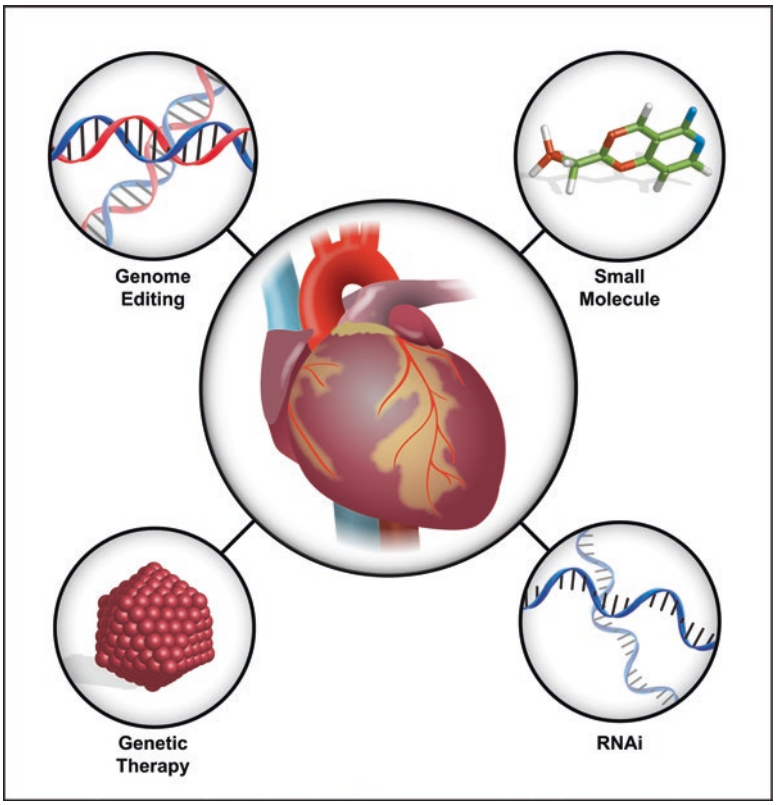

Fig. 10.4 Experimental therapeutics for sarcomeric cardiomyopathies. Small molecule therapeutics aimed at restoring contractility, metabolism, or Ca^{2+} handling. RNAi to knockdown the mutant mRNA levels to restore normal function. Gene therapeutics to replace mutant protein or restore sarcomere function. Genome editing as a means to eliminate the mutant allele

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Right Heart Failure

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_11

Introduction

The heart is a dynamic organ with chamber-specific features, including a distinct embryological derivation, vascular supply, molecular program, innervation, and architectural structure. The right heart is also distinctly separate from the left heart regarding response to stress, injury, and disease. Moreover, diseases such as genetic syndromes and pulmonary hypertension differentially affect the right heart. This chapter highlights the embryological origin of the right heart and emphasizes the right ventricle's adaptations in response to normal and pathological states. These changes underscore the capacity of the right heart to adapt to differential loads, structural changes, injury, and disease.

Regulatory Mechanisms Govern Right Heart Development

The heart is the first organ to develop during embryogenesis [1–3]. Following gastrulation, progenitor cells emerge from the anterior lateral mesoderm and coalesce at the midline to form the linear heart tube [2, 4]. Shortly thereafter, the linear heart tube initiates contractile activity, and further cellular proliferation promotes rightward looping of the developing heart (Fig. 11.1). As development progresses, distinct chambers are established, valves emerge from the cushions, and the myocardium becomes trabeculated (Fig. 11.1).

The embryonic heart is derived from progenitors that emerge from the primary (posterior) and secondary (anterior) heart fields (Fig. 11.1) [2, 4–6]. The derivatives of the primary heart field include the left ventricle and the atria, whereas the derivatives of the secondary heart field (SHF) include the right ventricle and the right ventricular outflow tract (OFT) [2, 5]. Previous studies by the Buckingham Laboratory showed that the secondary heart progenitors emerged from the splanchnic and pharyngeal mesoderm—ultimately, to contribute to the right ventricle, OFT, and ventricular septum [5]. Fate mapping studies demonstrated that the endocardium in the right ventricle and the OFT was also a derivative of the SHF. A number of transcriptional networks have been shown to be essential for SHF formation and their derivatives, including the LIM homeodomain protein, Islet-1 (Isl1) [4, 5, 7]. Mice lacking Isl1 are nonviable and lack a right ventricle and OFT. Likewise, Foxh1 null mice are nonviable and appear to lack a right ventricle and OFT. Similarly, the bHLH protein, Hand2, is expressed in the secondary heart field derivatives, and global deletion of Hand2 results in the formation of a single ventricle that lacks a distinct right ventricle and OFT. In addition to these networks, Mef2c, Tbx1, and Bop have also been shown to have an important role in the formation of secondary heart field derivatives [5, 7].

These studies are complemented by other transgenic studies using promoter-reporter constructs such as Nkx2-5, which serves to map cardiac progenitors and the primary and secondary heart field and their derivatives (Fig. 11.2) [2, 7, 8]. Collectively, these studies emphasize the importance of chamber-specific networks that govern progenitors from the secondary heart field and that perturbations of these networks contribute to congenital heart defects. These studies also emphasize the distinct nature of the developing right ventricle as well as the molecular and structural differences between the ventricular chambers.

The Right Ventricle

The right ventricle is a thin-walled, crescent-shaped, compliant chamber (Fig. 11.3). Its workload is significantly less as compared to the left ventricle, as the right ventricle pumps blood to the low-resistance and highly compliant pulmonary circulation [9]. In addition, the right ventricle behaves more like a volume pump rather than a pressure pump because of its lower volume-to-surface area ratio. Therefore, the right ventricle cannot handle an acute increase in pressure overload (acute pulmonary embolism). Right ventricular stroke volume has been shown to decrease rather linearly with an

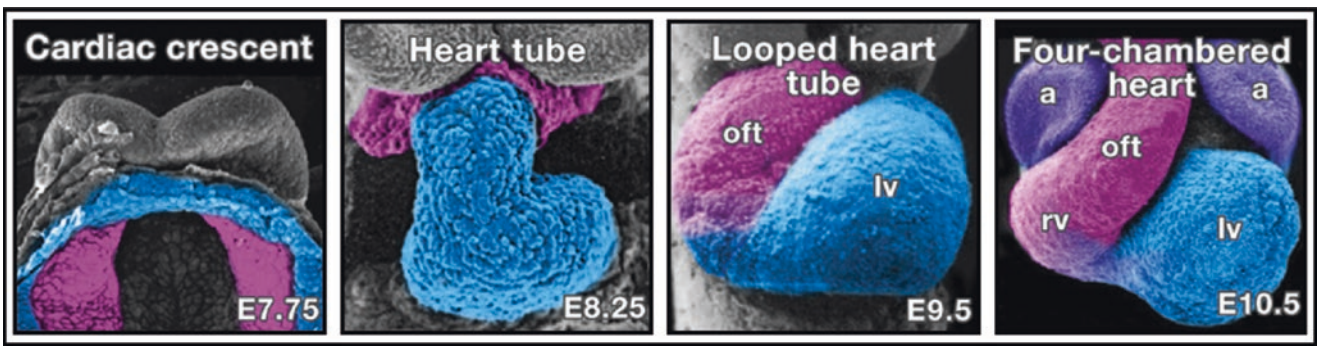

Fig. 11.1 The developing mammalian heart is derived from progenitors that emerge from the primary and secondary heart fields. Scanning electron microscopic images of the developing mouse heart demonstrating the derivatives of the primary and secondary heart fields. Note the primary (*blue*) and secondary (*pink*) heart fields at the cardiac crescent (E7.5 to E7.75), heart tube (E8.25), looped heart (E9.5), and four-chambered heart (E10.5). The atria are derivatives of the primary heart field. *oft* outflow tract, *lv* left ventricle, *a* atria, *rv* right ventricle

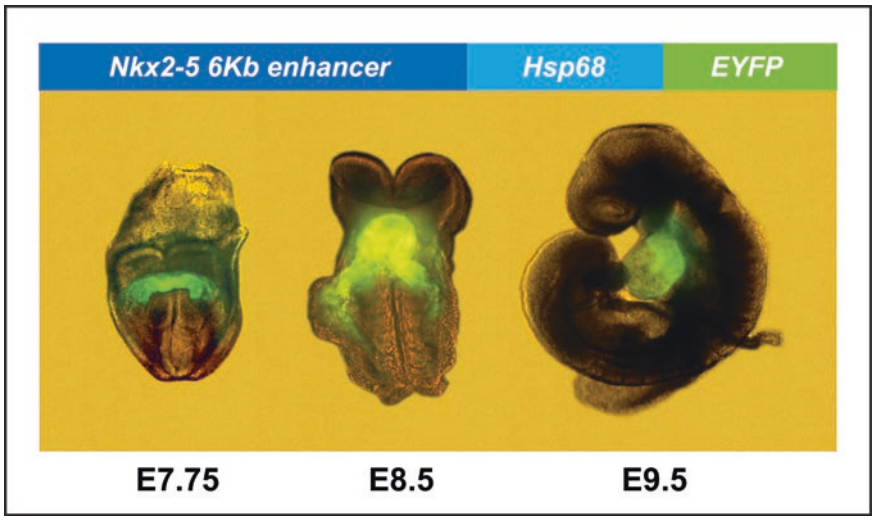

Fig. 11.2 Nkx2-5 is expressed in cardiac progenitors of the developing heart. Using a transgenic strategy, the Nkx2-5 upstream enhancer (6Kb fragment) was fused to a minimal promoter (Hsp68 or heat shock factor68) and the EYFP reporter to mark the progenitors associated with the cardiac crescent (E7.75), heart tube (E8.5), and looped heart at E9.5

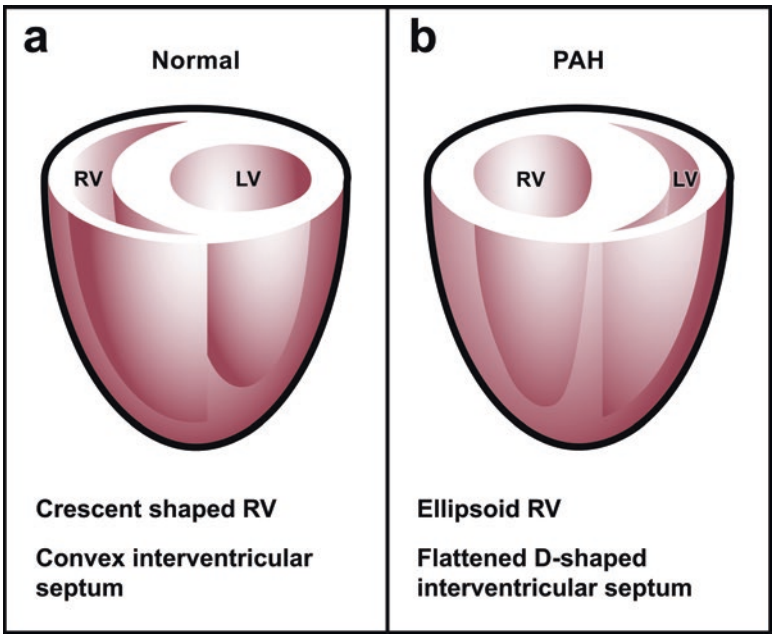

Fig. 11.3 Right ventricle in normal health and pulmonary hypertension. (**a**) The normal, healthy right ventricle is thin walled and crescent shaped. (**b**) Pulmonary arterial hypertension (PAH) increases right ventricular afterload, leading to compensatory hypertrophy and, eventually, dilatation. In the presence of pulmonary hypertension, the right ventricle becomes ellipsoidal with a flattened interventricular septum. *RV* right ventricle, *LV* left ventricle

acute increase in the afterload. In contrast, persistent pressure overload secondary to chronic pulmonary hypertension (PH) leads to right ventricular hypertrophy and enlargement (Fig. 11.3).

Right Heart Failure

Right heart failure resulting from right ventricular dysfunction can be broadly categorized into three different types: increased right ventricular afterload, cardiomyopathy affecting the right ventricular myocardium, and right-sided valvular heart disease. The afterload of the right ventricle consists of a steady component and a pulsatile component. The steady component—pulmonary vascular resistance (PVR)—is the afterload faced by the right ventricle to maintain forward flow, and the pulsatile component—the pulmonary arterial compliance—is the afterload faced by the right ventricle from the pulsatility of the pulmonary artery. Pulmonary vascular resistance accounts for 75–80 % of the total right ventricular afterload, and pulmonary arterial compliance accounts for the remainder of the 20–25 % of the total right ventricular afterload [10].

Pulmonary Hypertension

Pulmonary hypertension, defined as the mean pulmonary artery pressure ≥ 25 mmHg at rest (measured invasively), is the most common cause of right ventricular failure. In the presence of pulmonary hypertension, both the steady and pulsatile afterload of the right ventricle increases. Initially, the right ventricle adapts to the increased total afterload by compensatory hypertrophy. The right ventricle's

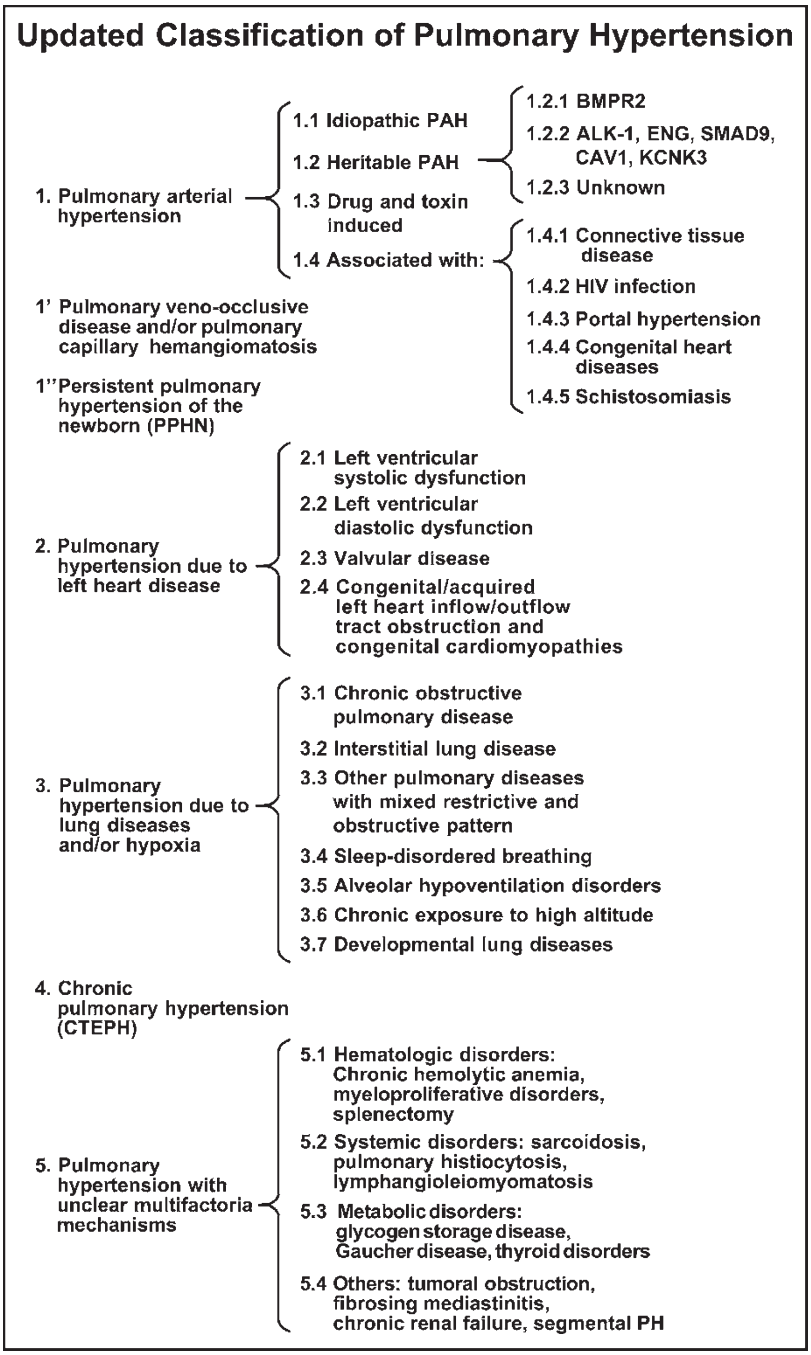

Fig. 11.4 Fifth World Health Organization classification of pulmonary hypertension. Pulmonary hypertension is classified into five categories based on the pathogenesis and mechanism of origin. *BMPR* bone morphogenetic protein receptor, *ENG* endoglin, *CAV* caveolin, *HIV* human immunodeficiency virus, *PH* pulmonary hypertension

compensatory hypertrophy decreases wall stress and increases contractility by the Anrep effect to maintain contractile function (Fig. 11.3). However, over time, the right ventricle dilates due to maladaptive remodeling and eventually fails. The mechanism behind the transition from adaptive, compensatory hypertrophy to maladaptive right ventricular (RV) dilatation is unclear. Right ventricular ischemia due to reduced epicardial blood flow (as a result of reduced perfusion gradient), capillary rarefaction, neurohormonal activation, and metabolic changes with increased anaerobic glycolysis and fatty acid oxidation have been proposed. In 2013, the World Health Organization (WHO) categorized pulmonary hypertension (PH) into five major groups based on pathophysiology and the underlying mechanism (Fig. 11.4).

Pulmonary Arterial Hypertension: WHO Category I PH

Pulmonary arterial hypertension (PAH), WHO category I PH, comprises a group of disorders characterized by endothelial cell dysfunction and smooth muscle hypertrophy of the small pulmonary arteries, leading to RV dysfunction,

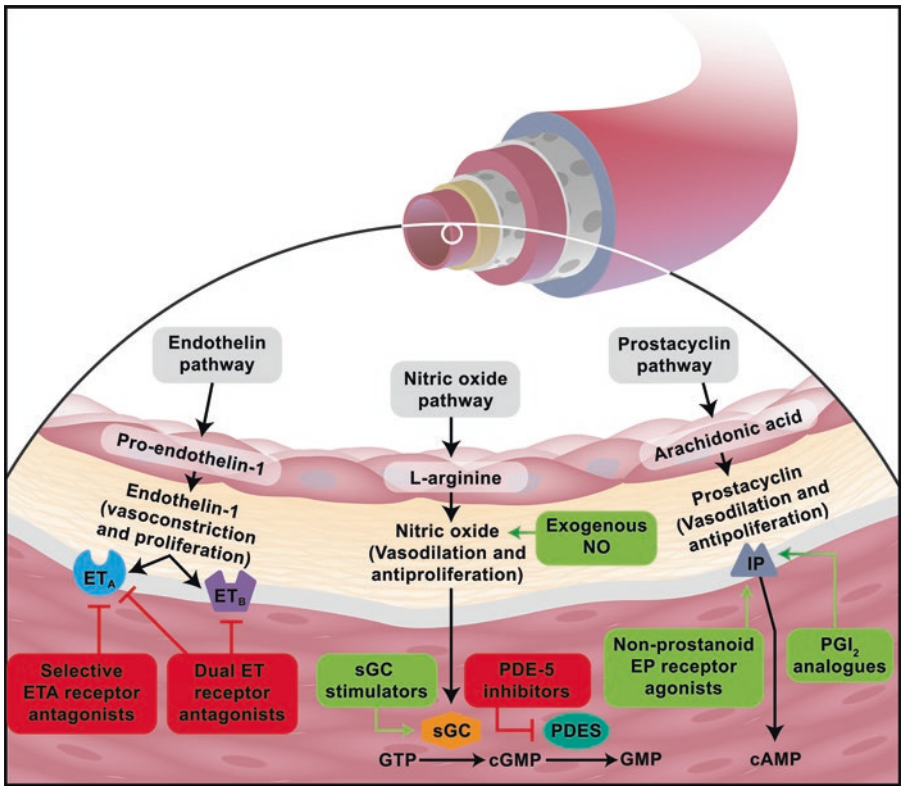

Fig. 11.5 Three major pathways implicated in the pathogenesis of pulmonary arterial hypertension (PAH). PAH is characterized by increased endothelin and decreased prostacyclin and nitric oxide in the small pulmonary arteries. *ET* endothelin, *NO* nitric oxide, *sGC* soluble guanylate cyclase, *PDE* phosphodiesterase, *PG* prostacyclin

right heart failure, and eventual death [11]. Remodeling of the resistance pulmonary arteries increases pulmonary arterial pressure (PAP) and pulmonary vascular resistance. This remodeling also decreases pulmonary arterial compliance, which collectively increases the afterload of the right ventricle. PAH is defined as mean PAP ≥ 25 mmHg, pulmonary capillary wedge pressure (PCWP) < 15 mmHg, and pulmonary vascular resistance (PVR) ≥ 3 Wood units. PAH can be idiopathic, hereditable, or associated with other conditions such as connective tissue disease, congenital heart disease, portal hypertension, HIV infection, anorexigen exposure, or schistosomiasis. PAH chiefly affects the small, resistance pulmonary arteries, which develop intimal hyperplasia, medial hypertrophy, adventitial proliferation, in situ thrombosis, and inflammation [12]. Capillary-like, angioproliferative vascular channels within the lumina of small muscular arteries, referred to as plexiform lesions, are pathognomonic of PAH [12].

The pathogenesis of PAH likely involves multiple pathways rather than a single mechanism [11]. The three main pathways implicated in the pathogenesis of pulmonary vascular remodeling include the endothelin, nitric oxide, and prostacyclin pathways (Fig. 11.5). Endothelial dysfunction characterized by an imbalance of vasoactive and vasodilator substances does occur in the small pulmonary arteries. Endothelin production increases, while synthesis of prostacyclin and nitric oxide decreases. Endothelin is a potent vasoconstrictor and a smooth muscle mitogen, whereas prostacyclin is a potent vasodilator that inhibits smooth muscle proliferation and has antiplatelet properties [11]. Nitric oxide, a potent vasodilator, inhibits smooth muscle proliferation and platelet activation. Thromboxane, serotonin, and vasoactive intestinal polypeptide have also been shown to be involved in the pathogenesis of PAH.

PAH also causes increased proliferation and decreased apoptosis of pulmonary artery smooth muscle cells. Various potential mechanisms shown to be involved in smooth muscle proliferation include normoxic activation of two transcription factors—hypoxia inducible factor (HIF)-1 alpha and nuclear factor of activated T cells (NFAT)—as well as decreased expression of the voltage-gated potassium channels Kv1.5 and Kv2.1, increased expression of the antiapoptotic protein survivin, and increased expression of transient receptor potential channels (TRPCs). Finally, the presence of inflammatory infiltrates and activation of pro-inflammatory cytokines suggest that inflammation may play a role in the pathogenesis of PAH (Fig. 11.6) [13].

Mutations in genes involved in the transforming growth factor beta (TGF-ß) pathway, bone morphogenetic protein receptor (BMPR2), activin-like kinase, and endoglin have been identified in patients with hereditable PAH [14]. Mutations in caveolin-1 and KCNK3 genes have also been identified in patients with hereditable PAH [14].

The incidence of PAH is about 2–7 cases per million; prevalence is 10–26 cases per million. Idiopathic or hereditable PAH is the most common cause of PAH, accounting for nearly 50 % of patients with PAH. Of the associated causes of PAH, connective tissue disease (mainly scleroderma) is the most common etiology [15–17]. The mean age of patients with idiopathic or hereditable PAH is 45–65 years. It predominantly affects females, with a 3:1 ratio. PAH remains a fatal disease with a relatively high mortality. In the

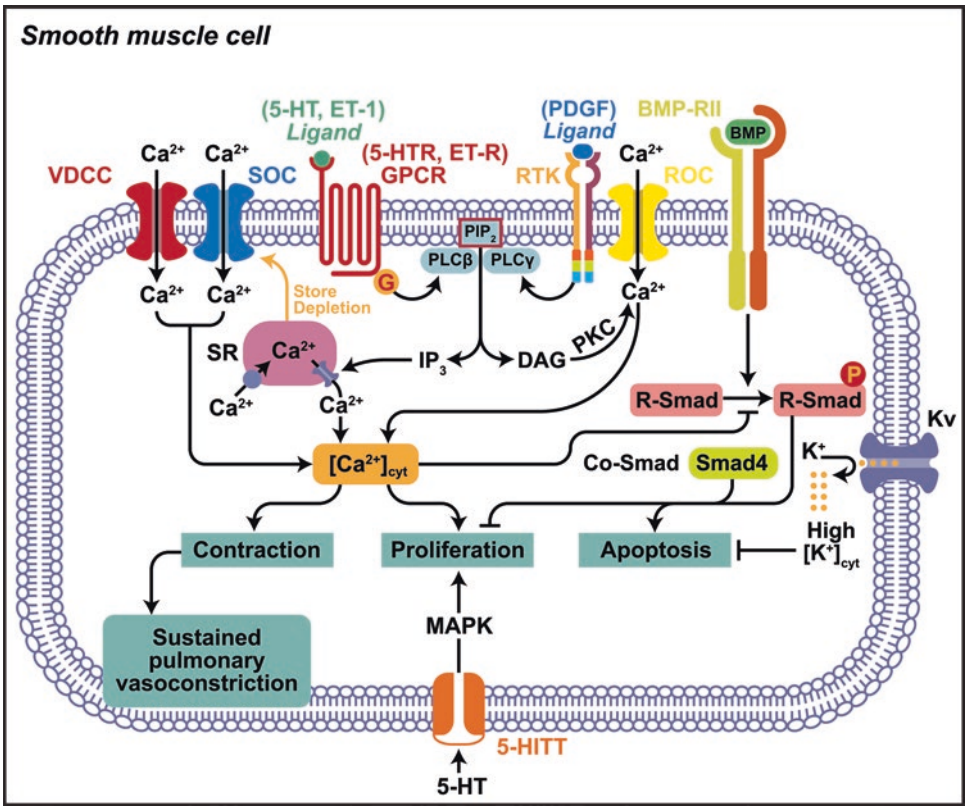

Fig. 11.6 Signaling pathways proposed in the pathogenesis of pulmonary arterial hypertension. *VDCCs* voltage-dependent calcium channels, *5-HTP* 5-hydroxytryptophan (serotonin), *5-HTR* serotonin receptor, *ET* endothelin, *ETR* endothelin receptor, *PDGF* platelet-derived growth factor, *BMPRII* bone morphogenetic protein receptor, *SOC* store-operated calcium channels, *MAPK* mitogen-activated protein kinase, *DAG* diacylglycerol, *GPCR* G protein-coupled receptor, *IP3* inositol n,5-trisphosphate, *PIP2* phosphatidylinositol bisphosphate, *PLC* phospholipase C, *PLCβ* PLC-beta, *PLCγ* PLC gamma, *PKC* protein kinase C, *RO* receptor-operated calcium channel, *RTK* receptor tyrosine kinase, *co-Smad* common-mediator Smad, *R-Smad* receptor-activated Smad signaling pathway

contemporary PAH registries, 1-, 3-, and 5-year survival rates were ~85 %, 69 %, and 61 %, respectively [18–22].

Clinical presentation is marked by exertional shortness of breath—the most common presenting symptom of PAH. Other symptoms include fatigue, chest discomfort, syncope, lower extremity swelling, abdominal distension, and weight gain. On physical examination, patients can have elevated jugular venous distension (JVD) with a prominent "a" wave, a palpable right ventricular heave, a loud second heart sound, a right-sided S4, and a holosystolic murmur secondary to tricuspid regurgitation. When right heart failure occurs, patients can have a prominent "v" wave in the JVD, a right-sided S3 gallop rhythm, hepatomegaly, ascites, and lower extremity edema.

Imaging studies are used to diagnose PAH. A chest X-ray can reveal a prominent central pulmonary artery, decreased peripheral pulmonary vascular markings, and reduced retrosternal space due to right ventricular hypertrophy [13]. EKGs may show right atrial enlargement, right ventricular hypertrophy, and right axis deviation. A transthoracic echocardiogram is the screening test of choice [13], and typical findings include elevated systolic pulmonary artery pressures estimated by Doppler imaging, right ventricular enlargement and hypertrophy, flattened (D-shaped) interventricular septum, reduced right ventricular systolic function, right atrial enlargement, and right-to-left shunt. Doppler estimates of PAP can be inaccurate and should not be used to make a definitive diagnosis of PH.

Patients should be screened for human immunodeficiency virus (HIV) infection, connective tissue disease, and portal hypertension. Pulmonary function tests, overnight polysomnography, ventilation-perfusion (V/Q) scan, and computed tomography (CT) pulmonary angiogram should be performed to exclude other causes of pulmonary hypertension. Right heart catheterization is the gold standard test for diagnosing PAH [13]. It helps to confirm the diagnosis, assess severity, and test for acute vasodilator response. PAH is defined as mean PAP greater than 25 mmHg at rest with a PCWP $\leq$ 15 mmHg and a PVR > 3 Wood units. During diagnostic right heart catheterization, acute vasodilator challenge is usually performed to identify a subset of patients with a positive response who will respond to calcium channel blocker therapy. Cardiac magnetic resonance imaging (CMRI) is gaining importance in the diagnostic evaluation of PH, especially to assess the functional status of the right ventricle. It provides an accurate and reproducible assessment of the right ventricular volumes, mass, and contractile function [23].

Treating patients with PAH includes general supportive measures and PAH-specific vasodilator therapy. PAH-specific therapies have been shown to improve functional capacity, quality of life, and hemodynamics, and reduce hospitalizations. PAH survival has improved significantly in the last two decades, but the exact reason for that improvement is unclear. Epoprostenol is the only drug shown to improve survival. None of the other 12 available PAH-specific therapies have been shown to improve survival.

Supportive treatment measures for PAH include supplemental nasal oxygen, diuretics for right heart failure, and long-term anticoagulation using warfarin, with a target INR of 1.5–2.5 [24, 25]. Long-term anticoagulation is recommended for patients with PAH, especially idiopathic PAH [13]. Digoxin has been shown to improve right ventricular contractility in PAH. Calcium channel blockers are indicated in patients with idiopathic PAH who have a positive response during acute vasodilator testing at the time of diagnostic right heart catheterization. Only 5–10 % of patients with idiopathic PAH will have a positive vasodilator response [15], but those who do will have a sustained reduction in pulmonary artery pressures and a better survival when treated with long-term oral calcium channel blocker therapy [26].

PAH-specific vasodilator therapies target the nitric oxide pathway, the endothelin pathway, and the prostacyclin pathway. Phosphodiesterase 5A inhibitors (PDE5A-inhibitors) increase cyclic guanosine monophosphate, which has vasodilatory, antiproliferative, and proapoptotic effects. Soluble guanylyl cyclase stimulators increase cyclic guanosine monophosphate by stimulating the enzyme-soluble guanylyl cyclase independent of nitric oxide. Sildenafil and tadalafil are two PDE5A-inhibitors approved for patients with PAH. Both drugs reduce mean PAP, increase cardiac output, and decrease PVR associated with an increase in 6-min walk distance and improvement in functional class both with short-term and long-term therapy [27–29]. Riociguat is a soluble guanylate cyclase stimulator that increases 6-min walk distance and time to clinical worsening [30].

Bosentan, sitaxsentan, ambrisentan, and macitentan are the endothelin receptor antagonists available for treatment of PAH. Bosentan and macitentan are dual endothelin receptor antagonists that block both the endothelin A and B receptors, whereas ambrisentan and sitaxsentan are selective endothelin A receptor antagonists. All four endothelin receptor antagonists have been shown to increase 6-min walk distance, improve functional class, and increase the time to clinical worsening [31, 32]. Unlike other endothelin receptor antagonists, in a long-term, event-driven trial, macitentan was shown to reduce morbidity and mortality [33].

Parenteral prostacyclin therapy is the treatment of choice for PAH patients with WHO functional class (FC) IV symptoms. Epoprostenol requires continuous intravenous infusion because of its very short half-life of only 3–5 min, and it is unstable at room temperature. Treprostinil has a longer half-life, and it is stable at room temperature; thus, it can be administered either by subcutaneous or intravenous routes. Epoprostenol and treprostinil improve exercise capacity, hemodynamics, and quality of life, but epoprostenol is the only therapy that has been shown to improve survival in a randomized and double-blind controlled trial [34–36]. Treprostinil can also be administered by inhalation [37]. Treprostinil diolamine is a sustained release oral formulation of treprostinil and is approved as a first-line therapy in PAH patients who are not receiving any background PAH-specific therapy [38].

Lung transplantation is a potential therapeutic option for patients with PAH who do not respond to pulmonary vasodilator therapy. There is no consensus on single-lung transplant vs. double-lung transplant. In addition, patients with severe right ventricular failure may need combined heart-lung transplantation [13].

Left Heart Disease: Pulmonary Venous Hypertension (PVH)—WHO Category II PH

Pulmonary venous hypertension is defined as mean pulmonary arterial pressure ≥ 25 mmHg in the presence of pulmonary artery wedge pressure (PAWP) >15 mmHg [39]. Pulmonary venous hypertension can be associated with left ventricular systolic dysfunction, diastolic dysfunction, and left-sided valvular heart disease. Pulmonary hypertension due to left heart disease is more prevalent than other WHO categories of pulmonary hypertension [40].

Elevated left ventricular filling pressure leading to reactive pulmonary arterial vasoconstriction and pulmonary vascular remodeling results in pulmonary hypertension in left heart failure [41]. An increase in left-sided filling pressure leads to a passive increase in pulmonary artery pressure to maintain forward flow. During this initial stage, there is no structural or physiological abnormality in the precapillary resistance arterioles. Thus, transpulmonary gradient, pulmonary vascular resistance, and diastolic pulmonary artery pressure gradient remain within normal limits. This is referred to as isolated postcapillary pulmonary venous hypertension [42]. In this chapter, we will refer to this state as "postcapillary PH." However, prolonged elevation in left-sided filling pressure causes pulmonary arterial vasoconstriction and intrinsic pulmonary arteriolar remodeling [43, 44]. This results in a disproportionate increase in pulmonary artery pressure, elevated pulmonary vascular resistance, and diastolic pressure gradient [42, 45]. The Fifth World Symposium on Pulmonary Hypertension classified pulmonary hypertension from left heart disease based on a diastolic pressure gradient as isolated postcapillary (<7 mmHg) or combined postcapillary and precapillary (≥7 mmHg) PH [46].

The prevalence of pulmonary hypertension and right heart failure is based on the underlying etiology of left heart disease (left ventricular systolic dysfunction, diastolic dysfunction, or valvular heart disease) and on the method used to diagnose PH (echocardiography or right heart catheterization). Pulmonary hypertension is more common in left ventricular diastolic dysfunction (18–83 %) compared to left ventricular systolic dysfunction (35–47.5 %) [47–55]. The prevalence of right heart failure due to pulmonary hypertension from left heart disease is not well reported. Recent data suggest that right heart failure occurs in about 30 % of patients with pulmonary hypertension due to left heart

disease [50, 56, 57]. PH also commonly complicates both mitral stenosis and regurgitation [58–60]. PH is common in isolated aortic stenosis but less common in aortic regurgitation [61–64].

The presence of pulmonary hypertension and right heart failure is associated with increased mortality in patients with left heart disease regardless of the underlying etiology. Using echocardiography, the elevated (estimated) systolic pulmonary artery pressure in patients with left ventricular systolic dysfunction is associated with a higher risk of mortality, cardiac transplantation, left ventricular assist device implantation, or heart failure hospitalization [53, 54, 65]. Similar trends have been shown in patients with left ventricular diastolic dysfunction [47, 66]. The presence of right heart failure has incremental prognostic value over pulmonary hypertension for adverse outcomes [56, 65, 67–69]. The presence of pulmonary hypertension also predicts poor outcomes in patients with mitral and aortic valve disease [70–78].

Pathophysiology of PVH and Right Heart Failure

Elevated left-sided filling pressure due to restrictive physiology and functional mitral regurgitation is the major mechanism for the development of PH and subsequent right heart failure in patients with left heart disease [48, 79, 80]. Other risk factors include: polymorphism in the promoter region of the serotonin transporter gene, older age, female gender, left atrial enlargement, atrial fibrillation, and decreased pulmonary artery compliance [53, 81, 82]. Risk factors for developing right heart failure include: male gender, atrial fibrillation, the presence of coronary artery disease, lower systemic arterial pressures, and lower left ventricular ejection fraction [56].

The treatment of pulmonary hypertension and right heart failure secondary to left heart disease is mainly based on treating the underlying left heart disease process. The role of PAH-specific therapies in patients with pulmonary hypertension due to left heart disease is unclear and is currently not recommended. In addition to the lack of efficacy data, these drugs pose safety concerns as they have been associated with increased mortality in patients with left ventricular systolic dysfunction. Theoretically, these therapies could cause pulmonary edema by increasing pulmonary blood flow in the presence of elevated left-sided filling pressures [83–85]. Of all the various PAH-specific therapies, phosphodiesterase-5-inhibitors (PDE5-inhibitors) have been studied the most in PH-HFpEF (heart failure with preserved ejection fraction) [86, 87], but the results from these trials are mixed. Thus, none of the currently approved PAH-specific therapies, including PDE-5 inhibitors, have been approved for pulmonary hypertension and right heart failure in patients with left heart disease.

Cor Pulmonale: WHO Category III PH and Right Heart Failure

Cor pulmonale is defined as the combination of right ventricular hypertrophy and/or failure with pulmonary hypertension that results from lung disease, impaired ventilation, or environmental hypoxia [88]. Chronic obstructive pulmonary disease (COPD) is the most common cause of cor pulmonale. The restrictive lung diseases associated with cor pulmonale include: idiopathic pulmonary fibrosis, sarcoidosis, and connective tissue-related interstitial lung disease [88]. Other conditions associated with cor pulmonale include: obstructive sleep apnea, obesity hypoventilation syndrome, and hypoxic high-altitude sickness [88].

Cor pulmonale accounts for 10–30 % of all heart failure admissions in the United States. The estimated prevalence of cor pulmonale in patients with chronic respiratory disease varies widely across different studies based on the definition of PH, the diagnostic modality used to categorize PH, and the severity of the underlying lung disease. Dyspnea is the most common symptom of cor pulmonale, but clinical recognition is difficult as most patients with chronic lung disease often have dyspnea. The presence of other symptoms such as chest pain, lightheadedness, syncope, and worsening dyspnea may indicate the presence of cor pulmonale. Accurate diagnosis of cor pulmonale requires right heart catheterization (RHC) because Doppler-based estimation of PAP can be inaccurate, particularly in patients with chronic lung disease [89]. Importantly, the development of cor pulmonale in patients with COPD and other lung diseases is associated with increased mortality [90].

The first line of treatment for cor pulmonale is long-term oxygen therapy. Chronic alveolar hypoxia is the major determinant of pulmonary vascular remodeling, elevated pulmonary artery pressure, and increased pulmonary vascular resistance in patients with chronic lung disease [91]. Long-term oxygen therapy decreases chronic alveolar hypoxia and, ultimately, decreases pulmonary vasoconstriction and right ventricular afterload, leading to increased right ventricular contractility and increased cardiac output. The role of pulmonary vasodilators in cor pulmonale is unclear. In theory, worsening hypoxia with pulmonary vasodilator therapy is a concern due to increased ventilation perfusion mismatch [88]. Given the lack of efficacy and the theoretical risk of hypoxia, PAH-specific vasodilator therapies are currently not approved for the treatment of cor pulmonale. Digoxin can be used to increase right ventricular contractility, but the efficacy of digoxin in cor pulmonale has not been studied systematically. Diuretic therapy provides symptomatic benefit by decreasing intravascular volume and right ventricular preload. Lung transplantation is the definitive treatment for patients who are less than 65 years of age and are not inotrope dependent. Right ventricular function improves after single- or double-lung transplantation [88].

Pulmonary Thromboembolic Disease

Acute pulmonary embolism can cause acute right ventricular failure and cardiogenic shock [92]. The right ventricle is more sensitive to pressure overload than volume overload; hence, an acute increase in pulmonary artery pressure from an acute massive or sub-massive pulmonary embolism leads to reduced right ventricular contractility and right heart failure. Thrombolytic therapy, in addition to systemic anticoagulation, is recommended in patients that present with acute pulmonary embolism and severe hypotension defined as systolic blood pressure less than 90 mmHg [92]. Over time, about 5 % of patients with acute deep venous thrombosis and/or pulmonary embolism develop chronic thromboembolic disease, which can lead to chronic right heart failure due to increased right ventricular afterload [93]. Pulmonary endarterectomy is the treatment of choice for patients who have operable chronic thromboembolic disease (proximal disease) [93]. For those with distal, inoperable, chronic thromboembolic disease, riociguat, a soluble guanylyl cyclase stimulator, has been shown to improve exercise capacity and reduce clinical worsening and right heart failure-related hospitalization [94]. Percutaneous pulmonary balloon angioplasty is an alternative option for patients with inoperable chronic thromboembolic disease [93].

Right Myocardial Ventricular Infarction

Acute right ventricular myocardial infarction (MI) can lead to right heart failure. It usually occurs in the setting of inferior wall myocardial infarction, as both the inferior wall of the left ventricle and the right ventricle are supplied by the right coronary artery. Isolated right ventricular MI is extremely rare [95, 96]. The incidence of right ventricular myocardial infarction varies from 10 to 50 % in patients with inferior wall myocardial infarction. The classic clinical triad of right ventricular myocardial infarction includes hypotension, elevated jugular venous distension, and clear lung fields. Electrocardiogram reveals ST-segment elevation in the right-sided chest leads (V3R and V4R). The main line of treatment for right ventricular infarction is timely revascularization of the right ventricle, either percutaneously or surgically, as indicated [95, 96]. Cardiogenic shock due to acute right ventricular infarct responds to intravenous fluid administration, as these patients are highly preload dependent. Diuretics should be avoided. In general, regardless of revascularization, acute right ventricular myocardial infarction does not lead to chronic right heart failure unless it's accompanied by significant pulmonary vascular disease [95, 96].

Arrhythmogenic Right Ventricular Dysplasia

Arrhythmogenic right ventricular dysplasia (ARVD) is a hereditary progressive cardiomyopathy characterized by fibrofatty replacement of the myocardium leading to ventricular arrhythmias and progressive right heart failure [97]. While ARVD predominantly affects the right ventricle, the left ventricle can also be involved, especially in the subepicardial surface. The exact pathogenesis of ARVD is unclear, but mutations in desmosomal proteins (desmoplakin and plakoglobin) have been associated with ARVD. The prevalence of ARVD varies from 1:2500 to 1:5000, and it predominantly affects males between the second and fifth decades [97].

Common clinical symptoms of ARVD are palpitations, syncope, and sudden cardiac death. Ventricular tachyarrhythmia is the predominant manifestation [97]. Progressive right ventricular systolic dysfunction leading to chronic right heart failure can occur but is less common (<10 % of patients). Diagnosis of ARVD is challenging [98]. Various diagnostic criteria have been recommended for accurate diagnosis of ARVD. Cardiac magnetic resonance imaging is the imaging modality of choice; however, identification of fibrofatty infiltration in the right ventricular free wall can be difficult, as it is very thin and less muscular. Endomyocardial biopsy is usually not helpful because of the sampling error due to patchy involvement of the right ventricle. Immunohistochemical staining for desmoplakin and plakoglobin in the right ventricular endomyocardial biopsy samples has been proposed for early diagnosis of ARVD in specialized centers [98].

The treatment of choice for ARVD patients with ventricular tachyarrhythmia is implantation of an automatic intracardiac defibrillator. The long-term survival of ARVD patients who receive an intracardiac defibrillator, for either primary or secondary prevention of ventricular tachyarrhythmia, is generally favorable as tachyarrhythmia is the predominant clinical manifestation. Cardiac transplantation is the treatment of choice for a minority of ARVD patients who develop progressive right ventricular dysfunction and right heart failure. Currently, there is no FDA-approved, long-term, implantable, right-sided ventricular assist device for chronic right heart failure. The role of medical therapy with neurohormonal modulation and aldosterone receptor antagonists in ARVD is limited [99].

Right-Sided Valvular Heart Disease

Over time, tricuspid regurgitation, either primary or secondary, leads to right ventricular volume overload, right ventricular dysfunction, and right heart failure. Secondary tricuspid regurgitation due to pulmonary hypertension or right ventricular cavity and/or annual dilatation is much more common than primary tricuspid regurgitation. Primary tricuspid regurgitation is rare; its causes include infective endocarditis, carcinoid heart disease, rheumatic heart disease, tricuspid valve prolapse, trauma, and certain appetite-suppressant drugs.

Carcinoid heart disease occurs in nearly 50 % of patients with carcinoid tumors, which are rare neuroendocrine tumors secreting vasoactive substances that include

serotonin, histamine, bradykinin, 5-hydroxytryptophan, 5-hydroxytryptamine, and atrial natriuretic peptide [100]. It predominantly occurs in the gastrointestinal tract. Carcinoid heart disease is characterized by deposition of plaque-like fibrous tissue—typically in the valves and/or the endocardium of the right side of the heart. The left side of the heart is generally not affected by carcinoid heart disease. The vasoactive substances secreted by the carcinoid tumor are metabolized in the pulmonary circulation. On the right side of the heart, both the tricuspid and pulmonic valves are equally affected. Over time, tricuspid regurgitation and/or pulmonic valve regurgitation causes right ventricular volume overload, right ventricular dysfunction, and, eventually, right heart failure. Removing the primary carcinoid tumor is the definitive treatment. Patients with severe valvular heart disease can benefit from valve repair or replacement [100].

Conclusions

The right heart is distinct from the left heart regarding its developmental origin, structural organization, molecular regulation, and functional role. Pulmonary hypertension, myocardial infarction, genetic disease, and carcinoid can all promote right heart failure and, thereby, impact patients' morbidity and mortality. Intense interest is focused on developing new therapies to impact disease progression, but the current state of therapeutic development remains at an early stage. Developing patient registries and using imaging technologies and molecular analyses will provide a deeper understanding of the mechanisms and, ultimately, new therapies for right heart failure.

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Neuromuscular Cardiomyopathies

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_12

Neuromuscular disorders are a diverse and heterogeneous group of diseases that affect the nervous system and/or muscle function. More than 80 distinct neuromuscular disorders exist, which include the muscular dystrophies.

Muscular dystrophies comprise more than 30 genetic disorders characterized by progressive degradation of striated muscles. While many individual muscular dystrophies exist, with varying ages of onset, severity, and patterns of muscle weakness, they share a genetic and pathophysiological origin. That shared origin is a mutation in a gene encoding one of the many structural cytoskeletal proteins that play a critical role in muscle function.

The primary presenting symptom in muscular dystrophies is skeletal muscle weakness. However, cardiac muscle, another type of striated muscle, is similarly affected in many of the muscular dystrophies.

Cardiomyopathies associated with muscular dystrophies are an increasingly recognized manifestation of these neuromuscular disorders and play a significant role in morbidity and mortality in these disease processes. The most common muscular dystrophies to have cardiac involvement include the dystrophinopathies, Duchenne and Becker muscular dystrophies, and myotonic dystrophies.

Dystrophinopathies: A Historical Perspective

The earliest detailed descriptions of muscular dystrophies were by Meryon in England in 1852 and by Duchenne in France in 1868 [1, 2]. They identified a disease that affected young boys with severe muscular weakness and an abnormal increase in calf size. Duchenne obtained muscle biopsies of these boys and noted fatty-fibrous replacement of the skeletal muscle. For this contribution, the disease that he described was named after him: Duchenne muscular dystrophy (DMD).

In 1886, Gowers described the way that a child affected with muscular dystrophy uses his arms to rise from the ground [3]. While DMD had been known as a clinical entity since the 1860s, its cause was not elucidated for more than 100 years. In a landmark discovery in 1986, Louis Kunkel's laboratory identified the gene responsible for causing Duchenne muscular dystrophy and, in 1987, showed that mutations resulting in the absence of the 427-kDa rodlike protein dystrophin caused DMD [4, 5].

These major advancements enabled development of diagnostic and genetic testing as well as the establishment of disease models that have facilitated our knowledge of DMD. While a number of questions remain about the muscular dystrophies, the rich history of discovery has significantly accelerated our knowledge of DMD since the mid-1980s.

Dystrophinopathies: Inheritance

DMD is the most common form of muscular dystrophy, affecting 1 of every 5000 boys born in the United States [6–9]. It results from an inherited or spontaneous mutation of the dystrophin (DMD) gene. The *Dystrophin* (*DMD*) gene is a 2.5-Mb gene located on chromosome Xp21.1 [5, 7, 10]. Dystrophin is among the largest known genes, encoding a 14-kb transcript with 79 exons (Fig. 12.1).

The 11-kb cDNA encodes a 3685 amino acid dystrophin protein of 427 kDa. The full-length dystrophin gene has three

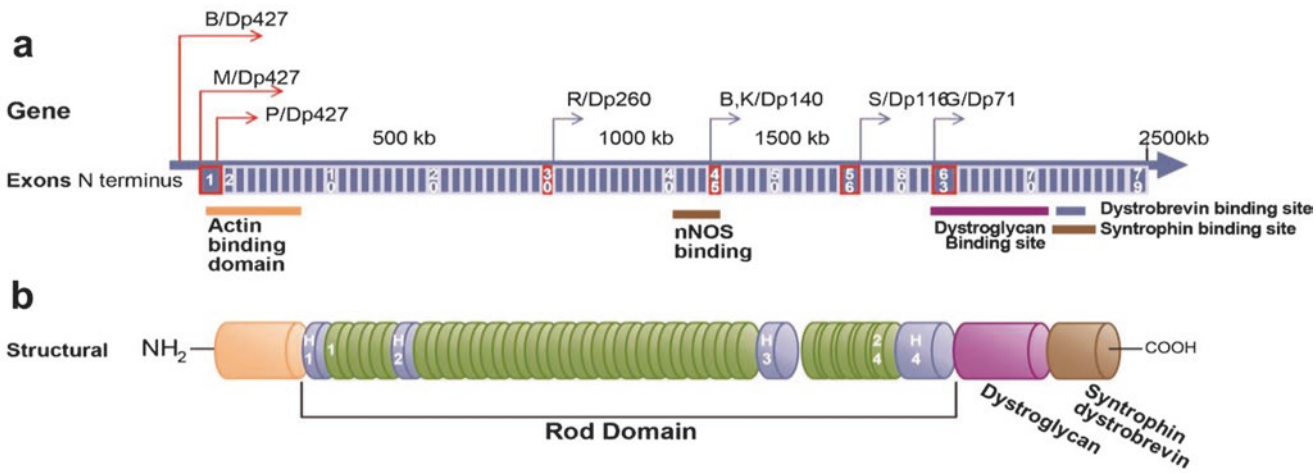

Fig. 12.1 *Dystrophin* gene and protein. (**a**) The 79 exons of the full-length *dystrophin* gene with promoters for the alternatively spliced isoforms with *red arrows* and *boxes* specific for each promoter. Full-length *dystrophin* promoters include M, muscle promoter; B, brain promoter; and P, purkinje promoter. The isoforms for other shorter dystrophin isoforms include Dp260, which is expressed in the retina (R); Dp140, which is expressed in kidney (K) and brain (B); Dp116, which is expressed in Schwann cells (S); and the ubiquitously expressed Dp71. (**b**) The protein structure of dystrophin, which includes the actin-binding site at the N-terminus and the dystroglycan complex protein-binding site at the C-terminus. The rod domain contains 24 spectrin-like repeats with four hinge regions

gene promoters: (1) the M promoter produces the Dp427m isoform, which is located in the skeletal and cardiac muscle; (2) the B promoter produces Dp427c, which is located in the brain; and (3) the P promoter produces Dp427p, which is in the brain's Purkinje cells [11–13]. Other non-full-length dystrophin isoforms are produced, including Dp260 (retina), Dp140 (brain and kidney), and Dp71 (ubiquitous) [14–17].

An out-of-frame mutation of one or several of the 79 exons in the full-length dystrophin gene results in an absence of a functional dystrophin protein, which is the hallmark finding in DMD. DMD is inherited in an X-linked recessive manner, where a female carrier with one X chromosome carrying the DMD mutation has a 50 % chance of passing on the mutated X chromosome to her son. Female carriers can also have symptoms based on their X inactivation. While the majority of DMD mutations are inherited, spontaneous mutations account for 30 % of DMD cases [18].

Dystrophin and DGC Organization

The 79 exons code for dystrophin, a 427-kDa protein that is expressed in the skeletal muscle, cardiomyocytes, and brain [7]. Dystrophin, a rod-shaped cytoplasmic protein, connects the dystroglycan complex (DGC) to the intracellular contractile apparatus and extracellular matrix (ECM) of the cell (Fig. 12.2) [19]. Dystrophin is similar to spectrin and other structural proteins and consists of two ends separated by long, flexible rodlike regions. The N-terminus binds actin and the C-terminus binds to glycoproteins in the sarcolemma. The role of dystrophin is to stabilize the plasma membrane by transmitting forces generated by the sarcomeric contraction to the ECM.

The DGC is a multimeric complex composed of glycated integral membrane proteins and peripheral proteins that form a structural link between the f-actin cytoskeleton and the ECM in both the cardiac and skeletal muscle [20–23]. The DGC is comprised of cytoskeletal proteins, dystrophin, syntrophins, dystroglycans, sarcoglycans, DGC-associated proteins, neuronal nitric oxide synthetase, and dystrobrevin [24–26]. The fully nucleated DGC provides mechanical support to the skeletal or cardiac plasma membrane during contraction. Loss of function or absence of one or several of these DGC proteins leads to plasma membrane fragility.

DMD and Becker muscular dystrophy (BMD) arise from mutations in dystrophin. Other forms of muscular dystrophies arise from mutations in the DGC components. In the skeletal muscle, the DGC is located at regular intervals in structures known as costameres, whereas in the cardiac muscle, the DGC is not located in discrete costameres [27]. The composition of the DGC in the skeletal muscle and cardiac myocytes may be different and differentially altered in dystrophin deficiency [28].

Pathogenesis and Physical Findings

The skeletal muscle and hearts lacking functional dystrophin are mechanically weak, and contraction of the cell (skeletal myocytes and cardiac myocytes) leads to membrane damage [29, 30]. Loss of membrane integrity leads to a cascade of increased calcium influx into the cell and eventual cell death.

Clinically, the loss of dystrophin manifests as progressive muscle weakness [19, 31]. Symptoms are first noted in early childhood and include calf pseudohypertrophy, an inability to stand without using the arms for assistance (Gowers sign), toe walking, and difficulty keeping up with peers. As the disease progresses, the skeletal muscle becomes increasingly weak, causing atrophy and contractures that subsequently result in the loss of ambulation by the age of 10–12. Patients with DMD have markedly elevated serum levels of creatinine kinase (CK), a muscle protein, due to ongoing muscle damage. Creatinine kinase levels may be 10–100 times the normal limit in patients with DMD, and elevated CK levels are a diagnostic sign [32]. DMD diagnosis can be confirmed by muscle biopsy demonstrating the absence of dystrophin (Fig. 12.3) and by genetic testing for dystrophin mutations.

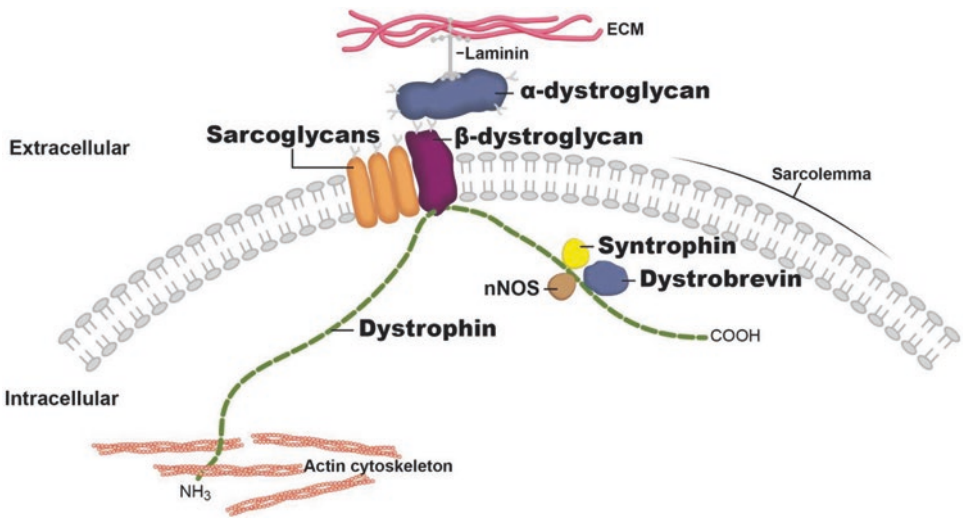

Fig. 12.2 Schematic diagram of the dystroglycan complex (DGC). The DGC spans the sarcolemma and links the cytoplasmic actin cytoskeleton to the extracellular matrix via dystrophin. The transmembrane components of the DGC include sarcoglycans, beta-dystroglycan, and extracellular alpha-dystroglycan which binds laminin. The cytoplasmic components include dystrophin (or utrophin) which binds dystrobrevin, syntrophin, and nitric oxide synthase

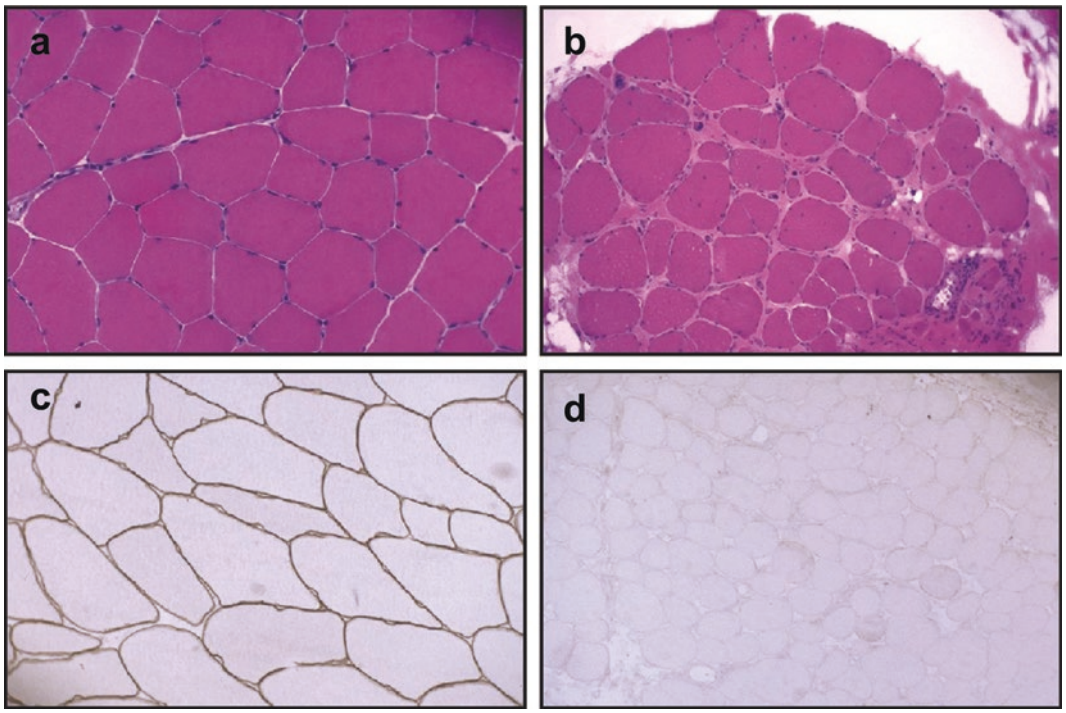

Fig. 12.3 Absence of dystrophin in the DMD skeletal muscle. Photomicrographs of cross sections of the normal and DMD human skeletal muscle. (**a**) Normal muscle biopsy shows relatively uniform fiber diameter, peripherally located nuclei with no fiber degeneration, inflammation, or endomysial fibrosis. (**b**) DMD muscle biopsy shows varied fiber diameter, inflammation, and necrotic change with fat and fibrous replacement of the normal muscle tissue. (**c**) Normal muscle biopsy stained for dystrophin, which is located at the plasmalemma (*brown*). (**d**) DMD muscle biopsy stained for dystrophin, demonstrating the absence of dystrophin expression

Survival

Historically, this progressive muscle weakness resulted in the loss of ambulation by 10–12 years of age and death during the second decade of life mainly due to respiratory failure. However, with the advent of nocturnal ventilation, spinal surgery, and steroid treatment, the life expectancy of boys with DMD has increased to the late 20s to early 30s [33] (Fig. 12.4). While respiratory problems used to be the major cause of death in DMD patients, cardiomyopathy now is the predominant cause of death in these patients [34].

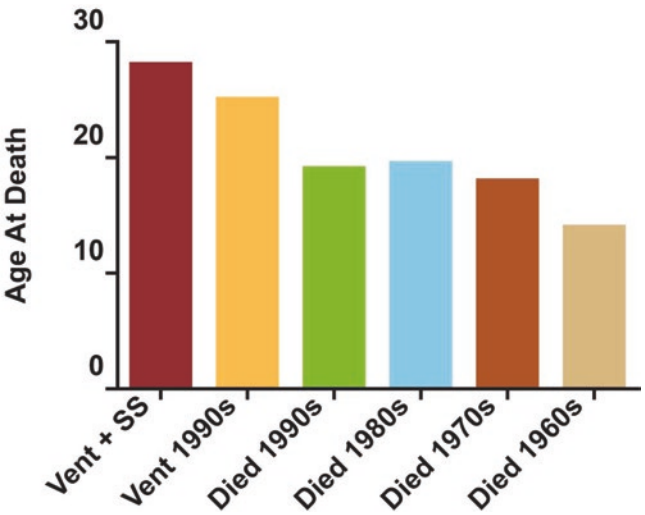

Fig. 12.4 Interventions that prolong survival in Duchenne muscular dystrophy. A marked increase in survival of DMD patients has been observed with addition of steroids, ventilation, and spinal surgery . Adapted from [33]

Treatments

Advances in management, namely, corticosteroid treatments, spinal stabilization, and improved pulmonary support, have significantly improved life expectancy of boys/men with DMD to the late 20s and early 30s [33]. Glucocorticoids are one of the mainstays of treatment for DMD and have been shown to improve muscle strength and function and pulmonary function in patients with DMD [35–39].

Corticosteroid Treatments

Glucocorticoids are recommended for patients with DMD who are age 5 or older who are not gaining motor skills or have a decline in motor skills [40]. While the precise mechanism of glucocorticoid therapy in preserving strength is not known, it is postulated that the mechanisms may include inhibition of muscle proteolysis, stimulation of myoblast proliferation, membrane stabilization, an increase in myogenic repair, and a reduction in inflammation [41–46]. The current glucocorticoid protocols that have been tested in randomized clinical trials include daily prednisone 0.75 mg/kg/day,

intermittent prednisone 0.75 mg/kg/day 10 days on and 10 days off, and daily deflazacort 0.9 mg/kg/day [47].

Side effects with prednisone and prednisolone include weight gain, Cushingoid appearance, short stature, delayed puberty, and increased risk of osteoporosis and fractures. Patients prescribed steroids should receive preventive measures such as calcium and vitamin D supplementation to reduce bone loss.

Deflazacort is another steroid used with DMD patients; it may have a more limited side effect profile compared to prednisone [48]. At press time, deflazacort is not approved by the US Food and Drug Administration (FDA), so it is not available in the United States. The FDA granted it fast-track status in 2015. Steroid therapy has also been demonstrated to preserve cardiac function in DMD patients in a retrospective study [49].

While steroids are known to be beneficial, no consensus exists on the ideal dosing strategy, age of initiation, or duration of therapy for glucocorticoids in DMD. The FOR-DMD randomized control trial aims to answer the question of ideal dosing strategy by enrolling 300 DMD patients (4–7 years of age) who have not previously received steroids and randomizing them to one of the three dosing regimens listed above.

Spinal Stabilization

Scoliosis and kyphosis are common, progressive sequelae of DMD, occurring near the time the patient loses ambulation. Spinal deformities further decrease pulmonary function as measured by forced vital capacity intervention such as spinal stabilization surgery [50]. Thus, spinal stabilization surgeries using Harrington rods and other techniques have been used with DMD patients to help maintain or improve pulmonary function and improve patient comfort [51, 52].

Pulmonary Support

Respiratory complications occur frequently in patients with DMD as they lose respiratory muscle strength, leading to decreased ventilation and increased risk for pneumonia, atelectasis, and respiratory failure [53]. Before rigorous pulmonary screening and intervention, the majority of deaths in end-stage DMD occurred as a result of respiratory failure and infections.

It is recommended that patients with DMD see a pulmonologist and obtain pulmonary function testing by age 10 and then twice yearly after loss of ambulation or when the vital capacity is less than 80 % of predicted or after the age of 12 [54, 55]. Noninvasive nocturnal mechanical ventilation is offered first at night to treat sleep-related breathing problems and hypoventilation, which are common in patients with DMD [55, 56]. Nocturnal ventilation has improved survival in patients with DMD [57]. Once respiratory weakness progresses past nocturnal ventilation, full ventilator support can be initiated.

Cardiac Involvement in DMD

Nocturnal ventilation and spinal stabilization surgery have reduced respiratory-related deaths, but also increased DMD cardiomyopathy due to the advanced age of DMD patients [33, 57, 58]. Cardiac involvement is nearly ubiquitous in older DMD patients, as more than 90 % of young men over the age of 18 have evidence of cardiac dysfunction [34]. Dilated cardiomyopathy typically has an onset in the mid-teen years and progressively remodels and contributes to the demise of DMD patients [34, 59] (Fig. 12.5). Distinct dystrophin mutations have been correlated to an increased incidence of cardiomyopathy and possible response to treatment [60].

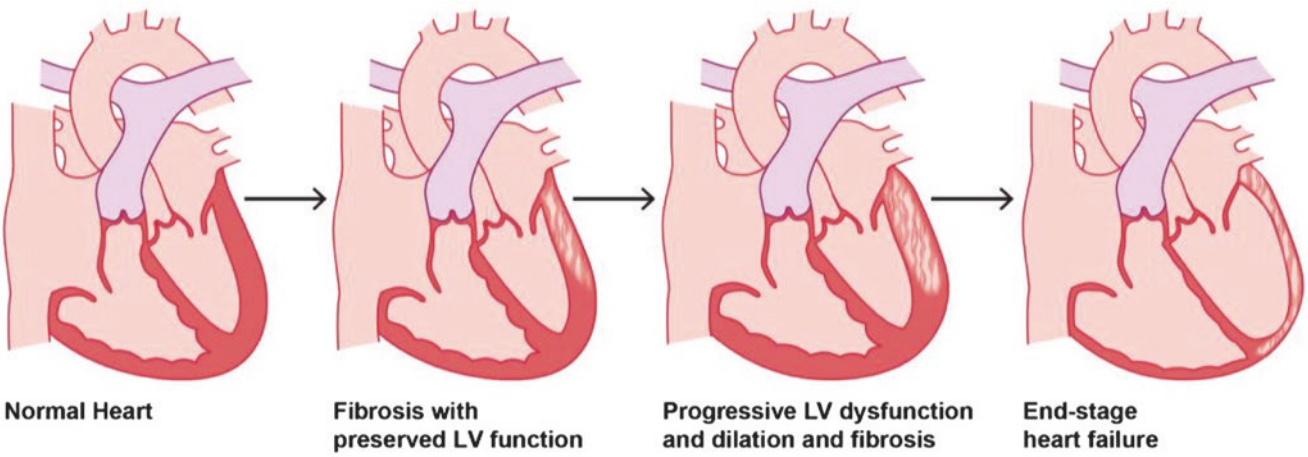

Fig. 12.5 DMD cardiac disease progression. DMD cardiomyopathy disease progression. Initially, DMD patients have structurally normal hearts. Subsequently, DMD patients develop fibrosis of the inferobasal wall as the earliest sign of myocardial involvement. Over time this leads to progressive fibrosis, left ventricular dysfunction, and dilatation leading to end-stage heart failure

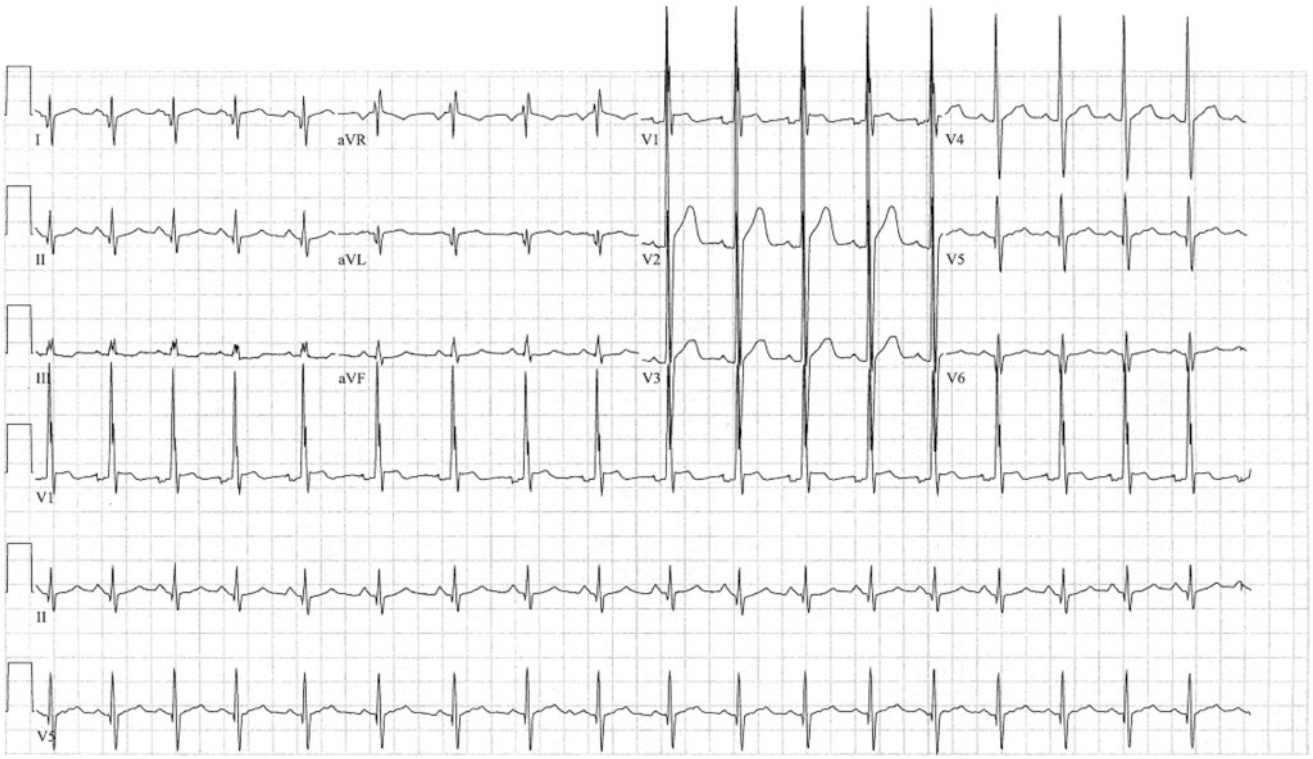

Fig. 12.6 Electrocardiographic changes in DMD. Electrocardiogram (ECG) from a patient with Duchenne muscular dystrophy. The ECG demonstrates sinus tachycardia; Q waves in leads I, aVL, and V4-6; and large R waves in V1 and V2

Recognition of cardiomyopathy in DMD patients can be challenging due to physical inactivity and other respiratory complaints that can obscure the diagnosis [61]. Currently, clinical guidelines recommend initial cardiac screening at the time of diagnosis of DMD, and every 2 years until age 10, and then yearly thereafter [40].

Most DMD patients will have abnormal electrocardiographic tracings. The classical pattern demonstrates tall R waves and increased R/S amplitude in lead V1, Q waves in the left precordial leads, right axis deviation, or complete right bundle branch block [62–64] (Fig. 12.6). These ECG findings correlate to the pathological studies that have shown a tendency to develop fibrosis in the heart's basal posterior wall in patients with muscular dystrophies and may reflect reduced electrical activity in the inferobasal wall [65]. ECG findings are believed to precede echocardiographic findings of cardiomyopathy, but no correlation between ECG findings, and the presence of cardiomyopathy has yet been established [62, 66].

Arrhythmias are a common cardiac involvement in patients with muscular dystrophies. Sinus tachycardia is a common finding in patients with DMD [67–69]. Dystrophic patients experience elevated heart rates even when compared to patients with other muscular dystrophies or deconditioned patients [69]. Pathological examination of the heart in dystrophic patients has shown fibrosis of the conduction system in addition to the myocardium [70], which may explain autonomic cardiac dysfunction in the DMD population [71, 72].

Additionally, sinus tachycardia may correlate with cardiac dysfunction in patients with DMD [73]. Dalmaz et al. reported that urinary catecholamines increased in DMD patients around the age of 10 years, which corresponded to the time of heart rate elevation and cardiac involvement [74]. In patients with DMD cardiomyopathy, atrial arrhythmias including atrial fibrillation, atrial flutter, and atrial tachycardias can occur. Ventricular tachycardia, premature ventricular contractions (PVCs), and other conduction abnormalities have been noted and are correlated with progressive ventricular dilation and dysfunction [75].

Cardiac Imaging in DMD

Cardiac imaging can be challenging in patients with end-stage DMD due to scoliosis, ventilation, and contractures. Imaging modalities commonly used include echocardiography and cardiac magnetic resonance imaging (MRI).

Echocardiography in DMD cardiomyopathy shows regional wall motion abnormalities in the posterior basal wall, left ventricular dilation, and overall reduced systolic function [76]. Current guidelines recommend obtaining an echocardiogram at the time of diagnosis or by age 6, with repeat echocardiograms every 1–2 years until age 10. After age 10, it is recommended that patients have an annual echocardiogram to assess left ventricular function [51]. While echocardiography is easily accessible, relatively quick, and a cost-effective imaging modality, it can be technically challenging in patients with DMD due to chest wall deformities, scoliosis, and respiratory dysfunction, thus limiting the diagnostic yield [77].

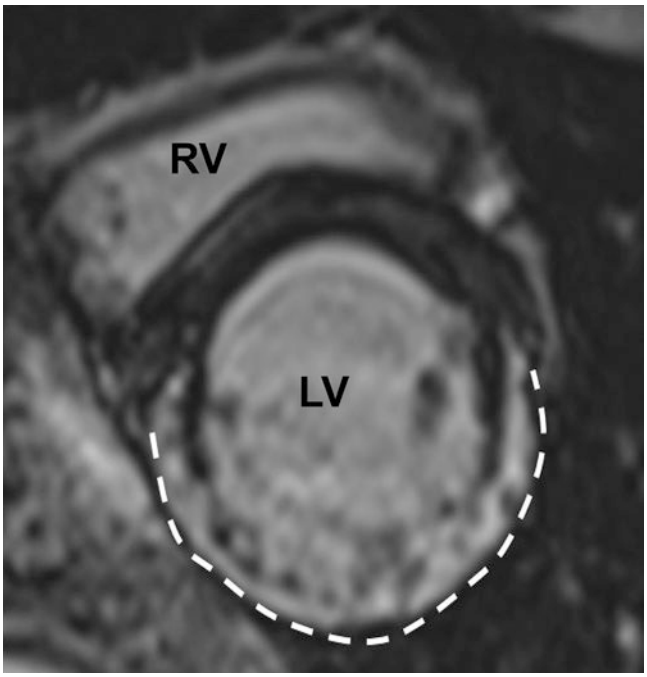

Fig. 12.7 Cardiac magnetic resonance imaging demonstrating dilated cardiomyopathy and fibrosis in a patient with DMD. Cardiac magnetic resonance delayed enhancement image in the basal short axis view performed on 1.5-T MRI. This image demonstrates near-transmural enhancement (*gray*) in the left ventricular basal-mid anterolateral, inferolateral, and lateral wall (area denoted by *dashed white line*) consistent with myocardial scar or fibrosis. This is in an 18-year-old male patient with Duchenne muscular dystrophy and exon 24 deletion with associated cardiomyopathy (LVEF 33 %)

CMR imaging has been used with DMD patients and can provide one of the most accurate assessments of left ventricular size and function [78–80]. Silva et al. performed gadolinium contrast-enhanced CMR on ten patients with dystrophinopathies (eight DMD and two BMD patients) and were the first to demonstrate late gadolinium enhancement (LGE) by CMR in a dystrophic heart. They further reported that, using echocardiography, LGE was present even with normal left ventricular function [71].

Pulchalski et al. subsequently performed a study of 74 patients with DMD; the majority had LGE in the posterobasal region of the left ventricle in a subepicardial distribution [81]. This pattern of LGE in the basal inferior and inferolateral walls is consistent with the pathological findings of fibrosis in the inferior basal wall (Fig. 12.7) [65, 82]. A large single-center study by Hor et al. retrospectively evaluated LGE in 314 DMD patients and demonstrated that LGE increased with age and with decreasing left ventricular ejection fraction [LVEF] [83]. Thus, CMR imaging may provide an earlier detection of cardiovascular involvement in DMD and enable accurate and reproducible quantification of left ventricular function and size and promote initiation of earlier cardioprotective treatment. While CMR has many imaging benefits for patients with DMD, it can also be challenging, especially in the pediatric population, due to the need for sedation, higher costs, and limited access to this type of specialized imaging.

Pharmacologic Treatment of Cardiomyopathy

Studies have shown the benefits of corticosteroid therapy and, as shown by echocardiography and cardiac MRI, support the notion that steroid treatment delays left ventricular dysfunction in DMD patients [59].

Duboc et al. evaluated the impact of angiotensin-converting enzyme (ACE) inhibitors, which have proven effective in asymptomatic adults with left ventricular dysfunction, and in patients with DMD with preserved left ventricular function [84]. The investigators randomized 57 children with DMD (mean age of 10.7 years) to the ACE inhibitor perindopril (2–4 mg/day) or placebo. At 3 years of follow-up, there was no significant difference in LV function between the children treated with perindopril or placebo. However, at the 3-year mark, all patients were switched to perindopril treatment and followed for an additional 2 years. After crossing over to perindopril at 2 years, there was no difference in mean LV function between those patients treated with perindopril initially versus those initially treated with placebo.

However, the initial placebo group had 8 of 29 patients with LVEF < 45 % and only 1 of 27 patients in the perindopril group ($p = 0.02$), which suggests that early treatment with perindopril was effective in preventing progression to left ventricular dysfunction in DMD. Subsequently, these patients were followed for 10 years, and in the initial placebo group, only 65 % of patients were alive versus 92.9 % in the initial perindopril group ($p = 0.013$), which emphasized that early use of an ACE inhibitor reduced mortality in patients with DMD [85].

Treatment guidelines recommend initiation of ACE inhibitors in patients with DMD only once LV dysfunction has developed [51], but based on the studies by Duboc et al., we recommend initiation of an ACE inhibitor before the development of left ventricular dysfunction in patients with DMD, as they are at high risk for developing left ventricular dysfunction (American College of Cardiology heart failure stages A and B) [84, 85]. Additionally, for those patients who are intolerant to ACE inhibitors, angiotensin receptor blockers (ARBs) can also be used. ARBs have been shown as effective as ACE inhibitors in DMD [86].

While the benefit of ACE inhibitors in DMD cardiomyopathy has been definitive, the efficacy of beta-blockers in DMD cardiomyopathy has been less clear. The use of carvedilol has been assessed in pediatric DMD patients with elevated atrial natriuretic peptide (ANP) or brain natriuretic peptide (BNP), and a low ejection fraction (EF < 40 %), as measured by echocardiography. No significant difference in carvedilol-treated patients was seen regarding symptoms of left ventricular dysfunction [87]. However, in a study by Rhodes et al., carvedilol was shown efficacious in patients with DMD cardiomyopathy [88].

When superimposed on background therapy of ACE inhibitors, the use of carvedilol in this patient population remains unclear. An analysis of 13 patients with DMD who

were treated with ACE-I versus ACE-I and carvedilol revealed a beneficial effect of beta-blocker therapy in increasing left ventricular shortening and decreasing left ventricular end-diastolic dimensions, as shown by echocardiography [89]. In contrast, a recent study by Viollet et al. tested ACE inhibitor alone versus ACE inhibitor and metoprolol, but in this study, low-dose beta-blocker was added only for heart rates above 100 bpm or if arrhythmias occurred [90]. The results of this study showed an improvement from pretreatment LVEF in both groups, but no difference between the treatment groups. Further research with larger groups of patients and more robust trial designs are needed to definitively address the use of beta-blockers in DMD. Based on current ACC/American Heart Association/Heart Failure Society of America guidelines, we recommend that beta-blockers be initiated in DMD patients with left ventricular dysfunction [91].

Spironolactone, an aldosterone inhibitor, is a standard heart failure therapy and has also been demonstrated in the mouse model to improve cardiomyopathy [92]. In a recently completed randomized double-blinded clinic trial, eplerenone, an aldosterone receptor antagonist versus placebo, was added to the background therapy of ACE inhibitors or ARBs in DMD patients with normal LV function to assess the efficacy of eplerenone in preventing cardiomyopathy in DMD.

Twenty patients were randomized to eplerenone and 20 to placebo. They were followed for 6 and 12 months using cardiac MRI. The primary endpoint at 12 months was change in left ventricular circumferential strain, which is a marker of contractility. At 12 months, the decline in LV circumferential strain was lower in the group treated with eplerenone than the placebo group, although there was no overall change in left ventricular function in either group [93]. This study, while small, demonstrated attenuation of progressive left ventricular dysfunction that occurs in DMD. And while this study is positive, further studies to assess the impact of eplerenone in DMD survival are warranted.

Cardiac Transplantation and Left Ventricular Assist Devices

The gold standard for treating end-stage or advanced heart failure remains cardiac transplantation. When a patient has heart failure with multisystem organ involvement and is not expected to be able to rehabilitate after cardiac transplantation, a heart transplant is not advised. These contraindications have limited the applicability of heart transplants for patients with muscular dystrophy.

Rees et al. were the first to describe heart transplantation in patients with muscular dystrophies in a single German center [94]. Of the 582 transplants performed, three patients with DMD and one patient with BMD underwent cardiac transplantation, with a mean duration of follow-up of 40 months. They described that these patients tolerated immunosuppression, had no difference in postoperative intubation, and were able to be rehabilitated [94].

Ruiz-Cano et al. described a Spanish single-center experience with heart transplantation in three patients with BMD who underwent cardiac transplantation with a mean follow-up duration of 57 months. These investigators also demonstrated that BMD patients had an intraoperative and postoperative course comparable to nonmuscular dystrophy patients undergoing heart transplantation [95].

Patane et al. described a single case of successful transplantation in a patient with cardiomyopathy secondary to BMD [96]. We performed a more recent multicenter registry analysis of cardiac transplantation from the Cardiac Transplant Research Database and identified 29 patients with muscular dystrophies. Of those, 15 had BMD and three had DMD and underwent cardiac transplantation between 1995 and 2005. We compared them to 275 nonmuscular dystrophy, non-ischemic patients who were matched for age, body mass index, gender, and race [97] and found no significant difference in survival at 1 or 5 years, transplant rejection, infection, or allograft vasculopathy between the muscular dystrophy and nonmuscular dystrophy patients.

These studies described comparable outcomes of cardiac transplantation in a small and select group of patients with DMD and BMD with end-stage cardiomyopathy. However, the functional status of these patients prior to transplantation was not known, and these studies may have a selection bias. Further research regarding cardiac transplantation in patients with DMD and BMD with end-stage cardiomyopathy is needed.

Given the scarcity of organs for heart transplantation, left ventricular assist devices (LVADs) have been proven effective in treating patients with end-stage or advanced heart failure as well. These devices are also applicable to a larger population, including those with muscular dystrophies, as they can be used as destination therapy without the need for transplantation [98, 99].

Two groups recently reported cases of successful implantation of LVADs as destination therapy in DMD patients [100, 101]. Amedeo et al. were the first to describe LVAD implantation in two pediatric DMD patients [100]. These investigators implanted the Jarvik 2000 LVAD in a 15-year-old boy with DMD who had inotrope refractory heart failure and in a 14-year-old boy with DMD who was bridged from extracorporeal membrane oxygenation to a Jarvik 2000 LVAD. The first patient was discharged 3 months after LVAD implantation and the second patient 6 months after LVAD implantation.

Ryan et al. subsequently described the HeartMate II LVAD implantation in a 29-year-old male patient with DMD and end-stage heart failure and a HeartWare LVAD implantation in a 23-year-old female symptomatic DMD carrier with end-stage heart failure [101].

LVAD as destination therapy is a potentially promising therapy to address end-stage heart failure in patients with dystrophin-deficient heart failure. However, postoperative complications including respiratory failure, rehabilitation, bleeding, stroke, and arrhythmias need to be evaluated further in this population. Extensive preoperative and postop-

erative management in an experienced center would be necessary for LVAD implantation in the DMD population. Larger studies are needed to evaluate the efficacy and outcomes in this population.

Becker Muscular Dystrophy and Cardiomyopathy

In 1955, German physicians Becker and Kiener described an X-linked muscular dystrophy with a much milder clinical course than DMD, which is now known as Becker muscular dystrophy [102, 103]. In 1984, the gene responsible for BMD was located on the X chromosome [104] and, subsequently, that mutations in the *DMD* gene resulted in BMD [105]. BMD has an incidence of 1:19,000 and is an X-linked recessive disorder resulting from a mutation of the dystrophin gene [106]. Compared to patients with DMD, who have a complete absence of dystrophin, dystrophin mutations in BMD tend to be in-frame and result in misfolded or abnormal and less-functional protein [107].

Patients with BMD have an age of onset that is typically later than those with DMD [108] (Table 12.1). While the muscular symptoms may be less severe, over 70 % of patients with BMD also develop cardiomyopathy [109, 110], and it is the leading cause of death in BMD patients [51].

Cardiomyopathy may be more severe in BMD patients than in DMD patients. This could be due to BMD patients being ambulatory much longer, placing greater stress on the heart [111–113]. The onset of cardiomyopathy is variable in BMD and is not correlated to skeletal muscle involvement [109, 114].

Cardiac magnetic resonance studies have shown a similar inferobasal fibrotic pattern in BMD and DMD patients [115]. Patients with BMD cardiomyopathy should receive standard medical heart failure therapy [91]. Given that BMD patients have a relatively milder skeletal muscle phenotype, several of these patients have received heart transplantation for severe cardiomyopathy with good outcomes (see Transplant/LVAD section) [94–97].

Carrier Status and Cardiomyopathy

While DMD and BMD affect males—given that they are inherited in an X-linked recessive manner—females can be carriers. The majority of DMD and BMD are inherited; thus, a significant number of females are carriers of DMD and BMD. Most female carriers of DMD and BMD are asymptomatic; however, female carriers can become symptomatic or become manifesting carriers. Manifesting carriers can have symptoms such as mild muscle weakness, elevated serum creatinine kinase, and, also, cardiomyopathy [116, 117]. Hoogerwaard et al. evaluated 90 women who were carriers of dystrophin mutations and identified 22 % with symptoms including muscle weakness and 18 % with evidence of a dilated left ventricle [118]. The age of onset for carriers is variable and the percent of symptomatic carriers has ranged from 2.5 to 22 % in prior studies [120].

X inactivation is the process by which one of the two X chromosomes in female cells randomly becomes transcriptionally inactive. It is postulated that carriers can become symptomatic based on the extent of random X inactivation of the normal X chromosome versus the dystrophic X chromosome. While DMD and BMD carriers have been identified to have cardiomyopathy, the prevalence and severity of disease are incompletely defined [118, 121–123]. We recommend that all female dystrophinopathy carriers be screened for cardiomyopathy.

Models of Muscular Dystrophy

Animal models of DMD have played an important role in elucidating mechanisms of dystrophin deficiency. The dystrophin-deficient mdx mouse, dystrophin/utrophin double knockout mouse (U-dko), and the golden retriever muscular dystrophy (GRMD) models are the most studied models regarding cardiac phenotype (Fig. 12.8).

The mdx mice arise from a naturally occurring nonsense point mutation in exon 23 of the *DMD* gene. This mutation results in the formation of a stop codon and the absence of

Table 12.1 Duchenne vs. Becker muscular dystrophy

	DMD	BMD
Dystrophin protein	Absent	Partially functional
Incidence	1:5000 male births	1:50,000
Mean age at onset	3–5 years	12 years
Mean age of becoming non-ambulatory	~12 years	~27 years
Mean life expectancy	Mid- to late 20s	40s
Cardiomyopathy (onset)	16–18 years	Variable, and cardiomyopathy may precede skeletal symptoms

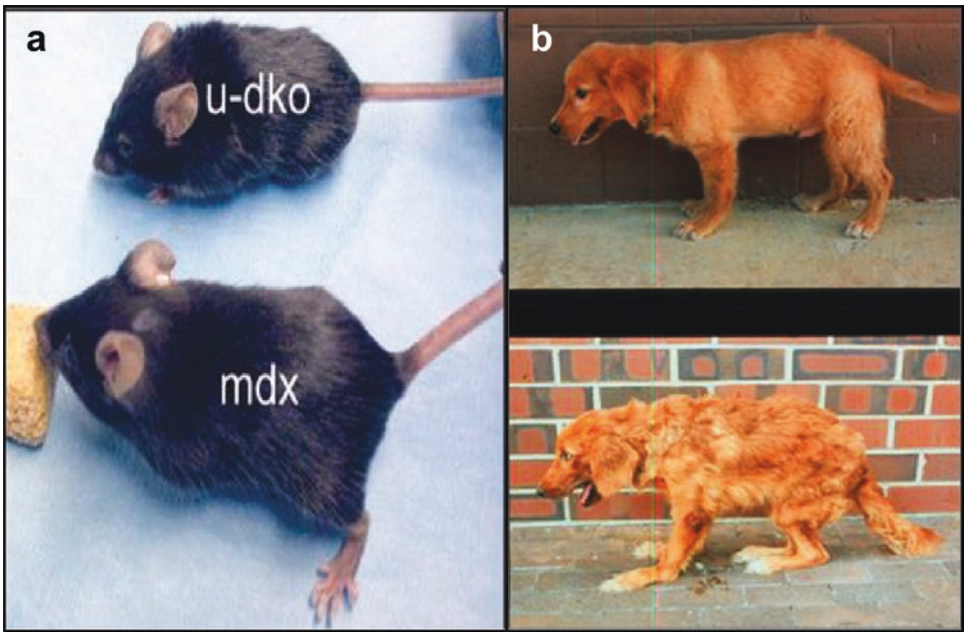

Fig. 12.8 Animal models for muscular dystrophy. (**a**) Mdx and utrophin/dystrophin double knockout mice demonstrating that age- and sex-matched U-dko mice are smaller than mdx mice. (**b**) Golden retriever muscular dystrophy dog model at 3 months (*top photo*) and at 6 months (*bottom photo*) demonstrating severe muscle loss with contractures (adapted from [124, 125])

full-length dystrophin [126, 127]. The skeletal muscle phenotype in these animals has been well characterized and is relatively mild. Young mice do not typically have any cardiac involvement, but after 10 months of age, they begin to develop signs of cardiomyopathy, including poor contractility, myocardial necrosis, and fibrosis, as well as echocardiographic and electrocardiographic changes [128, 129].

While a significant cardiomyopathy is not seen in younger mdx mice under normal conditions, various forms of stress, such as beta-adrenergic stress or pressure overload, demonstrate a cardiomyopathic phenotype [130–132]. Thus, the mdx mouse shares a similar genotype and some features of cardiomyopathy that are seen in patients with DMD. The mdx mice, however, do not develop cardiomyopathy until relatively late in comparison to patients, although the mdx mice have a mildly reduced lifespan compared to normal control mice [133].

In a recent study, Long et al. used the emerging technology of genome editing to genetically correct the dystrophin mutation in the mdx mouse [134]. The genome-edited mdx mice had between 2 and 100 % correction of the gene with this strategy. Mosaic mdx mice, with only 17 % correction of dystrophin by gene editing, had a nearly normal muscle phenotype [134].

Mdx/utrophin double knockout mouse model: Utrophin is an autosomal paralogue of dystrophin, which is upregulated in the mdx mouse [135]. The upregulation of utrophin in the mdx mouse likely compensates for the loss of dystrophin, thus producing a less severe phenotype. The utrophin and dystrophin double knockout mouse was generated to evaluate the impact of utrophin upregulation. Compared to the mdx mouse, the double knockout mouse model has a much more severe phenotype [136, 137]. Double knockout mice are smaller, with progressive muscle atrophy, and die prematurely at about 10 weeks of age. The double knockout mouse also develops a severe cardiomyopathy by 8 weeks, which is comparable to that of an aged mdx mouse [136]. The double knockout mouse may more closely represent human DMD.

Canine models: The canine model of dystrophin deficiency is a large animal model of DMD that more closely resembles human disease. The golden retriever muscular dystrophy (GRMD) dog model is one of the best-characterized dog models of DMD [138]. In 1988, Valentine et al. described a family of golden retrievers with male members affected by a severe neurodegenerative disorder with muscle weakness and gait abnormalities, and absence of dystrophin on muscle biopsy, which paralleled human DMD [138]. Subsequently, the mutation was identified to be a single mutation in the consensus splice site of intron 6, which leads to an out-of-frame mutation and absence of dystrophin during RNA processing [139].

GRMD dogs develop significant muscle weakness by 2 months of age with progressive weakness and also have a reduced lifespan [140]. GRMD dogs also develop a severe cardiomyopathy [141]. GRMD is a useful model to better understand DMD cardiomyopathy and test new therapies; however, the larger size of the GRMD dogs can increase maintenance costs and restrict their use [142]. GRMD colonies operate in the United States at the University of North Carolina at Chapel Hill and the Fred Hutchinson Cancer Center in Seattle. Other colonies exist in Brazil, France, Japan, and the Netherlands.

Human cell-based models: Animal models have been useful to evaluate the pathophysiology of DMD; however, they have limitations and do not fully recapitulate the disease phenotype observed in human patients. Obtaining human tissues, especially cardiomyocytes, is challenging and poses a risk to the patient. The advent of human inducible pluripotent stem cells (hiPSCs) in 2007 has been a major scientific development [143, 144].

hiPSCs represent a novel tool to study human genetic diseases though cellular reprogramming of patient-specific cells that retain the genetic composition and are pluripotent. hiPSCs have been used to study various cardiac diseases including hypertrophic cardiomyopathy and long QT syndrome [145, 146]. hiPSC disease modeling is a promising method to study DMD cardiomyopathy. Several hiPSC lines from patients with various mutations have been derived [147, 148]. We and other groups have successfully differentiated the DMD patient-specific hiPSC to cardiomyocytes. Modeling DMD cardiomyopathy using hiPSC is a promising method to elucidate the pathophysiology of DMD cardiomyopathy and test novel therapies [149].

Emerging Therapies

A major challenge for treating DMD is finding therapies that address dystrophin deficiency and that target both the cardiac and skeletal muscle. A number of promising emerging therapies include exon skipping, dystrophin mini-gene replacement, sealants, and gene-editing strategies.

Exon Skipping

DMD mutations are heterogeneous, but the majority of DMD arises from an out-of-frame deletion or duplication of one or several of the 79 exons within the *DMD* gene. These mutations affect the normal transcription of dystrophin mRNA open reading frame and, subsequently, prevent the full-length dystrophin protein from being transcribed. An exciting and novel therapy for the treatment of DMD involves exon skipping within the central rod domain. This can restore the normal mRNA reading frame and convert an out-of-frame mutation to a less severe, in-frame mutation, comparable to those seen in Becker muscular dystrophy. The exon-skipping process uses antisense oligonucleotides (AONs), which are short, synthetic fragments of nucleic acids.

The AONs bind RNA sequences that regulate RNA splicing, which enable a smaller but functional mRNA to be produced that lacks the exon mutation (Fig. 12.9). This strategy may be effective in 80 % of DMD mutations [150]. AONs for exon skipping target exon 51 of the *DMD* gene, which accounts for ~13 % of DMD mutations, including drisapersen (GSK-2402698, GlaxoSmithKline and Prosensa) and eteplirsen (AVI 4658, Sarepta Therapeutics), which are currently in clinical trials. These AONs have been tested in the mdx mouse and canine models. Intramuscular injections were found to be safe and restored dystrophin expression without significant side effects [151–155].

The initial phase I and II trials for both eteplirsen and drisapersen were promising in restoring dystrophin expression, but did not demonstrate a significant change in the primary endpoint of the 6-min walk test. Major side effects included renal toxicity with drisapersen and thrombocytopenia at high doses [156, 157]. These drugs are in ongoing phase III clinical trials.

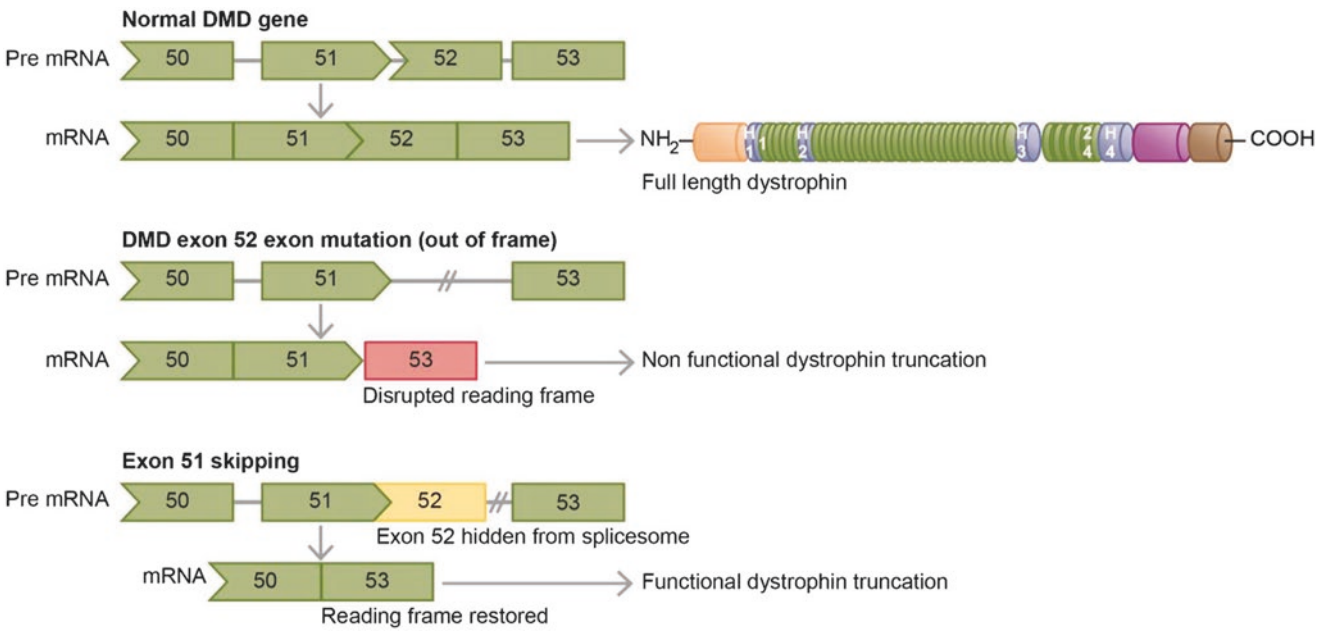

Fig. 12.9 Schematic of exon skipping. Dystrophin exons are spliced to form mature messenger RNA (mRNA), which results in the translation of a full-length, functional dystrophin protein. However, in classic mutations, such as in exon 52, this results in skipping of exon 52 during splicing. This leads to a disrupted reading frame that produces a truncated, nonfunctional dystrophin protein. Introduction of antisense oligonucleotide that skips exon 51 restores the reading frame and produces a truncated but functional dystrophin protein

Dystrophin Mini-gene Replacement

Given that dystrophin mutations lead to the complete absence of the functional dystrophin protein in DMD, one strategy to mitigate the disease sequelae is gene replacement therapy using recombinant adenoviral virus vectors (rAAVs). Compared to the exon-skipping strategy, currently available only for exon 51 skipping, gene replacement strategies can be beneficial for all patients with DMD regardless of their DMD mutation.

One limitation of the rAAV technology is the inability to deliver the large full-length dystrophin gene due to the limitations of packaging. The 2.4-Mb dystrophin gene is the largest single gene in the human genome, and as a result, cloning the 14-kb cDNA is challenging to introduce into delivery vectors [10, 158]. However, observing mildly affected BMD patients with very large dystrophin gene deletions led to the understanding that truncated dystrophins could be functional [105, 159]. This, in turn, led to the development of micro- or mini-dystrophins, which contain only the essential regions of the gene. They are functional and can be packaged within the rAAV [160] (Fig. 12.10).

rAAV6 vectors containing microdystrophin have been administered to dystrophin-deficient mice and demonstrated restoration of dystrophin, improved muscular function, and increased lifespan [161–164]. Dystrophin gene replacement therapy has been effective in mouse models, but in large animal models such as those using dogs and nonhuman primates, gene therapy efficacy has been limited due to the host immune response [165–170].

In a human preclinical trial of rAAV-mediated minidystrophin gene transfer, six DMD patients received intramuscular injections in the biceps brachii muscle. None of the patients demonstrated significant levels of dystrophin and one patient had a microdystrophin T-cell response within 15 days of injection [168, 169]. In addition to the T-cell-mediated response, humoral or antibody-mediated immune responses are also observed in large animal models of rAAV dystrophin delivery [171]. Dystrophic muscles have two features that promote the induction of an immune response, including cellular contents exposed to the environment due to muscle necrosis along with elevated immune effector cells [172–174].

Regarding cardiac gene transfer, delivery has been achieved through transendocardial injection of rAAV vectors in a nonhuman primate model where rAAV6 was more effective than rAAV 8 or 9 [175]. rAAV8 delivery via the internal jugular vein also demonstrated target gene expression after 2.5 months of infusion [176]. Although limited by immune side effects that may be overcome by immunosuppressant regimens, gene replacement therapy remains a promising therapy for DMD, including the associated cardiomyopathy.

Sealants

Dystrophin deficiency can lead to increased membrane fragility and is exacerbated by any mechanical stress. Yasuda et al. demonstrated that isolated dystrophin-deficient cardiomyocytes, when stretched, have reduced compliance and increased susceptibility to calcium overload [130]. Thus, increased membrane stability is a potential pathway to modify the disease sequelae related to membrane fragility seen in DMD patients.

Poloxamer 188 (P-188) is a triblock copolymer that is able to insert into damaged lipid bilayers and repair membranes. It has been used to stabilize red blood cell membranes in sickle cell disease [177]. This concept of membrane stabilization repair was applied to the mdx mouse receiving adrenergic stimulation with either dobutamine or isoproterenol as a stressor, and administration of P-188, which demonstrated improved left ventricular function and increased survival [130, 178].

The use of P-188 as a cardioprotective agent was also tested in the more severely affected golden retriever muscular

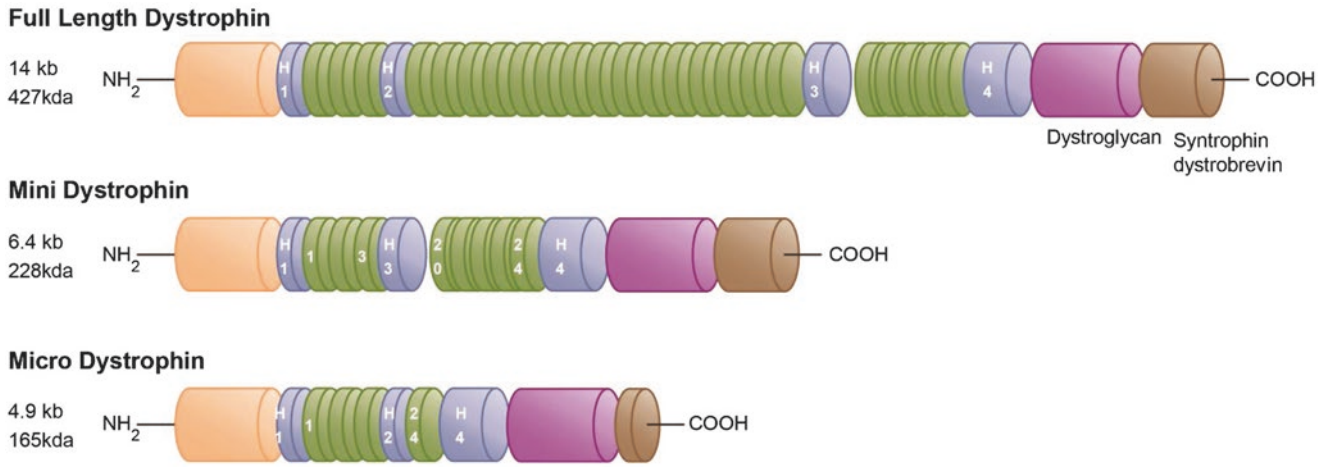

Fig. 12.10 Full-length dystrophin, mini- and micro-dystrophin constructs. Full-length dystrophin has a 14-kb cDNA, which results in a 427-kDa protein. Full-length dystrophin has an N-terminal actin-binding domain, a rod domain with 24 spectrin-like repeats and four hinge domains, and a C-terminal region that has dystroglycan, syntrophin, and dystrobrevin-binding domains. Examples of a mini- and a micro-dystrophin with rod domain deletions that are able to be cloned into recombinant adeno-associated viral vectors

dystrophy model where the dogs received an 8-week infusion of P-188. This infusion resulted in decreased fibrosis and prevention of left ventricular dilatation [142].

While P-188 has been shown to be cardioprotective in animal models, the daily doses may be a limitation. Furthermore, the sealant (P-188) does not address the absence of dystrophin. Additionally, the impact on the skeletal muscle has not been well described.

In one recent study, mdx mice given either a one-time or daily P-188 injection had a decline in skeletal muscle force generation [179]. While cardiac benefits in animal models have been demonstrated, further testing of P-188 on both the skeletal and cardiac function is needed.

Gene Editing

A new promising technology for DMD is gene editing. Gene editing can be mediated with CRISPR (clustered regularly interspaced short palindromic repeat)/CRISPR-associated systems (Cas) to alter the genome [180–182]. The CRISPR/Cas9 system binds to the target gene and generates a double-strand DNA break. It can then be replaced by the corrected gene sequence (Fig. 12.11). This system precisely removes the mutated gene of interest and replaces it with a functional copy of the gene.

Correction of DMD using gene editing targeted to exon 51 of dystrophin has been used to restore the dystrophin gene reading frame in DMD patient myoblasts [183]. The restored dystrophin reading frame enabled restoration of functional dystrophin expression in the DMD patient myoblasts [183]. In a recent study, gene editing using a CRISPR/Cas9 strategy was used in vivo to correct the *DMD* gene mutation in the germ line of mdx mice [134]. In the genome-edited animals, between 2 and 100 % of *DMD* gene correction was observed. In mosaic mdx mice with only 17 % correction of dystrophin by gene editing, a normal muscle phenotype was observed. This nascent technology has possible therapeutic benefits in patients with DMD. Further animal studies evaluating the cardiac function are needed.

Cell-based therapy is also another potential way to treat dystrophin deficiency. Therapeutic cells can be obtained from a donor bearing normal dystrophin or from the DMD patient, corrected ex vivo, reimplanted, and injected into the DMD patient. Skeletal muscle stem cells are known as satellite cells. They have been shown to respond to muscle injury by proliferating and restoring the muscle architecture [184]. Satellite cells are also easy to isolate and culture in vitro. Thus normal myoblast injections were first tested in mdx mice showing dystrophin-positive muscle cells [185, 186].

However, subsequent human clinical trials with myoblast transplantation have demonstrated only up to 10 % dystrophin-positive fibers [187–189]. Given the challenges with myoblast engraftment, survival, and migration, other cell types that have myogenic potential—including bone marrow-derived stem cells and CD133+ muscle stem cells—have been tested in DMD patients [190, 191]. However, further testing is required for these therapies. Vessel-derived stem cells have been used to treat mdx double knockout mice to prevent cardiomyopathy, but no human stem cell trials have been conducted to assess the efficacy of any stem cell therapies in DMD cardiomyopathy [192].

Myotonic Dystrophy

Myotonic dystrophies are among the most common inherited, adult-onset, muscular dystrophies that have multisystem impact. Myotonic dystrophies are characterized by myotonia or a delay in relaxation of muscle contraction. Myotonic dystrophy leads to skeletal muscle weakness and muscle wasting and, in end-stage disease, respiratory muscle

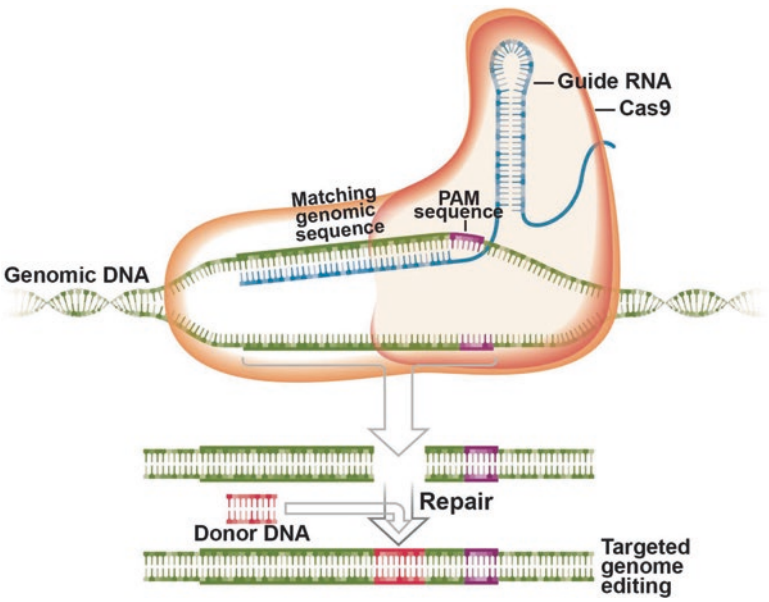

Fig. 12.11 A schematic of CRISPR/Cas9-mediated genome editing. Guide RNA is fused with the DNA sequence targeting the host gene of interest. The guide RNA recognizes specific regions on the host RNA and complexes with Cas9, which recognizes the PAM sequence on the target and exerts its endonuclease function to cause double-stranded breaks in the DNA. This triggers repair mechanisms, which enable the donor DNA to be inserted at the break site, and results in targeted genome editing

Table 12.2 Myotonic dystrophy type 1 vs. myotonic dystrophy type 2

	Myotonic dystrophy type 1	Myotonic dystrophy type 2
Gene	DMPK	ZNF9
Repeat	CTG	CCTG
Inheritance	Autosomal dominant	Autosomal dominant
Incidence	1:8000	13:100,000
Age of onset	20–40 years, also congenital and juvenile onset	30–60 years
Anticipation	Yes	Less
Cardiac involvement	Yes	Variable

weakness. Patients also have endocrine abnormalities that commonly include hypogonadism and insulin resistance. The gastrointestinal system is also impacted and dysphagia, reflux, and hypermotility are often noted. Central nervous system and ocular manifestations include cataracts, cognitive impairment, and hypersomnolence. Cardiac consequences of myotonic dystrophy are also prominent, and predominantly involve conduction abnormalities and arrhythmias, although cardiomyopathy is being increasingly identified [193].

In 1909, German physician Hans Steinert and English physicians Frederick Batten and H. P. Gibb described for the first time a muscular dystrophy that was characterized by myotonia, or involuntary muscle contraction and delayed relaxation, and muscle weakness [194, 195]. This disorder was initially called Steinert disease and, later, myotonic dystrophy.

In 1911, Griffith described a patient with myotonic dystrophy who had bradycardia with a heart rate of 30 bpm, and subsequently, other early clinical reports of cardiovascular abnormalities in muscular dystrophy were reported [196, 197]. Nearly 80 years later, the gene responsible for myotonic dystrophy was identified [198]. However, in 1994, a group of patients who had clinical features similar to what is now classified as myotonic dystrophy type 1, but without the gene mutation, were described [199, 200]. This was later classified as myotonic dystrophy type 2. The gene responsible for the pathogenesis was identified in 2001 [201]. The two genetically defined subtypes of myotonic dystrophies are myotonic dystrophy type 1 and myotonic dystrophy type 2 (Table 12.2).

Myotonic Dystrophy Type 1

Myotonic dystrophy type 1 is also known as Steinert disease and has an incidence of 1:8000 [202]. Myotonic dystrophy type 1 is the most common adult form of muscular dystrophy. It is further subdivided into three subtypes based on age of onset and severity.

Congenital DM1 typically occurs before the first year of life and is the most severe. It occurs primarily due to maternal transmission. Classical myotonic dystrophy type 1 is divided into childhood or adult onset. Adult-onset disease typically manifests in the second through fourth decades [203]. Myotonic dystrophy type 1 is caused by autosomal dominant inheritance of an abnormal expansion of a cytosine-thymine-guanine (CTG) trinucleotide repeat in the DMPK gene in chromosome 19 encoding for the protein dystrophia myotonica protein kinase [204]. The DM protein kinase is expressed in skeletal, cardiac, and smooth muscle cells. Normally, less than 37 CTG repeats exist, but in patients with myotonic dystrophy type 1, more than 50 to thousands of repeats may exist.

A direct correlation exists between an increasing number of CTG repeats and the age of onset and severity of neuromuscular and cardiac disease in myotonic dystrophy type 1. CTG repeats typically expand as it is passed from parents to offspring, resulting in a more severe disease phenotype in a process known as genetic anticipation.

Myotonic Dystrophy Type 2

Myotonic dystrophy type 2 is less common, with an incidence of 13:100,000 people. It has a similar autosomal inheritance pattern as myotonic dystrophy type 1, but type 2 is a result of a tetranucleotide CCGT repeat in the gene ZNF9 gene on chromosome 3 coding for zinc finger protein 9 [205]. The CCGT repeats in myotonic dystrophy type 2 are typically in the thousands. Myotonic dystrophy type 2 is typically adult onset and is less severe than myotonic dystrophy type 1.

Pathogenesis

In both myotonic dystrophies, the underlying molecular mechanism is similar. The gene including the abnormal repeat is transcribed into RNA, but not translated. The abnormal RNA accumulates in the nucleus and disrupts splicing of pre-messenger RNA into mature RNA through affecting RNA-binding proteins [206]. This process subsequently results in abnormal function of different genes including chloride channels needed for muscle function, cardiac troponin, and insulin receptors [207].

Myotonic dystrophy type 1 typically presents with muscle weakness and myotonia of the distal muscles. Patients may have a characteristic long face, male pattern baldness, and atrophy of the facial and jaw muscles. Myotonic dystrophy type 2 also manifests with myotonia and weakness, as well as the other systemic sequelae but at a later age and with less severity.

Cardiac involvement in these patients involves fibrosis and degeneration—typically affecting the conduction system as well as the myocardial tissue—leading to arrhythmias and cardiomyopathy. Conduction abnormalities occur in 75–80 % of myotonic dystrophy type 1 patients with more than 65 % of patients having abnormal ECGs [208]. Atrial and ventricular

arrhythmias are also common and affect 25% of patients with myotonic dystrophy. The conduction abnormalities and arrhythmias can cause sudden cardiac death, which accounts for more than one-third of deaths in these patients.

In a study of myotonic dystrophy type 1 patients, a correlation between CTG length and presence of arrhythmias and conduction abnormalities was noted [209]. Patients with myotonic dystrophy are also more likely to develop cardiomyopathies, with 20% of patients with myotonic dystrophy type 1 demonstrating left ventricular dilatation and 14% of patients with left ventricular dysfunction [210, 211]. In patients who have left ventricular dysfunction, medical therapy including ACE inhibitors and beta-blockers should be used. These therapies are standard for systolic dysfunction, and while they have not been tested in myotonic patients, the reverse left ventricular remodeling and survival benefit have been extrapolated to this population as well.

Mexiletine, a class Ib antiarrhythmic agent and a sodium channel blocker, is being used more commonly in myotonic patients for treatment of myotonia without increasing QRS duration or changing cardiac conduction [212]. AV nodal blocking agents for the treatment of arrhythmias should be used cautiously, given the bradyarrhythmias and conduction blocks seen in these patients.

Pacemaker and implantable cardioverter-defibrillator (ICD) therapy guidelines have specifically included the myotonic dystrophy population. Permanent pacemaker implantation is a class IIa indication in myotonic patients with an HV interval >100 ms and class IIb indication for any degrees of atrioventricular (AV) block regardless of symptoms [213]. ICDs are indicated in myotonic patients with ventricular tachycardia, and a wider indication may exist in this patient population [214].

Cardiac Involvement in Other Muscular Dystrophies

While patients with DMD, BMD, and myotonic dystrophy type 1 and type 2 have a known high incidence of cardiovascular involvement, many other muscular dystrophies including certain limb-girdle muscular dystrophies have known cardiac involvement. Facioscapulohumeral muscular dystrophies and other similar muscular dystrophies have unknown cardiac involvement. Table 12.3 summarizes the major inherited muscular dystrophies and cardiac involvement. Cardiac screening in patients with inherited muscular dystrophies is warranted, as many

12

Table 12.3 Cardiac involvement in muscular dystrophies

Muscular dystrophy	Inheritance	Gene	Protein	Cardiac involvement
Duchenne muscular dystrophy	XR	Xp21	Dystrophin	Yes
Becker muscular dystrophy	XR	Xp21	Dystrophin	Yes
Dystrophin mutation carriers	XR	Xp21	Dystrophin	Yes
Myotonic dystrophy type 1	AD	19q13	DMPK	Yes
Myotonic dystrophy type 2	AD	3q21	ZNF9	Yes
Emery-Dreifuss		Xq28	Emerin	Yes
Facioscapulohumeral	AD	4q35	Unknown	Unknown
LGMD1A	AD	5q31	Myotilin	Unknown
LGMD1B	AD	1q22	Lamin A/C	Yes
LGMD1C	AR	3p25	Caveolin-3	Unknown
LGMD2A	AR	15q15	Calpain-3	Yes
LGMD2B	AR	2p13	Dysferlin	Unknown
LGMD2C	AR	13q12	y-Sarcoglycan	Unknown
LGMD2D	AR	17q12	a-Sarcoglycan	Unknown
LGMD2E	AR	4q12	b-Sarcoglycan	Yes
LGMD2F	AR	5q33	d-Sarcoglycan	Unknown
LGMD2G	AR	17q11	Telethonin	Unknown
LGMD2H	AR	9q33	TRIM32	Unknown
LGMD2I	AR	19q	FKRP	Yes
LGMD2L	AR	11p12-p15	Anoctamin 5	Unknown

muscular dystrophies do have a high incidence of cardiac involvement, and in others, cardiac involvement is less well known.

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Heart Failure with Preserved Ejection Fraction (HFpEF)

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_13

Definition

Heart failure is a syndrome and not a disease. It has multiple causes and multiple phenotypes. It is never a "stand-alone" diagnosis. One of the two major phenotypes of heart failure is HFpEF. It also is not a stand-alone diagnosis, but rather a syndrome that manifests itself in several phenotypes.

HFpEF has been classically defined as a form of heart failure with a normal or small left ventricular internal dimension in diastole, typically measured by echocardiography [4–7]. Sometimes, but not always, there is an increase in the left ventricular wall thickness. Designating a name for this condition has been the subject of some debate [8]. In 1937, Fishberg described a form of cardiac insufficiency resulting from inadequate filling of the heart, which he termed "hypodiastolic failure" [9]. Over the ensuing years, particularly during the early cardiac catheterization era, the term "diastolic heart failure" became the preferred nomenclature [10].

This form of heart failure was largely referred to as diastolic heart failure for many years and was diagnosed primarily in the cardiac catheterization laboratory as a manifestation of alteration in the pressure-volume relationship of the LV. Diastolic heart failure is characterized by a disproportionate increase in LV pressure related to volume. Under normal conditions, any increase in volume is accompanied by an abrupt increase in left ventricular end-diastolic pressure (LVEDP) (Fig. 13.1) [11].

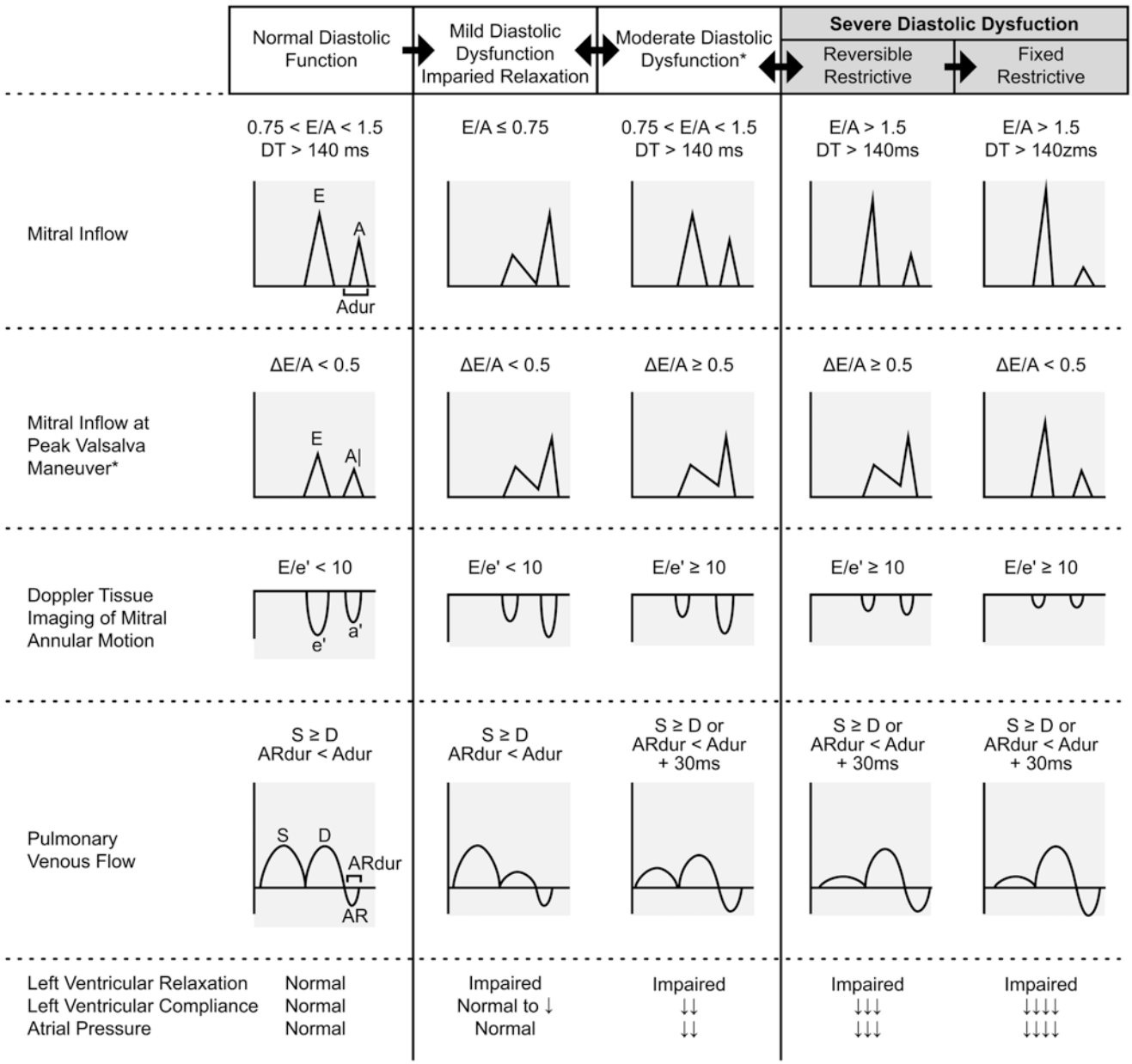

Fig. 13.1 Left ventricular pressure-volume loops in systolic and diastolic dysfunction (Adapted with permission from: Aurigemma GP, Gaasch WH. Clinical practice. Diastolic heart failure. N Engl J Med. 2004;351(11):1097–105)

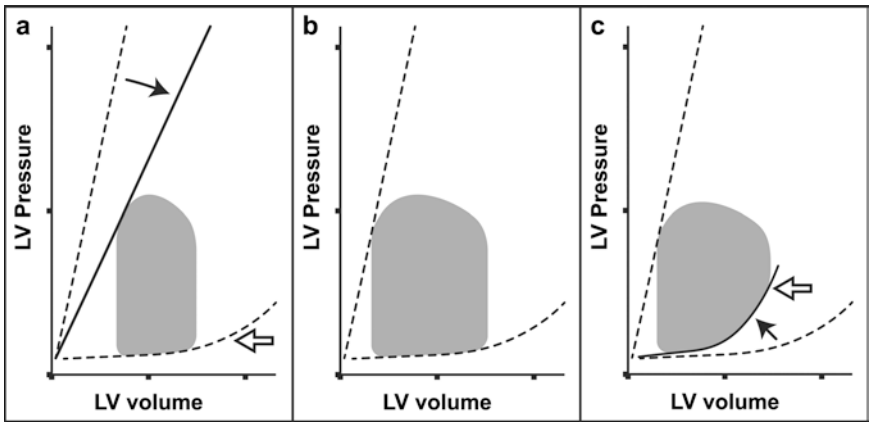

Fig. 13.2 (**a**–**c**) Doppler criteria for classification of HFpEF (Adapted with permission from: Redfield MM, Jacobsen SJ, Burnett JC, Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003;289(2):194–202)

However, problems with this terminology emerged during the early use of echocardiography. Some patients with presumed diastolic heart failure failed to manifest clear-cut echocardiographic evidence of impaired left ventricular (LV) filling. The situation became even more complex as clinicians began to realize that many, if not all, patients with systolic heart failure also manifest some echocardiographic features of impaired LV filling. Some patients were described as having classic diastolic heart failure in the absence of echocardiographic evidence of impaired LV filling. In fact, the most consistent echocardiographic finding of patients with HFpEF is an enlarged left atrium.

The typical place for diagnosing diastolic heart failure is no longer the cardiac catheterization laboratory. Echocardiography is now widely used to verify the diagnosis of heart failure, typically dividing it into HFpEF and HFrEF, depending on the clinical and echocardiographic findings. Numerous echocardiographic features help define impaired LV filling and diastolic heart failure (Fig. 13.2) [12–17]. However, none of these features are always present in every patient with HFpEF, and none are entirely reliable with regard to predicting an elevated LVEDP [18–20].

Although some investigators prefer the term heart failure with normal ejection fraction (HFnEF) [8], the term HFpEF has more recently become widely used in the American literature. Most contemporary studies indicate that patients with HFpEF typically have a normal-sized or even small left ventricle internal chamber dimension in diastole [3]. Left ventricular concentric hypertrophy is commonly present, but in some cases, the hypertrophy is eccentric, and other patients do not manifest left ventricular hypertrophy (LVH) at all.

Left atrial enlargement is very common in patients with HFpEF and is perhaps the first echocardiographic sign to herald the subsequent HFpEF. It often precedes the development of atrial fibrillation which is also common in HFpEF. Typically, the LV ejection fraction in patients with HFpEF is 50 % or greater, although some studies have defined it as 40 % or greater. Grade II or III diastolic dysfunction is usually observed by echocardiography, but this is highly variable and not evident in every case.

Invasive LV pressure monitoring in HFpEF indicates increased left ventricular end-diastolic filling pressure and a shift in pressure-volume relationship (Fig. 13.1). That is, the left ventricular end-diastolic pressure (LVEDP) is higher relative to the LV end-diastolic volume. This change in the relationship between LV pressure and volume is highly characteristic of an increase in LV chamber stiffness (referred to as k, an engineering term for chamber stiffness).

The LV in patients with HFpEF is clearly less distensible, thus allowing for an increase in the LVEDP, despite only a small increase in end-diastolic volume. Not only is the increase in chamber stiffness at the level of the left ventricle but evidence also indicates that the cardiac myocytes themselves are thickened and stiffer and have increased microtubular density. These changes at the cardiomyocyte level may render the cell stiffer. Moreover, increased collagen content is well known to occur in the hypertrophied left ventricle, and this undoubtedly also contributes to the increased chamber stiffness [21].

Classically, patients with HFpEF manifest early exercise intolerance, chronotropic incompetence, micro-endothelial dysfunction, and an inability to increase LV ejection fraction in response to inotropic stimuli such as exercise or dobutamine [1, 22, 23]. In essence, patients with HFpEF show reduced cardiovascular inotropic and chronotropic reserve and an inability to dilate the peripheral microvasculature in response to exercise. Because LVEDP tends to increase in these patients at rest and rises further with exercise, the left atrium (LA) may remodel and increase in size prior to clinical manifestations of heart failure. Atrial fibrillation and flutter are common comorbid conditions in patients with HFpEF and likely further impair diastolic filling, sometimes leading to signs and symptoms of acute heart failure and the need for hospitalization.

Patients with HFpEF manifest LVH, LA enlargement, and diastolic dysfunction. In many cases, LV mass is also increased. The increase in LA size is independently associated with increased morbidity and mortality in patients with HFpEF [24].

Some cardiology thought leaders believe that systolic and diastolic heart failures are different phenotypes of the same syndrome [25, 26]. It is possible that HFpEF and HFrEF are merely extremes in the spectrum of overlapping phenotypes,

and therefore, neither LV ejection fraction nor LV cavity dimensions can capture the wide variety of remodeling that goes on during the progression of heart failure. Many investigators, however, consider HFpEF and HFrEF as distinct phenotypes within the heart failure spectrum and that these two phenotypes have different responses to therapy. The latter view is currently most widely held. Others believe there is no intrinsic diastolic property that can explain the occurrence of heart failure with normal EF [27].

Despite this lack of complete agreement regarding the definition of HFpEF, nearly all cardiologists recognize it clinically as a particular type of heart failure that is increasing in incidence and that it is relatively resistant to conventional neurohumoral blocking therapy such as renin-angiotensin-aldosterone inhibitors and beta-adrenergic inhibitors.

It is likely that HFpEF consists of multiple subgroups expressing distinctly different phenotypes and underlying pathophysiologies [6, 28]. This highly variable syndrome and its many clinical varieties are perhaps what lead to confusion about its definition. It is not a single phenotype but has great heterogeneity within itself. These different phenotypes may respond differentially to various therapies [28].

Epidemiology and Comorbid Conditions

In 2010, 1 in 9 deaths in the United States were related to heart failure. About 5.1 million Americans above the age of 20 years have heart failure [29]. Heart failure accounts for 35 % of cardiovascular disease deaths. The prevalence of heart failure will increase by 46 % from 2012 to 2030, resulting in more than eight million people above the age of 18 years with heart failure. Probably more than half of these cases will be patients with HFpEF. It is widely believed that the prevalence of HFpEF is increasing with the aging population [17, 30, 31].

It is also widely agreed that HFpEF is more common in women than in men. The incidence of HFpEF is 6.6 % in women age 65–69 years old and is increased to 14 % in women over 85 years. Risk factors for the development for HFpEF include older age, female gender, hypertension, obesity, obstructive sleep apnea, diabetes, coronary artery disease, and being African American [17, 30]. Normal aging is associated with an increase in LV stiffness, even when blood pressure is controlled and LV mass is reduced [32]. Some experts believe that HFpEF is simply the result of the aging process, so it may not be amenable to conventional heart failure therapy. The overall prevalence of LV diastolic dysfunction as measured by echo in a random sample of the general population is as high as 27.3 % [33]. The so-called preclinical diastolic dysfunction clearly can progress to symptomatic HFpEF and may eventually become a target for therapeutic intervention [34]. About 40 % of all hospital admissions for heart failure are for patients with HFpEF [35]. In one report from 2005 to 2010, the proportion of hospitalizations for HFpEF increased from 33 to 39 % [35]. Two-thirds of patients with HFpEF will develop atrial fibrillation, which greatly complicates the syndrome and leads to frequent hospitalizations [36]. In one report, about 70 % of patients with HFpEF had angiographically proven coronary artery disease (CAD) [37]. Therefore, CAD is common in patients with HFpEF and is associated with an increase in mortality and some deterioration in LV function [37]. Although the prevalence of concomitant CAD may be 70 %, only about 40 % of patients with HFpEF have angina pectoris [37, 38]. Revascularization of patients with HFpEF and coronary artery disease (CAD) appears to improve survival, at least in one observational study [37]. With this information, one needs to consider the use of diagnostic coronary angiography in patients with HFpEF, even though many of these patients are elderly, frail, and poor candidates for diagnostic coronary angiography.

Diabetes mellitus occurs in about 40 % of patients with heart failure. It is common in patients with HFpEF and tends to occur in younger, more obese patients. Patients with HFpEF and diabetes mellitus are more often males and tend to have concomitant hypertension, renal dysfunction, pulmonary disease, and peripheral vascular disease [39]. Patients with diabetes also have more LVH and higher LVEDP than patients with HFpEF and no diabetes. Patients with HFpEF and diabetes have less exercise capacity compared to those who have no diabetes and are also more likely to be hospitalized.

It now seems clear that HFpEF is a syndrome with various phenotypes and is far from being a single clinical entity. It has different etiologies and presents as different subtypes with a wide spectrum of signs and symptoms. Some patients go on to develop pulmonary hypertension and some do not. Some develop symptomatic angina, and some do not. Some manifest concentric LV remodeling, while others do not. Patients appear to progress back and forth across the spectrum, making it unlikely that a single form of therapy will ever emerge as uniformly effective.

The mode of death in patients with HFpEF is cardiovascular in about 60 % of cases, with sudden death and heart failure death being most common [40]. This percentage of cardiovascular death (60 %) is less than what is typically reported in patients with HFrEF. This observation is in keeping with the notion that patients with HFpEF are older and have more non-cardiovascular (non-CV) deaths. The large number of non-CV deaths in patients with HFpEF is likely due to cancer and other maladies of old age. Performing an adequately powered randomized controlled trial of therapy for patients with HFpEF using CV death as an end point would require an unrealistic, large sample size. This may partly explain why clinical trials in HFpEF have failed to uncover successful therapy. It is possible that the lower rate of CV death in the HFpEF population in therapeutic trials to date has largely led to treatment neutrality. Because CV end points are less common in this population of patients, most trials of HFpEF therapy to date likely have been underpowered (Table 13.1).

Table 13.1 Key randomized controlled trials of HFpEF

Trial	Year	*N*	Ejection fraction	Primary outcome hazard ratio (95% confidence interval)	Comments
CHARM-PRESERVED Candesartan vs. placebo	2003	3023	>40%	Composite of CV death and HF hospitalization 0.86 (0.74–1.0); $P=0.051$	Significant reduction in HF hospitalization
PEP-CHF Perindopril vs. placebo	2006	850	Wall motion index of <1.4 equivalent to EF 40%	All-cause mortality or unplanned HF hospitalization 0.69 (0.47–1.01); $P=0.055$ at 12 months	Post hoc analysis showed a trend toward benefit with perindopril at 12 months
I-PRESERVE Irbesartan vs. placebo	2008	4128	>45%	All-cause mortality or hospitalization for CV cause 0.95 (0.86–1.05); $P=0.35$	None
TOPCAT Spironolactone vs. placebo	2014	3445	>45%	Composite of death from CV causes, aborted arrest, or hospitalization for HF 0.89 (0.77–1.04); $P=0.14$	Overall, the trial was considered neutral. However, patients treated in the United States did appear to benefit from this therapy. There appears to be international variation in the response to this therapy

Pathophysiology

General Concepts

HFpEF is no longer considered a single, unitary, pathophysiologic entity that will simply respond to therapies designed to improve increased LV filling pressures [41]. Rather, new paradigms are emerging for treating HFpEF that incorporate a myriad of mechanisms including coronary microvascular inflammation, reduced nitric oxide availability, reduced cyclic guanosine monophosphate (cGMP), reduced protein kinase G, and increased myocyte hypertrophy [42]. The hope is that uncovering new mechanisms will lead to improved therapies for patients with HFpEF. To date, we do not have an effective specific therapy for HFpEF, and the treatment still largely consists of diuretics and management of comorbidities. However, new molecules to treat HFpEF are under consideration and in early stages of clinical trials.

Patients with HFpEF are often elderly women who manifest hypertension, diabetes, and coronary artery disease. However, multiple phenotypes are possible and may include such comorbidities as disproportionate pulmonary hypertension, tricuspid regurgitation, right heart failure, and infiltrative/restrictive cardiomyopathy. It may be because of the wide spectrum of phenotypes that no therapy to date has proven uniformly effective for all patients with HFpEF [6].

13

Geometric Changes in Chamber Size and Wall Thickness

HFpEF is typically associated with significant LV remodeling that affects the LV and LA chambers, the cardiomyocytes, and the extracellular matrix. When pulmonary hypertension is present, the RV may hypertrophy and dilate, and tricuspid insufficiency may eventually ensue. LV remodeling is associated with normal or decreased LV end-diastolic volume, concentric chamber hypertrophy, increased wall thickness, and increased ratio of myocardial mass to cavity volume—all of which result in a steep diastolic pressure-volume relation (Fig. 13.1) [43–46]. Fifty to 66% of HFpEF patients have increased wall thickness and mass that is concentric in type [47, 48]. However, LVH is not essential to make the diagnosis of HFpEF, since patients with diabetes, CAD, and advanced age may develop HFpEF in the absence of LVH [11].

Other mechanisms of diastolic dysfunction include deficient early elastic LV recoil, blunted LV lusitropic response, and low LV preload reserve [45]. In normal individuals during diastole, the rapid pressure decay associated along with the "untwisting" and elastic recoil of the LV produces a suction effect that promotes ventricular filling by increasing the left atrium (LA) to LV pressure gradient. This tends to pull blood into the left ventricle. The suction process is augmented during exercise to compensate for the reduced diastolic filling period induced by the associated increase in heart rate. Systolic longitudinal and radial strain, systolic mitral annular velocities, and apical rotation are lower in patients with HFpEF, and these measurements fail to increase normally during exercise. In diastole, patients with HFpEF have reduced and delayed untwisting and reduced LV suction at rest and during exercise. Such changes can be measured using three-dimensional (3D) echo and strain calculations, but special software is required and the calculation can be time-consuming.

Other potential mechanisms contributing to the pathophysiology of HFpEF include [46, 49, 50]:

- Asynchrony of relaxation due to regional myocardial infarction
- Myocardial ischemia
- Chamber hypertrophy
- Myocardial and atrial fibrosis
- Conduction disease
- Geometric changes involving the LV chamber
- Microvascular coronary disease
- Atrial systolic dysfunction
- Atrial diastolic dysfunction
- Chronotropic incompetence
- Atrial fibrillation
- Supraventricular tachycardia

Diastolic dyssynchrony with or without electrical dyssynchrony has been observed in patients with HFpEF [51]. Whether or not dyssynchrony is an important contributor to the pathophysiology of HFpEF remains uncertain. It should be noted that cardiac resynchronization therapy (CRT) in patients with HFrEF and QRS duration of less than 130 ms does not reduce the rate of death or hospitalization and may increase mortality [52].

Cardiomyocyte and Extracellular Matrix

Patients with HFpEF have thicker cardiomyocytes with little or no change in cardiomyocyte length. This may result in decreased length/width ratio. Borbély et al. [44] have demonstrated thicker and shorter myocytes with increased myofibrillar density in patients with HFpEF compared to those with HFrEF. These myocyte changes correspond to the increase in LV wall thickness but appear not to alter LV volume. Although there is an increase in the amount of collagen in hearts of both patients with HFpEF and HFrEF, the thickness of the collagen bundles and the continuity of the fibrillar components of the extracellular matrix surrounding the cardiomyocyte are greater in HFpEF [46, 53].

Cellular calcium overload and/or adenosine triphosphate (ATP) depletion has been observed in HFpEF. The sarcoplasmic reticular reuptake of cytosolic calcium is abnormal and is associated with slower cardiomyocyte relaxation [45, 49].

Hemodynamic Abnormalities

Classically, patients with HFpEF manifest increased filling pressure either at rest, with exercise, or volume challenge. The elevated LVEDP is likely responsible for some of the dyspnea that the patients experience either at rest or with exertion, but this is not the complete story. Changes in active and passive relaxation of the LV also occur, which lead to alterations in negative dP/dt, or tau. The change in the pressure-volume relationship is a product of the increased stiffness of both the LV chamber and the abnormal myocyte structure and function.

There may be a molecular basis for the increased myocyte stiffness that is related to phosphorylation and dephosphorylation of the large intracellular cardiac myocyte molecule called titin [44]. A number of factors, including titin isoform switches (to a less compliant N2B isoform) and titin phosphorylation state, can affect passive myofiber stiffness, and perturbation in both has been described in HFpEF. Interaction of titin with other signaling molecules and with ion channels may also contribute to the effect of titin on diastolic stiffness. It is believed that alterations in titin may occur in concert with changes in the extracellular matrix, but this interaction is not well defined. Unfortunately, our understanding of the role of alteration in titin and titin interactions in patients with HFpEF is limited, and much remains to be clarified [44, 54].

Neurohumoral Abnormalities

The critical role of neurohumoral factors in regulating circulation and volume status in normal people and in patients with heart failure and reduced ejection fraction has been known for more than a century. The importance of neurohumoral activation in HFrEF pathophysiology was identified in the middle and latter part of the twentieth century and formed the basis for the neurohumoral hypothesis of heart failure [55, 56]. Major contributions to this understanding came from observational data collected in large, well-characterized populations of patients participating in systolic heart failure treatment trials [55, 57]. In many of these studies, plasma levels of vasoactive hormones including norepinephrine, renin, angiotensin II, aldosterone, vasopressin, and atrial natriuretic peptide were measured and found to be significantly increased compared with normal controls. These observations allowed for important insight into both the pathophysiology and the prognosis of patients with HFrEF [55, 57–59].

It is therefore well known that neurohumoral activation plays a fundamental role in the progression of HFrEF. Activation of the sympathetic nervous system, aldosterone, and the natriuretic peptide system is also known to occur in patients with HFpEF [60–62]. Although natriuretic peptide levels are lower in patients with HFpEF compared to patients with HFrEF, the plasma levels of catecholamines and aldosterone may be similarly increased. Whether other counter-regulatory hormones such as renin, angiotensin II, and endothelin are playing an active role in the pathophysiology of HFpEF remains to be determined. To date, clinical trials using angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor blockers have failed to demonstrate a survival benefit in patients with HFpEF (Table 13.1).

Risk Factors for HFpEF

Gender

Along with age, female gender is a potent risk factor for the development of HFpEF. Indeed, there appear to be important age-gender interactions, such that the prevalence of HFpEF increases more sharply with age in women than the prevalence of HF with a reduced EF [63, 64]. The reasons for the female predominance in HFpEF are not entirely clear, but women have higher vascular, LV systolic, and diastolic stiffness than men. Vascular and ventricular stiffness increases more dramatically with age in women [64]. Women develop greater wall thickness than men in response to an afterload stress such as aortic valve stenosis [65]. That is, for the same degree of aortic stenosis or hypertension, women may have more LVH than men.

Unique coronary vascular functional changes in women may also play a role in the pathophysiologic process of HFpEF. Microvasculature dysfunction, including inability to dilate the microvasculature in response to exercise, is an important feature of HFpEF. It is of interest that HFpEF is more common in women, as is coronary microvascular disease.

Age

Although cardiovascular disease may contribute to diastolic dysfunction in older people, studies have also suggested that the ability to fill the left ventricle during diastole deteriorates with normal aging [64]. The speed of left ventricular relaxation declines with age in men and women, even in the absence of cardiovascular disease.

Vascular, LV systolic, and LV diastolic stiffness increases with aging [64, 66]. Increases in vascular stiffness are likely related to effort intolerance in patients with HFpEF [23]. Structural cardiac changes with aging (e.g., increased cardiomyocyte size, increased apoptosis with decreased myocyte number, altered growth factor regulation [67], focal collagen deposition) and functional changes at the cellular level involving blunted beta-adrenergic responsiveness, excitation-contraction coupling, and altered calcium-handling proteins may also contribute to diastolic dysfunction with normal aging. At least one study has suggested that prolonged, sustained endurance training may preserve LV compliance with aging and help prevent HF in the elderly [68].

Growth differentiation factor 11 (GDF 11) has recently been shown to circulate in young mice and reverse age-related cardiac hypertrophy when there is cross circulation with an older mouse (parabiosis) [67]. This striking observation suggests that aging plays a prominent role in the development of cardiac hypertrophy and stiffness and that this process is potentially reversible [69, 70].

Diabetes Mellitus

Nearly half the patients with heart failure have diabetes mellitus, usually type II, and patients with HFpEF are no exception [39]. Diabetes is a potent risk factor for the development of heart failure. The prevalence of diabetes is seemingly similar in patients with HFpEF and HFrEF, suggesting that diabetes contributes to the pathophysiology of both [39]. Although diabetes predisposes to coronary artery disease, renal dysfunction, and hypertension, numerous studies suggest that there is a direct effect of diabetes and hyperglycemia on myocardial structure and function [71–73]. Myocardial contractile dysfunction in patients with diabetes is likely related to worsening cardiac mitochondrial function and mitochondrial dynamics [74]. These changes in contractile function observed in diabetic patients are not seen in obese patients at an early stage of insulin resistance [74].

Mechanisms responsible for increased diastolic stiffness of the diabetic heart are perhaps different than those changes found in patients with HFrEF. Altered cardiomyocyte resting tension is more important in HFpEF, whereas fibrosis and advanced glycation end products are more important in HFrEF [75]. Increases in passive trans-mitral LV inflow velocity measured by Doppler in diabetic patients are associated with the development of HFpEF and increased mortality, independent of hypertension or coronary artery disease [76]. Diabetic patients may develop cardiac steatosis, which can precede the onset of glucose intolerance and left ventricular dysfunction [73]. Lipid overstorage of human cardiomyocytes can be an early manifestation of type 2 diabetes mellitus and can be evident before the development of heart failure [73].

Other morphologic changes in the diabetic heart include myocyte hypertrophy, increased extracellular matrix (fibrosis), and intramyocardial microangiopathy. Functional changes, which may represent a continuum, include impaired endothelium-dependent and endothelium-independent vasodilation, impaired LV relaxation, increased passive diastolic stiffness, and contractile dysfunction.

Atrial Fibrillation and Frequent Premature Atrial Contractions

Atrial fibrillation is recognized as a frequent precipitant of acute heart failure in patients with HFpEF. Whereas atrial fibrillation may cause decompensated HF in patients with diastolic dysfunction, it is also true that diastolic dysfunction can provoke atrial fibrillation [77]. Thus, diastolic dysfunction, atrial fibrillation, and HFpEF are common and interrelated conditions that probably share common pathogenic mechanisms in the elderly. High-density premature atrial contractions, previously considered a benign entity, are now understood to likely be a precursor to the development of atrial fibrillation and may signal the forthcoming onset of atrial fibrillation and perhaps even stroke [78]. Excessive supraventricular ectopic activity is defined as ≥30 premature atrial contractions per hour or any episode of runs of ≥20 premature atrial contractions. To date we have insufficient data to know if treating this risk factor is appropriate or not.

Coronary Artery Disease

The reported prevalence of coronary artery disease or myocardial ischemia in patients with HFpEF varies widely, although a recent report of unselected patients using diagnostic coronary angiography indicated that 70 % of patients with HFpEF have significant underlying CAD [37, 79]. Although acute ischemia is known to cause transient diastolic dysfunction, the role of chronic coronary artery disease and myocardial infarction in patients with HFpEF is not precisely defined. Clearly, increased myocardial fibrosis from previous infarctions could contribute to the diastolic dysfunction. Patients with HFpEF and severe CAD may benefit from revascularization [37, 80].

Systemic Hypertension

Hypertension is perhaps the most commonly associated risk factor for patients to develop HFpEF. Chronically increased blood pressure is an important stimulus for cardiac structural remodeling and functional changes. The resultant hypertensive heart disease is characterized by LVH, increasing vascular and ventricular systolic stiffness, impaired relaxation, and increased diastolic stiffness. All of these factors are linked to the pathogenesis of HFpEF [81]. LVH is also known to be associated with a reduction in coronary vascular reserve. Therefore, patients with hypertension and LVH may manifest less coronary blood flow on demand, leading to transient myocardial ischemia.

Obesity

Obesity is associated with an increased risk for the development of heart failure. In general, patients with HFpEF are more often obese than are patients with HFrEF. The prevalence of diastolic dysfunction is increased in obese patients. Generalized adiposity not only imposes an adverse hemodynamic load on the heart but also is a source of a large number of biologically active peptide and non-peptide mediators.

These mediators appear to modulate a number of important bodily functions, including inflammation. Increased body mass index is a risk factor for the development of hypertension, diabetes mellitus, coronary artery disease, and atrial fibrillation. All of these are associated with HFpEF. Studies using tissue Doppler imaging or invasive LV pressure measurement have reported an association between diastolic dysfunction, elevated filling pressures, and obesity, even in the absence of a diagnosis of heart failure [82].

Renal Insufficiency

The critical impact of renal function on morbidity and mortality in patients with heart failure is well established [83]. Since patients with HFpEF tend to be older, one might expect they would have a lower glomerular filtration rate (GFR). Studies have shown no difference in the severity of renal dysfunction that occurs in patients with acute decompensated heart failure who have HFrEF versus HFpEF [29, 84, 85]. Furthermore, the incidence of worsening renal function during HF therapy is similar in patients with HFpEF and HFrEF [86]. Severe systemic hypertension (with or without bilateral renal artery stenosis) may lead to acute pulmonary edema, a well-recognized presentation for HFpEF [87]. Evaluation of the renal arteries should be considered in patients presenting with the triad of hypertension, renal dysfunction, and HFpEF.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is commonly associated with all types of heart failure including patients with HFpEF. Central sleep apnea may also occur in patients with HFpEF, but the response to therapy is more variable than with obstructive sleep apnea.

Clinical Presentation

One cannot easily distinguish HFrEF from HFpEF at the bedside. A careful history and physical examination are always indicated, but an echocardiogram is usually recommended in order to measure the ejection fraction. This measurement distinguishes HFpEF from HFrEF. Patients with acute HFpEF and HFrEF present similarly. The picture is typically dominated by severe dyspnea, tachypnea, diaphoresis, neck vein distension, rales, and peripheral edema. A third and fourth heart sound may be present, and the patient may have tachycardia and hypoxemia. An electrocardiogram should be obtained because a substantial proportion of patients may have atrial fibrillation [80, 88].

Diagnosis

- Careful history and physical examination
- Electrocardiogram
- Chest X-ray
- Echocardiogram
- NT-pro-BNP

The diagnosis of HFpEF is dependent on a careful history and physical and echocardiographic findings. The history and physical examination are consistent with the presence of heart failure, but do not distinguish or differentiate between HFpEF and HFrEF. A transthoracic echocardiogram should be performed to verify the diagnosis of HFpEF, unless it has been recently done. Generally speaking, natriuretic peptide levels are elevated both in patients with HFpEF and HFrEF, but tend to be somewhat lower in patients with HFpEF. The chest X-ray in patients with HFpEF tends to show a normal or small cardiac silhouette, whereby patients with HFrEF tend to demonstrate cardiomegaly. However, patients with LVH (common in HFpEF) frequently have cardiomegaly on chest X-ray. The electrocardiogram may indicate LVH in some patients with HFpEF, although this might occur in either HFpEF or HFrEF. Some patients may be candidates for coronary angiography, particularly if there is a history of coronary artery ischemia or angina. Other patients may be elderly and frail and have advanced kidney dysfunction and therefore might not be candidates for coronary angiography. When infiltrative cardiomyopathy disorders are being considered, cardiac magnetic resonance imaging may be helpful.

Treatment

No specific treatment is known to improve survival for patients with HFpEF. Therefore, the goal of therapy in patients with HFpEF and heart failure is to relieve symptoms and manage the comorbidities. Treatment usually includes intravenous loop diuretics and dietary sodium restriction. Fluid restriction is generally not imposed unless the patient is hyponatremic. Normal sinus rhythm should be restored when there is acute hemodynamic compromise, and blood pressure should be controlled. Comorbid conditions should be treated when possible [80, 88].

Prognosis

The prognosis of patients with HFpEF is very similar to patients with HFrEF. In a classic paper from Mayo Clinic, Owan and colleagues reported that the prognosis of patients with HFpEF is similar to those with HFrEF once the patient with HFpEF had been hospitalized for heart failure (Fig. 13.3) [29]. Therefore, HFpEF is a serious disorder with a prognosis that is very poor once symptoms develop. As with HFrEF, these patients tend to be repeatedly hospitalized and, therefore, require frequent and vigorous follow-up. Because these patients are often elderly and frail and may come from nursing homes, the level of evaluation must be tempered with knowledge of each patient's individual needs and condition.

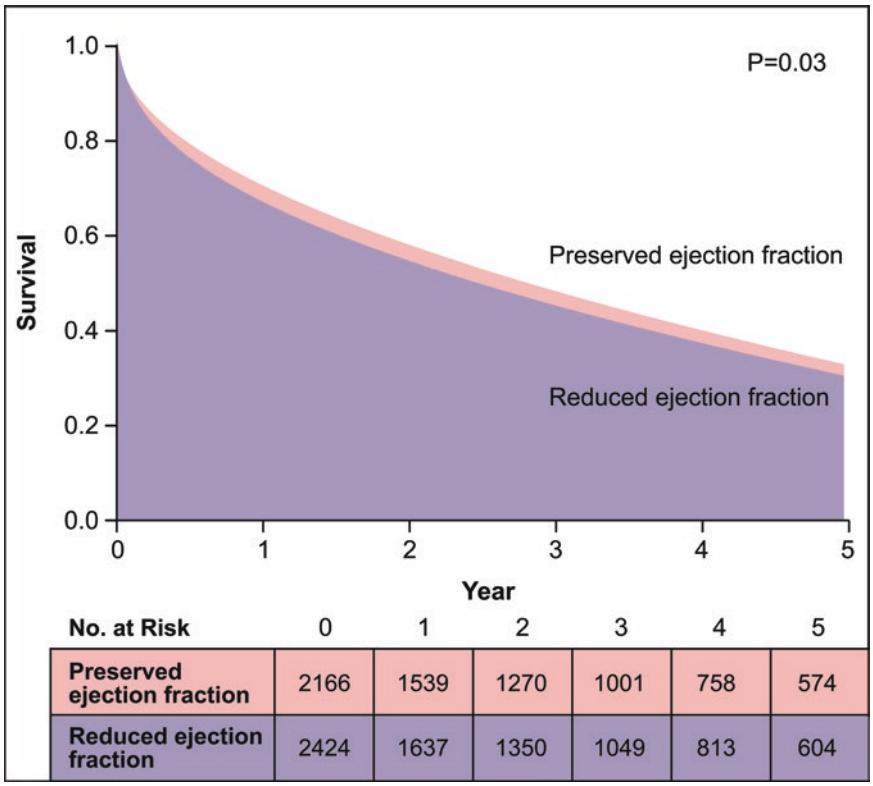

Fig. 13.3 Kaplan-Meier survival curves for patients with heart failure and preserved or reduced ejection fraction (Adapted with permission from Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006;355(3):251–9)

Future Directions

Although there are a number of interesting strategies that might benefit patients with HFpEF, most are in the very early stages of development. One new, ongoing trial, for example, is studying LCZ696. This novel therapy has recently been demonstrated to benefit patients with HFrEF by improving survival and decreasing hospitalization when compared to enalapril [89]. A current study—Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction (PARAGON-HF)—is randomizing patients with HFpEF to either LCZ696 or valsartan. LCZ696 is a molecule that contains valsartan, an angiotensin receptor-blocking agent, and neprilysin, a neutral endopeptidase inhibitor. The potential benefits of any new such therapy for patients with HFpEF remain speculative.

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Myocardial Viability and Imaging in the Failing Heart

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_14

Myocardial viability is the presence of living myocardial tissue. Viability means the absence of dead myocardium—necrosis in the acute setting or scar in the chronic setting. In ischemic cardiomyopathy with dysfunctional myocardium, viability denotes the presence of living myocardium despite the dysfunction due to coronary artery disease. The clinical implication that often accompanies viable myocardium, especially in the context of viability testing, is that it has the potential for functional recovery, often through coronary revascularization. Viability testing uses a technique to show the presence or absence of viable myocardium.

Myocardial Stunning and Hibernation

Myocardial stunning and hibernation are two concepts that describe dysfunctional myocardium that is viable and has the potential for functional recovery [1]. Myocardial stunning describes dysfunction that occurs in the setting of acute, nonlethal myocardial ischemia and can persist for several hours but, eventually, is followed by full functional recovery. Myocardial hibernation is a chronic state of myocardial post-ischemic dysfunction seen in patients with coronary artery disease (CAD) and is believed to result from repeated episodes of demand ischemia and cumulative stunning. Unlike myocardial stunning, functional recovery in myocardial hibernation occurs only after coronary revascularization. In pathophysiological terms, a severe reduction in coronary flow reserve is common in both stunning and hibernation, and functional recovery in hibernating myocardium after coronary revascularization is matched by restoration of an adequate coronary flow reserve [1].

The Need for Myocardial Viability Testing

In patients with coronary artery disease and left ventricular systolic dysfunction, determining which of them will benefit from revascularization is of obvious clinical significance. It is logical to assume that patients with dysfunctional but viable myocardium are more likely to benefit from revascularization than those with dysfunctional, nonviable myocardium. Thus, a diagnostic test that can distinguish between viable and nonviable myocardium is essential in the clinical assessment and management of patients with ischemic heart disease.

Imaging Modalities for Myocardial Viability Testing

Multiple imaging modalities test myocardial viability. The clinically used modalities include echocardiography, single-photon emission computed tomography (SPECT), positron emission tomography (PET), cardiac computed tomography (CCT) imaging, and cardiac magnetic resonance imaging (CMR).

Nuclear imaging targets cell membrane integrity using SPECT and evidence of metabolic activity with PET to distinguish viable from irreversibly damaged or scarred myocardium, whereas dead myocardium can be directly identified using magnetic resonance imaging. In contrast, contractile reserve to an inotropic agent (dobutamine) is a common technique used in echocardiography for viability imaging. This chapter describes all of the imaging modalities used for myocardial viability testing.

Echocardiographic Techniques of Viability Imaging

Myocardial viability imaging via echocardiography most often uses dobutamine stress echocardiography. Other techniques such as myocardial contrast echocardiography and strain imaging have not taken hold in day-to-day clinical practice.

Dobutamine Stress Echocardiography

Left ventricular contractile reserve, as assessed by dobutamine stress echocardiography (DSE), is a common technique used to identify viability of a dysfunctional myocardium. The traditional protocol starts with infusion of low-dose dobutamine, starting at 2.5 μg/kg/min and going up to 5, 7.5, 10, and 20 μg/kg/min [2]. A viable but ischemic segment of the left ventricle exhibits the classic "biphasic response," whereby improvement in regional function is seen at low dose (5–10 μg/kg/min) followed by deterioration at high dose (up to 40 μg/kg/min) [2]. Other possible responses of a dysfunctional myocardial segment to dobutamine include sustained augmentation with dobutamine dose escalation, functional deterioration without any improvement, and the absence of change in function [2]. Both biphasic and sustained recovery responses to dobutamine indicate viable myocardium; however, the former is highly predictive of functional recovery [2, 3], whereas the latter is not [4]. Sustained improvement to dobutamine infusion may suggest the absence of a flow-limiting stenosis and possibly an underlying cardiomyopathy as an explanation for the observed resting regional contractile dysfunction [4]. Increased myocardial blood flow accounts for the underlying mechanism by which dobutamine elicits improved contractile function without inducing ischemia [5, 6].

The sensitivity and specificity of DSE in detecting viable myocardium are 71–97 % and 63–95 %, respectively [2]. The diagnostic performance of DSE can be affected by several factors including resting tachycardia, duration of dobutamine infusion, degree of impairment of myocardial blood flow, left ventricular translational motion, and the presence of segmental wall motion abnormality largely due to subendocardial infarction [4]. Figure 14.1 demonstrates two examples of dobutamine stress echocardiography—Panel a, upper row, shows images obtained from the apical four-

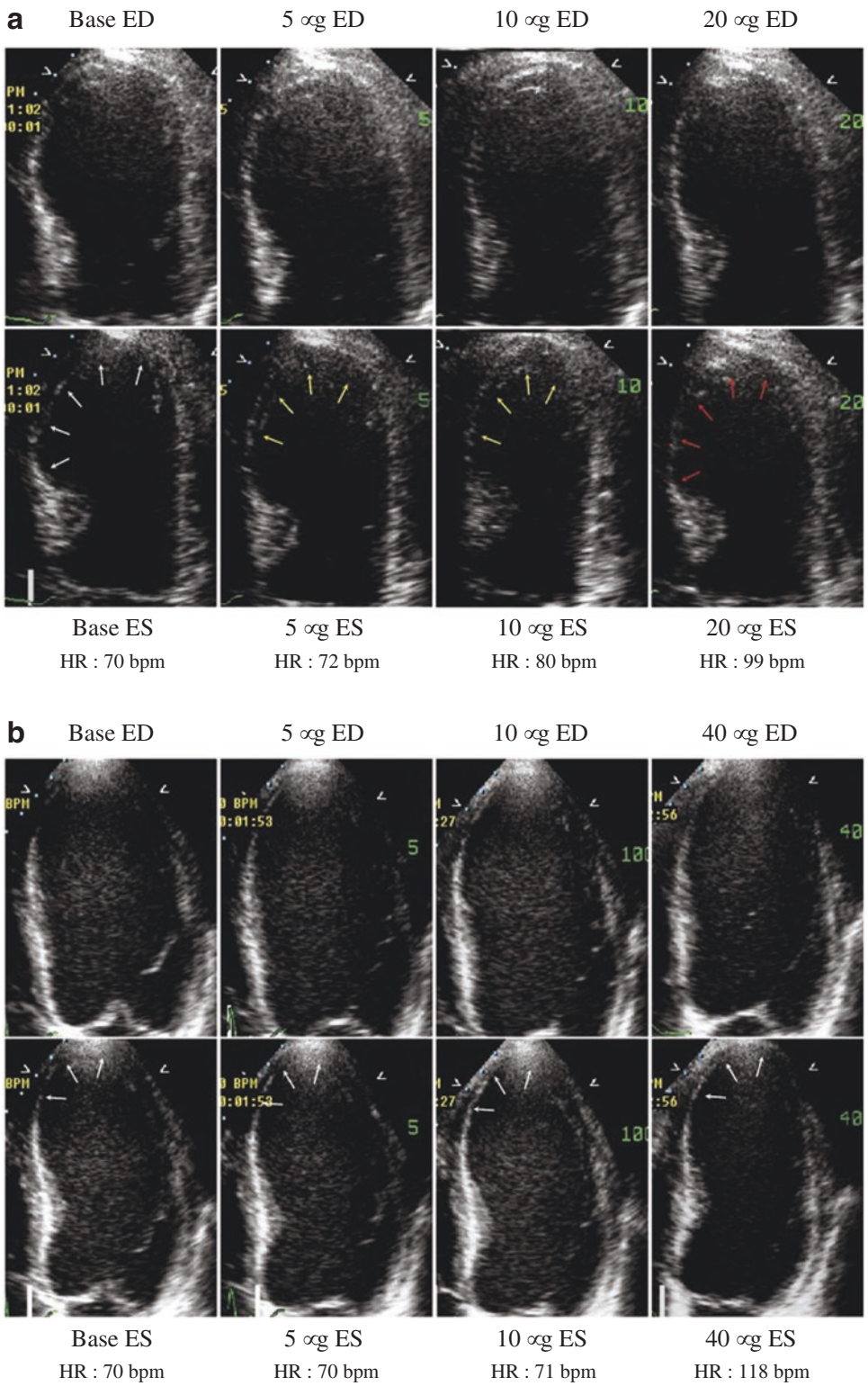

Fig. 14.1 This figure demonstrates two examples of dobutamine stress echocardiography. Panel **a**, *upper row*, shows images obtained from the apical four-chamber view in end diastole at baseline and during the infusion of 5, 10, and 20 µg/kg/min of dobutamine. The *lower row* shows the corresponding end-systolic images. The *yellow arrows* indicate segments improving function, whereas *red arrows* indicate deteriorating segments. The sequence illustrates a typical biphasic response in the distal septum and the apex, consistent with viable but dysfunctional (hibernating) myocardium. Panel **b**, *upper row*, shows images obtained from the apical four-chamber view in end diastole at baseline and during the infusion of 5, 10, and 40 µg/kg/min of dobutamine. The *lower row* shows the corresponding end-systolic images. The sequence shows the absence of inotropic reserve in the distal septum, consistent with nonviable or infarcted myocardium

chamber view in end diastole at baseline and during the infusion of 5, 10, and 20 µg/kg/min of dobutamine. The lower row shows the corresponding end-systolic images. The yellow arrows indicate segments improving function, whereas red arrows indicate deteriorating segments. The sequence illustrates a typical biphasic response in the distal septum and the apex, consistent with viable but dysfunctional (hibernating) myocardium. Panel b, upper row, shows images obtained from the apical four-chamber view in end diastole at baseline and during the infusion of 5, 10, and 40 µg/kg/min of dobutamine. The lower row shows the corresponding end-systolic images. The sequence shows the absence of inotropic reserve in the distal septum, consistent with nonviable or infarcted myocardium.

Myocardial Contrast Echocardiography

Another echocardiographic technique used in viability imaging is myocardial contrast echocardiography (MCE), which uses gas-filled microbubbles to evaluate the integrity of the microvasculature [7]. The basic protocol involves continuous intravenous infusion of microbubbles until a steady state is achieved and measurement of the rate of reemergence (myocardial blood flow velocity) and the concentration in tissue (myocardial blood volume fraction) following destruction with a high-power ultrasound pulse [8, 9]. Although widespread clinical use has been limited, MCE has been used to determine the extent of viable myocardial tissue and predict functional recovery after revascularization in acute coronary syndromes [10–12], as well as in chronic ischemic cardiomyopathy [13]. Figure 14.2 shows examples of myocardial contrast echocardiography in patients with viable (Panel a) and nonviable (Panel b) apical segments. An apical thrombus is also noted in the patient with an acute myocardial infarction (MI) depicted on Panel b.

Myocardial Strain Imaging

Strain, regional deformation, and strain rate (the rate of regional deformation)—either measured by tissue Doppler imaging or speckle tracking—are rapidly becoming indispensable echocardiographic tools for assessing regional left ventricular systolic function in various disease processes. Strain imaging has the potential to help avoid the common pitfalls inherent in DSE, such as the subjective nature of regional wall motion assessment and the challenge of discriminating between a segment that's actively contracting from one that's "tethered" [14, 15]. The use of strain imaging has identified multiple variables that favor myocardial viability and functional recovery. These include increase in peak systolic strain rate by more than 0.23/s [16], high-end-systolic strain [17], and a >9.5 % change in radial strain [18]. Limited data pertaining to the application of strain imaging for assessing myocardial viability exist, and further studies are warranted to clarify its clinical utility. Figure 14.3 shows an example of strain rate tracings at rest (solid line) and during dobutamine infusion (dotted line) for one cardiac cycle of a hypokinetic segment at rest, shown to be viable by 18-fluorodeoxyglucose (FDG) PET imaging. The peak systolic strain rate increased from 1.1 s^{-1} at rest to 2.0 s^{-1} during dobutamine stimulation.

Left Ventricular End-Diastolic Wall Thickness

Myocardial wall thinning occurs in areas of transmural myocardial infarction and is commonly considered a surrogate marker for the presence of nonviable tissue [19, 20]. The left ventricular end-diastolic wall thickness (EDWT) is easy to determine using two-dimensional (2D) echocardiography. In small, prospective studies involving patients with coronary artery disease and left ventricular dysfunction, EDWT > 6 mm was shown to have high sensitivity but low specificity to identify viable myocardium and predict functional recovery. The sensitivity of EDWT as an index of viability was improved by the addition of contractile reserve with dobutamine stress echocardiography [21, 22]. Similar findings were obtained when cardiac magnetic resonance imaging was used to measure EDWT using cutoff values greater than 5.5–6 mm [23]. However, a recent landmark cardiac magnetic resonance (CMR) imaging study showed that, among patients with coronary artery disease and regional wall thinning, limited scar burden was present in 18 % and was associated with improved contractility and resolution of wall thinning after revascularization [24]. Thus, myocardial thinning is potentially reversible and, therefore, should not be considered a permanent state. Similarly, EDWT is not a reliable predictor of viability.

Single-Photon Emission Computed Tomography

Single-photon emission computed tomography (SPECT) uses radiotracers to assess perfusion and cell membrane/mitochondrial integrity as hallmarks of viability. The two

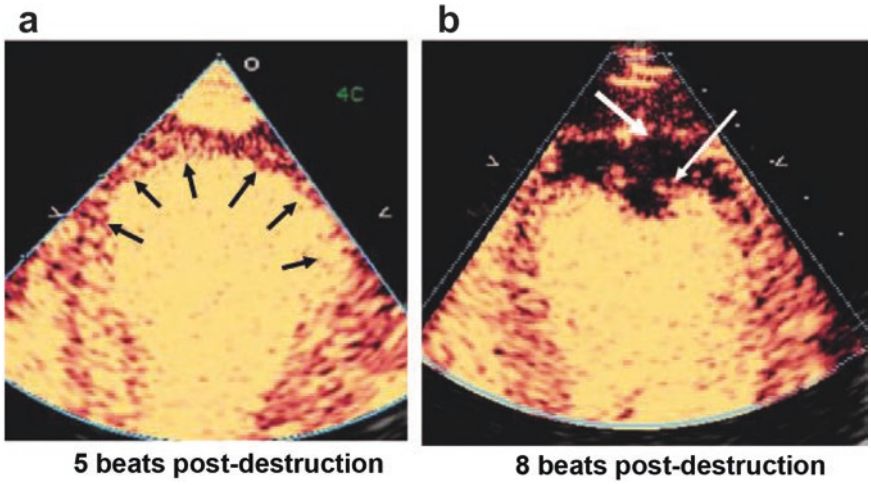

Fig. 14.2 This figure shows examples of myocardial contrast echocardiography in two patients with viable (Panel **a**) and nonviable (Panel **b**) apical segments. An apical thrombus is also noted in the patient with an acute myocardial infarction (MI) depicted on Panel **b**

radiotracers used most commonly with SPECT are thallium 201 (TI) and technetium 99m (Tc) [1]. TI is a potassium analog that is actively transported into myocytes by a Na/K ATPase-dependent mechanism, thus requiring an intact cell membrane. As TI kinetics are directly proportional to tissue blood flow, normal tissue has more rapid uptake and washout than underperfused, viable tissue. Myocardial TI is then exchanged continuously with the reservoir of systemic blood pool TI, with net efflux from the myocardium. Images obtained early after tracer injection reflect blood flow, whereas retention and redistribution of thallium over a 4–24-h period reflect intact cell membrane function and, thus, myocyte viability. TI redistribution in regions that initially had a perfusion defect is the hallmark of viability when using SPECT.

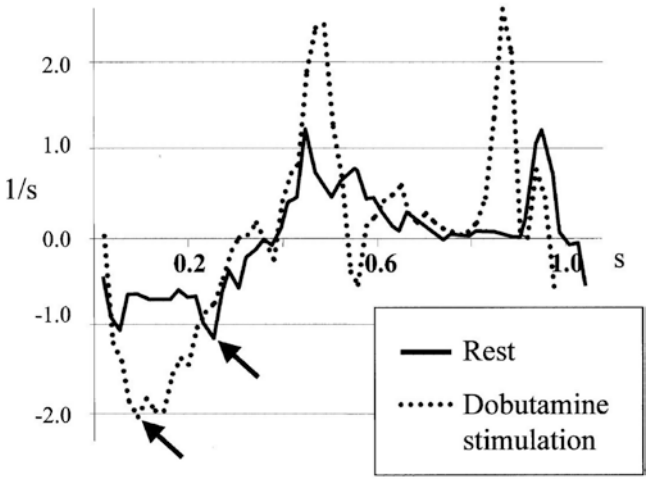

Fig. 14.3 This figure shows an example of strain rate tracings at rest (*solid line*) and during dobutamine infusion (*dotted line*) for one cardiac cycle of a hypokinetic segment at rest, shown to be viable by 18-FDG PET imaging. The peak systolic strain rate increased from 1.1 s^{-1} at rest to 2.0 s^{-1} during dobutamine stimulation

Numerous viability protocols have been described, which underscores the lack of standard criteria. Common protocols include stress redistribution, which provides information for both inducible ischemia and cellular viability and rest redistribution, which provides information on myocardial blood flow at rest and cellular viability. Whereas rest redistribution needs only one injection of TI, stress redistribution needs a reinjection of a small dose at rest, as the initial uptake of TI during stress may be severely reduced in some patients with significant CAD. The second injection during stress redistribution imaging can be done early (3–4 h) or late (8–72 h) following the initial injection.

Tc-labeled radiotracers (sestamibi and tetrofosmin) are widely used for performing stress myocardial perfusion imaging. Although accumulation and retention of Tc is a passive process driven by transmembrane electrochemical gradient, it still depends on mitochondrial membrane integrity. The usual stress protocols require modification (such as administration of nitrates) to optimize the radiotracer delivery to hibernating myocardium, particularly in patients with very severe left ventricular dysfunction. In general, TI is the radiotracer of choice with SPECT to assess viability [25].

Thallium protocols yield good positive and negative predictive values (70–90 % range) for recovery of function after revascularization. However, a pooled analysis of TI viability studies showed high sensitivity (88 %) but low specificity (49 %), suggesting overestimation of recovery by TI. SPECT has limited ability to differentiate between subendocardial

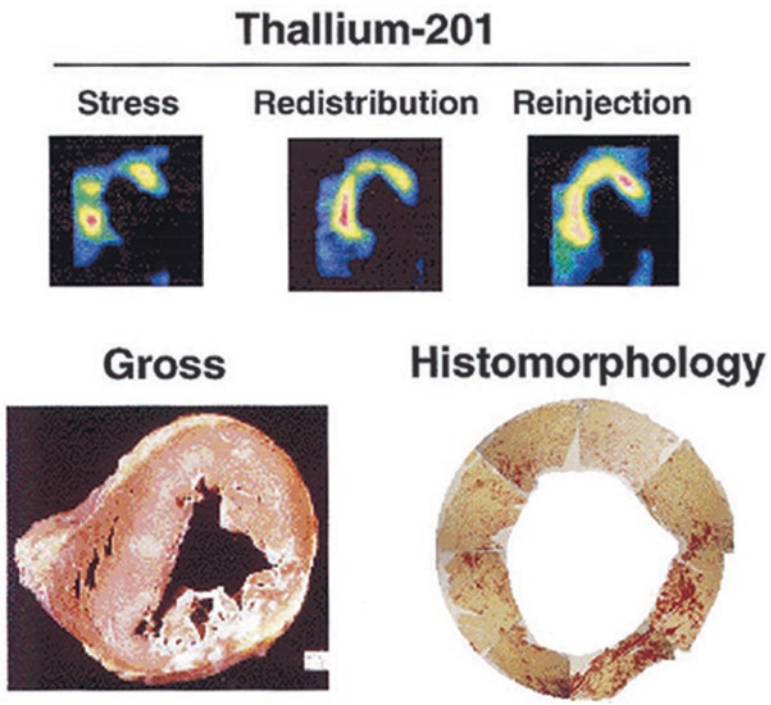

Fig. 14.4 This figure shows an example of a Tl viability study. The *top panel* shows Tl images at stress, redistribution, and reinjection. The *bottom panel* shows corresponding gross pathology and histopathology of a mid-ventricular slice. On the thallium study, extensive perfusion defects are visible in the anterior, septal, and inferolateral regions during stress. On redistribution, partial reversibility of the anterior region is seen, as well as complete reversibility of the septum and an irreversible defect in the inferolateral region. After thallium reinjection, complete reversibility of the septal and anterior regions is noted with a persistent irreversible defect in the inferolateral region. This is consistent with viability in the septal and anterior regions and infarct in the inferolateral region. On gross pathology, white fibrotic myocardium is visible in the inferolateral region, and histomorphologic analysis shows a significant amount of red-stained collagen intermixed within normal-looking myocytes in the same area

and transmural scars, primarily due to low spatial resolution. Figure 14.4 shows an example of a Tl viability study. The top panel shows Tl images at stress, redistribution, and reinjection. The bottom panel shows corresponding gross pathology and histopathology of a mid-ventricular left ventricular (LV) slice. On the thallium study, extensive perfusion defects are visible in the anterior, septal, and inferolateral regions during stress. On redistribution, partial reversibility of the anterior region is seen, as well as complete reversibility of the septum and an irreversible defect in the inferolateral region. After thallium reinjection, complete reversibility of the septal and anterior regions is noted with a persistent irreversible defect in the inferolateral region. This is consistent with viability in the septal and anterior regions and infarct in the inferolateral region. On gross pathology, white fibrotic myocardium is visible in the inferolateral region, and histomorphologic analysis shows a significant amount of red-stained collagen intermixed within normal-looking myocytes in the same area.

Positron Emission Tomography

Positron emission tomography (PET) uses separate positron-emitting radiotracers to assess perfusion and metabolism, based on the concept that metabolism is preserved relative to flow in hypoperfused but viable myocardium. Perfusion is assessed with N-13 ammonia, which needs an on-site cyclotron, or rubidium-82, which is produced by a generator. Metabolism is measured by uptake of 18-FDG, which is a glucose analog. It is transported into the cell and effectively fixed in the myocardium through phosphorylation by hexokinase [25].

Under normal fasting conditions, the myocardium mainly uses free fatty acids as the primary energy source. After a meal or glucose load, the combined effects of insulin and the increased glucose concentration result in viable myocardium preferentially switching to glucose as the preferred energy substrate. Importantly, myocardial ischemia may further increase the overall proportion of glucose utilization in the myocardium. FDG uptake into the myocardium is dependent on the insulin-sensitive glucose transporters that can be activated by either oral glucose loading or administration of insulin before tracer administration. This is the exact opposite of protocols used in oncology or for detection of cardiac sarcoidosis, where imaging is done in a fasting state to minimize FDG uptake by normal tissue.

Normal myocardium is characterized by normal flow, normal glucose uptake (matched perfusion/metabolism); infarcted, nonviable myocardium has both decreased flow and glucose uptake (matched perfusion/metabolism defect); hibernating but viable myocardium has reduced resting flow with normal or increased glucose uptake (mismatched perfusion/metabolism). Using this concept, myocardial segments assessed with PET show (1) normal flow/metabolism (viable), (2) mild-matched reduction in flow/metabolism (subendocardial scar), (3) severe-matched defect (transmural scar), or (4) mismatch with resting perfusion defect and preserved glucose uptake (hibernating but viable). Viability is denoted by greater than 50 % FDG uptake in a myocardial segment.

The accuracy of PET to predict functional recovery after revascularization is high, with positive and negative predictive values in the 80–90 % range. Importantly, this accuracy holds even in patients with severe left ventricular dysfunction. From a pooled analysis of studies investigating the value of preserved FDG uptake in predicting functional recovery, sensitivity was 88 % and specificity was 73 %. The extent of viability shown on PET needed to predict improvement in mortality after revascularization varies in different studies between 7 and 20 %. This reflects the fact that viability is not a binary figure but rather a continuum, where increasing hibernation implies both increased risk and increased potential for recovery. Benefits of PET imaging are superior spatial and temporal resolution, improved attenuation and scatter correction compared to SPECT, and the ability to image patients with severe renal disease and pacemakers/defibrillators who cannot have CMR imaging. Limitations of PET include limited availability, requirement of an on-site cyclotron for N-13 ammonia, the need to create a tightly controlled metabolic milieu, and suboptimal performance in diabetics due to reduced myocardial extraction of 18-FDG [25]. Figure 14.5 shows mid-ventricular short-axis images of resting blood flow (top panel) and 18-FDG uptake on PET (bottom panel) in a patient with LV dysfunction due to a recent MI in the left anterior descending territory treated initially with thrombolysis. Extensive reduction in resting blood flow in the anterior wall is seen with enhanced 18-FDG uptake (flow/metabolism mismatch pattern). This patient had improved LV function following surgical revascularization.

Cardiac Computed Tomography

Viability imaging with cardiac computed tomography (CCT) uses a premise similar to that for delayed-enhancement CMR with gadolinium, as iodine is also primarily an extracellular, interstitial agent with similar contrast kinetics [26]. Areas of myocardial damage provide an increased volume of distribution for contrast, thus showing contrast enhancement on repeat imaging about 10 min after contrast delivery. The typical CCT protocol includes two scans. The first scan is a routine coronary angiogram that visualizes the coronary arteries and myocardial first-pass perfusion. Hypoperfused myocardium due to coronary stenosis or infarction appears hypoenhanced due to slow contrast wash-in. The second scan, obtained about 10 min later (with no additional contrast injection), is performed to assess myocardial viability. Scar tissue will appear as hyperenhanced compared with surrounding viable myocardium. A major disadvantage of CCT for delayed-enhancement imaging is its low contrast-to-noise ratio, with poor contrast difference between normal and infarcted myocardium [26]. Currently, CCT perfusion is not used widely to assess viability. Figure 14.6 shows images from viability stud-

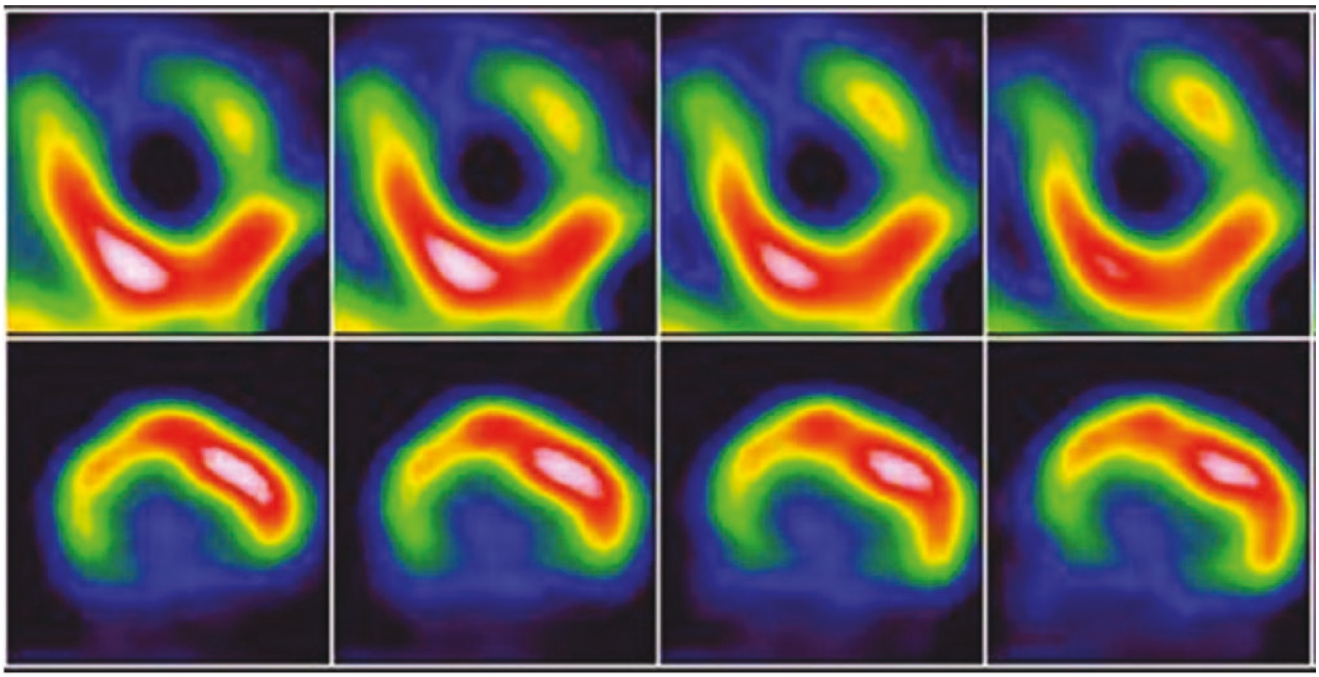

Fig. 14.5 This figure shows mid-ventricular short-axis images of resting blood flow (*top panel*) and 18-FDG uptake on PET (*bottom panel*) in a patient with LV dysfunction due to a recent MI in the left anterior descending territory treated initially with thrombolysis. Extensive reduction in resting blood flow in the anterior wall is seen with enhanced 18-FDG uptake (flow/metabolism mismatch pattern). This patient had improved LV function following surgical revascularization

ies by CCT compared to delayed-enhancement magnetic resonance imaging (DE-CMR) in the same patients.

Cardiac Magnetic Resonance

Cardiac magnetic resonance imaging provides information on viability by a technique called delayed enhancement cardiac magnetic resonance (DE-CMR). Using this technique, irreversibly injured myocardium is visualized as bright (hyperenhanced) regions. Hyperenhancement on delayed-enhancement images represents necrosis in the acute or scar tissue in the chronic myocardial infarction settings. Viable myocardium, either normal or reversibly injured, appears dark. Gadolinium-based contrast is injected intravenously at a dose of 0.075–0.20 mmol/kg body weight. If a stress and rest perfusion scan precede the viability scan, no additional contrast media injection may be necessary. Figure 14.7 shows typical cine and DE-CMR images.

Contrast agents currently used for the DE-CMR technique are gadolinium chelates. They are extracellular or interstitial agents as they leave the vascular bed and enter the extracellular or interstitial space, but not the intracellular space. In healthy, viable myocardium, the distribution volume (i.e., the volume available for contrast agent distribution) is small, because the intracellular space from healthy myocardial cells occupies a large portion of the tissue volume (about 75–80 % of the water space) and is unavailable to the contrast agent. In acute infarction, the ruptured cardiomyocyte membranes enable the gadolinium contrast agent to passively diffuse into the formerly intact intracellular space, resulting in an increased contrast agent concentration and "hyperenhancement." In chronic infarction, the myocardial tissue consists of dense scar with an increased extracellular or interstitial space between collagen fibers and, therefore, an increased distribution volume for the contrast agent relative to normal myocardium. Thus, a direct inverse relationship exists between the gadolinium contrast concentration within the myocardium and the percentage of viable myocytes (Fig. 14.8) [27].

About 10–15 min are needed between the injection of the contrast agent and the start of DE-CMR to allow the contrast agent to redistribute in the myocardium and sufficiently exit the blood pool. The goal of DE-CMR is to create images with high contrast between dead tissues, which accumulates excess gadolinium contrast compared to viable tissue, where the gadolinium contrast concentration is low [28]. DE-CMR has been shown to be highly effective in identifying the presence, location, and extent of irreversible myocardial injury in both acute and chronic settings [29].

DE-CMR is used clinically for differentiating patients with ischemic cardiomyopathy who have potentially reversible ventricular dysfunction and those with irreversible dysfunction. Patients with potentially reversible ventricular dysfunction are significantly more likely to benefit from coronary revascularization compared to those with irreversible dysfunction. The initial, landmark study by Kim et al. demonstrated that DE-CMR performed before coronary

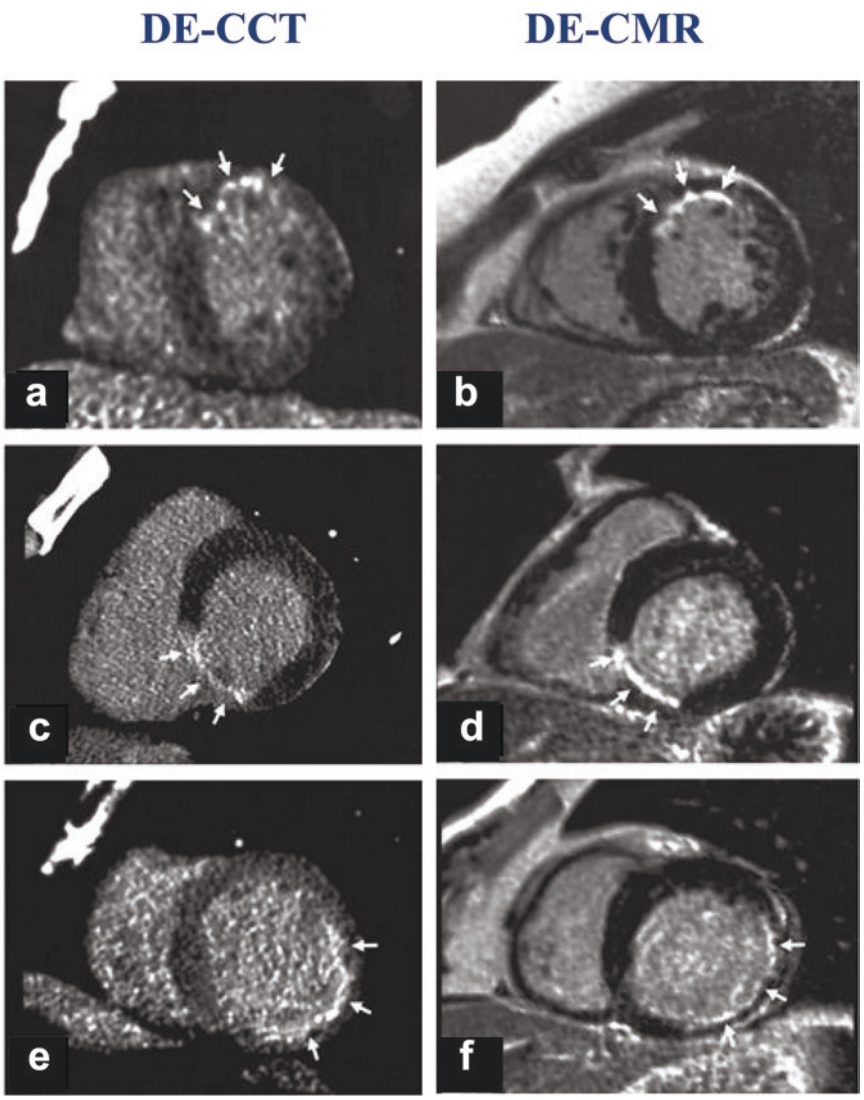

Fig. 14.6 This figure shows images from viability studies by CCT (Panels **a**, **c,** and **e**) compared to DE-CMR in the same patients (Panels **b**, **d,** and **f**)

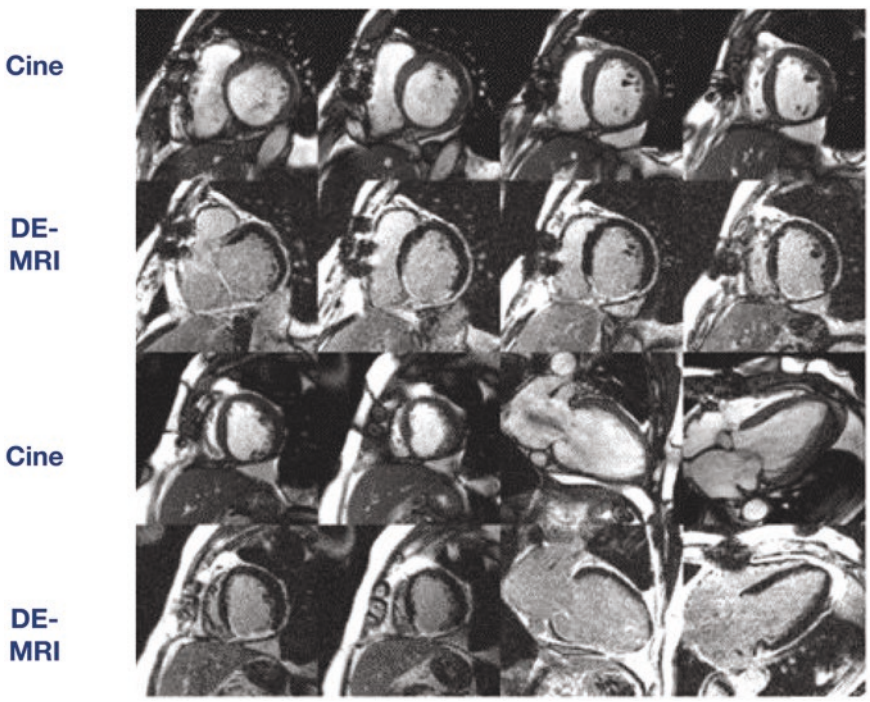

Fig. 14.7 This figure shows typical cine and corresponding DE-CMR images

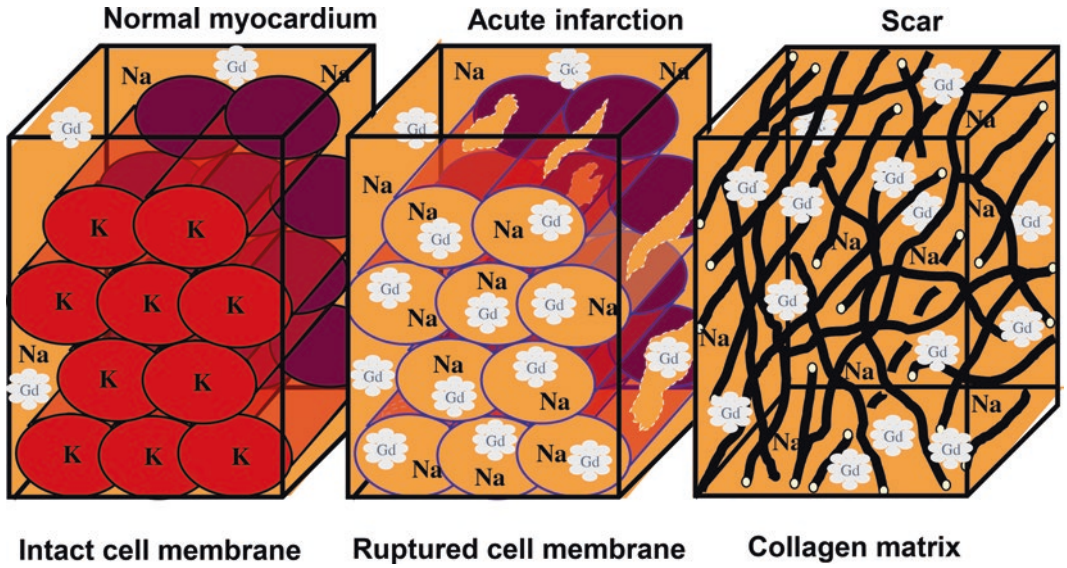

Fig. 14.8 This figure demonstrates the physiological basis of hyperenhancement in DE-CMR. In normal myocardium, two points should be noted. First, cardiomyocytes are densely packed, and the total tissue volume is predominantly intracellular (about 80 % of the water space). Second, gadolinium contrast does not cross cellular membranes and thus is limited to the extracellular (intravascular and interstitial) space. Thus, the volume of distribution of gadolinium contrast in normal myocardium is quite small (about 20 % of water space), and one can consider viable myocytes as actively excluding contrast media. In acutely infarcted regions, the myocyte membranes are ruptured, allowing gadolinium to passively diffuse into the formerly intact intracellular space. The result is an increased concentration of gadolinium at the tissue level resulting in hyperenhancement. Chronic myocardial scar is characterized by a dense collagenous matrix. However, at a cellular level, the interstitial space between collagen fibers may be significantly greater than the interstitial space between the living myocytes that is characteristic of normal myocardium. Thus, the concentration of gadolinium in scar is greater than in normal myocardium because of the expanded volume of distribution, and the regions of scar appear hyperenhanced. Thus, a direct inverse relationship exists between the gadolinium contrast concentration within the myocardium and the percentage of viable myocytes

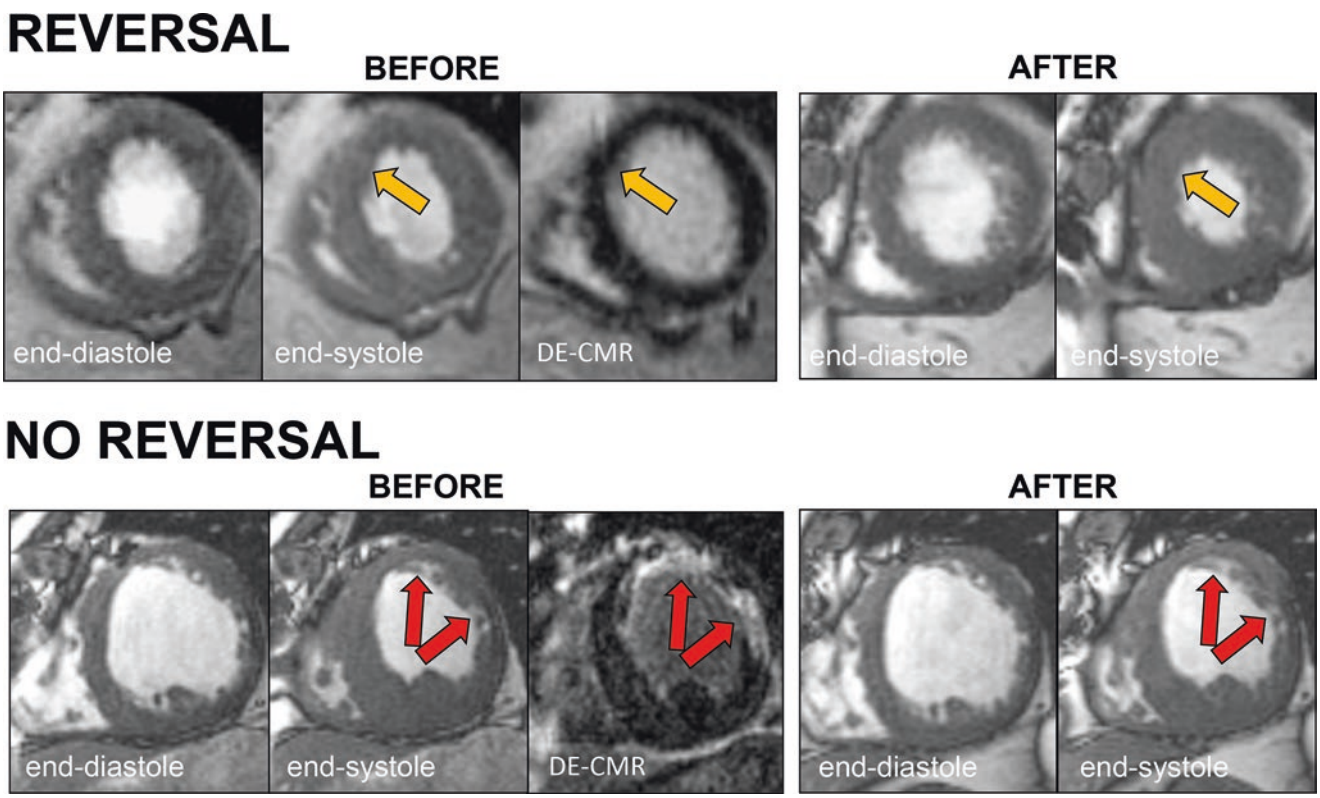

Fig. 14.9 This figure shows representative cine and DE-CMR images from two patients in the study by Kim et al. [30]. The *top row* shows a patient with significant viable myocardium and improved contractility after revascularization. The *bottom row* shows a patient without significant viable myocardium and a lack of functional recovery after revascularization

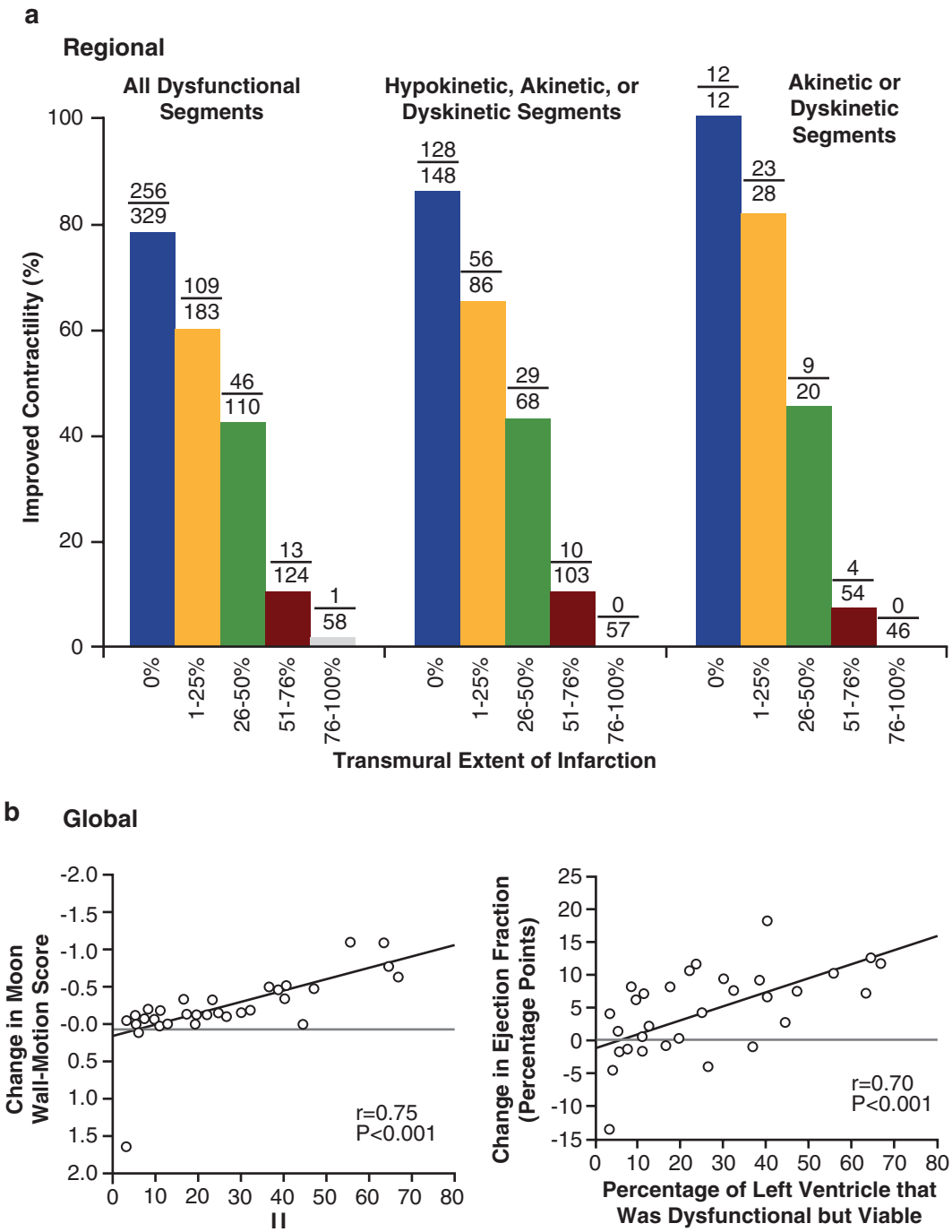

Fig. 14.10 This figure from the paper by Kim et al. [30] demonstrates the results of analyses of regional wall motion (Panel **a**) showing that improved contractility was inversely related to the transmural extent of infarction. Panel **b** shows that the extent of dysfunctional but viable myocardium calculated on a per-patient basis predicted the magnitude of improvement in global function after revascularization

revascularization could predict functional improvement [30]. Figure 14.9 shows representative cine and DE-CMR images from two patients in this study. Analyses of regional wall motion showed that improved contractility was inversely related to the transmural extent of infarction (Fig. 14.10, Panel a). The extent of dysfunctional but viable myocardium calculated on a per-patient basis predicted the magnitude of improvement in global function after revascularization (Fig. 14.10, Panel b). In the setting of acute myocardial infarction (MI), early reperfusion with primary percutaneous intervention or thrombolysis has been shown to result in salvage of ischemic but viable myocardium, long-term improvement in LV function, and longer survival. However, in the immediate post-MI setting, it is difficult to differentiate between myocardial dysfunction that is due to necrosis, and thus irreversible, and that due to stunning, which is reversible. Studies have shown the utility of DE-CMR in differentiating infarcted from viable myocardium soon after

acute MI and reperfusion therapy. Similar to findings in the chronic setting, the extent of viable myocardium as measured by DE-CMR was directly related to improvement in segmental function in a stepwise fashion [31]. Additionally, DE-CMR also provided the best predictor of improvement in global LV function: The percentage of the LV that was dysfunctional but viable was directly related to subsequent changes in LV wall thickening score and LV ejection fraction [31].

Advantages of CMR Over Other Modalities for Myocardial Viability Imaging

Unlike other imaging modalities, DE-CMR's major advantage is that it can simultaneously visualize the transmural extent of both viable and nonviable myocardium [32]. Other modalities used to assess myocardial viability, such as SPECT, only visualize the viable portion of the myocardium. The percentage of viability in a given segment is assessed indirectly and generally denotes the amount of viability in the segment normalized to the segment with the maximum viability or to data from a database of sex-specific controls. With DE-CMR, the percentage of viability can be assessed directly and expressed as the amount of viability in the segment normalized to the amount of viability plus infarction in that same segment (Fig. 14.11, Panel a) [32].

Direct visualization provided by DE-CMR of both live and dead myocardium provides important insights into myocardial thinning and the recovery of LV dysfunction. The differences in the way viability is measured can alter clinical interpretation, as illustrated in the patient example in Fig. 14.11, Panel b, showing long-axis DE-CMR images of a patient before and 2 months after revascularization. Although the akinetic anterior wall is thinned (diastolic wall thickness 5 mm; remote zone 9 mm), DE-CMR shows that there is only subendocardial infarction (1.5 mm thick). Direct assessment of viability would show that the anterior wall is predominately viable (3.5/5 mm = 70 % viable) with a high likelihood of wall motion recovery, whereas an indirect method would show that the anterior wall is predominately nonviable (3.5/9 mm = 39 % viable) with a low likelihood of functional recovery (Panel a). Cine views after revascularization demonstrate that the direct method is more accurate since there is functional recovery after revascularization.

This case runs counter to the commonly accepted clinical belief that thinned walls have no potential for recovery after revascularization. Prior reports have concluded that in patients with ischemic cardiomyopathy, regions with thinned myocardium represent nonviable tissue and therefore cannot improve in contractile function after revascularization. However, this example proves that thinning should not be equated with the absence of viability and that in some patients these regions can improve after revascularization. This was recently demonstrated elegantly by Shah et al. who studied 1055 patients with CAD referred for DE-CMR and found that 201 (19 %) had regional thinning [24]. Limited scar burden was present in 18 % of these thinned regions, and in these cases, revascularization led to improved contractility and resolution of wall thinning [24].

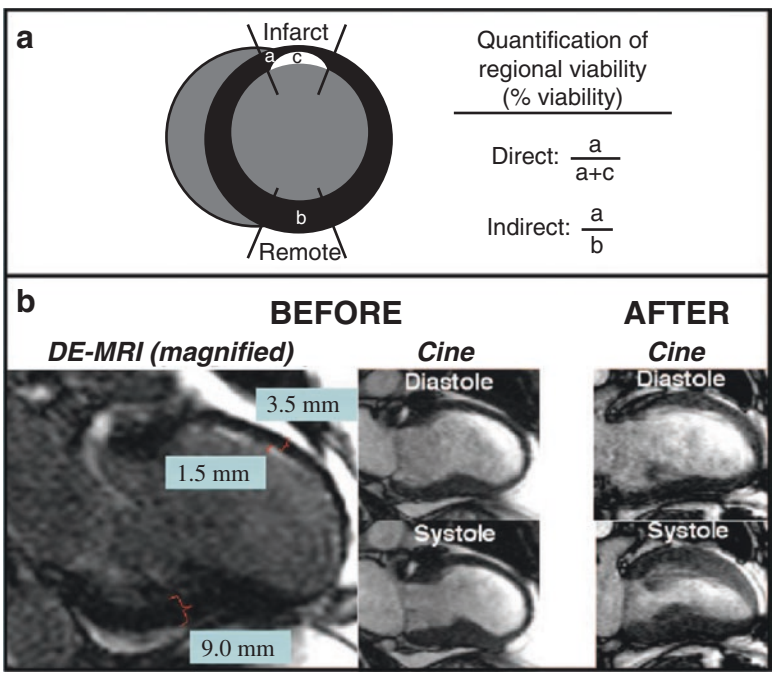

Fig. 14.11 This figure demonstrates the advantage of DE-CMR over other modalities for viability assessment by providing direct visualization of both live and dead myocardium. Panel **b** shows long-axis DE-CMR images of a patient before and 2 months after revascularization. Although the akinetic anterior wall is thinned (diastolic wall thickness 5 mm; remote zone 9 mm), DE-CMR shows that there is only subendocardial infarction (1.5 mm thick). Direct assessment of viability would show that the anterior wall is predominately viable (3.5/5 mm = 70 % viable) with a high likelihood of wall motion recovery, whereas an indirect method would show that the anterior wall is predominately nonviable (3.5/9 mm = 39 % viable) with a low likelihood of functional recovery (Panel **a**). Cine views after revascularization demonstrate that the direct method is more accurate since there is functional recovery after revascularization

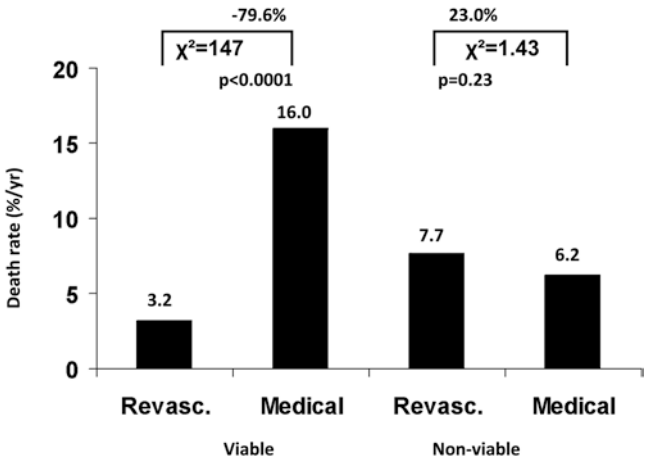

Fig. 14.12 This figure illustrates the importance of myocardial viability assessment. Allman et al. [33] pooled data from 24 studies examining late survival with revascularization versus medical therapy after myocardial viability testing in patients with severe coronary artery disease and left ventricular dysfunction. This meta-analysis in 3088 patients demonstrated that in patients with viability, revascularization was associated with a 79.6 % reduction in annual mortality (16 % vs. 3.2 %, $p < 0.0001$) compared with medical therapy. Patients without viability had intermediate mortality, trending to higher rates with revascularization versus medical therapy (7.7 % vs. 6.2 %, p = NS). Mean left ventricular ejection fraction at baseline was 32 ± 8 % and patients were followed for 25 ± 10 months

The Utility of Myocardial Viability Testing

The utility of myocardial viability testing in prognostication after revascularization has been evaluated in many small single-center studies, most of which were included in a meta-analysis. Results showed decreased annual mortality in patients with viable myocardium undergoing revascularization compared to those not undergoing revascularization [33]. In the meta-analysis of 24 studies that included 3088 patients with a mean left ventricular ejection fraction (LVEF) of 32 %, Allman et al. concluded that, in patients with significant viable myocardium, revascularization was associated with a 79.6 % lower annual mortality compared with medical treatment (3.2 % vs. 16 %, $P < 0.001$) (Fig. 14.12) [33]. Conversely, in patients without viable myocardium, survival rates were similar for revascularization and medical therapy (7.7 % vs. 6.2 %, P = ns) (Fig. 14.12). However, all the included studies were small, not randomized, and were retrospective, leading to potential patient selection bias. Additionally, the methodology, definitions of viability, and treatment regimens were not standardized among the studies.

The Surgical Treatment for Ischemic Heart Failure (STICH) trial was a randomized, multicenter, non-blinded trial funded by the National Institutes of Health's National Heart, Lung, and Blood Institute [34] In this study, 1212 patients with angiographically documented coronary artery disease suitable for surgical revascularization and associated left ventricular systolic dysfunction (defined as left ventricular ejection fraction ≤35 %) without medically refractory disabling angina or significant left main coronary artery stenosis were randomized to coronary artery bypass graft (CABG) surgery with intensive medical therapy, or to intensive medical therapy alone. The primary end point of all-cause mortality after a median follow-up of 56 months occurred in 41 % of patients randomized to medical therapy alone compared with 36 % randomized to CABG, which was not statistically significantly different (hazard ratio with CABG, 0.86; 95 % CI, 0.72–1.04; $P = 0.12$).

The STICH trial recommended post-randomization myocardial viability testing by dobutamine stress echocardiography and/or radionuclide imaging. While this was initially in the study protocol, it was made optional due to difficulty in recruitment. Eventually, 601 patients received a viability study. A significant association between viability and survival was identified on univariate analysis but not on multivariable analysis. In contrast with prior literature, assessing myocardial viability did not help in identifying patients with a differential survival benefit from CABG compared with medical therapy alone [35].

The authors pointed out several limitations to the viability sub-study of the STICH trial [35]. Less than 50 % of the 1212 study patients underwent viability testing. While the main study was a randomized trial, the viability study was not; the patients were not randomized to viability testing. Viability testing could have been performed before, on the day of, or after study enrollment. These factors may have led to enrollment bias and influenced downstream clinical decision-making. Only a small percentage of patients were determined not to have viable myocardium ($n = 114$; 19 %), which limited the power of the analysis to detect a differential effect of CABG, compared with medical therapy alone, in patients with viability versus those without viability. Only 54 patients without viability underwent CABG, and 60 patients without viability were treated with medical therapy alone. Most importantly, the viability studies were limited to SPECT and DSE imaging. The investigators did not incorporate other approaches, such as PET or DE-CMR. Thus, the results cannot be extrapolated to imaging modalities that were not tested in STICH, such as PET or MRI.

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Heart Failure Disease Progression

Cardiorenal Syndrome and Heart Failure

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_15

Introduction

Heart failure is one of the most important causes of cardiovascular morbidity and mortality. However, the adverse physiologic impact extends beyond the cardiovascular system, particularly to the kidneys. Renal dysfunction is well established as one of the most potent predictors of morbidity and mortality in heart failure patients [1, 2]. Similarly, heart failure is one of the most common complications of patients with renal dysfunction [3]. This chapter summarizes the cardiorenal syndrome (CRS) caused by heart failure. This is a complex topic, and readers with particular interest are referred to an excellent text with greater detail by Heywood et al. [4].

Definition

Because many early heart failure trials excluded patients with renal dysfunction, much of the data about cardiorenal syndrome comes from retrospective studies where worsening renal function was found in patients hospitalized for acute decompensated heart failure (ADHF) [5]. Although several definitions have been used for worsening renal failure, including an increase in creatinine ≥25 % from baseline, the most commonly used definition is the one shown to give the best sensitivity and specificity: an increase in serum creatinine (SCr) equal to or more than 0.3 mg/dl [6–8].

Initially, cardiorenal syndrome was defined as the progression of renal dysfunction secondary to heart failure [9]. However, cardiorenal syndrome can also be applied to patients with chronic or acute renal dysfunction who develop heart failure or other heart diseases. In 2008, Ronco et al. proposed a more general and concise definition [10]. The authors defined cardiorenal syndrome as "a pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of 1 organ may induce acute or chronic dysfunction of the other" [10].

Classification

Based on the above definition, cardiorenal syndrome has been divided into five categories depending on the initial compromised organ, acuity, and a patient's symptoms and physical status (Fig. 15.1) [10]:

1. *Cardiorenal syndrome type 1* (*acute CRS*): acute worsening of cardiac function leading to acute kidney injury (AKI) or dysfunction [11]. In this case, acute cardiovascular diseases like acute coronary syndrome, cardiogenic shock, and acute decompensated heart failure are the cause of acute renal dysfunction [10, 11].
2. *Cardiorenal syndrome type 2* (*chronic CRS*): chronic abnormalities in cardiac function causing progressive chronic kidney disease [10].
3. *Cardiorenal syndrome type 3* (*acute reno-cardiac syndrome*): acute kidney injury (abrupt or primary worsening) leading to cardiac dysfunction and/or injury. In this case, acute kidney injury can be related to ischemia or glomerulonephritis that causes acute cardiac injury or dysfunction such as acute decompensated heart failure, arrhythmia, or ischemia [10, 12].
4. *Cardiorenal syndrome type 4* (*chronic reno-cardiac syndrome*): primary chronic kidney disease that leads to chronic cardiac dysfunction including decrease in cardiac function, left ventricular hypertrophy, diastolic dysfunction, or increase in cardiovascular morbidity [10].
5. *Cardiorenal syndrome type 5* (*secondary CRS*): systemic condition (acute or chronic) causing simultaneous heart and kidney dysfunction. Some of these systemic conditions include sepsis, connective tissue disorders such as systemic lupus erythematosus, drugs, toxins, Wegener granulomatosis, diabetes mellitus, sarcoidosis, and amyloidosis [10, 13].

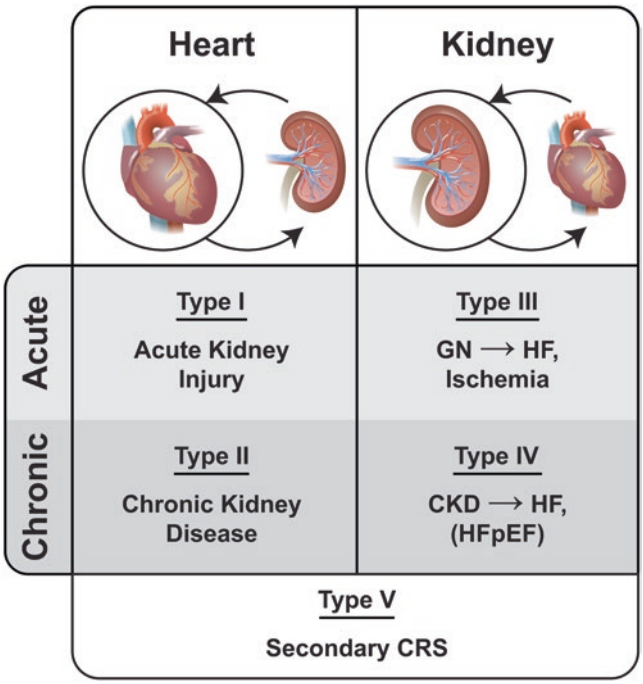

Fig. 15.1 Types of cardiorenal syndrome. Cardiorenal syndrome can be seen in an acute setting, such as when the hemodynamic changes of heart failure lead to acute kidney injury (type 1). Acute kidney injury such as glomerulonephritis (GN) can lead to heart failure (HF) or myocardial ischemia (type 3). The chronic hemodynamics of heart failure can also lead to chronic kidney disease (type 2), or chronic kidney disease (CKD) can lead to heart failure, commonly with preserved ejection fraction (HFpEF, type 4). Systemic conditions such as sepsis or diabetes can also cause simultaneous heart and kidney failure (type 5)

Epidemiology

The incidence of CRS varies by its type. Because cardiorenal syndrome type 5 is a newly recognized entity that may occur in different pathological processes, its incidence, prevalence,

and outcomes are not yet well defined [13]. Cardiorenal syndrome type 1 has been the most studied and, thus, the best characterized.

As previously mentioned, initial studies on cardiorenal syndrome were retrospective studies in patients admitted to the hospital with acute decompensated heart failure. Thus, we know that acute worsening of renal dysfunction occurs in 25–45 % of patients with acute decompensated heart failure, especially during the first 3 days after admission [11, 14]. For example, in the Acute Decompensated Heart Failure National Registry (ADHERE) that had more than 105,000 patients with ADHF, renal dysfunction was found in 30 %, and 21 % had a serum creatinine ≥2.0 mg/dl [15]. Less data are available for cardiorenal syndrome type 2, but in chronic heart failure patients, the prevalence of kidney dysfunction has been reported in up to 25 % of these patients (2), and stage III chronic kidney disease (CKD, defined as GFR < 60 ml/min/1.73 m^2), has been present in up to 60 % of patients with chronic heart failure [16].

Importantly, renal dysfunction is the most important predictor of mortality in heart failure patients, and worsening renal function is associated with increased hospital stays, cost of complications, and mortality at 5 years [16].

Pathophysiology

Broadly, several factors are thought to contribute to CRS (Fig. 15.2). The pathophysiology of cardiorenal syndrome is still not well understood, and most studies have focused on CRS type 1. Hemodynamic changes and neurohormonal activation have been implicated in the development of all five types of cardiorenal syndrome. Several mediators can play a role in CRS, including a hyperactive sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS), an imbalance between radical oxygen species (ROS) and nitric oxide, and an inflammatory response (Fig. 15.3) [3]. In fact, some studies have shown increased neurohormonal activity associated with tubular and myocardial damage in patients with CRS compared to those with heart failure who did not develop renal failure [17].

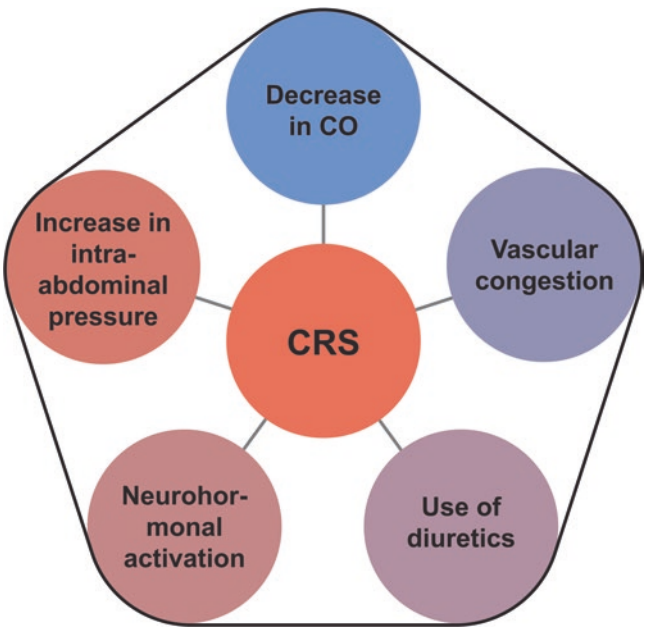

Fig. 15.2 Schematic summary of key factors leading to cardiorenal syndrome (CRS). *CO* cardiac output

Hemodynamic Abnormalities

1. *Low cardiac output*: The low cardiac output state seen in patients with heart failure, especially those with systolic dysfunction and related hypovolemia, leads to activation of arterial and intrarenal receptors in the kidneys. Activation of these receptors will cause non-osmotic release of arginine vasopressin that, in turn, leads to activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system. Activating both the RAAS and SNS results in water and sodium retention that causes systemic hypertension. This increase in systemic pressures in conjunction with increased renal arteriolar resistance results in decreased glomerular filtration rate (GFR). This is important because in patients with heart failure, GFR is an important predictor of survival [18]. Several medications used in heart failure can impact renal hemodynamics, causing worsening renal function. Thus, diuretic therapy increases the production of angiotensin II and leads to worsening renal hemodynamics, especially when the use of diuretics is related to hemoconcentration. In that case, patients experience a fivefold increase in worsening renal function [11, 19]. Also, medications such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists (ARBs), and aldosterone receptor antagonists can directly lead to worsening renal function in these patients.
2. *Vascular congestion*: Vascular congestion has been associated with poor prognosis in heart failure patients and with worsening renal function. Mullens et al. [20] observed that patients admitted with acute decompensated heart failure had central venous pressure higher than 18 mmHg at admission. This increased central venous pressure is transmitted to the renal vein with a subsequent decrease in GFR and an associated decrease in sodium excretion, decrease in renal flow, and an increase in renal interstitial pressure that is associated with tissue hypoxia [20–22]. In addition, the authors found a limited contribution of impaired cardiac index at admission in the development of worsening renal function in these patients, similar to a sub-analysis of the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial, where 193 patients were treated with pulmonary artery catheter-based therapy. Although the cardiac index improved in these patients, there was no significant

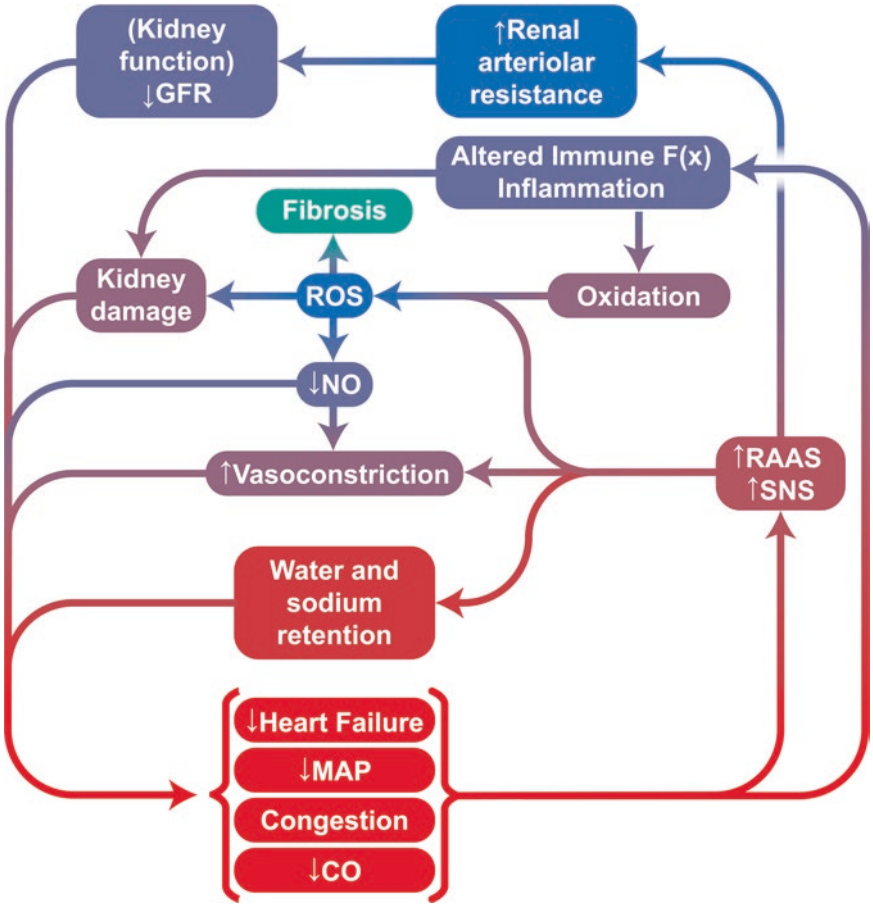

Fig. 15.3 Schematic representation of some of the factors involved in the cardiac-renal interactions. *GFR* glomerular filtration rate, *F(x)* function, *ROS* reactive oxygen species, *NO* nitric oxide, *RAAS* renin-angiotensin-aldosterone system, *SNS* sympathetic nervous system, *MAP* mean arterial pressure, *CO* cardiac output

improvement in renal function, and there was no correlation between pulmonary wedge pressure, systemic vascular resistance, and cardiac index with serum creatinine or GFR [16].

3. *Increase in intra-abdominal pressure*: An increase in intra-abdominal pressure equal to or higher than 8 mmHg has been associated with worsening renal function in patients with ADHF [23]. In a very small cohort, the same authors [Mullens et al.] showed that removing intra-abdominal fluid either by ultrafiltration (UF) or paracentesis is linked to improvement in renal function without a significant alteration in hemodynamic parameters [24]. The increase in intra-abdominal pressure is related to abdominal perfusion pressure (APP). Abdominal perfusion pressure is the difference between mean arterial pressure (MAP) and intra-abdominal pressure (IAP); APP = MAP − IAP [25].

Thus, patients with acute decompensated heart failure associated with congestion and who normally have a low MAP but experience an increase in IAP will have a low abdominal perfusion pressure, resulting in reduced perfusion to the abdominal organs [25]. Some studies have shown that APP is an independent predictor of adverse events in patients with intra-abdominal hypertension. An APP of at least 50 mmHg was shown to be a good predictor of survival in patients with abdominal trauma (sensitivity, 76 %; specificity, 57 %) [26].

Non-hemodynamic Factors

In addition to the hemodynamic changes seen during acute decompensated heart failure, other mechanisms have been implicated in the development of CRS type 1. Besides activation of the RAAS and SNS, other factors, including increased inflammatory response, apoptosis, and imbalance between reactive oxygen species and nitric oxide (NO) production, play a role [27]:

1. *Immune response*: Growing evidence supports activation of the immune system as part of development of heart failure [28–30]. Similarly, abnormalities in the immune system have been proposed as part of the mechanism leading to cardiorenal syndrome. In vitro studies of patients with CRS type 1 have shown significantly higher monocyte apoptosis and activation of caspase cascade in patients with heart failure who developed acute kidney injury compared with controls. In addition, patients with CRS type 1 have higher levels of inflammatory cytokines produced by monocytes, including interleukin-16 (IL-6) and IL-18 as well as tumor necrosis factor (TNF)-α [31]. These cytokines promote renal tubular epithelium injury and death leading to tubular damage that, similar to GFR, has been associated with worsening outcomes in heart failure patients [27, 32].
2. *Oxidative stress imbalance*: Heart failure patients have an increase in oxidative stress mediated by RAAS and SNS activation and related to a metabolic shift in the

cardiomyocytes. The activation of radical oxygen species is associated with cardiac damage and is related with negative effects on contractility, ion transport, and calcium handling in the cardiomyocytes [33]. The RAAS stimulates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation that results in ROS formation. This increase in ROS generation in response to RAAS activation is also related to kidney damage. Increased oxidative stress brings a decrease in NO and an increase in vasoconstrictor molecules including cyclooxygenase-mediated production of thromboxane A2. ROS also induces tissue fibrosis by promoting mesangial cell apoptosis and cellular hypertrophy. Finally, ROS causes loss of normal epithelial cell function in the tubules. This epithelial cell dysfunction is characterized by loss of cell adhesion, disruption of tubular basement membrane, and cell migration with invasion into the interstitium. Ultimately, chronic inflammation present in patients with heart failure and kidney dysfunction leads to a vicious cycle where increased inflammatory cytokines and persistent activation of RAAS and SNS lead to a continuous production of ROS and an oxidative stress imbalance that perpetuates the damage not just in the heart but also in the kidney [17].

It appears that CRS type 2 is the result of a vicious cycle among poor hemodynamics, persistent congestion, and neurohormonal abnormalities. These chronic changes lead to an increase in vasoconstrictive mediators, altered response to vasodilators, and a persistent inflammatory process marked by elevated cytokines, apoptosis, and ROS generation as well as vascular dysfunction manifested by arterial stiffness [10, 34]. In fact, some studies have shown that patients with cardiorenal syndrome type 2 have glomerular damage with evidence of podocyte damage [35].

This cross talk between the kidneys and the heart works both ways—implying that CRS type 3 also uses pathways similar to those of CRS type 1. Thus, in the presence of acute kidney injury, there is also activation of inflammatory cascades, oxidative stress with ROS generation, and caspase-mediated apoptosis that can cause distal organ damage [36]. In the setting of acute injury, tubular epithelial cells play an active role in handling inflammatory mediators and enable them to reach the systemic circulation. In addition, the renal vascular endothelial cells initiate inflammatory responses with an increase in endothelial permeability that facilitates leukocyte infiltration of the renal parenchyma. These functional abnormalities affect leukocyte trafficking, adhesion, and tissue extravasation in other organs including the heart—causing CRS type 3 [27].

However, immune and neurohormonal factors are not the only ones that cause cardiac injury in the setting of AKI. Indirect mechanisms that can lead to cardiac injury in these patients include fluid overload caused by renal dysfunction (leading to sodium and water retention with cardiac overload, venous congestion, and hypertension that could cause myocardial dysfunction and neurohormonal activation), electrolyte imbalance that can cause arrhythmias, acidemia that can disturb the cardiac metabolism, and uremic toxins that can lead to myocardial ischemia and organ dysfunction (Fig. 15.4) [37].

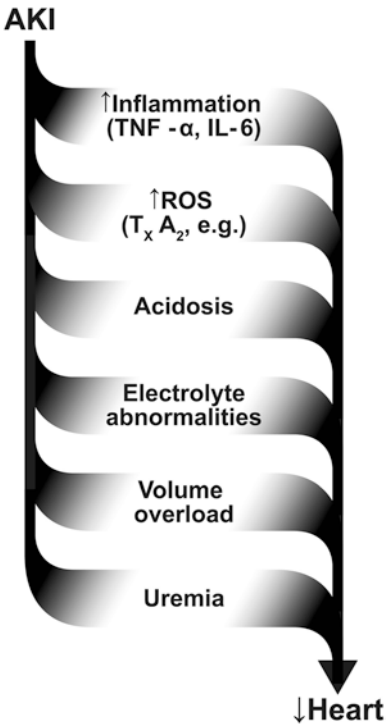

Fig. 15.4 Acute kidney injury (AKI) leads to a number of consequences, such as increased reactive oxygen species (ROS), which have an adverse impact on cardiac function

Diagnosis

The diagnosis of cardiorenal syndrome remains a challenge, especially in CRS type 1 where the increase in SCr sometimes reflects a preexisting kidney injury, and clinicians cannot prevent further renal injury.

Although measuring the glomerular filtration rate is commonly used to evaluate renal function, it may not adequately reflect the renal function in patients with cardiorenal syndrome. We have to remember that GFR is not reliable in acute states, given that the formulas used to estimate GFR have been validated in patients with stable renal function. In addition, other markers of renal function, such as serum creatinine, are influenced by several factors including age, sex, and muscle mass and reflect the GFR but not the tubular function. Then, using GFR or serum creatinine to assess renal function in patients with ADHF can be misleading and can sometimes lead to delay in diagnosis.

Early identification of cardiorenal syndrome certainly is important; several new biomarkers have been shown to be useful for this purpose, including neutrophil gelatinase-associated lipocalin (N-GAL) and cystatin C [3]. N-GAL is obtained using genomic and protein microarray technology [38]. It indicates accumulation of nephrotoxins and renal ischemia 48–72 h before the increase in serum creatinine is

noted in children with AKI and in adults before AKI or after cardiac surgery [38–40]. More importantly, N-GAL levels correlate with the degree of renal tubular damage and also are an early marker of renal injury in children admitted to the intensive care unit [41], in patients with contrast-induced nephropathy after percutaneous intervention [42], and in patients with acute pulmonary embolism [43].

In patients with cardiorenal syndrome, N-GAL, blood urea nitrogen (BUN), and BUN/creatinine levels were found to be significantly higher compared to patients with normal renal function and heart failure, so it helps to discriminate between patients with CRS and those without renal injury [17].

Cystatin C is a cysteine protease inhibitor (non-glycosylated protein) produced at a constant rate for almost all nucleated cells [44]. Its levels are not affected by age, sex, race, or muscle mass, which makes it more reliable than creatinine [44]. Cystatin C is also freely filtered by the kidney due to its low molecular weight, and it is neither secreted nor reabsorbed in the kidney, which makes it better for estimating GFR with a greater sensitivity than serum creatinine (93.4 % vs. 86.8 %) [44, 45]. Also, cystatin C has been found to be an independent predictor of adverse cardiovascular events in heart failure patients—even in patients with preserved renal function [46]. However, although cystatin C is more accurate than N-GAL, N-GAL provides earlier estimates of renal dysfunction [47].

In addition, several markers of inflammation found in heart failure patients have also been suggested to be related to development of cardiorenal syndrome. These inflammatory markers are myeloperoxidase [48], cytokines [49], and urine IL-18 [50]. Readers are directed to a review on the topic for more information on the role of biomarkers in the cardiorenal syndrome [51].

These newly recognized biomarkers are still experimental for diagnosing cardiorenal syndrome, and the most important tool for diagnosing CRS remains the clinical assessment. This assessment should be based on the presence of either acute or chronic heart failure with preserved or reduced ejection fraction associated with biochemical findings of renal dysfunction, including elevated SCr, worsening calculated GFR, or the presence of additional findings of renal damage including proteinuria with other simultaneous biomarkers that improve accuracy of the diagnosis (Nt-proBNP and N-GAL) [52, 53].

Management

Because patients with cardiorenal syndrome have been excluded from many heart failure trials, literature supporting appropriate management and treatment of cardiorenal syndrome is lacking and remains largely empirical. Most treatment plans focus on improving hemodynamic abnormalities and congestion (Fig. 15.5).

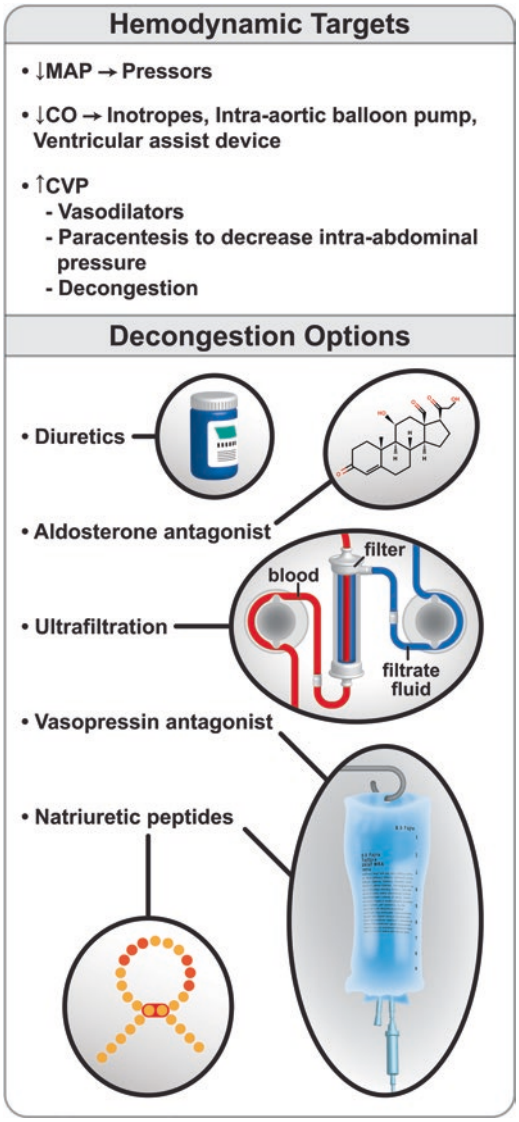

Fig. 15.5 Treatment of cardiorenal syndrome consists of optimizing hemodynamics and maintaining effective decongestion. *MAP* mean arterial pressure, *CO* cardiac output, *CVP* central venous pressure

Congestion Relief

Almost half of the patients admitted with a diagnosis of heart failure present with signs and symptoms of congestion [15], which plays an important role in the development of CRS. Consequently, it is critical to accurately assess the volume status of patients presenting with heart failure and worsening renal function. However, it is also vital to understand that, for some patients, there is a disconnection between the cardiac filling pressures and the intravascular volume. In the latter case, patients will present with no significant increase in weight but with a significant increase in filling pressures, likely secondary to changes in the splanchnic venous pool. These changes are caused by a persistent sympathetic activation that leads to vasoconstriction of the venous pool with

the subsequent volume shift to the systemic circulation and an increase in filling pressures [54]. When that happens, the clinician should use decongestion measures with caution to avoid intravascular volume depletion and worsening renal failure.

Regarding decongestion, several volume-control strategies have been attempted in patients with acute decompensated heart failure. These strategies include:

(a) *Diuretics*: Loop diuretics remain the most-used therapy for patients with ADHF, as demonstrated in the Acute Decompensated Heart Failure National Registry (15). Use of diuretics has been associated with improvement in symptoms, hemodynamics, and, in some cases, renal function, when they are tailored to relieve congestion [55]. However, there are not enough studies that formally evaluated the optimal dose, route of administration, and safety of diuretics. The Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE AHF) trial is probably the only large randomized clinical trial that evaluated the use of diuretics in heart failure patients. This trial failed to show any difference in symptoms or in change in renal function between patients who received continuous infusion vs. bolus of diuretics and those who received high dose vs. low dose [56].

The use of diuretics in ADHF has several caveats. First, some heart failure patients present with diuretic resistance, most likely due to a decrease in diuretic efficiency in the setting of a kidney dysfunction and low cardiac output that leads to poor renal perfusion. Some authors have proposed combination therapy with other diuretics like thiazides to decrease resistance and achieve progressive and gradual diuresis instead of aggressive diuresis to reduce hypovolemia [3]. Second, diuretics have been associated with worsening renal function in patients with acute decompensated heart failure and may increase the risk of complications when used in conjunction with other medications like angiotensin-converting enzyme (ACE) inhibitors [57].

Additional limitations of loop diuretics are related to neurohormonal activation mediated by an increase in RAAS activation, norepinephrine release, and electrolyte imbalance [58, 59]. Despite these limitations, recent studies like the CARRESS trial showed that stepwise pharmacological therapy with diuretics was as effective as ultrafiltration in managing congestion in ADHF patients [60]. In a post hoc analysis from CARRESS-HF and DOSE trials, neither a high dose nor a low dose of diuretics showed significant RAAS activation, and the plasma renin activity in the diuretic therapy group was lower than in the ultrafiltration group. This is important because the degree of RAAS activation has been related to worsening renal function and worse outcomes [61].

(b) *Ultrafiltration*: The main goal of ultrafiltration is mechanical removal of isotonic fluid from the venous compartment. Ultrafiltration is not associated with electrolyte imbalance or neurohormonal activation and could be beneficial in patients with diuretic resistance [62–64]. However, the role of ultrafiltration is controversial. Although some studies like the RAPID trial [65] and the UNLOAD [66] trial showed that UF can safely remove more fluid than high-dose diuretics, and with more weight loss and decrease in admissions for heart failure at 90 days, neither therapy showed a significant clinical benefit in terms of dyspnea or renal function. Ultrafiltration also was not beneficial in patients admitted to the intensive care unit with pulmonary catheter-guided therapy, and it was associated with a higher incidence of transition to renal replacement therapy and high in-hospital mortality despite improvement in hemodynamics [67]. In addition, the CARRESS-HF trial showed that the pharmacological therapy algorithm was superior to ultrafiltration for preserving renal function with less adverse events [60]. One explanation for these findings in the CARRESS-HF trial is that the ultrafiltration rate was constant in patients undergoing ultrafiltration. This could lead to transient episodes of intravascular volume depletion, which can also explain the higher levels of plasma renin activity in these patients compared those undergoing diuretic therapy [61]. Given that the results from ultrafiltration studies are contradictory, there is no clear consensus about the appropriateness of using ultrafiltration over diuretic therapy in ADHF patients.

(c) Vasopressin receptor antagonists: Vasopressin receptor antagonists can act on V2 and V1a receptors. V2 receptors are located in the distal tubules and collecting ducts; their function is increasing aquaporin-mediated water reabsorption [68]. V1a receptors, located in the peripheral vasculature, cause vasoconstriction [69]. Thus, V2 receptor blockers have a natriuretic effect, while V1a receptor antagonists affect the blood pressure. Tolvaptan is a V2 receptor-antagonist that was tested in the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) [70] and Efficacy of Vasopressin Antagonism in HF Outcome Study with Tolvaptan (EVEREST) [71] trials. In both studies, tolvaptan showed a beneficial effect on body weight loss, dyspnea, and edema as well as improvement of hyponatremia. However, there was no difference on primary end points including mortality and readmission rate for heart failure. Thus, although tolvaptan has not delivered a long-term beneficial effect in these patients, it has shown benefit in high-risk patients, including those presenting with poor prognostic factors such as hyponatremia. Conivaptan is a V1a/V2 receptor-antagonist that has shown an increase of diuresis in patients with ADHF without significant effect on blood pressure or heart rate [72]. However, despite these promising results, due to its lack of effect on mortality and heart failure readmissions, neither tolvaptan nor conivaptan has been approved for use in ADHF patients.

(d) *Adenosine antagonists*: Adenosine interacts with A1 receptors in several organs including the kidney (causing afferent arteriole vasoconstriction and tubuloglomerular feedback) and the heart (causing cardiac fibrosis and altered calcium handling) [73]. Initial studies with adenosine antagonists have shown their capacity to prevent further reduction in GFR and enhance the diuretic effect of furosemide [74]. However, the PROTECT trial did not show any benefit in reduction of primary end points, including readmission or death for heart failure, worsening heart failure symptoms, or renal impairment, and was associated with an increase in secondary effects including seizures and stroke [75]. The PROTECT trial was a placebo-controlled randomized study of the selective A1 adenosine receptor-antagonist KW-3902 for patients hospitalized with acute heart failure and volume overload to assess treatment effect on congestion and renal function.

(e) *Natriuretic peptides*: Brain natriuretic peptide (BNP) is a native peptide available for therapeutic use (nesiritide) and commonly used for diuretic resistance. Concerns were raised about its impact on renal function and mortality, but the A Study Testing the Effectiveness of Nesiritide in Patients With Acute Decompensated Heart Failure (ASCEND-HF) trial found a lack of impact on death, rehospitalization, or renal function in patients hospitalized for acute decompensated heart failure [76, 77]. Furthermore, a substudy found that nesiritide did not increase urine output in patients with ADHF [78]. With the clinical challenge of cardiorenal syndrome and diuretic resistance, interest in natriuretic peptides remains high in light of their combination of vasodilatory and natriuretic properties [79].

15

Improvement of Hemodynamics

As mentioned, patients with heart failure undergo significant hemodynamic changes. These changes contribute to worsening renal perfusion and activation of inflammatory responses that lead to glomerular and tubular damage in CRS. As important as relieving congestion, improving the patient's hemodynamics avoids worsening renal failure and breaks the vicious cycle that perpetuates kidney damage. To do so requires:

(a) *Decreasing intra-abdominal pressure*: An increase in intra-abdominal pressure is usually related to third-space accumulation of fluid leading to ascites. Therefore, paracentesis in patients with ADHF presenting with ascites has been associated with improvement in renal function and should be considered, especially in those patients refractory to medical treatment [25].

(b) *Avoiding hypotension and intravascular volume depletion*: In order to maintain an adequate glomerular filtration rate, the kidneys require a relatively good mean arterial pressure and intravascular volume. Achieving these renal hemodynamics during acute heart failure requires autoregulatory mechanisms with activation of the RAAS and SNS [80]. Aggressive diuresis and use of vasodilators and neurohormonal modulators like ACE inhibitors and aldosterone antagonists will affect these autoregulatory mechanisms, leading to a decrease in GFR and worsening renal function. Thus, it is very important to avoid hypotensive episodes as well as to titrate decongestion therapies to enable an adequate capillary refill [25, 54]. With insufficient evidence of an appropriate mean arterial blood pressure in these patients, some authors suggest it would be prudent to avoid mean arterial pressures below 65 mmHg. Below that reading, renal autoregulatory mechanisms start to fail. This is especially important when managing patients who have a history of chronic hypertension. They require higher blood pressures to maintain these autoregulatory mechanisms [54].

(c) Increasing cardiac output with maintenance of an appropriate effective circulatory volume is critical to restore organ perfusion and improve GFR. This improvement in cardiac output can be achieved by afterload reduction with vasodilators, improvement in contractility with inotropic therapy, or use of mechanical circulatory support. If tolerated, vasodilators should be used as the first line of therapy in these patients to improve cardiac output, given that its use is associated with better outcomes than in patients treated with inotropes [81, 82]. Inotropes can be used to improve cardiac output, but they have been associated with increased mortality and poor short-term prognosis [83–86]. Mechanical circulatory support with left ventricular assist devices (LVADs)—while never indicated based solely on the presence of cardiorenal syndrome—has shown improvements in renal function [87, 88]. Relaxin-2, a natural peptide that increases during pregnancy, is a potent renal vasodilator. Recently, serelaxin, a recombinant human relaxin-2, has shown rapid relief of congestion in acute decompensated heart failure patients. It is associated with an improvement in markers of cardiac, renal, and liver function with subsequent improvement in clinical outcomes by preventing organ damage [89]. Other strategies such as low-dose dopamine and nesiritide have failed to show a beneficial effect in these patients. Additional secondary effects such as tachycardia and hypotension could be deleterious in patients with renal dysfunction [90].

(d) *Considering sympathetic renal denervation*: Given the importance of the kidneys in SNS activation mediated by renal afferent and efferent sympathetic nerves, renal denervation therapy has emerged as a possible treatment alternative. Although large, randomized studies have failed to show improvement in primary outcomes [91], some small studies have shown that renal denervation therapy is associated with

improvement in a 6-min walk test and decreased diuretic use in patients with systolic heart failure [92]. Animal studies have also shown that renal denervation has a protective effect on the kidney and the heart that is independent of blood pressure changes—and that appear to be associated with the effect on the renin-angiotensin-aldosterone system [93]. However, despite these findings, there is no evidence that renal denervation therapy slows the progression of chronic kidney disease, and, in some cases, it has been associated with a deleterious effect on renal function [94].

Summary

In summary, cardiorenal syndrome is anticipated to be an area of active research. Improvements in our understanding of CRS' underlying mechanisms and most effective treatment options would have a major impact on caring for patients with heart failure.

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Neurohormonal Activation and the Management of Heart Failure

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_16

Introduction

Heart failure is a complex and usually progressive disease process in which structural and functional disturbances in the left ventricle are accompanied by activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) [1–3]. Before the 1970s, managing heart failure aimed at improving the functional deficit of the left ventricular pump and relieving the resultant fluid accumulation with diuretic therapy [4]. Although diuretic therapy has remained a mainstay of treatment, inotropic drug therapy was associated with adverse effects and no improvement in survival [5, 6]. Consequently, since the 1970s, pharmacologic management has shifted more toward reducing the vascular bed's opposition to left ventricular emptying and inhibiting the vasoconstrictor and growth-promoting influences of neurohormonal stimulation that leads to left ventricular structural changes or remodeling [7–10]. This shift in emphasis has resulted in reduced dependence on digitalis and other positive inotropic interventions and greater reliance on angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-adrenergic receptor blockers, aldosterone inhibitors, and newer agents that appear to inhibit vasoconstrictor and growth-promoting forces that contribute to the progression of the disorder [11–15].

This chapter addresses the evidence for neurohormonal activation in heart failure, data demonstrating a favorable effect of these neurohormonal modulators on the course of heart failure, and future therapeutic strategies that may be effective in slowing the growing burden of heart failure in the developed world.

Activation of the Renin-Angiotensin-Aldosterone System

The renin-angiotensin system (RAS) evolved as a defense mechanism to enable animals to migrate from saltwater to land, where it was necessary to preserve sodium and water critical for survival (Fig. 16.1). The RAS has traditionally been viewed as a renal system capable of monitoring the concentration of sodium in the renal tubules. If needed, it adjusts the production rate of angiotensin, which preserves sodium and supports blood pressure when intravascular fluid becomes depleted [16]. In support of this hypothesis, secretion of renin, which enhances angiotensin II production, is activated in the presence of a low-salt diet and suppressed when salt intake is high [17]. In more recent years, the RAS has also been shown to activate the production of angiotensin at local sites, particularly in the microvasculature, where its presence is critical in controlling vascular tone [18].

The adrenal cortex secretes aldosterone, a hormone also critically involved in renal tubular function, in response to changes in potassium concentration [19]. Since angiotensin stimulates the secretion of aldosterone, the RAS system is often referred to as the RAAS system. Aldosterone and angiotensin function in a coordinated fashion to control electro-

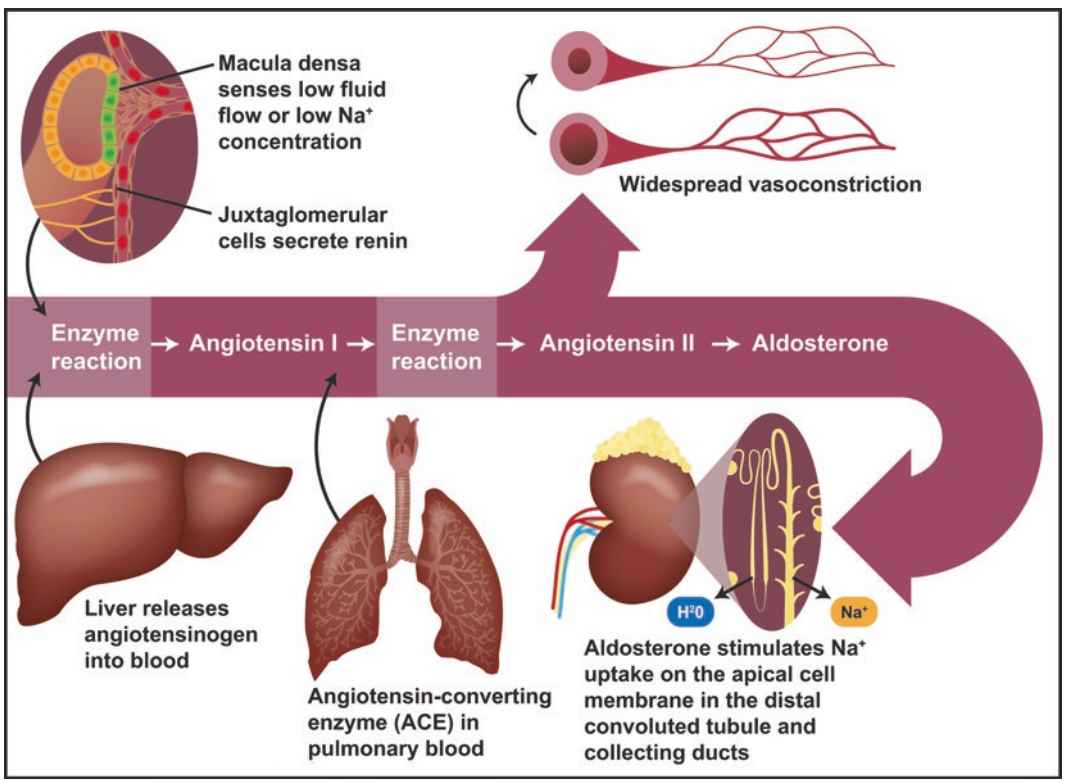

Fig. 16.1 Sequence of normal physiological events resulting from deprivation of salt

lyte excretion by the kidney and to support blood pressure when necessary [20].

These hormonal systems are all activated in patients with heart failure, probably not as an appropriate response to cardiac dysfunction but as a misguided signal suggesting the depletion of vascular volume and the need for fluid retention [21]. Indeed, the decrease in cardiac output often noted in heart failure may be perceived by arterial receptors as a decrease in cardiac output from volume depletion. The difference, of course, is that in dehydration, the total vascular volume is depleted, whereas in heart failure, the volume depletion is confined to the arterial system, while the venous system is more likely overexpanded.

Extensive hemodynamic and clinical outcome studies have confirmed the inappropriateness of hormonal activation. Drugs that interfere with the RAAS system produce dramatic improvements in cardiac performance and also slow the structural remodeling process in the left ventricle [22–27]. The magnitude of benefit of these pharmacologic agents has made these drugs an essential part of the recommended regimen to manage patients with chronic heart failure [28].

Activation of the Sympathetic Nervous System

The RAAS is predominantly a circulatory system, in which blood levels of the hormone exert direct effects on its target organs. The mediator of sympathetic nervous system (SNS) activity, predominantly norepinephrine, is released at adrenergic nerve endings and exerts its effect locally. Thus, circulating levels of the hormone, although a reflection of release at the nerve endings, do not provide accurate insight into the degree of local activation [29, 30]. Nonetheless, elevated circulating levels of norepinephrine correlate directly with the severity of heart failure and with shortened survival times [3].

The mechanism or mechanisms by which heart failure leads to sympathetic nervous system activation are not well understood. Reduced stroke volume or reduced rate of pressure rise in the aorta may influence baroreceptors and induce sympathetic activation (Fig. 16.2). Such a response to what may be perceived by the body as a reduction in arterial blood volume would appear to be an appropriate compensatory effort. Heart rate increases, myocardial contractility is augmented, the arterial system constricts to support blood pressure, and renal blood flow falls to inhibit volume loss. Traditionally, this sympathetic activation was believed critical in maintaining circulatory function in the setting of heart failure, but data in more recent years suggest that inhibition of the sympathetic nervous system response exerts a favorable effect on long-term prognosis in patients with heart failure [22–27], although some concern over its safety persists [31].

But a fundamental difference exists between the circulatory impact of activation of the RAAS and that of the SNS. RAAS stimulation activates angiotensin that exerts its

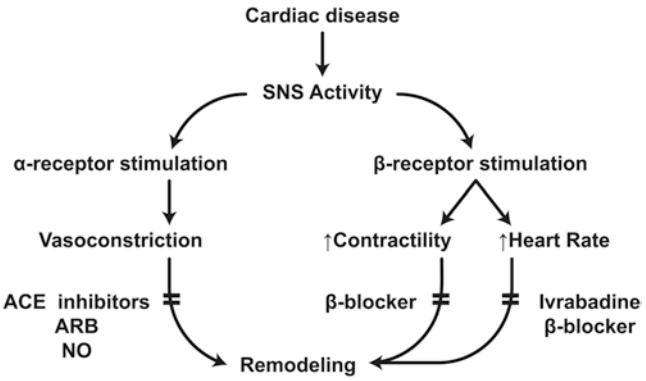

Fig. 16.2 Consequence of sympathetic activation in heart disease. The adverse consequences of vasoconstriction and cardiac stimulation can be counteracted by drug therapy, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), nitric oxide (NO) enhancement, and beta blockers (β-blockers)

effects on all circulatory beds. In contrast, SNS activation—through neural pathways and the release of norepinephrine—activates organ-specific receptors that exert quite distinctive effects. The most important of these are the alpha receptors that constrict the vascular smooth muscle and the beta receptors that stimulate the heart to increase its rate and its force of contraction [32]. These receptors respond independently to pharmacologic blockade [33].

Until the 1990s, the enhanced cardiac stimulation of beta receptors in heart failure was believed critical in maintaining cardiac output and perfusion of vital organs. When long-term trials with beta blockers, given in gradually escalating doses to minimize adverse effects on cardiac function, were shown to prolong life, it became apparent that cardiac stimulation was accompanied by progressive structural remodeling of the heart that shortened life expectancy [34, 35]. These drugs then began the transition from "contraindicated" to "mandated" therapy for heart failure with a dilated left ventricle [28].

The role of alpha receptor stimulation in heart failure remains more controversial. One would expect that alpha blockade to relax vasoconstriction, which impedes cardiac output in heart failure with a dilated ventricle, would be beneficial. Nonetheless, the vasodilator effect of alpha blockade does not appear to exert as much benefit on morbidity and mortality as does comparable vasodilation induced by drugs that activate nitric oxide (NO) [36]. Thus, alpha blockade is not advocated to enhance arterial dilation in heart failure. Furthermore, central inhibitions of the SNS by drugs that inhibit SNS activation have not improved outcomes [31, 37]. Consequently, the overall impact of sympathetic stimulation on the course of heart failure is uncertain.

Heart Failure and Cardiac Remodeling

Similar dysfunction of the left ventricle may occur in the presence of two rather distinct structural changes in heart failure (Fig. 16.3). In heart failure with a dilated ventricle

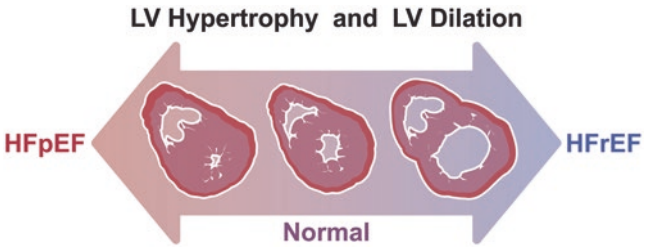

Fig. 16.3 The two distinct pathological processes associated with heart failure. Cross section of the normal left and right ventricle is shown in the center. In heart failure with a dilated ventricle (HRrEF) on the right, the left ventricle and right ventricle are both dilated. In HFpEF on the left, the left ventricular wall is thickened, the chamber size, normal or small, and the right ventricle usually dilated

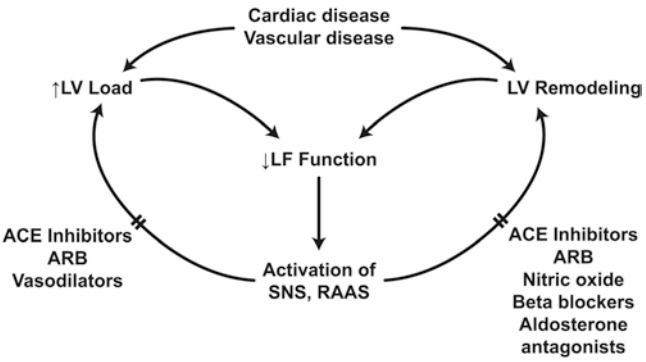

Fig. 16.4 Pathophysiological events contributing to progression of heart disease. Effective therapy inhibits the adverse consequences of both the functional and structural effects of neurohormonal activation

(HFDV)—often referred to as heart failure with a reduced ejection fraction (HFrEF)—the chamber is dilated, the wall sometimes thickened, the myocardial mass increased, and the wall motion greatly reduced. This pattern is common in patients who have suffered a prior myocardial infarction and also in patients with cardiomyopathy from nonischemic origins. The dilated chamber results from lengthening of myocytes as a result of new sarcomere growth longitudinally in series in the myocytes [38].

In heart failure with a non-dilated ventricle (HFNDV)—often referred to as heart failure with a preserved ejection fraction (HFpEF)—the chamber is not enlarged, but the wall is usually thickened. This pattern is commonly observed in elderly individuals, often women, and generally has a better prognosis than the dilated ventricle syndrome [39]. The sarcomere growth pattern in this syndrome thickens the myocyte because of sarcomere growth in parallel.

Neurohormonal activation occurs in both structural syndromes of heart failure, but the magnitude of activation is generally greater in the HFDV syndrome. Indeed, large-scale prospective studies have demonstrated the effectiveness of neurohormonal-inhibiting therapy with HFDV syndrome [22–27]. Attempts to document benefit of such therapy in the HFNDV syndrome have generally been disappointing [40–42]. These contrasting experiences have strengthened the hypothesis that the major therapeutic benefit of neurohormonal blocking therapy in heart failure is its inhibiting effect on the cardiac remodeling that contributes to chamber dilation (Fig. 16.1).

Treatment of Heart Failure

Treatment goals for symptomatic heart failure are twofold: (1) relieve the symptoms of heart failure and improve quality of life and (2) prolong life. Until the 1980s, managing chronic heart failure was limited to digitalis to enhance contraction of the failing left ventricle and diuretics to relieve the circulatory congestion that was manifested as shortness of breath and edema. Recognizing that vasoconstriction was placing a reversible impedance load on ventricular emptying, and that neural and hormonal stimulation was contributing to both vasoconstriction and adverse cardiac remodeling, led to the current universal recommendation that patients with heart failure associated with a reduced ejection fraction (HFrEF)—or HFDV—should be treated with one, two, or perhaps all of the following drugs: an ACE inhibitor, an angiotensin receptor blocker (ARB), a beta-adrenoceptor blocker, and an aldosterone inhibitor [28] (Fig. 16.4). Multiple large-scale trials have shown reduced mean morbidity and/or mortality when the effect of each of these drugs is compared to comparable patients managed without each of these drugs [22–27].

It is important to understand what these large-scale trials demonstrating efficacy mean for individual patients. They do not imply that all individuals with the disease process will benefit from the drug in question. Differing genetic and environmental factors render each individual and their disease process unique. In the population of individuals studied, the trial results imply that the benefit of randomized assignment to the study medication exerted greater benefit than harm on the end point selected for study. Some individuals may have been harmed, but more individuals in the population were benefited. All trials assess benefit in populations, not necessarily in individuals.

Given that caveat, guidelines use these large-scale trials as the basis for recommending treatment regimens for patients with heart failure, at least those having the baseline characteristics of those included in the trials. These recommendations probably do not apply to all individuals who meet the criteria, but in the absence of clear evidence for excluding specific individuals, the recommendations have come to be applied to all. The following analysis provides the mechanistic and trial basis for the currently recommended drug management of chronic heart failure. Unless otherwise stated, these recommendations are confined to patients with chronic, stable heart failure accompanied by a dilated left ventricle with a reduced ejection fraction.

Inhibitors of Angiotensin

The renin-angiotensin system is stimulated early in the heart failure syndrome, presumably as a change in renal sodium handling. Since angiotensin constricts the arterial microcir-

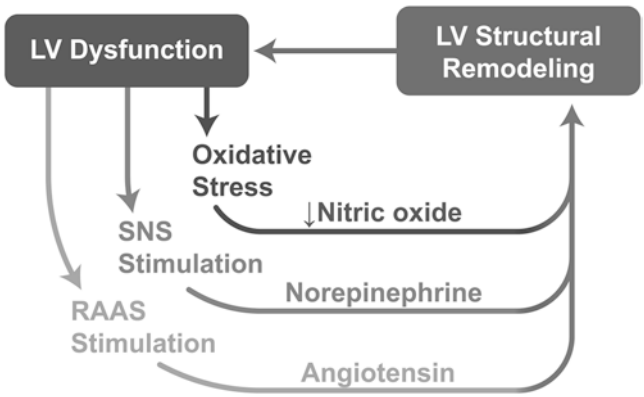

Fig. 16.5 Role of activation of the renin-angiotensin system (RAS), sympathetic nervous system (SNS), and oxidative stress in influencing left ventricular structural remodeling

culation and stimulates vascular smooth muscle growth, its inhibition improves left ventricular emptying and modestly enhances cardiac output [43] (Fig. 16.5). Furthermore, despite angiotensin's minimal effect on venous constriction, drugs that interfere with angiotensin action also reduce venous pressure. Elevated venous pressure contributes to shortness of breath and edema. It remains unclear how much of this venous effect is contributed by bradykinin stimulation and how much by sympathetic inhibition, which also may be mediated by angiotensin inhibition. Nonetheless, angiotensin inhibition improves the hemodynamics in heart failure, thus relieving symptoms and improving quality of life. Furthermore, because of angiotensin's role in stimulating both cardiac and vascular smooth muscle growth, its inhibition is accompanied by a reduced rate of left ventricular remodeling and improved long-term prognosis [11, 25].

The benefits of angiotensin inhibition can be gained with either an ACE inhibitor or an angiotensin receptor blocker. The sequence of their development led most ACE inhibitor trials to compare the various agents to placebo, where they were effective in reducing morbidity and mortality. In later ARB trials, however, the drugs were compared largely as additive to ACE inhibitors, where modest morbidity reductions could be shown but not necessarily a further reduction in deaths.

Important pharmacologic differences exist in the response to these two classes of drugs. ACE inhibitors reduce angiotensin II levels, at least transiently, and stimulate bradykinin. ARBs selectively block AT1 receptors but result in an increase in angiotensin II levels, thus potentially enhancing AT2 receptor-mediated responses. How these pharmacologic differences influence the short-term and long-term effects of these drugs is largely unknown.

Dosing of these angiotensin-inhibiting agents has traditionally been based on the response, that is, reduced blood pressure in managing hypertension. In heart failure, however, dosage has been based on the target doses achieved in long-term outcome studies. It has been suggested that dosing in hypertension should similarly be aimed at target doses rather than target responses [44]. Tolerability to these target doses is documented by gradual escalation of the dose. A dangerous reduction in blood pressure, or intolerable dizziness when standing, mandates reduction in the dose of these drugs. A modest rise in serum creatinine is a common observation when initiating therapy, but this azotemia is usually reversible and should not require dose reduction unless it becomes progressive.

It is likely that the benefits of ACE inhibitors and ARBs in managing heart failure represent a class effect of these drugs and likely apply to all members of the class. Drug marketing restrictions mandate, however, that only drugs that have undergone adequate controlled studies in heart failure can be labeled for use in that syndrome. Furthermore, specific dosing recommendations for any drug would depend on a clinical trial demonstrating efficacy of that target dose. With ARBs, there is little reason to suspect that individual drugs in that class exert a different spectrum of effects. With ACE inhibitors, however, differing effects may relate to tissue penetration. Some lipophilic agents may more effectively gain access to tissue compartments where the local renin-angiotensin system may be activated. Whether such local effects are of importance in the response to ACE inhibitors in heart failure is uncertain.

Beta-Adrenoceptor Blockade

Historically, the clinical benefit of beta blockers to treat heart failure was documented after ACE inhibitors became standard therapy. Their use, therefore, is generally recommended to supplement inhibitors of angiotensin effect. Furthermore, since beta blockers do not produce short-term improvement in hemodynamics nor short-term benefit in quality of life, their dosing requires gradual escalation to avoid adverse effects. Background angiotensin-inhibiting therapy probably enhances tolerability of the beta blockade. Thus, the general recommendation of initiating ACE inhibitor or ARB therapy first, and then initiating a beta blocker regimen, is rational.

Beta blockers' main site of action in heart failure is on inhibiting the left ventricular myocyte and collagen remodeling process (Fig. 16.5). This effect is associated with reduced ventricular volume and improved ejection fraction [25–27]. Thus, it is important to confine this pharmacologic approach to patients with dilated ventricles and a reduced ejection fraction.

The mechanism by which beta blockade inhibits remodeling remains controversial. If it relates exclusively to inhibition of the sympathetic nervous system, it is unclear why the benefits are not replicated by central sympathetic nervous system inhibition by drugs such as clonidine and moxonidine [31, 37]. Since a similar benefit on remodeling and outcome is associated with the use of ivabradine, a drug that slows heart rate without inhibiting the sympathetic nervous system [45], one hypothesis is that the benefit of beta blockers is mediated primarily through cardiac slowing.

Although the beneficial effect of beta blockers in heart failure is viewed largely as an effect of this class of drugs, indi-

vidual differences in the mechanism and site of action of beta blockers make it problematic to use agents that have not been adequately tested in this syndrome. Beta-1 selectivity and other pharmacologic properties of individual drugs vary widely and may impact their effectiveness in heart failure.

Aldosterone Inhibition

The role of aldosterone in the progression of heart failure is poorly understood. Levels of the circulating hormone are increased in heart failure, but that increase does not appear to be associated with worsened survival, as it is with renin activity and norepinephrine [46]. Nonetheless, inhibition of aldosterone action by drugs such as spironolactone and eplerenone in patients with heart failure appears to inhibit left ventricular remodeling and improves survival [47]. In heart failure, these drugs have been studied as supplements to background therapy, usually with an ACE inhibitor and a beta blocker. Therefore, these drugs are generally recommended to be added to the background regimen for heart failure, not to be used as primary therapy.

The most serious side effect to aldosterone-inhibiting therapy is a rise in serum potassium, potentially to lethal levels. Initiation of therapy therefore requires sequential monitoring of serum potassium to guard against a rise to levels above 5.5 mEq/L.

The major dilemma with aldosterone inhibition is whether it should be part of the standard regimen for all patients with heart failure and a dilated ventricle or whether it should be reserved for patients whose disease appears to progress despite standard background therapy. Clinical trials cannot resolve that dilemma because the benefit in a large-scale trial is probably confined to a small subset of the population that cannot be identified in the context of the study.

Nitric Oxide Enhancement

Nitric oxide is a normal product of endothelial function in the vasculature and probably endocardial function in the heart [48]. Its production maintains low vascular tone, inhibits vascular smooth muscle and myocyte growth (Fig. 16.5), and inhibits platelet aggregation in the vasculature [49]. In heart failure, as in most cardiovascular diseases, endothelial function is impaired and nitric oxide deficient. It is likely that neurohormonal activation plays a role in antagonizing nitric oxide activity.

The only therapy currently available as a nitric oxide enhancer is the combination of isosorbide dinitrate and hydralazine, available commercially as a combination tablet called BiDil. This combination tablet has been shown to be effective as a supplement to conventional therapy in enhancing quality of life and prolonging life in patients with heart failure and a dilated ventricle [50]. The effect in an earlier trial was enhanced in patients of African-American descent [51], and a trial specifically in African-Americans demonstrated a 43 % reduction in mortality [50]. Thus, the drug is approved for treatment of blacks with heart failure but has not been subjected to an adequate study in white patients, Asians, or Hispanics.

The rationale for its enhanced effect in blacks is based on the evidence that African-Americans more often have endothelial dysfunction with reduced nitric oxide activity [51]. How neurohormonal stimulation interacts with nitric oxide deficiency and how angiotensin inhibition and beta blockade may impact this interaction remain largely speculative. The potential importance of enhanced nitric oxide, however, should stimulate the development of other pharmacologic interventions to enhance this system, not only in patients with heart failure but also in those with other vascular diseases.

Early Versus Advanced Disease

Therapeutic interventions in patients with heart failure have generally been studied in advanced forms of the disease. This strategy is in part mandated by the regulatory need to document a reduction in morbid events, which are common enough in advanced disease to be targeted in therapeutic trials. This clinical trial strategy should not, however, inhibit the clinical goal of slowing progression of early disease to prolong healthy life. Thus, the lessons learned in trials of advanced disease can hopefully be applied to management strategies earlier in the disease process.

Neurohormonal stimulation can be documented in early stages of heart failure [52]; thus, neurohormonal-inhibiting therapy might be effective in slowing progression. Successful intervention at this stage would mean intervening in individuals who have a low likelihood of a short-term morbid event. End points other than death or serious morbid events would need to be selected. This strategy requires that the cost/benefit of such interventions be favorable and that the side effects and adverse consequences of the management strategy be acceptable.

Unresolved is the appropriate stage of early disease that justifies intervention. Should a dilated left ventricle without symptoms be treated, hopefully to delay its progression? Should minor symptoms of heart failure lead to aggressive multiple-drug therapy? Should such therapy be continued for life, for fear that its discontinuation will result in progressive left ventricular remodeling? Large-scale clinical trials would be needed to address each of these questions. But even then, the population-based evidence may be inadequate to advise individual patients on the best strategy for management.

As in nearly all aspects of patient management of complex disease processes, the best strategy is developed by a knowledgeable caregiver interacting with an individual patient. A caregiver's physiologic and pharmacologic insight should be a prerequisite. It must be supplemented by knowledge of clinical trial data and of guideline recommendations for an individual's background and disease process in order to formulate a tailored treatment plan.

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Structural Remodeling in the Development of Chronic Systolic Heart Failure: Implication for Treatment

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_17

Heart failure (HF) progresses through a process of structural remodeling of the heart to which neurohormonal and cytokine activation makes an important contribution. The term *ventricular remodeling* refers to deviation in ventricular architecture from normal, with changes in volume, wall thickness, and/or shape. This term was initially applied to the pathologic changes related to myocardial hypertrophy, fibrosis, and associated chamber dilation seen following a large myocardial infarction (MI) [1–3]. The term has also been used in other conditions associated with ventricular dilation and eccentric myocardial hypertrophy, referred to as dilated cardiomyopathy, and to conditions associated with concentric left ventricular (LV) hypertrophy with a normal or reduced chamber volume, as is seen in hypertensive heart disease. A large body of evidence now indicates that these forms of pathologic ventricular remodeling are independently associated with adverse clinical outcomes and, more importantly, that interventions that attenuate or reverse these changes are usually associated with improved clinical outcomes [4].

Remodeling Concept of Heart Failure

It is well known that the heart can enlarge or shrink in response to hemodynamic demands (Fig. 17.1) [5]. Critical to our understanding of HF are observations that HF is related to progressive alterations in the heart's structure and function. The earliest reference to the role of cardiac structure in development of HF dates back to the nineteenth century [6]. In *The Principles and Practice of Medicine*, William Osler pointed to hypertrophy as a step in the development of HF, since it is followed by a "period of broken compensation … that commonly takes place slowly and results from degeneration and weakening of the heart muscle" [7]. However, in the modern era, Linzbach has been credited for being the first to recognize that alterations in cardiac structure are the primary determinants of HF and that LV weight of about 200 g was critical in the natural history of the disorder [8].

In the 1960s, a different view of LV hypertrophy and enlargement began to emerge. In accordance with Laplace's law, which dictates that afterload-induced increases in

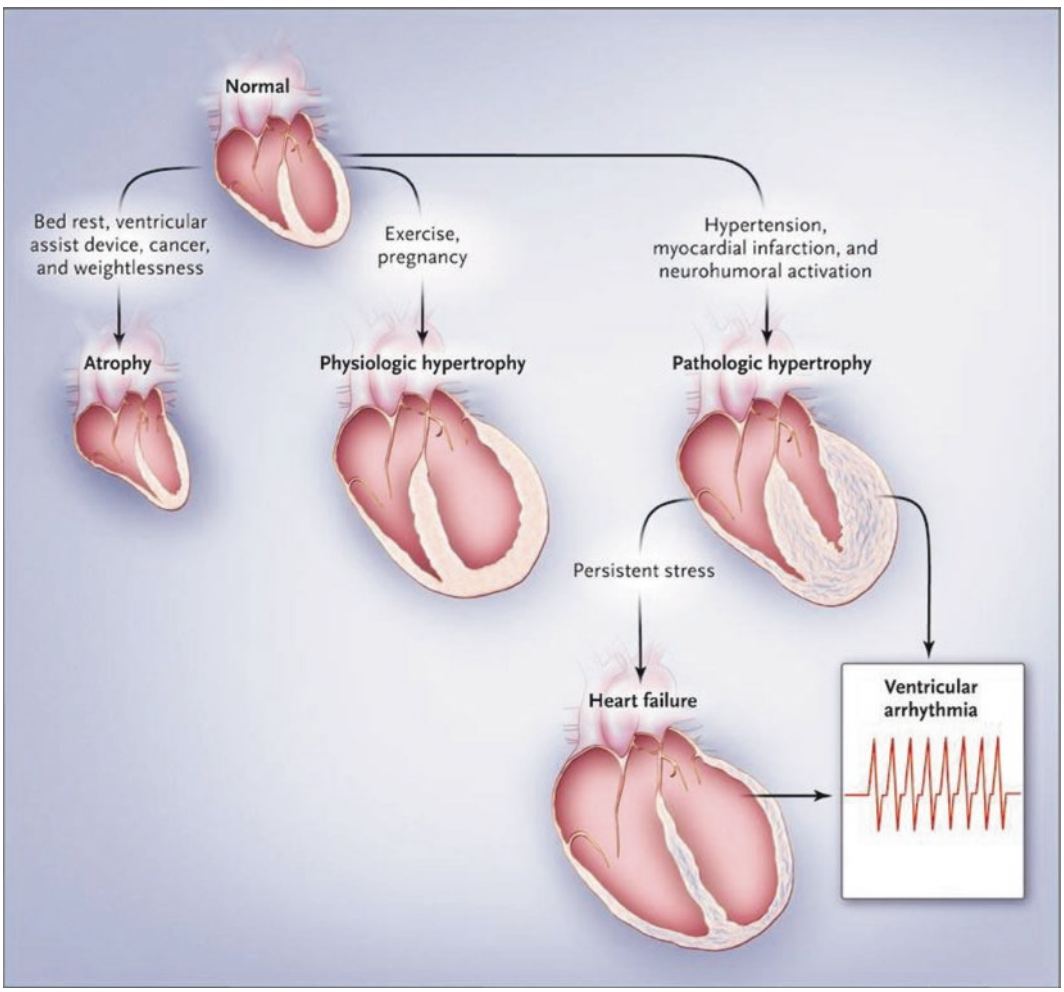

Fig. 17.1 Conditions leading to remodeling of the heart and resulting in atrophy or hypertrophy. Depending on the circumstances, remodeling can be normal or pathologic. Pathologic remodeling is associated with a propensity toward decompensation, ventricular dilatation, systolic dysfunction, and electrophysiologic changes leading to malignant ventricular arrhythmia. *Source*: Hill JA, Olson EN. Cardiac plasticity. N Engl J Med. 2008;358:1370–80

systolic wall stress are offset by increases in wall thickness, hypertrophic growth of the heart was seen as "compensatory" and, hence, beneficial [9, 10]. Animal models of pressure overload led Meerson to suggest that cardiac growth induced by biomechanical stress plays a protective role, at least in the short term [11]. Moreover, in the 1970s and 1980s, hemodynamic measurements in patients with valvular heart disease provided support for the concept of adaptive hypertrophic growth which, when "inadequate," could lead to systolic dysfunction [12–14].

Recent clinical studies have called into question the idea that structural changes of the ventricle are adaptive and protective. Progressive LV hypertrophy, enlargement, and cavity distortion over time have consistently been shown to be directly related to the deterioration of LV performance and an increase in mortality and morbidity [15–19], irrespective of the etiology of HF [20].

Current concepts of ventricular remodeling are largely derived from studies on patients and animal models of MI and hypertension [21–24]. Studies by Chanutin and Barsdale [25] on an experimental model of arterial hypertension demonstrated that LV weight and myocyte fiber diameter increased in relation to the severity of hypertension. Janice Pfeffer and her colleagues [26, 27] studied the relationship between LV mass and function over time, in the spontaneously hypertensive rat model. They demonstrated that despite continuous and marked LV wall thickening, the LV eventually dilates and then fails. At this stage, the stimulus for LV hypertrophy is not only elevated arterial pressure but also chamber dilatation that further aggravates the hemodynamic load by increasing wall stress. This seminal finding laid the foundation for the concept that regardless of the initial insult, ventricular dilatation may become a self-sustaining process of deterioration in LV structure and function.

A consensus statement helped define remodeling as the "genomic expression resulting in molecular, cellular and interstitial changes that are manifested clinically as changes in size, shape and function of the heart after cardiac injury" [28]. Remodeling process is regulated by mechanical, genetic, and neurohormonal factors [29]. The importance of ventricular remodeling has increased with the observation that agents such as inhibitors of the sympathetic and renin-angiotensin-aldosterone systems that have beneficial effects in HF also generally attenuate or reverse ventricular remodeling [30–34], whereas agents that fail to improve clinical outcomes either have no effect on remodeling or have been associated with adverse remodeling [4]. Ventricular remodeling has therefore emerged as a credible surrogate end point and an important therapeutic target in HF [35, 36].

Mechanisms of Left Ventricular Remodeling

Although ventricular remodeling may occur following any form of myocardial injury [20], most of our knowledge has been acquired from the study of remodeling following MI. Acute coronary occlusion in the clinical setting or in the experimental animal leads to loss of myocardial tissue, depression of myocardial function, and hypotension. This causes baroreceptor-mediated activation of a number of neurohormones that help stabilize the hemodynamics through an increase in heart rate, contractility, and fluid retention. However, continuous activation of these mechanisms, designed for short-term support of blood pressure [37], may lead to progressive LV remodeling and dysfunction. Two distinct phases have been identified following MI: early postinfarct LV remodeling and late progressive LV remodeling.

Early Postinfarct Left Ventricular Remodeling

Loss of regional wall function after acute MI results in an abrupt increase in loading conditions of the ventricle that brings on a unique pattern of remodeling involving the infarct area, the border zone, and the remote noninfarcted myocardium. Thinning and stretching of the acutely infarcted myocardium lead to infarct expansion, the first feature of LV remodeling [21, 22]. Although later thinning of the LV wall also occurs in the noninfarcted myocardium, the cellular mechanisms are different in the two regions. In the infarcted myocardium, wall thinning is pronounced and is a result of loss of myocytes, collapse of the intercellular space, and stretching of surviving myocytes [21–23, 38, 39]. This may lead to bulging of the infarct zone that can result in ventricular rupture, aneurysm, mitral insufficiency, and ventricular tachyarrhythmias. In the noninfarcted regions, myocardium thins because of a decrease in the number of myocytes across the wall [38, 39]. Two mechanisms—myocyte slippage [38] and myocyte loss from necrosis [40–42] and apoptosis [41, 43]—have been proposed to explain this decrease.

It has been suggested that "myocyte slippage" plays a major role in progressive chamber dilation leading to failure [8, 38, 44], although much of the literature mentioning this phenomenon is rather vague. This concept usually refers to slippage of myocytes past one another transversely or linear slippage of individual myofibrils within myocytes [44, 45].

Increased myocardial collagenase activity (see discussion under *Extracellular Matrix Remodeling* below) is believed to disrupt intermyocyte collagen struts, leading to side-to-side slippage of myocytes [46]. Such a process could reduce wall thickness and increase the volume of the ventricle. Linzbach [44] and others [38] have noted reduced numbers of myocytes across the wall as evidence of myocyte slippage. However, this explanation may be too simplistic. For a meaningful discussion of the slippage concept, we need to consider the three-dimensional nature of myocyte-to-myocyte interconnections. Each myocyte is connected to an average of 5–10 neighboring myocytes via end-to-end and side-to-side intercalated disks (Fig. 17.2) [47]. Slippage implies disruption of intercalated disks. Once the disks are disrupted, they may be unable to reconnect, resulting in poorly coordinated contractions.

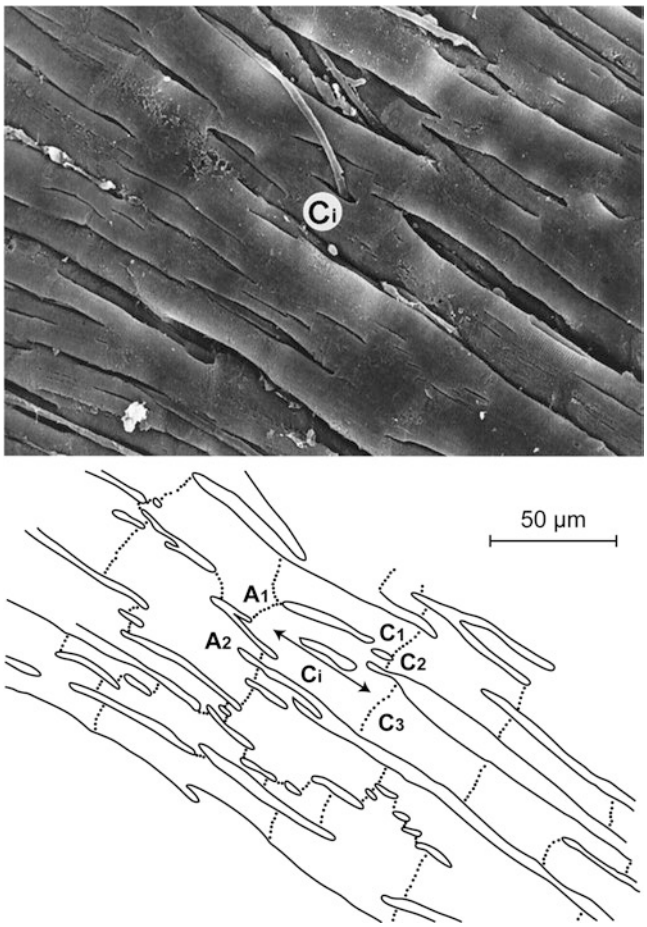

Fig. 17.2 Scanning electron micrograph (*top*) and a drawing (*bottom*) of the cardiac myocardial fibers. The cardiocyte Ci connects with five neighboring cardiocytes (A_1, A_2, C_1, C_2, and C_3). *Source*: Yamamoto S, James TN, Sawada K, Okabe M, Kawamura K. Generation of new intercellular junctions between cardiocytes. A possible mechanism compensating for mechanical overload in the hypertrophied human adult myocardium. Circ Res. 1996;78:362–70

Factors Affecting the Magnitude of Remodeling after Myocardial Infarction

The magnitude of infarct expansion and development of LV remodeling largely depends on the extent of myocardial damage and the loading conditions of the ventricle. In the rat infarct model, increase in LV diastolic volume is related to the size of the infarct and correlated with the extent of impaired systolic performance [48, 49]. A critical transmural infarct size of about 20 % of LV myocardium was necessary for significant infarct expansion [22]. It was observed more frequently in patients with a large anterior transmural infarction compared to an infarction in other regions of the LV [50–52]. Distortion of the ventricular contour leading to aneurysm formation is frequent in patients with infarct expansion and is associated with a much higher 1-year mortality than for patients with anterior infarction and comparably reduced ejection fraction (EF) but without aneurysm [53].

The loading conditions of the ventricle are also important in ventricular remodeling. Both early transient increase in afterload after an MI and sustained increase in afterload with aortic banding increased infarct expansion in animal models [54, 55]. Patients with hypertension and LV hypertrophy have increased morbidity and mortality after MI [56], and careful afterload reduction early in the course of MI may have important effects on LV remodeling by reducing infarct expansion and limiting infarct size [57].

Early establishment of patency of the infarct-related coronary artery and restoration of antegrade flow may also confer a beneficial effect on ventricular remodeling and long-term survival in patients with acute MI, whether accomplished pharmacologically [58] or mechanically [59]. However, the open-artery hypothesis that the restoration of antegrade flow in the infarct-related artery days, weeks, or even several months after MI would improve survival with or without improvement of LV function was not proved in the Occluded Artery Trial [60] and the Total Occlusion Study of Canada (TOSCA)–2 Trial [61].

Late Progressive Postinfarct Left Ventricular Remodeling

Early infarct expansion after MI may be followed by progressive ventricular dilatation and dysfunction over subsequent months and years, involving predominantly the noninfarcted segments. The mechanisms responsible for this inexorable deterioration of LV structure and function are not entirely clear but are related to continued activation of neurohormones and cytokines such as norepinephrine, angiotensin II, aldosterone, endothelin, and tumor necrosis factor. These factors, in combination with increased wall stress and mechanical stretch of the myocytes, upregulate a large number of signaling pathways, leading to structural and functional changes in the myocyte and nonmyocyte compartments that underlay a reduction in LV function and the progression of HF. In the discussion that follows, changes in these individual components will be described and their implications discussed.

Alterations in the Myocyte Compartment

The remodeling process results in important changes in the cardiac myocytes. These include myocyte hypertrophy, myocyte loss by necrosis [41, 42, 62] and apoptosis [41, 63–66], and changes in the structural proteins with downregulation of contractile and sarcomeric skeleton proteins and upregulation of cytoskeletal and membrane-associated proteins [67]. In addition, loss of myofilaments, nuclear enlargement, development of multiple small mitochondria, decrease in the T-tubular system, and sarcoplasmic reticulum are common histological features of the failing myocardium [68].

Myocyte Hypertrophy

Grossman and coworkers proposed that alterations in myocyte shape and size determine the type of cardiac hypertrophy [69]. In conditions with pressure overload such as aortic stenosis or hypertension, parallel addition of sarcomere causes an increase in myocyte cross-sectional area with no increase in myocyte length (Fig. 17.3) [70–72]. This leads to an increase in wall thickness and concentric LV hypertrophy (increase in ratio of wall thickness to chamber dimension) [69, 73]. In conditions with volume overload such as aortic and mitral regurgitation, ventricular volume and wall thickness increase proportionally, and this is associated with a corresponding proportional increase in both myocyte length and cross-sectional area (addition of sarcomeres both in parallel and series) [74] (Fig. 17.3). It appears that during the compensated stage of concentric LV hypertrophy, wall stress does not increase.

After a large MI, progressive LV dilatation is due to an increase in myocyte size which occurs predominantly by laying of sarcomeres in series, resulting in an increase in myocyte length, with only mild increase in width and cross-sectional area [75–78] (Fig. 17.4). This further increases cavity volume with no change or a decrease in wall thickness. Myocyte length is the major determinant of changes in LV size, and most of the increase in LV volume can be explained by an increase in myocyte length [75, 77–79]. Although LV mass increases, the increase in LV volume is proportionately greater, so that mass-to-volume ratio, an important determinant of wall stress, is reduced. The development of myocardial

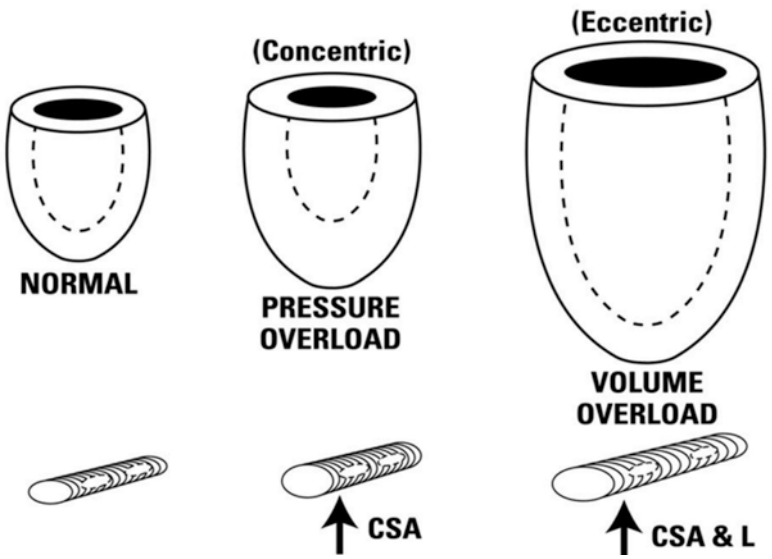

Fig. 17.3 Schematic representation of myocyte change in left ventricular concentric and eccentric hypertension. In pressure-overload hypertrophy, myocyte cross-sectional area (CSA) increases and the ventricular wall becomes thicker during the compensatory phase. In volume-overload hypertrophy, ventricular volume and wall thickness increase proportionally, and this is associated with a corresponding proportional increase in both myocyte length and CSA. CSA and L, cross-sectional area and length. *Source*: Gerdes AM. The use of isolated myocytes to evaluate myocardial remodeling. Trends Cardiovasc Med. 1992;2(4):152–5

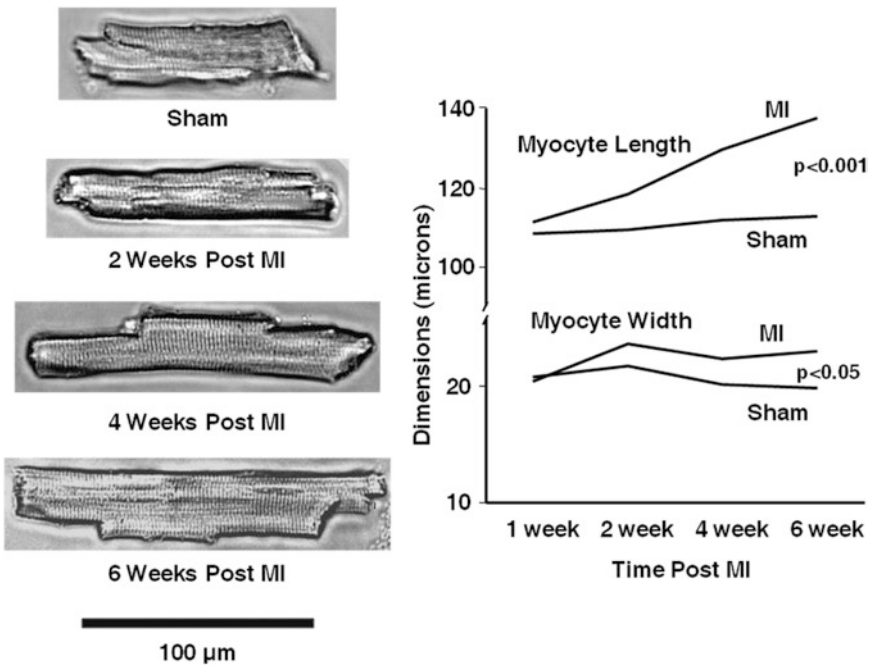

Fig. 17.4 Cardiac myocyte remodeling in the rat infarct model. Myocyte length and width from rats at 2, 4, and 6 weeks after myocardial infarction are compared to those from a sham-operated animal. Note the predominant increase in myocyte length as the major determinant of the increase in ventricular volume. *MI* myocardial infarction. *Source*: Anand IS, Liu D, Chugh SS, Prahash AJ, Gupta S, John R, Popescu F, Chandrashekhar Y. Isolated myocyte contractile function is normal in postinfarct remodeled rat heart with systolic dysfunction. Circulation. 1997;96(11):3974–84

hypertrophy after MI, therefore, results in eccentric hypertrophy (cavity dilation with a decrease in wall thickness to chamber dimension ratio) that increases wall stress.

In volume-overload conditions such as mitral and aortic regurgitation, ventricular hypertrophy remains appropriate and helps to maintain normal wall stress for variable periods of time. Transition from a compensated to a decompensated state is associated with further increase in chamber volume but no increase in wall thickness. This results in a decrease in mass-to-volume ratio and increase in wall stress. The cellular mechanisms responsible for this are not entirely clear, but they could be related to an arrest in growth of the myocytes in the transverse diameter, resulting in myocyte lengthening without further change in myocyte cross-sectional area. Studies of mitral regurgitation in the dog, and in patients at the time of mitral valve surgery, also show a decrease in myocardial myosin content proportional to the degree of LV dysfunction [74, 80]. Thus, reduced contractility in mitral regurgitation could, in part, be due to loss of contractile elements. Although aortic and mitral regurgitation are often considered together as volume-overload conditions, the two have their specific pathophysiologic features.

In aortic regurgitation, the sum of the regurgitant and forward stroke volume is ejected into the aorta in systole, resulting in a wide pulse pressure and systolic hypertension. Therefore, aortic regurgitation creates both volume and pressure overload on the left ventricle. Systolic wall stress is always higher in aortic regurgitation than in mitral regurgitation [81] and is often as high as in aortic stenosis (the classic pressure-overload condition) [82]. These different loading conditions in mitral and aortic regurgitation create two different types of ventricular geometry. In mitral regurgitation, there is an enlarged thin-walled left ventricle in which the mass-to-volume ratio is less than 1.0 [83]. In contrast, in aortic regurgitation, the mass-to-volume ratio is normal at 1.0 [84]. Whether the cellular hypertrophy at the onset of failure is different in these two conditions remains to be determined.

In pressure-overload conditions, concentric ventricular hypertrophy (thick wall, normal chamber volume, and high mass-to-volume ratio) helps to keep wall stress normal despite high ventricular pressure. Because systolic stress (afterload) is a major determinant of ejection performance, the normalization of systolic stress helps to maintain a normal stroke volume despite the need to generate high levels of systolic pressure [12]. Transition to failure is accompanied by progressive cavity enlargement and decline in the mass-to-volume ratio, resulting in eccentric ventricular hypertrophy. In spontaneously hypertensive rats, transition to failure is preceded by myocyte lengthening without an increase in myocyte cross-sectional area [70, 71].

Myocyte Death

Cell death is an important determinant of progressive cardiac remodeling and LV wall thinning. A reduction of contractile material is a prominent feature in HF, and myocyte loss may occur either by necrosis or apoptosis [41].

Myocyte necrosis: Necrosis generally occurs in the setting of catastrophic events such as MI or inflammation and is characterized by severe membrane alterations, release of cell breakdown products, and polymorphonuclear infiltration. However, slow myocyte loss by necrosis is also a common feature of chronic HF [40–42, 85]. During the progression of HF, activation of several neurohormones occurs, including norepinephrine, angiotensin II, and endothelin. These neurohormones are directly toxic to the myocardium and have been shown to cause myocyte necrosis in various animal models [86, 87]. Moreover, in patients with severe HF, circulating levels of troponin are often increased, suggesting ongoing myocyte necrosis [88, 89]. Myocyte loss through necrosis probably contributes to progressive LV dilatation and wall thinning. Even very low plasma concentrations of troponin are predictive of adverse outcomes in patients with chronic HF [88].

Myocyte apoptosis: Apoptosis or programmed cell death is an evolutionarily conserved process of cell death, wherein cells die without provoking significant inflammatory response. Evidence shows that apoptosis contributes to the progression of HF. Apoptosis occurs through a cascade of subcellular events including cytochrome c release into the cytoplasm and activation of proteolytic caspases [90]. Activated caspases lead to fragmentation of cytoplasmic proteins, including contractile apparatus [91]. Caspase-3 (the final executioner in the apoptotic cascade) overexpression or activation has been shown to directly reduce the contractile performance of the LV [92]. The degree of myosin cleavage with caspases correlated with the contractile performance of the heart [93]. It has been proposed that the release of cytochrome c from mitochondria and contractile protein loss in living heart muscle cells contributes to systolic dysfunction [90]. Apoptosis is involved at multiple points in the natural history of HF. This includes initial events like ischemia, infarction, and inflammation as well as those events occurring later in established LV dysfunction. Several of the factors implicated in the pathogenesis of HF such as myocardial stretch [94], norepinephrine [95], angiotensin II [96, 97], tumor necrosis factor-α (TNF-α), and oxidative stress [98, 99] may provoke apoptosis.

While the presence of myocardial apoptosis has been confirmed in end-stage human HF [65, 66] and in several animal models [41, 43, 63, 64], questions remain whether apoptosis is a cause or a consequence of HF. Myocyte apoptosis may be a factor in the transition from compensated to uncompensated HF [91]. This has been shown in several animal models of experimentally induced LV hypertrophy and HF [100–102]. Several studies have demonstrated the presence of apoptosis late after MI [103–105].

Alterations in Myocyte Structural Proteins

The complexity of events involved in the pathogenesis of ventricular remodeling cannot be solely attributed to myocyte hypertrophy and cell loss. The hypertrophied myocytes in the

remodeled failing heart also show alterations in most of the structural proteins (Table 17.1) [67]. Following is a brief description of the structural protein (Fig. 17.5), alterations that occur in HF proteins, and their functional consequences.

Contractile Proteins

The contractile apparatus includes thick filament myosin and thin filament complexes composed of α-actin, α-tropomyosin, and troponins C, I, and T. Ventricular remodeling involves transcriptional and translational downregulation of these proteins [67]. One of the earliest changes is a decrease in α-myosin heavy chain and an increase in β-myosin heavy chain [106].

Table 17.1 Myocyte protein families

Contractile proteins	Myosin, α-actin, α-tropomyosin, troponins C, I, and T
Sarcomeric skeleton	Titin, α-actinin, M-line proteins: M-protein, myosin-binding protein-C
Cytoskeletal proteins	Tubulin, desmin, nonsarcomeric actin
Membrane-associated proteins	Vinculin, talin, dystrophin, spectrin, integrins
Proteins of the intercalated disk	Connexins, cadherins, catenins

Source: Kostin S, Heling A, Hein S, Scholz D, Klovekorn W-P, Schaper J. The protein composition of the normal and diseased cardiac myocyte. Heart Fail Rev. 1998;2:245–60

Sarcomeric Skeleton Proteins

The contractile apparatus is kept in register by different proteins localized in the Z-disk, M-band of the sarcomere, and the giant filament molecule titin, which spans the entire half-sarcomere from the Z-disk to the M-line. The Z-disk is a region of overlapping tails of actin microfilaments cross-linked by α-actinin. The M-line is the region where the myosin tails are linked and organized by the M-line proteins—myomesin, M-line protein, and myosin-binding protein-C. Titin is anchored with its N-terminus at the Z-disk and reaches the M-line region with its C-terminal head portion where it interacts with M-line protein and with myomesin [107]. It spans the Z-disk of the sarcomere [108] and overlaps in the M-line region of the sarcomere [109], thus functioning as a molecular spring and a source of elastic properties of the cardiomyocyte (Fig. 17.5). The interplay between titin and actomyosin suggests a possible role for titin in the Frank-Starling mechanism of the heart [107]. Several studies have reported that the amount of titin is reduced in myocardium of patients with dilated cardiomyopathy, and this could be responsible for the altered ventricular compliance in this condition [110, 111]. Because titin is required for sarcomere formation, lack of titin may also contribute to contractile dysfunction of failing hearts [112].

Cytoskeletal Proteins

The cytoskeleton is a complex network of microtubules (primarily tubulin), nonsarcomeric actin, and intermediate filaments (primarily desmin). Tubulin is the protein of microtubules, which are hollow tubes formed from α- and

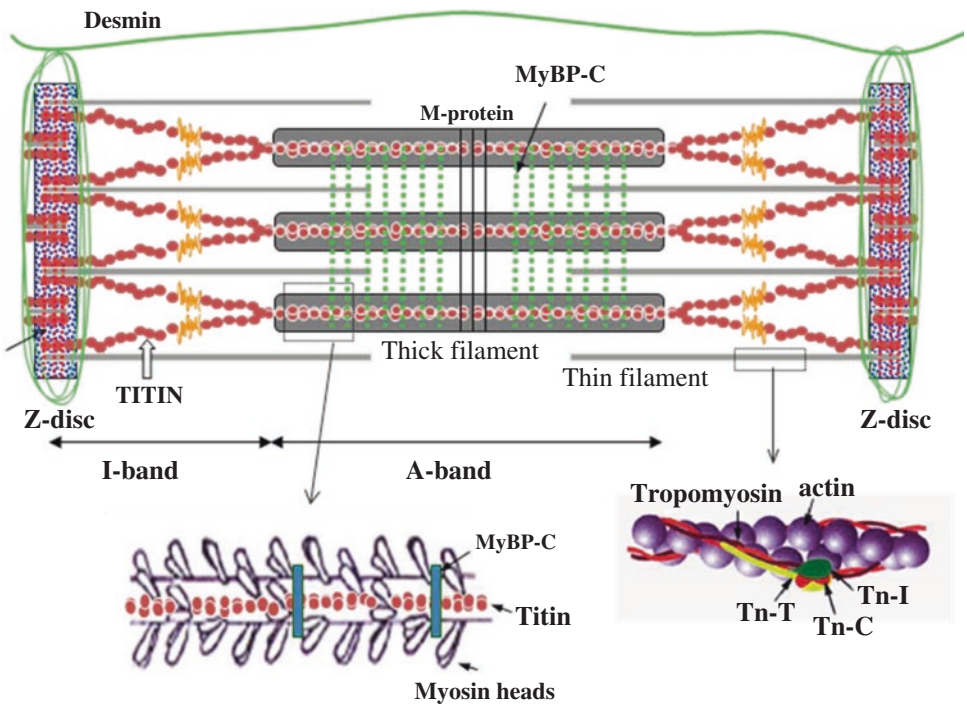

Fig. 17.5 Diagram of the myocyte sarcomeric proteins. (Courtesy of H. L. Granzier.) *MyBP-C* myosin-binding protein-C, *Tn-C* troponin C, *Tn-I* troponin I, *Tn-T* troponin T

β-tubulin surrounding the nucleus and spreading mostly in a longitudinal direction throughout the entire cell. The multifunctional roles of microtubules include mitosis, intracellular transport, organization of organelles, cell motility, determination of cell shape, receptor modulation, and signaling [113]. Desmin surrounds the Z-disks and connects the sarcomeres so that they are kept in register during contraction. Desmin filaments also link myofibrils to one another, to the sarcolemma, and to the nuclear envelope [114]. The desmin network plays a role in the underlying structural integrity of the myocyte, as well as participating in the signaling processes needed for integration of cellular responses to external and internal stimuli [114].

In failing human myocardium, both tubulin and desmin are increased [115]. The increase in these proteins mainly occurs in cells that lack myofilaments and could, therefore, help maintain cellular stability. Tubulin accumulation plays a role in certain models of pressure-overload hypertrophy [116]. In feline right ventricular hypertrophy resulting from pulmonary artery banding, isolated myocytes show contractile dysfunction and loss of compliance. These changes are accompanied by an increase in total and polymerized tubulin [117–119].

Desmin-related cardiomyopathies that have, as a hallmark, abnormal deposits of desmin aggregates are increasingly reported. A progressive increase of desmin protein and filaments was shown to accompany the transition from hypertrophy to HF [120]. Overexpression and altered distribution of desmin were also observed in dilated cardiomyopathy [115]. The absence of an intact desmin filament system may also be involved in cardiomyocyte hypertrophy and cardiac dilation with compromised systolic function [121]. Whether alteration in desmin quantity is a cause or a consequence of HF is not yet clear.

Membrane-Associated Proteins

Membrane-associated proteins include dystrophin, vinculin, talin, spectrin, and integrins, which are involved in fixation of sarcomeres to the lateral sarcolemma and stabilization of the T-tubular system [67, 122, 123]. Mutations of these proteins have been shown to cause dilated cardiomyopathy [124–126]. Dystrophin connects intracellular actin and extracellular laminin independent of integrin binding [127] and plays an important role in promoting the action of the cytoskeleton as a stabilizing force and as a mechanotransductor [128].

Intercalated Disk Proteins

The intercalated disk consists of three different types of specialized membranes: fascia adherens, desmosomes, and gap junctions [129]. Fascia adherens establish the longitudinal connections with the contractile filaments. The desmosomes are connected to intracellular desmin via desmoplakins. Connexins are four-pass transmembrane proteins that are assembled in groups of six to form hemichannels, or connexons, and two hemichannels combined to form a gap junction. Gap junctions are responsible for the orderly spread of electrical excitation from one myocyte to the next in the heart. Remodeling of gap junction and connexin expression is a conspicuous feature of human congestive HF and other cardiac conditions with a dysrhythmic tendency. Remodeling of gap junctions and reduced connexin43 levels may contribute to slowing of conduction [130, 131]. Evidence from experimental animals strengthens the case that gap junction remodeling is a key determinant of arrhythmias in the diseased heart [132, 133].

Alterations in the Nonmyocyte Compartment

Apart from the myocyte compartment, the chronically failing heart is characterized by iterations in the extracellular matrix (ECM), particularly by fibrous tissue formation [62]. Such an adverse accumulation of ECM raises myocardial stiffness and impairs contractile behavior [134].

Extracellular Matrix Remodeling

The extracellular matrix of the heart is made up of a number of structural proteins including fibrillar collagen, smaller amounts of elastin, laminin, fibronectin, and signaling peptides. The complex collagen three-dimensional weave, mainly consisting of type I collagen, interconnects individual myocytes through a collagen-integrin-cytoskeletal-myofibril arrangement. This network supports cardiac myocytes during contraction and relaxation and also provides a mechanism for translating individual myocyte shortening and force generation into ventricular contraction. It is also responsible for much of the ventricle's passive diastolic stiffness [135]. In both human and animal studies, progressive LV remodeling and dysfunction are associated with significant changes in the ECM [136–139]. The specific changes in serological markers of collagen turnover occurring in HF with preserved versus reduced systolic function need to be clarified [140].

The structural hallmark of prolonged pressure-overload hypertrophy is increased collagen accumulation between individual myocytes and myocyte fascicles (Fig. 17.6) [141, 142]. Thus, the highly organized architecture of the ECM undergoes significant alterations in collagen structure, composition, and geometry caused by increased collagen synthesis, postsynthetic processing, posttranslational modification, and decreased degradation and turnover. This "reactive" collagen deposition is characterized by both perivascular and interstitial fibrosis [135, 143, 144]. The changes in collagen homeostasis that occur during the development of chronic pressure-overload hypertrophy are directly associated with increased myocardial diastolic stiffness properties, which in turn cause abnormal diastolic filling [142, 145, 146]. Indeed,

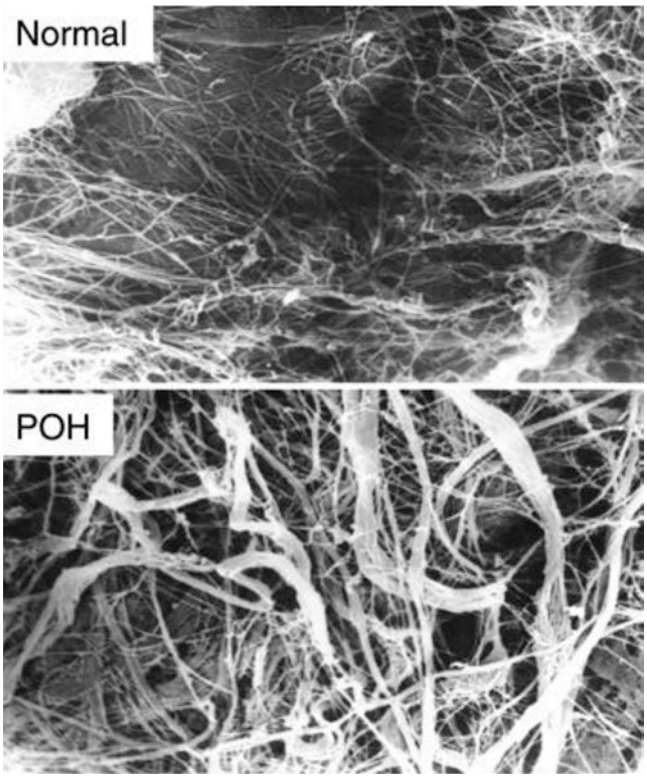

Fig. 17.6 Scanning electron micrographs taken from normal nonhuman primate left ventricular myocardium and following the induction of pressure-overload hypertrophy (POH). These microscopic studies demonstrate thickening of the collagen weave and overall increased relative content between myocytes with POH. *Source*: Abrahams C, Janicki JS, Weber KT. Myocardial hypertrophy in Macaca fascicularis. Structural remodeling of the collagen matrix. Lab Invest. 1987;56(6):676–83

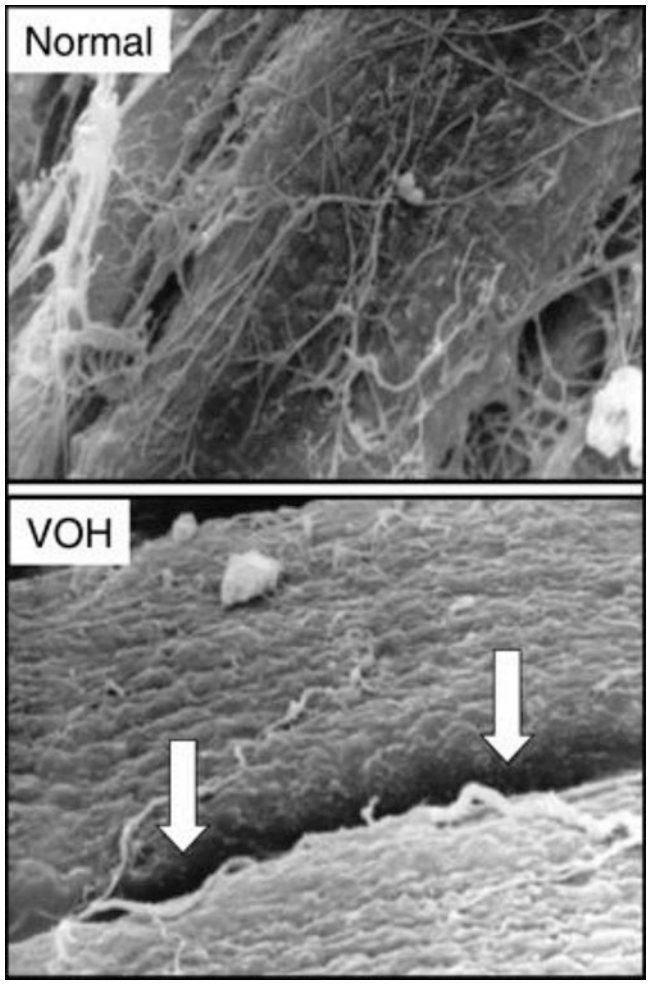

Fig. 17.7 Scanning electron micrographs taken from normal canine left ventricular myocardium following chronic mitral regurgitation that causes a volume-overload hypertrophy (VOH). In this model of VOH, a loss of normal ECM architecture was demonstrated between individual myocytes (*arrows*), and the collagen supporting network is poorly organized. *Source*: Spinale FG. Myocardial matrix remodeling and the matrix metalloproteinases: influence on cardiac form and function. Physiol Rev. 2007;87(4): 1285–342

clinical evidence suggests that progressive ECM accumulation and diastolic dysfunction are important underlying pathophysiological mechanisms for HF in patients with pressure-overload hypertrophy [147, 148].

Because of the persistently elevated preload in volume-overload hypertrophy, a much different pattern of ECM remodeling occurs. In large-animal models of volume-overload hypertrophy caused by chronic mitral regurgitation, the LV remodeling process is accompanied by increased degradation of collagen fibrils surrounding individual myocytes [80]. These changes in ECM support are associated with changes in isolated LV myocyte geometry where the cardiac cells increase in length. Representative scanning electron micrographs taken from a model of canine mitral regurgitation [149] are shown in Fig. 17.7 and show the profound differences in ECM structure and composition compared with normal myocardium. Increased ECM proteolytic activity likely contributes to the reduced ECM content and support and, thereby, facilitates the overall LV remodeling process [150].

Although the mechanisms by which increased degradation of collagen promotes LV dilatation and global LV dysfunction are not entirely clear, dissolution of the collagen weave may lead to increased elasticity and contribute to muscle fiber slippage and, therefore, an increase in chamber size [145]. Loss of collagen struts connecting individual myocytes could prevent transduction of individual myocyte contractions into myocardial force development, resulting in reduced myocardial systolic performance.

The ECM and, particularly, collagen are under dynamic control of two sets of proteins: those that favor degradation and those that tend to inhibit it. The dissolution or degradation of collagen is predominantly related to the activation of matrix metalloproteinases (MMPs), a family of zinc-containing proteins that includes collagenases, gelatinases, stromelysins, and membrane-type MMPs [150]. A critical control point for MMP activity is through the inhibition of the activated enzyme by the action of a group of specific

MMP inhibitors termed tissue inhibitors of metalloproteinases (TIMPs) [150]. The TIMPs are low-molecular-weight proteins that can combine noncovalently to active MMPs, inhibiting their activity [151, 152].

While the contributory mechanisms for the changes in plasma MMP levels remain speculative, an association between changes in plasma MMP levels to adverse LV remodeling has emerged. A Framingham Heart substudy showed that increased plasma MMP-9 levels were associated with LV dilation [153]. Elevated TIMP-1 plasma levels have been associated with major cardiovascular risk factors and with the presence of LV hypertrophy [153]. Furthermore, changes in plasma TIMP-1 levels have been associated with increased mortality [154]. However, it is likely that the changes in plasma MMP and TIMP levels observed in these studies will be influenced by the underlying etiology of the cardiovascular disease process and, therefore, that future studies will be needed. Furthermore, these studies only measured MMP and TIMP plasma levels at one point in time, so the temporal relation to the natural history of the LV remodeling process and progression to HF remains to be established.

Myocardial Fibrosis

Fibrosis in HF is an ongoing, active process of increasing collagen concentration and not simply a response to myocyte injury [134]. There are two types of fibrosis: reparative and reactive. Reparative fibrosis occurs in response to a loss of myocardial cells and is mainly interstitial. In contrast, reactive fibrosis is observed in the absence of cell loss as a reaction to changes in myocardial load or inflammation and is primarily perivascular. During ventricular remodeling, reactive and reparative fibrosis usually coexist. After MI, reparative fibrosis is organized as a scar and is surrounded by reactive fibrosis and myocyte hypertrophy [135].

The mechanisms responsible for fibrosis are still controversial. Fibrosis is not directly induced by myocardial stretch or mechanical overload. Chronic volume overload due to exercise training, atrial septal defect, or aortic insufficiency is not accompanied by ventricular fibrosis [155, 156]. In contrast, pressure overload is frequently associated with fibrosis. It has been proposed that ventricular fibrosis seen in arterial hypertension is caused by associated factors linked to this condition, such as ischemia [157] and neurohormones [134]. Humoral factors, particularly those of the renin-angiotensin-aldosterone system, are believed to be responsible for fibrosis. Angiotensin II and aldosterone have been implicated in the process as they stimulate collagen synthesis in cultured cardiac fibroblasts, and angiotensin II inhibits collagen degradation [158, 159].

Myocardial fibrosis has a number of deleterious effects on cardiac function. A two- to threefold increase in myocardial collagen content alters ventricular filling properties particularly by increasing diastolic stiffness; a fourfold or greater increase in fibrosis also affects systolic function [160]. Fibrosis contributes to ventricular arrhythmias because disproportionate collagen accumulation creates myocardial electrical heterogeneity. Fibrosis is therefore one of the major biological determinants of fatal issues in cardiac remodeling, including congestive HF, severe arrhythmias, and sudden death.

Changes in Global Structure and Function

The mechanical effects of LV remodeling set in motion several self-sustaining deleterious consequences. As the ventricle enlarges, LV geometry alters from a normal prolate ellipse to a mechanically disadvantageous spherical or globular shape. The result is an increase in meridional wall stress [161], abnormal distribution of fiber shortening, increase in oxygen consumption [161, 162], and abnormal myocardial bioenergetics [163]. The spherical shape of the LV leads to dilatation of the atrioventricular ring and stretching of the papillary muscles, resulting in functional mitral regurgitation [164], which contributes to a further decrease in forward cardiac output. Moreover, the high LV end-diastolic volume and pressure promote subendocardial ischemia that aggravates LV dysfunction and neurohormonal activation, decreases exercise capacity [165], and increases the risk of ventricular arrhythmias [166].

Compensatory Versus Maladaptive Remodeling

A fundamental question that must be addressed before embarking on a strategy to reverse hypertrophic and structural myocardial remodeling is whether remodeling is good or bad. Distinction is often made between a compensatory (adaptive) and a maladaptive process. An adaptive component enables the heart to maintain function in response to pressure or volume overloading in the acute phase of cardiac injury [167]. Acute distension of the viable myocardium and the operation of the Frank-Starling mechanism through an increase in sarcomere length are, therefore, entirely appropriate beneficial responses. Likewise, augmentation of chronotropic and inotropic activity through adrenergic receptor stimulation that tends to maintain pump function during the abrupt loss of contractile tissue can be considered compensatory.

Progressive LV dilatation after MI can also help to maintain stroke volume in the face of reduced contractile function and has been considered an adaptive and compensatory response [3, 168]. Under these circumstances, however, increased LV volume is not due to sarcomere stretch, but because of the addition of new sarcomeres in series [78]. Therefore, it is not a mechanism of enhancing contractility on the basis of Frank-Starling mechanism. Such a progressive remodeling and LV dilation does not normalize, but increases wall stress and is associated with a poor prognosis [19, 168].

Moreover, the prevention of very early LV dilation with the use of angiotensin-converting enzyme (ACE) inhibitors

and beta-blockers does not have any deleterious hemodynamic consequence [169–171]. Indeed, Sharpe et al. [169] have demonstrated that the attenuation of LV remodeling with early initiation of ACE inhibitors is associated with a greater increase in stroke volume as compared with a placebo. Furthermore, the prevention of remodeling by early initiation of an ACE inhibitor or beta-blocker, after MI, in selected populations with LV dysfunction [31, 34] and even in unselected populations [172] is associated with significant reduction in mortality and morbidity [34, 170, 173, 174]. Hence, ventricular remodeling and dilation after MI may be maladaptive from the very start and should be a target for aggressive antiremodeling therapy.

In contrast, an increase in ventricular mass that helps to normalize wall stress in aortic stenosis and hypertension may be an appropriate compensatory response. Because systolic stress (afterload) is a major determinant of ejection performance, normalization of systolic stress helps to maintain a normal EF while generating high levels of systolic pressure [12]. However, LV hypertrophy has been shown to be an important independent risk factor for mortality and morbidity [17]. Similarly, a proportional increase in chamber volume, wall thickness, and mass in mitral and aortic regurgitation normalizes wall stress and is an obligatory response to maintain a large stroke volume that is necessitated by the regurgitant volume. Until the initial volume and pressure overload is matched by adequate hypertrophy, the process may be considered adaptive and compensatory. Eventually, a mismatch occurs with progressive dilation and the process becomes maladaptive and decompensatory, and HF becomes clinically manifest [175, 176]. There is no data to indicate when the transition from possible adaptive to maladaptive remodeling occurs; such a transition and its time course can vary greatly. However, once established beyond a certain phase, remodeling likely contributes to progression of HF. Thus, whether remodeling is beneficial or deleterious cannot be viewed as a stereotypical process. Today's challenge is taking advantage of the adaptive features of the hypertrophic response while eliminating or at least minimizing the maladaptive consequences.

Reverse Remodeling

"Reverse remodeling" is a concept, where progressive LV dilatation and deterioration in contractile function are not simply arrested, but partially reversed. Two important questions related to reverse remodeling are: "Do myocytes have the ability to remove sarcomeres?" and "Is there any time line beyond which reverse remodeling cannot be achieved?"

Surgical and pharmacological experiments have confirmed that the regression of myocyte hypertrophy with removal of sarcomeres is possible. But insufficient data exist to address the second question. Remodeling is believed to be reversible early in the natural transition from hypertrophy to failure, whereas later, with the development of extensive fibrosis, accumulation of cytoskeletal proteins, and loss of the contractile filaments, an irreversible process sets in [111]. Several therapeutic approaches for HF have been shown to halt or even reverse the remodeling process.

Pharmacological Approaches

Numerous experimental studies have shown that modulating neurohormonal activation improves cardiac remodeling [177, 178]. McDonald et al. [179] showed that ACE inhibition and beta-adrenoreceptor blockade can reverse established ventricular remodeling in a canine model of discrete myocardial damage [179]. A significant reduction of LV mass and a trend in reduction of end-diastolic volume were found in both captopril- and beta-blocker-treated groups compared with the control group [179]. Tamura et al. [180] reported that the administration of angiotensin II type 1 receptor blockers produced significant reduction in myocyte volume, length, and cross-sectional area in rats with spontaneously hypertensive HF—below pretreatment values, suggesting true reverse remodeling, rather than simply arrested progression of myocyte hypertrophy [180]. Xu et al. [181] studied the effect of angiotensin II receptor blocker losartan combined with exercise training in a postinfarction rat model and demonstrated that exercise training after MI provides a beneficial effect on cardiac function and LV remodeling by altering the gene and protein expressions that regulate myocardial fibrosis. In contrast, such effects were only slightly improved by combining exercise and losartan [181].

ACE Inhibitors

The first class of medications shown to beneficially affect remodeling and clinical outcomes in patients with HF was the ACE inhibitors. In several trials performed in both asymptomatic and symptomatic patients with reduced EF, ACE inhibitors attenuated the progressive increase in end-diastolic and end-systolic volume compared with placebo-treated groups [32, 169, 182–184].

Beta-Blockers

In contrast to ACE inhibitors that attenuate LV remodeling, the use of beta-blockers has been associated with significant reduction in ventricular volumes and improvement in global LV function (reverse remodeling) [30, 31, 33, 185]. Beta-blockers were shown to reduce myocardial apoptosis which, at least in part, could explain their favorable effect on ventricular remodeling [186].

Aldosterone Receptor Blockers

Aldosterone receptor blockers have been shown to reverse LV remodeling following MI and in patients with HF [187, 188]. The 4E–Left Ventricular Hypertrophy Study [189] used cardiac magnetic resonance imaging (MRI) to compare LV mass regression by the selective aldosterone blocker eplerenone to the ACE inhibitor enalapril and the combination of eplerenone/enalapril in hypertensive patients with LV hypertrophy. Eplerenone was as effective as enalapril in

regression of LV hypertrophy and control of blood pressure. The combination of eplerenone and enalapril was more effective in reducing LV mass and systolic blood pressure than eplerenone alone [189]. In a single-site clinical trial, Chan and colleagues [190] demonstrated with serial cardiac magnetic resonance (CMR) that the addition of spironolactone to candesartan has significant beneficial effects on LV reverse remodeling in patients with mild to moderate chronic systolic HF.

Angiotensin Receptor Blockers

Several trials demonstrated the beneficial effect of angiotensin receptor blockers (ARBs) on LV remodeling. In the Valsartan Heart Failure Trial (Val-HeFT) [191, 192], valsartan therapy attenuated LV remodeling [193]. Stratification by baseline severity of remodeling showed that patients with worse LV enlargement and systolic function are at highest risk for an event, yet appear to gain the most antiremodeling effect and clinical benefit with valsartan treatment [194]. The Losartan Intervention For Endpoint (LIFE) study [195] showed that reduction in LV mass by angiotensin II blockade was independent of blood pressure reduction, indicating that the inhibition of the renin-angiotensin-aldosterone system has added benefits beyond blood pressure control [195].

Isosorbide Dinitrate-Hydralazine Combination

In the first Vasodilator-Heart Failure Trial (V-HeFT-I) [196], isosorbide dinitrate combined with hydralazine therapy compared with placebo in patients with HF treated only with digoxin and diuretic resulted in a sustained increase in LV EF that was associated with improved survival [196]. The African American Heart Failure Trial (A-HeFT) confirmed these findings, on top of ACE inhibitors and beta-blockers [197, 198].

Role of Cell Transplantation and Surgical Approaches in Heart Failure

Since about 2000 there has been an explosion of activity in the field of cell transplantation and of advanced surgical approaches in HF. These specialized areas are discussed in detail elsewhere in this book.

Cardiac Resynchronization Approach

Beneficial effects of cardiac resynchronization therapy (CRT) on survival, New York Heart Association (NYHA) functional class, exercise capacity, and quality of life are associated with significant improvement in LV remodeling as early as 1 month after device implantation [199–201] and with further, progressive reduction in LV volumes beyond 1 year in selective patients [202, 203]. The Cardiac Resynchronization-Heart Failure (CARE-HF) study demonstrated an early and sustained reduction in NT-pro-BNP with CRT that correlated with improvement in LV dimension and EF and mitral regurgitation [204].

Cardiac Constraint Devices

Preclinical studies have shown that passive ventricular containment with cardiac constraint devices halts progressive ventricular remodeling [205–207] and improves myocyte function and structure, as characterized by enhanced myocyte contraction and relaxation, decreased myocyte hypertrophy, and decreased interstitial fibrosis [205, 207]. Ventricular restraint prevents infarct expansion, improves borderzone function, and favorably modifies LV geometry and myocardial structure after MI [208–210]. Limited clinical experience with the Acorn CorCap Cardiac Support Device and the Paracor HeartNet Device has shown amelioration of symptoms and improvement in LV chamber dimensions and EF. However, the implantation of these devices was not associated with improved survival [211–213].

Conclusions

Ventricular remodeling is a complex process. It results from interactions between the initial myocardial injury and alteration in loading conditions and multiple mechanical and neurohormonal factors that are capable of modifying the cardiomyocyte phenotype and inducing changes in the extracellular matrix. Myocyte hypertrophy, cellular necrosis and apoptosis, interstitial fibrosis, and degradation of collagen are the major features of myocardial remodeling. Each of these components of the remodeling process contributes importantly to the development and progression of HF. At the level of the ventricular chamber, remodeling refers to changes in ventricular geometry, volume, and mass. Although, initially, it may be compensatory in certain pressure and volume-overload conditions, progressive ventricular remodeling is ultimately a maladaptive process contributing to progression of symptomatic HF and to an adverse outcome. After acute MI, however, progressive hypertrophy and remodeling of noninfarcted myocardium may be harmful from the start.

Ventricular remodeling had emerged as an important therapeutic target in HF. Treatment with the goal of slowing or reversing remodeling has been shown to improve long-term outcome. Additional research is needed to identify the molecular processes responsible for remodeling and to improve ways to inhibit this maladaptive growth response.

Future Directions

Enormous effort has been directed to identifying new therapeutic strategies with long-term efficacy in HF. The path is littered with successes and failures [4], yet advances in myocardial biology, stem cell research, pharmacologic developments, and mechanical devices hold promise for future treatments. A comprehensive understanding of ventricular remodeling is obligatory, since it reflects the basic mechanisms of HF development and progression.

Although multiple studies have documented that interventions with beneficial effects on HF also generally attenuate or reverse ventricular remodeling and that those failing to improve clinical outcomes either have no effect on remodeling or have been associated with adverse remodeling, few studies have examined the mechanism by which LV reverse remodeling is mediated. Questions remain as to whether the reversal of myocyte structural remodeling is accompanied by normalization of the biology of the failing myocyte and what the mechanisms of changes are at the myocyte level. Further research should focus on the molecular and cellular mechanisms involved in adverse and reverse remodeling, on optimizing therapies to prevent remodeling, and on identifying appropriate patient groups to target.

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Heart Failure Prevention

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_18

Introduction

Heart failure represents a major national and global burden on health care. As reported by the National Heart, Lung, and Blood Institute (NHLBI), 5.7 million adult Americans had heart failure in 2012, and that number is expected to rise by 46 % by 2030 [1]. In spite of the significant advancements in heart failure therapies with improved morbidity, the mortality rate is still unacceptably high, with a 1-year mortality rate of 29.6 % [2] and cumulative mortality of almost 50 % within the first 5 years after the initial diagnosis [3]. In addition, the burden of heart failure on health care remains colossal. Despite the decline in heart failure hospitalization rates, more than 80 % of the cases were hospitalized at least once and 43 % hospitalized at least four times [4]. Furthermore, more than 1.8 million office visits and 676,000 emergency room visits were attributed to heart failure in 2010 [1]. In 2012, the direct medical costs of heart failure exceeded $21 billion, with a projected increase of almost 127 % by 2030 [5].

Opportunely, heart failure is primarily a preventable disease. For example, 75 % of heart failure cases had predisposing hypertension, and the lifetime risk for people with a blood pressure (BP) > 160/90 mmHg is double that of those with a BP < 140/90 mmHg [6]. The Coronary Artery Risk Development in Young Adults (CARDIA) study identified hypertension, obesity, and systolic dysfunction as important risk factors amenable to prevention [7]. Therefore, the high morbidity, mortality, and health-care costs associated with heart failure mandate heart failure prevention as the future approach, rather than a focus on treatment of end-stage disease. This chapter outlines the common, preventable risk factors for heart failure and their clinical rationale.

Heart Failure Prevention and Hypertension

Hypertension is defined as a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg at two separate encounters or the need for an antihypertensive medication to control blood pressure [8]. The prevalence of hypertension in the United States among adults ≥20 years of age was estimated to be 32.6 % in 2012, translating to an estimated 80.0 million adults [1]. Its morbidity and mortality remain substantial. Hypertension is the leading cause of death in women and the second leading cause of death in men [9]. In 2011, more than 65,000 deaths were attributable to hypertension, which continue to rise [1]. Data from the NHLBI showed that hypertension is associated with shorter life expectancy [10]. In 2011, the estimated health-care costs of hypertension were approximately $46 billion annually, and by 2030, the cost is estimated to exceed $250 billion annually [1]. The risk factors for hypertension include age, diet (especially increased salt intake), smoking, male gender, alcohol consumption, obstructive sleep apnea, and African American race [11].

Consequently, hypertension has been shown to be a major risk factor for overall cardiovascular death, coronary artery disease and myocardial infarction, stroke, hypertensive cardiomyopathy, and heart failure. For example, about 69 % of patients with a history of myocardial infarction, 77 % of those with a history of stroke, and 74 % of those with a history of heart failure were previously diagnosed with hypertension as a major risk factor of their resulting illness [1].

One major sequela of hypertension is hypertensive cardiomyopathy and heart failure. Hypertensive cardiomyopathy represents a spectrum of pathological changes ranging from asymptomatic myocardial remodeling, heart failure with preserved ejection fraction (HFpEF, or diastolic heart failure), and heart failure with reduced ejection fraction (HFrEF) [12]. Interestingly, these myocardial changes are accompanied by dysfunctional neurohormonal pathways (renin-angiotensin-aldosterone system and sympathetic nervous system), contributing to a higher risk of heart failure development [13]. Mechanistically, chronic hypertension initially leads to increased cardiac hypertrophy—a maladaptive response to normalize wall stress and maintain stroke volume. Mechanical stretch of the cardiomyocytes and neurohumoral factors induce changes in intracellular signaling pathways, resulting in an increased protein synthesis and activation of specific genes promoting cardiomyocyte growth, eventually leading to left ventricular hypertrophy [14]. Ultimately, the ventricular hypertrophy results in prolonged systole at the expense of a reduction of diastole, which causes delayed myocardial relaxation principally compromising the coronary perfusion.

The increased myocardial oxygen demand from a combination of elevated afterload, increased ventricular hypertrophy, and prolonged systole, in addition to decreased perfusion, predisposes hypertensive patients to myocardial ischemia and negative remodeling. In the adverse myocardial remodeling, a disproportionate growth of the extracellular space, fibrosis, and endothelial dysfunction occurs. Therefore, an increase in interstitial collagen is associated with HFpEF, whereas a degradation of the collagen extracellular scaffolding, thinning of myocardium, and dilatation of the ventricular chamber would lead to HFrEF (Fig. 18.1). For example, in a retrospective cohort of 159 African Americans with concentric ventricular hypertrophy and hypertension, 18 % developed HFrEF after a follow-up of about 4 years [15]. The Cardiovascular Health Study showed that left ventricular hypertrophy diagnosed by echocardiography or electrocardiography was an independent risk factor for the development of HFrEF—independent of coronary artery disease [16]. It should be emphasized that ventricular hypertrophy is a strong predictor of cardiovascular morbidity and mortality, regardless of blood pressure values [17, 18].

Therefore, it is plausible to hypothesize that hypertensive cardiomyopathy is a preventable disease, at least in its early stages. In patients with left ventricular remodeling, controlling blood pressure could halt or reverse this cardiomyopathic process. In patients with established heart failure, blood

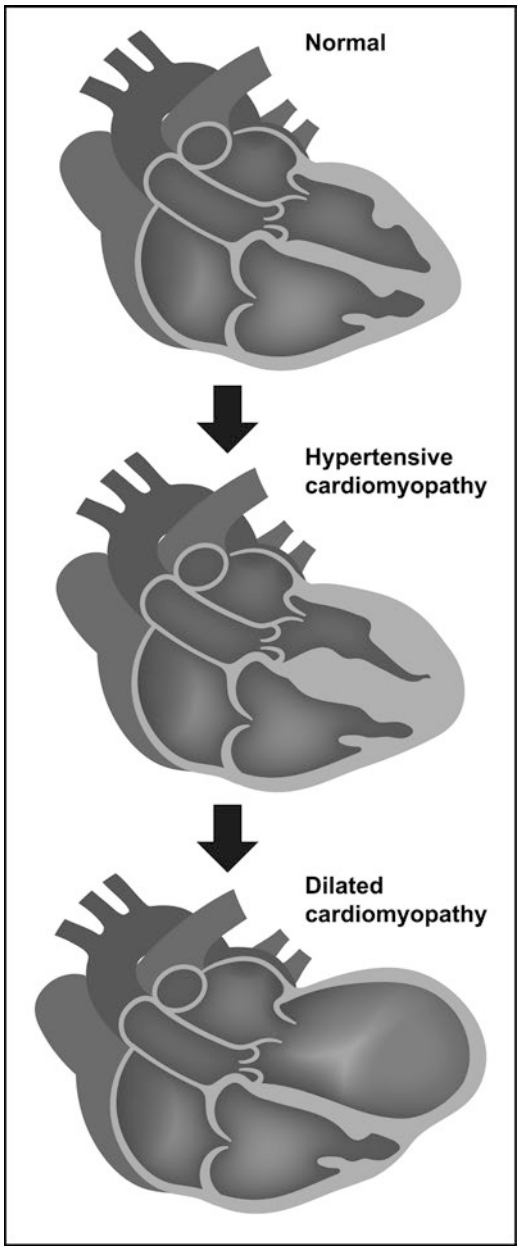

Fig. 18.1 The basic mechanism of negative remodeling and progression to dilated cardiomyopathy in hypertension

pressure control reduced the number of rehospitalizations, slowed the progression of disease, and improved overall mortality. In large-scale randomized prevention trials, antihypertensive therapy produced as much as a 50 % relative risk reduction in the incidence of heart failure [19–21]. Consistent with the Eighth Joint National Committee (JNC 8) and the European societies of hypertension and cardiology, antihypertensive medications should generally be initiated if the office systolic blood pressure is persistently ≥140 mmHg or the diastolic pressure is persistently ≥90 mmHg [8]. In 2015, results of the SPRINT trial (Systolic Blood Pressure Intervention Trial) showed that blood pressure control at 120/80 mmHg was associated with further significant cardiovascular risk reduction compared to blood pressure control at 140/90 mmHg [22].

Interestingly, multiple large-scale studies concluded that the degree of blood pressure reduction, not the choice of antihypertensive medication, is the major determinant of reduced cardiovascular risk in patients with hypertension. For example, the recent meta-analysis of 35 randomized controlled trials highlighted that antihypertensive medications effectively prevented new-onset heart failure, with a relative risk reduction of 37 %. It is further suggested that lowering blood pressure using calcium channel blockers is as effective in preventing "new-onset" heart failure as other antihypertensives [23]. Nonetheless, certain classes of antihypertensive medications are indicated in patients with heart failure. These are primarily angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARB), a combination of nitrates and hydralazine, and beta-blockers (BBs), given their proven mortality benefit in this population [24]. Aldosterone antagonists (especially spironolactone) are the cornerstone in resistant hypertension [25], and their administration has resulted in significant reductions in morbidity and mortality in HFpEF [26] and HFrEF [27].

Diabetes Mellitus and Heart Failure Prevention

Diabetes mellitus represents a significant health-care burden, affecting an estimated 450 million people across the globe in 2013 [28]. This endocrinological imbalance is associated with a myriad of cardiovascular conditions, including heart failure, with considerable morbidity and mortality [29]. As reported in the Framingham studies, diabetes mellitus is associated with five times increased risk in women and two times increased risk in men of attaining clinically significant heart failure [30]. Moreover, patients with diabetes mellitus aged 45–54 years are almost nine times more likely to develop heart failure [31]. The prevalence of heart failure in diabetic patients is greater than that of the general population [31, 32]; as such, every 1 % increase in glycosylated hemoglobin is linked to an 8 % increased risk of heart failure [33]. This is important, as the diagnosis of diabetes mellitus in heart failure patients is associated with a worse prognosis compared to heart failure patients without diabetes [34].

Although atherosclerotic coronary artery disease is the major cause of heart failure in diabetic patients, the pathogenesis of heart failure in this population remains multifactorial and includes diabetic cardiomyopathy, hypertensive cardiomyopathy, and atherosclerosis [35]. The entity of diabetic cardiomyopathy, first described by Rubler in 1972, represents the direct impact of insulin resistance and hyperglycemia on the myocardium, irrespective of the presence of significant atherosclerosis of epicardial vessels [36].

Disease progression in diabetic patients is unclear, but evidence suggests it starts with the formation of diabetic cardiomyopathy without any systolic or diastolic dysfunction.

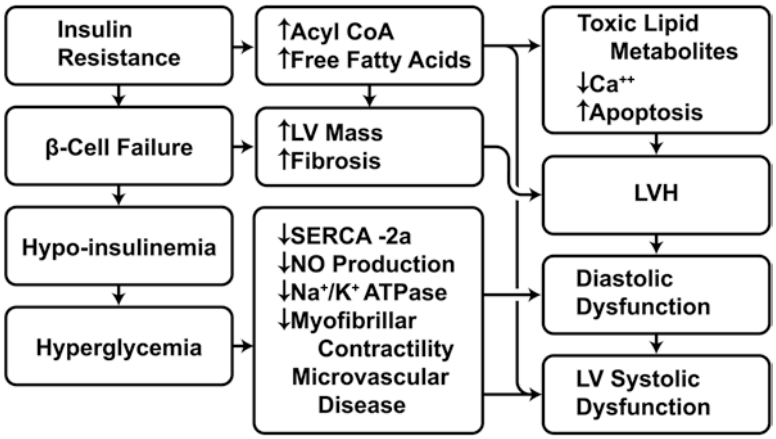

Fig. 18.2 A schematic of the molecular pathways involved in the development of diabetic cardiomyopathy in diabetes mellitus. *LV* left ventricle, *LVH* left ventricular hypertrophy

Both the Framingham study and the Strong Heart Study showed early evidence of left ventricular hypertrophy development associated with diabetes [37, 38]. Hypertrophy of cardiomyocytes is initially related to increased insulin levels and, subsequently, to insulin resistance [39]. One consequence of insulin resistance is an enhanced release of free fatty acids with a resultant reduction in myocardial glucose transporter expression and glucose uptake. This causes the activation of myocardial peroxisome proliferator-activated receptor-α that stimulates the transcription of multiple genes responsible for the increase in mitochondrial transport and oxidation [40]. In response to myocardial stress, fatty acids accumulate within the cardiomyocytes, and toxic lipid intermediates such as diacylglycerol and ceramides and myocytic apoptosis are produced.

Diabetes is also associated with abnormalities related to cardiomyocyte contractile protein expression and calcium (Ca) sensitivity. These abnormalities include a shift in myosin isoenzyme composition and the predominance of the fetal β myosin heavy chain expression with respect to α-myosin heavy chain [41]. Both lead to depressed ATPase activity of myofibrils and reduced contractile force. In addition, oxidative stress in cardiomyocytes incubated in a high-glucose medium has been shown to inactivate sarcoplasmic reticulum Ca-ATPase (SERCA) 2 activity. This hyperglycemic state results in inefficient sequestration of Ca in the sarcoplasmic reticulum, Ca overload in the cytosol, and impaired relaxation [42]. Ultimately, the formation of advanced glycation end products, lipid oxidation, impaired nitric oxide production, endothelial dysfunction, and microvascular remodeling will cause the early diastolic dysfunction evident in patients with diabetes.

Using tissue Doppler imaging, left ventricular diastolic dysfunction was observed in upwards of 75 % of asymptomatic diabetic patients [43]. As ventricular diastolic dysfunction progresses, activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system would favor myocardial fibrosis, apoptosis, vascular inflammation, and oxidative damage, leading to systolic dysfunction and dilated cardiomyopathy [44]. Individuals with diabetes mellitus characteristically develop atherosclerotic coronary artery disease at an early age that is also more likely to include the microvascular bed [45]. They also have decreased angiogenesis, leading to reduced collateral vessel formation, with increased risk of heart failure [46]. Finally, comorbidities that commonly accompany diabetes, such as hypertension, dyslipidemia, microvascular dysfunction, and renal impairment, may accelerate the progression of cardiac dysfunction toward end-stage heart failure [47] (Fig. 18.2).

From the earliest stages, a treatment strategy that decreased insulin resistance and hyperglycemia would prevent the progression of the cardiomyopathy [48]. Once there is evidence of cardiomyopathy, standard heart failure therapies should be implemented. However, it is unclear whether the mortality of diabetics with heart failure remains higher than their nondiabetic counterparts—in spite of the advanced therapies used. Ongoing discussion has addressed the intrinsic effects of oral antidiabetic drugs and protection from cardiovascular disease, including heart failure. The potential underlying mechanisms are speculative and complex. In 2015, the cardiovascular safety study of empagliflozin use in diabetes mellitus (EMPA-REG OUTCOME trial) showed that empagliflozin not only reduced the cardiovascular death rate (a 38 % relative risk reduction), but it also significantly reduced the risk of hospitalization for heart failure (a 32 % relative risk reduction) [49].

Heart Failure Prevention and Dyslipidemia

Dyslipidemia is a well-studied risk factor for coronary atherosclerotic disease, and it contributes to the incidence of ischemic cardiomyopathy and heart failure [50] and diabetes mellitus [51]. However, the direct effect of dyslipidemia on the myocardium remains controversial. Cardiomyocytes have limited lipid storage capacity, and excess fatty acids are shunted into non-oxidative pathways that generate toxic by-products leading to contractile dysfunction [52, 53]. Evidence has implicated high levels of free fatty acids and triglycerides in cardiotoxicity, and elevated levels of lipid fractions may be involved in cardiac remodeling and heart failure [54]. However, reports from observational studies on the

associations of triglycerides and total cholesterol (TC)/high-density lipoprotein (HDL) cholesterol ratio with incident heart failure have been inconsistent [51]. In the Multiethnic Study of Atherosclerosis (MESA) study, neither high triglyceride nor low HDL was a significant predictor of future occurrence of heart failure [55]. In a later report from the same study, lipid measurements were not associated with the occurrence of heart failure in individuals without diabetes mellitus. However, in diabetics, high triglyceride, low HDL, or high total cholesterol/HDL-C ratio were significantly associated with heart failure [51]. In other studies, low HDL but not high triglyceride was an independent predictor of heart failure in all patients [56, 57]. In the Physicians' Health Study, neither HDL nor TC/HDL ratio was independently associated with heart failure [54]. In the Framingham Heart Study, elevated levels of non-HDL, decreased levels of HDL, and a high TC/HDL ratio were associated with increased risks of heart failure [58, 59].

The effects of HDL on heart failure are less clear. Small- plus medium-diameter HDL particles are an independent predictor for chronic inflammation-related death and hospitalization and for coronary heart disease events in subjects initially free of overt cardiovascular disease. These findings support the hypothesis that smaller HDL particles having a diameter <9.4 nm have anti-inflammatory properties in the myocardium [60]. Due to these inconsistencies, a paucity of data governs the use of lipid-lowering agents in the primary or secondary prevention of heart failure.

The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) [61] and the GISSI-HF [62] randomized controlled trials were specifically designed to investigate the effect of statin (rosuvastatin) on the prognosis of patients with heart failure. In the CORONA study, patients were randomized to receive either rosuvastatin (10 mg) or placebo for a median follow-up of about 3 years. Despite a 45 % reduction of LDL, the primary cardiovascular end point of mortality was not significantly different compared to placebo. However, hospitalization due to heart failure was significantly reduced by rosuvastatin administration. Prognosis was improved among patients with plasma N-terminal B-type natriuretic peptide (NT-proBNP) levels in the lowest tertile, suggesting a benefit for patients with less-severe heart failure [61]. In the GISSI-HF randomized, double-blind trial, patients were randomized to rosuvastatin (10 mg) or placebo. Surprisingly, rosuvastatin failed to improve mortality despite a substantial reduction of LDL [62]. Subsequently, in a recently published meta-analysis of studies in primary and secondary prevention trials, statins modestly reduced the risks of nonfatal heart failure hospitalization and a composite of nonfatal heart failure hospitalization and death [63]. Nonetheless, as coronary artery disease is the determinant risk factor of heart failure, and often is caused by dyslipidemia, its treatment would ultimately reduce the incidence of heart failure (Fig. 18.3).

Prior large prospective clinical trials involving statins have provided clear evidence of the effect of LDL reduction on cardiovascular events. However, there remains a population of patients who need dyslipidemia therapy but have contraindications to or are intolerant of statins. Several agents are being developed with higher efficacy than statins. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors were developed to significantly impact on the LDL levels. The PCSK9 protein produced by the hepatocyte binds to the LDL-LDL receptor (LDLR) complex on the surface of the hepatocytes, resulting in its internalization. LDL binding to LDLR on the hepatocyte is the mechanism for eliminating LDL and other non-HDL molecules. However, when PCSK9 is bound to the LDL-LDLR complex, it leads to lysosomal catabolism of LDLR within the hepatocyte and prevents LDLR recycling [64]. By sequestering PCSK9, the PCSK9 inhibitors block the binding of PCSK9 protein to the LDLR. This prevents LDLR catabolism which, in turn, preserves LDLR recycling and increased receptor density on the hepatocyte surface. Increased LDLR density increases LDL binding and the clearance from the blood, resulting in reduced LDL serum levels.

In 2009, two PCSK9 inhibitors in the form of monoclonal antibodies alirocumab and evolocumab were used in clinical trials in humans, resulting in Food and Drug Administration approval in 2015. In the first published phase I trials on the use of PCSK9 inhibitor, alirocumab significantly reduced LDL cholesterol levels (as high as 60 %) in healthy volunteers and in subjects with familial or nonfamilial hypercholesterolemia [65]. Although the efficacy and safety of alirocumab and evolocumab have been demonstrated in multiple trials, clinical trials addressing their effects on cardiovascular outcomes, including heart failure, are underway [66].

Social Behavior and Prevention: Polysubstance Abuse

Cocaine-induced cardiomyopathy: Cocaine, benzoylmethylecgonine, is a potent neurostimulant used illicitly for recreation [67]. It is commonly nasally snorted or smoked. According to the World Health Organization (WHO), nearly 6.9 million individuals were estimated to have cocaine dependence in 2001, with 25,000 years of life lost due to dependency [68]. It is associated with multiple cardiovascular complications, including myocardial ischemia and infarction, cardiomyopathy, arrhythmias, stroke, and hypertension [69]. Cocaine-induced dilated cardiomyopathy remains a rare cause of heart failure [70]. The mechanisms underlying cocaine cardiomyopathy are not fully understood but are hypothesized to include sympathomimetic activation, increased calcium influx and oxidative stress, and myocardial ischemia [71].

Strong clinical suspicion should be considered in young men without traditional cardiovascular risk factors who are presenting with heart failure. While the management of cocaine cardiomyopathy is similar to other forms of dilated cardiomyopathy, BBs should be avoided. Left ventricular function will likely improve dramatically with abstinence [72]. Unfortunately, addiction and relapse are high, and left

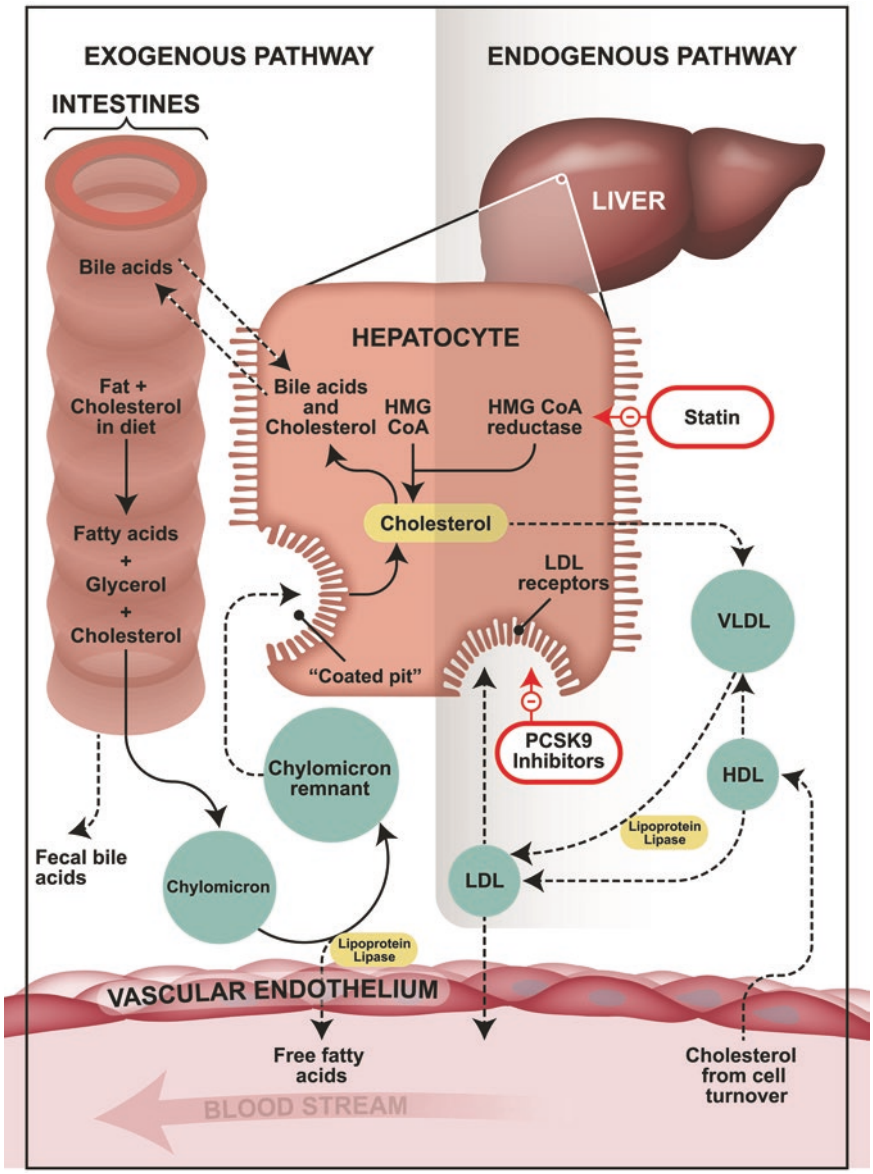

Fig. 18.3 Cholesterol metabolism pathway. Endogenous production of cholesterol begins via the mevalonate pathway where two molecules of acetyl coenzyme A (CoA) react to form acetoacetyl-CoA. This is followed by a second reaction between acetyl CoA and acetoacetyl-CoA to form 3-hydroxy-3-methylglutaryl CoA (HMG-CoA). This molecule is then reduced to mevalonate by the enzyme HMG-CoA reductase, which is the rate-limiting step of cholesterol synthesis—site of action of statins. Cholesterol is amphipathic, thus it is transported inside lipoprotein complexes in the bloodstream. There are several types of lipoproteins, including chylomicrons, very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), intermediate-density lipoprotein (IDL), and high-density lipoprotein (HDL). LDL particles are the major blood cholesterol carriers. Each one contains approximately 1500 molecules of cholesterol ester. LDL molecule shells contain just one molecule of apolipoprotein B100, recognized by LDL receptors in the peripheral tissues. Via binding of apolipoprotein B100, LDL receptors-LDL complexes concentrate in clathrin-coated vesicles that get internalized via endocytosis and directed for metabolism. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme that binds to the LDL receptor. In the liver, the LDL receptor scavenges the LDL molecules from the bloodstream. When PCSK9 binds to the LDL receptor, the receptor gets inhibited. If PCSK9 is blocked (site of action of PCSK9 inhibitors), more LDL receptors will be present on the surface of the liver and will remove more LDL cholesterol from the bloodstream, thus lowering LDL serum levels

ventricular dysfunction often persists, resulting in high mortality. Additional epidemiological studies are needed to fully assess its impact on health care (Fig. 18.4).

Androgenic steroid-induced cardiomyopathy: Anabolic steroids, also known as anabolic-androgenic steroids, are hormones with cyclic ring conformation with similar effects to endogenous androgenic steroids such as testosterone. Thus, they have androgenic properties, including the development of masculine male characteristics. They also increase protein production and accumulation, especially in skeletal muscles. Anabolic steroids were initially developed in the early nineteenth century as therapeutic options for patients with puberty disorders and cachexia [73]. However, it was not until the 1980s that the American College of Sports Medicine acknowledged their use by athletes to increase muscular mass and physical endurance [74].

Unfortunately, anabolic steroid abuse among athletes has dramatically increased—with the use of much higher doses for improved muscular appearance. One survey found that two-thirds of professional body builders have reported use of anabolic steroids to enhance performance [75]. These steroids cause several deleterious effects on the cardiovascular system, including cardiomyopathy, atherosclerosis, increased vascular tone, dyslipidemia, and sudden cardiac death [76]. Via their interaction with androgenic receptors in a dose-dependent response, anabolic steroids induce left ventricular hypertrophy, which progresses to dilated cardiomyopathy [77, 78].

Several studies showed that high doses of anabolic steroids such as nandrolone may lead to a phenotype similar to hypertrophic cardiomyopathy, followed by apoptosis which is mediated by intracellular Ca influx and mobilization [79, 80]. This ultimately leads to ventricular remodeling, failure, and sudden cardiac death. In animal models, although a short course (<2 weeks) of nandrolone improved postischemic myocardial performance in postconditioned myocar-

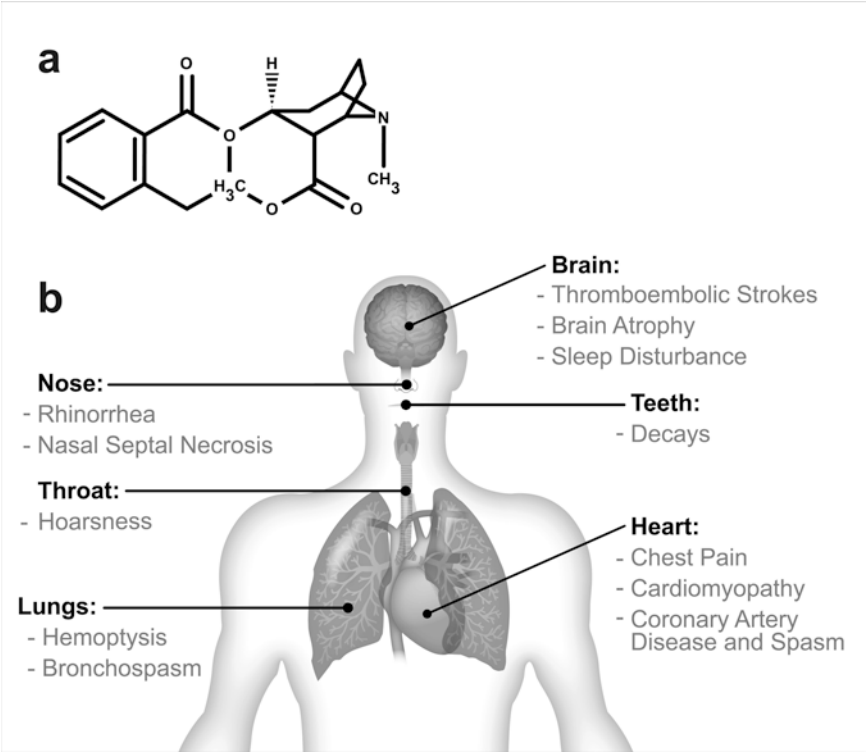

Fig. 18.4 Cocaine has an adverse impact on the heart. (**a**) The molecular conformation of cocaine. (**b**) The side effects of cocaine abuse

dium, the prolonged administration (>10 weeks) increased myocardial susceptibility to ischemia-reperfusion injury and abolished cardioprotection. This increased susceptibility might be related to steroid-induced hypertrophy or increases in the preischemic myocardial cAMP concentrations [81]. In addition, anabolic steroids have previously been linked to Takotsubo "stress" cardiomyopathy [82]. Finally, anabolic steroids induce a decrease in HDL by 20 % and an increase in LDL by 20 % due to lipolytic degradation of lipoproteins and their removal by receptors through modification of apolipoprotein A-I and B synthesis [83]. Thus, use of these steroids increases the risk for coronary artery disease and myocardial ischemia. Whether the abstinence of steroids would result in reverse remodeling of the myocardium is still unclear (Fig. 18.5).

Amphetamine-induced cardiomyopathy: Amphetamines, belonging to the phenethylamine class, are potent central nervous system stimulants used primarily for treating attention deficit hyperactivity disorder [84]. However, amphetamines are being used recreationally as an illicit drug [85]. The chronic use of amphetamines has been associated with the development of cardiomyopathy and systolic heart failure [86, 87]. The mechanism of the dilated cardiomyopathy is unclear but is likely driven by the adrenergic signaling pathway [72]. Amphetamines have a dopaminergic substrate with sympathomimetic qualities. They are also potent reversible inhibitors of monoamine oxidase-A, the neuronal enzyme that inactivates norepinephrine and dopamine [88]. In addition to causing hypertensive emergency or tachycardia, direct myocardial toxicity can lead to left ventricular failure, recurrent coronary vasospasm, and accelerated atherosclerosis [89, 90].

Autopsy studies of methamphetamine users have shown myocardial necrosis [91]. 3,4-Methylenedioxymethamphetamine, known as ecstasy, has been shown to cause myocarditis with inflammatory cellular infiltrates and necrosis [92]. Eventually, this drug causes eccentric left ventricular dilation and diastolic dysfunction, leading to systolic dysfunction. Although evidence has shown that the myocardial pathology may be reversible with early cessation of exposure to amphetamine [93], complete abstinence and standard heart failure therapy should be implemented.

Alcohol Abuse and Heart Failure Prevention

Excessive alcohol intake is the third leading cause of premature death among males aged 15–59 years in the United States [94]. Alcohol abuse, defined as three or more standard drinks per day, has been associated with cardiovascular disease. Cardiovascular complications include alcoholic cardiomyopathy, arrhythmias, and hypertension [95]. By comparison, daily consumption of low to moderate amounts of alcohol has beneficial effects on cardiovascular health and is associated with reduced all-cause mortality [96].

Alcoholic cardiomyopathy is an acquired dilated cardiomyopathy associated with long-term heavy alcohol consumption (>80 g of ethanol per day for at least 5 years) [97, 98]. Epidemiological studies that investigated the prevalence of alcohol abuse among heart failure patients have found high alcohol consumption in 3.8–47 % of dilated cardiomyopathy cases [99]. The relationship between alcohol intake and survival is described as a J-shape. More than moderate drinking—defined as up to one drink per day for females and

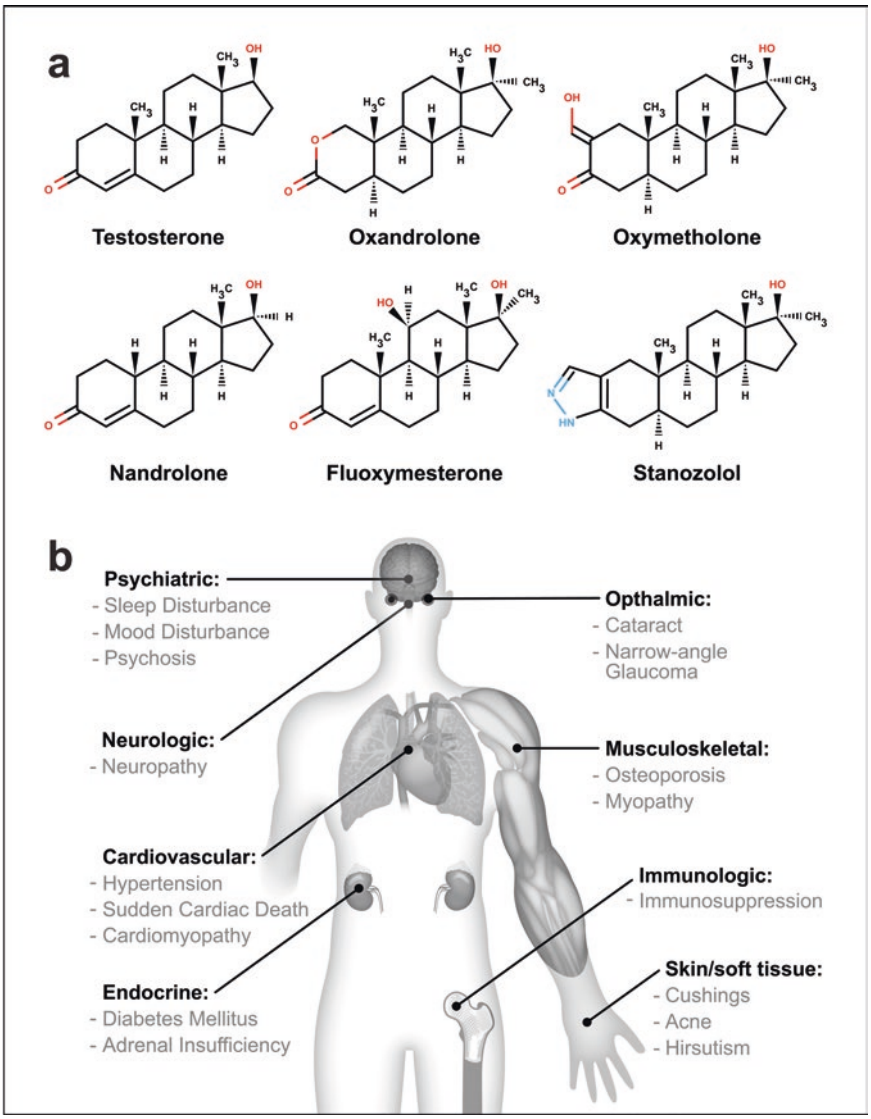

Fig. 18.5 Androgenic steroids have an adverse impact on the heart. (**a**) The molecular conformations of the more commonly used androgenic steroids, compared to testosterone. (**b**) The side effects of androgen abuse

up to two drinks per day for males—induces more harmful effects. Furthermore, low to moderate levels of alcohol intake are associated with improved cardiovascular health [100]. For example, the Atherosclerosis Risk in Communities (ARIC) study reports that males who consume up to seven drinks per week had a 20 % reduced risk of heart failure compared with nondrinkers. This effect was observed less frequently in females [101].

About 50 % of asymptomatic alcoholic subjects have a mild increase in left ventricular wall thickness without echocardiographic evidence of decreased myocardial contractility [102]. From another perspective, alcohol intoxication can produce acute asymptomatic left ventricular dysfunction even when ingested by healthy individuals in quantities typical of social drinking [103]. Binge drinking is associated with transient myocardial changes that are detectable by cardiac magnetic resonance imaging, elevated serum markers for myocardial injury such as troponins, and coronary arterial vasospasm [104]. However, the development of alcoholic cardiomyopathy is not only related to the mean daily alcohol intake but also to the duration of use [105]. Alcoholic cardiomyopathy is characterized by increased ventricular mass, diastolic dysfunction, left ventricular dilatation, and, eventually, systolic failure. Although cardiac magnetic resonance imaging is extremely useful in analyzing the cardiomyopathic heart, alcoholic cardiomyopathy does not have specific structural features compared to idiopathic dilated cardiomyopathy [106].

The early stages of alcoholic cardiomyopathy are characterized by spatial disorganization of the mitochondrial ultrastructure followed by irreversible mitochondrial damage and lipid accumulation [107]. Additional mechanisms of myocardial injury include apoptosis [108], excitation-contraction coupling dysfunction [109], decreases in contractile proteins and myofibrils [110], upregulation of the L-type calcium channels and calcium inflow [111], and activation of the renin-angiotensin system and the sympathetic nervous system [112]. Histologically, myocardial fibrosis, focal myocardial edema, endocardial fibroelastosis, and vascular thrombosis are abundant [113]. However, earlier mitochondrial changes seem more specific to alcohol ingestion [114].

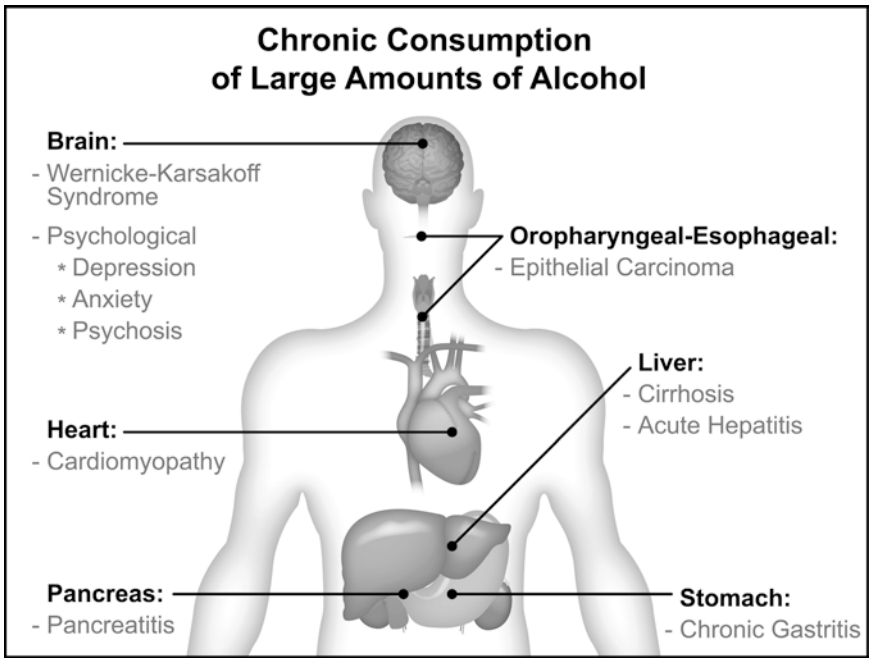

Fig. 18.6 Alcohol-induced cardiomyopathy. The side effects of chronic ingestion of excessive amounts of ethanol

Treatment of alcoholic cardiomyopathy is total and permanent abstinence from alcohol consumption [115]. Some studies have suggested that moderation of alcohol consumption may produce similar outcomes as abstinence. Though some studies have cited the lack of myocardial interstitial fibrosis as a potential indicator of reversibility, the limited data on morphometry have yielded mixed results [116, 117]. Small observational studies have suggested that left ventricular function improves in some patients with abstinence, as early as 6 months. A shorter duration of heart failure symptoms prior to abstinence may favor recovery [118]. These notions were illustrated in a prospective study of 55 men with a cardiomyopathy who consumed ≥100 g alcohol per day for at least 10 years [119]. During a 1-year follow-up, the improvement in systolic function was the same in abstainers and those who controlled their intake. In contrast, patients who continued to drink >80 g per day had a further deterioration in the ejection fraction.

In patients with asymptomatic left ventricular dysfunction, BBs and ACEIs/ARBs coupled with abstinence may halt or reverse the negative remodeling of the myocardium. Patients should also eat a balanced diet and correct any nutritional deficiencies.

The prognosis of alcoholic cardiomyopathy varies depending on the presence and extent of continued alcohol use. Patients who abstain from alcohol or continue moderate alcohol use have a prognosis better than or similar to that seen with idiopathic dilated cardiomyopathy, while continued heavy alcohol use is associated with a worse prognosis. In a study by Gavazzi et al., non-abstainers had a lower 7-year, transplant-free survival rate of 27 % compared with those who stopped drinking (45 %) or those with an idiopathic cardiomyopathy (53 %) [120]. Among patients with alcoholic cardiomyopathy, independent predictors of death include heart transplantation, atrial fibrillation, QRS duration >120 ms, and a lack of BB therapy [121] (Fig. 18.6).

Human Immunodeficiency Virus and Heart Failure Prevention

Human immunodeficiency virus (HIV) is a global pandemic affecting more than 40 million individuals worldwide [122]. With the introduction of antiretroviral therapy (ART), HIV infection has become a chronic disease with improved morbidity and mortality. One result of increased life expectancy, however, is that cardiovascular complications associated with HIV infection are becoming more significant. The constellation of cardiac sequelae includes HIV-associated cardiomyopathy, coronary artery disease, hypertension, and pulmonary hypertension [123].

The advent of ART has significantly changed the incidence and prevalence of cardiac complications—both as a result of HIV infection modulation and medication-related side effects [124]. For example, in the Strategies for Management of Anti-Retroviral Therapy (SMART) study, earlier initiation of ART resulted in decreased inflammatory markers (C-reactive protein, IL-6, and D-dimer), portending less cardiovascular events in the future [125]. Coronary artery disease was the third most common cause of death in HIV-infected patients [126]. Contrarily, the incidence of HIV cardiomyopathy is difficult to assess, because very few studies actually evaluated this outcome. A meta-analysis of 11 studies in the ART era showed a prevalence of systolic dysfunction of 8.3 % and diastolic dysfunction of 43.4 % [127]. The African Heart of Soweto Study investigated the impact of HIV infection on de novo occurrence of heart disease [128]. In that study, 9.7 % of newly diagnosed heart dis-

ease patients were identified as HIV positive. Of these patients, 38 % had clinically symptomatic HIV cardiomyopathy. Nonetheless, subclinical myocardial changes are likely underreported. For example, cardiac magnetic resonance imaging detected subtle systolic dysfunction, cardiac lipid deposition, and myocardial fibrosis in almost 100 % of HIV patients on ART therapy [129].

The pathophysiology of HIV cardiomyopathy is multifactorial and complex. It includes direct myocardial infection by HIV-1, toxicity from the ART therapy, coronary artery disease, opportunistic cardiac infections, and nutritional deficiencies [130, 131]. Infection of the myocardium with HIV-1 virus has been postulated as one of the key mechanisms for the development of impaired systolic and diastolic dysfunction [130]. Interestingly, in situ hybridization of HIV-1 using myocardial samples showed that the myocardial interstitial cells, rather than the cardiomyocyte, are primarily infected with the virus [132, 133]. This would ultimately culminate in an autoimmune response to myocardial epitopes and the generation of cardiomyocyte-specific autoantibodies. Furthermore, overexpression of tumor necrosis factor-alpha, reactive oxygen species, and other cytokines ultimately contribute to the more advanced systolic dysfunction [133, 134]. Mitochondrial toxicity, especially by zidovudine, clevudine, and lodenosine, has been shown to cause significant myocardial damage, starting with subtle cardiac abnormalities and leading to more symptomatic cardiomyopathy [135–137]. This is especially significant given the hypothesized synergistic effect with direct HIV myocardial infection. Deficiency of trace elements such as selenium has been associated with cardiomyopathy, as well [138].

Finally, HIV infection represents an independent risk factor for the development of coronary artery disease [139]. Consider that the incidence of acute myocardial infarction occurred at 11.13 per 1000 person-years in HIV patients compared with 6.98 per 1000 person-years in healthy controls [140]. This increased risk was multifactorial and attributed to the HIV virus itself, ART therapy, metabolic derangement, endothelial dysfunction, and high prevalence of recreational drug abuse such as cocaine and tobacco [139]. Not only do these patients have a high incidence of coronary artery disease but their risk of subsequent acute coronary syndrome remains significant. A meta-analysis of 11 studies focusing on acute coronary syndrome in HIV patients found that HIV patients admitted for acute coronary syndrome have a significant short-term mortality of 8 %, a significant long-term risk of myocardial infarction of 9.4 %, and a 20.1 % need for percutaneous coronary revascularization [141]. A landmark study has shown that ART was independently associated with a 26 % relative increase in the rate of acute myocardial infarction per year of exposure during the first 5 years of therapy [142]. However, in the SMART study, treatment interruption was associated with a 57 % increased risk of acute coronary syndrome [143]. More studies are needed to dissect the subpopulations primarily at risk.

Severe systolic dysfunction has a grave prognosis [144]. In a study by Felker et al., the hazard ratio for death was 5.86 compared with patients with idiopathic cardiomyopathy [145]. The impact of diastolic dysfunction on survival is yet to be elucidated. Unfortunately, little is known about the optimal therapy for HIV cardiomyopathy and the response of known heart failure medications in HIV patients. No randomized trials of heart failure medications have been performed at this date. Common recommendations include the use of beta-blockers, reverse remodeling agents, and afterload reduction. Refractory cases could be managed with chronic resynchronization device therapy [146]. However, mechanical circulatory support and even heart transplantation might be needed in end-stage cases [147]. Transplantation outcomes have been favorable, with no increases in acute rejection or worsening of HIV status with immunosuppression [148] (Fig. 18.7).

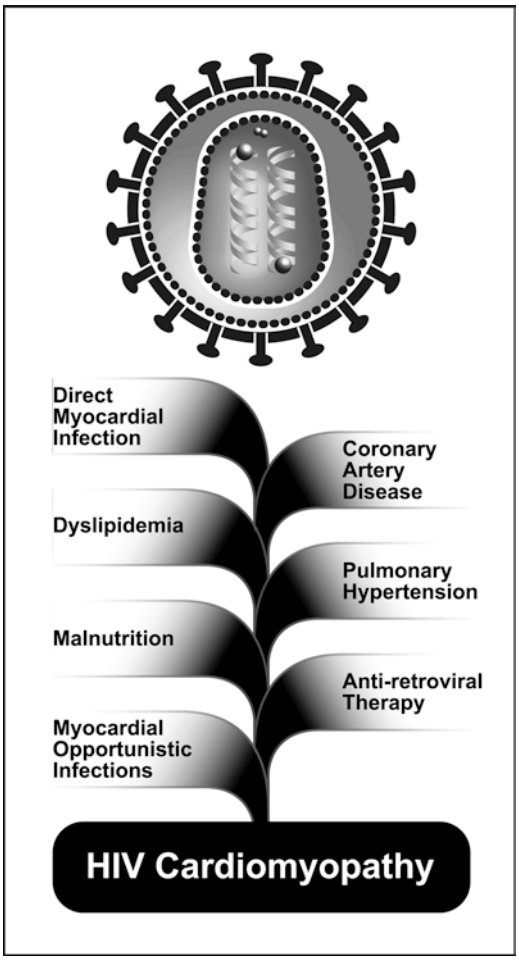

Fig. 18.7 HIV cardiomyopathy. The retrovirus HIV-1 has a constellation of effects on the cardiovascular system, in addition to direct myocardial damage. The end result is end-stage dilated cardiomyopathy. *HIV* human immunodeficiency virus

Cancer Therapeutics and Heart Failure Prevention

According to the National Cancer Institute, more than 14 million cancer survivors were estimated to be living in the United States in 2014, having a 60 % 5-year survival rate

[149]. Advances in therapeutics for childhood cancers have resulted in even more impressive improvements, with a 5-year survival exceeding 80 % [150]. Nevertheless, long-term side effects of these therapies are surfacing with prolonged survival rates. These side effects include chemotherapy-induced cardiomyopathy and heart failure, which have emerged as primary causes of morbidity and mortality in long-term survivors free of cancer [151]. For example, survivors of childhood cancer have more than 15 times the risk of developing heart failure compared to the general population [152]. Therefore, it is important to understand the pathophysiology of cancer therapeutics-related heart failure in an attempt to mitigate its occurrence and serve as a platform for therapeutic interventions.

Over the past several decades, distinct cardiotoxicity patterns have appeared that relate to specific therapeutics [153]. Due to the predictability of such toxicity, the American Heart Association has published guidelines that designate all cancer patients at risk of cardiotoxicity as stage A heart failure [154] and in need of aggressive cardiovascular risk modification in addition to chemotherapy-specific preventive measures.

Evidence suggests that prevention is far more efficacious than therapy. For example, in a recent study by Cardinale et al., the majority of patients with left ventricular dysfunction who were treated for heart failure within 4 months of their last anthracycline treatment had considerable improvement of left ventricular function than those who started treatment more than 6 months after chemotherapy [155].

Doxorubicin (Adriamycin) and its family of anthracyclines are antineoplastic agents with proven efficacy in treating hematological and breast malignancies. Given that this family of anthracyclines has the highest rate of myocardial injury, cardiotoxicity has been classically associated with this group of medications [156]. Although not based on long-term prospective studies, the cardiotoxicity can be divided into three phases: acute, subacute, and chronic. Acute cardiotoxicity starts within 24 h of administration and is usually asymptomatic. It occurs in 40–50 % of the cases. These include transient electrocardiographic changes such as nonspecific ST-T changes, QTc interval prolongation, premature atrial and ventricular contractions, and mild cardiac troponin leak. Subacute cardiotoxicity is characterized by interstitial myocardial edema and cellular infiltration. The chronic form may not become evident until 20 years after the last administration and is associated with progressive left ventricular dysfunction with a 50 % 5-year mortality rate [157–159].

The molecular mechanisms associated with the cardiomyopathy include oxidative stress, myofibrillar disintegration, topoisomerase-2b inhibition, endothelial apoptosis, and intracellular calcium dysregulation [160]. Interestingly, cardiomyopathy development is largely dose dependent [161] but may occur at low doses due to increased susceptibility. For example, female gender, young age, coadministration of other cardiotoxic drugs, mediastinal radiotherapy, and other comorbidities represent strong clinical risk factors indicating susceptibility [162]. Since the deleterious effects of doxorubicin on the myocardium are often not detected until years after cancer remission, the greatest impact is on pediatric cancer survivors [150].

Sunitinib, sorafenib, and bevacizumab are vascular endothelial transduction pathway inhibitors used in the treatment of solid tumors. The incidence of cardiomyopathy for these agents can be up to 13 % across clinical trials [163]. Not only did these agents directly cause cardiotoxicity, they have been implicated in the development of clinically significant hypertension, as well [164]. Trastuzumab is a tyrosine kinase inhibitor monoclonal antibody used in HER2+ breast cancer patients. Coadministration with anthracyclines has resulted in heart failure in about 27 % of cases [165]. Finally, the radiation used as an adjuvant or primary therapy can result in a myriad of effects on the heart. This includes restrictive cardiomyopathy and diastolic heart failure, pericardial disease, and valvular dysfunction [166].

Early detection of myocardial damage might enable implementation of preventive measures that could reduce the likelihood of further ventricular decompensation. Cardiac biomarkers such as cardiac troponins and atrial natriuretic peptides (ANPs) can be important indicators of myocardial injury and can provide useful diagnostic information, especially when used in combination with myocardial imaging studies [167]. Serial echocardiographic monitoring is generally used as a first-line imaging modality [168]. Left ventricular systolic function can be evaluated traditionally using the ejection fraction or, more recently, by speckle echocardiography.

For example, in the National Surgical Adjuvant Breast and Bowel Project (NSABP), a randomized phase III trial of trastuzumab in the 1830 cancer patients with HER2-positive breast cancer, borderline low ejection fraction at baseline carried a hazard ratio of 6.72 for the subsequent occurrence of heart failure [169]. Subsequently, in the Herceptin Adjuvant (HERA) trial, a lower baseline ejection fraction was reported to be a risk factor for adverse cardiac outcomes, including cardiovascular mortality, cardiomyopathy, and heart failure [170]. From another prospective, speckle analysis is a useful measure of myocardial deformation, which is an intrinsic mechanical property of the myocardial tissue. Reduced radial strain is associated with the onset of early histological damage and myocardial injury, offering an earlier method of detection compared to standard assessment of ventricular function [171].

Although echocardiography remains the cornerstone of cardiotoxicity screening, cardiac magnetic resonance imaging is evolving as a more superior and sensitive imaging entity for diagnosis and follow-up in the field of cardio-oncology. It offers the advantage of earlier cardiotoxicity detection—within weeks of administration [159]. Signs of cardiotoxicity primarily include myocardial edema, as it appears on T2-weighted images [172, 173]. T2 images are performed with a dual-echo technique at our institution (the

University of Minnesota) to improve potential detection of signal abnormality relative to normal myocardium. In fact, a recent study showed that 11 % of cancer survivors were misdiagnosed as having normal global systolic function on echocardiography, while they were abnormal on magnetic resonance imaging [174] (Fig. 18.8). Finally, cardiac magnetic resonance imaging can be particularly valuable in detecting myocardial fibrosis, a chronic manifestation of cardiotoxicity. Further investigation is needed to fully assess its impact on patient outcomes in the coming years.

With all this evidence, several groups of investigators have supported efforts to prevent the occurrence of advanced cardiomyopathy, rather than treatment of end-stage disease. Currently, dose modulation is the single most important strategy to prevent cardiomyopathy in patients undergoing chemotherapy. Several studies have reported that a lower weekly dosage, or even continuous infusion, will suppress tumors adequately while limiting cardiotoxicity [175].

BB and ACEI medications have been successfully used when cardiomyopathy develops [155]. A recent meta-analysis of the role of cardioprotective therapy for primary prevention of cardiotoxicity with chemotherapy reviewed 12 randomized controlled trials and two observational studies [176]. Prophylaxis with an ACEI, BB, or dexrazoxane was found to be beneficial in improving the primary outcome which was primarily heart failure and ejection fraction decline. The current practice most often dictates closely following patients at risk during treatment for their cancer and starting treatment for asymptomatic left ventricular dysfunction as detected by one of the imaging modalities. Once there are signs of cardiomyopathy, standard heart failure therapy should be implemented, starting with medical therapy. In its severe forms, refractory cases can benefit from cardiac resynchronization therapy, durable mechanical circulatory support, and transplantation [177]. Transplantation is particularly relevant given the history of malignancy. Nonetheless, it is an acceptable treatment option for patients with intractable cardiac failure secondary to chemotherapeutic agents. Fortunately, it has been shown that survival is comparable with all other heart recipients and that tumor recurrence after transplantation is rare, even with immunosuppression [178]. Guidelines regarding the duration of a cancer-free interval before listing should be reexamined on an individual basis, with input from the oncologist and consideration of type of tumor, stage, grade, and response to initial therapy.

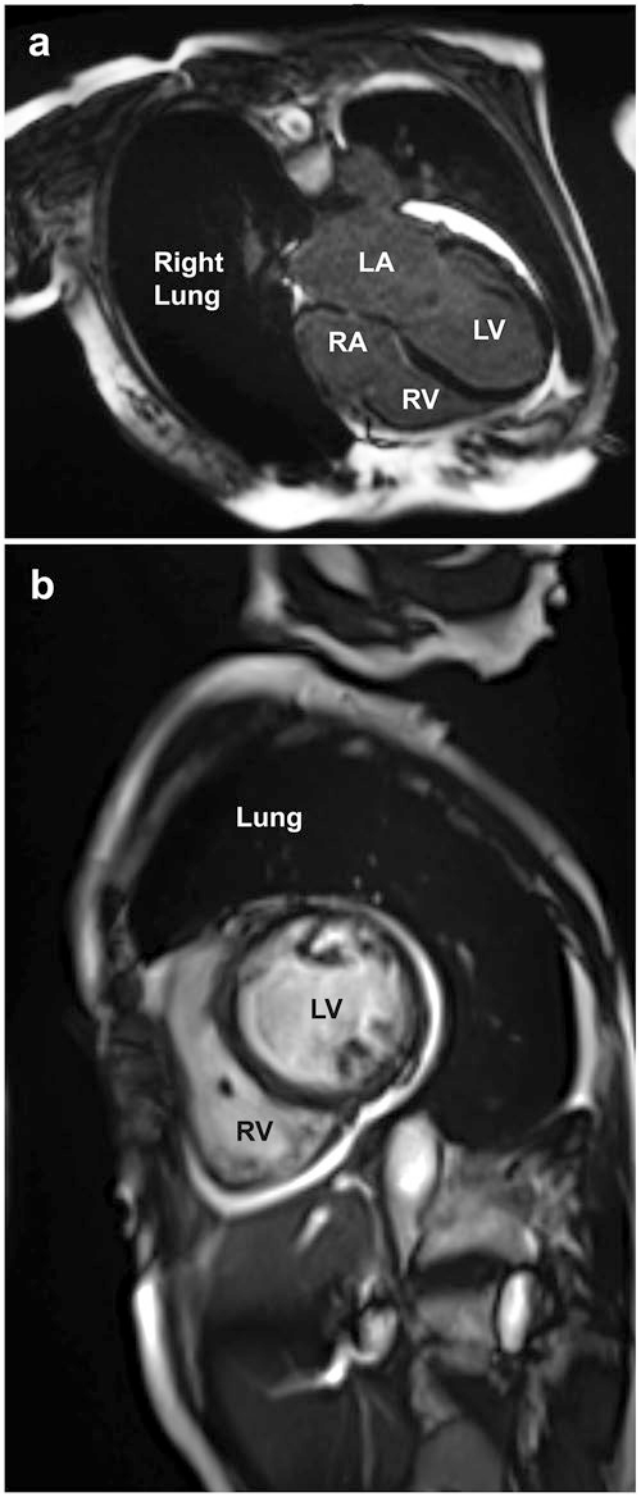

Fig. 18.8 Magnetic resonance imaging of chemotherapy-induced cardiomyopathy. (**a**) T1 image demonstrating the cardiac structures in a four-chamber view. In later stages, it presents with a dilated left ventricle (LV) with reduced ejection fraction. (**b**) Late gadolinium-enhanced image (short axis view) showing the lack of overt fibrosis in the myocardium

Summary

Heart failure is becoming one of the most challenging cardiovascular pathologies, not only because it is associated with a high mortality but also due to repetitive hospital admissions. In order to change this devastating prognostic trajectory, early detection of heart failure is important. Moreover, identifying the risk factors for heart failure is vital. Eliminating or reducing risk factors and treating them adequately will not only reduce morbidity and mortality but also maintain patients' quality of life and reduce health-care costs. This disease is also preventable by aggressively managing hypertension, dyslipidemia, obesity, and diabetes mellitus.

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Arrhythmias in Cardiomyopathy

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_19

Introduction

The morbidity and mortality of patients with most types of cardiomyopathy are related to either pump failure with end-organ dysfunction or arrhythmia-induced death or decompensation. While arrhythmia can complicate the course of a cardiomyopathy with subsequent increase in mortality and morbidity, cardiomyopathy can either be exacerbated or induced by arrhythmias. It can be challenging to quantify the effect of an arrhythmia on left ventricular function or cardiac output or how much the ventricular function will ameliorate after treating an arrhythmia. In our experience, there is usually a component of both a baseline cardiomyopathy and some exacerbation of variable scale caused by the arrhythmia. Treating both ends of this vicious cycle is essential in providing the best chances of recovery. Hence, adequate and prompt therapy of arrhythmias in patients with cardiomyopathy needs to be an essential and initial part in the multidisciplinary approach to these patients.

In this chapter, we are going to review the arrhythmias seen in patients with multiple types of cardiomyopathy and the therapeutic options available. While it is challenging to cover all the cardiomyopathies exhaustively, we are going to discuss the most common and compelling cardiomyopathies known to have a strong association with arrhythmias, while excluding the lone arrhythmic disorders seen without structural heart disease.

Atrial Tachyarrhythmias in Cardiomyopathy

It is well known that atrial arrhythmias often complicate the treatment of patients with cardiomyopathy and heart failure. It is often difficult to determine in a given clinical scenario whether the arrhythmia is the result or the cause of the cardiomyopathy, the classic "chicken or the egg" conundrum. We will first examine the role of atrial arrhythmias complicating or exacerbating cardiomyopathy before turning to an examination of arrhythmia as a cause of cardiomyopathy, the so-called arrhythmia-induced cardiomyopathy (AIC).

Atrial arrhythmias can exacerbate both systolic heart failure or "*h*eart *f*ailure with *r*educed *e*jection *f*raction" (HFrEF) and "*h*eart *f*ailure with *p*reserved *e*jection *f*raction" (HFpEF). We will primarily discuss atrial fibrillation (AF). While less frequent than AF, atrial flutter (AFL), atrial tachycardia (AT), and reentrant supraventricular tachycardia (SVT) may all decompensate or cause a cardiomyopathy.

Atrial Arrhythmias Complicating Treatment of Cardiomyopathy

It can be difficult to determine the primary abnormality in a patient presenting with both an atrial arrhythmia and left ventricular (LV) dysfunction. Even in patients with a previous diagnosis of cardiomyopathy, atrial arrhythmias may result in further deterioration of LV systolic function. In these patients, both atrial arrhythmias and cardiomyopathy must be treated simultaneously.

The ATRIA study found HF to be a more powerful predictor of AF than age, valvular heart disease, hypertension, diabetes, or prior myocardial infarction [1]. There is a direct correlation between the New York Heart Association (NYHA) functional class and the risk of AF [2]. The onset of atrial fibrillation complicates the management of HF and increases the risk of hospital admission for decompensation. Yamada and colleagues found that 20–35 % of patients admitted for decompensated HF were in AF. Of the patients, AF was new in onset in one-third [3].

Atrial Fibrillation and the Risk of Sudden Cardiac Arrest (SCA)

Atrial fibrillation is associated with an increased risk of SCA in a variety of populations [4]. Whether the risk of SCA associated with AF is due to a direct proarrhythmic effect with regard to ventricular arrhythmias or indirectly by worsening HF remains unsettled. If AF is in itself proarrhythmic, this would suggest that therapies to prevent AF (i.e., rhythm-control strategy) might be successful in lowering the risk of SCA. There is evidence to suggest that AF may be proarrhythmic with regard to ventricular arrhythmias. First, the rapid heart rates associated with AF result in a shortening of ventricular refractoriness [5]. Somberg and coauthors reported that programmed stimulation resulted in the induction of ventricular tachycardia in 25 of 26 dogs only during AF but not when the stimulation was performed during sinus rhythm [6]. Finally, the irregular pattern of ventricular activation that occurs with AF increases the risk of "short-long-short" sequences known to be proarrhythmic [7]. In fact, the study by Gronefeld et al. demonstrated that patients with AF had a higher incidence of short-long-short preceding ventricular arrhythmias as compared to patients with sinus rhythm (50 % vs. 16 %, $P = 0.002$) [8].

Atrial Fibrillation Complicating Device Therapy for Heart Failure

A significant number of cardiomyopathy patients will undergo placement of an implantable cardioverter defibrillator (ICD) for either primary or secondary prevention of sudden cardiac arrest (SCA). Studies have shown that patients with AF at the time of ICD placement have a higher rate of inappropriate ICD therapy, appropriate ICD therapy, as well as increased mortality [9, 10]. Aggressive efforts to control the heart rate during AF could conceivably reduce the risk of inappropriate shocks, but it is less clear what effect a heart rate-control strategy would have on mortality or appropriate ICD therapy. However, there is a paucity of data to suggest a rhythm-control strategy is more effective in this regard than a rate-control strategy.

Cardiac resynchronization therapy (CRT) improves symptoms and mortality in patients with HF, beyond the survival improvement seen with ICD therapy alone. There is conflicting data regarding the effects of AF on the efficacy of CRT. Khadjooi and colleagues reported on 295 consecutive NYHA Class III–IV HF patients and AF receiving CRT in a prospective observational study [11]. They found that patients with AF had similar improvement in symptoms, prognosis, and echocardiographic measures of remodeling as did patients in sinus rhythm. It should be noted that although patients in sinus rhythm had a higher percentage of biventricular pacing, the AF patients had a percentage of biventricular pacing of >87%. Linde and MUSTIC investigators reported similar degrees of response to CRT in patients with AF compared to those in sinus rhythm [12]. However, the average heart rate between the two groups at baseline was similar, 75 ± 13 beats per minute (bpm) in the patients in sinus rhythm versus 74 ± 5 for those in AF. Leclercq et al., on behalf of the MUSTIC investigators, reported on CRT in patients with permanent AF [13]. Again, the AF patients in this study had slow ventricular rates that require device placement.

Other investigators reported that patients with AF did not respond as well to CRT. A multicenter prospective observational study, the Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry (CERTIFY), followed 7384 consecutive CRT patients for a median of 37 months. The largest group, 6046 patients, had sinus rhythm. There were 895 patients with AF rate controlled using drug therapy and 443 patients with AF and atrioventricular junction ablation. Patients treated with heart rate-slowing drugs had higher total and cardiac mortality [14]. Given the lack of a control group, the investigators could not comment on the proportional improvement with CRT in each group or determine if, despite poorer outcomes, the AF plus rate control with drug group had a benefit from CRT.

Atrial Flutter and Atrial Tachycardia in Heart Failure

Although AF is the most common arrhythmia seen with HF, atrial flutter (AFL) and atrial tachycardia (AT) are not infrequent. AFL can be difficult to control with antiarrhythmic drugs. Rate control in AFL and AT is also frequently difficult. Ablation of AFL is highly efficacious with a low risk of major complications. Ablation should be considered a first-line therapy for HF patients with either symptomatic AFL or when there is suspicion that AFL is causing a further reduction in systolic function.

There is little data to guide management decisions regarding treatment of AT in cardiomyopathy patients. In selected patients treatment with antiarrhythmic drugs may be successful, although the only approved drugs available for use in this setting are amiodarone or dofetilide [15]. Ablation for AT is also reasonable as a first-line therapy and in patients in whom drug therapy was either unsuccessful or not tolerated.

Arrhythmia-Induced Cardiomyopathy (AIC) and Treatment

Atrial arrhythmias are well known to lead to decompensation of patients with cardiomyopathy. What is less well appreciated is that atrial arrhythmias may in fact be the cause of the cardiomyopathy. This has been referred to as *arrhythmia-induced cardiomyopathy* (AIC). Arrhythmia-induced cardiomyopathy can be induced by ventricular arrhythmias as well as atrial arrhythmias [16].

Atrial Fibrillation as a Cause of AIC

Atrial fibrillation is the most common cause of AIC in adults. In patients with HFrEF, AF may result in a component of AIC. In other patients AF is the cause of the cardiomyopathy. This distinction is not always a simple matter. If the patient has a known underlying cardiomyopathy prior to presenting with AF, the AF is most likely a contributing factor.

However, in a patient who presents with a new dilated cardiomyopathy *and* new AF, the possibility that the AF is the cause of the cardiomyopathy should not be discounted. As in AF patients in general, there continues to be a debate with regard to whether a rate-control or rhythm-control strategy is superior. In patients perceived to have AIC due to AF, there is the added concern that AIC may not be caused by elevated heart rate alone. Other factors such as irregularity of ventricular activation, exacerbation of diastolic failure via loss of active atrial contraction, and worsening of mitral regurgitation may all play a role as well.

The studies reviewed above have demonstrated that ablation therapy for AF in HF is feasible. Most also demonstrate that successful ablation therapy is associated with an improvement in heart function [17–20]. In high-volume centers, with acceptable rates of serious complications, ablation therapy for AF-associated AIC should be considered, especially if the rhythm is not well controlled with antiarrhythmic drug therapy. The data is less clear that this approach is superior to AVJA and CRT pacing. In our practice the approach to treatment of AF in the setting of AIC is highly individualized, taking into account patients' wishes and their overall functional status and comorbidities. It is our practice to, at the least, consider ablation therapy as an option in these patients. In general, unless the patient declines or due to comorbidities there is no reasonable choice of an antiarrhythmic drug, pharmacologic control of the AF is attempted first.

Atrial Flutter as a Cause of AIC

As discussed earlier, AFL is more difficult to rate control. Ablation therapy for AFL is highly efficacious and of low risk. In patients felt to have AIC due to AFL, ablation of the arrhythmia is the treatment of choice.

Supraventricular Tachycardia (SVT) as a Cause of AIC

Ablation therapy is the treatment of choice for any patient with symptomatic reentrant supraventricular tachycardias (atrioventricular nodal reentrant tachycardia or accessory pathway-mediated tachycardias); this is especially true in patients suspected of AIC due to SVT.

Atrial Tachycardia as a Cause of AIC

As with AF, the approach is highly individualized in a given patient. Ablation therapy being the first choice is very dependent on patient preference. In our experience, younger patients, or patients who are not on any prescription medications, tend to gravitated toward an ablation approach.

Management of Atrial Arrhythmias in Cardiomyopathy

Rate Control Versus Rhythm Control in Cardiomyopathy

In 2014 the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society published guidelines for the management of AF [15]. In regard to patients with HF who develop AF, they conclude that "a rhythm control strategy is not superior to a rate control strategy." In reaching this conclusion, the authors reference the work of Roy and colleagues [21]. This randomized multicenter trial compared a rhythm-control strategy versus a rate-control strategy in patients with HF. They followed 1376 patients for a mean of 37 months, 682 patients in the rhythm-control arm and 694 patients in the rate-control arm. There was no statistical difference in cardiovascular death, all-cause death, stroke, or worsening HF between the two arms on an intention-to-treat basis. Ten percent of the rate-control patients crossed over to the rhythm-control strategy due to worsening HF. A higher percentage, 21 %, crossed over from the rhythm-control to the rate-control arm due to an inability to maintain sinus rhythm. Rhythm control was achieved using pharmacologic agents. As with previous studies comparing rhythm- versus rate-control strategies, the adequacy of control of AF is an issue. Fifty-eight percent of the rhythm-control patients had at least one episode of AF during follow-up. The prevalence rate of AF at 4 years of follow-up in the rhythm-control arm was 27 % as compared to prevalence rates of 59–70 % in the rate-control arm [21].

Other studies, however, have demonstrated the benefit of a rhythm-control strategy. The CAFÉ-II trial randomized 61 patients to either rhythm control with amiodarone versus rate control in patients with symptomatic persistent AF and HF [22]. In this study a rhythm-control strategy resulted in significantly more improvement in left ventricular function, quality of life, and N-terminal pro-B-type natriuretic peptide levels when compared to a rate-control strategy.

Moreover, studies have compared atrioventricular junctional ablation (AVJA) versus rate control with drugs, AVHJA versus catheter ablation of AF, as well as catheter ablation of AF versus control patients in the setting of HF. In 2004, Hsu and colleagues reported on a series of 58 consecutive patients with persistent AF and HF treated with catheter ablation compared to 58 matched control patients with persistent AF without HF who underwent ablation therapy [17]. The study showed that ablation therapy for AF in HF patients was feasible and was as likely to be successful compared to patients without HF. They also found that HF patients had significant improvement in left ventricular function, improvement in symptoms, exercise capacity, and quality of life.

Khan et al. compared catheter ablation of AF to AVJA and cardiac resynchronization therapy (CRT) in a multicenter randomized trial [19]. Ablation therapy was found to be superior to AVJA and CRT in patients with drug-resistant persistent AF.

CAMTAF was a single-center, randomized, non-blinded study. The patients in this trial had persistent AF [18]. Twenty-six patients were randomized to ablation therapy and 24 to the rate-control arm. Strict HR control (resting HR < 80 bpm and moderate exercise HR < 110 bpm) was required in the rate-control arm. Freedom from AF after a single ablation procedure was achieved in 10 of 26 patients (38 %). Twenty-one of 26 patients (81 %) were free from AF 6 months after the last ablation therapy. At 1 year 19 of 26 patients (73 %) remained AF free. There were two serious complications (stroke, tamponade) in the ablation arm for a 7.7 % risk of major complication *per patient* or 4.7 % *per procedure*. At 6 months the patients in the ablation arm showed better improvement in ejection fraction, functional capacity, and HF symptoms.

A recent review by Ganesan and colleagues looked at the results of ablation therapy for AF in patients with left ventricular (LV) systolic dysfunction [20]. They identified 19 studies totaling 914 patients with LV systolic dysfunction who underwent ablation therapy for AF. The single procedure success rate was 57 %. The overall success rate (multiple procedures and use of antiarrhythmic drugs) was 82 %. The mean improvement in ejection fraction was 13 %. Seven of the studies demonstrated improvements in exercise capacity and quality of life as well.

In the most recent 2014 guidelines, catheter ablation was considered as "reasonable to treat symptomatic AF in selected patients with significant LV dysfunction and HF." Indications for ablation therapy of AF are given in these guidelines but not specifically for patients with HF.

Concern has been expressed that many of the studies cited may suffer from patient selection bias. The results of the Ablation vs. Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD/CRT-D (AATAC-AF) should be available soon and may help better define this issue (ClinicalTrials.gov Identifier: NCT00729911).

Summary of Treatment Options for Atrial Arrhythmias in Cardiomyopathy

The following approaches are largely based on the 2014 AF guidelines but include minor modifications based upon the authors' own clinical practice [15].

Treatment of Cardiomyopathy/HF

- All patients should be on guideline-based therapy for their cardiomyopathy.

Prevention of Thromboembolic Complications

- The CHA_2DS_2-VASc score should be used to assess the risk of thromboembolic complications, except in patients with valvular AF or patients with HCM.
- With regard to thromboembolic risk, AFL patients are treated the same as AF patients.
- In patients with nonvalvular AF, the newer novel oral anticoagulants should be considered.

Rate Control of AF in Cardiomyopathy Patients

- In patients with HFrEF beta-adrenergic receptor blockers should be used for heart rate control.
- Digoxin, in combination with a beta-blocker, can be helpful, especially in patients with decompensated HF. There continues to be concern that the use of digoxin in AF patients may be associated with increased mortality. If digoxin is used, the serum level should be monitored and kept ≤0.9 ng/ml [23].
- In patients with HFpEF or HCM, non-dihydropyridine calcium channel antagonists are reasonable rate-control agents. Their long-term use should be avoided in patients with HFrEF.
- Intravenous amiodarone is reasonable for heart-rate control when other agents have been unsuccessful or contraindicated.
- Atrioventricular junction ablation for heart-rate control is reasonable. However, the current guidelines state this should only be considered in patients in whom the heart rate could not be controlled with drugs. We recommend attempting a rhythm-control approach before pursuing AVN ablation. In patients with reduced EF, CRT pacing either via a pacing system or ICD should be considered *unless* the cardiomyopathy is felt to be arrhythmia induced.
- It should not be forgotten that, when feasible, a rhythm-control strategy (including ablation therapy of AF) also controls the heart rate.

Rhythm Control of AF in Cardiomyopathy

- In the absence of clearly demonstrable superiority of either rate-control or rhythm-control strategy, patient preference, comorbidities, and goals need to be carefully considered.
- Before embarking on a rhythm-control strategy, any precipitating factors, including HF, should be treated.
- In patients with HFrEF only amiodarone and dofetilide are considered acceptable antiarrhythmic drug choices.
- In patients with ischemic cardiomyopathy but without HF, dronedarone and sotalol are also reasonable.
- In patients with HCM, amiodarone or disopyramide is considered the drug of choice.
- Ablation therapy for AF should be considered for symptomatic patients who do not tolerate antiarrhythmic drug therapy or in whom drug therapy for rhythm control has failed. This is an area of ongoing investigation in which clinical practice patterns may be expected to continue to evolve.

Summary of Treatment Options in Adults with AIC

- Patients with AIC should receive standard guideline-based treatment for LV systolic dysfunction. Whether to continue HF-based therapy after resolution of AIC is a question that remains unresolved.
- Patients with AF or AFL should be treated with oral anticoagulation based on their CHA_2DS_2-VASc score.
- In patients with AIC secondary to AFL or SVT, except in rare circumstances, ablation therapy is the preferred approach.
- In patients with AIC secondary to AF, the superiority of rate control versus rhythm control remains a topic of debate. What is clear is that a lenient approach to heart rate control in AIC is inappropriate. Current guideline recommendations indicate that AVJA should only be done after an attempt at rate control with drugs [15]. There appears to be increasing evidence that rhythm control through ablation therapy may have advantages over both rate-control and pharmacologic rhythm-control strategies. This remains controversial, and clinical practices continue to evolve rapidly.
- In patients with AIC secondary to AT, arrhythmia control with an antiarrhythmic drug and ablation are both reasonable, depending on the individual patient and circumstances.

While it may seem obvious, nonetheless it is important to emphasize that in a patient with AIC, control of the arrhythmia, by the most appropriate means in a given circumstance, is of paramount importance.

Ventricular Tachyarrhythmias in Cardiomyopathy

Premature Ventricular Complexes

Premature ventricular complexes (PVC) are the most common arrhythmia in patients with normal heart function and are often considered benign without structural heart disease. However, in the presence of cardiomyopathy, their prognostic

value becomes dependent on the presence and extent of underlying structural disease in patients with cardiomyopathy [24, 25]. While the presence and decompensation of a cardiomyopathy can cause an increase in PVCs and while most patients with frequent PVCs will not develop cardiomyopathy, frequent PVCs or idiopathic ventricular tachycardia can induce or exacerbate a cardiomyopathy [26]. A PVC can also interfere with cardiac resynchronization therapy and decrease its efficacy.

PVC-Induced Cardiomyopathy

Frequent PVCs can induce a cardiomyopathy in patients without structural heart disease and can exacerbate cardiomyopathy in patients with baseline structural disease [27–29]. This relationship has been confirmed on the basis of reversal of the cardiomyopathy with suppression of the PVCs [30, 31]. The mechanism of PVC-mediated cardiomyopathy is not fully understood. Potential mechanisms include ventricular dyssynchrony, abnormal ventricular filling from the post-PVC pause, and abnormal calcium handling from the short or variable coupling intervals.

The most prominent predictor of cardiomyopathy appears to be a high PVC burden, variably defined as ranging from >10,000 to 25,000 PVCs/day and as >10–24 % of total heartbeats/day [26, 32]. The most accepted cutoff in the 2014 EHRA/HRS/APHRS Expert Consensus on Ventricular Arrhythmias is 10,000 PVCs/day [33]. Decreasing the PVC burden to <5000/day can improve ventricular function [30]. This threshold is helpful when elimination of all PVCs may not be possible in the setting of multiform PVCs. Other PVC characteristics including male sex, increased body mass index, higher PVC coupling interval dispersion, and interpolated PVCs have not been reproducible in all studies.

Therapy for PVC-induced cardiomyopathy should be targeted at suppressing or eliminating the PVCs. It includes antiarrhythmic therapy and catheter ablation. Beta-blockers are frequently considered as first-line therapy because of the low side effect profile, but have limited effectiveness. Dofetilide, mexiletine, sotalol, or amiodarone may be more effective, but with the greater risk of side effects and proarrhythmia. Medical therapy is reserved for patients who fail or are reluctant to undergo catheter ablation.

Catheter ablation has become as the definitive and first-line therapy for PVC-mediated AIC, with success rates ranging from 70 to 90 % [27]. The much better efficacy of ablation therapy over medical therapy is proven in a recent randomized trial [34]. The elimination of a high PVC burden (>10 % or 10,000 PVCs/24 h) in patients with impaired LVEF can be associated with improvement of function, even when structural cardiac abnormalities are present [35].

PVCs Interfering with Cardiac Resynchronization Therapy (CRT)

A high biventricular pacing percentage above 95–98 % of all ventricular beats was associated with a significant reduction in mortality [36]. Frequent PVCs in patients with CRT pacemakers and defibrillators can interfere with biventricular pacing and decrease it below 95 %. Successful ablation of PVCs can improve the efficacy of cardiac resynchronization therapy in nonresponders [37]. In this patient population, a pre-ablation PVC burden of >22 % was associated with a significant improvement in LV function.

Ventricular Tachycardia

Ischemic heart disease is the most common cause of sustained ventricular tachyarrhythmias. In particular, polymorphic ventricular tachycardias (VTs) leading to ventricular fibrillation (VF), or primary VF itself (. Fig. 19.1) due to acute coronary ischemia, are probably the most common causes of sudden cardiac death (SCD). Approximately 20 % of patients with a primary prevention ICD and 45 % of patients with secondary prevention ICD receive an appropriate ICD intervention within the first 2 years following ICD implantation. Additionally, VT storm, defined as 3 or more VT episodes within a 24 h period, may affect 4 % and 20 % of primary and secondary prevention patients, respectively. Moreover, ICD shocks and even appropriate ATP has been linked to increased mortality in this population.

Apart from acute ischemia, ventricular tachyarrhythmias may also occur as a result of structural heart disease that causes localized disturbances of electrical activation in the myocardium or conduction system. In severe disease, left ventricular function may be markedly impaired resulting in an ischemic cardiomyopathy.

The most common structural disturbance leading to tachyarrhythmia susceptibility is scar remaining after a prior myocardial infarction due to obstructive coronary artery disease. However, ventricular scars leading to reentrant VT also occur in nonischemic cardiomyopathies, including idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy, infiltrative heart disease (e.g., sarcoidosis), right ventricular dysplasia (also now known as right ventricular cardiomyopathy), and postrepair of congenital heart disease or valvular heart disease.

Reentry involving the regions of myocardial scar noted above is the basis for most instances of sustained monomorphic VT in patients with structural heart disease. In such cases, the scar zone contains viable fibers that provide for the slow conduction that is a necessary requirement for sustained reentry. These slow conduction zones and sometimes the coexisting conduction pathways sustaining the arrhythmia can be identified by "electro-anatomic mapping" in the electrophysiology laboratory and subsequently modified by radiofrequency ablation to diminish VT susceptibility.

Bundle branch reentry is an important but less common form of reentry mostly seen in nonischemic dilated cardiomyopathy, but can be occasionally seen in ischemic cardiomyopathy. Typically, bundle branch reentry (■ Fig. 19.2) occurs in the setting of severe cardiomyopathy in which there is usually a combination of both conduction system disease and marked ventricular dilatation. The reentry in these cases uses the bun-

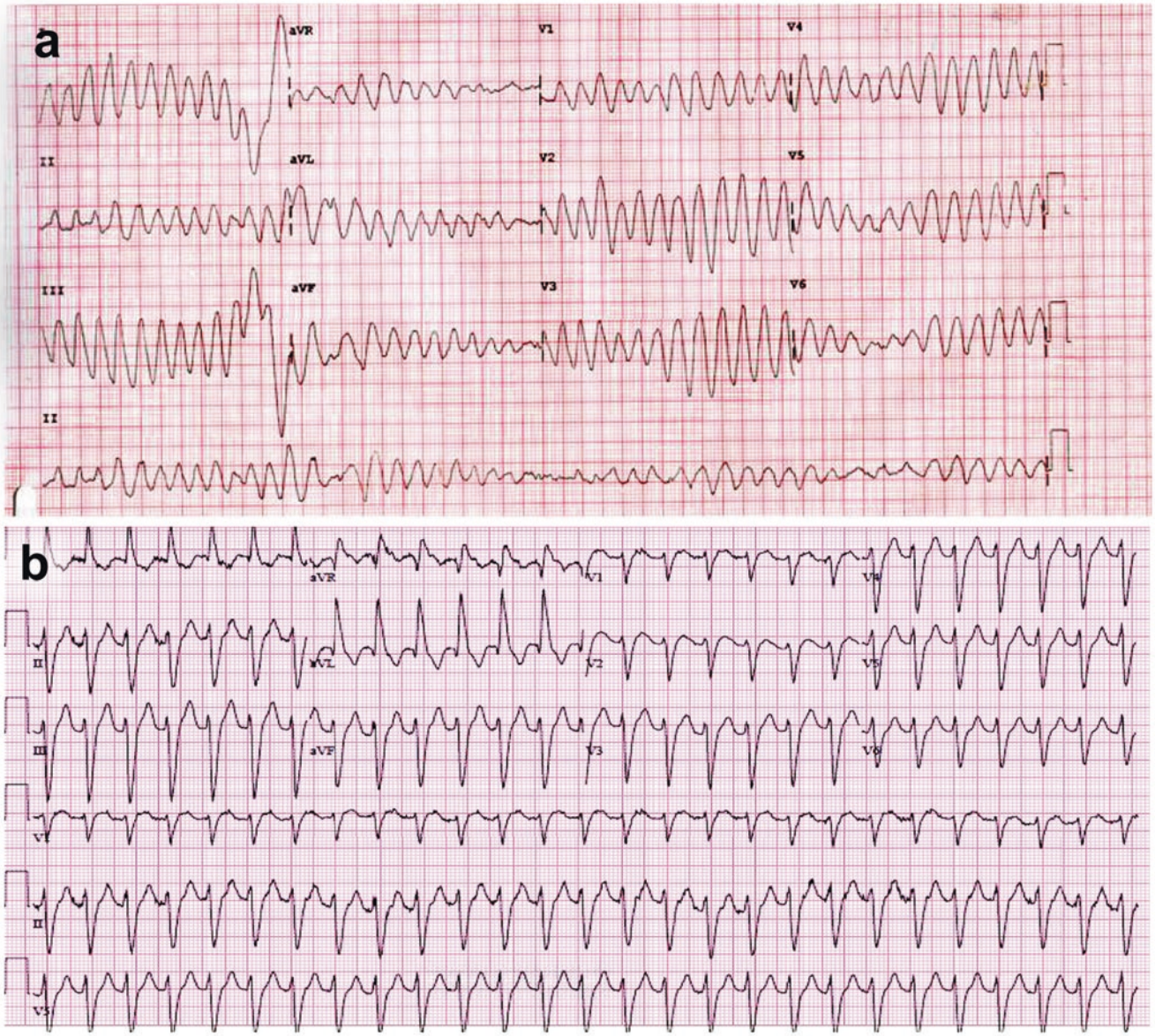

Fig. 19.1 (**a**) ECG exhibiting polymorphous VT that was determined to be torsades de pointes, (**b**) ECG showing sustained scar-related monomorphic VT. *ECG* electrocardiogram, *VT* ventricular tachycardia

dle branches. Most often anterograde ventricular activation occurs over the right bundle branch, with retrograde conduction back over the usually diseased left-sided conduction system. The conduction system disease in conjunction with a dilated ventricle allows for the necessary electrical circuit size that permits sustained reentry. Recognition of this arrhythmia is important because it is amenable to catheter ablation therapy by transecting the bundle branches (usually the right bundle as it is a more discrete target) [38, 39].

Management of VT includes antiarrhythmic therapy and ablation therapy. In the era of defibrillators, VT manifests the most with ICD shocks. Patients who present with an ICD shock should be first evaluated to rule out obvious reversible causes: electrolyte abnormalities, device interrogation to make sure it is an appropriate shock, decomposition of heart failure, ischemic workup especially in patients with ischemic cardiomyopathy, and polymorphic VT. It should be mentioned that ischemia can manifest with monomorphic VT, challenging the old dogma just mentioned. Moreover, beta-blocker therapy needs to be optimized. Once a reversible cause is ruled out and/or treated, medical antiarrhythmic therapy is usually the first-line therapy and needs to be tailored to the type of cardiomyopathy. Antiarrhythmic therapy is detailed in a separate section. Of note, if a patient presents with a single ICD shock with no recurrence, it is reasonable to defer therapy until a significant recurrence since VT burden tends to sometimes wax and wane without intervention.

Ablation therapy for VT related to cardiomyopathy is slowly gaining momentum and is currently considered in patients with recurrent VT resistant to antiarrhythmic medical therapy [40]. Although the occurrence of VT increases mortality in patients with structural heart disease, there is

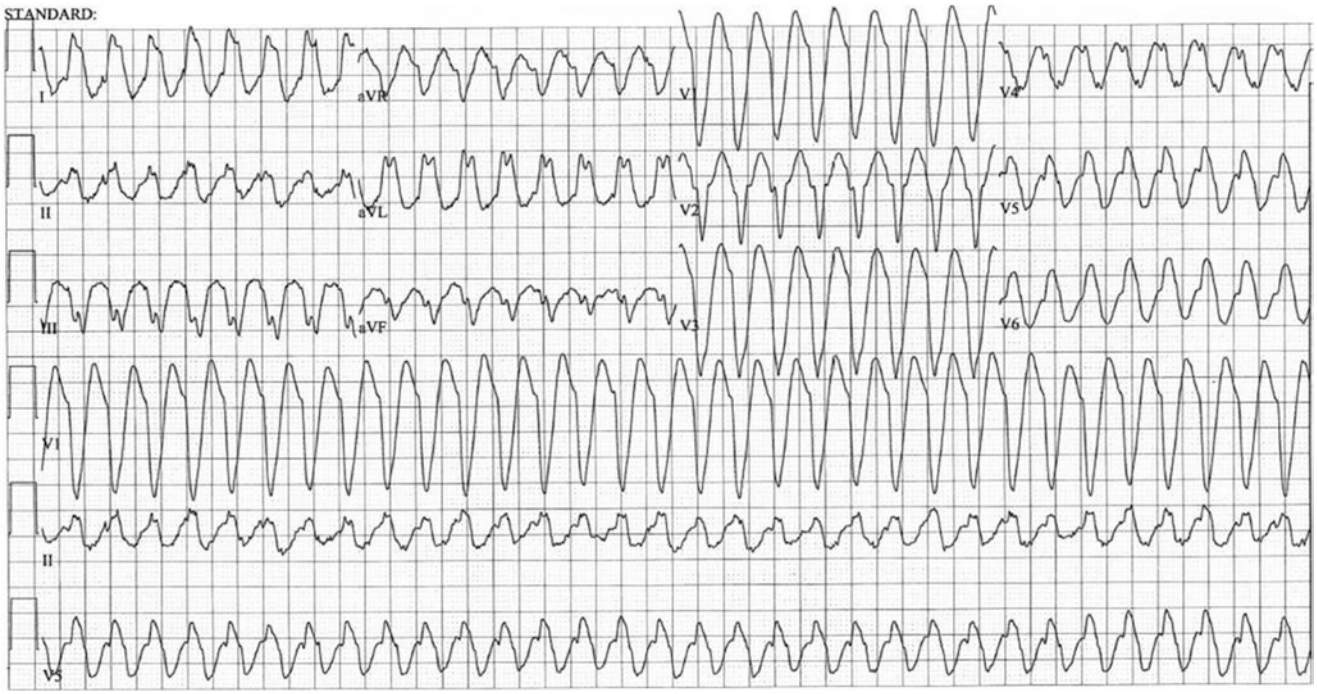

Fig. 19.2 ECG showing bundle branch reentry VT in a patient with conduction system disease. *VT* ventricular tachycardia

still debate whether VT suppression, especially with VT ablation, affects mortality.

There are two main approaches to VT ablation with ramifications of each. The first is based on activation mapping, which includes inducing the clinical VT and using 3D and conventional mapping techniques to define the circuit and ablate the area responsible for sustaining the tachycardia. This is limited by the fact that only about 10 % of the VTs are hemodynamically stable enough to have time for mapping while in VT. The percentage of VTs amenable to this approach increased with the advent of hemodynamic support such as an intra-aortic balloon pump, the CARDIOHELP system (Maquet Cardiopulmonary AG, Hirrlingen, Germany), and IMPELLA (Abiomed, Danvers, MA). This method is limited by the potential vascular complications with hemodynamic support and the potential of stunning the myocardium with subsequent severe decompensation of heart failure from prolonged times in VT during the ablation. The second method consists of substrate modification, with the advantage of performing ablation in sinus rhythm without prolonged time in VT. The goal is to homogenize the scarred area in order to eliminate potential slow conduction channels responsible for sustaining VT. There are a multitude of approaches within substrate modification, which is out of the scope of this chapter. Overall, most operators use a hybrid approach between the two methods that permits targeting of the clinical VT and prevents future potential circuits.

We will review the efficacy of VT ablation with each of the most common clinical scenarios.

Ablation Therapy for VT in Ischemic Cardiomyopathy (ICM)

Two main relatively large prospective randomized clinical trials examine the outcomes after VT ablation in patients with ICM [41, 42].

SMASH-VT included 128 patients with recently implanted ICDs for secondary prevention and with primary prevention ICDs who had received a single appropriate therapy [41]. Freedom from recurrent VT/VF resulting in appropriate ICD therapy after 2 years of follow-up was significantly higher in the ablation arm (88 % versus 67 %; HR 0.35; 95 % CI 0.15–0.78; $P = 0.007$) compared with controls.

The second landmark trial was the Ventricular Tachycardia Ablation in Coronary Heart Disease (VTACH) study that enrolled 110 patients with hemodynamically stable VT, prior MI, and reduced left ventricular ejection fraction (LVEF), who were randomly assigned to catheter ablation and ICD versus ICD alone [42]. After 2 years, the ablation arm had less VT/VF (47 % versus 29 %; HR 0.61; 95 % CI 0.37–0.99; $P = 0.045$) and fewer appropriate ICD shocks per patient year (mean 0.6 ± 2.1 versus 3.4 ± 9.2 shocks; $P = 0.018$).

There are a multitude of retrospective studies with various success rates and effects on mortality. The main limitation is the largely heterogeneous ablation techniques adopted. There are two ongoing VT ablation studies for ICM patients, the VANISH and BERLIN trials, that will also study mortality [43, 44]. Two other trials, STAR-VT and PARTITA, will include both ICM and NICM patients [45, 46].

Ablation Therapy for VT in Nonischemic Cardiomyopathy (NICM)

Unlike ICM, where the underlying substrate is relatively well defined based on the affected coronary artery, patients with NICM have heterogeneous substrates that include different degrees of involvement of the mid-myocardium and epicardium, usually in the perivalvular regions.

To date, there are no prospective randomized trials describing outcomes of VT ablation in patients with NICM. In general, patients with NICM have higher rates of acute procedural failure and long-term VT recurrence after ablation therapy compared to patients with ICM. The HELP-VT study was a prospective observational European single-center study that enrolled 63 patients with NICM and 164 patients with ICM treated with VT ablation [47]. VT-free survival rates at 1-year follow-up were 40.5 % for NICM and 57 % for ICM. One large single-center retrospective observational study included 226 patients with NICM treated with VT ablation. The composite endpoint of death, heart transplantation, or hospitalization for VT recurrence at 1 year (after the last ablation) was 31 % [48].

Role of the Implantable Cardioverter Defibrillator

Patients with either ischemic or nonischemic cardiomyopathy have an increased risk of SCD due to ventricular tachyarrhythmias. SCD is also the leading cause of mortality in patients with heart failure (HF) and occurs at a rate six to nine times that seen in the general population.

The Role of Implantable Cardioverter Defibrillator (ICD) Therapy in Cardiomyopathy

In general, a systolic dysfunction worsens (i.e., the left ventricular [LV] ejection fraction becomes lower), and the severity of HF becomes more marked. In LV dysfunction of NYHA Class I and II and moderate III severity, SCD is most often due to VF, and ICD therapy has proved highly effective. However, as LV function deteriorates further (severe NYHA Class III and Class IV), the propensity for bradyarrhythmic deaths increases (particularly pulseless electrical activity). Inasmuch as the most prominent bradyarrhythmias in this setting are associated with pulseless electrical activity (PEA), they are not amenable to ICD therapy. Prevention of the latter scenario requires that both medical therapy to slow deterioration of LV function and ICD therapy to terminate VF events be employed in concert at an early stage of patient care.

Given the worrisome susceptibility to SCD in patients with diminished LV ejection fraction (particularly <35 %) and heart failure, the ICD has emerged as an important life-saving treatment option. Randomized trials have consistently shown that ICD implantation reduces mortality in HF patients with reduced left ventricular function, as well as in patients who have suffered a cardiac arrest [49–51] (Tables 19.1 and 19.2). Further, ICD therapy has always proved superior to antiarrhythmic drug therapy. Two broad categories of patients are candidates for ICD therapy: (a) secondary SCD prevention and (b) primary SCD prevention.

Secondary SCD Prevention

Secondary prevention refers to the prevention of SCD in patients who have survived a prior cardiac arrest or sustained VT. If the initial arrhythmic event was not due to a clearly reversible or temporary cause (such as an electrolyte disturbance, a transient hypoxia due to respiratory failure, or an acute coronary ischemia episode that can be addressed), then there is a high risk (>40 %) of experiencing a recurrent episode of VT or VF in the next 2 years [52]. In such cases, several clinical trials have shown that ICD use results in improved survival compared with antiarrhythmic agents. By way of summarizing these observations, a meta-analysis of secondary prevention trials (*AVID* [Antiarrhythmics Versus Implantable Defibrillators], *CASH* [Cardiac Arrest Study Hamburg], and *CIDS* [Canadian Implantable Defibrillator Study] [51, 53, 54]) demonstrated that ICD use was associated with a 50 % relative risk reduction for arrhythmic death and a 25 % relative risk reduction for all-cause mortality [55] (Table 19.1).

Primary SCD Prevention

Primary SCD prevention refers to the use of ICDs in individuals who are at risk for, but have not yet experienced, an episode of sustained VT, VF, or resuscitated cardiac arrest. Early primary prevention trials focused on patients with ischemic cardiomyopathy (*MADIT-I* [Multicenter Automatic Defibrillator Implantation Trial], *MUSTT* [Multicenter Unsustained Tachycardia Trial], *MADIT-II* [Multicenter Automatic Defibrillator Implantation Trial-II], *CABG-Patch* [Coronary Artery Bypass Graft Patch Trial]) [49, 56–58]. These prospective, randomized, multicenter studies showed benefit of ICD therapy for primary SCD prevention and improved total survival in patients with ischemic cardiomyopathy (Table 19.2). Initial trials of ICD therapy for primary prevention in patients with nonischemic cardiomyopathy (*CAT*, the Cardiomyopathy Trial) and *AMIOVIRT* (amiodarone versus implantable cardioverter defibrillator) showed no survival benefit, but were limited by small sample size [59, 60]. However, subsequent larger trials (*DEFINITE*, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation, and *SCD-HeFT*, Sudden Cardiac Death in Heart Failure Trial) have extended the evidence of ICD benefit to patients with nonischemic cardiomyopathy and have demonstrated decreased mortality from prophylactic ICD implantation in this patient group [50, 61] (Table 19.2).

Given the high risk of SCD in the early post-myocardial infarction (MI) period (e.g., in the Valsartan in Acute Myocardial Infarction Trial [*VALIANT*], the risk of sudden

Table 19.1 Major randomized clinical ICD trials (secondary prevention)

Study	Year	Inclusion criteria	Patients, *n*	ICD, *n*	Mean follow-up (month)	Main result
AVID [5]	1997	Any of (1) VF, (2) VT with syncope, or (3) VT with severe symptoms and EF ≤ 40 %	1016	507	18	ICD therapy resulted in 31 % RR reduction in mortality (CI 10–52 %), $P = 0.002$
CASH [7]	2000	Cardiac arrest secondary to ventricular arrhythmia	288	99	57	ICD therapy resulted in nonsignificant 23 % RR reduction in mortality (CI lower bound–11 %), $P = 0.08$
CIDS [8]	2000	Any of (1) VF, (2) out-of-hospital cardiac arrest requiring defibrillation or cardioversion, (3) VT with syncope, (4) VT ≥ 150 bpm with symptoms and EF ≤ 35 %, or (5) unmonitored syncope with subsequent VT	659	328	36	ICD therapy resulted in nonsignificant 20 % RR reduction in mortality (CI—8–40 %) $P = 0.142$

Table 19.2 Major randomized clinical ICD trials

Primary prevention in ischemic cardiomyopathy						
Study	Year	Inclusion criteria	Patients, *n*	ICD, *n*	Follow-up (mo)	Main result
MADIT [10]	1996	EF ≤ 35 %, MI ≥ 3 weeks before entry, NSVT, inducible sustained VT on EPS, NYHA I–III	196	95	27	ICD therapy resulted in 54 % RR reduction in mortality (CI 18–74 %), $P = 0.009$
CABG [12] Patch	1997	EF ≤ 35 %, abnormal SAECG, epicardial ICD during CABG	900	446	32	ICD therapy did not reduce mortality, $P = 0.64$
MUSTT [11]	1999	EF ≤ 40 %, MI 1 month before entry, asymptomatic NSVT	704	161	39 (median)	ICD therapy resulted in 55 % RR reduction in mortality (CI 37–68 %), $P = 0.001$
MADIT-II [4]	2002	EF ≤ 30 %, MI 1 month before entry, NYHA I–III	1232	742	20	ICD therapy resulted in 31 % RR reduction in mortality (CI 7–49 %), $P = 0.016$
SCD-HeFT [3]	2005	EF ≤ 35 %, 3 months of optimal medical therapy, NYHA II–III	2521 total, 1310 ischemic	829 total, 431 ischemic	45.5 (median)	Overall, ICD therapy resulted in 23 % RR reduction in mortality (CI 4–38 %), $P = 0.007$; in ischemic patients, ICD therapy resulted in nonsignificant 21 % RR reduction in mortality (CI—4–40 %), $P = 0.05$. No evidence of effect modification by etiology
Primary prevention in ischemic cardiomyopathy: early after MI						
DINAMIT [16]	2004	EF ≤ 35 %, within 6–40 days of MI, depressed HRV, or average Holter HR ≥ 80 bpm, NYHA I–III	674	332	33	ICD group had a significant decrease in risk of death due to arrhythmia, $P = 0.009$ but a significant increase in risk of non-arrhythmic death, $P = 0.02$. ICD therapy did not reduce all-cause mortality, $P = 0.66$

IRIS [17]	2009	EF ≤ 40 %, within 5–31, HR—90 bpm or NSVT ≥ 150 bpm, NYHA I–III	898	445	37	ICD group had a significant decrease in sudden cardiac death, $P = 0.049$ but a significant increase in risk of non-sudden cardiac death, $P = 0.001$. ICD therapy did not reduce mortality, $P = 0.78$
Primary prevention in nonischemic cardiomyopathy						
CAT [13]	2002	EF ≤ 30 %, new-onset DCM, NYHA II–III	104	50	66	ICD therapy did not reduce mortality, $P = 0.55$
AMIOVIRT [14]	2003	EF ≤ 35 %, DCM, asymptomatic NSVT, NYHA I–III	103	51	36	ICD therapy did not reduce mortality, $P = 0.80$
DEFINITE [15]	2004	EF ≤ 35 %, NSVT, NYHA I–III	458	229	29	ICD therapy resulted in nonsignificant 35 % RR reduction in mortality (CI—6–60 %), $P = 0.08$
SCD-HeFT [3]	2005	EF ≤ 35 %, 3 months optimal medical therapy, NYHA II–III	2521 total, 1310 ischemic	829 total, 431 ischemic	45.5 (median)	Overall, ICD therapy resulted in 23 % RR reduction in mortality (CI 4–38 %), $P = 0.007$; in ischemic patients, ICD therapy resulted in nonsignificant 21 % RR reduction in mortality (CI—4–40 %), $P = 0.05$. No evidence of effect modification by etiology

RR = relative risk, CI = 95 % confidence interval, EF = left ventricular ejection fraction, NYHA = New York Heart Association Class, DCM = dilated cardiomyopathy, Mo = month, SAECG = signal-averaged ECG, HRV = heart rate variability

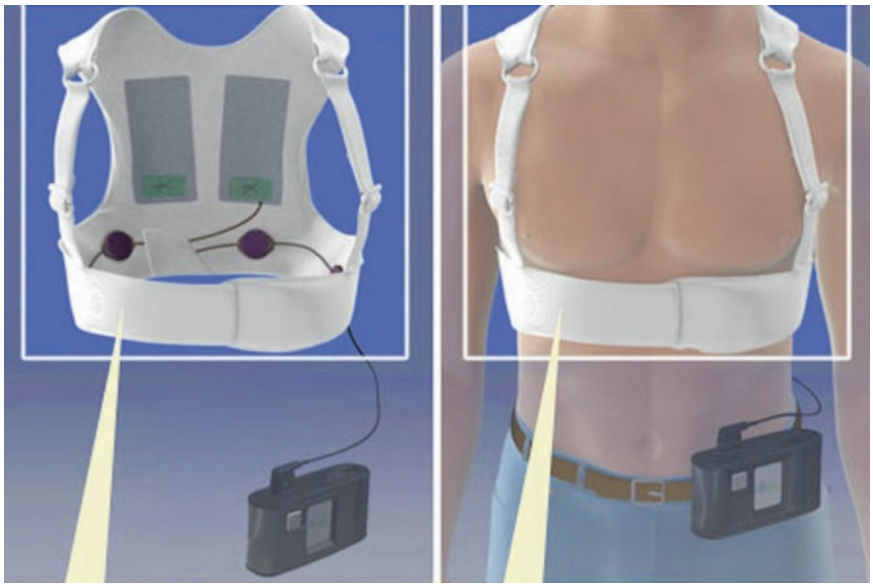

Fig. 19.3 Life Vest, wearable cardiac defibrillator (WCD), ZOLL Medical Corporation, Pittsburgh, PA, USA

death was highest in the first 30 days after an MI) and the benefits of ICD therapy in patients with cardiac dysfunction due to MI, the consideration arose that ICD implantation would be beneficial early after MI [52]. However, two separate randomized trials have failed to show the benefit of ICD implantation within 30–40 days after MI (*DINAMIT*, *IRIS*) [62, 63] (Table 19.2). Subsequent analysis of *VALIANT* and *DINAMIT* has demonstrated a possible pathophysiologic mechanism for the absence of benefit of ICD implantation in the early period after MI [52, 62]. In *DINAMIT*, only 50 % of the sudden deaths were attributable to arrhythmia, whereas mechanical causes of SCD (e.g., LV rupture, acute mitral regurgitation) were common in the other half of patients. Similarly in *VALIANT*, in the first month after MI, 80 % of sudden cardiac deaths appeared to be due to recurrent MI or myocardial rupture, and presumed arrhythmia-induced SCD only accounted for 20 %. By 1 year, the proportions of sudden deaths due to non-arrhythmia versus arrhythmia causes were equal, and over time there appeared to be a very gradual increase in the proportion of sudden deaths due to arrhythmia (approximately 60 % at 30 months). Therefore, early implantation of an ICD in this patient population would not be expected to significantly impact deaths. These observations have led to specific recommendations regarding "waiting periods" between the occurrence of an acute event and the placement of an ICD. In fact, after these studies, CMS (Center for Medicare & Medicaid Services) ruled that there should be at least 40 days of waiting period after MI before ICD implantation. In addition, due to the possibility of EF improvement in patients who underwent revascularization or in whom there were reversible causes of NICM (myocarditis, postpartum cardiomyopathy, etc.), CMS requirements demand at least 90 days waiting period after revascularization and/or newly diagnosed and medically treated NICM before ICD implantation [64].

Not infrequently, the waiting time rules and exposure to risk that they necessitate cause patients and physicians to be very uncomfortable. The introduction of more widespread use of wearable ICDs (WCD) (Fig. 19.3) has substantially reduced risk of SCD in these waiting periods. Recently Epstein et al. reported findings in 8453 patients who had a WCD prescribed in the first 3 months post-MI [65]. A total of 133 patients (1.6 %) received 309 appropriate shocks from their WCD. Of these patients, 91 % were resuscitated from a ventricular arrhythmia. With 40-day and 3-month waiting periods in patients post-MI, the WCD successfully treated SCD in 1.4 %, and the risk was highest in the first month of WCD use.

Recommendations for Implantable Cardioverter Defibrillators (Tables 19.3 and 19.4)

Recommendations on the use of the ICD in clinical practice have been provided in four important guideline documents sponsored by the American College of Cardiology (ACC), the American Heart Association (AHA), Heart Rhythm Society (HRS), and the European Society of Cardiology (ESC) [66–68]. Current ICD indications and recommendations are summarized in Tables 19.3 and 19.4 [69].

Recommendations for Wearable ICD (WCD)

WCDs are recommended for patients with accepted indications for ICD implantation but who also have (usually temporary) contraindications for such a procedure [65, 70]. The most common are those in the CMS mandated "waiting periods" after acute MI or revascularization. Other temporary contraindications include an infected ICD system that requires explanation with the need for long-term antibiotic treatment. A second group of WCD candidates comprises

Table 19.3 Recommendations for implantable cardioverter defibrillators (2012 ACCF/AHA/HRS Focused Update Incorporated into the ACCF/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities) [24]

Class I	Level of evidence
• ICD therapy is indicated in patients who are survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes.	A
• ICD therapy is indicated in patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable.	B
• ICD therapy is indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study.	B
• ICD therapy is indicated in patients with LVEF less than or equal to 35 % due to prior MI who are at least 40 days post-MI and are in NYHA functional Class II or III.	A
• ICD therapy is indicated in patients with nonischemic DCM who have an LVEF less than or equal to 35 % and who are in NYHA functional Class II or III.	B
• ICD therapy is indicated in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF less than or equal to 30 %, and are in NYHA functional Class I.	A
• ICD therapy is indicated in patients with non-sustained VT due to prior MI, LVEF less than or equal to 40 %, and inducible VF or sustained VT at electrophysiological study.	B
Class IIa	Level of evidence
• ICD implantation is reasonable for patients with unexplained syncope, significant LV dysfunction, and nonischemic DCM.	C
• ICD implantation is reasonable for patients with sustained VT and normal or near-normal ventricular function.	C
• ICD implantation is reasonable for patients with HCM who have 1 or more major† risk factors for SCD.	C
• ICD implantation is reasonable for the prevention of SCD in patients with ARVD/C who have 1 or more risk factors for SCD.	C
• ICD implantation is reasonable to reduce SCD in patients with long-QT syndrome who are experiencing syncope and/or VT while receiving beta-blockers.	B
• ICD implantation is reasonable for non-hospitalized patients awaiting transplantation.	C
• ICD implantation is reasonable for patients with Brugada syndrome who have had syncope.	C
• ICD implantation is reasonable for patients with Brugada syndrome who have documented VT that has not resulted in cardiac arrest.	C
• ICD implantation is reasonable for patients with catecholaminergic polymorphic VT who have syncope and/or documented sustained VT while receiving beta-blockers.	C
• ICD implantation is reasonable for patients with cardiac sarcoidosis, giant cell myocarditis, or Chagas disease.	C

(continued)

Table 19.3 (continued)

Class IIb	Level of evidence
• ICD therapy may be considered in patients with nonischemic heart disease who have an LVEF of less than or equal to 35 % and who are in NYHA functional Class I.	C
• ICD therapy may be considered for patients with long-QT syndrome and risk factors for SCD.	B
• ICD therapy may be considered in patients with syncope and advanced structural heart disease in whom thorough invasive and non-invasive investigations have failed to define a cause.	C
• ICD therapy may be considered in patients with a familial cardiomyopathy associated with sudden death.	C
• ICD therapy may be considered in patients with LV non-compaction cardiomyopathy.	C
Class III	Level of evidence
• ICD therapy is not indicated for patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year, even if they meet ICD implantation criteria specified in the Class I, IIa, and IIb recommendations above.	C
• ICD therapy is not indicated for patients with incessant VT or VF.	C
• ICD therapy is not indicated in patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up.	C
• ICD therapy is not indicated for NYHA Class IV patients with drug-refractory congestive heart failure who are not candidates for cardiac transplantation or CRT-D.	C
• ICD therapy is not indicated for syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease.	C
• ICD therapy is not indicated when VF or VT is amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with the Wolff-Parkinson-White syndrome, RV or LV outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease).	C
• ICD therapy is not indicated for patients with ventricular tachyarrhythmias due to a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma).	B

Table 19.4 HRS/ACC/AHA expert consensus statement on the use of implantable cardioverter defibrillator therapy in patients who are not included or not well represented in clinical trials (2013) [25]

• In patients with abnormal cardiac biomarkers that are not thought to be due to an MI and who otherwise would be candidates for implantation on the basis of primary prevention or secondary prevention criteria, implantation of an ICD *is recommended*.
• Implantation of an ICD within the first 40 days following acute MI in patients with preexisting systolic ventricular dysfunction (who would have qualified for a primary prevention ICD) is *not recommended*.
• In patients who, within 40 days of an MI, develop sustained (or hemodynamically significant) ventricular tachyarrhythmias >48 h after an MI and in the absence of ongoing ischemia, implantation of an ICD *is recommended*.
• Implantation of an ICD for primary prevention is *not recommended* with in the first 3 months after initial diagnosis of NICM.
• If recovery of left ventricular function is unlikely, implantation of an ICD for primary prevention can be useful between 3 and 9 months after initial diagnosis of NICM.

patients under investigation for a disease with a high risk of arrhythmic death or pending definitive diagnosis (e.g., those with inheritable arrhythmic disorder who are awaiting results of confirmatory testing or survivors of a cardiac arrest of unclear (and potentially treatable or reversible) origin). The third group consists of patients with severe heart failure awaiting cardiac transplantation and, finally, patients having a condition that temporarily places them at high risk of an arrhythmic death (e.g., patients with a low LVEF resulting from potentially reversible condition such as a newly diagnosed dilated cardiomyopathy (that could be due to transient myocarditis) or an ischemic cardiomyopathy in the early period after revascularization or in the early period after a MI).

Antiarrhythmic Drug Therapy for Atrial and Ventricular Tachyarrhythmias in Cardiomyopathy

The apparent antiarrhythmic effects of certain compounds have been recognized for well over 250 years. Cardiac glycosides and quinine are perhaps the earliest examples. However, most of the antiarrhythmic drugs (AADs) currently in use have been introduced in only the last 35–40 years. Currently, AADs remain a mainstay for termination and prevention of atrial fibrillation (AF) and provide useful adjunctive therapy for certain forms of ventricular tachycardia (VT). Few, however, have proved effective for ventricular fibrillation prevention (with the possible exception of amiodarone and perhaps bretylium).

The primary goals of current AAD therapy have been the reduction of frequency, duration, and severity of arrhythmia episodes. Unfortunately, on the negative side, most AADs have cardiac and noncardiac adverse effects that limit their clinical utility in important segments of the patient population, particularly those with more than minimal left ventricular (LV) dysfunction and/or heart failure.

Overview of Current Antiarrhythmic Drugs

Table 19.5 summarizes the most widely available antiarrhythmic drugs using the Vaughan Williams classification which focuses on each drug's principal cardiac channel effects. However, it is recognized that drug actions are much more complex than the Vaughan Williams approach allows and that actual drug effects on arrhythmias are not readily predicted by the classification. Given this important limitation, an attempt has been made to provide a more comprehensive and precise classification of drug effects [71, 72]. This effort (the so-called Sicilian gambit), while scientifically robust, is necessarily complex and as a result has largely been neglected in recent years.

Excluding beta-adrenergic blockers, calcium channel blockers, and cardiac glycosides, the majority of available "membrane-active" antiarrhythmic drugs exert predominant effects on cardiac sodium or potassium currents. The first of the orally available membrane-active agents to have a prominent place in therapeutics was quinidine and its congeners (derived from quinine). Procainamide became available in the early 1950s. Thereafter, at least in the USA, there was a long delay before the emergence of disopyramide in the late 1970s. Flecainide, encainide (the latter now withdrawn from the US market), ethmozine, mexiletine, tocainide (also withdrawn), imipramine, bretylium/bethanidine (not used to any extent), and amiodarone appeared in the 1980s. Propafenone, sotalol, dofetilide, dronedarone, and ivabradine followed.

Encainide, like flecainide, is a Vaughan Williams Class 1C agent (Table 19.5), but its use was discontinued in many countries (but not all) after CAST (Cardiac Arrhythmia Suppression Trial) revealed increased death rate in the treatment group [73]. Flecainide remains available due to additional studies showing benefit in supraventricular tachycardias, particularly atrial fibrillation (AF).

Tocainide is an orally available lidocaine "look-alike," but its use was undermined by an excessive number of adverse effects (especially hematologic). Imipramine (a long-used QT-prolonging tricyclic antidepressant) was, surprisingly to many, incorporated in the pre-CAST pilot study (CAPS), but was never a serious antiarrhythmic drug contender, and reasonably dropped by the wayside as far as cardiac arrhythmia therapy was concerned in the mid-1980s [74]. Bretylium was developed in the 1970s and proved to be an interesting antifibrillatory drug and was commercially available for parenteral use in the USA. The principal indication for bretylium was termination of refractory VF and VF prevention during acute care scenarios. However, while bretylium has an excellent inotropic profile, it induced profound postural hypotension and was difficult to use; in addition, it was not available for oral administration. Bethanidine (which had been widely used as an antihypertensive drug for many years and may still be used in some countries) has bretylium-like antifibrillatory properties [75]. However, although orally absorbable, very cheap, and widely available in the world, it is also difficult to use due to induction of postural hypotension. Techniques were devised to minimize the postural hypotension limitation, but given the emergence of amiodarone, the impetus to use bethanidine largely evaporated.

Sodium channel-blocking drugs (Table 19.5) are often called membrane-stabilizing agents because they decrease the excitability of cardiac tissue. Typically, these drugs exhibit use dependence. This means that the predominant effect on conduction (sodium channel blockade) is seen at rapid heart rates. On the ECG, QRS widening due to conduction slowing is often observed.

Drugs with major effects on blocking potassium currents prolong the action potential duration and refractory periods. Quinidine, procainamide, disopyramide, sotalol, and dofetilide are primarily potassium channel-blocking drugs that display reverse use dependence such that repolarization is prolonged at slow heart rates. The latter effect predisposes these drugs to lengthen the QT interval most dramatically

Table 19.5 Vaughan Williams classification

Class	Drugs	Channel(s) blocked	Mechanism(s)
Ia	Quinidine	I_{Na}, I_{Kr}, acetylcholine	(Na^+) channel block (intermediate association/dissociation) and K^+ channel-blocking effect
	Procainamide		
	Disopyramide		
Ib	Lidocaine	I_{Na}	(Na^+) channel block (fast association/dissociation)
	Phenytoin		
	Mexiletine		
	Tocainide		
Ic	Encainide	I_{Na}, β	(Na^+) channel block (slow association/dissociation)
	Flecainide		
	Propafenone		
	Moricizine		
II	Carvedilol		Beta-adrenergic blockers
	Propranolol		
	Esmolol		
	Timolol		
	Metoprolol		
	Atenolol		
	Bisoprolol		
III	Amiodarone	I_{Kr}, I_{Na}, I_{Ca}, β, α, acetylcholine	K^+ channel blocker
	Sotalol	I_{Kr}, β	Sotalol is also a beta-blocker
	Ibutilide	I_{Kr}, I_{Na} agonist	Amiodarone has Class I, II, III, and IV activity
	Dofetilide	I_{Kr}	
	Dronedarone	I_{Kr}, I_{Na}, I_{Ca}, β, α, acetylcholine	

(continued)

Table 19.5 (continued)

Class	Drugs	Channel(s) blocked	Mechanism(s)
IV	Verapamil		Ca^{2+} channel blockers
	Diltiazem		
	Ivabradine	I_f	Inhibition of the funny channel

Sodium channels (I_{Na}): fast Na^+, phase 0 depolarization of non-pacemaker cardiac action potentials
Potassium channels
Transient outward (I_{to}): contributes to phase 1 of non-pacemaker cardiac action potentials
Delayed rectifier (I_{Kr}): phase 3 repolarization of cardiac action potentials
Calcium channels (I_{Ca}): slow inward, long-lasting current; phase 2 non-pacemaker cardiac action potentials and late phase 4 and phase 0 of SA and AV nodal cells; important in vascular smooth muscle contraction
β beta antagonist; α alpha antagonist
I_f: funny current

during bradyarrhythmias and increase susceptibility to triggering torsade-de-pointes (TdP) ventricular tachycardia.

Apart from their electrophysiological effects, most available antiarrhythmic drugs also exhibit negative inotropic effects, thereby limiting their applicability in patients with diminished LV function (i.e., most patients with structural heart disease) and/or heart failure. Disopyramide and procainamide are perhaps the most negatively inotropic agents. On the other hand, quinidine, dofetilide, bethanidine (not used), and amiodarone are perhaps the most innocent agents in this regard.

Due to their negative inotropic effects, Class 1C agents and dronedarone are generally not used in LV dysfunction/heart failure patients. On the other hand, quinidine (not often used these days), dofetilide, sotalol, and amiodarone are generally acceptable in heart failure, but patient response must be carefully monitored. Other factors limiting AAD use in individual patients include the mechanism of clearance of the agent and how that might be affected by systemic disease (◘ Table 19.6). By way of example, elimination of both sotalol and dofetilide is highly dependent on renal function status, and their dosages must be adjusted accordingly. Similarly, AAD plasma concentrations may be altered by the presence of other AADs. Perhaps the quinidine-digoxin interaction was the earliest important AAD-AAD interaction to be identified, and it may have contributed to many cases of the so-called quinidine syncope (see later).

Role of Specific Antiarrhythmic Drugs

Treatment of most paroxysmal supraventricular tachycardias (SVTs) is now focused predominantly on mapping and ablation, since ablation offers a cure, whereas AADs offer only palliation. Currently, AADs are primarily used for AF and to some extent for other primary atrial tachycardias (AT).

Quinidine, procainamide, and disopyramide are no longer widely used for the treatment or prevention of AF or ATs in developed countries. Although these drugs can be useful, their adverse effects and the presence of better tolerated alternatives have undermined their use; consequently, they are not discussed further in this section. Amiodarone, despite its multiple numerous side effects and lack of supportive US Food and Drug Administration labeling, has become ubiquitous in the AF population, but careful follow-up is mandatory to assess for development of adverse effects (◘ Table 19.6). Amiodarone is discussed in more detail below.

Flecainide

Flecainide, in addition to its prominent conduction slowing effect due to sodium channel-blocking activity (which may widen the QRS complex), also has mild IKr (rapid component of the delayed rectifier potassium channel) blocking effects, but is not generally associated with significant QT prolongation.

Flecainide is contraindicated in individuals with prior myocardial infarction and reduced LV function because of increased ventricular proarrhythmia risk [15]. It is also potentially hazardous in patients with conduction system disease, as it may predispose to aggravating the severity of atrioventricular (AV) block or sinus node dysfunction. Consequently, flecainide is rarely used for VT, since VT patients often have underlying LV dysfunction and/or conduction system disease. However, flecainide may be useful for prevention of AF in patients without severe structural heart disease. In this circumstance, flecainide may reduce recurrences and/or slow atrial rate in ongoing AF or AT.

On a cautionary note, it is important to recognize that flecainide-induced conduction slowing in AF patients may have unexpected adverse consequences. Flecainide (as well as other AADs, such as propafenone) can slow and regularize AF resulting in new-onset atrial flutter (so-called Type 1C flutter) [76]. The occurrence of "1C flutter," which typically exhibits a slower atrial rate than does conventional atrial flutter, can result in a paradoxical increase of ventricular rate due to lesser block at the AV node level. The outcome may be substantial clinical distress. Thus, flecainide must be used in conjunction with a beta-blocker or calcium channel blocker to slow AV nodal conduction in the event 1C flutter develops.

In AF, flecainide may be used as first-line therapy in patients without structural heart disease. Oral flecainide (200–300 mg) has been used as a "pill-in-the-pocket" approach in patients who have infrequent AF and are capable of recognizing onset of an episode so they know to take the medication (preferably within an average of 30 min of arrhythmia onset).

Class IC antiarrhythmic agents such as flecainide are no longer recommended as therapy for VT in patients with ischemic heart disease or LV dysfunction from any cause. This limitation arose as a result of the CAST trial findings which showed that both all-cause mortality and arrhythmic death were increased with both encainide and flecainide. This exclusion of flecainide has been extended to nonischemic cardiomyopathy patients as well, despite the fact that they were not evaluated in CAST.

As a rule, flecainide tends to be well tolerated. However, common non-cardiovascular side effects include dizziness and visual disturbance in 5–10 % of patients [77].

Propafenone

Propafenone has beta-adrenergic blocking properties in addition to its 1C sodium channel-blocking activity. It also has mild negative inotropic and chronotropic effects.

In AF and AT, propafenone may be used as first-line therapy in patients without structural heart disease (typically 150 mg BID). High-dose oral propafenone (450–600 mg) has also been used as a "pill-in-the-pocket" approach in paroxysmal AF patients. As with flecainide, propafenone should be partnered with an AV nodal-blocking drug. Propafenone is not recommended for most VT patients with LV dysfunction.

Table 19.6 Antiarrhythmic drug dosing and side effects

Antiarrhythmic drug	Metabolism/dose	Major non-cardiovascular toxicity	Major cardiovascular toxicity
Quinidine	• Hepatic CYP3A4 (70 %), renal (30 %) • Sulfate, 600 three times a day • Gluconate, 324–648 every 8 h	Thrombocytopenia, cinchonism, pruritus, rash	QRS prolongation with toxic doses, torsades de pointes (not dose related)
Propafenone	• Hepatic • 150–300 every 8 h • Sustained release 225–425 twice a day	Metallic taste, dizziness	Atrial flutter with 1:1 conduction; ventricular tachycardia; may unmask Brugada-type ST elevation; contraindicated with coronary disease
Flecainide	• Renal/hepatic CYP2D6 • 50–100 mg twice a day	Dizziness, headache, visual blurring	Atrial flutter with 1:1 conduction; ventricular tachycardia; may unmask Brugada-type ST elevation; contraindicated with coronary disease
Sotalol	• Renal: 80–120 mg twice a day • Maximum dose 240 mg twice a day	Bronchospasm	Bradycardia, torsades de pointes
Dofetilide	• Renal/hepatic CYP3A4 • 500 μg twice a day • Renally dose adjusted	None	Torsades de pointes
Amiodarone	• Hepatic; half-life 50 days • Oral load 10 g over 7–10 days, then 400 mg for 3 weeks, then 200 mg/day • Intravenous: 150–300 mg bolus, then 1 mg/min infusion for 6 h followed by 0.5 mg/min thereafter	Pulmonary (acute hypersensitivity pneumonitis, chronic interstitial infiltrates); hepatitis; thyroid (hypothyroidism or hyperthyroidism); photosensitivity; blue-gray skin discoloration with chronic high dose; nausea; ataxia; tremor; alopecia	Sinus bradycardia
Ibutilide (intravenous)	• Hepatic CYP3A4 • 1 mg intravenous over 10 min; repeat after 10 min if necessary	Nausea	Torsades de pointes
Dronedarone	• Renal, hepatic, gastrointestinal • 400 mg twice a day	Anorexia; nausea; hepatotoxicity	Bradycardia
Mexiletine	• Hepatic • 200 mg three time a day	Dizziness, heartburn, nausea, nervousness, trembling, unsteadiness	Bradycardia
Disopyramide	• Hepatic • 125 mg four times a day	Dry mouth, constipation, Urinary retention, blurred vision	Negative inotrope Hypotension

The major non-cardiovascular adverse effects of propafenone include a metallic taste as well as dizziness and visual disturbances. High-dose oral propafenone (450–600 mg) has been used as a "pill-in-the-pocket" approach in patients who have infrequent AF and are capable of recognizing onset of an episode, preferably within an average of 30 min of arrhythmia onset.

Sotalol

Sotalol is a potassium channel (IKr) blocker and beta-blocker with minimal non-cardiovascular side effects and a high rate of utilization. Sotalol is cleared by the kidneys and is prescribed twice daily unless the creatinine clearance is low (between 30 and 60 mL/min) when single daily dosage is used. It is often started as an inpatient at a dose of 80 mg twice daily and up-titrated with attention to QT prolongation. The potassium channel-blocking effect increases with increasing dosage, and, as a result, the risk of torsade-de-pointes ventricular proarrhythmia (TdP) increases at a higher dosage.

Initially, sotalol was approved for treatment of AF with a recommendation for inpatient initiation. However, most recent guidelines allow for it to be started as an outpatient [15]. The Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) initiated either sotalol or amiodarone in the outpatient setting during AF without adverse effect and with an equivalent rate of restoring sinus rhythm [76]. In the OPTIC trial examining the potential to reduce shock frequency in secondary prevention ICD recipients, amiodarone plus beta-blockers was shown to be superior to monotherapy with sotalol or beta-blockers [78].

Sotalol is considered reasonable as first-line therapy for patients with coronary artery disease and relatively preserved left ventricular function. Sotalol may also be considered as an option for first-line therapy in VT, particularly in patients in whom beta-blockade is tolerated. The principal sotalol side effects parallel those of most beta-blockers and include fatigue, bronchospasm, and dyspnea. Sotalol can also exacerbate sinus node dysfunction (◘ Table 19.6).

Dofetilide

Dofetilide is also primarily an IKr blocker, without other clinically significant electrophysiological effects. It is cleared by the kidneys and must be dosed according to creatinine clearance (◘ Tables 19.1 and 19.2). It was approved for use in the USA in 2000 with a 3-day mandatory in-hospital loading period. ◘ Figure 19.4 shows an onset of TdP during inpatient dofetilide loading. Dofetilide is more effective for the maintenance of sinus rhythm in AF patients than it is for restoring sinus rhythm [79].

Dofetilide is a reasonable first-line therapy choice in AF/AT patients in whom coronary artery disease is present and especially if associated with LV dysfunction. It has been demonstrated to be relatively safe in the settings of heart failure and post-myocardial infarction populations [80, 81]. Dofetilide is not recommended for use in VT; however, it has been used off-label when other more conventional options are contraindicated.

The principal risk factors for dofetilide adverse effects (particularly TdeP) include hypokalemia, hypomagnesemia, female gender, baseline prolonged QT interval, or congenital long-QT syndrome and concomitant use of other QT-prolonging therapies. It is one of the few antiarrhythmics that have little if no effect on sinus node function.

Amiodarone

Amiodarone is the most commonly prescribed antiarrhythmic drug for AF/AT, despite not having been approved by the US FDA for that indication. Amiodarone is a complex iodinated compound that acts on multiple channels including antagonism of α- and β-adrenergic receptors (◘ Fig. 19.2). It is the most effective antiarrhythmic drug currently available, but its ease of use is limited by a myriad of non-cardiovascular side effects [82]. The major cardiovascular side effect of amiodarone is sinus bradycardia, with a higher risk of pacemaker requirement in women [83].

QT prolongation is common with amiodarone but fortunately is very rarely associated with TdP (<0.5 %) [84]. The combination of amiodarone with the CYP3A4 substrate simvastatin has been associated with an increased risk of myositis [85]. Conversely, this risk seems to be smaller when amiodarone is combined with pravastatin, which does not use the cytochrome P450 system for metabolism. The most important drug-drug interaction with amiodarone occurs with potentiation of the anticoagulant effect of warfarin through inhibition of CYP2C9. In addition, amiodarone can reduce digoxin clearance.

Amiodarone is orally well absorbed with high bioavailability, but it may also be administered as an intravenous agent; the parenteral form has been used for terminating AF, but in reality it is only weakly effective for this purpose [86]. On the other hand parenteral amiodarone is a very effective agent for slowing ventricular response in AF.

A major limitation of amiodarone is its exceedingly long half-life, 58 days (range 15–142 days). As a result, it takes a long time to "load" amiodarone and also a long time to eliminate it if side effects become an issue. As rule, amiodarone can be loaded orally over the course of 3–4 weeks. A day or two of parenteral loading (0.5–1 mg/min IV) may help accelerate loading and is generally well tolerated.

EMIAT and CAMIAT evaluated amiodarone use in patients recovering from myocardial infarction (MI) [87, 88]. EMIAT was a European randomized double-blind placebo-controlled trial to assess whether amiodarone reduced all-cause mortality (primary endpoint) and cardiac mortality and arrhythmic death (secondary endpoints) in survivors of myocardial infarction with a LV ejection fraction (LVEF) of 40 % or less. CAMIAT was a Canadian randomized double-blind placebo-controlled trial designed to assess the effect of amiodarone on the risk of resuscitated ventricular fibrillation or arrhythmic death among survivors of myocardial infarction with frequent or repetitive PVCs. Both reports found that incidences of cardiovascular death and arrhythmic death or resuscitated cardiac arrest were significantly lower in patients receiving both beta-blockers and amiodarone than in those not receiving beta-blockers, with or without amiod-

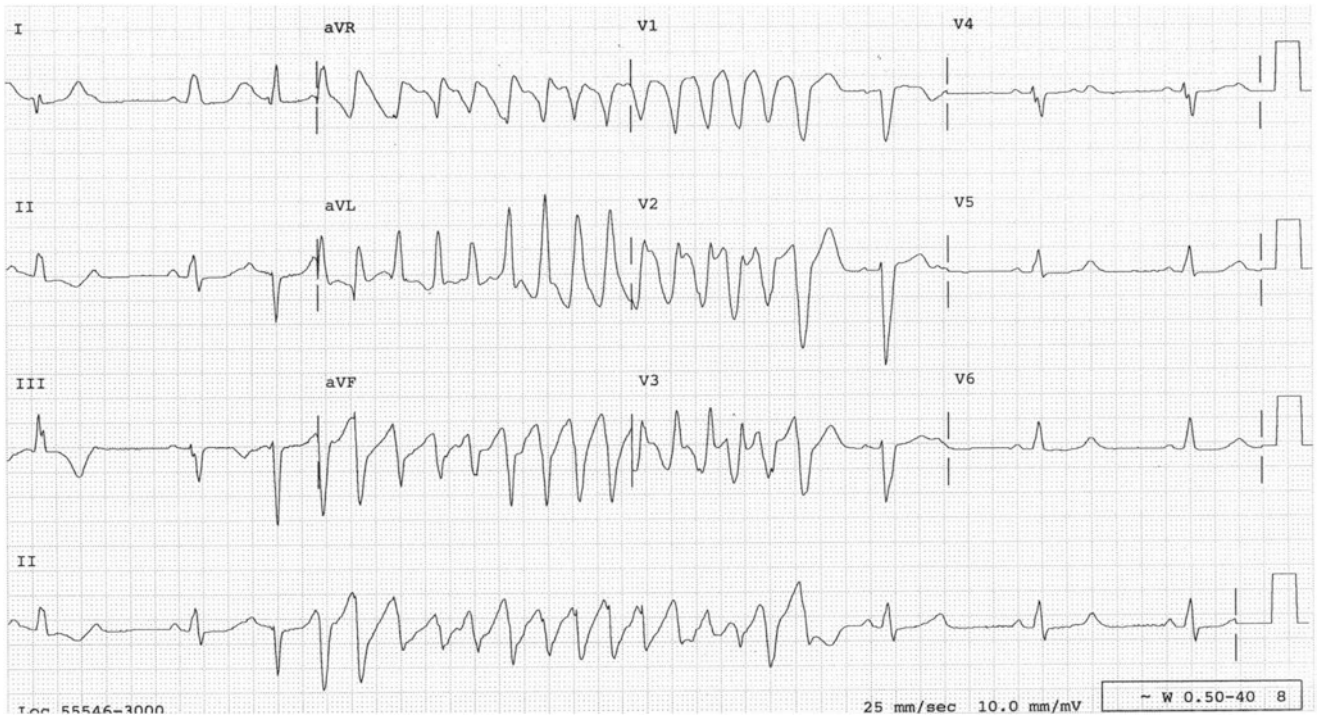

Fig. 19.4 50-year-old male with a history of ischemic cardiomyopathy with EF 20–25 % with a single-chamber ICD and difficult-to-control AF who presented as an elective admission for attempted chemical cardioversion with dofetilide. Two hours after his second dose of dofetilide, the patient developed torsades de pointes and received a shock from his ICD. Note the long-short sequence prior to initiation of tachycardia

arone. TdP occurred in less than 1 % of patients in the EMIAT and CAMIAT trials.

In the case of AF treatment, amiodarone should be reserved as second-line therapy if coronary artery disease is associated with LV dysfunction because of the severity of potential adverse effects. However, despite this admonition, in clinical practice amiodarone seems to have become the first choice AAD for AF prevention. Oral amiodarone can also be used to convert AF to sinus rhythm, but effectiveness is unpredictable.

In VT amiodarone should be a second-line agent for patients who are intolerant or not candidates for sotalol. However, amiodarone is often used as a first-line agent, especially in patients with an excessive ICD shock burden. Increasingly, however, ablation may be preferred to drug therapy in this situation.

Dronedarone

Dronedarone is the first of a group of drugs that have been designed to resemble amiodarone but with fewer non-cardiovascular side effects. It is similar in structure to amiodarone with the addition of a Methanesulfonamide group and the absence of iodine moieties (Fig. 19.2). An initial study, ANDROMEDA, which was designed to assess the effect of dronedarone on mortality in patients with advanced congestive heart failure, disappointingly revealed increased mortality in the dronedarone-treated group [89]. The drug is therefore contraindicated in patients with decompensated congestive heart failure. Subsequent efficacy studies and a major safety study in healthier patients with AF and without decompensated heart failure have shown no significant extra-cardiovascular toxicities and a reduction in hospitalizations and cardiovascular mortality associated with this drug [90]. However, the PALLAS study indicated that dronedarone may be less desirable in patients with permanent AF [91].

In AF patients, dronedarone may reasonably be considered as first-line therapy in patients with intermittent AF but without structural heart disease. With regard to VT, dronedarone has been shown to be effective in suppressing ventricular tachyarrhythmias in animal studies and in case reports of patients with refractory VT/VF episodes. However, the results of ANDROMEDA and PALLAS have raised doubts about the safety of this medication in patients with more than modest severity structural heart disease.

Other Drugs Used in VT

Beta-adrenergic blockers are almost a routine part of VT preventive treatment as they are deemed first-line therapy for their established survival benefit in patients with systolic heart failure or those who have recently suffered an acute MI [92]. In addition, beta-blockers are indicated in the treatment of certain ion channelopathies, such as congenital long-QT syndrome and catecholaminergic polymorphous VT (CPVT) [93].

Mexiletine

Currently, mexiletine is the most commonly used Class I antiarrhythmic agent, but is only rarely used as a stand-alone AAD. It was used in 20 % of patients who received adjuvant antiarrhythmic treatment in the ICD arm of the AVID trial [94]. As a Class IB antiarrhythmic agent (lidocaine-like), it does not seem to carry the increased mortality risk associated with the Class IC drugs. This mortality aspect is based on observational data with the Class IB drug lidocaine from the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-I and GUSTO-IIb) trials [95]. On the other hand, mexiletine is often poorly tolerated due to gastrointestinal side effects.

Ethmozine (Moricizine)

In the Cardiac Arrhythmia Suppression Trial (CAST), ethmozine showed only a nonsignificant increase of mortality from 5.4 to 7.2 %. This is in line with other class IC antiarrhythmics [73]. Ethmozine is only rarely used in current US clinical practice.

Drugs Less Often Used or Under Development

Quinidine

Originally, quinidine was derived from the bark of the cinchona plant and was identified as a potential antiarrhythmic drug more than a century ago. It has important vagolytic and α-blocking effects with an intermediate sodium channel-blocking action at rapid heart rates and higher concentrations. It has a prominent potassium channel-blocking effect at slower heart rates and normal concentrations resulting in QT interval prolongation and increased TdP susceptibility (the basis for what was once called "quinidine syncope" although the concomitant use of cardiac glycosides may have contributed).

Quinidine has a long history for termination and prevention of AF, but is only rarely used for that purpose these days as other more readily tolerated agents are available. Similarly, quinidine is no longer used for VT due to the risk of torsade de pointes. However, quinidine's blocking effect on the Ito current (cardiac transient outward potassium current) has generated interest as a potential therapy for Brugada syndrome and idiopathic ventricular fibrillation [96]. Its non-cardiovascular adverse effects include diarrhea as well as cinchonism (tinnitus and headache) and thrombocytopenia.

Disopyramide

Disopyramide is a sodium channel-blocking drug with potent anticholinergic and negative inotropic effects. The anticholinergic effects have led to its recommendation for patients with vagally induced AF despite little supporting evidence [15]. However, because of its negative inotropic effects, disopyramide should be avoided in patients with left ventricular dysfunction as it can aggravate heart failure. In addition, given its powerful anticholinergic side effects, it should be avoided in the setting of narrow-angle glaucoma, prostatic hypertrophy, or myasthenia gravis.

Disopyramide is not recommended due to the risk of TdP in patients with structural heart disease. On the other hand, it may have a particular niche application in hypertrophic cardiomyopathy (HCM) in which its negative inotropic properties may act to diminish outflow obstruction [97].

Ibutilide

Ibutilide is an intravenous IKr blocker that also enhances the late inward sodium current [98]. Ibutilide is ≈50 % effective at restoring sinus rhythm in recent onset AF patients. It is slightly more effective for atrial flutter than for AF. Patients must be monitored closely for QT prolongation and TdP for at least 2 h after infusion.

Procainamide

Procainamide (◘ Table 19.5) is a Class 1A agent which is available for both oral and parenteral administration. Although not often used for this purpose, it remains a reasonable alternative, when administered intravenously, for pharmacological termination of new-onset atrial fibrillation. Long-term procainamide use is now rare as the drug is associated with many adverse effects, including hypotension, QT prolongation with TdP, and a lupus-like syndrome. As a result, procainamide's use has declined substantially in recent years.

Ivabradine

Ivabradine is a so-called "funny current" (I_f) blocker that has the effect of slowing the heart rate. It has been approved for heart failure but also finds "off-label" use for reducing heart rate in the syndrome of inappropriate sinus tachycardia and may also have some benefit in postural orthostatic tachycardia syndrome (POTS) [99].

Ranolazine

Ranolazine is a novel antianginal drug with multiple ion channel-blocking antiarrhythmic activities. It is a piperazine derivative with a chemical structure similar to lidocaine; its most potent ion channel-blocking effect is on late sodium currents, and it has modest capacity to prolong the QT interval on ECG.

In the MERLIN-TIMI 36 trial, despite causing modest QT prolongation, ranolazine was shown clinically to reduce arrhythmia episodes, including non-sustained VT, by ambulatory cardiac monitoring in patients presenting with acute coronary syndrome [100]. Based on limited but positive clinical experiences with ranolazine, it appears to be beneficial as add-on therapy in patients with recurrent VT events while on a Class III antiarrhythmic agent. Currently, an ongoing trial is examining the utility of ranolazine for reducing the risk of ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators (ICDs).

Azimilide

Azimilide has been undergoing clinical study for many years and remains an investigational Class III antiarrhythmic agent that blocks both the rapid (IKr) and slow (IKs) components of the delayed rectifier cardiac potassium current. In the SHIELD trial, both symptomatic tachyarrhythmias terminated by antitachycardia pacing and appropriate ICD therapies for VT/VF episodes were reduced in patients receiving azimilide [101]. However, the ALIVE trial did not reveal significant differences in all-cause, cardiac, or arrhythmic mortality [102].

Upstream Therapies

Upstream therapies are primarily focused on AF prevention. The concept is to prevent the development of atrial electrical and mechanical remodeling and thereby reduce AF susceptibility. Data support use of ACE inhibitors (ACEI) or angiotensin-receptor blocker (ARB) for primary prevention of new-onset AF in patients with heart failure HF with reduced LVEF [103]. However, this application of these agents is already implied given the Class I indication for use of ACEI/ARB for the treatment of systolic dysfunction assuming no apparent contraindication (e.g., poor renal function) [104].

ACEIs and ARBs have been studied for both primary and secondary prevention of AF. In particular, angiotensin-receptor blockers have been studied for the reduction of new-onset AF in patients with hypertension but without significant structural heart disease [105]. On the other hand, there are not as yet conclusive data to support the use of aldosterone inhibitors for the primary or secondary prevention of AF.

The impact of statins as upstream therapy has been the subject of several systematic reviews [106]. The outcomes for the primary or secondary prevention of AF have been conflicting. Administration of statins may reduce postoperative AF in patients undergoing coronary artery bypass graft surgery [107].

Overall therapy with an ACE inhibitor, ARB, or statin is not proven beneficial for primary prevention of AF in patients without cardiovascular disease [108]. Nonetheless, these drugs are commonly indicated as concomitant treatment for associated comorbidities (e.g., hypertension) in patients with or without structural heart disease.

Arrhythmias in Specific Conditions

Valvular Cardiomyopathies

The 2014 AHA/ACC/HRS Guideline defined *nonvalvular* AF as AF in the absence of any of the following: rheumatic mitral stenosis, mechanical or bioprosthetic heart valve or mitral valve repair [15]. This aligns closely with the definition used by Lip and colleagues in their development of what would become the CHA_2DS_2-Vasc score. In that investigation, patients were selected from the Euro Heart Survey on AF populations who were "without mitral stenosis or previous heart valve surgery" [109].

Most readers will be aware that the trials of the so-called novel oral anticoagulants or NOACs excluded patients with valvular AF. For that reason, NOACs were only approved by the US Food and Drug Administration for use in patients with nonvalvular AF. Unfortunately, the trials for these agents defined "valvular AF" in different ways, so that, for example, a patient with severe aortic stenosis would have been excluded from the dabigatran trial, whereas in the rivaroxaban trail, only hemodynamically significant mitral stenosis or prosthetic heart valves were excluded. These differences were recently discussed in detail in a review by De Caterina and Camm [110]. This review also highlights the fact that the highest risk of thromboembolic complications in AF and concomitant valvular heart disease occurs in mitral stenosis. There is little evidence that other types of valvular heart disease increases the risk of thromboembolic complications related to AF. In fact, there is evidence that mitral regurgitation may confer protection from thromboembolic complications in AF [110].

While far from settled, from a practical standpoint, in patients with AF, *valvular heart disease* refers primarily to (a) mitral stenosis, (b) prosthetic heart valves, or (c) mitral valve repair. It should be noted that only the North American guidelines define valve repair as "valvular AF."

Arrhythmias Associated with Disorders of the Atrioventricular (AV) Valves

Any disorder of the AV valves, either regurgitant or stenosis, that results in an increase in atrial strain and size will result in an increased risk of atrial arrhythmias. Not surprisingly, the primary arrhythmia seen in disorders of one, or both, of the AV valves is AF. Typical and atypical atrial flutters, as well as ectopic atrial tachycardia, can also be seen. Of note, it is also possible that AF may, itself, result in AV valve regurgitation [111].

Management of AF in the setting of AV valve diseases is not fundamentally different than in any other population with AF besides thromboembolic prophylaxis reviewed above.

Patients with AV valve disease are usually not at increased risk of ventricular arrhythmias, unless the valvular heart disease has resulted in a cardiomyopathy. Ventricle incisions are unusual in modern AV valve surgery, but in older patients with a history of AV valve surgery, if a ventriculotomy was performed, the resulting ventricular scar can predispose to ventricular arrhythmias.

Arrhythmias Associated with Ebstein's Abnormality

Ebstein's abnormality of the tricuspid valve is uniquely associated with an increased risk of AV accessory pathways (AP). Patients with Ebstein's anomaly frequently have multiple accessory pathways. They may have AV reentrant using the AP in both the retrograde direction resulting in a narrow-complex supraventricular tachycardia (SVT) or in the antegrade direction resulting in a wide-complex tachycardia. The latter can be difficult to distinguish from ventricular tachycardia [112].

Treatment of AP-mediated tachycardia is primarily catheter ablation. In infants and small children, antiarrhythmic drug therapy should be used to delay catheter ablation until the child has an opportunity to grow.

Surgical Treatment of AF During Valve Surgery

Roughly 40–50 % of patients undergoing mitral valve surgery have a history of AF. Atrial fibrillation after mitral valve surgery is associated with worse outcomes. In centers with experienced operators, the Cox-Maze procedure can be performed in mitral valve or mitral valve plus tricuspid valve surgery with no increase in operative mortality or morbidity [113].

The 2014 Guideline document gives surgical ablation of AF in selected patients undergoing cardiac surgery (not just mitral valve surgery), for other reasons a consensus Class IIa indication [15].

Conduction Abnormalities After Aortic Valve Replacement/Intervention

Surgical replacement of the aortic valve is associated with a significant risk of postoperative conduction abnormalities including complete heart block (CHB). In one single-center study, 8.5 % of patients undergoing isolated aortic valve required permanent pacemaker placement (PPM) [114]. Transcatheter aortic valve replacement (TAVR) has also been found to carry a significant risk of post-intervention conduction system disease and CHB, influenced by a variety of factors including type of valve used, depth of implantation, degree of calcification, and pre-procedure conduction system disease, among others. The need for PPM after TAVR is higher than after surgical valve replacement [115].

In the AHA/ACC/HRS 2008 Guidelines for Device-Based Therapy, CHB or high-degree second-degree postoperative AV block, when not expected to improve, was considered a Class I indication for PPM [66]. TAVR is not specifically mentioned in the 2008 AHA/ACC/HRS guidelines. The European Society of Cardiology published Guidelines on Cardiac Pacing in 2013 that included TAVR in its recommendations for pacing after cardiac surgery [116]. Pacing for high-degree or complete AV block after cardiac surgery or TAVR was given a Class I indication. A 7-day period of observation for recovery of AV conduction was suggested, but in patients with poor escape rhythms, shortening of the observation period was deemed acceptable.

Whether the appearance of new LBBB post-TAVR is an indication for PPM remains a subject of debate. In our experience the decision to pace in this situation is often dependent on the operator, the institution, and the wishes of the patient.

Hypertrophic Cardiomyopathy

Atrial Arrhythmia in Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is reviewed elsewhere in this chapter. However, a few salient points should be emphasized. Patients with HCM who develop AF (or AFL) should be started on oral anticoagulation, assuming no contraindication to such, regardless of their CHA_2DS_2-VASc score. This is a Class I (LOE: B) recommendation in the 2014 guidelines. Antiarrhythmic drug therapy with amiodarone or disopyramide with a beta-adrenergic receptor blocker or a non-dihydropyridine calcium antagonist was given a Class IIa (LOE: C) indication [15]. Catheter ablation for AF in HCM when drugs fail or are not tolerated was given a similar indication.

Ventricular Arrhythmia and Sudden Cardiac Death in Hypertrophic Cardiomyopathy

The substrate for ventricular arrhythmias in HCM lies in the disorganized, chaotic architecture of myocardial cells and the connective tissue. Management of VT begins with avoidance of potential triggers for VT and sudden cardiac death (SCD). Patients with unequivocal or probable HCM should not participate in most competitive sports [117]. While beta-adrenergic blockers and non-dihydropyridine calcium channel blockers are often used to improve symptoms, primarily angina or dyspnea [118], available data does not support a significant role for these drugs in the prevention of VT or SCD [119]. The implantable cardioverter defibrillator (ICD) is the current mainstay for SCD protection. Antiarrhythmic drugs, such as sotalol and amiodarone, may be added empirically as adjunctive therapy to manage VT causing ICD shocks.

Early descriptions of HCM from tertiary care centers estimated the annual mortality to be as high as 6 % [120], but larger, community-based studies suggest that most patients have a more benign course with an annual mortality of 1 % or less [120, 121]. Risk factors have been identified from observational studies and registries. Not surprisingly, HCM patients at highest risk for SCD are survivors of a prior SCD or sustained ventricular tachyarrhythmia [118]. These patients are candidates for ICD implant for secondary prevention [65].

Nearly 90 % of HCM patients will have premature ventricular contractions (PVCs), and 30 % will have non-sustained ventricular tachycardia (NSVT) on ambulatory monitoring [122]. There arrhythmias pose a management dilemma to physicians. NSVT has a high negative predictive value (95 %) but low positive predictive value (10–20 %) for SCD [122, 123]. The significance of ventricular arrhythmias

may be age-dependent, with younger patients being at higher risk. In one study of 531 HCM patients, the odds ratio of SCD in patients ≤30 years of age with NSVT was 4.35 (95 % CI: 1.54–12.28, $P = 0.006$) compared with 2.16 (95 % CI: 0.82–5.69, $P = 0.1$) in patients >30 years of age [124]. An electrophysiologic study (EPS) to test for inducibility of VT is of little value in risk stratification: polymorphic VT and ventricular fibrillation (VF) are often induced, which are considered nonspecific endpoints [120, 125, 126].

Expert consensus has identified major risk factors for SCD in HCM patients [65, 118]. In general, these seem to be more significant in younger patients and include NSVT, family history of SCD, syncope, massive LVH (wall thickness is ≥30 mm), and a hypotensive or flat blood pressure response to exercise. Other factors that have been proposed or considered include young age at diagnosis, degree of late gadolinium enhancement on cardiac MRI, and degree of left ventricular outflow tract obstruction [118]. Genetic testing is of limited value for risk stratification because of the large number of mutations, many of which may be novel to a given family [118].

While there is general consensus on the identity of the major risk factors, their positive predictive value is low. Although the annual risk of SCD in a community-based HCM population may be 1 % or less, at least one risk factor may be found in nearly 50 % of HCM patients [119]. Even a single major risk factor can be significant, however. In one retrospective ICD study, 35 % of HCM patients with an ICD implanted for primary prevention on the basis of a single identified risk factor received an appropriate ICD therapy [127].

US Guidelines provide broad latitude for ICD therapy in HCM patients. ICD implantation is considered "reasonable for patients with HCM who have 1 or more major risk factors for SCD" [65]. A European Task Force on SCD reserves their strongest recommendation for a primary prevention ICD in HCM patients to those with two or more risk factors but still provides that a single risk factor may be sufficient to decide to place an ICD [126]. The new HCM Risk-SCD calculator, which could be accessed at http://doc2do.com/hcm/web-HCM.html, was based on recommendation of the 2014 European guidelines for ICD. The ICD should be considered if the annual risk is >6 %, may be considered between 4 and 6 %, and should generally not be indicated if <4 % [128, 129]. Although this risk score performed better than the 2003 and 2011 guidelines, it still missed some high-risk patients in one cohort and overestimated the risk in another [130, 131].

There are no randomized trials of ICD therapy specific to HCM patients. In one retrospective study of 506 HCM patients with ICDs, 20 % had appropriate therapies with an intervention rate of 10.6 % and 3.6 % per year in secondary and primary prevention patients, respectively [127]. While appropriate ICD therapy does not equate to lives saved, it is argued that the discrepancy in HCM may be less than in ischemic heart disease. Due to the disorganized and thick myocardium, VT is poorly tolerated; moreover, polymorphic VT or VF may be unlikely to terminate spontaneously [119]. A meta-analysis of 2190 HCM patients with ICDs (mean age, 42 years; 83 % for primary prevention) across 16 studies showed a low annualized rate of cardiac and noncardiac mortality (0.6 % and 0.4 %, respectively). The rate of appropriate and inappropriate ICD intervention was 3.3 % and 4.8 % per year, respectively [132].

Ultimately, the decision to implant an ICD is an endeavor that requires discussion of the potential risks and benefits with each individual patient. The difficulty of these decisions is evident in an international registry of HCM patients under 20 years of age. Of 224 ICD patients (188 primary prevention), appropriate therapy was frequent (43 patients, 19 %), as were complications (91 patients, 41 %). A single risk facture identified some primary prevention patients at risk and the number of risk factors (1, 2, or 3) did not predict the likelihood of ICD therapy [133].

Catheter ablation of VT currently has only a very limited role in HCM patients. Polymorphic VT and VF, as opposed to monomorphic VT, are frequent and are not amenable to current mapping techniques. During EPS, polymorphic VT and VF were induced more than three times more frequently than monomorphic VT [134]. Stored electrograms in ICDs show that approximately half of the appropriate ventricular therapies are for VF [127]. In addition to mapping challenges, the thick, hypertrophic myocardium limits the effective delivery of radiofrequency energy to potentially critical myocardial sites. Nevertheless, a combination of epicardial and endocardial approaches may offer an option for the control of monomorphic VT in highly selected patients [135].

Arrhythmogenic Right Ventricular Cardiomyopathy

ARVC (also referred to as arrhythmogenic right ventricular dysplasia (ARVD), ARVD/C, or ARVC/D) is an inherited cardiomyopathy characterized by fibro-fatty replacement of portions of the myocardium, usually most evident in the right ventricle (RV). Patients may develop VT and SCD, particularly in association with exercise. Patients with ARVC may have multiple morphologies of VT, typically of "left bundle branch block morphology" reflective of RV origin [136, 137]. ARVC is inherited as an autosomal dominant trait caused by mutations in a variety of genes predominantly encoding proteins composing desmosomes. Given their role in cell-cell connection, defects in desmosomes may become clinically relevant at an earlier time in the thin-walled RV than the left ventricle (LV) [138]. Early pathologic studies showed a predilection for myocardial thinning, scarring, and aneurysm formation in the RV infundibulum, apex, and inflow regions [136, 139]. Electroanatomical mapping of the RV demonstrates areas of low voltage consistent with scar and correlating with myocardial scaring that may be identified by cardiac MRI [137, 139, 140].

Although VT and sudden death may occur at rest in patients with ARVC, there is a clear association with exertion. Athletes with a "definite," "borderline," or "possible"

diagnosis of ARVC are recommended not to participate in most competitive sports [117]. Beta-blockers are often used to attenuate sympathetic stimulation, although there is currently no evidence that they reduce mortality or ventricular arrhythmias [141]. Surprisingly, the clinical significance of VT in a given ARVC patient is uncertain. Mortality was low in early series of ARVC patients with VT who were treated primarily with antiarrhythmic drugs and very few ICDs [142, 143]. ARVC patients frequently have preserved LV function so VT may be better tolerated and may be less likely to degenerate into VF. Nevertheless, there is general consensus that ARVC patients with prior cardiac arrest, sustained VT, or VF should undergo ICD implant [65, 126]. Antitachycardia pacing is highly effective in terminating VT in ARVC patients and may reduce ICD shocks [144]. Available data from small studies of ARVC patients support the use of ICDs in such secondary prevention patients [144–147].

Guidelines support ICD implantation for primary prevention of sudden cardiac death in ARVC patients felt to be at high risk but, as opposed to HCM, consensus is lacking on the specific factors that identify high-risk individuals [65]. Retrospective ICD studies have variously identified predictors of subsequent ICD therapies that include a history of syncope [148] and NSVT and inducibility of sustained VT or VF [149] or spontaneous VT [144]. Interestingly, although considered a potential risk factor [126], a family history of SCD due to ARVC was not found to be a predictor of risk in multivariate analysis in several studies [144, 148, 149].

A meta-analysis of 610 primary and secondary prevention patients in 24 studies showed an annualized rate of appropriate and inappropriate ICD therapies of 9.5 % and 3.7 %, respectively. ICD-related complications were frequent (20.3 %), such as largely difficult lead placement and lead malfunction [150]. ICD implantation may be challenging in ARVC patients. Lead placement may be difficult due to low-voltage electrograms in the RV. Fatty infiltration and inflammatory changes in the RV may increase the risk of perforation [145, 148–150].

Although ablation is not considered a primary therapy for VT, it is an important adjunctive therapy to reduce ICD shocks. In contrast to HCM, in ARVC patients, VT is frequently monomorphic, sustained, and inducible with PES and may be hemodynamically stable. These features render VT more amenable to catheter ablation. Large and/or multiple regions of ventricular scarring, however, provide substrate for multiple forms of ventricular tachycardia. In more challenging cases such as these, "substrate modification" may successfully ablate VT. In these techniques mapping is performed during sinus rhythm to identify and target "potential" reentrant circuits [151].

The acute success rate of VT ablation may be increased with the addition of epicardial ablation techniques to the more traditional endocardial approach [152, 153]. The potential value of this approach is suggested by early morphologic studies of ARVC that showed that the pathologic process appears to begin, or is at least more extensive, in the epicardium and then extends toward the endocardium [137, 139]. Although ablation techniques may acutely reduce VT occurrence in ARVC, the continued progression of the pathologic process may still limit long-term VT-free survival.

Antiarrhythmic drugs alone have not been shown to reduce the risk of sudden death but are often used as adjunctive therapy to reduce shocks from ICDs. A report from the North American ARVC Registry showed that neither beta-blockers nor sotalol reduced the risk of ventricular arrhythmias, while amiodarone (used in only ten patients) had superior efficacy in preventing ventricular arrhythmias [141].

Arrhythmia-Induced Cardiomyopathy in Children

Children are not shrunken adults. They neither present with the same arrhythmias as adults nor is the approach to management necessarily the same as in adult patients. While we have a large number of adults with congenital heart disease and arrhythmias in our practice, we do not hesitate to refer to a pediatric electrophysiologist when appropriate.

Outcomes in children or infants with dilated cardiomyopathy are poor [154]. The search for reversal causes, such as AIC, must be rigorous. Supraventricular tachyarrhythmias are more common than ventricular arrhythmias in children. Consequently, in the pediatric population, AIC is more commonly caused by atrial.

Atrial Tachycardia (AT) as a Cause of Pediatric AIC

Ectopic atrial tachycardia is an uncommon arrhythmia in infants and children, but it is associated with AIC. Koike et al. reported on a small series of nine patients in 1988 with what they referred to as "atrial automatic tachycardia." Over half the patients in that series had dilated cardiomyopathy. They also noted that 33 % of the patients had spontaneous resolution of their arrhythmia [155].

A more recent multicenter retrospective review of 249 patients with focal atrial tachycardia (FAT) reported a 28 % incidence of dilated cardiomyopathy [156]. They found an overall rate of resolution of the FAT in 89 %. Antiarrhythmic drug therapy was utilized in 154 patients. The most common agent used was a β-blocker in 53 %, with an efficacy rate of 42 %. Antiarrhythmic drug therapy controlled the FAT in 72 %. Catheter ablation controlled the FAT in 80 % of the patients. The authors highlight the wide variation in approaches. Similar to the study by Koike, this study also found that the FAT resolved spontaneously in approximately one-third of the patients [156].

Permanent Junctional Reciprocating Tachycardia (PJRT) as a Cause of Pediatric AIC

PJRT is a reentrant tachycardia mediated by an unusual accessory pathway. This is a "long RP" tachycardia seen in infants and children. PJRT is often incessant. Because PJRT

can occur in infants, the first manifestation may be AIC and HF. In a recent review, 7 % of the case presented as hydrops in neonates. The rhythm rarely resolves spontaneously. Fortunately, it is amenable to catheter ablation, thought control with an antiarrhythmic may be used initially to allow for growth of the child prior to catheter ablation [157].

Junctional Ectopic Tachycardia (JET) as a Cause of Pediatric AIC

Junctional ectopic tachycardia is most often seen after surgery for congenital heart disease [158]. Less commonly it occurs in the absence of surgery. The nonsurgical form of JET is associated with high morbidity and mortality [159]. JET is often incessant and has been associated with AIC. Although the focus is often near the atrioventricular junction, catheter ablation is effective and can be performed with an acceptably low risk of inadvertent high-degree or complete AV block [159]. As in PJRT, medical control may be attempted in order to delay catheter ablation and allow the child to grow.

Summary of Treatment of Pediatric AIC

- As in adults with AIC, pediatric patients with AIC should also be treated with standard therapies for LV systolic dysfunction.
- Medical management is often required in order to allow for growth of the patient prior to catheter ablation.
- In atrial tachycardia, spontaneous resolution is seen in a substantial portion of patients, making medical control and delay in catheter ablation reasonable.
- Junctional ectopic tachycardia and PJRT rarely resolve spontaneously. Catheter ablation is frequently required.

Arrhythmias Related to Cardiac Sarcoid (CS)

Symptomatic cardiac involvement in patient with systemic sarcoidosis occurs in about 55 of patient; however, asymptomatic involvement can be 25 % based on autopsy or up to 55 % based on cardiac imaging. The main arrhythmic disorders observed are conduction abnormalities and ventricular tachycardia. CS may be difficult to differentiate from other forms of NICM, such as ARVC. Unlike ARVC, CS typically presents with more extensive LV scar and can have septal involvement. A full review of arrhythmia management in patients with CS was recently published in the 2014 HRS Expert Consensus Statement on the Diagnosis and Management of Arrhythmias Associated with Cardiac Sarcoidosis [160].

Conduction Abnormalities

Atrioventricular nodal (AV) block at various degrees is a common presentation of patients with CS. The most recent 2013 guidelines for device-based therapy included three CS-specific recommendations, all class IIa: a pacemaker is useful even if the AV block is transient, immunosuppression can be useful for Mobitz II and complete AV bloc, and ICD can be considered in patients with an indication for a permanent pacemaker [69]. Immunosuppression with corticosteroids reversed AV conduction in an average of 47 % of patients. When implanting a pacemaker, it is prudent to implant the device first and wait for the incision to heal before starting on immunosuppressants to decrease the risk of device infection.

Management of Ventricular Arrhythmias

In general, two main mechanisms are implicated in VT in patients with CS. VT can reentry around fixed scar in burned-out areas of myocardium and is typically monomorphic. The second mechanism is inflammation causing either monomorphic or polymorphic VT. The role of immunosuppression is controversial, with some studies showing decrease in arrhythmia burden, while others failed to benefit. Moreover, there are reports showing corticosteroids can exacerbate VT initially and can be linked to aneurysm formation. Theoretically, corticosteroids would be beneficial for arrhythmias in the initial inflammatory phase of the disease. The initial therapy of VT also includes antiarrhythmics including amiodarone and sotalol.

The largest published study of ablation therapy for VT in patients with CS included 21 patients [161]. The rate of complete acute procedural success was relatively poor, and freedom from VT after 1 year after a single ablation was only 25 % (37 % after multiple procedures). Ablation was effective, however, in acutely terminating VT storm in 78 %. Currently, VT ablation is considered for VT storms and high VT burden refractory to immunosuppressive and antiarrhythmic medical therapy.

Risk of SCD and Role of ICD

There is a paucity of data and factors to risk stratify patients with CS. For patients with an LVEF <35 % or history of VT/VF arrest, the need for an ICD is clear based on the major primary and secondary prevention trials. Most studies show that patients with normal RV and LV function have very low event rate. However, mild LV dysfunction does not seem to be benign. In the biggest cohort of patient with CS and ICDs reported, most of the patients who received appropriate shocks had an LVEF >35 % [162]. Hence, ICD implant may be considered (Class IIb) in patients with EF between 35 and 50 % despite immunosuppressive therapy. Otherwise, an CID can be useful (Class IIa) in patients with CS and an indication for a pacemaker implantation, history of unexplained syncope, or inducible sustained VT, irrespective of LVEF. The value of EP study is controversial (Class IIb), although an inducible VT is accepted as a Class IIa indication [160].

Arrhythmias in Patients with Left Ventricular Assist Devices (LVAD)

LVADs have been used increasingly in the management of medically refractory end-stage heart failure after the Randomized Evaluation of Mechanical Assistance for the

Treatment of Congestive Heart Failure trial (REMATCH) demonstrated a survival benefit from LVADs in patients with advanced end-stage heart failure [163]. These currently serve as a bridge to recovery in fulminate myocarditis or massive MI, as bridge to transplant, or as destination therapy. Patients with LAD still experience a significant burden of arrhythmias both in the postoperative period and later after recovery. Since most of the hemodynamic load is carried by the LVAD, one would suspect that the impact of arrhythmias would be minimal. However, both atrial and ventricular arrhythmias continue to impact these patient symptoms and quality of life.

Atrial Arrhythmias in Patients with LVAD

Atrial arrhythmias in LVAD patients comprise mostly of AFL and AFib. AFL can be a classic cavo-tricuspid isthmus-dependent flutter but may also be scar related from atriotomies performed during LVAD implantation or earlier cardiac surgeries. AFib is present in close to 50 % of the patients with LVAD in a study of 106 patients [164]. While paroxysmal AFib was not found to be associated with increased mortality, HF hospitalizations, bleeding, or thromboembolism, persistent AFib was an independent predictor of the composite endpoint of death or HF hospitalization, driven mostly by an increased risk of HF hospitalizations [164]. This suggests that the immediate hemodynamic impact of AFib on LVAD patients is likely to be minimal, but the more chronic presence of AFib and its burden might either affect the RV function or have a primary chronic hemodynamic impact in this patient population. There was no increase in bleeding or thromboembolism with persistent AFib, but thromboembolic events happened at higher INR in patients with AF [164]. Another study of 389 patients with LVAD showed that the presence of preoperative AFib was associated with an increased risk of thromboembolism after LVAD implant [165]. Both studies favor using a higher INR target of 2–3 rather than 2–2.5 in patients with LVAD. The latter study did not show a mortality impact from AFib but did not dichotomize patients into paroxysmal or persistent AFib.

In our experience, even paroxysmal AFib still impacts the quality of life in a limited number of patients, in which a rhythm-control approach with medical or ablation therapy should be considered. Intervention on AFib or AFL with ablation can positively impact their quality of life and RV function [166, 167].

Ventricular Arrhythmias in Patients with LVAD

Sustained ventricular arrhythmias (VA) are still frequent in up to 52 % of the LVAD population. They are often well tolerated but can still cause hemodynamic collapse and thromboembolism [168, 169]. The presence of preexisting VAs, cause of cardiomyopathy, device type, indication for support, and duration of follow-up have been found to be associated with the risk of post-LVAD VAs [170–173]. VAs are generally divided into two main categories that have different etiology distribution and different priorities for management options.

Early arrhythmias occur in the first 2–4 weeks after LVAD implant. They are mostly due to suck-down events, altered early repolarization, mechanical trauma and apical irritation caused by LVAD cannula, perioperative adrenergic stimulation and the use of adrenergic agonists, or simply recurrence of ventricular arrhythmias recorded before the LVAD implant. These arrhythmias tend to decrease in frequency in the initial recovery period. There is growing evidence that LVAD-induced unloading of the left ventricle may reduce the risk of VA through reverse electrophysiological remodeling and reduction of QRS and QT intervals [174]. The management of the early VAs consists of targeting their mechanism: fluid management with focus on the right ventricular function, reinitiating and advancing beta-blocker therapy as soon as deemed tolerable, antiarrhythmic therapy, and autonomic modulation like left stellate ganglion blockade in order to temporize VAs through the postoperative recovery period [175]. In select cases where the above measures are ineffective and the patient cannot tolerate frequent VAs that are hindering his recovery, ablation therapy can be considered (Fig. 19.5).

Late VAs occur after the first month post-LVAD implant. Only a minority (less than 15 %) of VAs are related to the inflow cannula. The majority of VAs are related to intrinsic myocardial scar present before the LVAD implant [176]. This agrees with the fact that the recurrence of post-LVAD VAs is higher in patients with secondary prevention ICDs compared to patients with primary prevention ICDs [177]. Management still includes ruling out suck-down events by interrogating the LVAD; manage the fluid status and RV function first before considering more invasive approaches. Antiarrhythmic medications can be tried as a first-line therapy. However, most of these patients are already on some

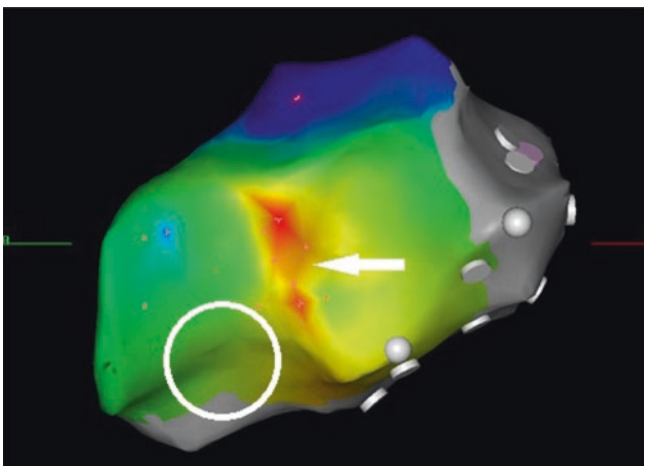

Fig. 19.5 Activation map of a pleomorphic VT induced by mechanical irritation of the cannula on the mid to distal lateral wall of the left ventricle. VT was refractory to beta-blockers and antiarrhythmics. The mechanism was confirmed with intracardiac echocardiography. Cannula location is illustrated with the *white circle*. Ablation at that level (*arrow*) inhibited VT. Patient had no recurrences, and we avoided revising the cannula because of cannula-induced VT

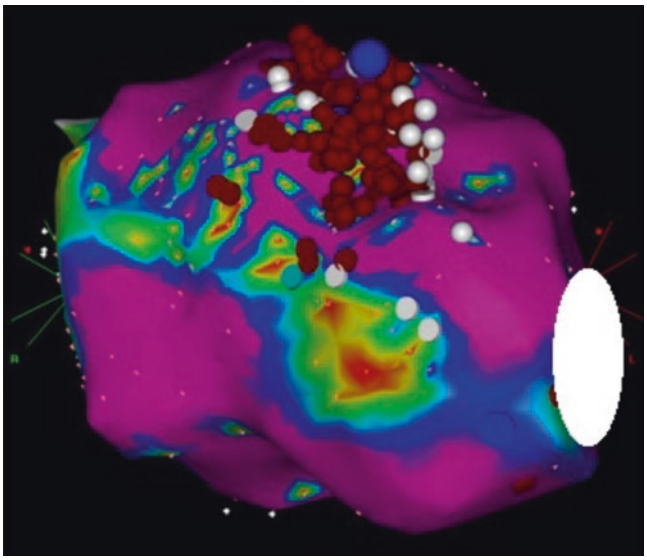

Fig. 19.6 Patient with ischemic cardiomyopathy with VT storm more than 1 month after LVAD implant, refractory to multiple antiarrhythmic medications, and beta-blockers. The LVAD cannula is represented by a *white circle*. The location of the VT (*blue dot*) was away from the cannula in a scar area located in the mid-anterior wall of the LV. Ablation at that location terminated VT storm and provided a more stable recovery

kind of antiarrhythmic medication before their implant and ablation therapy should be considered in refractory patients and especially in patient with hemodynamic compromise, high VA burden, and subsequent ICD shocks. Consideration should be given to increasing the threshold for therapy on the ICD by elevating the heart rate on the VT or VF detection zones and increasing detection times. VT ablation has a good acute success rate of 86 % for the first procedure, a recurrence rate of 33 % with limited follow-up [176, 178] (Fig. 19.6).

The association of VAs to mortality after LVAD implant is controversial, so is the utility of ICDs in increasing survival [179–181]. A recent meta-analysis of observational studies including 1179 patients found that post-LVAD VAs were associated with increased all-cause mortality at 60, 120, and 180 days, but only pre-LVAD VAs were independent risk factors of post-LVAD all-cause mortality [182]. This suggests that, while post-LVAD VAs are an indicator of worse outcomes, it might not be a direct cause. Studies are ongoing to assess the utility of ICD in patients with LVAD.

It is also important to recognize the potential for LVAD and ICD interaction. There have been several reports on electromagnetic interference of the HeartMate II LVAD with the ICD telemetry inhibiting communication between the ICD and its programmer in select ICD models [183]. The ICD lead characteristics can also be affected with a decrease in R-wave amplitude, a decrease in impedance, and an increase in capture threshold [183, 184]. This can lead to failure to sense VAs, failure to capture, and inappropriate pacing caused by undersensing. ICD interrogation should be performed after LVAD implant to detect these changes. The ICD can be tested to make sure it can detect VA and deliver therapy, and the lead should be revised if needed. However, the risks or revision should be weighed against the risks of infection in a patient population where the efficacy of the ICD is questioned, especially in patients with biventricular VADs and in patient close to being transplanted.

Autonomic Modulation for Arrhythmia Control

Several studies have shown that imbalance in the cardiac autonomous system and sympathetic nerve sprouting around the myocardium play a significant role in the genesis of VT/VF [185]. Sympathetic hyperactivity outside the heart has also been associated with increased incidence of VA [186]. Neuromodulation, designed to either increase the parasympathetic tone or decrease the sympathetic tone, is emerging as a viable therapy to treat refractory arrhythmias. It includes spinal cord stimulation, thoracic epidural anesthesia, renal denervation, and cardiac sympathetic denervation.

The effect of spinal cord stimulation in suppressing ventricular arrhythmias has been shown in animal models and in case reports in humans [187, 188]. This method has not shown a significant effect on cardiac remodeling in heart failure in a randomized feasibility study [189]. Although this study is not definitive, it is unclear whether this method is going to be studied further.

Renal denervation has shown additional benefits on top of AFib ablation in patients with persistent AFib and severe hypertension. The benefit of renal denervation for VT/VF was shown only in case studies [190, 191]. Ongoing studies include evaluation of renal sympathetic denervation (Renal Sympathetic Denervation to Suppress Ventricular Tachyarrhythmias [RESCUE-VT] and Renal Sympathetic Denervation as an Adjunct to Catheter-based VT Ablation [RESET-VT]) as adjuvant therapy to prevent recurrent VA [192, 193].

Cardiac sympathetic denervation was studied in left or bilateral stellate ganglia blockage (alcohol or RF ablation of ganglia or injection of anesthetic) or resection. Left and bilateral cardiac sympathetic denervation has been shown to acutely reduce the burden of ICD shocks and control VT storm in a small number of patients [194, 195]. Left versus bilateral stellate ganglia surgical resection was compared in a retrospective study of 41 patients [196]. There was a more decrease in ICD shock and VT burden in the bilateral resection arm. The risks of the procedure included change in sweating pattern in 10 %, ptosis in 2 %, and skin sensitivity in 12 % of the patients. The randomized PREVENT VT study (Cardiac Denervation Surgery for Prevention of Ventricular Tachyarrhythmias) is analyzing bilateral cardiac sympathectomy for the control of refractory VAs [197].

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Peripartum Cardiomyopathy

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_20

Introduction

Perhaps one of the most significant and reversible physiological responses involving the cardiovascular system is observed during pregnancy. Most pregnant women experience these changes without the need for medical intervention, and therapeutic advances have decreased pregnancy-associated complications over the past decades. However, peripartum cardiomyopathy (PPCM) has emerged as a serious and life-threatening disease. In this chapter, we review the physiological adaptations associated with pregnancy and comprehensively address the etiology and treatment of peripartum cardiomyopathy. Active basic and clinical research initiatives have uncovered new therapies that may have a major impact on the morbidity and mortality of this disease.

Maternal Physiologic Adaptive Changes to Pregnancy

To effectively diagnose and treat peripartum cardiomyopathy requires an appreciation of the maternal adaptive responses to pregnancy. These physiologic changes impact the rheological, hemodynamic, vascular, and coagulation systems. Rheological changes include expansion of the plasma volume and red blood cell mass. In animal models, plasma renin activity increases, and atrial natriuretic peptide levels decrease during pregnancy [1]. These hormonal changes, identifiable as early as the fourth week of pregnancy, are associated with systemic vasodilation and increased vascular capacitance (Fig. 20.1). The disproportionate increase in red blood cell mass to plasma volume is accompanied by a decrease in the hematocrit. The increase in total body volume results from an increase of about 1000 mEq in sodium retention and in water by 6–8 l [2]. This expansion in volume is distributed between the maternal space (intracellular and extracellular), the fetus, and the amniotic fluid. The expansion in plasma volume begins during the first month of gestation and continues to 30–34 weeks, after which it remains relatively stable [3]. The average expansion in plasma volume (by 1.1–1.6 l) corresponds to a plasma volume of 4.7–5.2 l at term and represents a 30–50 % increase compared to the nonpartum state.

The expansion in red blood cell mass, stimulated by an increase in erythropoietin, begins in the third month of gestation. A marked increase in blood volume occurs during the second trimester and a slight increase through the third trimester [4]. The extent of change in red blood cell mass is dependent on whether the mother is taking iron supplementation. With iron supplementation, the red blood cell mass increases 20–30 % (250–450 ml); with no iron supplementation, the red blood cell mass increases only 15–20 % [5]. This physiological anemia of pregnancy is due to the disproportionate increase in plasma volume compared to red blood cell mass. The decrease in blood viscosity is a protective response that reduces resistance to blood flow through the placenta and thereby reduces the workload of the maternal heart. The expansion of blood volume to 50 % above the nonpregnant state helps protect the mother in the event of hemorrhage at the time of delivery. Vaginal delivery is associated with a 500 ml blood loss for a single fetus and upwards of 1000 ml for twins [4]. Immediately after delivery, a reverse transfusion of 500 mL takes place from the uteroplacental organs or unit into the maternal circulation. Maternal red blood cell mass and plasma volume gradually return to normal levels during the first 2 months after delivery. The hematocrit begins to increase within 3 days following delivery.

Numerous hemodynamic changes associated with pregnancy occur, including an increase in cardiac output, a decrease in vascular resistance, and a reduction in systolic and diastolic blood pressures (Fig. 20.1) [6]. Pregnancy is associated with an increase in cardiac output of 30–50 %, much of which occurs during the first 2 months of pregnancy

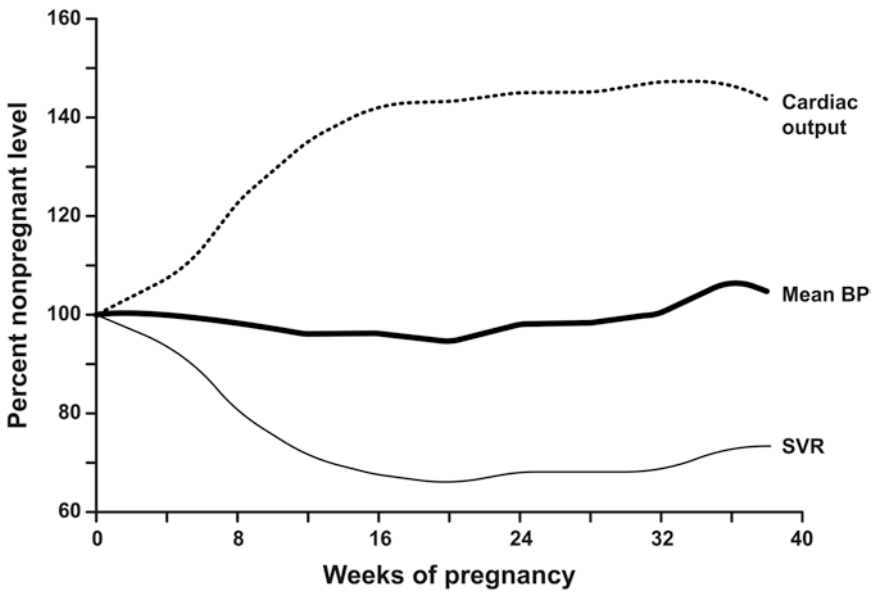
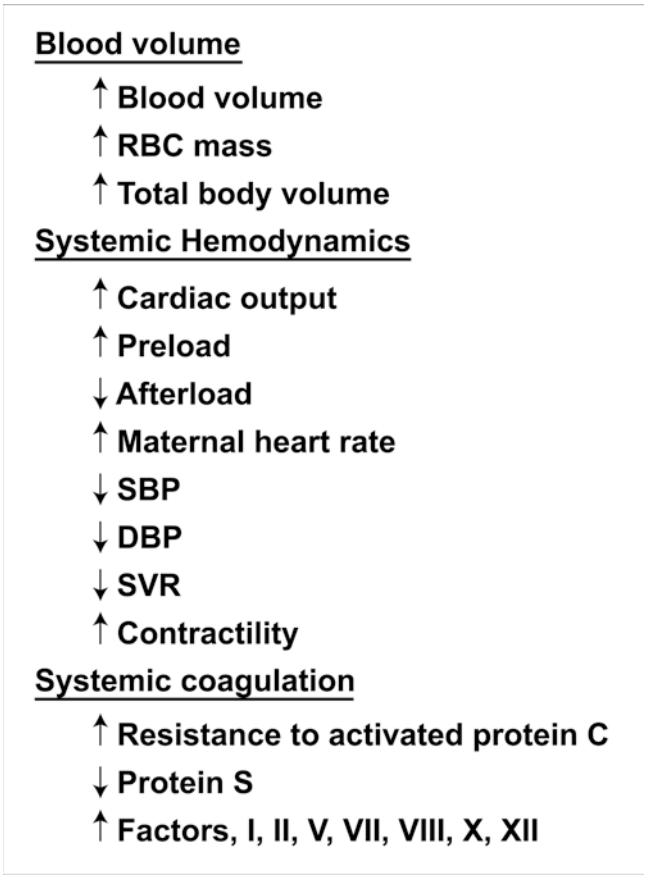


Fig. 20.1 Increased cardiac output is observed during pregnancy. Schematic highlighting the changes in cardiac output and systemic vascular resistance throughout the course of pregnancy

[7]. The increase in plasma volume results in a rightward shift on the Frank-Starling curve, with an increase in preload and greater stroke volume. The decline in systemic vascular resistance leads to a decrease in afterload. The increase in preload, the decrease in afterload, and the increase in basal heart rate of 15–20 bpm all result in an increase in cardiac output [8].

Augmentation of stroke volume is a greater contributor to cardiac output early in pregnancy, whereas an increase in heart rate accounts for the augmentation in cardiac output during the later stages of pregnancy. Importantly, left ventricular ejection fraction (LVEF) does not change significantly during pregnancy, and, thus, a reduction in ejection volume is pathologic. The reduction in systemic vascular resistance is due to the low resistance of the uteroplacental unit and from general vasodilation [9]. Potential mechanisms resulting in vasodilation include a decreased response to pressors (angiotensin II and norepinephrine) as well as increased endothelial prostacyclin [10], increased nitric oxide [11], and increased arterial compliance (■ Fig. 20.2) [12]. The decrease in systemic vascular resistance is associated with a reduction in both systolic and diastolic pressures [9]. In normotensive women, the systolic and diastolic pressures decline until the 21st week of pregnancy (about 5–10 mmHg below baseline) and gradually return to the baseline level during the third trimester [13].



■ **Fig. 20.2** Cardiovascular physiological responses to pregnancy. Table outlining changes in blood volume, hemodynamics, and coagulation during pregnancy

Central venous pressure does not change during pregnancy because the increased plasma volume can be accommodated by the low-resistance vascular circuit [14]. Similarly, the pulmonary arterial and pulmonary capillary wedge pressures are not significantly impacted, owing to the fall in pulmonary vascular resistance. Maternal cardiac output depends on posture. The cardiac output is greater in the left lateral decubitus position and decreases as much as 25–30 % in the supine position. The changes in cardiac output are related to changes in preload, which can be impacted whether the uteroplacental unit is compressing the inferior vena cava. The supine hypotensive syndrome is associated with a decrease in pulse pressure and can produce a physiologic reflex tachycardia. Cardiac output is not equally distributed among the organs. Uterine blood flow increases from 50 to 60 ml during the first trimester and to 450–750 ml at term. Blood flow is also preferentially directed to the kidneys for removing maternal and fetal waste and to the skin for facilitating maternal temperature control.

Pregnancy is associated with vascular changes and changes in coagulation factors. Vascular changes include fragmentation of reticular fibers, a decrease in acid mucopolysaccharides, loss of normal corrugation of elastic fibers, and hypertrophy and hyperplasia of smooth muscle cells [15]. Reports of both aortic dissection and coronary dissection are more prevalent during gestation than during the nonpregnant state. While pregnancy is considered a hypercoagulable state, it represents the net effect of competing processes. Favoring thrombolysis is a resistance to activated protein C and a reduction in protein S [16]. Favoring an increase in coagulation is the increase in multiple factors—I, II, VII, VIII, X, and XII—and an increase in inhibitors of fibrinolysis (PAI-1 and PAI-2) (■ Fig. 20.2) [17, 18]. While the hypercoagulable state is a physiological response and is protective in the setting of maternal hemorrhage, it poses an increased risk of venous thrombosis (deep venous thrombosis of lower extremities and pulmonary embolism).

Labor and delivery produce additional physiological adaptive hemodynamic changes [19, 20]. Uterine contractions result in the transfer of blood from the sinusoids into the maternal systemic circulation. An increase in the maternal cardiac output results from an increase in both stroke volume and pulse [21]. The cardiac output increases 15 % during the early phase of labor and 25 % during the active phase of labor. Cardiac output increases 50 % in the second stage of labor when the woman is actively pushing. Following delivery, the uterus involutes, resulting in additional autotransfusion and up to an 80 % increase in cardiac output above the prelabor value. The augmentation in cardiac output and stroke volume remain markedly elevated during the hours after delivery. Cardiac output and systemic vascular resistance return to baseline over the next 3 months.

Uterine contractions result in a 15–25 % increase in systolic and a 10–15 % increase in diastolic blood pressure. The blood pressure and heart rate changes occur during the second stage of labor, when the woman is pushing, similar to the changes that occur during the Valsalva maneuver. At the

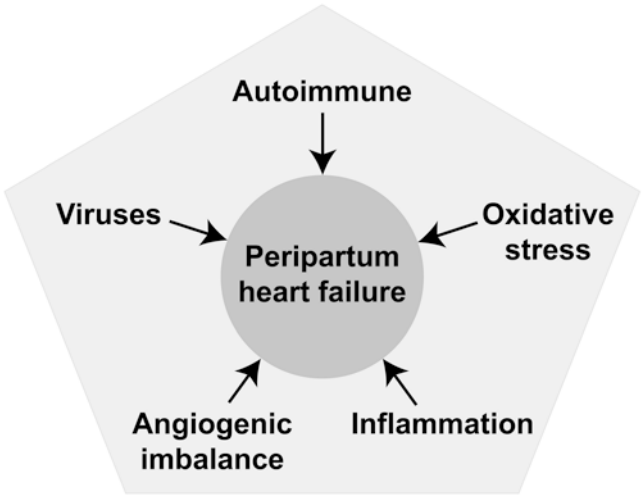


Fig. 20.3 Causes of peripartum cardiomyopathy. Schematic highlighting the most common causes of peripartum cardiomyopathy, including autoimmune issues, viral infections, inflammation, oxidative stress, and angiogenic perturbations

onset of pushing, a brief increase in left ventricular output takes place. The straining phase that follows is associated with a decrease in venous return, right and left ventricular volumes, stroke volume, mean arterial pressure, and pulse pressure. A reflex tachycardia results. Following the release of the strain, the left ventricular volume further declines. Completion of the strain brings an increase in stroke volume, an increase in arterial pressure, and a decrease in the heart rate.

The cardiovascular symptoms and physical findings associated with pregnancy are noteworthy. Innocent hyperpnea (breathlessness), reduced exercise tolerance, bruisability, basal rales that clear with coughing, and edema are common and not pathological. The arterial pulse is characterized by a rapid rise and collapse starting in the first trimester and resembles a water hammer pulse. While the jugular venous pressure remains normal, the *x* and *y* descents become more prominent during the second trimester. As the uterus enlarges, the heart is shifted anteriorly and laterally, and the apical impulse shifts to the fourth intercostal space in the midclavicular line. The heart rate and blood pressure increase. The heart sounds augment, and S1 splits widely. Similarly, S2 splits widely during the latter stage of pregnancy (Fig. 20.3). While an S3 is frequent, an S4 is pathologic. A systolic ejection murmur, moderate in intensity, can be auscultated over both the tricuspid and pulmonic and tricuspid areas. The mammary soufflé is unique to pregnancy and is auscultated over the breasts in the third trimester—and can either be systolic or continuous.

Definition of Peripartum Cardiomyopathy

Peripartum cardiomyopathy has been recognized as a clinical syndrome since the 1930s. Various definitions have been proposed by national organizations, both in the United States and Europe [22–25]. In 2000, a National Heart, Lung, and Blood Institute (NHLBI) workshop set forth the following diagnostic criteria for peripartum cardiomyopathy:

- The development of heart failure (HF) in the last month of pregnancy or within 5 months postpartum
- The absence of another identifiable cause of HF
- The absence of recognizable heart disease prior to the last month of pregnancy
- Left ventricular systolic dysfunction demonstrated by classical echocardiography criteria (LVEF < 45 %, fractional shortening <30 %, or both, with or without an LV end-diastolic dimension >2.7 cm/m^2 body surface area) [22].

In 2010, the European Society of Cardiology (ESC) Working Group on Peripartum Cardiology expanded the definition of peripartum cardiomyopathy by describing it as an idiopathic cardiomyopathy with the following features:

- The development of heart failure toward the end of pregnancy or in the months following delivery
- Absence of another identifiable cause for heart failure
- LVEF < 45 %, with either a dilated or normal-dimension left ventricle [25]

Importantly, the definition of peripartum cardiomyopathy excludes heart failure that occurs during the early stages of pregnancy. Pregnancy-associated cardiomyopathy (PACM) has been used to describe a dilated cardiomyopathy (DCM) occurring during the earlier stages of pregnancy [26].

Incidence and Risk Factors of Peripartum Cardiomyopathy

The incidence of peripartum cardiomyopathy varies widely around the world. Epidemiologic studies published since 2010 estimate the incidence of peripartum cardiomyopathy in the United States to range from 1:1141 to 1:4350 live births [27–32]. Peripartum cardiomyopathy is more frequent, with an incidence ranging from 1:300 in Haiti to 1:1000 in South Africa [33, 34]. The epidemiologic variance has been attributed to a wide variety of factors including hypertension and dietary intake. The Nigerian tradition of ingesting kanwa (dried lake salt) while lying on heated mud beds twice a day for 40 days during pregnancy is thought to be responsible for the strikingly high incidence of peripartum cardiomyopathy in that country.

About 45 % of cases worldwide are identified within 1 week of delivery and 75 % of cases within 1 month. A retrospective survey (2004–2011) of nationwide inpatient hospitalizations found the overall incidence of peripartum cardiomyopathy to be 10.3 per 10,000 (or 1 in 968) live births [35]. Over that 8-year period, the incidence increased from 8.5 to 11.8 per 10,000 live births ($P_{trend} < 0.001$). The major adverse event rate was 13.5 %. Researchers observed an increase in cardiogenic shock from 1.0 % in 2004 to 4.0 % in 2011 ($P_{trend} < 0.001$) and in mechanical circulatory support ($P_{trend} < 0.05$). In-hospital mortality averaged 1.3 % per year

with a statistically insignificant increase from 0.7 % in 2004 to 1.8 % in 2011.

Various risk factors have been identified for peripartum cardiomyopathy:

- Maternal age > 30 years: Peripartum cardiomyopathy has been reported in the United States in women with a mean age ranging from 27 to 33 [26, 28, 29, 31, 32, 36].
- African race: In epidemiologic studies, Africans have represented anywhere from 19 to 93 % of peripartum cardiomyopathy patients. In most of the studies, it was difficult to distinguish the racial makeup from the geographic source of patients. In a case–control study, Gentry et al. found African-American women had a 15.7-fold higher relative risk of peripartum cardiomyopathy than non-African-Americans [26, 28, 29, 31, 32, 36, 37].
- Hypertension: The vast majority of studies have cited hypertension as a risk factor for peripartum cardiomyopathy, with an incidence varying from 15 to 68 % (mean 23 %) [26, 29, 31, 32, 38, 39]. This is in contrast to the 8 % incidence of hypertension in pregnancy in the absence of peripartum cardiomyopathy [40]. The diagnosis of hypertension can often cloud the diagnosis of peripartum cardiomyopathy because the presenting symptoms of heart failure can be attributed to either hypertension, preeclampsia, or eclampsia. However, in young women, hypertension is unlikely to produce systolic dysfunction.
- Multiparity: Early data suggested multiparity was a risk factor for peripartum cardiomyopathy [36]. Recent studies have found peripartum cardiomyopathy to be associated with the first or second pregnancy in the majority of cases [9, 16, 18, 41]. Pregnancy with multiple fetuses: The incidence of multiple births in the United States is estimated to be 3 % [42]. Epidemiologic studies of peripartum cardiomyopathy have observed multiple births in 7–14.5 % of pregnancies [9, 15, 18, 19, 41].
- Maternal cocaine use: In a small case report series, cocaine use during pregnancy was associated with peripartum cardiomyopathy [43].
- Oral tocolytic therapy: Mendelson reported an association between chronic terbutaline therapy and peripartum cardiomyopathy. Among 15 gravidas who had peripartum heart failure, four had received terbutaline tocolysis for at least 4 weeks. All four of these patients subsequently recovered LV function [43].

Etiology of Peripartum Cardiomyopathy

The etiology of peripartum cardiomyopathy remains poorly defined. Cardiovascular risk factors (hypertension, diabetes, and smoking) as well as pregnancy-related factors (maternal age, number of pregnancies, number of fetuses, medications, and malnutrition) have been implicated. The pathogenesis, like the risk factors, is not well understood. Various mechanisms have been postulated including increased oxidative stress, cleavage of prolactin to an angiostatic N-terminal 16-kDA prolactin fragment, and impaired vascular endothelial growth factor (VEGF) signaling, resulting from upregulation of soluble forms like tyrosine kinase 1 (sFLT1) which may all be contributing factors for peripartum cardiomyopathy (Fig. 20.3).

Oxidative stress and prolactin: Oxidative stress reflected by increased serum levels of oxidized low-density lipoprotein (LDL) has been implicated in the pathophysiology of peripartum cardiomyopathy. Oxidative stress activates cathepsin D in cardiomyocytes, and cathepsin D cleaves prolactin into an angiostatic 16-kDa proapoptotic subfragment. Mice with a knockout in the cardiac tissue-specific signal transducer and activator of transcription 3 (STAT3) have increased cleavage of prolactin and develop peripartum cardiomyopathy [44]. The 16-kDa prolactin fragment inhibits endothelial cell proliferation and migration, induces endothelial cell apoptosis, disrupts capillary structures, promotes vasoconstriction, and impairs cardiomyocyte function (Fig. 20.4) [45]. The 16-kDa prolactin isoform also promotes microRNA-146a expression in endothelial cells and results in anti-angiogenic effects (Fig. 20.4). Increased levels of microRNA-146a have been found in women with peripartum cardiomyopathy [45]. Increased levels of soluble death receptor sFas/Apo-1, a proapoptotic serum marker, have also been identified in women with peripartum cardiomyopathy [46]. When bromocriptine, a dopamine D2 receptor agonist that inhibits lactation, was administered to knockout STAT3 mice, peripartum cardiomyopathy could be prevented [44]. This observation has formed the basis for early studies of bromocriptine and may offer a treatment strategy for women who develop peripartum cardiomyopathy (Fig. 20.4) [47–51].

Inflammation: Evidence suggests that inflammation plays a role in the development of peripartum cardiomyopathy. Women afflicted with peripartum cardiomyopathy have higher serum levels of the soluble death receptor sFas/Apo-1, C-reactive protein, interferon gamma (IFN-g), tumor necrosis factor, and interleukin 6 (IL-6) [44, 46, 52, 53]. Serum levels of Fas/Apo-1 and C-reactive protein have been shown to correlate with the severity of peripartum cardiomyopathy [46]. Pentoxifylline, an anti-inflammatory drug, was associated with a clinical benefit in a single nonrandomized study of 58 women with peripartum cardiomyopathy [54].

Angiogenic imbalance: Cardiac angiogenic imbalance has been implicated in the development of peripartum cardiomyopathy. Mice that lack cardiac peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1alpha, a powerful regulator of angiogenesis, develop profound PPCM [55]. Importantly, the PPCM is entirely rescued by pro-angiogenic therapies (i.e., VEGF). In humans, the placenta in late gestation secretes soluble FLT1, an inhibitor of VEGF, and this is associated with subclinical cardiac dysfunction. Preeclampsia and multiple previous pregnancies are associated with excess anti-angiogenic signaling and abnormally high levels of sFLT1, which can be identified in the serum of women with peripartum cardiomyopathy.

Autoimmune response: The autoimmune system may contribute to the pathophysiology of peripartum syndrome. Fetal cells can be found in maternal peripheral blood, and the

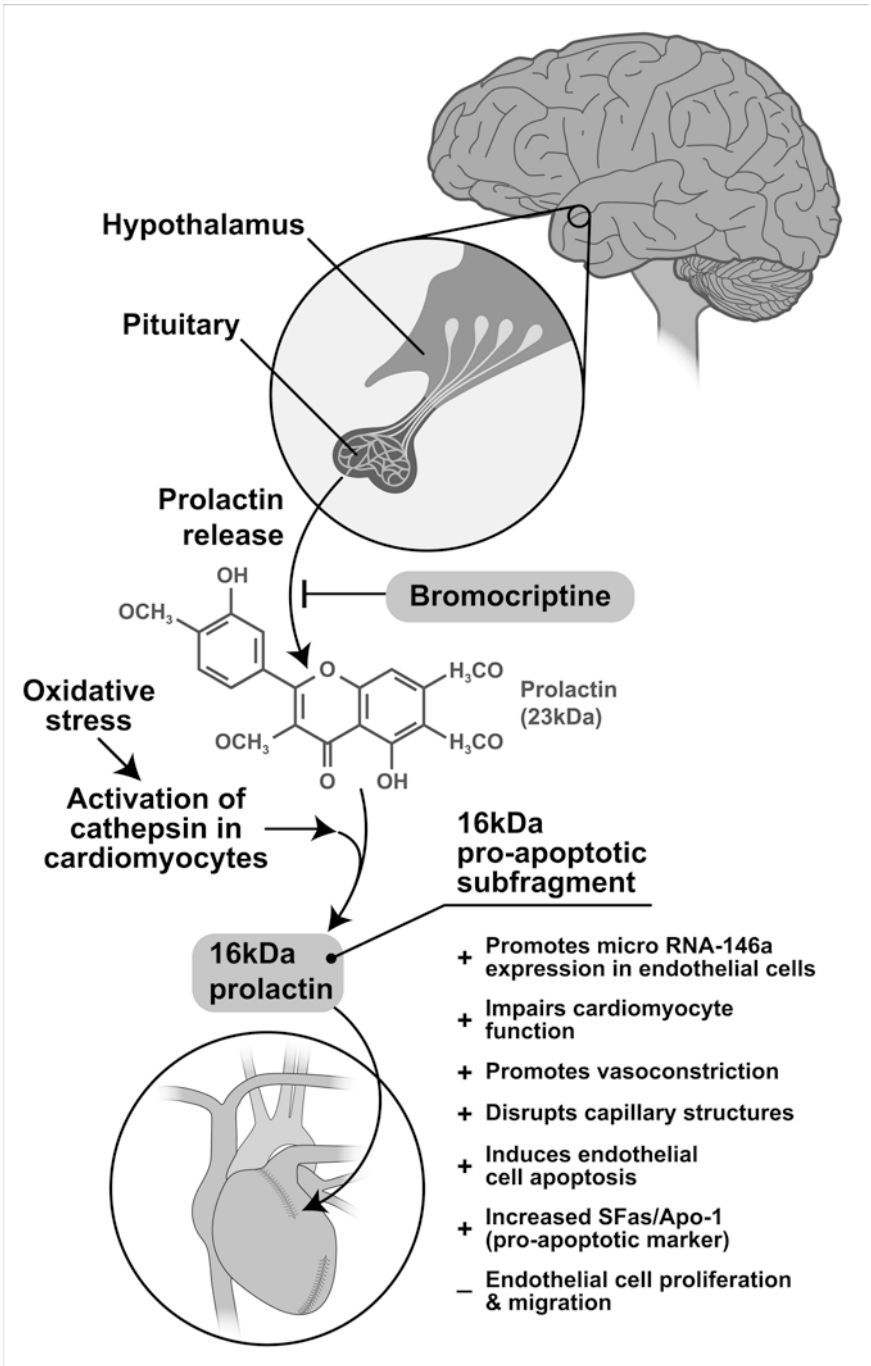


Fig. 20.4 Bromocriptine as a therapy for peripartum cardiomyopathy. Schematic highlighting the release and functional impact of prolactin. Blockade of prolactin with the dopamine-2D agonist bromocriptine has been shown to prevent the onset of cardiomyopathy in mice and a small clinical cohort of women at high risk for cardiomyopathy. The women had a documented peripartum cardiomyopathy in a previous pregnancy. Note that increased serum levels of 16-kDa prolactin and increased cathepsin D activity have been shown to be associated with peripartum cardiomyopathy. Bromocriptine eliminates the 16-kDa prolactin form, which has a number of deleterious effects on the endothelium and the myocardium

influx of fetal cells into the maternal circulation increases during parturition [56, 57]. Potentially, these cells could migrate to the maternal heart and trigger an autoimmune response leading to cardiac dysfunction. Women with postpartum cardiomyopathy have increased serum levels of autoantibodies to cardiac tissue proteins [58]. Studies have identified autoantibodies against myosin heavy chain, adenine nucleotide translocator, and branched-chain alpha-ketoacid dehydrogenase [59, 60]. A study of 39 Nigerian women with peripartum cardiomyopathy compared to controls failed to show a difference in serum immunoglobulins, cardiac muscle antibodies, and circulating immune complexes [61]. Further research is warranted to determine whether fetal antigens are promoting an autoimmune response in the maternal heart.

Viruses and myocarditis: The extent to which viruses and myocarditis may contribute to peripartum cardiomyopathy remains controversial. The first case report ($n = 3$) of myocarditis among patients with peripartum cardiomyopathy was reported by Melvin et al. in 1982 [62]. Endomyocardial biopsies from five of 11 Nairobi women with peripartum cardiomyopathy found "healing myocarditis"—mild inflammatory cell infiltration within the myocardium with foci of necrosis

and variable amounts of hypertrophy and fibrosis [63]. In a study of 26 patients with peripartum cardiomyopathy, endomyocardial biopsy revealed viral genomes (human parvovirus B19, Epstein-Barr virus, and human cytomegalovirus) in eight (30.7 %) individuals associated with interstitial inflammation [64]. Midei investigated 26 consecutive patients with peripartum cardiomyopathy and found myocarditis in 14 (78 %) of the patients. Ten of these patients were treated with immunosuppressive therapy with a 90 % recovery rate [65].

Genetic Association of Peripartum Cardiomyopathy

Efforts to establish a genetic susceptibility to peripartum cardiomyopathy have been hampered by the low frequency of this condition. In one of the first reports, Pierce et al. identified 3 of 17 probands with peripartum cardiomyopathy who had a family history of this condition [66]. Several small case reports subsequently identified peripartum cardiomyopathy in 2 or 3 first-degree relatives [50, 67, 68]. The presence of a dilated cardiomyopathy in other male relatives diminished the argument for genetic susceptibility. Recent family studies indicated that selected cases of peripartum cardiomyopathy may represent a form of familial dilated cardiomyopathy [69, 70]. van Spaendonck-Zwarts et al. reviewed their database of 90 families with dilated cardiomyopathy and found peripartum cardiomyopathy in 6 % of the sample [70]. They next performed cardiovascular testing of first-degree relatives of three peripartum cardiomyopathy patients who failed to recover and found dilated cardiomyopathy in all three families. Genetic analyses revealed a mutation (c.149A_G, p. Gln50Arg) in the gene encoding cardiac troponin C (*TNNC1*) segregating with disease in a DCM family with a member having PPCM. In another family-based genetic study, Morales et al. investigated 4110 women from 520 pedigrees in the Familial Dilated Cardiomyopathy Research Project database and found 45 cases of peripartum cardiomyopathy or pregnancy-associated cardiomyopathy. Evidence of familial clustering with dilated cardiomyopathy was observed in 23 unrelated cases. Nineteen of these cases were resequenced for known dilated cardiomyopathy genes and six carried mutations. These studies suggest a genetic association between peripartum cardiomyopathy and dilated cardiomyopathy.

Clinical Presentation of Peripartum Cardiomyopathy

The diagnosis of peripartum cardiomyopathy is based on the presentation of heart failure toward the end of pregnancy or in the first 5 months following delivery in the absence of identifiable etiology and in the setting of reduced left ventricular systolic function (LVEF < 45 %). The clinical presentation of peripartum cardiomyopathy can be insidious in onset or acute, and the New York Heart Association (NYHA) classification can vary based on the reduction in LVEF. Typical symptoms include dyspnea, cough, and fatigue. Other common symptoms include lower extremity edema, orthopnea, paroxysmal nocturnal dyspnea, palpitations, and dizziness. Less common symptoms include nocturia, right-upper-quadrant pain, chest pain, postural hypotension, and syncope. Frequently, the symptoms of peripartum cardiomyopathy are confused with other conditions or diseases and lead to a delay in diagnosis [71].

Physical exam findings are similar to those observed in the setting of congestive heart failure. The patient appears tachypneic and tachycardic; blood pressure may vary based on volume status and the severity of cardiac dysfunction. The jugular venous pressure is elevated, a right ventricular heave can be palpated, the apical pulse is displaced inferolaterally, and an S3 or summation gallop may be appreciated. Murmurs of tricuspid and mitral regurgitation can be auscultated. Pulmonary rales are present, hepatojugular venous reflex can be noted, extremities are cool to palpation, and lower extremity edema is evident.

The electrocardiographic findings are nonspecific. Frequently, sinus tachycardia, supraventricular tachycardia (SVT, atrial fibrillation or atrial flutter), and nonspecific ST and T wave changes can be observed [33, 72]. Other possible pathological findings include LV hypertrophy, left atrial enlargement, and left bundle branch block. Chest X-ray findings include cardiomegaly, pulmonary venous congestion, frank pulmonary edema, and pleural effusions [32]. B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are elevated as a result of increased left ventricular diastolic dysfunction [52]. Forster et al. observed markedly elevated mean NT-BNP levels in 36 peripartum cardiomyopathy patients compared to 21 controls (1727 vs. 339, $P < 0.0001$) [52].

Cardiovascular imaging is essential to establish the diagnosis of peripartum cardiomyopathy. Echocardiography has been used at baseline to define the cardiomyopathy and serially to determine patient prognosis [31, 73–75]. The echocardiographic criteria for idiopathic dilated cardiomyopathy set forth by an NHLBI-sponsored workshop in 1992 included a left ventricular ejection fraction less than 45 % or M-mode fractional shortening less than 30 %, or both, with a left ventricular end-diastolic dimension greater than 2.7 cm/m^2 [75]. The American Society of Echocardiography endorses the biplane method of disks to calculate both left ventricular volumes and ejection fraction [76]. Endocardial borders are traced using the apical four-chamber and two-chamber views (oriented at 90 = degree angles with similar long axis dimensions) at end-diastole and end-systole. These echocardiographic features were incorporated into the subsequent definitions of peripartum cardiomyopathy [22, 74]. The degree of left ventricular systolic function and dilation may vary from mild to severe and may be accompanied by right ventricular systolic dysfunction and dilation as well. Additional echocardiographic findings include moderate to severe mitral regurgitation and tricuspid regurgitation, increased pulmonary artery pressures, pulmonary

regurgitation, and left ventricular thrombus. Serial echocardiographic evaluations following the baseline study—prior to discharge, 6 weeks, 6 months, and annually—for both prognostic assessment and to assess response to pharmacologic therapy [25]. In one study of 32 peripartum cardiomyopathy patients, a fractional shortening value less than 20 % and a left ventricular end-diastolic dimension 6 cm or greater at the time of diagnosis was associated with a more than threefold higher risk for persistent left ventricular dysfunction [31].

Cardiac magnetic resonance imaging (MRI) has become a valuable tool for assessing cardiomyopathy. Cardiac MRI is more accurate than echocardiography in assessing chamber volumes and ventricular function, as well as LV thrombus. While the administration of intravenous gadolinium can help distinguish myocarditis from idiopathic dilated cardiomyopathy, gadolinium crosses the placenta, and 0.04 % of the maternal dose can be found in breast milk. The 2013 American College of Radiology and the European Society of Radiology statements on safe MRI practices discourage the use of IV gadolinium during pregnancy unless it is absolutely essential [77, 78]. Because less than 1 % of the contrast medium ingested by the infant is absorbed from its gastrointestinal tract, the expected systemic dose absorbed by the infant from the breast milk is less than 0.0004 % of the intravascular dose given to the mother [79]. While the risk is considered remote, the concern can be alleviated by instructing the mother to discontinue breastfeeding for 24 h after administration of gadolinium.

Differential Diagnosis of Peripartum Cardiomyopathy

By definition, peripartum cardiomyopathy is a diagnosis of exclusion and, as such, requires the clinician to consider alternative diagnoses. Patients with idiopathic dilated cardiomyopathy have identical symptoms but present in either the first or second trimester. They also have nonspecific findings on ECG, evidence of congestion on chest X-ray, elevated BNP, and reduced left ventricular ejection fraction. Patients with familial dilated cardiomyopathy likewise present with heart failure by the second trimester. They report heart failure among family members and often have markedly dilated left ventricles with reduced ejection fraction. Genetic testing remains a research tool and is not routinely employed in clinical practice. Human immunodeficiency virus (HIV)-associated cardiomyopathy is a well-described entity, typically with reduced left ventricular ejection fraction but not significant left ventricular dilatation. Women with preexisting hypertension may present with heart failure. Classically, the ECG shows left ventricular hypertrophy. Echocardiography may similarly show left ventricular hypertrophy with either preserved left ventricular systolic function (heart failure with preserved ejection fraction or diastolic dysfunction) or dilated cardiomyopathy. Acquired valvular heart disease such as rheumatic mitral stenosis may be unmasked in the first or second trimester of pregnancy and can be confirmed by echocardiography. Acute myocardial infarction secondary to spontaneous coronary dissection and acute pulmonary embolism can also present with heart failure and cardiogenic shock.

Congenital heart disease, as categorized by the World Health Organization, ranges from Class I (low risk) to Class IV (pregnancy contraindicated) [80]. Pregnant women with underlying cyanotic heart disease, moderate to severe left-sided valvular stenosis, aortic root dilation, and reduced left ventricular ejection fraction are at greatest risk. WHO Class I conditions include mild, uncomplicated valvular lesions (pulmonary stenosis, patent ductus arteriosus, and mitral valve prolapse) as well as successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, and anomalous pulmonary venous drainage). WHO Class II lesions include unrepaired atrial or ventricular septal defects and repaired tetralogy of Fallot. WHO Class II–III lesions include mild left ventricular impairment, hypertrophic cardiomyopathy, native or tissue valvular heart disease not considered WHO I or IV, Marfan syndrome without aortic dilatation, aorta <45 mm in aortic disease associated with bicuspid aortic valve, and repaired coarctation of the aorta. WHO Class III conditions include mechanical valves, systemic right ventricle, Fontan circulation, unrepaired cyanotic heart disease, other complex congenital heart disease, aortic dilatation (40–45 mm) in Marfan syndrome, and aortic dilatation (45–50 mm) in aortic disease associated with bicuspid aortic valve. WHO Class IV conditions (pregnancy contraindicated) include pulmonary arterial hypertension of any cause, severe systemic ventricular dysfunction (LVEF < 30 %, NYHA III–IV), previous peripartum cardiomyopathy with any residual impairment of left ventricular function, severe mitral stenosis, severe symptomatic aortic stenosis, Marfan syndrome with dilatation of the aorta >45 mm, and aortic dilatation >50 mm in aortic disease associated with a bicuspid aortic valve, and native severe coarctation of the aorta.

Treatment of Peripartum Cardiomyopathy

Acute management: The initial management of peripartum cardiomyopathy, directed at oxygenation and hemodynamic support, is comparable to the management of heart failure in pregnancy [81]. Supplemental oxygenation should be provided to ensure that oxygen saturation remains above 95 %. If nasal cannula and non-rebreather facemask prove inadequate, then noninvasive ventilation with a positive end-expiratory pressure of 5–7.5 cm H_2O should be instituted. Intravenous furosemide (risk category C), with an initial dosage of 20–40 mg, should be administered to patients with hypervolemia on exam. IV nitroglycerin (starting at 10–20 up to 200 mg/min) can be initiated in patients with a systolic blood pressure (SBP) > 110 mmHg and can be used with caution in patients with an SBP between 90 and 110 mmHg. IV nitroglycerin (risk category B) is preferred over IV nipride (risk category C) which may be associated with thiocyanate toxicity.

Cardiogenic shock, as manifested by low cardiac output and hypoperfusion [hypotension, cool/clammy skin, low urine output (<0.5 ml/kg/h), mental status changes, hepatic dysfunction], may require the combination of vasodilator and inotropic therapy. Dopamine (risk category C) is an inotrope with a dose-dependent effect on the peripheral vasculature. Dobutamine (risk category B) combines the inotropic and vasodilator properties. Vasopressors such as phenylephrine and norepinephrine should be avoided because their vasoconstrictor properties impair cardiac output, and they can impair uterine blood flow.

There is limited experience with mechanical support devices—intra-aortic balloon pump (IABP) counterpulsation [82, 83], left ventricular assist devices (LVADs) [84–88], and extracorporeal membranous oxygenation [89]—in the setting of pregnancy. The intra-aortic balloon pump is less invasive and does not require anticoagulation, but provides only mild augmentation in cardiac output. Percutaneous and surgically implanted left ventricular devices significantly augment cardiac output (2.5 = 5.0 L/min), are more invasive, are associated with greater risk, and require anticoagulation. Both the IABP and percutaneous LVAD devices such as the Impella have the added risk of radiation exposure associated with fluoroscopy. The LVAD can serve as a bridge to transplantation among women who do not recover from cardiomyopathy or may be removed if left ventricular function recovers.

Cardiac transplantation has been successfully performed in peripartum cardiomyopathy patients [90–92]. The incidence of cardiac transplantation for peripartum cardiomyopathy ranges from 0 to 11 % [31, 32, 93]. Rasmusson et al. reported on cardiac transplantations performed on 69 women from 29 US hospitals [94]. The risk of rejection was higher for women without prior pregnancies but similar among women who had previously given birth. The cumulative incidence of mortality and allograft vasculopathy was lower among women who had been transplanted for peripartum cardiomyopathy.

Chronic management: The pharmacological treatment of peripartum cardiomyopathy patients following delivery is identical to the treatment of idiopathic dilated cardiomyopathy [81]. Special consideration should be given to pharmacological therapy as several of the commonly used medications for idiopathic dilated cardiomyopathy are either untested or contraindicated in pregnancy [80]. Both angiotensin II receptor blockers and angiotensin-converting enzyme (ACE) inhibitors are contraindicated (risk category D) and pose the risks of renal or tubular dysplasia, oligohydramnion, growth retardation, ossification disorders of the skull, lung hypoplasia, contractures, large joints, anemia, and intrauterine fetal death. Spironolactone (risk category D) can have antiandrogenic effects and cause oral clefts during the first trimester and is therefore contraindicated. Eplerenone remains unclassified because of limited experience. As an alternative, the combinations of hydralazine (risk category C) and isosorbide dinitrate (risk category B) may be used to treat cardiomyopathy. Beta blockers (risk category B) have not been shown to have teratogenic effects but may produce hypoglycemia and bradycardia in the fetus and may result in intrauterine growth delay. β-1 selective drugs may be preferred because β-2 agents could have an anti-tocolytic effect. Hydrochlorothiazide (risk category B) and furosemide (risk category C) have both been used in pregnancy. Excessive diuretic use may lead to oligohydramnion. Unfractionated heparin (risk category B) can be utilized during pregnancy, whereas coumadin (risk category D) poses the risk of embryopathy during the first trimester and fetal hemorrhage throughout the pregnancy. The decision for anticoagulation in the setting of peripartum cardiomyopathy must take the maternal and fetal risks into consideration.

Device therapies: Limited data exist regarding the use of defibrillators and cardiac resynchronization therapy for managing peripartum cardiomyopathy. Saltzerg et al. investigated the outcomes among 107 peripartum cardiomyopathy patients who were outfitted with a wearable cardiac defibrillator for about 120 days [95]. None of the patients received an appropriate shock for ventricular tachycardia/ventricular fibrillation. However, three patients (2.8 %) died following removal of the wearable cardiac defibrillator. Neither the 2013 ACCF/AHA Guideline for the Management of Heart Failure [81] nor the European Society of Cardiology Guidelines for Peripartum Cardiomyopathy [25] provides specific recommendations regarding device therapy in this patient population. In contrast to a dilated cardiomyopathy with unknown prognosis, a substantial proportion of women with peripartum cardiomyopathy recover left ventricular function. Therefore, implantation of a device poses risks and incurs expenses without a proven clinical benefit. If one extrapolates the guidelines for patients with dilated cardiomyopathy to women with peripartum cardiomyopathy who do not recover left ventricular function after 6 months of optimal medical therapy, an implantable cardiac defibrillator should be considered. Similarly, for peripartum cardiomyopathy patients who have persistent left ventricular dysfunction (LVEF < 35 %) associated with NYHA Class III or IV heart failure and a QRS duration >120 ms, cardiac resynchronization should be considered.

Experimental therapies: Biologically plausible data suggest bromocriptine could be used in the treatment of peripartum cardiomyopathy [44, 47, 49, 50]. In animal models, oxidative stress activates cathepsin D in cardiomyocytes, and cathepsin D cleaves prolactin into an angiostatic 16-kDa proapoptotic subfragment. This fragment is associated with the development of peripartum cardiomyopathy. By inhibiting prolactin, bromocriptine may facilitate recovery. Silwa performed a prospective, single-center, randomized study of 18 patients with peripartum cardiomyopathy in which ten of the patients received bromocriptine in addition to the standard of care. Patients receiving bromocriptine had a greater recovery of LVEF (27–58 %; $P = 0.012$) compared with those receiving the standard of care (27–36 %, P = NS) at 6 months. Among the five deaths, only one occurred in the bromocriptine

group. Myocardial infarction has been reported in postpartum cardiomyopathy patients taking bromocriptine, emphasizing the need to consider anticoagulation, particularly when the LVEF is severely depressed [96].

Maternal Delivery

A paucity of literature addresses the timing of delivery and the mode of delivery in a woman with peripartum cardiomyopathy. The patient care team should include the obstetrician, a heart failure specialist, an anesthesiologist, intensivist, and a neonatologist. The first decision is whether to proceed with the pregnancy or to terminate it. If the woman proceeds with the pregnancy, frequent monitoring and pharmacologic intervention may be required to ensure heart failure does not worsen and that LV function remains stable. Both vaginal delivery and cesarean section should be considered. Cesarean section poses risk of hemodynamic fluctuation, blood loss, infection, respiratory and thromboembolic complications, and potential damage to pelvic organs. However, the use of invasive hemodynamic and urine monitoring provides for a controlled environment. Either continuous spinal anesthesia or combined spinal and epidural anesthesia may be used. Vaginal delivery avoids these anesthesia and surgical risks, but may be complicated by supine hypotension, blood loss, and exacerbation of heart failure associated with pushing during the second stage. In general, vaginal delivery is preferred for women with stable postpartum cardiomyopathy where the risk to the fetus is minimal, and cesarean section is preferred in the setting of decompensated heart failure. The left lateral position has been recommended in cases of vaginal delivery to avoid decreased blood return associated with compression of the inferior vena cava. In the setting of decompensated heart failure, the woman may not be able to lie flat, and a sitting-up position may be required. If spontaneous delivery cannot be achieved, either low forceps or vacuum-assisted delivery can be employed to decrease the time the woman is pushing in the second stage. During the third stage of delivery, a single intramuscular dose of oxytocin may be administered. However, ergometrine is contraindicated. Following delivery, autotransfusion may exacerbate heart failure and requires the administration of intravenous furosemide.

Complications/Prognosis of Peripartum Cardiomyopathy

A large number of epidemiologic studies have evaluated the outcomes of women with peripartum cardiomyopathy. Two retrospective, population-based studies have been performed in the United States, the larger of which included 171 patients [28, 29]. In addition, there have been both prospective and retrospective case series from single centers in the United States [31, 32, 93, 97], South Africa [33, 46, 53, 98], Haiti [34, 99], Brazil [100], and Turkey [101]. None of the studies enrolled more than 100 patients. Additional data came from a single survey of 100 women in the United States with peripartum cardiomyopathy [102].

In one of the earliest studies, Demakis et al. reported the long-term (average 10.7 years) outcomes of 27 patients with peripartum cardiomyopathy [36]. About 50 % of the patients had normal-sized hearts 6 months after diagnosis; two-thirds had Class I symptoms, and the remaining one-third had Class II NYHA symptoms. Among the patients who had persistent cardiomegaly, 85 % died of congestive cardiac failure. Their average survival was 4.7 years. Their clinical course included repeated admissions for congestive cardiac failure as well as pulmonary and systemic embolism.

Goland et al. performed a retrospective review on 182 patients with peripartum cardiomyopathy and noted at least one major adverse event among 25 %, including death (13), heart transplantation (11), temporary circulatory support (4), cardiopulmonary arrest (6), fulminant pulmonary edema (17), thromboembolic complications (4), and defibrillator or pacemaker implantation (10) [103]. One-third of the patients had residual brain damage following cardiopulmonary arrest or a cerebrovascular event. Risk factors associated with major adverse events included delay in diagnosis, LVEF < 25 %, and non-Caucasian race.

Amos et al. performed a retrospective analysis on 55 patients with peripartum cardiomyopathy (1990–2003) with a mean initial LVEF of 25 % and an average follow-up of 43 months [39]. The LVEF improved in 62 % of patients, remained unchanged in 25 %, and worsened in 4 %. The LVEF was over 45 % at 2 months after diagnosis in 75 % of the patients. Although no mortality was observed, 10 % of patients required cardiac transplantation. Factors associated with lack of recovery at initial assessment were a left ventricular end-diastolic dimension >5.6 cm, the presence of LV thrombus, and African-American race. The baseline LVEF did not predict recovery of LV function.

Safirstein et al. categorized 55 peripartum cardiomyopathy patients into two groups based on whether or not they recovered LV function (LVEF > 50 %) [38]. The presence of gestational hypertension (gHTN), EF ≥ 35 % at diagnosis, breastfeeding, and postpartum diagnosis were all significantly associated with recovery of systolic function.

Chapa et al. performed a chart review of 32 patients (1988–2001) with peripartum cardiomyopathy to determine whether echocardiography findings at the time of diagnosis were predictive of persistent cardiac dysfunction [31]. Left ventricular dysfunction was defined by echocardiography as fractional shortening less than 30 % and left ventricular end-diastolic dimension of 4.8 cm or more. Recovery of LV function was noted among 41 % of the patients. A fractional shortening value less than 20 % and a left ventricular end-diastolic dimension 6 cm or greater at the time of diagnosis were associated with a more than threefold higher risk for persistent left ventricular dysfunction. The ability of baseline echocardiographic parameters to predict which patients will recover from peripartum cardiomyopathy has been challenged by other studies [34, 39, 41].

In summary, the prognosis of peripartum cardiomyopathy patients is highly variable and difficult to predict. While peripartum cardiomyopathy is considered to have a better prognosis than other cardiomyopathies, it has become an increasingly recognized cause of pregnancy-related maternal mortality [104]. Recovery of LVEF > 50 % at 6 months ranges from 45 to 78 % [38, 39, 103]. Among patients followed for an average of 30 months, the greatest recovery occurred within the first 6 months after diagnosis [26]. Among patients who do not recover LV function, the prognosis is dismal, with mortality resulting from sudden cardiac death or progressive heart failure.

Future Pregnancies

Several retrospective observational studies have documented the outcomes of women with peripartum cardiomyopathy who have subsequent pregnancies. While all of these studies are small in size, they do highlight the likelihood of recurrence and a marked increased risk of morbidity and mortality. Elkayam et al. reported on 44 women with peripartum cardiomyopathy who had recurrent pregnancy. Left ventricular function had recovered among 28 women; 16 women had residual left ventricular function at the time of their next pregnancy. Among women who recovered left ventricular function, LVEF declined from 56 ± 7 % to 49 ± 10 % ($P = 0.002$); among women who had not recovered left ventricular function, the LVEF declined further (36 ± 9 % to 32 ± 11 %, $P = 0.08$). A decrease of more than 20 % occurred in 21 % of women who had recovered left ventricular function and 25 % who had not recovered left ventricular function. Heart failure was more than twice as frequent (44 % vs. 21 %) among women who had not recovered LVEF prior to the recurrent pregnancy. The mortality rate was 0 % among women who had recovered left ventricular function and 19 % among women who had not recovered LV function ($P = 0.06$). Both the frequency of premature delivery (37 % vs. 11 %) and therapeutic abortion (25 % vs. 4 %) were higher among women who had depressed left ventricular function going into the recurrent pregnancy.

Habli et al. assessed the prognostic value of ejection fraction at the index and subsequent pregnancy on long-term outcome among 70 patients with peripartum cardiomyopathy (PPCM) who had no subsequent pregnancy ($n = 33$), a successful subsequent pregnancy ($n = 21$), or who elected to terminate a subsequent pregnancy ($n = 16$) [105]. Patients were further dichotomized with an LVEF cut point of 25 %. Among the patients who had no subsequent pregnancy, those who had LVEF > 25 % had no further symptoms, whereas 50 % of the women with LVEF < 25 % were placed on the cardiac transplantation list. Among the women who terminated the subsequent pregnancy, there were no cardiac issues among the women with LVEF > 25 %; 63 % of the women with LVEF < 25 % were placed on a cardiac transplantation list. Among the women who had a successful repeat pregnancy, four of the 19 women (21 %) with LVEF > 25 % had worsening symptoms, and both of the patients with an LVEF < 25 % required transplantation.

In a separate study, Mandal et al. investigated 42 peripartum cardiomyopathy patients, six of whom had a repeat pregnancy [106]. Of the six women with subsequent pregnancies, the patient with persistent cardiomyopathy died after delivering a stillborn baby. The remaining five cases with normal left ventricular functional status had favorable fetal outcomes; however, the mothers experienced morbidities such as symptoms of heart failure (two cases) and one of them progressed to persistent cardiomyopathy.

Fett et al. prospectively enrolled 61 patients with peripartum cardiomyopathy into a registry between 2003 and 2009 [107]. Of 26 pregnancies with an LVEF < 55 % prior to pregnancy, relapse occurred in 12 pregnancies (46.2 %). Of 35 pregnancies with an LVEF ≥ 55 % prior to the pregnancy, relapse occurred in six (17.1 %) ($P < 0.01$). Among nine women who demonstrated adequate contractile reserve on exercise stress echocardiography, there was no recurrence of heart failure.

Together, these observational studies provide insight into the prognosis of women with peripartum cardiomyopathy who have a subsequent pregnancy. A substantial proportion of these women will experience recurrent heart failure, and the prognosis is far worse among women who did not recover left ventricular function following the initial insult. Cardiovascular complications were less frequent among those women who underwent therapeutic abortion. Women with prior peripartum cardiomyopathy should be advised of the risks associated with recurrent pregnancy. Women with residual left ventricular dysfunction should be strongly discouraged from becoming pregnant. For those women who recover left ventricular function, a trial off of ACE inhibitors and angiotensin receptor blockers should be considered before becoming pregnant. During pregnancy, serial evaluation for heart failure with NT-BNP and echocardiography is warranted.

Summary

Peripartum cardiomyopathy is a deadly disease. Basic science and clinical studies have enhanced our understanding of the temporal course of the disease and the effect of conventional therapies including pharmacotherapies, devices, and orthotopic heart transplantation. Recognition of the disease and early implementation of therapies have positively impacted patient morbidity and mortality. Education and involvement of advanced heart failure subspecialists have helped guide therapies and patient decisions. Emerging therapies hold tremendous promise but warrant testing using a prospective, double-blinded study.

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Advanced Therapies for Heart Failure

Advanced Therapies: Cardiac Resynchronization Therapy for Heart Failure

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_21

Abbreviations

6 MW - 6-minute walk
ACCF - American College of Cardiology Foundation
AF - Atrial fibrillation
AHA - American Heart Association
AV - Atrioventricular
CRT - Cardiac resynchronization therapy
CRT-D - Cardiac resynchronization therapy-defibrillator
CRT-P - Cardiac resynchronization therapy-pacemaker
CS - Coronary sinus
ESC - European Society of Cardiology
HF - Heart failure
HFSA - Heart Failure Society of America
HQ - High quality (evidence)
HR - Hazard ratio
HRS - Heart Rhythm Society
ICD - Implantable cardioverter defibrillator
IVCD - Intraventricular conduction delay
LA - Left atrium, left atrial
LBBB - Left bundle branch block
LoE - Level of evidence
LQ - Low quality (evidence)
LV - Left ventricle, left ventricular
LVEF - Left ventricular ejection fraction
LVESVI - Left ventricular end-systolic volume index
m - meters
MRI - Magnetic resonance imaging
ms - Milliseconds
NYHA - New York Heart Association
OPT - Optimal pharmacologic heart failure therapy
Q-LV interval - Time from QRS onset on surface ECG to local activation on left ventricular (or coronary sinus) lead
QOL - Quality of life
QRSd - QRS duration
RA - Right atrium, right atrial
RBBB - Right bundle branch block
RV - Right ventricle, right ventricular
SoR - Strength of recommendation
VO_2 - Oxygen consumption
VT - Ventricular tachycardia

Cardiac resynchronization therapy (CRT) refers to the application of multisite ventricular pacing with the goal of normalizing left and right ventricular timing (i.e., resynchronizing) that has been disturbed by heart disease. Current CRT methods are imperfect, but they do represent a major advance in managing systolic heart failure (HF). As an "advanced" therapy, CRT offers the advantages of both being widely available (as opposed to, e.g., ventricular assist devices or heart transplantation) and having abundant data supporting its clinical utility (as opposed to, e.g., the current state of stem cell therapy). Further, to the extent that CRT improves inotropy, it is unique in that, unlike pharmacologic inotropic agents such as dobutamine [1] or milrinone [2], it does not increase—and may decrease—mortality.

Several early pacing studies showed that the choice of ventricular pacing site impacts hemodynamic performance, although the optimal pacing site was not consistent across studies [3]. In 1970, Tyers demonstrated in dogs that multisite ventricular pacing, particularly combining right ventricular (RV) apex, left ventricular (LV) apex, and RV outflow tract, improved cardiac output compared to single-site ventricular pacing. It was postulated that cardiac function was improved by decreasing the time for complete ventricular activation compared to single-site ventricular pacing [4]. Gibson and colleagues [5] used the rate of ball movement of a Starr-Edwards valve in patients immediately after aortic valve replacement to show that, in humans, biventricular pacing consistently increased LV contractile force compared to either LV or RV pacing alone. Subsequent studies examined the acute hemodynamic effects of biventricular pacing in greater detail [3, 6].

In the end, realization of the clinical value of attempting to "resynchronize" contraction of the right and left ventricles in an HF patient with left bundle branch block (LBBB) is credited to Cazeau and colleagues. In a landmark case study, these authors used a coronary sinus (CS) lead, in addition to endocardial right atrial (RA) and RV leads, to pace the left atrium (LA), and an epicardial lead to pace the LV [7].

Ventricular Activation and Systolic Function

Normal activation and contraction of the LV depends on rapid conduction through the Purkinje system to produce near-simultaneous activation of the LV endocardium. This is reflected in an electrocardiogram (ECG) as a normal duration and morphology of the QRS complex. However, in disease, a complex interaction occurs between cardiomyopathic processes and electrical activation. Infarction, inflammation, or hypertrophy may produce mechanical dyssynchrony and may involve the Purkinje system to produce electrical dyssynchrony. Alternatively, or in addition, electrical dyssynchrony may result from a primary disruption in the electrical activation of the LV. Examples include a left bundle branch block (LBBB) or iatrogenic cause due to single-site right ventricular pacing, which produce delayed recruitment of contracting myocardium.

Dyssynchronous contraction may have immediate adverse hemodynamic effects in a ventricle with preexisting disease that might otherwise be tolerated in a normal ventricle. Sometimes, however, electrical dyssynchrony itself may induce adverse structural remodeling of the ventricle, producing systolic dysfunction even in a previously normal ventricle. For instance, among patients with normal baseline QRS duration who received a permanent pacemaker for sinus node dysfunction, the percentage time of ventricular pacing strongly predicted HF hospitalization [8]. Similarly, among patients with atrioventricular (AV) junction ablation and pacemaker implantation for atrial fibrillation (AF), up to 50 % developed LV dyssynchrony [9]. Moreover, even naturally

occurring LBBB itself may induce dilated cardiomyopathy that may be reversed with "reversal" of LBBB using CRT [10].

Under current guidelines, CRT may be appropriate for 5–10 % of patients with HF [11]. Nonetheless, in spite of the potential benefit of CRT, 20–40 % of patients are nonresponders, depending on the criteria used to define response (e.g., a 10 % increase of LV ejection fraction) [12]. Efforts to improve the CRT response rate include refining patient selection, developing new techniques for lead delivery, minimizing likelihood of phrenic stimulation, assuring that biventricular pacing is present >95 % of the time, and optimizing pacemaker programming (i.e., AV interval, interventricular interval) after implant.

CRT is typically achieved by using at least two leads targeted to activate and recruit left ventricular myocardium (usually the interventricular septum from the RV and the epicardial surface of the posterior or lateral base of the LV via the coronary veins) essentially simultaneously (Fig. 21.1). Ideally, the AV delay is programmed short enough to maximize the percentage of beats with full biventricular pacing (preferably 95–100 %), while keeping the AV delay long enough that diastolic filling is not impaired.

This chapter focuses primarily on the hemodynamic aspects of CRT in HF. Less attention is given to the electrophysiological aspects of CRT, e.g., whether patients should receive CRT as part of a pacemaker-only system (CRT-P) or a defibrillation system (CRT-D) in which an LV pacing lead is added to an implantable cardioverter defibrillator (ICD).

Clinical Outcomes with CRT

Functional Endpoints

In early randomized trials of New York Heart Association (NYHA) Class III–IV patients (Multisite Stimulation in Cardiomyopathies, MUSTIC [13]; Multicenter InSync Randomized Clinical Evaluation, MIRACLE [14]; MIRACLE ICD [15]; Contak CD [16]); and NYHA Class II patients (MIRACLE ICD II [17]), CRT improved one or more measures of clinical function such as 6-minute walk (6 MW) distance, peak oxygen consumption (VO_2), quality of life (QOL) based on standardized questionnaires, and NYHA functional class.

In recent years, greater focus has been given to additional measures of "benefit," especially those indicating a diminished cost of care. Thus, reduction in hospitalization is a measure of clinical response and reflects the economic benefit of therapy. Although a few early trials (MUSTIC [13], MIRACLE [14]) showed a decrease in hospitalization with CRT, others did not (MIRACLE ICD [15], Contak CD [16]). More recently, larger trials have employed a composite primary endpoint, using all-cause mortality plus a measure of HF or other cardiovascular morbidity (Table 21.1).

In the Cardiac Resynchronization-Heart Failure (CARE-HF) trial [21], 813 patients (94 % NYHA Class III, 6 % NYHA Class IV) were followed for a mean of 29.4 months. Patients were randomized to standard pharmacologic therapy alone for treatment of HF or with drug therapy plus a CRT pacemaker (CRT-P). The addition of CRT therapy significantly decreased the primary endpoint of death from any cause or an "unplanned hospitalization for a major cardiovascular event" (39 % vs. 55 %,

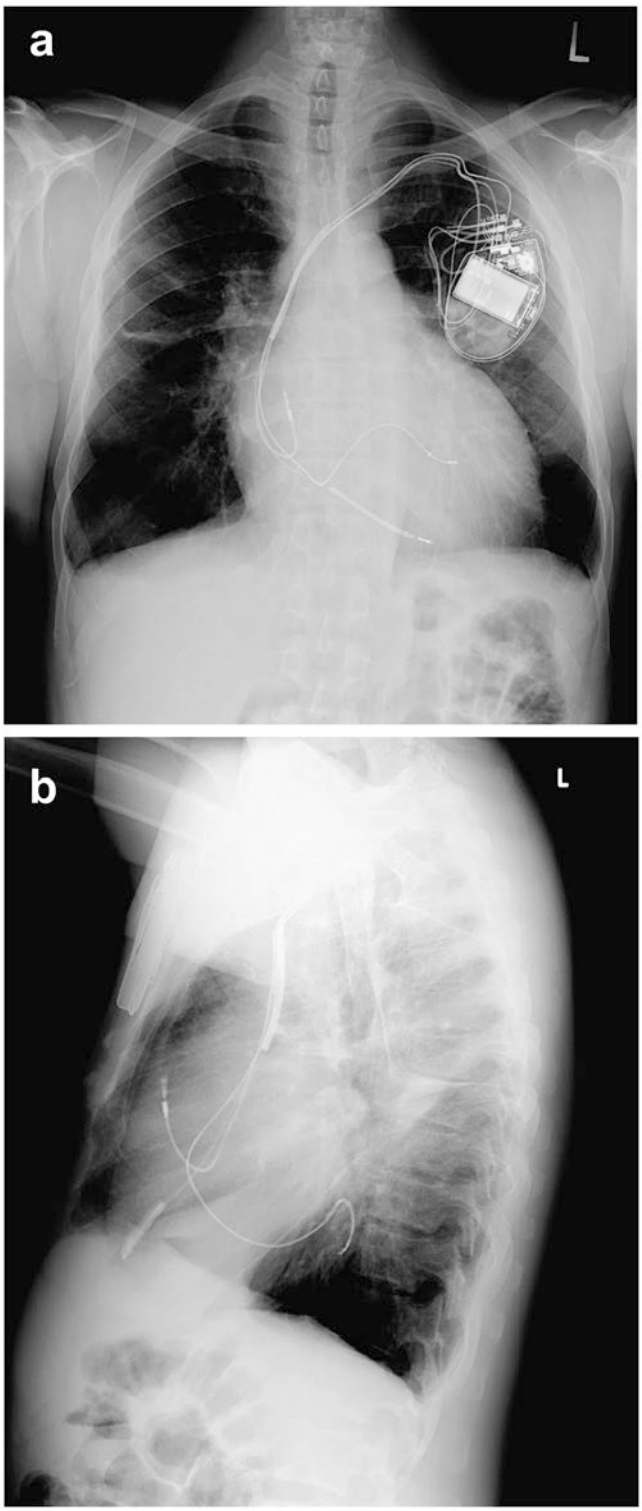

Fig. 21.1 (**a**) Posterior-anterior and (**b**) lateral chest radiographs of an implantable defibrillator system with cardiac resynchronization therapy (CRT-D). The right ventricular lead has two defibrillation coils, one in the right ventricle and one in the superior vena cava. The right atrial lead has a J-shaped curve. The lateral view shows that the coronary sinus lead is in the posterior aspect of the left ventricle, while the right ventricular lead is anterior to the left ventricle

Table 21.1 Named clinical trials cited (includes secondary analyses)

Acronym or short name	Trial name	Reference(s)
Adaptive CRT	Adaptive Cardiac Resynchronization Therapy	[18]
APAF	Ablate and Pace in Atrial Fibrillation	[19]
BLOCK-HF	Biventricular Versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block	[20]
CARE-HF	Cardiac Resynchronization-Heart Failure	[21–23]
CLEAR	Clinical Evaluation on Advanced Resynchronization	[24]
COMPANION	Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure	[25]
Contak CD	Same (name of device used in trial)	[16]
DAVID	Dual Chamber and VVI Implantable Defibrillator Trial	[26]
EchoCRT	Echocardiography Guided Cardiac Resynchronization Therapy	[27]
FIRST	Flolan International Randomized Survival Trial	[1]
InSync III	(Name of device used in trial)	[28]
LESSER-EARTH	Evaluation of Resynchronization Therapy for Heart Failure	[29]
MADIT II	Multicenter Automatic Defibrillator Implantation Trial II	[30]
MADIT-CRT	Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy	[31–37]
MIRACLE	Multicenter InSync Randomized Clinical Evaluation	[14]
MIRACLE ICD (AKA InSync ICD)	Multicenter InSync ICD Randomized Clinical Evaluation	[15]
MIRACLE ICD II (AKA InSync ICD II)	Multicenter InSync ICD Randomized Clinical Evaluation II	[17]
MOST	Mode Selection Trial	[8] (secondary analysis)
MUSTIC	Multisite Simulation in Cardiomyopathies	[13]
MUSTIC-AF	Multisite Simulation in Cardiomyopathies-Atrial Fibrillation	[38]
PATH-CHF	Pacing Therapies in Congestive Heart Failure	[39]
PATH-CHF II	Pacing Therapy for Chronic Heart Failure II	[40]
PAVE	Post AV Nodal Ablation Evaluation	[41]
PROMISE	Prospective Randomized Milrinone Survival Evaluation	[2]
RAFT	Resynchronization-Defibrillation for Ambulatory Heart Failure Trial	[42]
RAFT-AF	Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (AF subgroup)	[43]
RETHINQ	Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS	[44]
REVERSE	Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction	[45–48]
RHYTHM II	Resynchronization for HemodYnamic Treatment or Heart Failure Management II	[49]
RHYTHM II ICD	Resynchronization for HemodYnamic Treatment or Heart Failure Management II Implantable Cardioverter Defibrillator	[50]
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial	[51]
SMART-AV	SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy	[52, 53]
STARTER	Speckle Tracking Assisted Resynchronization Therapy for Electrode Region	[54]
TARGET	Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy	[55]
TRIP-HF	Triple Resynchronization in Paced Heart Failure Patients	[56]
Ventak CHF	(Name of device used in trial)	[57]

HR 0.63, 95 % CI 0.51–0.77, $p<0.001$). Subgroup analysis showed that CRT reduced unplanned hospitalization for a major cardiovascular event ($p<0.001$) and unplanned hospitalization for worsening HF ($p<0.001$).

The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial [25] assigned 1520 patients in a 1:2:2 randomization pattern to optimal pharmacological HF therapy (OPT) alone, OPT plus CRT-P, or OPT plus a CRT defibrillator (CRT-D). Inclusion criteria included left ventricular ejection fraction (LVEF) ≤ 35 %, NYHA Class III or IV, and a QRS duration (QRSd) ≥120 ms. The main observation of COMPANION was that compared to OPT alone, CRT-P decreased the risk of the primary composite endpoint of time to death or hospitalization for any cause (HR 0.81, $p=0.014$), as did CRT-D (HR 0.80, $p=0.01$).

The findings in the studies noted above were subsequently extended to patients with less severe HF. The Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) trial [31] followed 1820 patients (85 % NYHA Class II, 15 % NYHA Class I) for a mean of 2.4 years. Patients were randomized to a conventional ICD or a CRT-D device. CRT significantly decreased the combined endpoint of death from any cause or nonfatal HF event (17.2 % vs. 25.3 %, HR 0.66, 95 % CI 0.52–0.84, $p=0.001$). The superiority of CRT was driven by a 41 % reduction in the risk of HF events ($p<0.001$).

The Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) [42] followed 1798 patients (80 % NYHA Class II, 20 % NYHA Class III) for a mean of 40 months. Patients were randomized to implantation of either a CRT-D or an ICD without CRT. CRT decreased the primary combined outcome of death from any cause or hospitalization for HF (33.2 % vs. 40.3 %, HR 0.75, 95 % CI 0.64–0.87, $p<0.001$) and a secondary endpoint of hospitalization for HF ($p<0.001$). In the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial [45], 610 patients (82 % NYHA Class II, 18 % NYHA Class I) were followed for 12 months. Patients received either a CRT-P or CRT-D and were randomized to having CRT turned on or off for a mean follow-up period of 40 ± 20 months. The primary endpoint was a composite HF score that judged patients to be improved, unchanged, or worsened. In this scheme, a statistically nonsignificantly higher percentage of patients worsened with CRT ($p=0.1$). On the other hand, the time to first hospitalization for worsening HF was a prospective secondary endpoint and was significantly delayed by CRT (HR 0.47, $p=0.03$).

Some trials have demonstrated CRT to be associated with improvement in LV systolic function and favorable electrical remodeling. The MIRACLE [14], Contak CD [16], MIRACLE ICD II [17], and MADIT-CRT [31] trials showed statistically significant improvement in LVEF with CRT. The REVERSE trial [45] was prospectively powered to use the left ventricular end-systolic volume index (LVESVI) as a secondary endpoint that assessed LV remodeling. Compared with controls, CRT was associated with significantly greater reduction in LVESVI (−18.4 ± 29.5 ml/m^2 vs. −1.3 ± 23.4 ml/m^2, $p<0.0001$) and significantly greater increase in LVEF at 12 months.

Effects on Mortality

CRT and systems for implantable defibrillation have an independent beneficial impact on mortality in appropriately selected patients. Trials examining the effect of CRT on mortality may compare medical therapy with CRT-P or CRT-D with ICD. Some trials have compared medical therapy with CRT-P or CRT-D. The vast majority of trials examined mortality as part of a composite endpoint (typically combined with hospitalization, HF exacerbation, or hospitalization for HF) or as a secondary endpoint.

As mentioned previously, the COMPANION trial [25] examined patients (LVEF ≤ 35 %, NYHA Class III or IV, QRS duration ≥120 ms) randomized to OPT alone, OPT plus CRT-P, or OPT plus CRT-D. Death from any cause was a secondary endpoint with a mean follow-up duration of about 15 months. Compared with medical therapy (i.e., OPT), CRT-P showed a trend toward lower total mortality of 24 % ($p=0.059$), while CRT-D showed a significant, 36 % reduction in total mortality ($p=0.003$). The latter observation was consistent with contemporary trials that were showing a benefit to implantation of an ICD as primary prevention in patients with reduced LVEF and HF [30, 51].

The CARE-HF trial [21] was the first to show a mortality benefit that could be solely attributed to CRT. As a principal secondary endpoint, the study demonstrated a significantly lower rate of death from any cause in the medical therapy plus CRT-P group compared to medical therapy alone (20 % vs. 30 %, $p<0.002$). All-cause mortality was used as the primary endpoint in an extended follow-up assessment (mean 37.4 months) of patients in the CARE-HF trial and showed that CRT significantly decreased mortality compared to medical therapy (HR 0.60, 95 % CI 0.47–0.77, $p<0.0001$) [22].

The RAFT trial [42] examined whether adding CRT to ICD provides an additional benefit, given that the mortality benefit of primary prevention ICD in patients with systolic HF was already well established. Patients were randomized to receive ICD or CRT-D. Adding CRT reduced the death rate from any cause by 25 % (HR 0.75, 95 % CI 0.62–0.91, $p=0.003$).

Several smaller studies, and at least one large study (MADIT-CRT [31]), have not shown a significant decrease in total mortality. A recent meta-analysis of 25 trials (9082 patients), of which the COMPANION, CARE-HF, RAFT, and MADIT-CRT trials accounted for 59 % of the total population, concluded that there was a reduction in all-cause mortality with CRT for patients with Class II–IV congestive HF [58].

Patient Selection for CRT

Appropriate patient selection maximizes the likelihood of a favorable response to CRT therapy. Initial studies showed benefit among patients with systolic dysfunction and NYHA Class III and IV HF symptoms [13–15, 21, 25]. Subsequent studies expanded the role of CRT to NYHA Class II patients [17, 31, 45]. These studies have included NYHA Class I patients, but the number of patients has been small so that data supporting broad use of CRT in these patients is less

robust. At the same time, accumulating evidence has allowed refinement of indications for CRT so that the highest level of recommendations for CRT is reserved for patient subgroups that are gradually narrowing. In particular, patients in sinus rhythm with the longest QRS duration (>150 ms) and LBBB with nonischemic cardiomyopathy [32] have the highest likelihood of favorable CRT response. Individual patients in atrial fibrillation appear less likely to respond to CRT.

QRS Duration

Most clinical trials of CRT used QRS duration ≥120 ms as an inclusion criterion, and initial guidelines used this measure in recommendations for patient selection for CRT. Since the degree of QRS prolongation should, to a large extent, reflect the severity of electrical dyssynchrony, it seems reasonable to expect that patients with the longest QRS duration would have the greatest potential for clinical benefit from CRT. Several clinical trials included subgroup analyses based on QRS duration. Many showed that the benefits of CRT were limited to those patients with QRS duration longer than approximately 150 ms. Two published meta-analyses using the same five studies (COMPANION, CARE-HF, REVERSE, MADIT-CRT, and RAFT) concluded that the benefit of CRT was demonstrated in patients with QRS duration ≥150 ms, but not in patients with QRS duration <150 ms [59, 60].

Although the COMPANION trial showed that CRT decreased the risk of the combined endpoint of death from any cause or first hospitalization for any cause in patients with QRS duration >120 ms (LVEF ≤ 35 %, NYHA Class III–IV), subgroup analysis showed the benefit was seen only in patients with the longest QRS duration and not in patients with QRS duration of 120–147 ms [25]. The REVERSE trial showed that CRT produced overall favorable structural remodeling at 1 year among patients with QRS duration ≥120 ms (LVEF ≤ 40 %, NYHA Class I–II). Subgroup analysis, however, showed no benefit in LVESVI for QRS duration <140 ms, but significant benefit for QRS duration of 140–160 ms, and greater benefit for QRS duration >160 ms [46].

In the MADIT-CRT trial, CRT significantly decreased the primary endpoint of death from any cause or a nonfatal heart failure event in patients with QRS duration ≥130 ms (LVEF ≤ 30 %, NYHA Class I or II). In a prespecified subgroup analysis, however, the benefit was seen in patients with QRS duration ≥150 ms (about 65 % of the enrolled patients), but not in patients with QRS duration < 150 ms [31]. In the RAFT trial, CRT significantly decreased the primary outcome of death from any cause or hospitalization for HF in patients with QRS duration ≥120 ms (LVEF ≤ 30 %, NYHA Class II or III), but a prespecified subgroup analysis showed the benefit to be limited to patients with QRS duration ≥150 ms [42].

Other trials have shown benefit among patients with QRS duration of 120–150 ms. In the extended follow-up of patients in the CARE-HF trial, a prespecified subgroup analysis showed that CRT significantly decreased the primary endpoint of all-cause mortality whether the QRS duration was 120–159 ms or ≥160 ms [22]. In the MIRACLE trial, QRS duration was treated as a continuous variable and did not influence the significant improvements in the primary endpoints: 6 MW distance, QOL score, and NYHA functional class by CRT [14]. In the REVERSE trial [47], the favorable and significant effect of CRT on LVESVI showed a fairly linear relationship with baseline QRS duration that began at about 120 ms. In the same study, clinical response measured with a "clinical composite score" (including mortality, hospitalization for HF, whether the patient crossed over or discontinued double-blind treatment due to worsening HF, change in NYHA class, and patient global assessment) showed a similar relationship.

In view of these analyses, the European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Heart Rhythm Society (HRS), and the Heart Failure Society of American (HFSA) revised their guidelines for CRT to limit a Class I or "recommended" indication for those patients with QRS duration >150 ms [11, 61, 62]. Indications remain for QRS duration of 120–150 ms, but at a lower level of recommendation (Class IIa or "may consider") and/or a lower level of evidence base. QRS duration is, of course, a continuous variable and may be viewed as an indicator of the likelihood and/or magnitude of clinical response to CRT. Guideline revisions reflect clinical findings and the level of evidence supporting these findings. Of concern to caregivers, however, is that these interpretations may be used by third-party payers to limit coverage for procedures and, most importantly, may limit patients' accessibility to therapies. A thoughtful, invited debate has been published on the application of QRS duration data to clinical practice [63, 64].

Some single-center studies have used various imaging techniques to identify mechanical dyssynchrony in the face of QRS duration < 120 ms. In spite of this, at least three multicenter studies do not support the use of CRT in such patients. The Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (RETHINQ) study examined the effect of CRT in 172 patients with LVEF ≤ 35 %, NYHA Class III HF, QRS duration ≤130 ms, and evidence on echocardiography of mechanical dyssynchrony. CRT did not improve peak VO_2 (the primary endpoint) or quality of life [44]. The Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT) study examined patients with LVEF ≤ 35 %, NYHA Class III or IV, and echocardiographic evidence of dyssynchrony. All patients received a CRT-D with CRT randomized "on" or "off." The study was stopped prematurely for futility after 809 patients had been enrolled. CRT did not reduce the composite endpoint of death or HF hospitalization and may have increased mortality [27].

The Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) trial examined patients with LVEF ≤ 35 %, QRS duration < 120 ms, and symptoms of HF as indicated by 6 MW distance <400 m due to HF symptoms. There was no prerequisite for LV dyssynchrony. The trial was stopped prematurely as CRT was associated with a significant decrease in the 6 MW distance, and there was a nonsignificant trend toward increased HF hospitalization [29]. It may

be that the electrical synchrony provided by the Purkinje system that produces a narrow QRS complex is undermined by biventricular pacing that does not employ the Purkinje fibers. Thus, CRT may actually lengthen QRS duration.

In the LESSER-EARTH trial, CRT increased QRS duration at 6 months by 41.5 ms [29]. Thus, CRT produces a degree of electrical dyssynchrony in those patients with QRS duration < 120 ms. In essence, current technology cannot duplicate the rapid, "synchronized" ventricular activation that the intact conduction system provides, but nevertheless may remain advantageous if the conduction system is sufficiently impaired.

QRS Morphology

Under normal conditions, the last part of the LV to be activated is the posterior base [65]. LBBB prolongs LV activation while isolated right bundle branch block (RBBB), i.e., without fascicular delay in the LV, lengthens QRS duration without delaying LV activation. As such, patients with LV systolic dysfunction might be predicted to be more likely to respond to CRT if they have an underlying LBBB rather than RBBB. Data from CRT studies are consistent with this expectation, an outcome that is helpful since LBBB is more common than RBBB among patients with LV systolic dysfunction [33].

Subgroup analysis of MADIT-CRT [34] and REVERSE [47] studies showed that the favorable response to CRT was limited to patients with baseline LBBB. It was not seen in patients with RBBB or nonspecific intraventricular conduction delay (IVCD). Subgroup analysis of RAFT [42] showed a weak interaction between treatment and QRS morphology. In fact, patients with LBBB appeared to derive greater benefit than patients with nonspecific IVCD.

A meta-analysis of 5356 patients in COMPANION, CARE-HF, MADIT-CRT, and RAFT showed a highly significant reduction in adverse clinical events (mortality from any cause or hospitalization either for HF or, in some studies, other causes) among patients with LBBB. No benefit was seen among all patients with non-LBBB conduction abnormalities or when subdivided to RBBB and nonspecific IVCD [66]. A study of patients with baseline RBBB pooled from the MIRACLE and Contak CD found no benefit from CRT in any subjective or objective measure at 3 or 6 months except for NYHA class. However, control patients also showed a significant improvement in NYHA class at 6 months, consistent with a placebo effect [67].

Atrial Fibrillation

CRT is contemplated for patients with AF in two major scenarios: (1) patients with HF and a hemodynamic indication for CRT who have concurrent AF and (2) AF patients with a rapid ventricular rate who are being considered for AV junction ablation and permanent pacing. Although AF is a common arrhythmia in HF patients [33], the vast majority of patients enrolled in CRT trials have been in sinus rhythm. The limited data addressing use of CRT in patients with HF and permanent AF have been largely disappointing.

The MUSTIC trial was an early, single-blind crossover trial examining the clinical efficacy of CRT using 6 MW distance as the primary endpoint [13]. Secondary endpoints were peak VO_2, QOL, hospitalizations, patients' preferred study period, and mortality. The original study examined patients in sinus rhythm.

Using the same protocol, MUSTIC subsequently recruited the first and, to date, only trial of CRT in HF patients specifically with AF [38]. Patients had NYHA Class II HF, persistent AF (defined as >3 months), and a slow ventricular rate that necessitated ventricular pacing. Fifty-nine patients began the trial but, due to a high drop-out rate, only 37 completed both crossover phases. In the intention-to-treat analysis, none of the clinical endpoints were met. Nevertheless, blind questioning at the end of the study showed 84.6 % of patients preferred the period during which they received CRT ($p < 0.001$). On-therapy analysis showed CRT to improve 6 MW distance ($p = 0.05$) and peak VO_2 uptake ($p = 0.04$).

The RAFT trial [43] included 229 patients with permanent AF randomized to ICD or CRT-D, the largest population of AF patients in whom CRT has been evaluated to date. It found no difference in the primary endpoint of a composite of death or HF hospitalization. Likewise, there was no difference in cardiovascular death or 6 MW distance. It did show a trend favoring CRT with respect to fewer HF hospitalizations and a greater improvement in the Minnesota Living with Heart Failure score. A recent meta-analysis of 23 observational studies of response to CRT in AF patients concluded that CRT benefits are attenuated in AF patients, with a lower response rate compared to patients in sinus rhythm (RR 1.32, 95 % CI 1.22–1.55, $p = 0.001$) [68].

AF may pose a number of hurdles that contribute to limited CRT response (Table 21.2). One of the key factors is the need to maintain a very high percentage of biventricular pacing, typically targeting 92 % or higher [69, 70]. Indeed, even though eligible patients in the RAFT trial were required to have bradycardia that necessitated pacing (resting heart rate ≤60 bpm and ≤90 bpm after a 6 MW test), two-thirds had <95 % and half had <90 % CRT pacing [43]. These numbers, in fact, probably overestimate the amount of effective biventricular pacing as some of the so-called paced beats will be fusion or pseudofusion beats.

Better results have been reported when CRT is combined with AV junction ablation for patients with AF. This strategy may ameliorate a component of tachycardia-mediated cardiomyopathy and maximizes biventricular pacing by eliminating conducted beats that produce fusion. The Post AV Nodal Ablation Evaluation (PAVE) study [41] enrolled patients with chronic AF undergoing AV node ablation for medically refractory rapid ventricular rates and randomized them to receive a single-chamber pacemaker with its lead in the RV apex ($n = 81$) or a CRT device consisting of pacing leads in the right ventricle and coronary sinus ($n = 103$). This was not a heart failure study, as the groups had an initial

Table 21.2 Potential barriers to CRT success in AF

Patient related
AF patient generally older, sicker, more comorbidities
Poor LV function due to long-standing AF may be less responsive than that caused by rapid ventricular rates
Electrophysiologic
Rapid VR and short RR intervals reduce % CRT
Actual % CRT may be < apparent % CRT due to fusion
Hemodynamic
Inability to provide AV optimization

CRT cardiac resynchronization therapy, *AF* atrial fibrillation, *LV* left ventricle, *VR* ventricular response, *RR* R wave to R wave

LVEF of 45 ± 15 % and 47 ± 16 %, respectively. CRT patients showed greater improvement in the primary endpoint of change in 6 MW distance over 6 months following implant ($p = 0.04$). There was no difference in the secondary endpoint of QOL assessment. The LVEF in the CRT group was significantly higher (by 5 % absolute) than the RV pacing group after 6 months ($p < 0.05$) due to an LVEF decrease in the RV pacing group that did not occur in the CRT group.

The Ablate and Pace in Atrial Fibrillation (APAF) trial [19] enrolled patients with permanent AF who either (1) underwent a previously planned AV junction ablation to control high ventricular rates or (2) had permanent AF, drug refractory HF, and depressed LV function and in whom a clinical decision had been made to perform AV junction ablation and implantation of a CRT device. All received a CRT device (CRT-P or CRT-D at the enrolling physicians' discretion) but were randomized to RV or CRT pacing. After a mean 20-month follow-up, the primary composite endpoint of HF death, HF hospitalization, or worsening HF was significantly lower in the CRT groups ($p = 0.005$).

Total mortality was similar in both groups. The patients were analyzed in two subgroups: 25 % met contemporary United States [71] and European [72] guidelines for CRT (LVEF ≤ 35 %, QRS width ≥120 ms, and NYHA Class ≥III) and 75 % did not meet these guidelines. The primary endpoint was significantly lower (i.e., improved outcome) in both subgroups when treated with CRT rather than RV pacing.

The favorable response to CRT seen in these "ablate-and-pace trials" [19, 41] vs. HF trials that included AF patients reflects several important factors. First, AV junction ablation maximizes the percentage of time with biventricular pacing (limited, with normal pacemaker function, only by the quantity of ventricular ectopy). Second, as noted previously, even when AF patients were selected for bradycardia, the time spent with biventricular pacing was limited [43]. Third, AF patients receiving AV junction ablation in addition to CRT therapy may benefit by alleviating any component of tachycardia-mediated LV dysfunction. Finally, ablate-and-pace trials compare the electrical remodeling effects of RV and CRT pacing that may produce structural remodeling. That is, electrical dyssynchrony caused by RV pacing (or LBBB, or high-burden ventricular ectopy) may cause mechanical dyssynchrony.

By their nature, ablate-and-pace trials assess the extent to which CRT may prevent such electrical dyssynchrony. On the other hand, HF patients enrolled in CRT trials who also have AF may primarily have mechanical dyssynchrony (e.g., from ischemic heart disease, hypertensive heart disease, myocarditis) with secondary electrical dyssynchrony. Such patients may have a hemodynamic improvement with CRT, but they may be less likely to have favorable mechanical remodeling.

AV Block and/or Frequent Ventricular Pacing

The potential detrimental effects of RV-only pacing have been described in pacemaker and ICD studies. Dual-chamber pacing modes are designed to maintain AV synchrony over a wide range of sinus rates so that, in the setting of prolonged AV conduction or AV block, the ventricle is paced at the sinus rate.

The Mode Selection Trial (MOST) showed that in patients with sinus node dysfunction, dual-chamber pacing, and normal LV function, RV pacing >40 % of the time was associated with a 2.6-fold increased risk of HF hospitalization compared to patients with less RV pacing [8]. The Dual Chamber and VVI Implantable Defibrillator (DAVID) trial showed that in ICD patients with LVEF < 40 % but without an indication for anti-bradycardia pacing, patients with RV pacing due to a dual-chamber ICD system are more likely to develop HF than patients with an ICD that minimizes RV pacing by only doing so when the ventricular rate is less than 40 beats per minute without attempting to maintain AV synchrony [26]. The Biventricular Versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK-HF) trial showed that in patients with LVEF < 50 % who require ventricular pacing due to AV block, CRT was associated with a significantly lower risk of death or HF than RV-only pacing [20].

Indications

Table 21.3 summarizes the most recent guidelines for HF patients in sinus rhythm from cardiac societies in the Western world, ACCF/AHA/HRS [73], ESC [11], HFSA [61], and Canadian Cardiovascular Society (CCS) [74]. In general, the various guidelines are congruent.

Based on the most recent data, most societies have limited their highest level of recommendation for CRT to those patients with QRS duration ≥150 ms with an LBBB in sinus rhythm. Some evidence indicates that patients with nonischemic, rather than ischemic, cardiomyopathy have better response to CRT [32], but such distinction is not included in current guidelines. The CCS has adopted a QRS duration ≥130 ms for its recommendations, and the HFSA reserves its highest recommendations for "non-RBBB" morphology.

Table 21.3 Indications for CRT: part I, patients in *sinus rhythm*

	NYHA class	ACCF/AHA/ HRS 2012 (SoR/LoE)	ESC 2013 (SoR/LoE)	HFSA 2011[a] (SoR/LoE)	CCS 2013 (SoR/LoE)
EF ≤ 35 %				"non-RBBB"	
LBBB	II	I, B	I, A	I, A	
QRS ≥ 150 ms[c]	III	I, A	I, A	I, A	
QRS > 150 ms[d]	Ambulatory IV	I, A	I, A	IIb, B[b]	
EF ≤ 35 %	II	IIa, B	I, B	IIb, B	
LBBB	III	IIa, B	I, B	IIb, B	
QRS 120–149 ms[c]	Ambulatory IV	IIa, B	I, B	IIb, B	
QRS 120–150 ms[d]					
EF ≤ 35 %	II	IIb, B	IIa, B		Weak, LQ
Non-LBBB	III	IIa, A	IIa, B		Weak, LQ
QRS ≥ 150 ms[c]	Ambulatory IV	IIa, A	IIa, B		Weak, LQ
QRS > 150 ms[d]					
EF ≤ 35 %	II	**III**, B	IIb, B	IIb, B	
Non-LBBB	III	IIb, B	IIb, B	IIb, B	
QRS 120–149 ms[c]	Ambulatory IV	IIb, B	IIb, B	IIb, B	
QRS 120–150 ms[d]					
EF ≤ 35 %					Strong, HQ
LBBB					Strong, HQ
QRS ≥ 130 ms					Strong, HQ
EF ≤ 30 %	**I**	IIb, C			
LBBB					
QRS > 150					
Ischemic etiology					

Indications as determined by the above cardiovascular societies are listed with their "strength of recommendation" (SoR) and the "level of evidence" (LoE). For the strength of recommendation, the shorthand adopted by ACCF/AHA/HRS and ESC was applied to HFSA recommendations, as their systems were virtually identical:
I: "should be done," "beneficial," HFSA category "is recommended"
IIa: "reasonable," HFSA category "should be considered"
IIb: "may be considered," HFSA category "may be considered"
III: "no benefit," "harm," HFSA "is not recommended"
For level of evidence, ACCF/AHA/HRS, ESC, and HFSA have similar distinctions:
A: multiple populations evaluated
B: limited populations evaluated
C: very limited populations evaluated, expert opinion
CCS assigns strength of recommendation as "strong" or "weak (conditional)," and quality of evidence as "high" (HQ), "moderate," "low" (LQ), or "very low."
[a]HFSA Guidelines do not always list QRS morphology within its tables but indicate in text that "patients with LBBB appear to derive the most benefit from CRT" and that "patients with RBBB appear to derive minimal to no benefit from CRT"
[b]HFSA did not specify a requirement for sinus rhythm in this situation. Based on context, this may have been an unintended omission
[c]ACCF/AHA/HRS, HFSA
[d]ESC

Table 21.4 Indications for CRT:part 2

	NYHA class	ACCF/AHA/HRS 2012 (SoR/LoE)	ESC 2013 (SoR/LoE)	HFSA 2011[a] (SoR/LoE)	CCS 2013 (SoR/LoE)
Atrial fibrillation EF ≤ 35 % Frequent V pacing required and near-100 % bi-V pacing can be achieved pharmacologically or with AV junction ablation			IIa, B May add AV junction ablation to CRT to increase ventricular pacing	QRS ≥ 120 ms	
	II		–	IIb, B	
	III		IIa, B (QRS ≥ 120 ms)	IIb, B	
	Ambulatory IV		IIa, B (QRS ≥ 120 ms)	–	
	No distinction	IIa, B			Weak, LQ "otherwise suitable" for CRT
Chronic pacing EF ≤ 35 % Frequent (e.g., >40 %) pacing	III Ambulatory IV	IIa, C New device Upgrade non-CRT	I, B Upgrade non-CRT	IIb, C Reduced EF with frequent pacing	Weak, LQ ("chronic" RV pacing)
			IIa, B De novo CRT for HF, reduced EF, when high percentage of ventricular pacing is expected		
Other					
QRS < 120 ms			**III**, B		
QRS < 150, non-LBBB	I II	**III**, B **III**, B			
Poor survival		**III**, C			

Indications as determined by the above cardiovascular societies are listed with their "strength of recommendation" (SoR) and the "level of evidence" (LoE). For the strength of recommendation, the shorthand adopted by ACCF/AHA/HRS and ESC was applied to HFSA recommendations, as their systems were virtually identical:
I: "should be done," "beneficial," HFSA category "is recommended"
IIa: "reasonable," HFSA category "should be considered"
IIb: "may be considered," HFSA category "may be considered"
III: "no benefit," "harm," HFSA "is not recommended"
For level of evidence, ACCF/AHA/HRS, ESC, and HFSA have similar distinctions:
A: multiple populations evaluated
B: limited populations evaluated
C: very limited populations evaluated, expert opinion
CCS assigns strength of recommendation as "strong" or "weak (conditional)," and quality of evidence as "high" (HQ), "moderate," "low" (LQ), or "very low."
[a]HFSA Guidelines do not always list QRS morphology within its tables, but indicate in text that "patients with LBBB appear to derive the most benefit from CRT" and that "patients with RBBB appear to derive minimal to no benefit from CRT"

For patients with HF and atrial fibrillation, all societies support CRT at their second-highest level of recommendation (Table 21.4). ESC Guidelines include a Class IIa recommendation that AV junction ablation should be performed in AF patients with CRT but who cannot otherwise achieve near-100 % biventricular pacing [11]. All societies' guidelines support the use of CRT when HF patients require a high percentage of ventricular pacing, but the level of recommendation varies among the societies (Table 21.4).

Implantation

General Approach

The RV pacing (or defibrillation) lead is often placed first. Most patients receiving a CRT system will presumably have LBBB so that bumping the right bundle while probing for the coronary sinus may put the patient in complete heart block. If used, an RA pacing lead may be placed next, or it may be placed after the LV lead. The coronary sinus is cannulated with any of a number of soft-tipped sheathes. A balloon-tipped catheter may be used to occlude or nearly occlude the coronary sinus. Contrast dye is injected to define the coronary venous anatomy (Fig. 21.2). A suitable vein is selected and a pacing lead is advanced to its target. Angioplasty wires may be directed into the selected vein and the lead is advanced using over-the-wire technique.

A wide variety of lead designs have been used to overcome the difficulties of obtaining a stable lead position in the coronary sinus with satisfactory pacing characteristics (Fig. 21.3). Coronary sinus leads may have multiple electrodes to provide multiple potential pacing sites for long-term management. Likewise, modern CRT generators allow multiple pacing configurations because of potential difficulties in obtaining satisfactory pacing at implant and at future follow-up. These pacing configurations include between LV electrodes or between an LV electrode and a non-LV site such as an RV pacing electrode, a defibrillator coil, or the generator itself.

In the large clinical trials, implant success rates range from 89 to 97 % [14, 15, 17, 45]. Many factors may prevent successful coronary sinus lead placement (Table 21.5). In such cases, an epicardial LV lead may be placed surgically. Some surgeons may be able to place leads robotically to minimize the size of the incisions. Epicardial pacing leads have a higher failure rate than endocardial leads. In our institution, the surgeon places two epicardial leads so that if a lead fails, a "back-up" lead may be available without resorting to a repeat thoracotomy.

LV Lead Positioning

The posterior or lateral wall of the LV is typically targeted for lead placement while avoiding an apical position [11]. The posterolateral region is usually the last portion of the LV activated in the presence of a normal QRS [65]. Endocardial mapping has shown that the region of late activation in the presence of an LBBB is more heterogeneous, possibly reflecting different causes of LBBB. Latest activation was the posterolateral base in roughly half of patients studied, and the fraction increases to two-thirds if the mid-posterolateral wall is included [75].

Given that the RV lead is typically placed apically, a basal posterolateral LV lead position satisfies an intuitive sense that the leads should be implanted far apart in "opposite" positions of the LV. Some clinical data tends to support this notion. A calculated, composite distance between the RV and

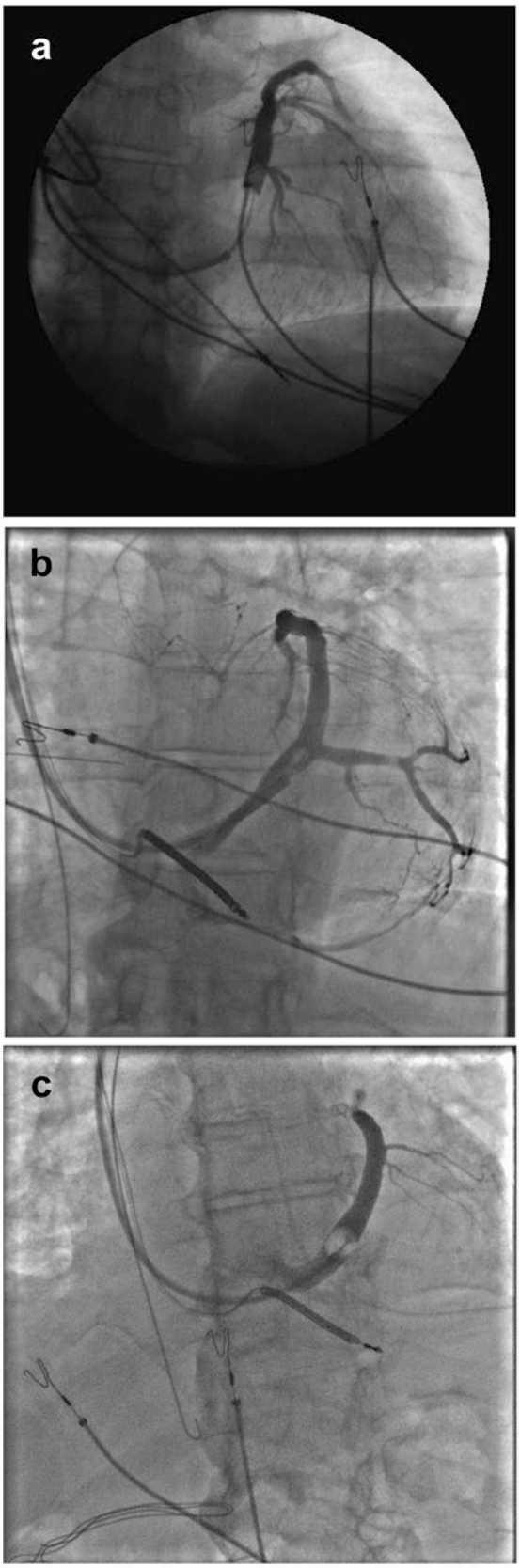

Fig. 21.2 (**a**–**c**) Coronary sinus venograms from three patients show substantial variation in the number, size, and location of cardiac veins. Lead placement positioning at an optimal target may be straightforward, moderate to extremely difficult, or, in some cases, not possible

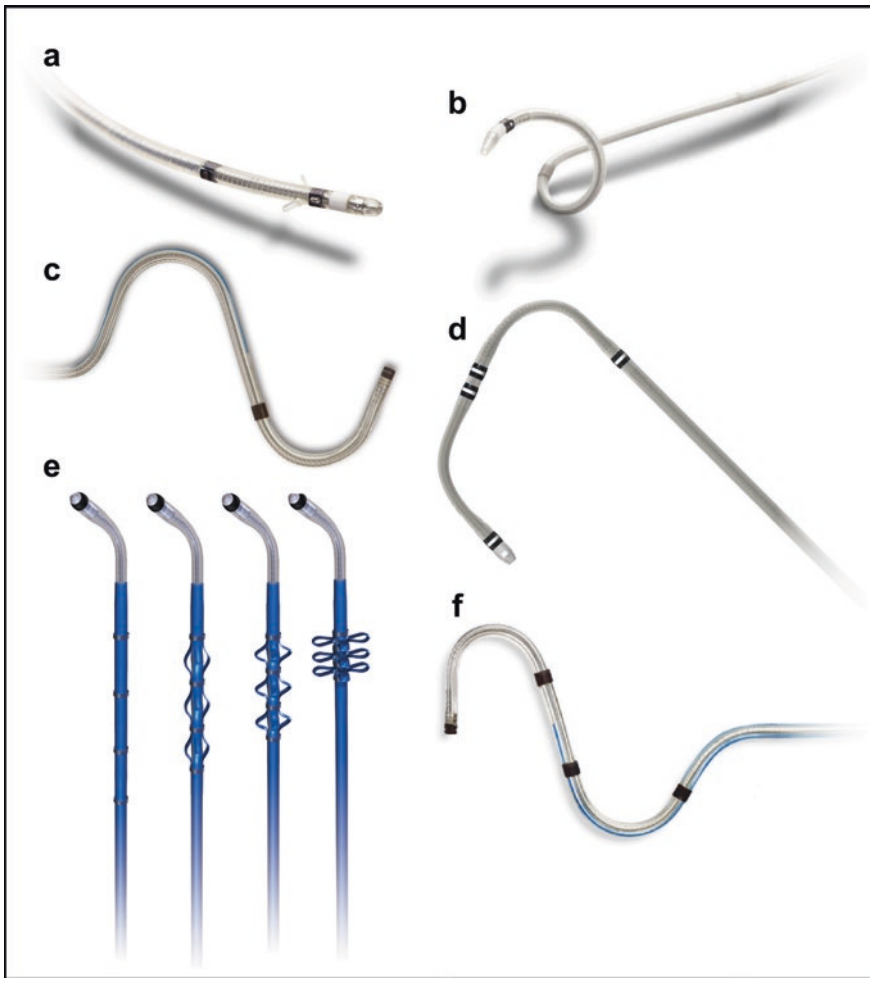

Fig. 21.3 The coronary sinus poses challenges for locating a satisfactory site for pacing and maintaining a pacing lead in a stable position. A variety of strategies in lead design have been employed to achieve these goals, and each manufacturer offers several design options; a few are shown here. (**a**) Soft tines may stabilize a lead in a relatively small-caliber vessel. (**b–d**, **f**) A variety of soft preformed lead shapes apply gentle pressure to the vessel walls and maintain a stable lead position in the majority of coronary veins. (**e**) A lead with soft, deployable fins serves as an "active fixation" mechanism for use in large-caliber veins that would not otherwise maintain a stable lead position. This mechanism may pose challenges if an infected CRT system requires explant. (**d**, **f**) Leads have recently been approved with multiple (in this case, four) electrodes for pacing at different sites along the lead that may be selected or changed after implant. Images are not to the same scale (*Sources*: (**a**) EasyTrak®2 left-heart lead; (**b**) Acuity® Spiral left-heart lead, reproduced with permission of Boston Scientific; (**c**) QuickFlex™ μ left ventricular lead with Optim™ Insulation; (**f**) Quartet™ left-heart lead, reproduced with permission of St. Jude Medical; (**d**) Attain Starfix® left-heart lead; (**e**) Attain® Performa left-heart lead, reproduced with permission of Medtronic, Inc.)

Table 21.5 Obstacles to successful placement of coronary sinus leads

• Inability to locate or cannulate coronary sinus
• Venous branches in targeted region lacking, too small, or too tortuous for lead placement
• Inability to capture targeted myocardium, e.g., infarcted myocardium
• Inability to achieve secure lead placement; venous branches too large
• Diaphragmatic, phrenic nerve, or chest wall capture

LV leads (derived from posterior-anterior and lateral chest X-rays) correlates with the magnitude of measured conduction delay to the LV lead and to the degree of favorable reverse LV remodeling by CRT [76].

An acute hemodynamic study showed better LV systolic performance when CRT included LV free wall rather than LV anterior wall pacing [40]. A retrospective review of 233 CRT implants at two medical centers showed more improvement in functional capacity and LVEF when the LV lead was placed in lateral and posterolateral branches of the coronary sinus, rather than anterior branches [77]. In the MADIT-CRT study, a basal or mid-ventricular position of the LV lead was associated with superior outcomes compared to an LV apical position [35]. The REVERSE study compared LV lead placement in lateral vs. nonlateral positions and apical vs. non-apical positions. More favorable LV remodeling and time to death and/or first hospitalization for HF was achieved when the LV lead was in a lateral, non-apical position [48]. On the other hand, the COMPANION trial showed no difference in clinical improvement or survival between anterior, lateral, and posterior positions of the LV lead [78].

As opposed to "empiric" anatomical position of the LV lead, some studies have attempted to "target" the optimal position for individual patients using various techniques to identify the region of latest activation, either electrically or mechanically. In contrast to previously mentioned studies in which imaging techniques fail to identify patients with normal QRS duration who may respond to CRT, identification of dyssynchrony in patients with prolonged QRS duration may aid in patient selection and/or in LV lead positioning.

During LV lead placement, the longest Q-LV interval—the time from the onset of the QRS complex on the surface ECG to the local electrical activation on the LV lead—may be used to identify late LV activation. Suggestive evidence may be found among 426 patients in a substudy of the SmartDelay

Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy (SMART-AV) trial. Q-LV intervals were measured at implant; longer intervals were associated with more reverse remodeling [52]. This relationship persisted when the Q-LV was corrected for QRS duration, an important observation since the study did not use Q-LV intervals to select the final pacing site. Long QRS durations identify responders to CRT, so that longer Q-LV intervals might identify patients more likely to respond favorably to CRT.

Alternatively, late mechanical activation may be identified with various imaging modalities including echocardiography (initially tissue Doppler imaging and, more recently, speckle tracking), nuclear imaging, and magnetic resonance imaging (MRI) [79]. For example, the Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy (TARGET) trial [55], a two-center study with 220 patients, and the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region (STARTER) trial [54], a single-center study with 187 patients, randomized patients to LV lead placement guided by speckle tracking strain imaging to identify the site of the latest mechanical LV activation vs. standard, unguided LV lead placement. In both studies, guided lead placement was associated with a significantly lower rate of the combined endpoint of all-cause mortality and HF hospitalization and more frequent incidence of reduction in left ventricular end-systolic volume.

Complications

Implanting a standard permanent pacemaker or implantable defibrillator carries risks of bleeding, infection, pneumothorax, perforation, pericardial effusion, tamponade, diaphragmatic (phrenic nerve) stimulation, and the need for a repeat operation (e.g., for lead dislodgement). The addition of a left ventricular lead increases the complexity of the implant procedure. The increased time needed for implantation and the additional hardware implanted increases the risk of infection.

Complication rates at implant and in follow-up are higher with CRT devices compared to non-CRT devices [42, 80, 81]. Accessing the coronary sinus carries a risk of perforation and increases the possibility of pericardial effusion and tamponade. The reported incidence of coronary sinus dissection ranges from 0.5 % to about 4 % [14, 15, 17, 45]. The risk of diaphragmatic or chest wall stimulation is higher than standard device implantation because the epicardial location of the LV lead can stimulate these structures either directly or through phrenic nerve capture.

The caliber of coronary veins is highly variable. The vast majority of leads intended for CS implantation have no means of fixation within the coronary venous system other than soft tines or preformed curves in the lead that provide counterpressure against the sides of the vessel. As a result, LV lead dislodgement is more common than RV or RA leads that have a means of positive fixation. Among trials that specifically report the need for LV lead revision, LV lead dislodgement ranged from about 4 to 7 % [14, 17, 31, 45].

Implant techniques and tools have improved over time. Clinical trials have documented the presence of a learning curve for CRT implantation. In three trials conducted by the same sponsor and reported in 2002, 2004, and 2005, the median time to CS cannulation, median time to first acceptable LV lead position, and median fluoroscopy time improved with experience [80]. Finally, because patients receiving a CRT device have reduced systolic function and may be NYHA Class III or "ambulatory" Class IV, their hemodynamic status may be tenuous, and they may be at increased risk for sedation and/or general anesthesia.

CRT Follow-Up: Optimization

Rather than discuss the standard follow-up of a cardiac implantable electrical device such as a CRT-D or CRT-P, the following discussion focuses on the approximately one-third of patients with CRT devices who do not show clinical improvement after implant. For purposes of discussion, it is assumed the patient has optimal pharmacologic therapy and is compliant with the regimen. It is also assumed that comorbidities have been addressed and that the CRT system is functioning properly in terms of pacing and sensing thresholds.

Post-implant optimization strategies have included (1) achieving near-100 % biventricular pacing, (2) optimizing LV lead positioning, (3) programming the AV delay to maximize atrial filling (AV optimization), and (4) trying to overcome LV dyssynchrony by altering the timing of RV and LV pacing, including the extreme case of LV-only pacing.

Fundamental to CRT success is maximizing the percentage of ventricular beats with full biventricular pacing. Clinical studies have demonstrated decreased benefit to CRT when biventricular pacing drops below 92 % or even 98 % [69, 70]. Increased biventricular pacing may be achieved by pharmacologically prolonging AV conduction, by AV junction ablation, or by shortening the programmed AV delay—but not so short that diastolic filling becomes impaired. Empirically programmed AV delays are typically 100–120 ms [11]. It is important to remember that the percentage of biventricular pacing reported by the implanted CRT-P or CRT-D includes ventricular beats with fusion and pseudofusion that do not provide effective ventricular resynchronization.

All possible efforts are presumed to have been taken to identify and use the optimal site for LV pacing at the time of initial implant. Nevertheless, and not infrequently, a coronary sinus lead will migrate to an anatomically suboptimal position or to a position in which the pacing threshold is inadequate. Almost none of the available coronary sinus leads have an active fixation mechanism that prevents lead movement. Not infrequently, a patient's coronary venous anatomy will not provide a usable vein in the presumed optimal LV location. In this situation, in our institution, a coronary sinus lead will be placed in the best possible location. If the patient does not have an adequate response to CRT, sur-

gical placement of an epicardial LV lead may be pursued. Within the past year of this writing, LV leads have become available with four individual electrodes along their length, enabling selection of different electrode pairs to pace at different locations along the coronary vein—instead of a single unipolar or bipolar pacing site at the end of the lead.

Refinements in the programming of pacemaker timing have been made in an attempt to improve acute hemodynamics and, ultimately, long-term clinical response. Two basic strategies are available: (1) appropriate selection of AV delays may improve ventricular filling (AV optimization) and (2) some implanted devices allow nonsimultaneous pacing of the RV and LV to further attempt to overcome dyssynchrony of ventricular contraction (VV optimization).

Several modalities have been used to achieve AV and VV optimization. Echo Doppler studies can assess LV filling and/or ventricular dyssynchrony [28, 82]. Algorithms built into pacemakers may use intrinsic AV intervals and QRS duration to attempt to predict the optimal programmed AV delay [53]. Algorithms built into pacemakers may use the time delay between intrinsic RV and LV activation to predict the optimal timing for RV vs. LV pacing [83]. Some pacemakers have built-in hemodynamic sensors to direct AV and VV optimization [24, 84].

While AV and/or VV optimization appeared promising in early single-center and observational studies, most multicenter studies have shown either modest [28, 49, 82] or no additional benefit [50, 53, 83] to optimization. Likewise, two recent meta-analyses have shown no benefit [85] or limited benefit [86] to optimization. The 2013 ESC Guidelines on CRT concluded that "current evidence does not strongly support the performance of AV and VV optimization routinely" in all CRT patients [11]. Nevertheless, it may be reasonable to attempt in nonresponders [87]. A recent, nonrandomized, retrospective analysis of one study suggests that frequent longitudinal optimization may be beneficial to CRT patients [24].

Other Issues

Is CRT Antiarrhythmic or Proarrhythmic?

Several studies have addressed whether CRT, with its potential to produce favorable LV remodeling, might reduce ventricular arrhythmias. Likewise, the hemodynamic benefits that accrue from positive LV remodeling may extend to reducing left atrial pressures and reduce atrial arrhythmias. Clinical studies have produced conflicting findings in both areas.

In an early, blinded crossover trial, CRT was associated with reduced ICD therapy compared with no CRT [57]. Device upgrades, i.e., adding an LV lead to a standard defibrillator, reduced ventricular arrhythmias in some studies [88, 89], but not others [90]. There was no difference in ventricular arrhythmias in the Contak CD study (a short, double-blind crossover of implanted defibrillators with CRT-on vs. CRT-off) [16] or in the 6-month MIRACLE ICD trial [15]. With longer follow-up (2 years) in the MADIT-CRT trial, patients with the most favorable remodeling, as judged by echocardiographic response, had a significant reduction in ventricular arrhythmias compared to low responders or those without CRT [36].

An intriguing suggestion has been made that the nonphysiological ventricular activation sequence caused by epicardial pacing of the LV may increase the transmural heterogeneity of repolarization that may prolong the QT interval and predispose to torsade de pointes. Epicardial pacing increased dispersion of repolarization in an animal model and increased QT interval in patients [91]. A few case reports of torsade de pointes have appeared [91, 92]. The clinical impact may be small. One study on the combined data in the Contak CD and MIRACLE ICD studies showed that CRT did not reduce monomorphic ventricular tachycardia (VT) and produced only a nonsignificant increase in polymorphic VT that was associated with a disproportionate number of episodes in a few patients [93].

Less data are published on CRT and atrial arrhythmias. Some show a decrease in atrial tachyarrhythmia, including AF [94, 95], while others show no decrease in AF burden with CRT [23, 96]. A secondary review of data from the MADIT-CRT trial showed no difference in the 3-year cumulative probability of atrial tachyarrhythmias (including AF) in patients with CRT-D compared to patients with ICD only. On the other hand, patients who had a significant reduction in left atrial volume (defined as ≥20 % reduction in left atrial volume 1 year after CRT) at 2.5 years after CRT had significantly less atrial tachyarrhythmias than low responders (<20 % reduction in left atrial volume) or patients with ICD only ($p = 0.03$) [37].

LV-Only Pacing

Among patients with intact AV conduction, several studies have examined the utility of LV-only pacing, rather than biventricular pacing. The lateral wall of the LV is paced, while the septal wall is activated by the native conduction system. Early studies of acute hemodynamics [6] and chronic pacing [97] showed similar benefits between biventricular CRT and single-site LV pacing.

One of the earliest multicenter clinical trials of CRT, Pacing Therapies in Congestive Heart Failure (PATH-CHF), was a single-blind crossover study of single-site ventricular pacing (36 LV and 4 RV, selected by the most effective acute hemodynamic response) and biventricular pacing with an intervening period of no pacing. Both methods showed similar improvements over no pacing, based on exercise capacity, NYHA functional class, and QOL indices [39].

Two recent meta-analyses collectively encompassing six studies (four in common) show LV-only pacing to be noninferior to biventricular pacing in terms of clinical status (6 MW distance, peak VO_2, NYHA class) [98] as well as

all-cause mortality and hospitalization [99]. Patients were in sinus rhythm in these studies, providing an opportunity to appropriately time the delivery of the LV pacing stimulus to coordinate with septal activation.

The vast majority of patients in these studies had baseline LBBB (required in three studies, about 90 % in two studies, and 100 % in the LV-only pacing group of the remaining study). Some recent studies suggest that LV-only pacing timed to fuse with right bundle conduction may have benefits over biventricular pacing in patients with normal AV intervals, but that biventricular pacing may be preferable in patients with prolonged AV conduction [18]. The utility of pacing systems with a ventricular lead only in the coronary sinus may be problematic due to a higher risk of dislodgement with coronary sinus leads and in patients in whom a defibrillation lead is indicated. Nevertheless, LV-only pacing may be an attractive option for children and young adults facing decades of pacing and multiple pacing systems [11].

Future Directions

Among patients meeting criteria for CRT implantation, 5–10 % of attempted CS lead placements are unsuccessful. Among those with successful CRT implantation, about one-third fail to have a significant beneficial clinical response.

Continuous refinements in implanting tools and techniques will continue to improve implant success rates. New, multipolar CS leads will provide greater flexibility in programming, particularly if capture thresholds in the selected configuration deteriorate during follow-up. Small studies have shown promise in pacing the LV from multiple, well-distributed LV sites, and similar studies are in progress [56]. LV endocardial pacing is of particular interest in that it could overcome the limitations imposed on epicardial pacing by the coronary venous anatomy and by maintaining endocardial-to-epicardial activation of the LV. The need for transseptal delivery and the thrombotic risk of such leads are technical challenges to overcome.

Simple, "leadless" pacemakers are in early use for single-chamber pacing. These are small units in which the entire pacemaker is delivered to the RV and secured to the endocardium. Wireless technology offers the possibility of delivering multiple devices to multiple chambers, with their individual operation coordinated to produce cardiac resynchronization.

Vagal nerve stimulation is an intriguing area of research in HF therapy. Although this does not involve CRT or even traditional cardiac pacing, it incorporates pacing technology. A stimulating electrode is implanted on the cervical vagus nerve and is attached to a stimulating unit. A standard intracardiac pacing lead is used to sense bradycardia and provides closed-loop feedback to limit vagal stimulation. Animal models [100, 101] and early clinical work [100] suggest that vagal nerve stimulation may improve cardiac function and clinical status.

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Ventricular Assist Devices for Advanced Heart Failure

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_22

Introduction

Despite monumental advances in medical therapy, systolic heart failure has a 5-year mortality rate as high as 50 % [1] and a mortality rate greater than 80 % if complicated by cardiogenic shock [2]. For patients with end-stage or advanced heart failure (stage D heart failure [3]), orthotopic heart transplantation became the only definitive therapy [4]. While orthotopic heart transplantation is associated with excellent survival, this therapy is limited by a lack of donor organs [5]. Therefore, intense interest has focused on alternative therapies, including mechanical circulatory support [i.e., ventricular assist devices (VADs)], which has achieved excellent results [6–9]. This chapter examines the dynamic and expanding use of ventricular assist devices for the treatment of advanced heart failure, including the rationale, patient selection, and complications associated with VADs.

Physiology of Ventricular Assist Devices

VADs were initially developed in the 1960s as a means to "assist" patients who could not be weaned from cardiopulmonary bypass following cardiac surgery [10]. They were not meant to be a ventricular replacement. Michael DeBakey, MD, implanted the first device in 1963 to treat cardiogenic shock postcardiotomy [11]. Since then, much interest has been generated to create the optimal assist device that can be durable, completely implantable for independence, and physiologically compatible with the recipient (Fig. 22.1).

All pumps generate flow against an opposing pressure; VAD pumps can be divided into two main categories: continuous flow (fluid dynamic) and pulsatile flow (positive displacement). Fluid dynamic pumps propel fluids by inducing thrust using a spinning mechanism and force blood radially, compared to positive displacement pumps, which move fluids by decreasing a chamber volume to expel fluid through an apparatus. Like the muscular positive displacement pumping mechanism of the native heart, pulsatile flow pumps offer the advantage of generating consistent flow against higher vascular resistance in a pulsatile fashion [12].

Initially, positive displacement pumps were used with the intention to keep the pulsatility, a physiological phenomenon of normal circulation. However, the large size and low durability of pumps such as the HeartMate XVE (HM-XVE) fueled further research regarding the need for pulsatility in the circulation. Since the flow through the capillaries is nonpulsatile in normal circulation, other than serving to decrease the stagnation and thrombosis of the aortic cusps, the pulsatility function was deemed dispensable [13]. To prove this theory, there has been great interest in how nonpulsatile flow affects the splanchnic and cerebral circulations. In animal shock models, liver and kidney perfusion improved with nonpulsatile flow. Cerebral autoregulation was also maintained with no pulse [14]. Although the short-term clinical outcomes remain similar [15], the long-term effects of nonpulsatile flow remain unclear [16].

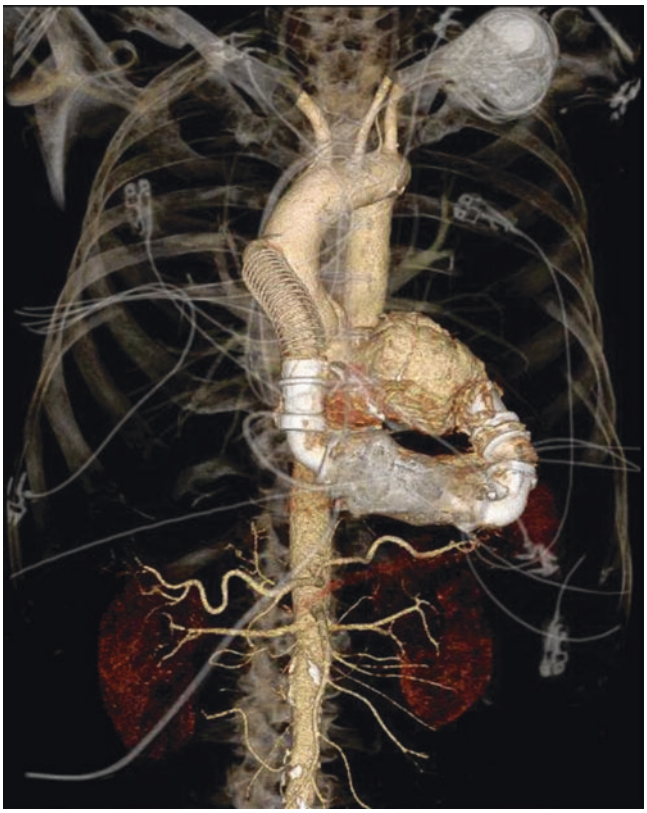


Fig. 22.1 VAD support for the patient with end-stage heart failure. Three-dimensional computed tomography thoracic scan demonstrating the HeartMate II and its inflow cannula, pump, and outflow cannula

Physiologically, unloading the ventricle with a VAD induces multiple changes in the myocardium. VAD assistance has generally induced positive remodeling and improvement in the contractility of the myocardium [17]. Changes in myocyte size, extracellular matrix, calcium handling, and myocardial energetics have been improved following VAD implantation [18, 19]. In fact, few studies have reported on explantation of VADs after a few years of support [20–22]. In a recent study by Baldwin et al., surgical explantation of 27 cases after about 500 days of support was performed at Baylor College of Medicine, with favorable outcomes [21].

History of Ventricular Assist Devices

In 1966, the first successful implant of a VAD in a patient with post-cardiopulmonary bypass cardiogenic shock was performed at Baylor College of Medicine in Houston [11]. In 2001, the HeartMate XVE was Food and Drug Administration (FDA) approved as the first pulsatile left VAD (LVAD) for bridge to transplantation (BTT). The REMATCH trial was a prospective, randomized multicenter study that compared

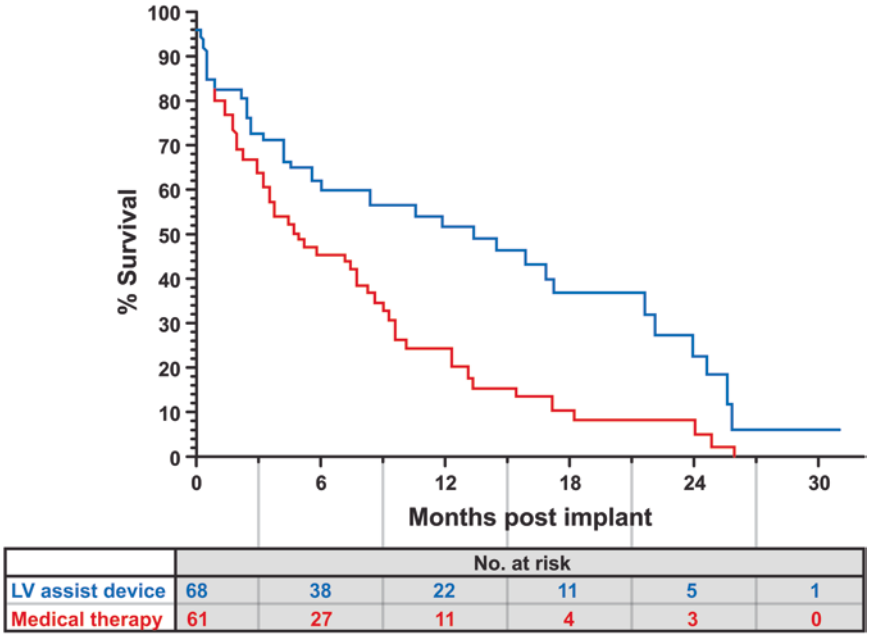


Fig. 22.2 REMATCH trial reveals a survival benefit of patients supported by VAD. Kaplan-Meier survival curve of patients with VAD support (HeartMate XVE) versus patients supported by parenteral inotrope therapies reveals a survival benefit in those patients with VAD support [6]

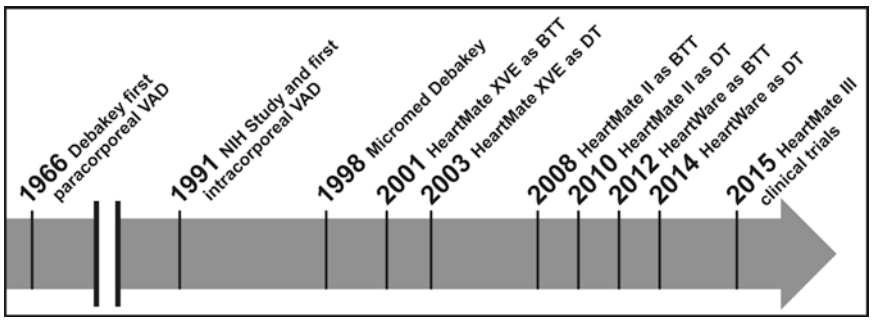


Fig. 22.3 Historical milestones associated with VAD development. Over a 50-year period, innovations associated with device development have resulted in improved VADs that have contributed to an acceptable quality of life for patients with advanced heart failure

the HM-XVE LVAD versus optimal medical therapy for patients not considered eligible for cardiac transplantation [6] (Fig. 22.2). Patients randomized to LVAD support had a 50 % increase in 1-year survival. Thus, in 2003, LVAD therapy was approved by the FDA as either BTT or destination therapy (DT). However, early pump failure limited the use of pulsatile pumps. The concept of continuous flow pumps (CF-LVADs) was developed in 1988 from a collaborative effort between Baylor College of Medicine and NASA [23]. After 10 years of development, the first CF-LVAD (MicroMed, DeBakey) was implanted in a human [24].

As the technology matured, the HeartMate II (HM II) LVAD was the first CF-LVAD to be approved by the FDA as BTT in 2008 and then DT in 2010. This advancement had a significant impact on survival and outcomes; the 1-year survival with the HM II VAD exceeded 80 %, making it a viable alternative to heart transplantation [8]. The centrifugal CF-LVAD HeartWare pump (HVAD) was developed in 2005 and FDA approved in 2012 as BTT and in 2014 as DT. The completely redesigned HM III was introduced in 2015 and became part of the MOMENTUM III randomized controlled trial [25] (Fig. 22.3).

Patient Referral and Work-Up

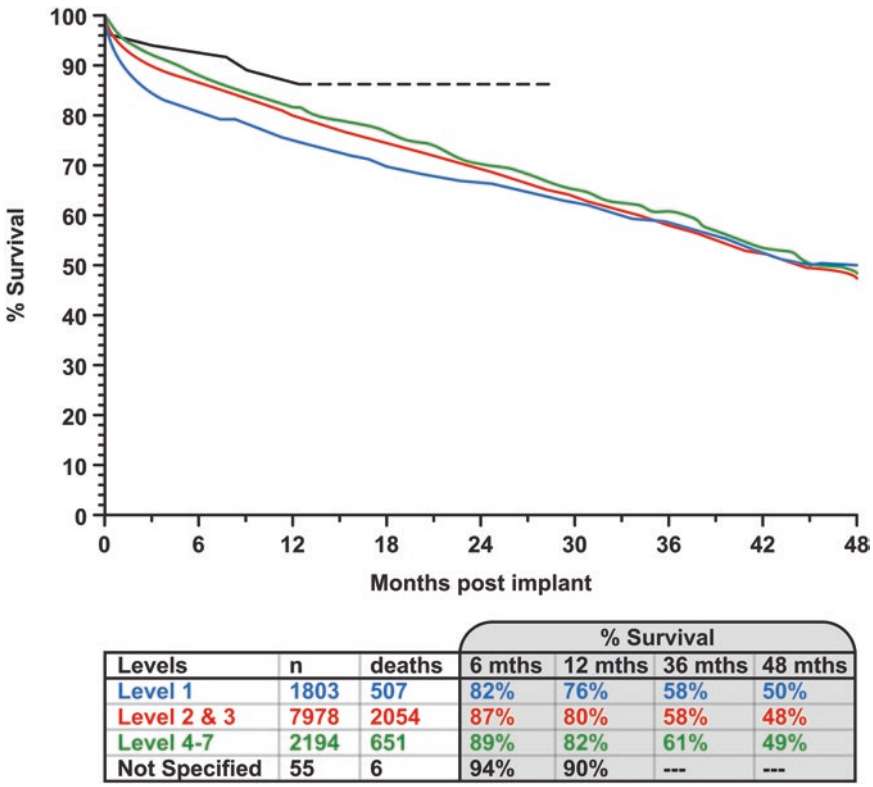
Patients eligible for transplantation—or ineligible but with end-stage disease and unable to wait on the transplant waiting list—are referred for LVAD implantation. For 1992–2000, the International Society for Heart and Lung Transplantation reported that 12 % of transplant recipients were mechanically supported with an LVAD pretransplantation, compared to 28 % from 2006 to 2012 [26]. End-organ damage, despite maximal medical therapy, including inotropic support or inotropic support dependency with anticipated long waiting times for heart transplantation, is the major indication for CF-LVAD implantation.

These cases correspond to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles 1–3. The INTERMACS is a US-based registry of patients receiving mechanical circulatory support (MCS) device therapy, including durable LVADs [27]. The INTERMACS scale assigns patients with stage D heart failure into seven levels according to hemodynamics and individual functional capacity (Table 22.1). Patients in acute cardiogenic shock are assigned INTERMACS profile 1 (Fig. 22.4).

Table 22.1 INTERMACS profiles

INTERMACS profile	Description	Details
1	Cardiogenic shock (crash and burn)	Hemodynamic instability despite inotropic support
2	Progressive decline (on inotropes)	Slow decline despite inotropic support
3	Stable on inotropes	Stable but inotrope dependent
4	Stable but symptomatic on oral therapy	Symptomatic at rest or during activities of daily living
5	Stable but exertion intolerant	Symptomatic with minimal exertion
6	Stable but physically limited	Symptomatic after few minutes of exertion
7	NYHA class III symptoms	Symptomatic with moderate exertion

NYHA New York Heart Association



			% Survival			
Levels	n	deaths	6 mths	12 mths	36 mths	48 mths
Level 1	1803	507	82%	76%	58%	50%
Level 2 & 3	7978	2054	87%	80%	58%	48%
Level 4-7	2194	651	89%	82%	61%	49%
Not Specified	55	6	94%	90%	---	---

Fig. 22.4 Stratification of patients and survival post-VAD implantation. Kaplan-Meier survival curves depicting the survival post-ventricular assist device implantation, stratified by the INTERMACS profile. Note that profiles 1–3 were associated with significantly worse mortality, compared to the other groups. *Source*: Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, Miller MA, Baldwin JT, Young JB. Seventh INTERMACS annual report: 15,000 patients and counting. J Heart Lung Transplant. 2015;34(12):1495–504

These patients are primarily supported with short-term MCS such as extracorporeal membrane oxygenation (ECMO), percutaneous axial VADs (Impella), or intra-aortic balloon counterpulsation and are then transitioned to more permanent support after they stabilize. These patients did poorly if they immediately received a durable LVAD, but most patients transitioning to a VAD in this scenario become relatively more stable and thus fall into INTERMACS profiles 2 and 3 (Fig. 22.4). Irrespective of the profile, implantation can be divided into one of four groups: BTT, DT, bridge to decision (BTD), or bridge to recovery (BTR). The BTT designation is intended to support the patients on the waitlist until their transplant. On the other hand, the DT designation is intended to support the patients not eligible for transplantation at the time of implantation.

Separation of LVAD patients into BTT or DT can be challenging. During their acute illness, many patients may fall into a gray zone with a clinical status that improves over time and with the potential of listing for transplantation. These patients are frequently designated as BTD. In an attempt to normalize end-organ function that precludes long-term cardiac replacement therapies such as heart transplant or durable LVAD, these patients are often supported using temporary MCS such as percutaneous temporary VADs or ECMO. The

risk factors for their increased mortality include large body weight (body mass index > 30 kg/m^2), older age (>75 years), cardiogenic shock, and the need for a right ventricular assist device [28]. Thus, a multidisciplinary team should carefully make the decision for these subgroups.

Bridge to Transplantation

Durable LVADs were primarily developed as a DT in patients ineligible for heart transplantation. Concerns about long-term performance and safety, however, prompted the FDA to restrict the initial use of such devices (HM-XVE) to patients who were eligible for a transplant, leading to the concept of BTT. This led to the development of more durable, smaller, and totally implantable devices, permitting a normal quality of life. The American Heart Association (AHA) guidelines recommend CF-LVAD implantation as BTT in patients awaiting heart transplantation who have become refractory to medical therapy (Class IB). Patients with refractory heart failure and hemodynamic instability expected to improve with time or who experience restoration of an improved hemodynamic profile should be considered for urgent MCS as a BTD (level of evidence C) [3, 29]. The European Society of Cardiology (ESC) recommends a CF-LVAD as BTT in selected patients with end-stage heart failure despite optimal medical therapy and who are otherwise suitable for heart transplantation to improve morbidity and mortality while awaiting transplantation (Class I, level of evidence B) [30] (Table 22.2).

Establishing the time frame for implantation is critical to balance the risks and benefits. The prognostic implications of the INTERMACS profiles provide guidance for the indications and the optimal timing of implantation. Currently, BTT is a major indication for CF-LVAD implantation, with a myriad of advantages pertaining to transplantation. In the seventh annual INTERMACS registry report, 53.5 % of the primary VAD implantations in 2014 were for BTT [27]. One of the major advantages of implantation for BTT is the possibility to decrease the pulmonary pressures, leading to potential improvements in posttransplant outcomes and even to listing patients who were previously not eligible for listing (BTD) [31]. LVAD implantation also recovers end-organ perfusion and enables patients' nutritional and functional status improvements. However, the timing of relisting heart transplant candidates who received an LVAD as a BTT remains an issue. An interval of about 6 months after implantation is recommended in cases of pulmonary hypertension [32]; however, no general consensus exists for patients who receive BTT LVAD for other reasons. Although it has been consistently shown that LVADs reduce mortality while patients are on the transplant waiting list [5, 33], controversy remains regarding whether device implantation as a BTT affects posttransplantation outcomes [34, 35]. BTT LVAD therapy is likely more cost-effective in patients at high to medium risk, with an expected long waiting time before transplantation. The excellent results achieved by CF-LVADs, the increased mortality rate for heart transplantation caused by the more liberal donor criteria, and the considerable mortality on the waiting list of nonsupported patients have led to the hypothesis that LVAD implantation should be viewed as the primary treatment of stage D heart failure, followed by heart transplantation only in eligible patients [36, 37].

Destination Therapy

With the extremely limited pool of cardiac allografts, CF-LVADs are becoming a more attractive and readily available method of support for stage D heart failure patients. Only after the development of the HM-XVE has the practice pattern begun to evolve toward DT. Although it showed improved survival, morbidity related to LVAD implantation was not insignificant. Thus, expansion of DT only began after the approval of the HM II LVAD by the FDA, and, since 2012, the number of DT implants has surpassed the number of BTT implants. In 2014, 45.7 % of implants were designated as DT [27]—interestingly, surpassing the number of heart transplants, as well.

The community of advanced heart failure specialists gain experience evaluating and treating patients, but determining which patient and the timing of device implantation continues to evolve. Indications for DT include chronic inotrope dependency, optimal medication non-tolerance, end-organ hypoperfusion, frequent rehospitalization, frailty, and exercise cardiopulmonary stress testing with VO_2 of 14 mL/kg/min or <50 % age-predicted maximum. The decision to implant a CF-LVAD as DT can be challenging, and the long-term complications associated with VAD therapy should be contrasted with current signs and symptoms of progressive heart failure treated with medical therapy alone [29]. Again, INTERMACS profiling could guide the decision-making process. For example, the benefits of CF-LVAD therapy outweigh the risks in INTERMACS profiles 1–3. In contrast, implanting a device in INTERMACS profiles 4–6 predicts greater survival after LVAD implantation compared with INTERMACS 1–3, but carries with it the adverse event burden in a patient whose mortality is less acute (Fig. 22.4).

The results of the HeartMate II post-approval study for DT patients showed 1-year survival of 82 % for patients with INTERMACS levels 4–7 versus 72 % for levels 1–3 [38]. These survival rates were significantly lower than the 88 % 1-year survival for the BTT patients, but the difference may result from the younger age of the BTT patients and their fewer number of comorbidities [39]. Currently, 80 % of the approved device implants as BTT or DT are for patients in INTERMACS levels 1–3. The benefit of device implantation in more compensated INTERMACS profiles (4–7) remains unclear. This question is being evaluated in the REVIVE-IT (Randomized Evaluation of VAD InterVEntion before Inotropic Therapy) trial. This study is a National Heart, Lung, and Blood Institute (NHLBI)-sponsored prospective, randomized trial for evaluating HM II as DT in New York Heart Association (NYHA) functional class III heart failure

Table 22.2 Mechanical circulatory support guidelines published by the American Heart Association (AHA), the Heart Failure Society of America (HFSA), and the European Society of Cardiology (ESC)

AHA 2012 guidelines [29]	Evidence
MCS for BTT indication should be considered for transplant-eligible patients with end-stage HF who are failing optimal medical, surgical, and/or device therapies and at high risk of dying before receiving a heart transplantation	Class I, level of evidence B
Implantation of MCS in patients before the development of advanced HF (i.e., hyponatremia, hypotension, renal dysfunction, and recurrent hospitalizations) is associated with better outcomes. Therefore, early referral of advanced HF patients is reasonable	Class IIa, level of evidence B
MCS with a durable, implantable device for permanent therapy or DT is beneficial for patients with advanced HF, high 1-year mortality resulting from HF, and absence of other life-limiting organ dysfunctions, who are failing medical, surgical, and/or device therapies and who are ineligible for heart transplantation	Class I, level of evidence B
Elective rather than urgent implantation of DT device can be beneficial when performed after optimization of medical therapy in advanced HF patients who are failing medical, surgical, and/or device therapies	Class IIa, level of evidence C
Urgent nondurable MCS is reasonable in hemodynamically compromised HF patients with end-organ dysfunction and/or relative contraindications to heart transplantation/durable MCS who are expected to improve with time and attain restoration of an improved hemodynamic profile	Class IIa, level of evidence C
These patients should be referred to a center with expertise in the management of durable MCS and patients with advanced HF	Class I, level of evidence C
Patients who are ineligible for heart transplantation because of pulmonary hypertension related to HF alone should be considered for bridge to potential transplant eligibility with durable, long-term MCS	Class IIa, level of evidence B
Careful assessment of RV function is recommended as part of the evaluation for patient selection for durable, long-term MCS	Class I, level of evidence C
Long-term MCS is not recommended in patients with advanced kidney disease in whom renal function is unlikely to recover despite improved hemodynamics and who are therefore at high risk for progression to renal replacement therapy	Class III, level of evidence C
Long-term MCS as a bridge to heart-kidney transplantation might be considered on the basis of availability of outpatient hemodialysis	Class IIb, level of evidence C [75]
Assessment of nutritional status is recommended as part of the evaluation for patient selection for durable, long-term MCS	Class I, level of evidence B
Patients with obesity (BMI >30 to <40 kg/m^2) derive benefit from MCS and may be considered for long-term MCS	Class IIb, level of evidence B
Assessment of psychosocial, behavioral, and environmental factors is beneficial as part of the evaluation for patient selection for durable, long-term MCS	Class I, level of evidence C
Evaluation of potential candidates by a multidisciplinary team is recommended for the selection of patients for MCS	Class I, level of evidence C
HFSA comprehensive HF practice guidelines [75]	
Patients awaiting heart transplantation who have become refractory to all means of medical circulatory support should be considered for an MCS device as a BTT	Level of evidence B
Permanent mechanical assistance with an implantable LVAD may be considered in highly selected patients with severe HF refractory to conventional therapy who are not candidates for heart transplantation, particularly those who cannot be weaned from intravenous inotropic support at an experienced HF center	Level of evidence B

AHA 2012 guidelines [29]	Evidence
Patients with refractory HF and hemodynamic instability and/or compromised end-organ function with relative contraindications to cardiac transplantation or permanent MCS expected to improve with time or restoration of an improved hemodynamic profile should be considered for urgent MCS as a bridge to decision; these patients should be referred to a center with expertise in the management of patients with advanced HF	Level of evidence C
ESC guidelines 2012 [30]	
An LVAD or BiVAD is recommended in selected patients with end-stage HF despite optimal pharmacological and device treatment and who are otherwise suitable for heart transplantation, to improve symptoms and reduce the risk of HF hospitalization for worsening HF and to reduce the risk of premature death while awaiting transplantation	Class I, level of evidence B
An LVAD should be considered in highly selected patients who have end-stage HF despite optimal pharmacological and device therapy and who are not suitable for heart transplantation, but are expected to survive >1 year with good functional status, to improve symptoms and reduce the risk of HF hospitalization and of premature death	Class IIa, level of evidence B

MCS mechanical circulatory support, *HF* heart failure, *DT* destination therapy, *RV* right ventricular, *BMI* body mass index, *HFSA* Heart Failure Society of America, *BTT* bridge to transplantation, *LVAD* left ventricular assist device, *ESC* European Society of Cardiology, *BiVAD* biventricular assist device

patients [40]. The goal of this ongoing study is to determine the clinical efficacy and cost of CF-LVAD implantation as DT in a less-sick patient population, given the challenging decision of LVAD implantation as DT.

In general, a number of clinical risk factors portend poor survival and might exclude a patient from LVAD candidacy. These risk factors include advanced age, previous cardiac surgery, renal failure, and right ventricular failure. Elderly patients (>65 years of age) tolerate CF-LVAD implantation poorly during acute decompensation. Nonetheless, outcomes in this population are generally favorable over a long period. Most importantly, the decision to implant a DT CF-LVAD, as opposed to pursuing ongoing medical therapy, implies that the patient is expected to make a successful postimplant recovery, is at a point in disease progression at which end-organ damage is reversible, is expected to benefit from a reduction in mortality, and, importantly, has an improved quality of life.

Complications of Ventricular Assist Devices

As clinical experience expands and patients live longer with VADs, more complications are being encountered, and management methods continue to evolve. The most common complications of VAD therapy include gastrointestinal (GI) bleeding, pump thrombosis, stroke, aortic valve insufficiency, and right ventricular failure.

The mechanisms of GI bleeding, which occurs in up to 40 % of cases [41], include acquired von Willebrand factor deficiency, mucosal arteriovenous malformations (AVMs), and chronic anticoagulation therapy [42]. Decreased or absent pulsatility with increased shear stress leads to subsequent angiodysplasia and the development of AVMs. The fragility of these capillaries leads to bleeding, which is exacerbated with anticoagulation [43]. Unfortunately, treatment options remain limited and predominantly include cessation of anticoagulation and antiplatelet therapy, endoscopy with control of visualized bleeding sources, and off-label medication use including subcutaneous octreotide injections [44] and oral thalidomide [45]. Effective use of these agents is being extrapolated from small retrospective studies; randomized studies are being undertaken.

Another major complication is pump thrombosis (Fig. 22.5). Proper inflow and outflow cannula positioning, anticoagulation, and antiplatelet therapies are needed to prevent thrombus formation within the pump. Delayed initiation, inadequate dosing, or cessation of anticoagulation therapy may be associated with thrombus formation within the pump, leading to pump failure. The initial HM II trials considered an international normalized ratio (INR) of 2–3 and a full-dose 325 mg aspirin (ASA) as standard therapy. Low thrombotic and high bleeding rates led to modification of these standards; an INR of 1.8–2.2 and an ASA dose of

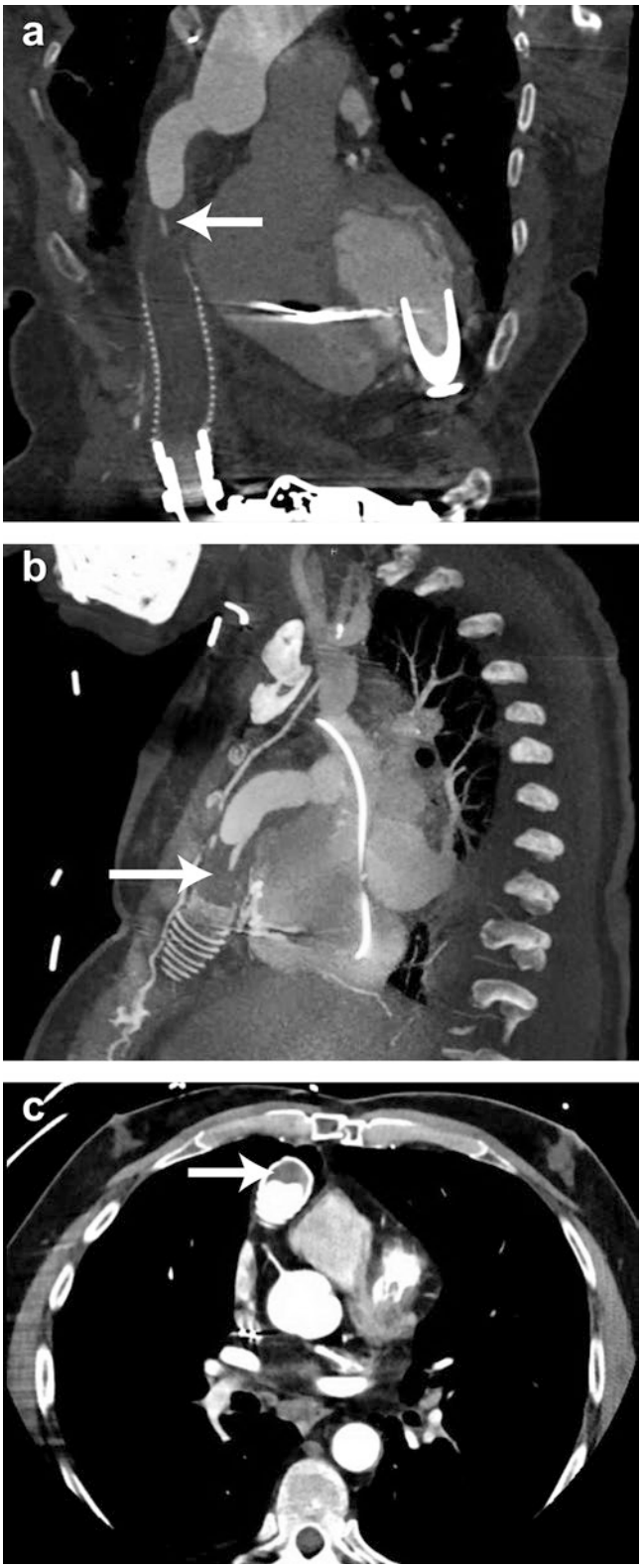


Fig. 22.5 Computed tomographic images demonstrating pump thrombosis. (**a**) Coronal view revealing an outflow cannula thrombus (*arrow*). (**b**) Sagittal view with pump and outflow cannula thrombus (*arrow*). (**c**) Transverse view with laminar outflow cannula thrombus (*arrow*)

81 mg were proposed. However, the recent increase in the incidence of thrombosis [46] led to new guidelines [47]. All risk factors remain unclear, but include driveline infection, obesity, younger age, and female sex [48]. Increased inflow cannula angulation and increased depth of the pump pocket have also been contemplated as risk factors of pump thrombosis [49]. Work-up includes measuring the serum levels of biomarkers of hemolysis such as lactate dehydrogenase and plasma-free hemoglobin. Newer ramp echocardiographic studies have been used with the notion that high speeds do not decompress the left ventricle as well in the presence of thrombosis [50]. Management includes intravenous unfractionated heparin or argatroban infusion, thrombolytic therapy, intensified chronic anticoagulation, and pump exchange via the subcostal/substernal approaches [51].

Self-administered hardware maintenance remains the cornerstone of device longevity. Patients with CF-LVADs are tethered by a driveline that emerges from the anterior abdominal wall and is connected to the portable controller (Fig. 22.6). Care of the driveline is critical to avoid infection that can have devastating consequences. Regimens of weekly or biweekly sterile dressing changes are required [52]. With the onset of a driveline infection, an aggressive treatment plan is implemented to avoid the need for pump exchange or urgent transplantation. Oral or parenteral antibiotics, surgical debridement, and pump exchange or explantation might be eventually needed [53].

The CF-LVAD is designed to be implanted at the apex (inflow cannula), with the outflow cannula anastomosed to the ascending aorta. Flow from this cannula is antegrade with some retrograde flow to the aortic valve, leading to increased pressure in the dependent sinuses of Valsalva. This increased pressure likely leads to leaflet fusion and prolapse, culminating in the development of late aortic insufficiency. This is primarily due to complete unloading of the ventricle when the pump speed is high enough, such that there is little or no ejection through the native aortic valve. Incidence of late de novo insufficiency has been estimated to be as high as 43.1 % in HM II vs. 65.7 % in HW recipients [54]. Non-opening of the aortic valve was strongly associated with de novo regurgitation development [55]. Treatment options include decreasing the flow through the device, afterload reduction, and valvular replacement. Surgical techniques include complete valve closure, repair, or complete replacement with tissue prosthesis [56, 57].

Early right ventricular (RV) failure and progressive decline of RV function are common complications of CF-LVAD implantation. With an incidence of up to 44 % [58], RV failure has been associated with higher mortality and morbidity [59]. It may lead to impaired LVAD flow, difficulty in weaning from cardiopulmonary bypass, decreased tissue perfusion, and, ultimately, multi-organ failure and death. Thus, identifying CF-LVAD patients at risk for RV failure postoperatively is crucial and most often unclear.

Understanding the basic physiology of the right ventricular system would ultimately guide management. The RV is connected to a highly compliant pulmonary vascular system, so it acts as a high-volume low-pressure pump rather than a pressure pump. RV stroke volume (SV) is equal to left ventricular SV, but at 25 % of the stroke work. Thus, it is very sensitive to a change in afterload [increased pulmonary artery pressure (PAP)], but is more tolerant of a hypervolemic state. The RV is more resistant to ischemia compared to LV due to lower coronary flow at rest and oxygen extraction. However, both ventricles are dependent on one another, so any change in compliance, shape, or size of one ventricle can affect the other [60]. Preoperatively, patients may present

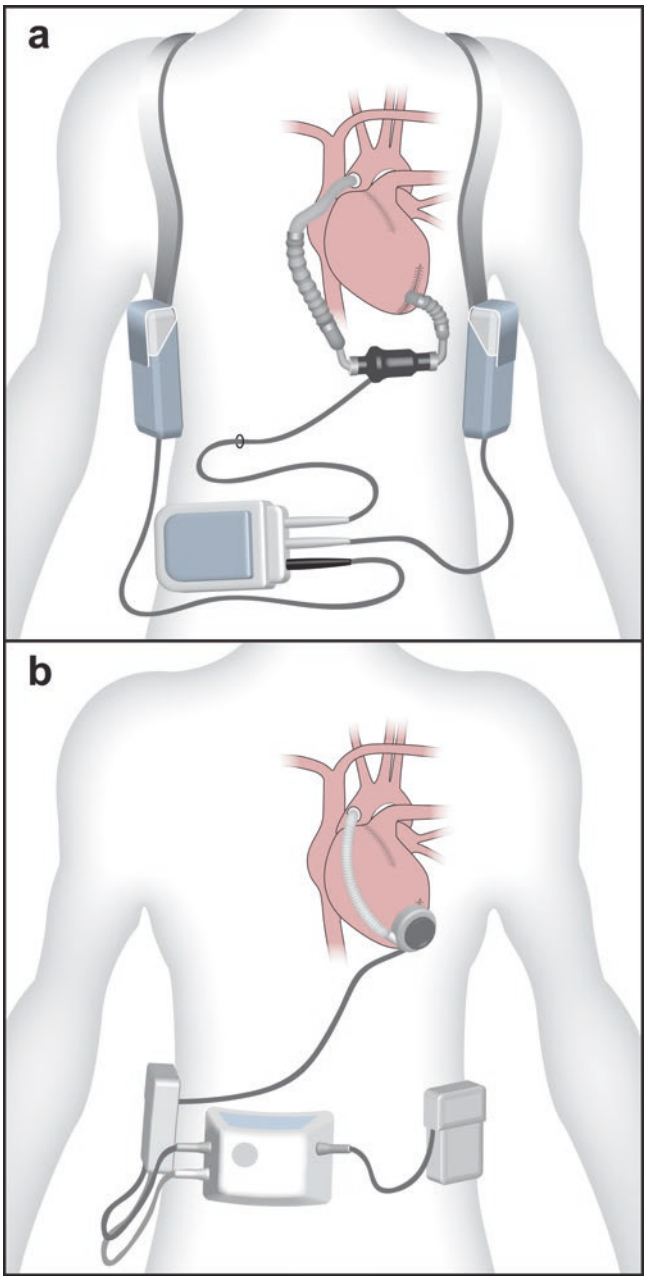


Fig. 22.6 A schematic drawing demonstrating the components of the most commonly used ventricular assist device systems. (**a**) HeartMate II and (**b**) HeartWare. With both of these VADs, the system consists of the implanted hardware, a driveline emerging from the anterior abdominal wall connected to a controller, and a battery pack

with a wide range of signs and symptoms of RV failure—from being relatively asymptomatic to highly decompensated. In these patients, RV failure is defined as the inability of the RV to fill and eject normally or as the inability of the RV to provide the pulmonary circulation with adequate blood flow in the presence of a normal central venous pressure (CVP). Postoperatively, RV failure can be defined as the inability of the RV to provide enough preload for the CF-LVAD despite maximal medical therapy.

In 2012, the INTERMACS proposed a set of universal criteria for RV failure post-LVAD implantation [61]. RV failure can also be classified according to the time of occurrence as intraoperatively, early, or late if it occurs >14 days postimplantation. Intraoperative RV failure is recognized when the cardiac index remains less than 2.0 L/min/m^2 and CVP is greater than 20 mmHg. The preoperative risk factors for postoperative RV failure include CF-LVAD destination (DT > BTT or BTR), female sex, presence of end-organ dysfunction, existence of preoperative hemodynamic instability, arrest at any time in the preoperative period, mechanical ventilation, malnutrition, severe RV systolic dysfunction, and RV strain, as demonstrated on preoperative imaging, and the presence of increased pulmonary vascular resistance (PVR), with hemodynamic parameters such as elevated CVP (≥15 mmHg), low right ventricular stroke work index (RVSWI) ≥ 300 mmHg mL/m^2, low pulmonary arterial pressure (PAP), low mean arterial pressure, and high PVR. Other risk factors include nonischemic cardiomyopathy, reoperation, presence of severe tricuspid regurgitation, and presence of pulmonary embolism [58, 62]. The need to optimize volume status, contractility, and RV afterload perioperatively is the cornerstone for preventing RV failure [63]. The use of intravenous inotropes such as milrinone, epinephrine, or dobutamine can be initiated, which allows for pulmonary vasodilation. Inhaled nitric oxide (NO) and phosphodiesterase inhibitors can be used to reduce PVR, as well.

If all the medical interventions have failed to improve RV function, then MCS may eventually be needed. Temporary MCS devices such as CentriMag, Abiomed, and TandemHeart have been used in acute reversible cases or more durable devices such as PVAD and HVAD in "more likely irreversible" cases (Fig. 22.7). Pulmonary artery balloon pumps and venoarterial ECMO for RV support are alternative short-term therapies. However, ECMO does not unload the ventricles as effectively as an RVAD and it has a high rate of complications [64]. Therefore, risk assessment for RV failure should be performed preoperatively to assess the need for initial biventricular assist device (BiVAD) implantation or total artificial heart. Fortunately, the transplant community is becoming more aware of the major risk factors, and the need for RVAD during LVAD implantation has decreased significantly. From 2006 to 2014, the implantation rate has decreased to 5.2% and may represent improved patient selection for LVAD devices [27].

Finally, the thrombotic and hemorrhagic complications, most notably stroke, are the principal sources of morbidity and mortality associated with VAD implantation [65]. The incidence of stroke among patients with CF-LVADs is about 17% per year. However, the risk factors are still unclear, as traditional factors do not seem to affect those risks [66, 67]. In the perioperative period, early thrombus formation in a new pump is a risk factor for stroke, although early power surges are not associated with subsequent stroke [68]. Other risk factors include systemic infection, which has increased the risk of stroke by nearly twofold [69]. Nonetheless, the risk might be elevated with preexisting medical conditions such as atrial fibrillation, elevated blood pressure, and mechanical factors associated with the device itself, including the deposition of fibrin material on the rotor, the permanent closure of the aortic valve, and the positioning of the inflow and outflow cannulas.

However, little is known regarding how traditional risk factors influence the risk of stroke, such as a previous stroke, hyperlipidemia, diabetes mellitus, and smoking. It is unclear whether the VAD patient population is particularly vulnerable to stroke, primarily due to the extremely high risk of hemorrhagic transformation and the inability to fully image the brain given the magnetic resonance-incompatible hardware. The risk factors for hemorrhagic stroke have also not been well characterized in the VAD population except for systemic infection, platelet counts, and antithrombotic therapy. Evaluation should include history and physical examination, computed tomography imaging of the head, and other vascular imaging.

Treatment decisions for acute hemorrhagic stroke patients are based on whether the patient has had a primary hemorrhagic stroke or hemorrhagic transformation. The decision to reverse a coagulopathy can be challenging, as it is plausible that rapid reversal of the coagulopathy could culminate in major pump thrombosis. The presence of hemorrhagic conversion, however, changes the treatment approach. If neuroimaging is more consistent with hemorrhagic transformation of an ischemic stroke, then the coagulopathy typically is reversed if bleeding remains active or has led to significant cerebral edema. Early decompressive hemicraniectomy for large ischemic strokes provides substantial mortality benefit in patients <60 years of age. Many patients with a CF-LVAD who develop a stroke will require future cardiac procedures, including device exchange or cardiac transplantation. Thus, candidacy for transplantation or a switch of designation to DT requires careful consideration [70].

Types of Durable Ventricular Assist Devices

Figure 22.7 and Table 22.3 list the various durable VADs that were used previously or currently or are under investigation. Pulsatile flow LVADs (HM-XVE) are first-generation volume displacement VADs, which used a diaphragm and unidirectional valves to replicate the pulsatile cardiac cycle through diastolic filling and systolic emptying of the device. Due to their large size, significant adverse events, and limited durability after 2 years of support, HM-XVE production has been discontinued.

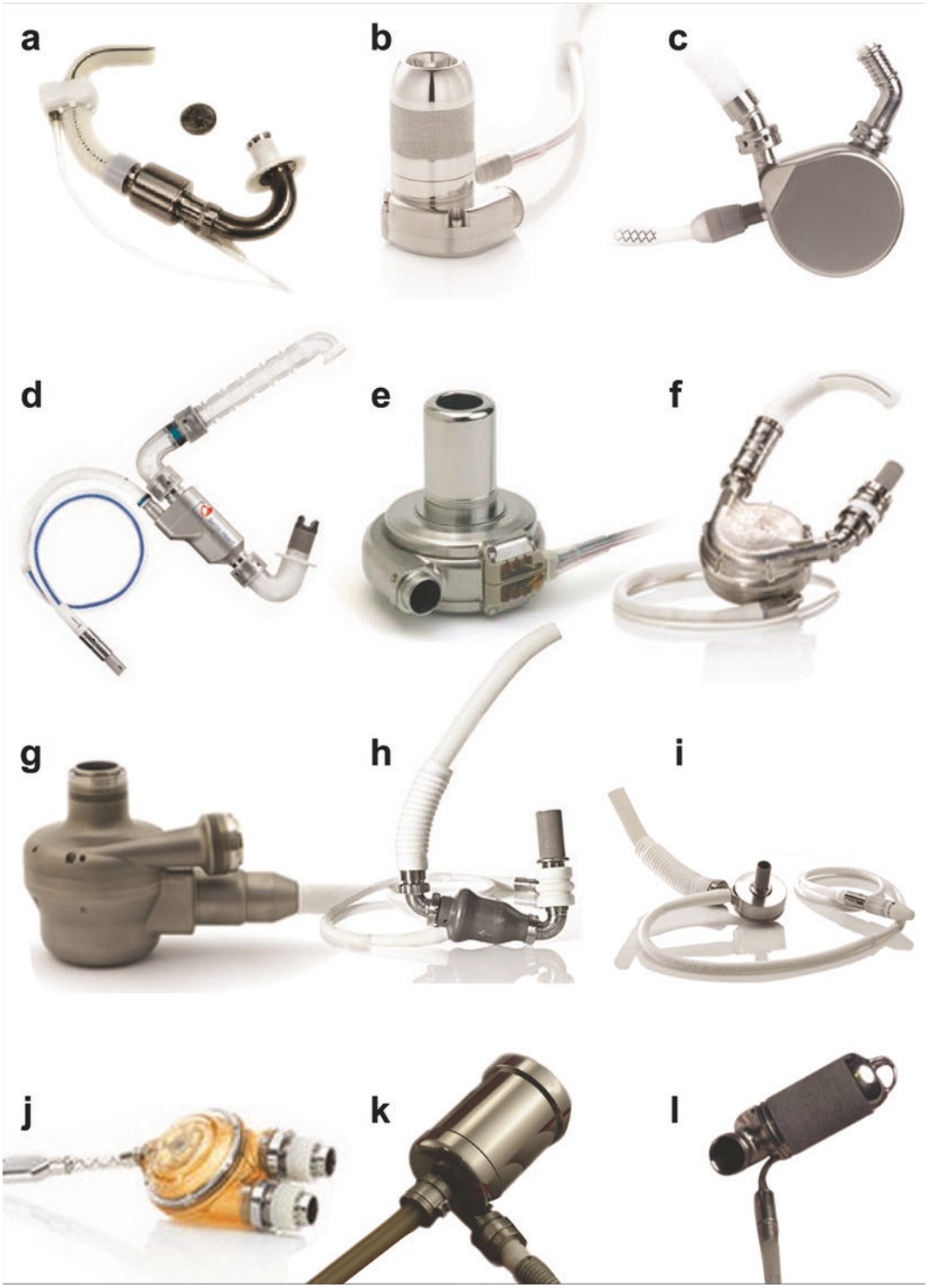


Fig. 22.7 Ventricular assist devices (approved and investigational) used in humans. (**a**) HeartAssist 5. (**b**) MVAD. (**c**) DuraHeart. (**d**) Incor. (**e**) HVAD. (**f**) HeartMate XVE. (**g**) Evaheart. (**h**) HeartMate II. (**i**) HeartMate III. (**j**) PVAD. (**k**) MiTiHeart. (**l**) Jarvik 2000

Continuous-flow LVADs are second- and third-generation pumps with valves that use a permanent magnetic field designed to rapidly spin a single impeller supported by mechanical or magnetic bearings. Second-generation axial pumps have the impeller outflow directed parallel to the axis of rotation. The rotor spins on mechanical or contact-free bearings. Third-generation centrifugal pumps have the impeller outflow directed perpendicular from the axis of rotation. In CF-LVADs, pump blood flow is directly proportional to rotor speed and inversely proportional to the pressure differential between the left ventricle and aorta.

Axial flow pumps show a steep and inverse linear relationship between flow and head pressure. In contrast, this relationship is flatter and more susceptible to head pressure

Table 22.3 Durable ventricular assist devices (approved, investigational, and discontinued VADs)

Device	Manufacturer	Flow—design	Status—USA
HeartMate XVE	Thoratec	Pulsatile—centrifugal	Discontinued
Excor Pediatric	Berlin Heart	Pulsatile—external membrane	Investigational
PVAD	Thoratec	Pulsatile—centrifugal	Approved
IVAD	Thoratec	Pulsatile—centrifugal	Approved
HeartAssist5	ReliantHeart	Continuous—axial	Investigational
HeartMate II	Thoratec	Continuous—axial	Approved
Incor	Berlin Heart	Continuous—axial	Investigational
Jarvik 2000	Jarvik Heart	Continuous—axial	Approved
VentrAssist	Ventracor	Continuous—centrifugal	Discontinued
Novacor	World Heart	Pulsatile—centrifugal	Discontinued
HeartMate III	Thoratec	Continuous—centrifugal	Investigational
MiTiHeart	MiTiHeart Corporation	Continuous—centrifugal	Investigational
HVAD	HeartWare	Continuous—centrifugal	Approved
DuraHeart	Terumo	Continuous—centrifugal	Investigational
Evaheart	Evaheart, Inc.	Pulsatile—centrifugal	Investigational
MVAD	HeartWare	Continuous—centrifugal	Investigational

changes in centrifugal pumps. With the same change in pressure, centrifugal pumps generate larger changes in flow, ranging from 0 to 10 L/min, whereas the axial flow pump flow ranges from 3 to 7 L/min. Centrifugal pumps have a more pulsatile waveform, more accurate flow estimation, lower risk of suction, and more dependency of device flow on loading conditions. The MOMENTUM III trial was initiated in 2015 to evaluate the efficacy of a new LVAD system (HeartMate III), compared to the HeartMate II. This prospective, multicenter, non-blinded trial aims to recruit cases destined as BTT or DT. The HM III is a centrifugal third-generation pump with minor pulsatility (Table 22.3).

Right Ventricular Assist Device (RVAD)

RV failure represents a challenging pathology with poor outcomes. The right ventricle was long ignored by the medical community, in part due to the difficulty to fully assess the right heart and the notion that the right heart's only functional role was to serve as a conduit of deoxygenated blood [71]. Normally, the pulmonary vasculature is a low-pressure, high-capacitance system, with lower vascular resistance than the systemic vasculature. The right ventricular myocardium is thin and more compliant, allowing the RV to accommodate large variations in venous return without significantly altering cardiac output. The systolic pressure of the RV is about 25 mmHg, which is approximately one-fifth the systolic pressure generated by the left ventricle. The RV appears triangular shaped on longitudinal imaging sections and crescent shaped in cross sections, and its contractility is primarily longitudinal in a peristaltic fashion [72, 73].

Etiologies of RV failure include primary causes, such as RV myocardial infarction, arrhythmogenic right ventricular cardiomyopathy, congenital disease, valvular disease, and infiltrative cardiomyopathies. Secondary causes include LVAD-induced pulmonary hypertension, pulmonary embolism, and sepsis. RV failure is a strong mortality predictor in the presence or absence of left ventricular failure and is associated with mortality rates of approximately 40 % [74]. Postoperative RV failure after CF-LVAD implantation is particularly significant, as it carries a mortality rate of more than 40 %, and implies the likely need for RV MCS [63].

Unfortunately, therapies remain limited with suboptimal efficacies. Therapeutic options include pharmacological treatment, MCS, and cardiac transplantation. The complex geometry of the RV and its intricate interactions with the left ventricle make it particularly challenging for RVAD implantation. If optimization of volume status and inotropic support do not adequately improve the RV function, higher levels of MCS are required. RV support can be temporary (using ECMO or CentriMag), or long term, although there currently is no CF-VAD approved by the FDA for RV support. Multiple centers have used paracorporeal PVAD, off-label use of HVAD, or conversion to total artificial heart. For patients ineligible for transplantation, permanent RVAD

should be considered, but their mortality remains high [63]. RVADs should be avoided in the setting of significantly elevated PVR, as the increased flow of blood from the RVAD into the pulmonary circulation might lead to severely elevated pulmonary pressures and lung injury without effectively increasing cardiac output.

Summary

In summary, MCS device development has a rich history marked by pioneering investigators and courageous patients. The innovation has translated to methods to help patients with end-stage heart failure. Today, VAD therapy in well-selected patients confers a superior survival benefit but still has associated complications. In the near future, the use of VADs for DT will increase and will likely become the primary therapy for end-stage heart failure. Engineering initiatives will focus on developing an internal, battery-powered generator and strategies to decrease thrombotic and bleeding complications. The future for MCS holds tremendous promise.

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Regenerative Mechanisms of the Adult Injured and Failing Heart

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_23

Introduction

Cardiovascular disease is the number one cause of death worldwide and in the United States [1–3]. While myocardial infarction and other myocardial insults (myocarditis, toxin-induced cardiomyopathy, genetic diseases, etc.) are common, they frequently progress to heart failure due to progressive loss of cardiomyocytes [4]. Previous studies have established that many adult mammalian organs have a tremendous regenerative capacity (e.g. skin, skeletal muscle, bone marrow, liver, intestine) but the adult heart's capacity is more limited [5, 6]. Recent studies have challenged this dogma. They suggest that lower organisms have the capacity for cardiac regeneration and may be useful in defining key regulatory mechanisms that govern repair and regeneration [7]. Therefore, intense interest has been directed to defining regenerative signaling cascades and factors that may ultimately be modulated and enhance the regeneration of the adult human heart. This chapter provides a general overview of the field and highlights mechanisms, pathways, and factors that may serve as a platform for regenerative therapies.

Regenerative Capacity of Lower Organisms: The Newt

Regeneration of the adult heart is commonly observed in a variety of invertebrate species [7], but vertebrate species typically have a more limited capacity for regeneration [5]. One advantage of studying the regenerative capacity of lower organisms is uncovering evolutionarily conserved regenerative pathways and mechanisms. The rationale for this strategy is that conserved pathways, which induce regeneration in lower organisms, may provide clues to the mechanisms that have evolved in mammals that have resulted in a more limited regenerative capacity and that these efforts may uncover opportunities to stimulate regeneration. For example, the newt and salamanders are well known for their ability to regrow their tail or limbs following amputation. This ability is most likely conserved as a mechanism to escape predators, but it appears that the regenerative capacity of the newt and salamanders is also observed in other organs such as the retina, mandible, and heart [8].

This capacity for cardiac regeneration in the adult newt was first noted by Oberpriller and Oberpriller in the 1970s [9, 10]. While earlier experimental studies characterized the cellular proliferation and mitosis in hearts of frogs and even neonatal rodents [11, 12], Oberpriller and Oberpriller, using electron microscopy, were the first to definitively demonstrate cardiomyocyte mitosis and proliferation in response to injury in the newt [9]. In these studies, the Oberprillers rigorously examined the response of the adult newt following an apical resection of about 10–15 % of the heart. They described the sequence of events following injury, including the formation of an apical thrombus, followed by necrosis and macrophage activation leading to complete regeneration of the amputated heart. Interestingly, these investigators noted that this regenerative process required a 1- to 2-week period before cardiomyocytes began to proliferate. During this initial period, a dedifferentiation process occurs in the border zone of the resected tissue, resulting in the reversion of differentiated cells back to a committed progenitor stage [13, 14]. Upon dedifferentiation, these progenitors reenter the cell cycle, proliferate, and eventually differentiate to add new cardiomyocytes and restore the cellular architecture. The dedifferentiation process likely involves changes in the extracellular matrix (ECM) components, and these changes in the ECM may partly drive the regenerative process [15].

The process of cardiomyocyte proliferation in the newt is not very different from mammalian cardiomyocytes. One of the major differences between the adult newt and mouse cardiomyocytes is the fraction of mononucleated cardiomyocytes, which is more than 95 % in newt, but less than 20 % in mice [16, 17]. Humans have a more equal distribution—with about 75 % mononucleated cardiomyocytes [18]. Another important difference between newt and mammals is the fraction of adult cardiomyocytes that will proliferate in culture. When adult newt cardiomyocytes are isolated and cultured, the majority of cardiomyocytes will reenter the cell cycle (S-phase) and begin to proliferate [14, 17]. However, only one-third of the cells that begin to proliferate actually complete the cell cycle with cytokinesis [14]. This finding suggests that not all cardiomyocytes in the newt heart have an equal capacity for dedifferentiation and participation in the cardiac repair process.

Although the newt has been and continues to be an important animal model for the study of cardiac regeneration, the limitations of this model include the inability to use genetic technologies (e.g., transgenesis, gene disruption, genetic fate mapping, etc.), the imprecise maintenance conditions for breeding, and preference for aquatic vs. terrestrial life cycle [19, 20]. However, with the introduction of gene-editing strategies, such as CRISPR-/Cas9-mediated gene targeting, these limitations may be addressed. Nevertheless, the tremendous regenerative capacity of the adult newt heart serves as a magnet to capture the interest of investigators focused on the definition of mechanisms that govern adult heart repair and regeneration.

Regenerative Capacity of Lower Organisms: The Zebrafish

The zebrafish has largely replaced the newt as a regenerative model (◘ Fig. 23.1) [21]. This interest in the zebrafish is mainly due to the ability to monitor the transparent embryo throughout development [22]. A second major advantage is the ease with which the zebrafish can breed, as it produces hundreds of fertilized eggs at each clutch. Third, the zebrafish genome has been sequenced [23]. Fourth, the availability of genetic tools to either generate transgenic zebrafish models, the use of forward genetics as a screening tool for phenotypes, the use of reverse genetics to inhibit gene expression

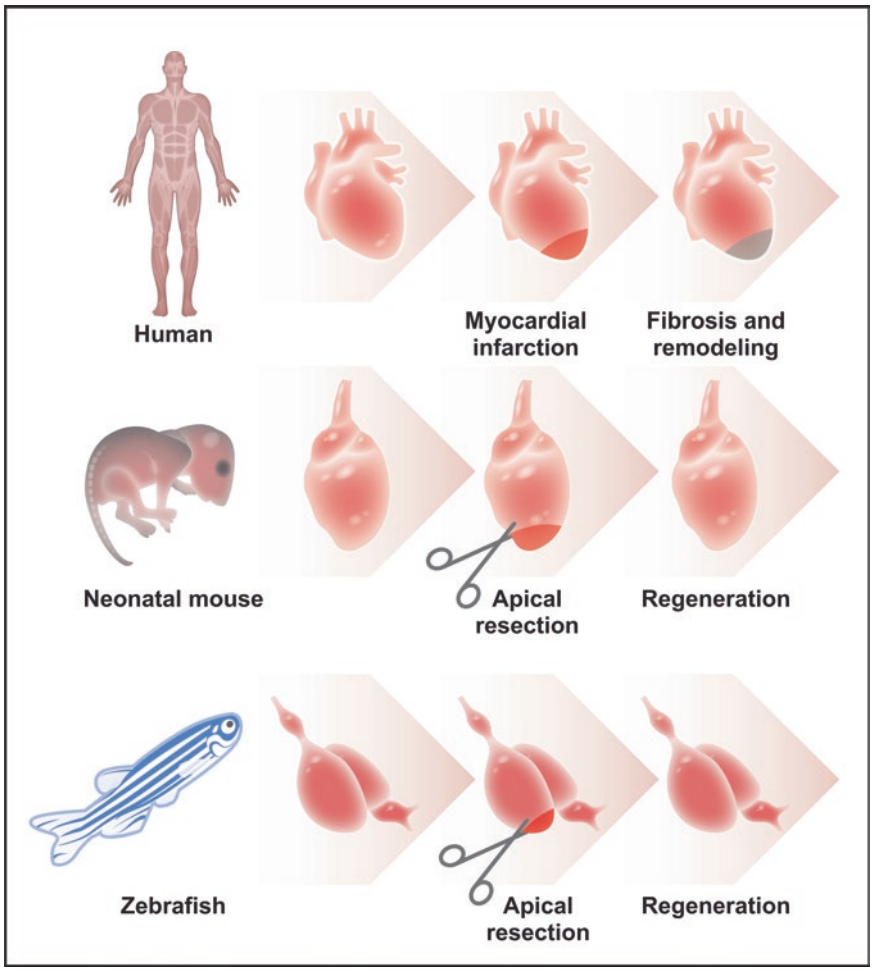

Fig. 23.1 Differential regenerative capacity of model organisms. The differential capacity of cardiac regeneration is schematized in the adult human, neonatal mouse, and zebrafish. *Top panel* outlines the typical response of the human heart to myocardial infarction, which results in the generation of a scar. However, both neonatal mice and zebrafish have the ability to repair the damaged myocardium and completely restore normal myocardial architecture. This regenerative capacity in neonatal mice and zebrafish is mainly a result of existing cardiomyocytes reentering the cell cycle and proliferating

using morpholino-mediated knockdown of gene expression, or the use of gene-editing strategies to produce mutant models have collectively established the zebrafish as one of the most widely used vertebrate models.

A seminal publication in 2002 by Poss et al. demonstrated that zebrafish have the same ability as newts to regenerate their adult heart following apical resection [24]. Similar to the newt, the zebrafish retains the ability to stimulate cardiomyocyte proliferation to regenerate lost or destroyed myocardium. Following this study, the zebrafish model received intense interest as a model organism for the study of cardiac regeneration, as it proved relatively easy to address major questions about the mechanisms that govern heart regeneration in lower organisms.

One of the important questions addressed using the zebrafish model was the origin of the newly formed cardiomyocytes in response to injury [25]. Although research in the newt suggested that dedifferentiation of adult cardiomyocytes followed by cellular proliferation was the main mechanism for the addition of new cardiomyocytes in response to injury, it was unclear whether these mechanisms were also operational in zebrafish. Theoretically, at least three separate origins of newly formed cardiomyocytes were predicted based on studies in both zebrafish and mice [26]. In mice, studies revealed that cardiac progenitor cells (CPCs) reside in the adult heart that can differentiate into all major lineages present in the heart [27, 28]. It was also shown that epicardial cells could contribute cardiomyocytes during development and may be a source of cardiomyocytes following injury [29–32]. Finally, the proliferation of existing cardiomyocytes to give rise to new cardiomyocytes as established in the newt was a possibility.

An important approach to discern these different possibilities was the use of a genetic lineage-tracing strategy. Here, a genetic driver was used to express the bacteriophage protein Cre recombinase, which could also be engineered to be expressed in an inducible manner to allow temporal control following the addition of tamoxifen. This (inducible) protein could then recognize specific palindromic DNA sequences called loxP sites and recombine two spatially separated loxP sites to a single loxP site, thereby deleting the intermediate DNA sequences. This approach was used to determine the contribution of progenitor cells, epicardial cells, and cardiomyocytes to heart regeneration following apical resection in zebrafish [25].

The initial report that described heart regeneration in response to apical resection showed that a 60-day period is required for the heart to completely regenerate [24].

Interestingly, during the first week, no new cardiomyocytes formed, and at least a 1-week period is required before immature cardiomyocytes appear. Frequently, as much as a 2-week period was required before mature cardiomyocytes arose from cellular proliferation events in the injured/regenerative region.

The origin of these newly formed cardiomyocytes was determined using a lineage-tracing strategy. The first attempt used a non-inducible cardiomyocyte-driven dual-fluorescent reporter that expressed both green fluorescent protein (GFP) and red fluorescent protein (RFP) [29, 33]. This initial report extrapolated the protein folding and degradation kinetics under baseline conditions where GFP was folded and also degraded more rapidly compared to RFP. Based on these kinetics, the appearance of GFP-expressing cells 7 days post-injury (that do not yet express RFP) was interpreted as evidence that the cardiomyocytes must be derivatives of undifferentiated progenitor cells, although the exact source of these progenitors was never established [29].

While initial data suggested that the newly formed cells arose from progenitor cells, since they were GFP^+ and RFP^-, the same investigators later reinterpreted these data after obtaining results with a newly generated double-fluorescent reporter line and concluded that the newly produced cardiomyocytes were likely derivatives of existing cardiomyocytes [25]. This conclusion was further corroborated by an additional line of evidence using a *Gata4* enhancer to drive Cre recombinase [25]. This enhancer was only active during zebrafish development and, in response to injury, specifically in cardiomyocytes. Again, newly formed cardiomyocytes were shown to be derived from existing cardiomyocytes. A third line of evidence included the use of an inducible Cre recombinase that was activated specifically in cardiomyocytes, but only 5 days before the injury. Again, all newly formed cardiomyocytes showed activity of the reporter that was activated just before the induced injury.

Finally, a completely independent line of evidence used an epicardially activated genetic driver for genetic lineage tracing. It was hypothesized that a subfraction of the newly formed cardiomyocytes were derived from the epicardium. A transgenic line was generated to express inducible Cre recombinase under the control of transcription factor 21 (Tcf21), a known epicardial marker in mammals [34]. Although epicardial cells contributed many cells to the newly formed heart tissue, none of these labeled cells ever differentiated into cardiomyocytes. The majority of epicardial cells differentiated into perivascular cells after a process reminiscent of epithelial-to-mesenchymal transition during development.

Having established that the majority of, if not all, newly formed cardiomyocytes in response to apical resection in adult zebrafish were derivatives of existing cardiomyocytes, it was important to determine whether this process involved many cardiomyocytes that simultaneously undergo this process or whether it represents only a subfraction of these cells. To address this question, a multicolor fluorescent transgenic reporter line called Brainbow was generated [35]. This reporter line expressed three different fluorescent proteins in different quantities in response to activation of Cre recombinase. This system generated a number of distinct colors by overlaying the relative presence of all three colors. Using this transgenic reporter in response to an inducible cardiomyocyte-specific Cre driver, it was shown that a limited number of clonal cells contributed to distinct cardiomyocyte lineages in the developing zebrafish heart, giving rise to three distinct muscle lineages: primordial, trabecular, and cortical cardiomyocytes. Importantly, following apical resection, only a limited number of clones were responsible for the majority of regenerated myocardium [35].

Current research focuses on the underlying signaling pathways that govern the regenerative process following apical resection (Fig. 23.2). An important difference between apical resection in zebrafish and mammalian cardiac injury is the absence/presence of scar tissue [15, 36]. A generally held notion is that the scarred region is not conducive to regeneration, but rather it is needed to maintain the architectural and structural integrity of the heart following injury. The repair process in mammals is characterized by the initial formation of the scar (presumably to limit free wall rupture) and most likely limits vascularization, nutrient delivery, and cardiomyocyte proliferation [37]. Therefore, it is hypothesized that scar formation limits cellular proliferation.

To further examine this hypothesis in zebrafish, investigators have used cryoinjury to produce necrotic cardiomyocyte death in about 20 % of the ventricle, resulting in an injury comparable to the size of the injury produced following apical resection. However, in contrast to apical resection, a scar is formed in response to the cryoinjury due to the extensive necrosis of cardiac tissue [38]. While the underlying mechanisms are not completely defined, the zebrafish is capable of regenerating this necrotic scar, although the repair process requires a 4-month period instead of a 2-month period, and a small fibrotic scar persists. This near-complete regeneration is dependent on TGF-β signaling [39].

These studies further emphasize the merit in examining the mechanistic differences in scar formation and resolution between mammals and zebrafish and may serve as a platform for the discovery of new therapeutics to enhance regeneration after myocardial infarction in mammals [40].

Regenerative Capacity of Lower Organisms: The Mouse

The notion that mammalian hearts cannot fully regenerate in response to injury has been recently challenged [41]. Using a similar approach as in the newt and zebrafish, an apical resection of the mouse heart was performed (Fig. 23.1). However, instead of performing the procedure on adult mice, the apical resection was performed on neonatal mice the day following birth [41]. Surprisingly, these neonatal mice survived a 15–20 % resection of the heart, and complete regeneration

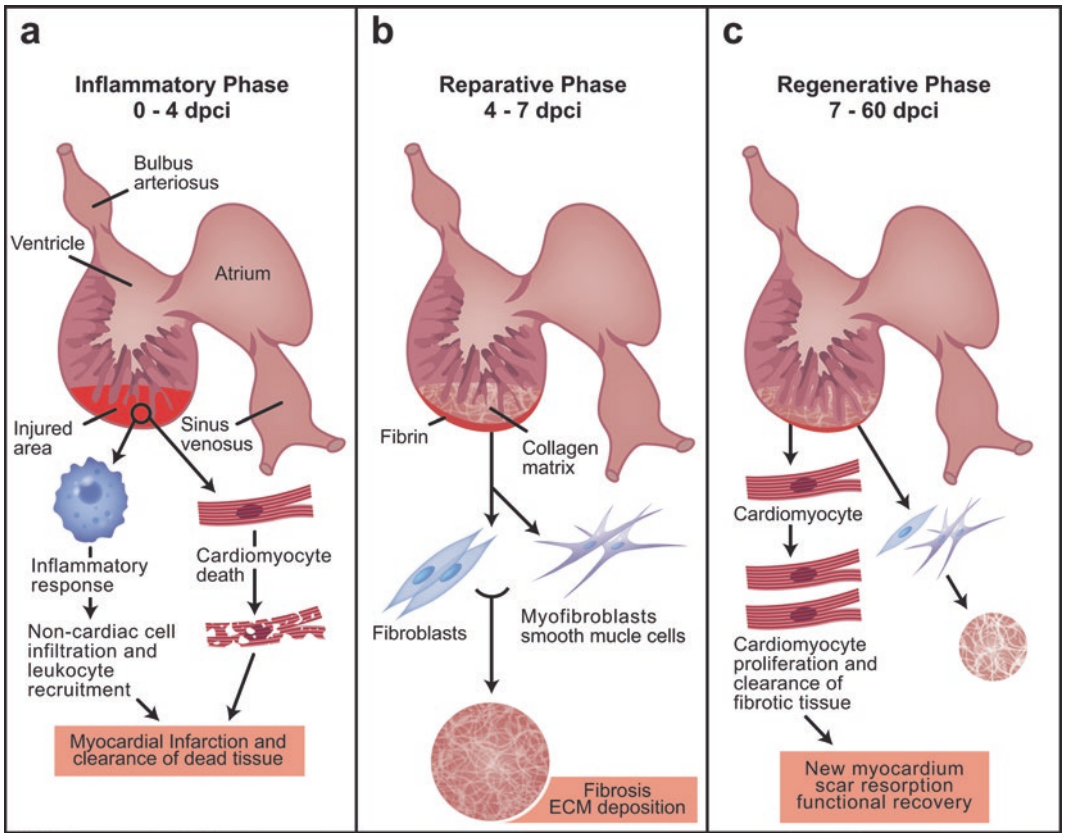

Fig. 23.2 Cardiac regeneration in zebrafish. Schematic outlining the phases of zebrafish heart regeneration. Upon apical resection, three phases of regeneration are recognized. (**a**) Phase 1 begins immediately after cardiac injury, when a blood clot is formed and an inflammatory response is initiated. Meanwhile, dead cardiomyocytes are cleared. (**b**) The second phase begins the reparative process, where (myo)fibroblasts migrate and deposit extracellular matrix. This phase is also characterized by the activation and dedifferentiation of border-zone cardiomyocytes. (**c**) The last phase results in cellular regeneration. Cardiomyocytes begin to proliferate and replace lost myocardium. Furthermore, deposited extracellular matrix and fibrosis are removed to eventually give rise to a completely restored myocardial structure. Dpci indicates days post cardiac injury. Adapted from Chablais F, Jazwinska A. The regenerative capacity of the zebrafish heart is dependent on TGFβ signaling. Development. 2012 Jun;139(11):1921–30. doi: 10.1242/dev.078543. Epub 2012 Apr 18

was observed without scar formation. Again, as observed in the newt and zebrafish, the genesis of many of the newly formed cardiomyocytes in the neonatal mouse was from pre-existing cardiomyocytes. While this robust regenerative response could be observed during the first several postnatal days, by 7 days following birth, the heart was unable to fully regenerate and was noted to have extensive scar formation following apical resection. Therefore, it appears that the extensive regenerative capacity in neonatal mice is fully dependent on the retained ability of the neonatal cardiomyocytes to proliferate. By postnatal day 7, this ability is largely extinguished due to ongoing maturation and inability of the existing cardiomyocytes to reenter the cell cycle.

Moreover, these studies also determined the relative rapid regenerative response in neonatal mice. Adult newt and zebrafish require at least 30–60 days for complete cardiac regeneration in response to apical resection, but neonatal mice have already completed the regenerative process by day 21 [41, 42]. This may be due, in part, to the accelerated stimulation of cardiomyocyte proliferation, as the 7-day post-resection period is marked by a large number of cardiomyocytes that stain positive for either BrdU, a thymidine analog, or for phospho-Histone H3, a marker of the G2/M cell cycle phase.

One important difference that was uncovered between the apical resection at postnatal day 1 vs. 7 was the associated immune response [43]. This response included the magnitude and type of immune cells that responded to the inflamed myocardium, which was distinct and included increased numbers of monocytes and macrophages infiltrating shortly after myocardial injury. Further evidence for the importance of these immune cells was provided using a clodronate-mediated macrophage depletion experiment, which resulted in myocardial scarring in response to apical resection, even in neonatal mice. The extent of innate immunity as an important mediator of regeneration after myocardial infarction is unknown. However, it is noteworthy that galectin-3-expressing cells (a marker for macrophages) are present in high numbers in failing hearts, especially those that are fibrotic [44, 45].

Cardiac Stem and Progenitor Cells During Embryogenesis

The heart is one of the first organs to form during embryonic development [46]. A well-defined cascade of transcription factors and progenitor cells has been shown to be essential for cardiac development [47]. The necessity of the heart is highlighted as embryos without a properly developed heart will not survive beyond mid-gestation (mice) or the first trimester (human) [48]. The heart is a derivative of the mesodermal germ layer that receives cues (i.e., growth factors) from adjacent lineages (i.e., endodermal derivatives). Before specification of the heart begins, a number of factors are activated to initiate migration of cells that emerge from the primitive streak and populate the heart fields (Fig. 23.3) [47]. The factors that regulate migration and specification during this developmental stage are not completely defined, but from zebrafish it appears that retinoic acid signaling, Wnt signaling, Notch signaling, and other pathways collectively function to specify fates and organogenesis [49–53]. Additional factors regulating mesodermal specification include Nodal and BMP as they signal to activate Brachyury and Flk1 [54]. These factors modulate mesodermal progenitors to differentiate to form hemangioblast precursor cells under immediate specification by Etv2 [55, 56].

The second wave of mesodermal progenitors, under the influence of reduced Wnt/β-catenin signaling, activates the earliest marker of cardiac progenitor cells, Mesp1 [57, 58]. However, Mesp1 is a broadly expressed mesodermal marker, and genetic lineage-tracing studies using a Mesp1-Cre transgenic mouse model label all mesoderm-derived cells in the murine heart as well as a number of other noncardiac mesodermal derivatives [57]. Mesp1 is expressed during gastrulation, when progenitor cells are migrating from the primitive streak to form the splanchnic mesoderm, where they eventually fuse together in the midline to form the cardiac crescent.

At this stage of development, cell fates are still pliable as genetic deletional studies (i.e., global loss of Etv2) in mice result in increased numbers of cardiac progenitors. During formation of the cardiac crescent, two distinct populations of cardiac progenitors exist—those residing in the first heart field and those in the second heart field (Fig. 23.3). The main difference that distinguishes the two populations is the level of exposure to different growth factors. The cells in the first heart field are exposed to higher levels of BMP and FGF signaling, while Wnt signaling is inhibited. The combined action of these morphogens results in cardiac differentiation of the first heart field progenitors as they begin to express cardiac markers, including Nkx2-5 and Gata4. Given the position in relation to the aforementioned morphogens, the progenitors in the second heart field remain undifferentiated and begin to express the second heart field marker, Isl1.

Following the onset of Isl1 expression, the second heart field progenitors begin to differentiate and express Nkx2-5 and other cardiac markers. As a portion of the second heart field, a specialized group of cells in the posterior aspect of the second heart field will develop and become the pro-epicardium under the influence of BMP and FGF signaling [59]. These signaling pathways initiate Twist expression with subsequent activation of Wt1, Tbx18, scleraxis, and semaphorin 3D. These pro-epicardial cells will envelope the heart to ultimately form the epicardium. Epicardially derived cells will undergo epithelial-to-mesenchymal transformation

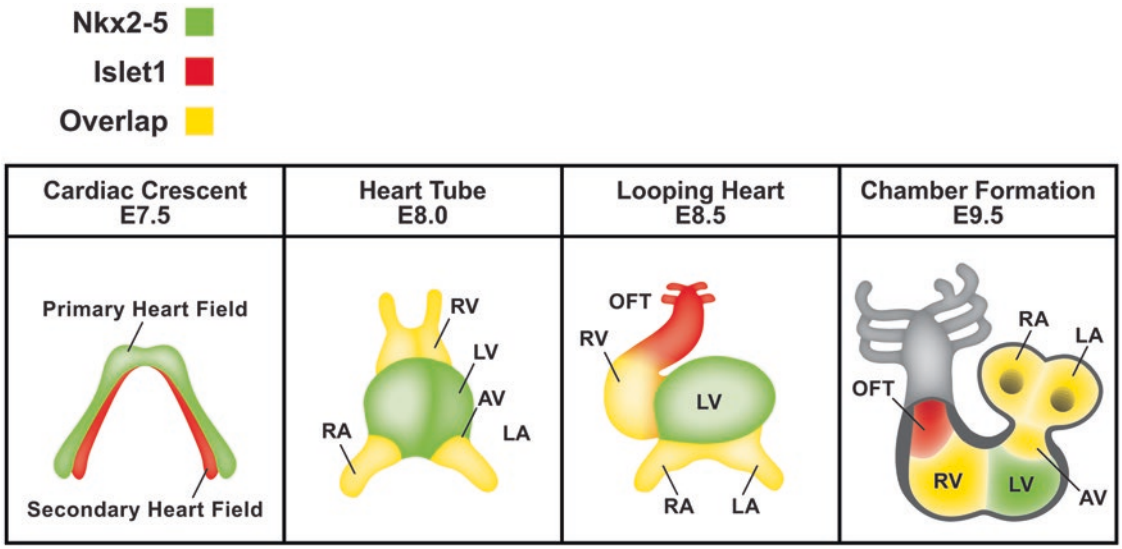

Fig. 23.3 Contribution of different developmental cardiac progenitor populations to the fully developed heart. Different developmental stages are schematized from murine cardiac development, where cardiac progenitor populations are identified by Nkx2-5 or Isl1 expression in the primary or secondary heart field. Over the course of 2 days, these progenitor populations will form the 4-chambered mammalian heart with contributions of Nkx2-5 progenitors in all 4 chambers, while Isl1 progenitors mainly contribute to the right ventricle and outflow tract. *E* indicates murine day of development; *RV* right ventricle, *LV* left ventricle, *LA* left atrium, *RA* right atrium, *AV* atrioventricular canal, *OFT* outflow tract

(EMT) to invade the heart and differentiate into smooth muscle cells, fibroblasts, and cardiomyocytes [60].

An additional source of progenitor cells that contribute cells to the developing heart is derived from the cardiac neural crest [61]. These ectodermal cells are generated as neural crest, but later migrate under the influence of semaphorins to the outflow tract of the heart, where they are responsible for septation of the aorta and pulmonary artery and will give rise to vascular smooth muscle cells that line the large arteries [62, 63]. In addition, these cardiac neural crest cells provide the neurons that enable parasympathetic innervation of the heart [64]. While the cardiac neural crest was shown to contribute cardiomyocytes to the developing zebrafish heart, this may not be observed in the mammalian heart [61, 65–67]. Despite the abundant presence of these sources of progenitor cells that together form the heart during development, it is unclear whether they also contribute to newly formed cardiomyocytes in the adult mammalian heart following injury.

Developmental Cardiac Progenitors and Regeneration

Most adult tissues harbor somatic stem cells that aid in ongoing maintenance and regeneration following injury [5]. Some of these somatic stem cells have a developmental origin, such as the hematopoietic stem cell, which is derived from fetal liver hematopoietic stem cells that invade the bone marrow niche during the later stages of murine development [68]. After arrival in the bone marrow niche, the majority of these hematopoietic stem cells become quiescent and are reactivated in response to distinct cues [69]. Similarly, the adult satellite cells that form the somatic stem cells for skeletal muscle are derived from the same dermomyotome as the developmental muscle progenitors that give rise to embryonic myoblasts [70]. Recent evidence suggests that the heart may also harbor a limited number of these developmentally derived progenitor cells [6]. It is unclear whether these progenitors are cells that were never fully differentiated but are already fully committed to become cardiomyocytes or whether they are uncommitted progenitor cells that continue to have the capacity to give rise to all cell types in the heart [71].

During development, Nkx2-5 is the most specific and widespread marker of progenitor cells that will ultimately generate cardiomyocytes [72, 73]. Using a Nkx2-5-GFP reporter transgenic mouse line, it was determined that these developmental progenitors represent a bipotential pool of uncommitted cells that give rise to cardiomyocytes and smooth muscle cells [74]. Surprisingly, a number of these uncommitted progenitor cells resided in the postnatal heart, with numbers decreasing from 5 % at 1–2 weeks of age to less than 0.3 % of nonmyocytes at 8 weeks [75]. Recent studies have identified a Tgf-β signaling pathway that regulates the proliferation of these progenitor cells, both in vitro and in vivo [76]. Specifically, the inhibition of Tgf-β family receptors Alk4, Alk5, and Alk7 significantly enhanced both the numbers of Nkx2-5 progenitor cells and their differentiation toward cardiomyocytes. Moreover, the inhibition of Tgf-β receptor 1 enhanced cardiomyoblast proliferation and differentiation in vivo following myocardial infarction and improved cardiac function [76]. To what extent new cell formation was responsible for the improvement in cardiac function is not clear. Nevertheless, these exciting findings provide a platform for using embryonically derived progenitor cells that remain in the adult heart for regenerative strategies.

A second population of embryonic progenitors express the transcription factor Islet1 (Isl1) [77]. During development, the Isl1-expressing progenitors are generated in the second heart field. While recent data suggest a more widespread expression pattern for Isl1, its role in the first heart field is less prominent. The phenotype of *Isl1* null mice, which lack a right ventricle and outflow tract, emphasizes the importance of this factor in the second heart field [78, 79]. Since Isl1-expressing cells are essential for the formation of the right ventricle and the outflow tract, they are important developmental progenitor cells. Interestingly, not all of the Isl1-expressing progenitor cells differentiate during development [80]. The majority of progenitor cells differentiates during cardiac development and can no longer be identified by Isl1 expression at the time of birth, but a limited number of cells remain positive for Isl1 expression (500–600 per rat heart). $Isl1^+$ progenitor cells have the potential to differentiate into endothelial cells and smooth muscle cells, as well as cardiomyocytes in vivo and in vitro. Importantly, both in rodents and in humans, postnatal $Isl1^+$ cardioblasts have been identified and shown to have the same capacity to differentiate into different cardiac lineages as embryonic $Isl1^+$ progenitor cells. Moreover, a recent study identified a small molecule that enhanced the renewal of $Isl1^+$ progenitor cells [81]. Importantly, these studies defined a triphasic role for Wnt signaling during cardiomyocyte differentiation. That is, prior to specification of cardiac progenitor cells, Wnt signaling is inhibited to allow a maximal number of progenitor cells. During the progenitor cell phase, when these cells are actively proliferating, Wnt is stimulated to maximize the number of progenitors. But immediately thereafter, Wnt signaling is once again inhibited; otherwise, cardiomyocyte differentiation will be suppressed. This time-sensitive dependency on Wnt signaling has been used during embryonic stem cell and induced pluripotent stem cell differentiation to generate cardiomyocytes [82–84]. Although these findings have uncovered a critical dependency on Wnt signaling during cardiac progenitor cell proliferation, and while the $Isl1^+$ progenitor cells display multi-lineage differentiation potential, the overall number of $Isl1^+$ progenitors that reside in the postnatal heart is most likely too small to produce significant cardiac regeneration, even if the numbers are enhanced in response to Wnt signaling [80, 85].

A third population of embryonic progenitors that could potentially be employed for cardiac regeneration is the epicardial-derived progenitor cells [30, 86, 87]. As previously outlined, during development, epicardial progenitor cells contribute limited numbers of cardiomyocytes to the

developing heart. This was clearly shown using Wt1 as an epicardial-specific marker [30]. Genetic lineage-tracing studies demonstrated that Wt1-derived cells generate cardiomyocytes during development. Moreover, it was shown that Wt1 cells have the ability to contribute cardiomyocytes during post-myocardial infarction cardiac remodeling [31]. While the levels of new cardiomyocyte formation were not quantified, the Wt1 lineage was shown to contribute cardiomyocytes. However, this contribution only occurred when the heart was pretreated (before initiation of myocardial infarction) with thymosin β4. Subsequent studies that attempted to replicate these findings could not identify newly established cardiomyocytes in the absence of thymosin β4 priming [31, 32].

Genetic Networks and Signaling Pathways During Cardiac Development

A plenitude of transcription factors has been studied during cardiac development for their role in cardiac morphogenesis [88, 89]. Many of these cardiac transcription factors can cause congenital heart defects when perturbed or mutated [90]. For example, mutations in the transcription factors Gata4 and Nkx2-5 can cause septal defects (atrial, ventricular, or combined) or even tetralogy of Fallot [91]. As previously noted, Nkx2-5 is a critical transcription factor during cardiac development and is one of the first transcription factors that specify cardiac progenitor cells [73]. Gata4 becomes expressed in cardiomyocytes early after Nkx2-5 and is also a critical transcription factor for cardiomyocytes [92, 93]. Genetic deletion of Nkx2-5 or Gata4 in mouse embryos results in cardiac developmental defects and lethality early after formation of the heart [72, 92, 93]. A third transcription factor that has a crucial role during cardiac development is Tbx5 [94]. Again, deletion of this gene in mouse embryos results in embryonic lethality soon after formation of the heart [95]. Mutations in Tbx5 result in Holt-Oram syndrome and are associated with a combination of atrial septal defects and digit abnormalities [96].

Although all of these transcription factors are critically important for cardiac development, their role during cardiac regeneration is not clear [97]. The most prominent strategy that uses these transcription factors for regenerative purposes aims to transdifferentiate fibroblasts to cardiomyocytes [98]. This is performed by overexpression of a set of at least three transcription factors in combination, including Gata4, Mef2c, and Tbx5, as discussed later in this chapter.

A gene network that has gained more attention in recent years for its potential role in regeneration is the Hippo signaling pathway [99]. This pathway was originally described in Drosophila and was shown to be important for the determination of organ size during development [100]. Although the upstream activator of this kinase-signaling cascade has not been firmly established, it is clear that the activation of Hippo (Mst1/2 in mammals) leads to phosphorylation and activation of the downstream kinase, Warts (Lats1/2 in mammals), which in turn can phosphorylate and inactivate Yorkie (Yap/Taz in mammals) [99]. During development, it was determined that perturbation of this signaling cascade leads to increased heart size due to enhanced and persistent proliferation of cardiomyocytes [101]. These findings are consistent with previous results in Drosophila, and also in other organ systems, indicating that the Hippo signaling pathway is involved in regulating organ size. While the precise mechanisms of regulation are not entirely clear, it has been shown that Hippo signaling could affect both differentiated cells, as well as progenitor cells [99]. Thereby, the overall effect of uninhibited Hippo-mediated gene expression could be cumulative, resulting in more progenitor cells and more differentiated cells.

Importantly, the developing heart regulates its size via both mechanisms. However, to the extent Hippo signaling could also play a role in the adult heart was not entirely clear.

The downstream effectors of the Hippo signaling pathway in mammals are Yap and Taz. To determine the importance of Yap in the developing and postnatal heart, conditional deletion cardiac mutants were generated, resulting in early postnatal lethality, indicating important roles for Yap in the heart [102]. In addition, transgenic strategies were used to express a constitutively active form of Yap in the adult heart [103, 104]. Interestingly, the activation of YAP stimulated cardiomyocyte proliferation and enhanced cardiac regeneration after experimental myocardial infarction. This is likely due to the direct effect on cardiomyocyte proliferation, since neonatal mice can completely recover from an experimental myocardial infarction due to the capacity of neonatal cardiomyocytes for proliferation [41, 105].

One week after birth, when neonatal cardiomyocytes no longer proliferate, experimental myocardial infarction no longer results in complete regeneration, but rather in scar formation [41, 42]. Importantly, activation of YAP was capable of inducing cardiac regeneration both 1 week and 4 weeks after birth, circumventing the proliferative block of most postnatal cardiomyocytes. These results were further confirmed using adeno-associated virus (AAV)-mediated activation of Yap in adult mice [103]. Finally, these results have been replicated and expanded to include additional regulators of the Hippo pathway, including the miR302-367 cluster as critical regulators of cardiomyocyte proliferation and cardiac regeneration [106].

Cellular Turnover in the Adult Mammalian Heart

The heart consists of multiple cell types, and, during homeostasis, all of these cell populations have low turnover rates [107]. The regulation of cellular turnover in the heart is unknown. Whether a stem cell population exists that orchestrates these proliferative events depending on demand or whether they are individually regulated by dedicated progenitor cells is an area of intense interest [6, 71, 108, 109]. Histological examination of mitotic figures has identified dif-

ferences in the normal turnover rates, not only of certain cell types, such as cardiomyocytes vs. endothelial cells, but also involving anatomically distinct regions of the heart [11, 12]. For example, the atria appear to be more amenable to proliferative stimuli than the cardiac ventricles. For most cell types, the assessment of mitotic figures or even incorporation of DNA nucleosides such as BrdU or EdU is sufficient to assess their turnover rate. However, cardiomyocytes have a peculiar characteristic that allows them to undergo endoreduplication, which increases ploidy per nucleus by undergoing DNA synthesis without mitosis, or by completing mitosis to generate two nuclei without undergoing cytokinesis [6, 110]. The mechanisms underlying this characteristic are not clear, and distinct species differences exist regarding the abundance of binucleated vs. mononucleated cardiomyocytes [110, 111]. To assess new cardiomyocyte formation, a number of recent technological advances have enabled an assessment of the turnover rates of cardiomyocytes.

Carbon Dating of Resident Cardiomyocytes

An innovative experimental approach was undertaken in 2009 to evaluate cellular proliferation and turnover in the adult heart [112] (Fig. 23.4). Radiocarbon dating is a well-known technology used to determine the age of biological materials [113]. ^{14}C is generated in the atmosphere, incorporated into plants by photosynthesis, and constantly exchanged during the life of animals, plants, or humans who ate the animals or plants. After plants or animals die, the amount of ^{14}C slowly decays over time at a constant rate. This constant rate is used to determine age by comparing the atmospheric levels of ^{14}C to the measured levels in the tested sample.

This technology has been used reliably to determine the age of fossils. Recently, this approach was adopted to determine the age of individual human cardiomyocytes. During the Cold War, aboveground nuclear testing released a pulse of ^{14}C into the atmosphere. This pulse was finite as all aboveground nuclear tests were eliminated following the Nuclear Test Ban Treaty in 1963. Therefore, this ^{14}C atmospheric pulse allowed investigators to determine the age of human cells [114]. Initially, the investigators established a protocol to distinguish cardiomyocyte nuclei from non-cardiomyocyte nuclei based on troponin expression [115]. In addition, the analyses were performed to account for increases in nuclear ploidy.

Using this strategy, the overall rates of renewal as detected by ^{14}C dating were relatively low, but measurable [112] (Fig. 23.4). About 1 % new cardiomyocytes were formed

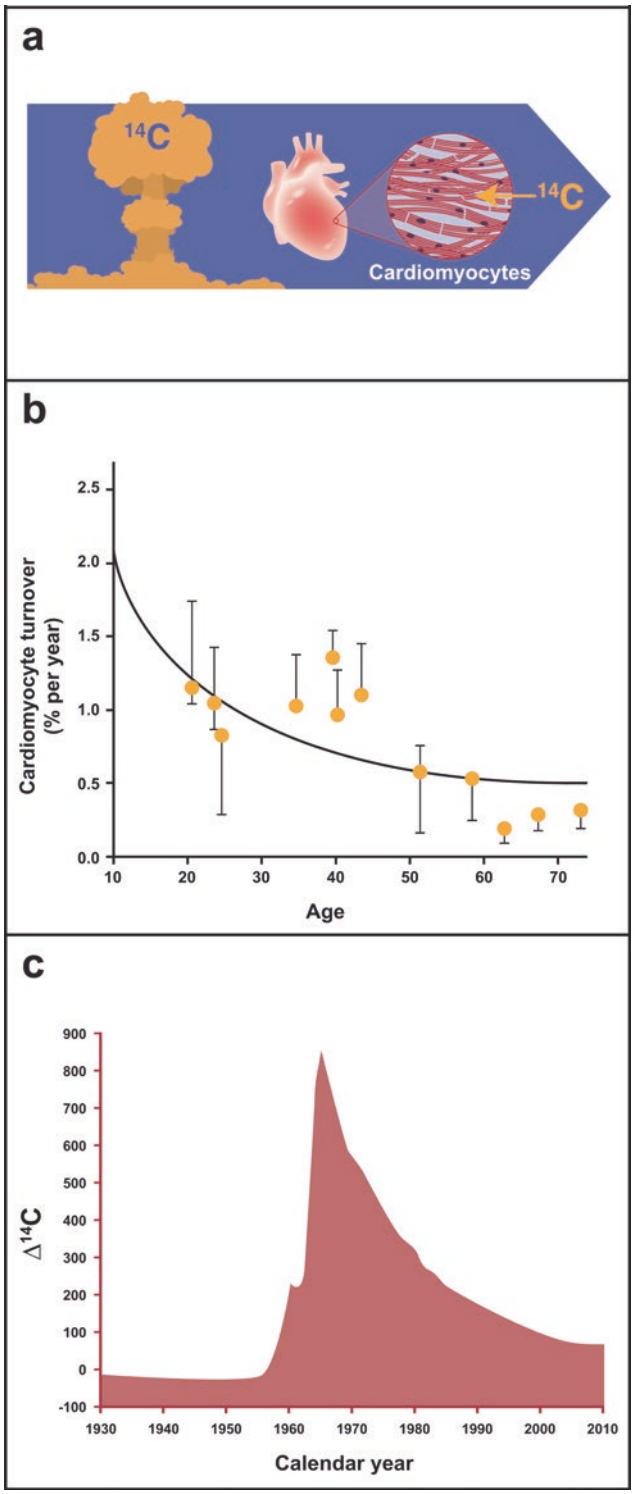

Fig. 23.4 Radiocarbon dating of cardiomyocytes. (**a**) Based on the large increase in atmospheric ^{14}C levels due to aboveground nuclear bomb testing in the twentieth century, the levels of ^{14}C found in cardiomyocyte nuclei can be used to determine the birth date of cardiomyocytes. (**b**) Birth dating of cardiomyocytes is enabled by the large increase in atmospheric ^{14}C followed by its sharp decline after the 1963 Nuclear Test Ban Treaty, as the biosphere absorbed the carbon. The biosphere-incorporated ^{14}C will be incorporated into the food we consume and the ^{14}C is incorporated into our cells. Especially long-lived cells such as cardiomyocytes will allow precise birth dating based on measured ^{14}C levels compared to atmospheric levels.

Fig. 23.4 (continued) (**c**) Based on the measured ^{14}C content in cardiomyocyte nuclei, combined with the calendar age of the individual from which these cardiomyocytes were acquired and the use of mathematical modeling, a yearly cardiomyocyte turnover rate is estimated at about 0.5–1 %. Adapted from Bergmann O, Bhardwaj RD, Bernard S, Zdunek S, Barnabé-Heider F, Walsh S, Zupicich J, Alkass K, Buchholz BA, Druid H, Jovinge S,Frisén J. Evidence for cardiomyocyte renewal in humans. Science. 2009 Apr 3;324(5923):98–102

per year, which leads to more than half of the heart being replaced over the average lifetime of humans. Although yearly renewal rates may be low, the total amount of renewed myocardium over a lifetime is likely to be important for cardiac function. Therefore, these studies emphasized that any perturbation in the regenerative capacity of the heart may lead to a reduction in cardiac function. Importantly, these findings provide convincing evidence of cardiomyocyte turnover and ongoing renewal of the heart, albeit at low levels [116].

The rates established by ^{14}C dating of individual cardiomyocyte nuclei in humans were recently reproduced in mice using a separate strategy. Here, a novel approach was used to feed mice thymidine, a nucleoside that is incorporated into DNA during DNA synthesis and cellular proliferation [117]. However, instead of feeding mice regular thymidine, the authors used ^{15}N thymidine, an isotope that is relatively rare in nature (0.3 %). An advanced imaging modality (multi-isotope imaging mass spectrometry) was used to quantify the ratio between ^{15}N and ^{14}N. Using this strategy, any signal that exceeded the natural ratio was clearly visible [117]. This method was first validated using the kinetics of intestinal crypt stem cells that continuously cycle to produce new cells. Further, the method was used to falsify the immortal strand hypothesis, which suggested that new DNA strands were preferentially segregated in 1 daughter cell [117]. When the investigators applied this new imaging modality to quantify the numbers of cardiomyocytes that undergo proliferation at baseline and following injury, they noted that the total proliferation rates were very low, with calculated renewal rates of just below 1 % per year during normal aging [109].

Genetic Models

The ability to quantify cardiomyocyte renewal is difficult due to the complex nature of cardiac tissue [6, 118, 119]. The sizes of cells are not uniform, and non-cardiomyocyte nuclei are in close proximity to cardiomyocytes. Furthermore, the non-cardiomyocyte fraction has a greater tendency to undergo proliferation compared to cardiomyocytes [107]. These characteristics make it difficult to assign a given nucleus to a cardiomyocyte in histological sections. To correctly identify cardiomyocyte nuclei, a genetic mouse model that specifically expresses a nuclear localized β-galactosidase protein in cardiomyocytes was used to precisely quantify the cardiomyocyte renewal rates at baseline and following injury [119, 120]. This genetic mouse model was combined with injection of tritiated thymidine to precisely measure DNA synthesis in cardiomyocytes [120].

The rates reported using this genetic mouse model were very low, which reflected that they were established from a single injection of thymidine. However, when these rates were extrapolated to yearly renewal rates, they were estimated to be about 1 % per year. One important caveat, however, is the observation that cardiomyocytes can undergo endoreduplication, which results in positive nuclei that are not indicative of cardiomyocyte renewal. It is further appreciated that, in response to pathological stimuli such as hypertension or following myocardial infarction, there would be a hypertrophic response of cardiomyocytes with low-level stimulation of proliferation resulting in increased ploidy [110, 111, 121].

A clear positive correlation was shown between cardiomyocyte size and DNA content. Yet any increase in DNA synthesis does not necessarily mean an increase in the number of cardiomyocytes. Quantification of the regenerative response following an injury was even more difficult due to increased numbers of immune cells invading the heart that were often positive for incorporated DNA nucleosides such as BrdU or ^{3}H-thymidine. All these factors complicated precise quantification of new cardiomyocyte formation [6, 121].

With advances in genetic manipulations in mice, a new strategy was devised to more accurately assess whether new cardiomyocytes are actively being formed by existing cardiomyocytes or by non-cardiomyocytes. To that end, a cardiomyocyte-specific inducible Cre line was combinatorially mated to a double reporter that expressed β-galactosidase in all cells at baseline, but GFP upon recombination [108]. After induction of recombination in adult mice, a maximum of 85 % of all cardiomyocytes was recombined to express GFP.

The hypothesis that was being tested stated that if cardiac progenitor cells were important contributors of new cardiomyocytes, then there would be an increase over time of non-GFP-expressing cardiomyocytes, since the Cre recombinase was only induced in already existing cardiomyocytes. So any newly generated cardiomyocytes from progenitor cells would not express GFP. However, no statistically significant increase was noted up to a year after labeling, indicating no contribution of progenitor cells to new cardiomyocyte formation during normal aging in mice [108]. In response to injury, however, a significant increase in the number of GFP^- cardiomyocytes was noted, with as much as 15 % new cardiomyocytes being generated from non-cardiomyocytes.

Although these data were initially interpreted as unequivocal evidence of new cardiomyocyte formation by progenitor cells, the investigators of this study reinterpreted their data in light of the fact that the majority of proliferative events that gave rise to new cardiomyocytes were actually not occurring in GFP^-, but in GFP^+ cardiomyocytes [109]. Therefore, no good explanation exists for the observed increase in GFP^- cardiomyocytes. If they were progeny from a progenitor cell pool, this pool was most likely depleted due to lack of ongoing renewal, given the absence of DNA duplication events in GFP^- cardiomyocytes. Other lines of evidence suggest that both cardiomyocytes and non-cardiomyocytes could contribute new cardiomyocytes to the adult heart. For example, recent evidence suggested that cardiac cell therapy—where cells were injected (either intravenous or intracardiac) following myocardial infarction—resulted in the activation of

endogenous progenitor cells that were stimulated to generate new cardiomyocytes [122, 123].

Another line of evidence provided direct proof that cardiomyocytes were capable of generating new cardiomyocytes in the adult mouse heart [124]. In these studies, the authors used a genetic mouse model that exchanged reporter cassettes between sister chromosomes during mitosis. This strategy enabled the direct visualization of newly formed cells that had completed cytokinesis, although the labeling efficiency was difficult to assess. The results showed that new cardiomyocytes were being formed from existing cardiomyocytes. The main discrepancy with previous findings was the lack of increased new cardiomyocyte formation in response to myocardial infarction.

The data from these studies provide convincing evidence that existing cardiomyocytes can give rise to new cardiomyocytes during normal aging. The majority of data suggest that injury such as myocardial infarction also induces new cardiomyocyte formation, although there are some conflicting data. Importantly, the reported rates of new cardiomyocyte formation from existing cardiomyocytes are mostly in agreement with each other and suggest cardiomyocyte turnover occurs at a rate of about 1 % per year in both mice and humans [109, 112]. While this low level of ongoing renewal may not be physiologically relevant for cardiac function in the mouse (which has a lifespan of 2–3 years), it would have a major impact in humans, with an average lifespan of over 70 years. This ongoing renewal may very well be extremely important to maintain normal cardiac function.

Endogenous Cardiac Progenitors

In addition to cardiomyocytes serving as a source for generating new cardiomyocytes, as discussed in the previous section, there is convincing evidence that the adult heart contains a limited number of uncommitted progenitor cells [27, 28, 71, 125] (Fig. 23.5). These progenitor cells can be extracted from the heart, mostly based on marker gene expression, and maintained in their undifferentiated state in cell culture [27, 28]. Upon activation, these cells undergo differentiation both in vitro and in vivo to give rise to new cardiomyocytes, endothelial cells, and smooth muscle cells. The developmental origin of these progenitor cells is not known, and a number of different markers have been used to identify progenitor cells, with limited overlap between these populations [71].

The c-kit-Expressing Progenitor Cell Population

The most extensively studied marker of cardiac progenitor cells is the tyrosine kinase receptor, c-kit [126] (Fig. 23.5). This receptor is a well-known marker of hematopoietic progenitor cells, both in mice and humans [127–129]. It is also expressed on Leydig cells in the testes, on melanoblasts and melanocytes in the skin, the interstitial cells of Cajal in the intestine, etc., where the exact function of c-kit-expressing cells is incompletely defined [130–132]. Based on the hypothesis that states that markers of progenitor cells in one tissue

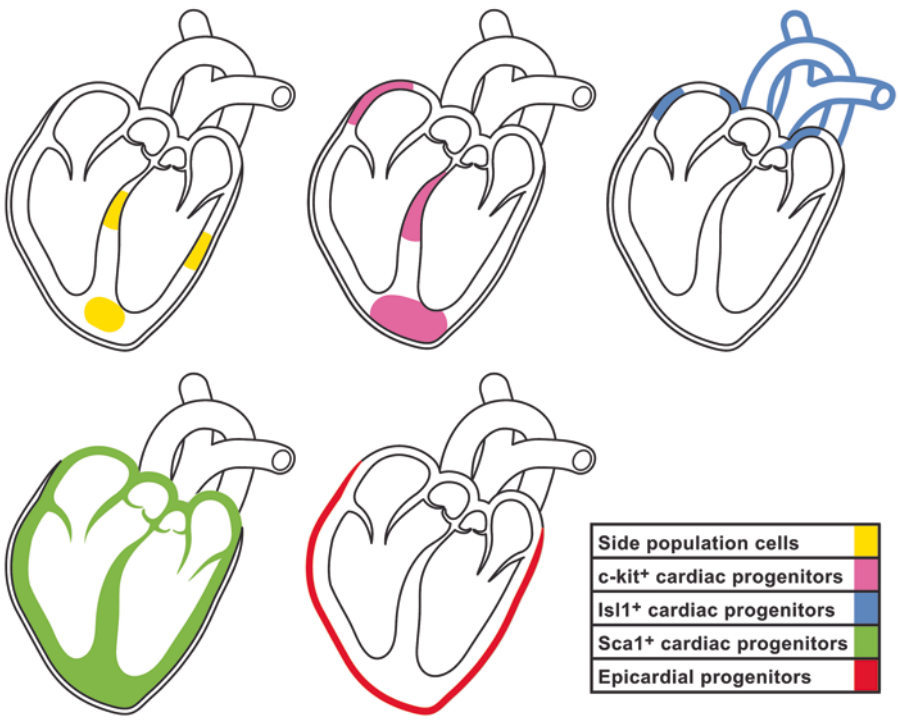

Fig. 23.5 Endogenous cardiac progenitor cells in the adult heart. As many as five distinct progenitor populations have been identified in the adult mammalian heart. Depicted is a schematic representation of these five progenitor populations and their reported anatomic distribution and abundance. To the extent that any of these progenitor populations contribute to endogenous cardiac repair remains to be determined (*RA* right atrium, *LA* left atrium, *RV* right ventricle, *LV* left ventricle)

also mark progenitor cells in another tissue, c-kit cardiac progenitor cells were identified in 2003 [27]. These cardiac progenitor cells were isolated based on the absence of the panhematopoietic lineage marker, CD45, and the presence of c-kit (lin$^-$c-kit$^+$). In culture, these lin$^-$c-kit$^+$ CPCs could be maintained in a proliferative undifferentiated state, they were clonogenic, and, importantly, they could be differentiated into all three major cardiac cell lineages: cardiomyocytes, endothelial cells, and smooth muscle cells. Furthermore, upon injection of undifferentiated CPCs into the infarcted rodent heart, they readily differentiated and improved cardiac function and repaired the infarct by approximately 70 %.

The existence of uncommitted c-kit$^+$ CPCs in the rat has been confirmed in other species, including mouse, dog, pig, and humans [133–135]. The isolation procedures vary somewhat and range from the immediate isolation using magnetic sorting beads to obtain lineage-negative, c-kit-positive cells, to the plating of isolated non-cardiomyocytes overnight before the selection of lineage-negative, c-kit-positive cells [27, 136, 137]. A strong argument for the progenitor status of c-kit CPCs is that they can be grown (or expanded) clonally in an undifferentiated state and then differentiated to the three main cardiac lineages: cardiomyocytes, endothelial cells, and smooth muscle cells [27, 133, 137].

A number of studies have identified factors that have a role in forming the niche for c-kit progenitor cells in the heart [138–140]. Since these progenitor cells are capable of both proliferation and differentiation, their control should be governed by intrinsic and extrinsic cues to guide cell fate decisions. In the bone marrow, supporting cells that interact with the hematopoietic stem cells provide these cues and maintain them in a quiescent state [141, 142]. While the precise requirements for the hematopoietic niche are also incompletely defined, recent evidence suggests tight interactions with a single mesenchymal stromal cell, together with supporting endothelial cells, are critical for the formation of a niche and to provide cues for cell cycle reentry and cell division, ultimately leading to either self-renewal and/or differentiation [141, 143].

The major benefit of the hematopoietic system is the availability of a depletion strategy followed by transplantation and homing of stem cells to the hematopoietic niche [144]. This, however, is not possible in the heart. Therefore, it has been more difficult to identify factors that regulate the cardiac stem cell niche [145]. Although the stem cell niche in the heart is less well defined, a number of factors are known to play important roles. First, a number of studies have characterized the cardiac progenitor cell niche and consistently find fibronectin present in the extracellular matrix surrounding the progenitor cells [27, 146]. Second, to the extent there is an interaction with supportive cells, as has been described for the hematopoietic stem cell niche, these cell-cell interactions in the cardiac progenitor cell niche are unclear. Several reports have shown connexin43 expression on CPCs and an interaction with the surrounding myocardium and other cells, but how these interactions regulate CPCs is not known [139, 147]. One potential mechanism is the exchange of genetic material, such as miRNAs through gap junctions. Active exchange of miRNAs to guide differentiation decisions has been demonstrated between cardiomyocytes and CPCs [148]. However, these experiments were performed in cell culture, with no in vivo proof of such an exchange mechanism.

In addition to niche factors that may promote CPC proliferation or differentiation, it is hypothesized that various signaling pathways are likely to have a role in CPC differentiation [53, 149–151]. One of the most prominent pathways suggested to have a role is the Notch signaling pathway. Notch signaling has been described as an important receptor for proliferation and differentiation in other organ systems [152, 153]. For example, in hematopoietic stem cells, the activation of Notch signaling initiates erythroid differentiation. In other organs, Notch signaling has been shown to be important in regulating cell fate and cellular proliferation [153]. In the heart, Notch signaling has been shown to initiate cardiomyocyte differentiation while repressing vascular differentiation [150].

The molecular mechanism underlying these events involves direct binding on the internally cleaved active Notch receptor domain to RBP-Jk, which in turn binds to the Nkx2-5 promoter to initiate cardiomyocyte differentiation. Moreover, the inhibition of Notch signaling in neonatal mice was sufficient to cause dilated cardiomyopathy due to reduced numbers of cardiomyocytes, suggesting a crucial role of Notch signaling in the maturation of the early postnatal heart.

A second marker of CPC differentiation that initiates vascular differentiation is the expression of the vascular endothelial growth factor (VEGF) receptor, Kdr [154]. In both human and mouse CPCs, the expression of Kdr coincided with CPCs that would adopt vascular endothelial fates, while Kdr-negative CPCs showed a higher tendency to differentiate toward a cardiomyocyte fate.

Although these initial studies have uncovered some potentially important signaling events, the lack of genetic models to evaluate the impact of signaling networks specifically in CPCs has limited our understanding of the pathways that govern CPC lineage specification. Recently, however, a mouse model was engineered where Cre recombinase was knocked into the murine Kit locus. This genetic mouse model was initially used for genetic lineage tracing to determine the extent that CPCs generate differentiated cells in the developing and adult heart [155]. Surprisingly, CPCs contributed minimally to the generation of cardiomyocytes, even after myocardial injury, while the main cell type generated by c-kit CPCs was endothelial cells. These genetic mouse models will prompt more mechanistic studies focused on cell-autonomous factors within CPCs that drive cell fate decisions. However, to date, the exact mechanisms regulating cardiac progenitor cell proliferation and differentiation remain largely unknown.

Sca1 Cardiac Progenitor Cells and Side Population Cells

In addition to c-kit-expressing CPCs, other markers have been used to isolate cardiac progenitor cells. Sca1 expression has been used to identify an alternative progenitor cell population in murine hearts [28]. The expression of Sca1 and c-kit resembles expression of these two markers on hematopoietic stem cells, although the overlap in expression of these two markers on cardiac progenitor cells is limited. Sca1 is expressed in a greater number of cells than c-kit, and most of these are vascular or perivascular cells. Based on published literature, the ability of murine Sca1-expressing CPCs to differentiate into cardiomyocytes is more limited than c-kit$^+$ CPCs [27, 28].

Given the widespread expression of Sca1 in the heart, not all of these cells are considered progenitor cells. The Sca1-expressing cells that do not express the endothelial marker Pecam1 (CD31) are typically considered CPCs. These Sca1$^+$CD31$^-$ CPCs can be isolated, cultured under undifferentiated conditions, and have the ability to differentiate into cardiomyocytes upon injection into the infarcted mouse heart. Moreover, the deletion of Sca1 has been shown to negatively impact cardiac function and is associated with increased Wnt signaling, suggesting an important role for endogenous Sca1 progenitor cells in normal cardiac performance [156].

More recently, an attempt to perform genetic lineage tracing of Sca1 cardiac progenitor cells indicated cardiomyocyte differentiation from Sca1 CPCs [157]. However, the genetic strategy that was used may have overestimated the abundance of cardiomyocyte differentiation due to more widespread expression of the genetic driver than endogenous Sca1 expression [6]. Whether humans express Sca1 is widely debated, but we know the Sca1 antibody has been used to isolate human cardiac cells [158, 159]. Upon isolation, these human cardiac cells appear to be progenitor cells with the ability to proliferate and differentiate into cardiomyocytes. More importantly, these human cardiac progenitor cells promote cardiac repair upon transplantation into mouse hearts post-myocardial infarction and differentiate into cardiomyocytes [159]. To date, no clinical trials have been performed using Sca1$^+$ cardiac progenitor cells.

A third source of endogenous cardiac progenitor cells is not based on the expression of a single marker, but the extrusion of the DNA dye, Hoechst 33342, in a subset of cardiac cells (Fig. 23.5). It allows for the isolation of these cells using flow cytometry (fluorescence-activated cell sorting, FACS) [160]. These cells sort to the side of the main population, hence their designation as side population (SP) cells. A number of ABC (ATP-binding cassette) transporter proteins (also referred to as multidrug resistance proteins) have been identified as conferring the capacity to extrude the DNA dye, most notably Abcg2 and Mdr1 [161].

The abundance of SP cells in the heart is relatively low, and, typically, multiple hearts are pooled to isolate cardiac SP cells. SP cells express other markers, such as Sca1 and CD31, supporting the notion that SP cells are a specialized subpopulation of Sca1 CPCs [162, 163]. When isolating cardiac SP cells, they are maintained in an undifferentiated state and can be made to differentiate toward cardiomyocyte fates by addition of oxytocin or the histone deacetylase inhibitor trichostatin A or by coculture with adult rat ventricular cardiomyocytes [67, 125, 162, 164, 165]. Transplanted SP cells can home to the infarcted heart and differentiate into multiple cardiac lineages, such as cardiomyocytes, endothelial cells, and smooth muscle cells [166]. Given the lack of a clear molecular marker for side population cells, there is currently no proof of the contribution of SP cells, in vivo, to promote endogenous cardiac repair [6, 161].

Epicardial Progenitor Cells

In recent years, the epicardium has received intense interest as an important source of progenitor cells (Fig. 23.5). Especially during development, it was shown that the epicardium contributes multiple cell types to the developing heart, including cardiomyocytes, fibroblasts, and smooth muscle cells [30, 167]. The source of these various cell types can be traced by different epicardial markers, including Wt1 and Tbx18 [30, 86, 87]. During development, these epicardial progenitor cells contribute various cell types to the heart, but the extent to which this occurs in the adult injured heart is unclear.

A recent study identified Wt1-derived cells as epicardial-generated cardiomyocytes after myocardial infarction [31]. However, a different study was unable to confirm these results using the same mouse model to perform genetic lineage tracing [32]. The only difference between these two studies was the administration of thymosin β4 before the onset of myocardial infarction—in the case when Wt1-derived cardiomyocytes were detected. The exact function of thymosin β4 in this context is not clear, but, previously, thymosin β4 was shown to ameliorate cardiac remodeling through the activation of integrin-linked kinase and Akt and to support survival of cardiomyocytes in culture [168].

Although the cells responsible for cardiac repair may no longer express the epicardial marker gene in the adult, it is still conceivable that the epicardium deploys a number of progenitor cells during development that, upon injury, can be activated to initiate cardiac repair. Evidence to support this notion used strategies similar to the ones used to analyze hematopoietic cells. It was reported that the heart contains mesenchymal cells that can form colonies similar to bone marrow mesenchymal cells [169]. These colonies are formed by undifferentiated cells that can differentiate into many cardiac cell types, including cardiomyocytes, endothelial cells, and smooth muscle cells. The extent to which these pro-epicardial-derived, colony-forming mesenchymal cells contribute to cardiac repair in the adult heart remains an unsettled question.

Reprogramming Strategies

Although cardiac progenitor cells reside in the adult heart, their regenerative capabilities are insufficient to repair the damaged heart following a severe insult such as a myocardial infarction [170]. Regeneration with cardiomyocytes and a vascular support system would be preferable, but the post-injured heart typically is marked by scar tissue and fibroblasts [171, 172]. One clever strategy takes advantage of these large areas of fibrosis in an attempt to convert the fibroblasts into cardiomyocytes (Fig. 23.6).

Fibroblast-to-Cardiomyocyte Transdifferentiation

The epigenetic landscape that was schematized by Waddington in 1940 (*Organisers and Genes*) of how an uncommitted stem cell differentiates into fully committed and terminally differentiated cells consists of a slope with ridges and valleys [173]. The uncommitted cells can only go down the slope through the valleys and were presumed to lack the ability to overcome the interspersing ridges. However, in recent years, this notion has been challenged. A classic example of fate conversion is the differentiation to skeletal muscle cells when MyoD is expressed in mouse embryonic fibroblasts [174]. These experiments designated MyoD as a master regulator of skeletal muscle cell fate [175]. Although MyoD is indeed a powerful regulator of fate, most other cell types (or lineages) are not instructed by the expression of a single gene.

Nevertheless, these results led to the notion that lineage-specific transcription factors may be sufficient to drive trans-differentiation. Most notable was the identification by Yamanaka and coworkers of four factors that promoted the conversion of fibroblasts back to a stem cell state [176]. Given the success of conversion to an undifferentiated state by forced expression of a set of genes, other investigators began

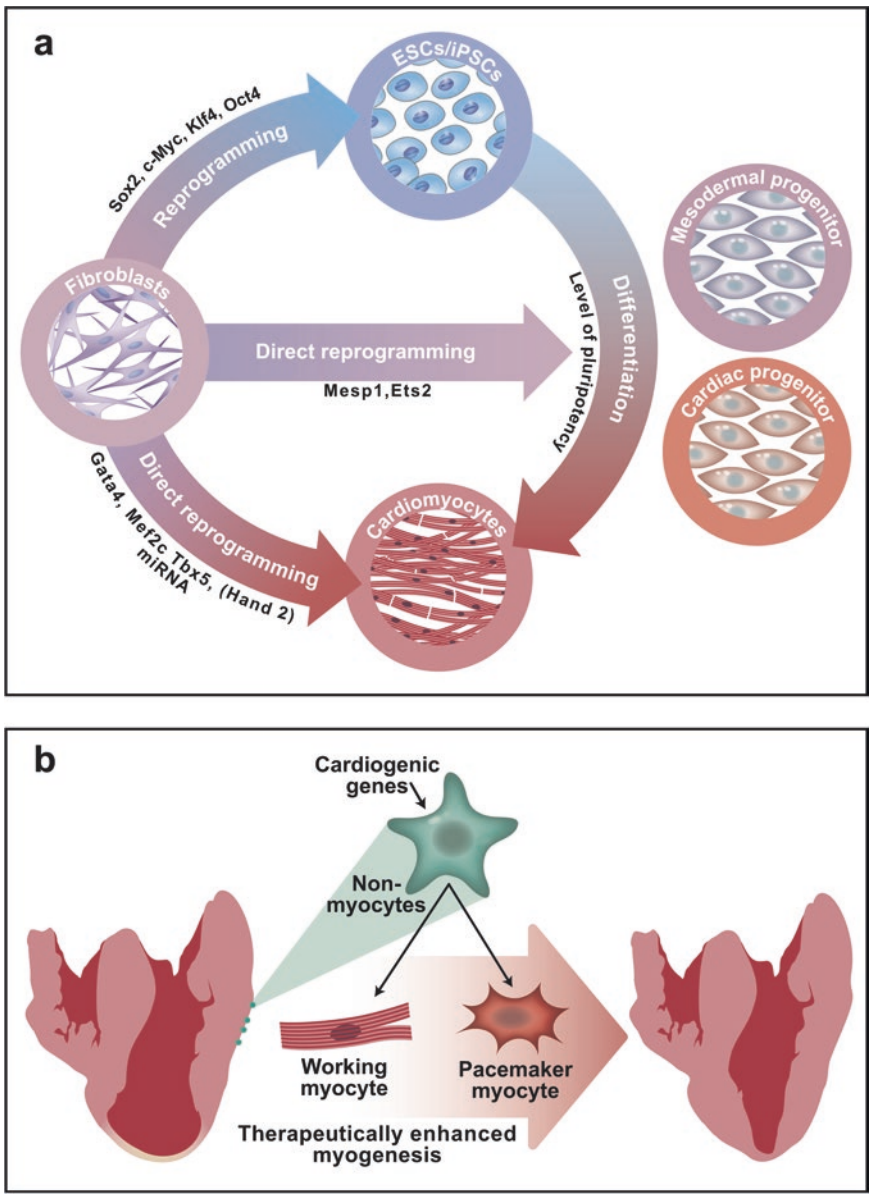

Fig. 23.6 Reprogramming strategies to generate cardiomyocytes. (**a**) A number of strategies to generate more cardiomyocytes are currently used in basic research. Fibroblasts can be converted to pluripotent cells that are then differentiated to cardiomyocytes. Alternatively, to prevent potential carcinogenic effects of undifferentiated pluripotent cells that might remain after differentiation, fibroblasts can be directly converted to cardiac progenitor cells. Finally, fibroblasts can be converted to cardiomyocytes on a one-to-one basis, which eliminates the requirement of proliferation and, thereby, likely diminishes the risk for cancer. Whether this final strategy can have the efficiency needed for a functional impact remains to be determined. (**b**) Direct reprogramming of fibroblasts to various specialized cardiomyocytes, including Purkinje and pacemaker cells, might aid in circumventing potential arrhythmogenic effects of direct reprogramming

to explore the notion of direct conversion of fibroblasts to terminated lineages by forced expression of a set of genes. Studies undertaken in Doug Melton's laboratory demonstrated that exocrine pancreatic cells could directly convert into insulin-producing β cells through forced expression of three transcription factors: Pdx1, Ngn3, and Mafa [177], without the need for an intermediate progenitor cell. Following these initial reports, other differentiated cells were generated by direct conversion, such as neurons and cardiomyocytes [98, 178].

For conversion of fibroblasts into cardiomyocytes, a set of three transcription factors was initially identified using mouse fibroblasts [98]. Forced expression of Gata4, Mef2c, and Tbx5 was sufficient to convert fibroblasts into cardiomyocyte-like cells. A number of cells began to express cardiomyocyte markers, such as myosin heavy chains and troponin, yet only a subfraction of these reprogrammed cells demonstrated spontaneous contractions.

Lineage-tracing studies using a plethora of Cre recombinase drivers showed absence of a transitional progenitor cell during the fibroblast-to-cardiomyocyte conversion, suggesting direct conversion. After the initial findings, other groups verified the findings and were able to convert fibroblasts to cardiomyocytes by forced expression of a set of defined factors [179]. Interestingly, the combination of factors used varied among the different studies, although Gata4, Mef2c, Tbx5, and/or Hand2 are most efficient in their conversion of murine fibroblasts to a cardiomyocyte fate. One study used microRNAs to induce fate conversion [180].

A major drawback and potential limitation for translational strategies using direct conversion, however, has been the low rates of fibroblast conversion to beating cardiomyocytes. Similar to the induction of pluripotency, not all cells that received the conversion factors will undergo conversion. The rates of conversion to myosin heavy chain and troponin-expressing cells are reported to be in the order of 1–2 %. The number of cells that spontaneously contract is even lower. Despite these initial drawbacks, the exciting fields involving reprogramming have received intense interest to decipher additional strategies to enhance the conversion rates to beating cardiomyocytes. In the case of induced pluripotency, for example, transduction with retroviral vectors has been shown to activate an innate immunity response, and this intracellular signaling response promotes the successful conversion of fibroblasts to induced pluripotent cells [181].

The extent to which additional pathways are important in the successful conversion of fibroblasts to cardiomyocytes is unclear. However, the stoichiometry between the different factors used for direct conversion is important [182]. When a polycistronic retroviral vector was used to drive simultaneous expression of Gata4, Mef2c, and Tbx5, it resulted in higher expression of Mef2c relative to Gata4, and Tbx5 which was more efficient than any other combination for the conversion of fibroblasts to cardiomyocytes.

Interestingly, this higher Mef2c stoichiometry combined with selection for retroviral expression increased the yield of beating cardiomyocytes. It is likely that additional factors can be defined to modulate the efficiency of cardiomyocyte conversion. Indeed, a recent study outlined the conversion of murine fibroblasts to cardiomyocyte-like cells without the use of transcription factors. Instead, the overexpression of a set of microRNAs was used to induce conversion. Similarly, the transduction of miRNAs 1, 133, 208, and 499 was sufficient to induce conversion of murine fibroblasts into cardiomyocyte-like cells [180]. Furthermore, the addition of a JAK (Janus activated kinase) inhibitor enhanced conversion tenfold. The mechanism associated with this conversion strategy using miRNAs compared to transcription factor-mediated conversion is unclear.

The conversion strategy of a fibroblast-to-cardiomyocyte phenotype was first shown in murine fibroblasts and appeared to successfully convert cardiac and tail-tip fibroblasts. However, recent studies have shown that human fibroblasts need additional factors for conversion to cardiomyocytes [183–185]. In recent years, a number of publications defined the factors needed to convert human fibroblasts into beating cardiomyocytes. The precise mix of factors varied among the studies that refined the reprogramming cocktail to convert human fibroblasts to cardiomyocytes, although the core factors Gata4 and Tbx5 were always present. One study replaced Mef2c with Hand2, and suggested Hand2 is more potent in driving conversion. The other commonality is the ability of myocardin to enhance reprogramming in human cells. Importantly, spontaneously beating human fibroblast-derived cardiomyocytes were not observed in any study, although contractility could be evoked by field stimulation, and calcium cycling reminiscent of human cardiomyocytes could be measured.

In Vivo Delivery of Reprogramming Factors

The ultimate goal of reprogramming fibroblasts to cardiomyocytes is to use the high fibroblast content in the human heart, especially after myocardial infarction, to increase the total numbers of cardiomyocytes. With more cardiomyocytes present in the heart, the workload would be lower per cardiomyocyte, thereby improving cardiac function. The further hope is that increased cardiomyocyte content, especially in scar-rich regions, will enhance vascular regeneration—given the well-known role of cardiomyocytes in promoting a microvascular endothelial network to provide oxygen and nutrients.

Since reprogramming does not occur through an intermediary progenitor cell and has been shown to be independent of proliferation, the risks of tumor formation as a result of reprogramming strategies are deemed extremely low, unlike the potential risk associated with cell transplantation therapies. Given the relatively low efficiency of reprogramming fibroblasts to cardiomyocytes in vitro, it was thought that in vivo rates would likely be limited. However, in vivo transduction with either Gata4, Mef2c, and Tbx5 (GMT) or with the addition of Hand2 or even injection of four different miRNAs all proved to be relatively efficient in converting

fibroblasts into cardiomyocytes [179, 186, 187]. All three strategies were able to show improvement in cardiac function in response to fibroblast reprogramming after myocardial infarction. Moreover, all three studies that have successfully reported in vivo conversion of fibroblasts to cardiomyocytes to date have provided evidence for good contractile properties of newly formed cardiomyocytes—something that was extremely difficult to achieve in vitro. These results suggest that the local environment of the infarcted heart, or perhaps the presence of a surrounding network of cardiomyocytes and endothelial cells, enhances the conversion to more mature cardiomyocytes that contribute to the overall contractile force generated by the heart.

Given the lack of good and reliable fibroblast markers, it is difficult to prove that newly formed cardiomyocytes were derived from a fibroblast. However, the use of retroviral vectors that require cell cycle activation for integration reduced the likelihood of activation in cardiomyocytes. Conversion of fibroblasts into cardiomyocytes was confirmed by using genetic lineage tracing with the currently available fibroblast markers Postn, Fsp1, or Tcf21 driving Cre recombinase expression.

These data provided convincing evidence that in vivo conversion of fibroblasts into cardiomyocytes has merit and may be a valuable strategy that could significantly enhance the level of cardiac regeneration obtained after myocardial infarction. The translational strategy to obtain conversion in humans is, as of yet, undecided, and multiple strategies could be envisioned, including transduction using adeno-associated vectors at the time of coronary reperfusion during percutaneous coronary intervention.

Engineering Strategies to Promote Cardiac Repair

In addition to the strategies outlined above, such as the conversion of fibroblasts to cardiomyocytes, and activation of endogenous progenitor cells, approaches with translational potential include engineering strategies to promote cardiac repair. A number of engineering strategies are underway to either stimulate cardiac regeneration or replace lost myocardium [188–190]. The most prominent strategies are discussed below.

Tissue-Engineered Scaffolds

Research using scaffolds for the delivery of cells, factors, or biomaterials (i.e., polymers) has received considerable attention. Investigators have focused on identifying the ideal substrate for tissue engineering strategies and including cardiomyocytes and the supporting endothelial and smooth muscle cells required to provide oxygen and nutrient supply to the cardiomyocytes. One of the earliest attempts focused on developing engineered cardiac tissue emerged from the laboratory of Thomas Eschenhagen, MD [191]. His team designed a strategy where cardiomyocytes were mixed with collagen fibrils in a mold to form a tissue-engineered ring that was attached to a cyclic stretch apparatus to stimulate contraction of this cardiac tissue ring. These results provided the first reproducible tissue-engineered cardiac constructs that could be easily generated from isolated neonatal or adult cardiomyocytes.

Interestingly, the 3D architecture of the contractile rings promoted further differentiation of neonatal cardiomyocytes and induced a higher-order connectivity between cardiomyocytes through gap junctions, leading to concerted electrical activation and contractile force. These contractile rings represent an ideal platform to test a multitude of pathways in cardiomyocytes in a more natural environment due to the 3D organization of the constructs. Moreover, the cardiomyocytes are aligned in a similar longitudinal organized pattern, as they would be in a normal heart. Furthermore, the engineered tissues are currently used as a platform for drug testing, as well as unraveling pathophysiological mechanisms that underlie genetic forms of cardiomyopathy or to decipher the impact of different signaling pathways [192].

Although these engineered cardiac tissues have merit for testing and identifying the requirements to generate contractile tissues, individual constructs are not easily used for transplantation purposes to replace lost myocardium after myocardial infarction. And while individual contractile rings are likely insufficient, a strategy of combining five individual rings into a single patch was employed in rat hearts after myocardial infarction [193]. The five rings were contracting in synchrony after stacking them on top of each other and stimulating contraction in vitro. After culturing the stacked loops, they were sewn onto the infarcted rat heart, and the rats were allowed to recover for 4 weeks. The results showed electrical integration of the transplanted tissue with the host myocardium. Moreover, the transplanted hearts showed improved reverse remodeling and increased contractile performance and overall cardiac function.

Another prominent strategy to generate patches for transplantation purposes is to grow cardiomyocytes in 2D sheets, detach the sheets, and layer them on top of each other [194]. This approach makes it possible to generate patches that are about four layers thick. Anything beyond a couple of layers will likely not be viable, since this would require a vascular network to provide oxygen and nutrients for survival. However, up to four layers of cardiomyocyte sheets could likely survive without a pre-designed vascular bed. When transplanted, these sheets remain intact and survive as full-thickness sheets, even when implanted under the skin. Moreover, transplantation of two-layer sheets onto the heart leads to electrical and mechanical coupling between the host heart and the transplanted sheet [195]. These results were very encouraging for the potential regenerative capacity of cell sheets.

An alternative strategy is the use of the decellularized heart preparation [196] (Fig. 23.7). Using a detergent, the isolated heart (mouse, rat, pig, and human) can be completely decellularized. The remaining scaffold can then be

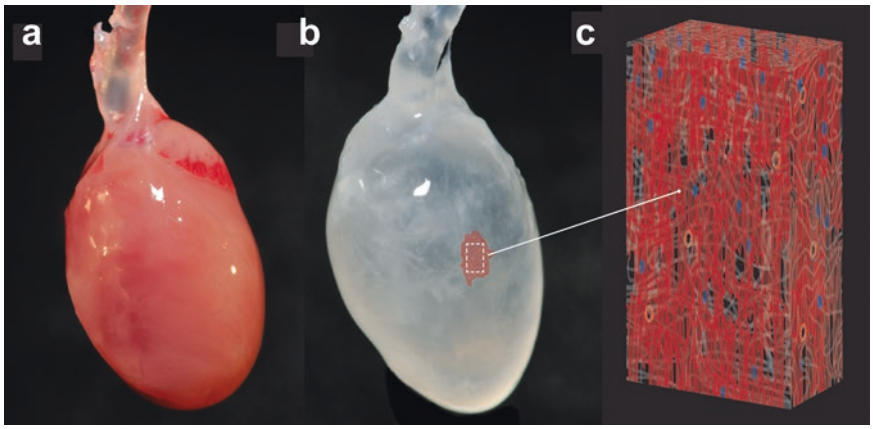

Fig. 23.7 Decellularized hearts as a platform for engineering new heart tissue. A normal heart (**a**) can be decellularized using detergent-containing solutions (**b**). This decellularized matrix can then be used to seed new cells for repopulation, ultimately generating functional 3D cardiac tissue (**c**)

recellularized to produce a contractile, intact heart [197]. This model may have merit for the repair of injured hearts or it may serve as an important model to examine cell-cell interactions, the role of the ECM, differentiation cues, and/or small molecule therapies as a platform for preclinical studies. Furthermore, efforts have begun to examine the utility of decellularized patches, decellularized/recellularized vascular conduits, and the decellularized scaffold/ECM as promoters of cardiomyocyte differentiation. Future studies will continue to explore the role of the ECM and cardiovascular pathophysiology.

Summary

Regenerative medicine is a dynamic field that holds tremendous promise. Studies have firmly established that the adult mouse and human hearts have the capacity for cardiomyocyte turnover and replacement. Moreover, signaling pathways and factors have been shown to modulate the capacity of cardiomyocyte proliferation. While cardiac progenitors reside in the adult heart, their role during aging and following injury remains unclear, but represents an area of investigation that is receiving intense interest. Perhaps one of the field's greatest discoveries is the ability to reprogram fibroblasts to cardiomyocytes in vitro and in vivo. Collectively, these discoveries, along with bioengineering scaffolds, provide a platform to launch the cardiovascular regenerative program toward preclinical and clinical applications that will revolutionize the field of advanced heart failure and potentially benefit millions of patients [198].

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Cell Therapy and Heart Failure

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_24

Introduction

The only definitive therapy for advanced heart failure is orthotopic heart transplantation. Cardiac transplantation is limited by the availability of donor organs (approximately 2200 donor hearts are available each year in the USA). Due to the limited supply of donor organs, other novel therapies have recently been explored including cellular replacement therapy. Somatic cell therapy (SCT) has been a proven and effective therapy for a number of chronic diseases. These therapies include the delivery of blood products, skin grafts, islet transplants, and bone marrow transplants. These successful cellular replacement therapies have provided a platform for the treatment of other chronic diseases such as heart failure. Over the past 15-year period, a number of cell sources have been utilized for the treatment of ischemic cardiac injury and advanced heart failure with variable results. In this chapter, we will examine the cell sources, delivery methods, results of clinical studies and highlight the areas of opportunity for further investigation. Overall, this is an embryonic field, which holds tremendous promise and has a number of hurdles. Perhaps an appropriate quote which characterizes the SCT field is the following:

» I have never promised anything but blood, tears, toil, and sweat. Now … It is not even the beginning of the end, but it is, perhaps, the end of the beginning.
Winston Churchill
November 10, 1942

Bone Marrow Transplantation as a Prototype for Cellular Therapy

Perhaps one of the most transformative innovations over the past 50-year period was bone marrow transplantation. Ever since the first successful bone marrow transplant in 1967 by Dr. Robert Good and his colleagues at the University of Minnesota, this therapy has been successfully utilized for the treatment of blood cell dyscrasias, hematological cancers, solid tumor cancers, metabolic diseases (i.e., Hurler syndrome), autoimmune diseases (dyskeratosis congenita), and many other debilitating diseases [1]. This pioneering initiative in 1967 by Good and his colleagues was the world's first allogeneic bone marrow transplant in a 5-month-old infant with sex-linked lymphopenic immunological deficiency [2]. These and many other discoveries have culminated in the treatment of more than 50,000 patients worldwide annually using bone marrow transplantation [3]. While this life-saving therapy improves survival, there are side effects of immunosuppression agents and complications associated with the therapy (i.e., graft vs. host disease, graft failure, recurrence of disease, organ toxicity, etc.) [4]. Moreover, cell sources include the use of bone marrow aspirates, peripheral blood mobilized stem cells and human umbilical cord blood stem cells (first utilized in 1988) for bone marrow transplantation [5, 6]. Collectively, the disease-free period and/or cure of the respective diseases using bone marrow transplantation in the pediatric and adult patient population is continuing to improve. Therefore, this established therapy provides the rationale and feasibility for uses of SCT for other chronic diseases (Fig. 24.1).

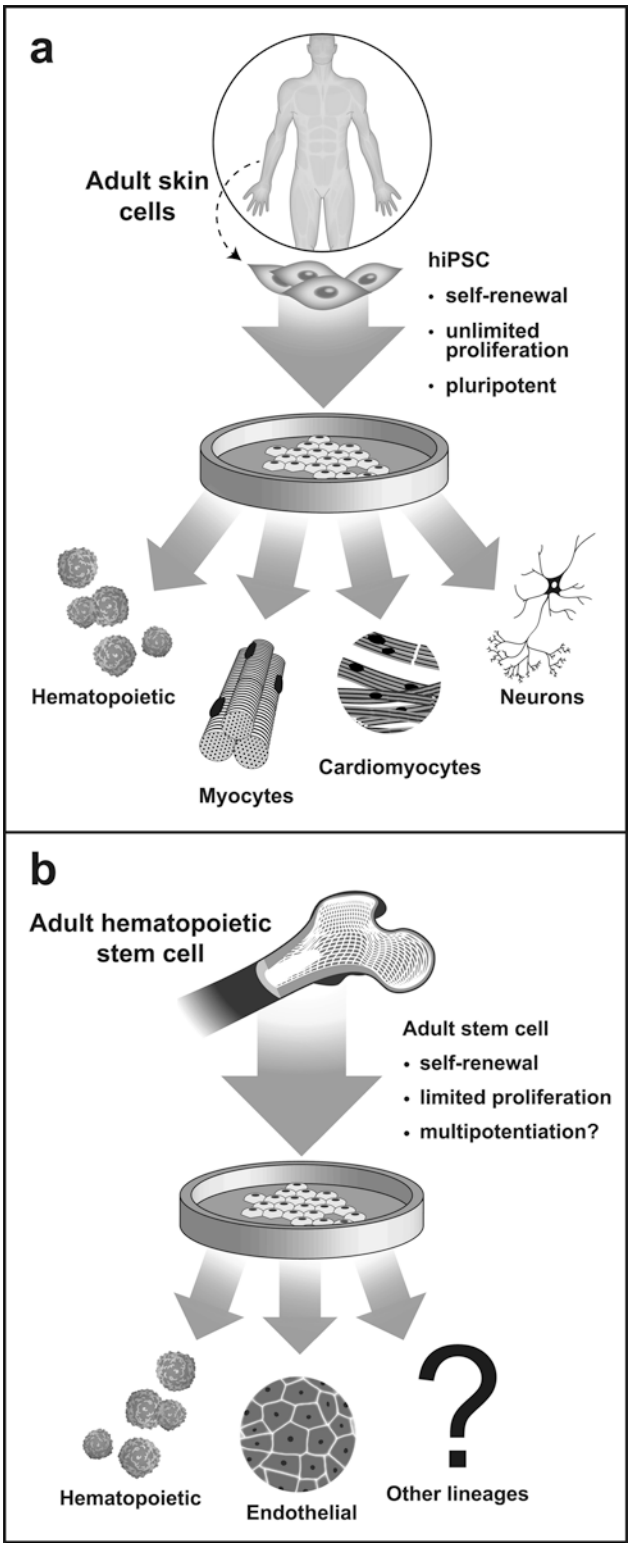


Fig. 24.1 Distinct differences are observed between pluripotent (**a**) and multipotent (**b**) stem cell populations. Schematic highlighting the major differences between pluripotent (i.e., ESC and hiPSC) versus multipotent (i.e., myogenic stem cells, c-kit stem cells, MSCs, SP cells, etc.) stem cell populations

Allotransplantation of Pancreatic Islets

Diabetes mellitus is a heterogeneous disease with a subpopulation of patients having such brittle disease that control with insulin supplementation is inadequate with patients having life-threatening episodes (i.e., seizures, hypoglycemic events, coma, etc.). Due to the limited number of pancreatic organs available for transplantation, isolated islets have been utilized with success. Initial studies were undertaken at the University of Alberta in Edmonton, Canada, with limited success in the 1970s [7]. More recently, increased success has been achieved using the Edmonton Protocol, which uses an enzyme cocktail for pancreatic digestion that is more protective of the fragile islets obtained from cadaveric organs [8]. Typically, one million islets are delivered into the portal vein of the diabetic recipient using ultrasound guidance. Following portal vein delivery, these allogeneic islets are embolized in the liver. This Edmonton protocol has increased insulin independence from approximately 15 to 80% following alloislet transplantation [8, 9]. Future studies will further examine the impact of the Edmonton protocol and other sources of islet tissues including human-induced pluripotent stem cell (hiPSC)-derived islets or porcine islets for the treatment of diabetes [10]. Collectively, these SCT strategies focused on BMT and alloislet transplantation serve as a platform to experimentally examine the safety and efficacy of SCT for cardiovascular disease (Fig. 24.1).

Cell Sources for SCT for Cardiovascular Disease

Embryonic Stem Cells (ESCs)

Embryonic stem cells were first isolated from the inner cell mass of the mouse blastocyst in 1981 [11]. ESCs have an unlimited proliferative capacity, a normal karyotype, and maintain high telomerase activity. These cells are pluripotent as they are able to differentiate into all three germ layer derivatives and able to give rise to every lineage with the exception of the extraembryonic cells [11, 12]. They have been an invaluable tool for the generation of gene disruption models in the mouse model system. Human embryonic stem cells (hESCs) were first isolated by Dr. Jamie Thomson and his colleagues in 1998 [13]. Due to ethical issues surrounding the isolation of hESCs from human embryos, the NIH developed guidelines (2009) to guide NIH-funded research and established an NIH hESC Registry [14]. Studies utilizing mouse and human ESCs have demonstrated efficient and directed cardiomyocyte differentiation (Fig. 24.1) [15, 16]. Previous studies have demonstrated positive results using hESC-derived cardiomyocytes as a cell therapy source for cardiac regeneration in small animal models [17]. Recently, preclinical studies utilized a nonhuman primate model and delivered 1 billion hESC-derived cardiomyocytes following myocardial injury with evidence of remuscularization [18]. While these studies produced promising results, they were limited by the large number of cells needed for delivery, arrhythmic complications of the graft, maturation of the donor cell population, and the need for immunosuppression therapy.

Human-Induced Pluripotent Stem Cells (hiPSCs)

Recent scientific advances have demonstrated the capacity of adult somatic cells (i.e., skin cells) to be reprogrammed using defined transcription factors into pluripotent stem cells, known as human-induced pluripotent stem cells (hiPSCs) [19–21]. In 2006, the Yamanaka laboratory identified 24 transcription factors that were differentially enriched in mouse embryonic stem cells [22]. Yamanaka's research team determined that the combination of Oct4, Sox2, Klf, and c-Myc, when virally transduced into mouse fibroblasts, reprogrammed the fibroblasts into embryonic-like stem cells. Therefore, these cells were termed induced pluripotent stem cells [22]. In 2007, this technology was translated into the development of human iPSCs by both the Yamanaka and Thomson laboratories independently [20, 21]. Importantly, the hiPSCs retain the genetic blueprint of the patient and can be differentiated into a variety of cell types. This innovative technology allowed for an unprecedented opportunity to study human diseases in vitro and to develop and test novel cell therapies.

The ability to generate high purity, functional cardiomyocytes is a transformative step in the development of cardiac disease models. The current understanding of embryonic cardiac development and differentiation of embryonic stem cells has been applied to the development of several differentiation protocols that reliably direct hiPSCs to the cardiac lineage (Fig. 24.1) [23–25]. These differentiation protocols include the temporal modulation of the BMP, TGF-β/activin/nodal, WNT/β-catenin, and FGF pathways to specify hiPSCs to a cardiac fate in a multistep process involving epithelial to mesenchymal transition, mesodermal and cardiac specification resulting in functional cardiomyocyte-like cells. While cardiomyocytes can be derived from hiPSCs, the gene expression profiling and physiological characterization indicate that they are immature (i.e., fetal-like cardiomyocytes). Compared to adult human cardiomyocytes, the hiPSC-derived cardiomyocytes are smaller, circular rather than rod-like shaped and have a less organized sarcomeric structure resulting in decreased force generation [25–27]. hiPSC-derived CMs develop more organized cardiac sarcomeric structure during differentiation, but have a morphology that is more comparable to fetal cardiomyocytes than rod-shaped adult cardiomyocytes. Additionally, hiPSC-derived CMs express genes such as smooth muscle actin, connexin 45, and MLC2a are expressed in immature cardiomyocytes. Similar to immature or fetal cardiomyocytes, hiPSC-derived CMs do not have well-developed T-tubules, and they rely primarily on glucose for metabolism and have less mature calcium handling [26, 27]. Strategies to generate more mature hiPSC-derived

CMs are a research focus and will be essential for future advancement of the field.

While a number of small animal models have evaluated the capacity of hiPSC-derived cardiomyocytes for remuscularization of the injured heart, recent preclinical studies have been examined using the porcine model. In these studies, hiPSC-derived cardiomyocytes, endothelial cells, and smooth muscle cells were delivered using a fibrin patch following cardiac injury in the porcine model [28]. These hiPSC-derived cells survived and improved heart function without inducing any ventricular arrhythmias. Collectively, these results support the notion that hiPSC-derived cell populations have a tremendous potential as a cell source for cardiac repair and regeneration.

Bone Marrow Mononuclear Cells and CD34$^+$ Cells

Bone marrow transplants are performed worldwide and have been shown to be a proven therapy for terminal diseases. Initially, the bone marrow donor cell population was harvested directly as a bone marrow aspirate and characterized based on the quantification of CD34$^+$ cell populations. CD34 is a transmembrane sialomucin protein that has a functional role in cell-cell adhesion and cellular migration [29]. It is expressed on long-term hematopoietic stem cells in humans. Numerous studies have demonstrated the capacity of bone marrow mononuclear cells to participate in cardiac repair following injury [30, 31], and an equal number have demonstrated that this cell population does not participate in cardiac regeneration following injury (Fig. 24.1) [32–34]. These controversies are ongoing, but the consensus at this time is that the bone marrow mononuclear cells are less effective in assuming a cardiac fate and regenerating injured myocardium.

Mesenchymal Stem Cells (MSCs)

MSCs have several unique features that make them attractive candidates for cell transplantation. First, they are easily accessible and expandable, as they could serve as an "off the shelf" allogeneic product, which would be cost-effective and available at the time of urgent interventions. Importantly, these cells appear to be immunoprivileged as they lack MHC II and B-7 costimulatory molecule expression and therefore have limited T-cell responses [35–39]. Yet, they are considered to directly inhibit inflammatory responses via paracrine mechanisms including the production of transforming growth factor beta-1 and hepatocyte growth factor [40, 41]. Previous studies using small animal (i.e., rodents) and large animal models (i.e., porcine) have shown short-term beneficial effects following the delivery of MSCs into the post-injured heart. These MSC-mediated effects include increased vasculogenesis, decreased scar burden, reverse remodeling, and improved cardiac function [42–44]. Again, controversial results have confronted this field as studies undertaken in Robert Kloner's laboratory, using a rat model of post-infarction LV remodeling, found that the beneficial effects on left ventricular function were short term and were absent after 6 months post-MSC delivery [45].

c-Kit-Expressing Cells

Beltrami et al. isolated cells expressing the tyrosine kinase receptor for stem cell factor (also referred to as steel factor or c-kit or CD117) from the interstitium of the adult rat heart [46]. The highest density of these lineage negative (lin$^-$), c-kit$^+$ stem cells was in the atria and ventricular apex. These cells were characterized as self-renewing, clonogenic, and multipotent. Further, they had the ability to differentiate into multilineages, including cardiomyocytes, endothelial cells, and smooth muscle cells. Moreover, the delivery of these c-kit-expressing clonogenic stem cells following myocardial injury improved left ventricular function and supported the notion that they contributed to myocardial regeneration. Recently, the same laboratory expanded their analyses to include preclinical studies using large animal models. They have demonstrated that the canine model also harbors a c-kit-expressing stem cell population in the adult heart that is clonogenic, multipotent, and capable of activation following injury. In response to myocardial injury, these c-kit-expressing stem cells were shown to be activated by cytokines and home to areas of injury to participate in repair and regeneration [47]. These preclinical studies have been extended to the study of the human heart. A similar c-kit-expressing stem cell population (c-kit-positive but negative for the expression of the hematopoietic and endothelial antigens including CD45, CD31, and CD34) has been isolated from the adult human heart and has been shown to be multipotent (capable of forming myocyte, smooth muscle cell, and endothelial cell lineages) in vivo and in vitro [48]. Moreover, studies have established that these human c-kit-expressing cardiac stem cells undergo both symmetrical and asymmetrical cell divisions [48]. Importantly, these results have generated intense interest and are being validated by other cardiac stem cell laboratories. For example, van Berlo et al. utilized genetic labeling strategies and demonstrated that c-kit-expressing stem cells were able to daughter cardiomyocytes, yet this was a rare event [49]. These investigators demonstrated that c-kit-expressing stem/progenitors primarily daughtered the endothelial cell population (as opposed to the cardiomyocyte lineage) within the adult mouse heart. These studies underscore the ongoing controversies associated with the stem cell/progenitor cell field.

Myogenic Stem Cells

The adult skeletal muscle has a resident stem cell population that is capable of complete regeneration and restoration of the myogenic architecture following an injury that destroys

up to 90 % of the skeletal muscle [50]. This resident stem cell population is also referred to as the satellite cell pool; these stem cells are located in close approximation to the multinucleated myofiber. These satellite cells are sandwiched beneath the basal lamina and the plasmalemma (which expresses dystrophin) and constitute 2–5 % of all nuclei (in the skeletal muscle) [50]. Satellite cells express the transcription factor Pax7 as well as other markers including c-met, CD34, VCAM, α7-integrin, syndecan 3/4, and other proteins. Satellite cells are capable of tremendous cellular proliferation and self-renewal and can assume both a quiescent and activated state. Activation of these satellite cells is mediated by an Fgf-CK2-mSds3-Foxk1-Foxo/Sox/Tgfb-p21 network [50, 51]. Studies have demonstrated that the delivery of a single isolated myofiber which contains as few as seven myogenic stem cells was capable of muscle regeneration and generated 100 new myofibers containing thousands of myonuclei [52]. These animal studies provided a platform for human clinical studies using human myoblasts for cardiovascular disease (Fig. 24.1).

Cardiospheres

In 2004, Messina et al. isolated undifferentiated cells that proliferated as self-adherent clusters (termed *cardiospheres*) from subcultures of postnatal atrial or ventricular human biopsy specimens and also from murine hearts [53]. These cardiospheres varied in size (20–150 μm) and were observed to beat spontaneously in culture. The cardiosphere-forming cells had the properties of adult cardiac stem cells as they were clonogenic, they expressed stem and endothelial progenitor cell antigens/markers (c-kit, Sca-1, CD31, and Flk-1), they were capable of long-term self-renewal, and they could differentiate in vitro and in vivo into myocytes and endothelial cells [53]. Importantly, these cardiospheres represented a heterogeneous cell population that was expanded in vitro. The expansion of the cardiosphere-forming cells resulted in more than 1 million human cardiospheres within a several-month period. These studies provided a platform for further studies undertaken in the Marban laboratory [54]. Cardiospheres and cardiosphere-derived cells express antigenic characteristics of stem cells at each stage of processing, as well as proteins vital for cardiac contractile and electrical function [54]. Human and porcine cardiosphere-derived cells cocultured with neonatal rat ventricular myocytes exhibited biophysical signatures characteristic of myocytes, including calcium transients synchronous with those of neighboring myocytes [54]. Moreover, the delivery of cardiosphere-derived cells following myocardial injury resulted in improved myocardial function compared to their respective controls.

Sca-1 and Side Population (SP) Cells

Resident murine cardiac progenitors have also been isolated on the basis of stem cell antigen-1 (Sca-1) expression [55]. These Sca-1-expressing CPCs were small interstitial cells that lacked hematopoietic lineage markers such as CD45, B220, TER119, or Flk-1, and they lacked c-kit expression, supporting the notion that they were distinct from the c-kit stem cell population. Studies verified that the Sca-1-expressing CPC population expressed the vascular marker CD31 and the cardiogenic transcription factors including GATA4, MEF2C, and TEF-1 (but lacked expression of NKX2-5). A subpopulation of these Sca-1-expressing CPCs activated cardiac genes, but did not exhibit spontaneous contractile properties in response to DNA demethylation with 5-azacytidine [55]. Studies were further undertaken to examine the capacity of the Sca-1 CPCs to form cardiomyocytes independent of fusion to the differentiated host cardiomyocytes, using genetic mouse models (Cre/Lox and the R26R genetic mouse models) for cellular labeling. Genetically labeled Sca-1 CPCs isolated from the αMHC-Cre transgenic mouse model and delivered into injured hearts of R26R (resulting in the labeling of all host cells with LacZ) mice. Two weeks following injury, the animals were sacrificed, and the hearts were examined for Cre and LacZ expression. Interestingly, approximately half of the cells expressing αMHC-Cre did not express LacZ, suggesting that the Sca-1-expressing cells were capable of myocardial differentiation independent of fusion to existing (host) cardiomyocytes [55]. Additional studies from other laboratories (Matsura and coworkers) have also isolated Sca-1$^+$ cells from adult murine hearts and demonstrated that they were capable of differentiation into beating cardiomyocytes in the presence of oxytocin but not 5-azacytidine [56]. These Sca-1 CPCs were heterogeneous, but a subpopulation was capable of effluxing Hoechst 33342 dye. Due to their ability to efflux Hoechst 33342 dye, these cells were described as a side population using flow cytometry and were termed SP cells. Subsequently, these SP cells have been isolated from a number of lineages including adult bone marrow, skeletal muscle, the lung, and mouse ESCs. These respective SP cell populations were multipotent when placed in a permissive environment. The ability of the SP cells to efflux the Hoechst dye was due to the presence of multidrug resistance (MDR) proteins. Studies have demonstrated that Abcg2 was a member of the ATP-binding cassette (ABC) transporters (also known as multidrug resistance proteins) and was the molecular determinant for the SP cell phenotype [57]. Both specific (FTC) and nonspecific (calcium channel blockers such as verapamil) blockers of Abcg2 prevented Hoechst 33342 dye exclusion. Abcg2-expressing SP cells participate in cardiac development and reside in the adult mouse heart [57]. Following injury, these Abcg2-expressing cardiac SP cells increased in number and formed fetal cardiac-like cells. In addition to serving as a marker for the SP cell population, Abcg2 has a cytoprotective function in response to oxidative stress. Moreover, previous studies have demonstrated that HIF2α is a direct upstream regulator of the *Abcg2* gene [58]. These results support the notion that CPCs in the adult heart likely have a cytoprotective mechanism that promotes survival following injury. To date, whole-genome analyses using microarray platforms have examined the molecular signature of adult cardiac SP cells, adult bone

marrow SP cells, adult skeletal muscle SP cells, and SP cells isolated from ESCs [59]. As expected, cardiac SP cells express Abcg2, Sca-1, and c-kit. They also have induction of signaling pathways including the Notch signaling pathway and the Wnt signaling pathway, which are characteristics of a number of other stem cell populations [59]. Yet, the cardiac SP cells largely lacked expression of hematopoietic markers (CD45 and TER119). Other laboratories have also isolated the SP cells from mouse hearts based on their ability to exclude Hoechst 33342 dye and have shown they differentiate into cardiomyocytes after coculture with rat cardiomyocytes [57, 60].

Stem Cell and Progenitor Cell Consortium for Cardiovascular Disease

To establish an interactive and collaborative network for the acceleration of discoveries, the National Heart, Lung, and Blood Institute at the National Institutes of Health established the NHLBI Progenitor Cell Biology Consortium [61]. One of the goals of this consortium was to gain an understanding of the mechanisms that direct stem and progenitor cells to a cardiac fate. Importantly, this network provided an infrastructure for the field and addressed issues including but not limited to:

1. The definition of a hierarchy of somatic stem and progenitor cells that reside in the adult heart
2. The definition of transcriptional networks, epigenetic networks, and microRNA networks that direct stem cells and progenitors toward a cardiac fate
3. Provided protocols for stem/progenitor cellular characterization and cardiomyocyte differentiation pathways
4. Established strategies to reprogram somatic cells (i.e., fibroblasts) to cardiomyocytes
5. Established fate-mapping strategies to define the contribution of selected stem/progenitor cell populations to the cardiac lineage during development and following myocardial injury
6. Compared specific cardiac and hematopoietic stem/progenitor cells using FACS, transcriptional, microRNA, functional, or epigenetic analyses

SCT studies have variable results. More than 2000 patients have received SCT for cardiovascular disease, and studies support the notion that the safety profile for SCT is favorable. However, while the first study using SCT for cardiovascular disease was performed more than 10 years ago, there has been a variable and, at best, only a modest benefit from such therapy. These initial studies utilized the delivery of skeletal myoblasts at the time of surgical revascularization [62]. These skeletal myoblasts survived the delivery into the injured heart, and they differentiated to form skeletal muscle in the cardiac milieu. Unfortunately, the newly formed skeletal muscle was not electrically synchronized with the host cardiomyocytes, and therefore there were a number of arrhythmogenic events requiring implantable cardioverter defibrillator (ICD) support. Therefore, due to the lack of integration and the inability of skeletal myoblasts to transdifferentiate to form cardiomyocytes, SCT using skeletal myoblasts has received less interest.

Due to the remarkable success of bone marrow transplantation for the treatment of hematopoietic diseases, studies were undertaken to examine the safety and effectiveness of unfractionated bone marrow mononuclear cells to transdifferentiate to a cardiomyocyte fate. One of the first randomized clinical studies compared mobilized stem cells with bone marrow mononuclear cells delivered 5 days following percutaneous coronary intervention [63]. One year following SCT, there was a modest decrease in infarct area in patients receiving either cell population. A comparable modest improvement in cardiac function was observed in the Reinfusion of Enriched Progenitor cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) study which examined 204 patients with bone marrow mononuclear SCT following percutaneous coronary intervention (PCI) at a 1-year follow-up period compared to control patients [64]. The Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration (BOOST) trial delivered bone marrow mononuclear cells (intracoronary route) 5 days following PCI and observed no significant difference in LV function between experimental vs. control patients [65]. Similarly, no significant improvement in cardiac function was observed in the Autologous Stem cell Transplantation in Acute Myocardial Infarction (ASTAMI) study ($n = 100$) following intracoronary delivery of bone marrow mononuclear SCT 6 days following PCI at a 3-year follow-up [66]. Moreover, little functional improvement was demonstrated in the NHLBI-supported Cardiovascular Cell Therapy Research Network (CCTRN) studies (TIME, LATE TIME, and FOCUS) which examined the use of SCT (bone marrow mononuclear cells) for ischemic cardiovascular disease [32–34]. In contrast to these SCT studies using bone marrow mononuclear cells, Haddad et al. demonstrated that intracoronary delivery of $CD34^+$ cells in patients with DCM has an average increase of LVEF of 5 % over a 5-year follow-up period [67]. Overall, while selected studies have demonstrated a modest improvement, it is generally agreed that many of the bone marrow-derived cell populations have not resulted in remuscularization of the heart. These data further emphasize the limited plasticity of somatic cell populations.

Another bone marrow-derived stem cell population is the mesenchymal stem cell (MSCs) ($CD73^+$, $CD90^+$, $CD105^+$, $CD34^-$, $CD45^-$, HLA-DR^-, $CD14^-$, $CD11b^-$, $CD79a^-$, $CD19^-$) population. While MSCs are believed to be immunoprivileged and have increased plasticity (able to daughter endothelial cells, osteoblasts, chondrocytes, adipocytes, etc.), a limited number of clinical studies have utilized this cell population for acute ischemic cardiomyopathy [68, 69]. In a small, Phase I study ($n = 53$), patients were randomized to receive placebo or allogeneic MSCs following an acute injury (i.e., MI) which resulted in a modest cardiac functional improvement at 6 months following delivery [70]. Moreover,

adipose-derived MSCs were delivered (intracoronary) in 14 patients following ST segment elevation MI (APOLLO study) resulting in a reduction of the scar burden and modest cardiac functional improvement [71]. In contrast to the pilot studies using MSCs for acute ischemia, more than six studies are underway or have been published using this cell population for chronic ischemic dilated cardiomyopathy. Several of these studies from the Hare laboratory (PROMETHEUS and POSEIDON studies) have demonstrated beneficial effects [72, 73]. In the POSEIDON study, which utilized autologous and allogeneic MSCs, there were decreased scar burden and ventricular volumes in both groups [72]. In the PROMETHEUS study, autologous MSCs were delivered at the time of surgical revascularization (i.e., CABG), which resulted in decreased scar tissue with increased perfusion, wall thickness, and systolic strain at 18 months following delivery [73]. Currently, Phase III clinical studies are in progress, which will enroll more than 1500 patients with chronic heart failure to receive intramyocardial delivery of MSCs.

Similarly, limited functional improvement was observed in the CADUCEUS study that examined SCT (intracoronary delivery of autologous cardiospheres) for ischemic CHF [74]. While only modest functional changes were observed, reduced scar burden and reversed structural remodeling of the injured human heart were noted. In addition, more recent studies have focused on the cardiosphere-mediated release of exosomes. These exosomes (cellular vesicles which have a diameter of approximately 50 nm) have been postulated to contain growth factors, mRNAs, miRs, double-stranded DNA, and antifibrotic factors that may promote structural changes of the injured heart (Fig. 24.2) [53]. Alternatively, these exosomes may also harbor factors that stimulate the endogenous cardiac progenitors to participate in new vessel and remuscularization of the heart following cardiosphere delivery (Fig. 24.2). Similarly, the SCIPIO study delivered c-kit$^+$(lin$^-$) cardiac stem cells in 33 patients, and the CELLWAVE study (bone marrow mononuclear cells; $n = 103$) demonstrated improved LVEF in patients with ischemic heart disease [31, 74–77].

Alternative cell sources include the use of hESC and hiPSC lines (Fig. 24.1). Previous studies have demonstrated the use of hESC-derived retinal support cells delivered into the eyes of patients with macular degeneration, which appeared to be safe and have encouraging results [78]. While hESC- or hiPSC-derived cardiomyocytes have not been utilized in clinical studies for patients with heart failure, nonhuman primate studies have shown that the delivery of a large number of hESC-derived cardiomyocytes results in remuscularization of the injured heart but has associated arrhythmogenic events [18, 79]. These hESC and hiPSC sources continue to lag behind others but may have increased potential for remuscularization of the injured heart compared to other cell sources.

Collectively, the variable results of SCT for cardiovascular disease may be multifactorial. These varied results may represent differences in the selection of cell source (i.e., CD34$^+$ cells, bone marrow mononuclear cells, mesenchymal stem cells, c-kit-/lin$^-$-expressing cells, cardiospheres, umbilical cord blood stem cells, skeletal myoblasts, etc.), cell processing and storage, mode of delivery [i.e., intracoronary, intramyocardial (endocardial vs. epicardial delivery), venous (coronary sinus), arterial, etc.], endpoints (3 months to 5 years), timing of delivery and disease etiology (i.e., delivery during the acute post-MI period, chronic ischemic coronary artery disease, nonischemic DCM, etc.), patient selection (age of patient, gender of patient, presence of comorbidities such as diabetes mellitus or tobacco use, and biomarker status), and cell source (autologous vs. allogeneic sources) (Fig. 24.3). These pilot studies with limited patient numbers and one or

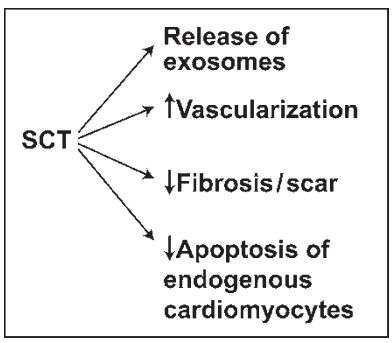


Fig. 24.2 Somatic cell therapy has a number of possible roles following the delivery into an organ of interest. Schematic highlighting the possible impact of SCT other than remuscularization

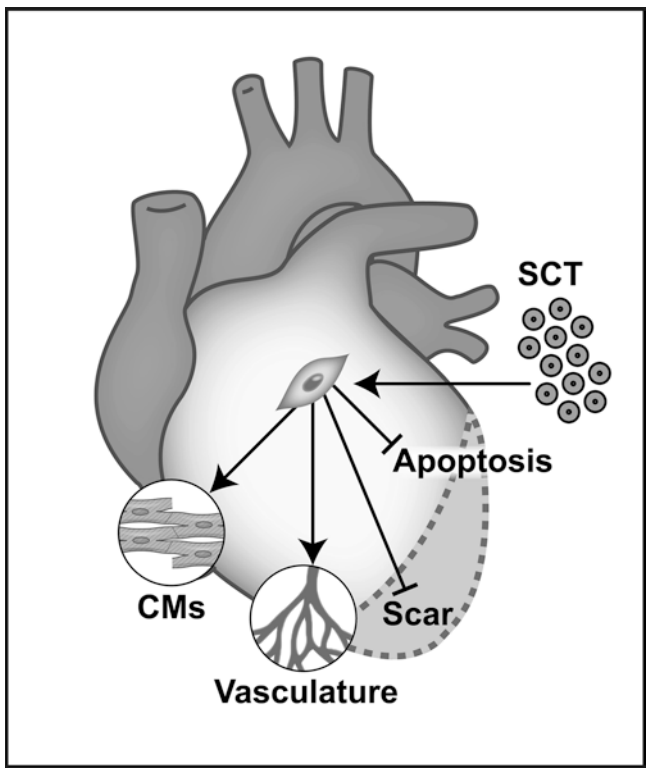


Fig. 24.3 Somatic cell therapy may mobilize endogenous cardiac progenitors. A proposed role for SCT is that the exogenous cells may mobilize endogenous cardiac progenitors to the area of myocardial injury and repress fibrosis/scar or apoptosis (infarct extension) or promote neovascularization or remuscularization

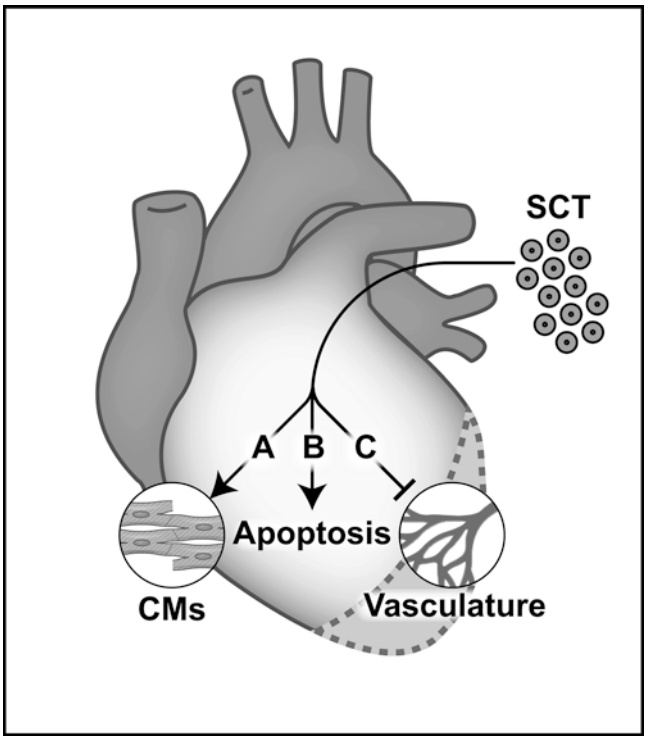


Fig. 24.4 Somatic cell therapy may have a number of roles following myocardial injury other than remuscularization. (*A*) SCT may promote remuscularization. (*B*) SCT may inhibit apoptosis of endogenous cardiomyocytes located at the border region of the site of injury. (*C*) SCT may promote vascularization at the border region of the injured myocardium

more of the above variables may be important contributors to the uneven response of SCT for cardiovascular disease. To further emphasize the challenges facing SCT, we will further highlight issues pertaining to the proposed mechanisms, the mode of cell delivery, and the ideal cell population for SCT and cardiovascular disease.

Proposed mechanisms of action for SCT. This limited cardiovascular functional response may also reflect the mechanisms of action for SCT. For example, SCT may directly provide cellular replacement therapy (i.e., remuscularization), promote new vessel formation, decrease scar formation, or promote autocrine/paracrine signals that facilitate the recruitment of endogenous intracardiac or extracardiac progenitors (Fig. 24.4). While controversy surrounds whether SCT has direct cardiogenic potential, studies support the hypothesis that the modest beneficial effects of SCT may be mediated by autocrine and/or paracrine factors [80, 81]. These autocrine/paracrine factors may initially be provided by the donor cells that are delivered and later by the host myocardium itself. Alternatively, SCT may mobilize myocardial factors that have the potential to modulate architectural or structural changes of the diseased heart (Figs. 24.2, 24.3, and 24.4). The controversy surrounding the mechanisms of SCT and its modest cardiovascular effect is fueled, in part, by findings that cell retention and engraftment following myocardial delivery is disappointingly low (Fig. 24.5). The lack of cellular retention in the host organ (i.e., heart) suggests that the myocardial milieu plays an important role in the viability of stem cells as a cardiac microenvironment that promotes cellular retention (i.e., cardioprotection with the release of antiapoptotic factors, stem cell recruitment factors, and proangiogenesis factors) (Fig. 24.2) while promoting decreased inflammation and fibrosis, which may be beneficial for SCT and other pharmacotherapies (Figs. 24.3 and 24.4).

Mode of Delivery

The mode of delivery of SCT for cardiovascular disease has involved multiple strategies. Initial strategies included an intramuscular delivery (i.e., intracardiac injection of cells) at the time of open heart surgery [82]. Typically, the cells would be delivered at the time of surgical coronary artery revascularization or device implantation (i.e., mechanical circulatory support device such as left ventricular assist device or LVAD therapy) (Fig. 24.6). This strategy requires a major intervention (surgical procedure) and complicates the assessment of SCT as the primary intervention may provide a significant improvement in cardiac function (separate from any effect of SCT). An alternative strategy is the intracoronary delivery of the cells utilizing a catheter-based delivery system (Fig. 24.6). While a number of studies have utilized this intracoronary delivery approach, the sludging of cells, ischemia, and inability to deliver the cells to the region of injury (due to a lack of vascularization of the injured myocardium) are potential experimental obstacles [83, 84]. Nevertheless, this delivery mode (i.e., intracoronary) appears to be safe. Other delivery modes include peripheral intravenous or intra-arterial delivery, retrograde delivery via the coronary sinus, or endocardial delivery using a NOGA catheter-based system (Fig. 24.6) [70, 85–87]. While these and other approaches have all proven to be relatively safe, it is unclear whether one strategy is superior to the others. The ideal delivery mode would be one that involves minimal intervention, promotes the delivery of the cells to the region of benefit (i.e., injury border zone of the heart), limits untoward effects, and is easily accessible.

Ideal Cell Population for SCT

Previous studies have utilized an array of cell populations for SCT for cardiovascular disease. These studies have utilized autologous and allogeneic cell populations, which include skeletal myoblasts, bone marrow mononuclear cells, $CD34^+$ cells (isolated from bone marrow and from peripheral blood), cytokine-stimulated peripheral stem cell populations, mesenchymal stem cells, cardiospheres, and c-kit-expressing cardiac progenitors. The ideal cell population would be one that is readily available, immunoprivileged, allogeneic, and resistant to a proinflammatory environment, does not require in vitro cellular expansion, and has stem cell characteristics

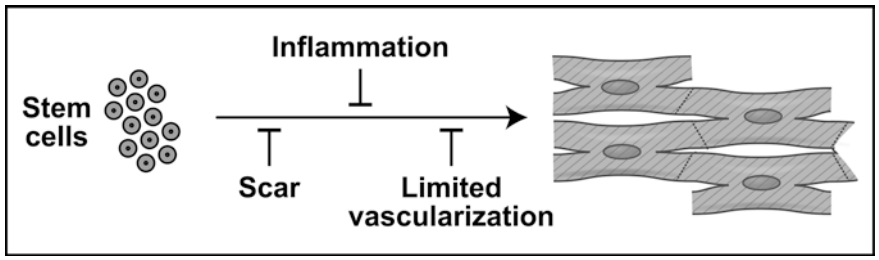
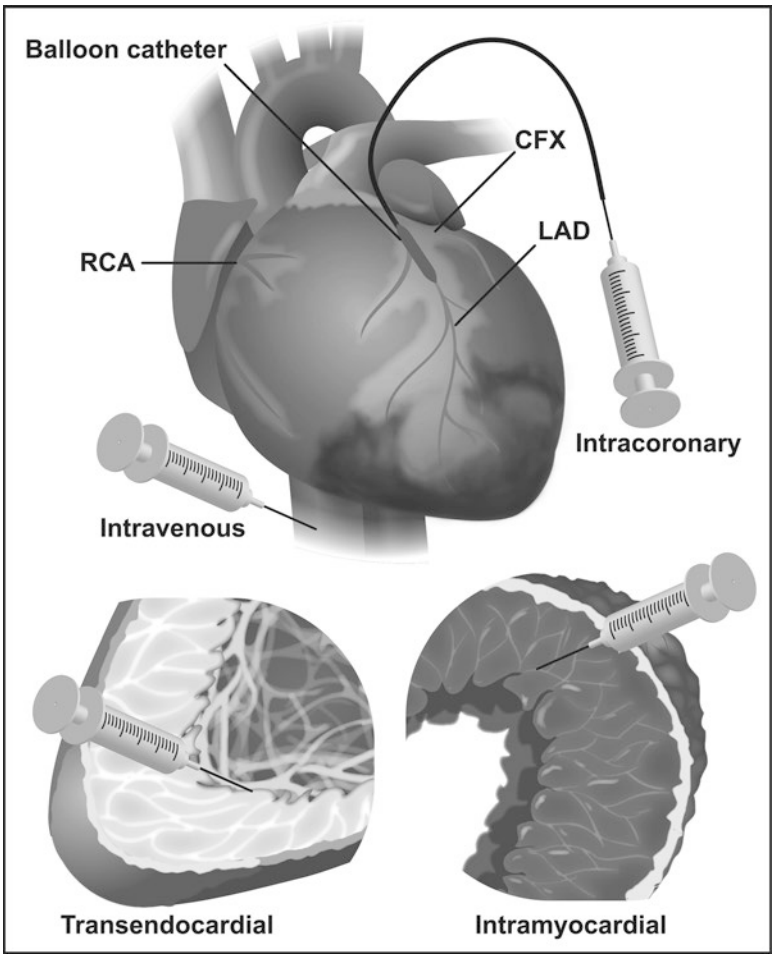


Fig. 24.5 Somatic cell therapy for myocardial injury is associated with limited cell survival following delivery. Schematic outlining the possible causes of limited survival of exogenously delivered cells (SCT) into the injured myocardium. Limited cell survival following delivery may be due to ongoing inflammation (following myocardial injury), impaired vascular supply to provide nourishment to new cells, and increased fibrosis/scar following injury

Fig. 24.6 Somatic cell therapy can be delivered to the injured heart using a number of strategies. Schematic highlighting the mode of delivery of exogenous cell sources (SCT) following myocardial injury



(increased proliferative capacity and plasticity to generate several distinct lineages). Other cell sources may include hiPSC-derived cardiac progenitors, hiPSC-derived cardiomyocytes, hiPSC-derived differentiated cocktail of cardiac progenitors, endothelial progenitors, smooth muscle progenitors, and human umbilical cord blood stem cells. Importantly, cell sources will continue to be selected and improved over time in a comparable fashion to that observed for bone marrow transplantation.

Gaps in Knowledge and Challenges for the Future

To further examine these mechanistic questions and accelerate cell-based therapies for cardiovascular disease, the National Heart, Lung, and Blood Institute funded the Cardiovascular Cell Therapy Research Network (CCTRN) that includes investigators at seven institutions (Minneapolis Heart Institute/University of Minnesota; Stanford University;

Texas Heart Institute; University of Louisville; Indiana University; University of Florida, Department of Medicine; and University of Miami) across the USA [88]. This network and other ongoing clinical studies/trials collaborate with bench investigators to define the patient population that benefits from cell therapy (i.e., ischemic vs. nonischemic dilated cardiomyopathy), the optimal cell population (autologous vs. allogeneic vs. EPCs, skeletal muscle satellite cells, bone marrow mononuclear cells, MSCs, cardiospheres, etc.), mode of delivery (intracoronary, intravenous, intramyocardial, etc.), cell preparation (cultured and possibly reprogrammed vs. freshly isolated cells), numbers of cells delivered, site of delivery (infarct related artery, border region of injured myocardium, distant ventricular delivery, atrium, etc.), mechanisms of action of cell therapy (paracrine effect to limit apoptosis, promote neovascularization, promote myocardial regeneration, limit fibroproliferative response), and the role of multiple or serial interventions with cell delivery. These studies will further benefit from the design of FDA-approved cell-labeling strategies that will allow for the detection of single cells using imaging technologies. Moreover, cell therapy studies performed in combination with patches or scaffolds and ventricular assist devices used as a bridge to transplant will allow histological analyses of the explanted heart at the time of transplant. These technologies will allow new mechanistic insights regarding the use of cellular therapy for treatment of cardiac failure.

Summary

In summary, SCT for cardiovascular disease has yielded variable results. For this field to move forward, increased standardization of protocols, double-blinded studies, and an enhanced understanding of the mechanisms that govern exogenous or endogenous cardiac progenitors for myocardial replacement or repair will be essential. Future studies will require an adequately powered, large, double-blinded, clinical study with well-defined primary and secondary endpoints to ultimately address whether SCT reduces morbidity and improves survival in patients with cardiomyopathy.

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Cardiac Transplantation

History of Cardiac Transplantation: Research, Discoveries, and Pioneers

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_25

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Introduction

Medical innovations are fueled by disease and premature death. Except for 1918 when influenza claimed more lives, cardiovascular disease has been the number one cause of death in the US every year since 1900 [1–3]. Furthermore, congenital heart disease (CHD) is the most prevalent genetic disease of live-born children [3, 4] (Figs. 25.1 and 25.2). Cardiovascular and CHD can progress to end-stage heart disease, and the only definitive therapy for advanced heart failure is heart transplantation.

Through the work of many innovative surgeons and scientists, heart transplantation has become commonplace [5–7]. Pivotal inventions such as cardiopulmonary bypass and the refining of anastomotic techniques made heart transplantation technically possible. The development of preservation solutions and effective immunosuppression regimens made heart transplantation successful [7]. This chapter reviews the research, experiments, and technology that led to modern-day heart transplant surgery.

Fig. 25.1 Congenital heart disease is the most common genetic defect. C. Walton Lillehei, MD, examines a child with congenital heart disease requiring corrective surgery and temporary pacemaker support. Photograph SEPS licensed by Curtis Licensing, Indianapolis, IN. All rights reserved.

Fig. 25.2 Congenital heart disease is the most common genetic defect. Children with congenital heart disease were hospitalized for long periods of time and received visits from entertainers who would visit the patients in the hospitals

Early Innovators and Cardiovascular Medicine

In the early 1900s, many considered the repair of blood vessels an impossibility. Alexis Carrel, MD (June 28, 1873–Nov. 5, 1944), led the way in small vessel vascular surgery, which promoted organ transplantation [6]. As a medical student, Carrel first became interested in vascular anastomosis after the president of France died from a laceration of the portal vein. At the time, the death of the president was believed inevitable because the procedure to repair blood vessels was unknown [6]. Dr. Carrel reviewed experiments by Mathieu Jaboulay that involved the repair of divided carotid arteries with an everting mattress technique. This technique was not reproducible on small vessels so Carrel began working on vascular anastomotic experiments and published a manuscript on his technique in 1902 [5, 6].

After he experienced a minor setback in his medical career, Dr. Carrel moved to Chicago in 1904 and began work with Charles Guthrie, MD (Sept. 26, 1880–April 1963), at the University of Chicago [5–7]. There he refined his triangulation method of vascular anastomosis using fine needles and sutures treated with petroleum jelly. While at the University of Chicago, Drs. Carrel and Guthrie demonstrated that veins could be used as a viable substitute for arteries by replacing sections of carotid artery with the jugular vein [5, 6]. They also proved that a vein patch could tolerate arterial pressures. Using these techniques, they published a manuscript in 1905 detailing the successful transplantation of a dog's kidney into the neck of another recipient dog using these refined surgical skills [5, 6]. The kidney functioned normally after transplantation; however, the dog died later of infection. Drs. Guthrie and Carrel subsequently transplanted the thyroid gland, kidneys, and ovaries from one dog to another as well as the heart of a small dog into the neck of a larger dog with witnessed contractions following implantation.

In 1906, Dr. Carrel moved his research to the Rockefeller Institute in New York [6]. There he established that blood vessels could be preserved in cold saline for days to weeks, reimplanted, and maintain their function. This was his entry into experiments on tissue preservation—so important in organ transplantation. Dr. Carrel pursued different methods of tissue and organ preservation such as heating and dehydration and storing tissues in glycerin, formalin, or petroleum jelly. By 1909, Dr. Carrel had successfully transplanted other organs in animals, such as the adrenal gland, spleen, intestine, heart/heart-lung block, and limbs [5, 6]. His groundbreaking work focused on transplantation earned him the Nobel Prize in 1912.

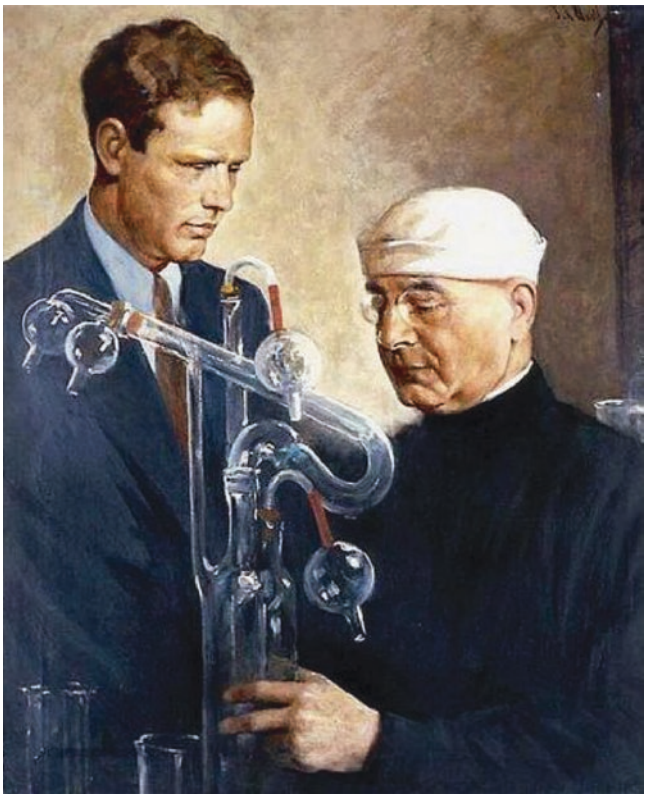

Fig. 25.3 Early research initiatives focused on the pump oxygenator. The famous aviator Charles Lindbergh worked with Nobel Prize winner Alexis Carrel in the laboratory

In 1929, he developed protocols for organ perfusion. These initial experiments failed due to infection of the perfused organ. With the aid of renowned pilot Charles Lindbergh (Feb. 4, 1902–Aug. 26, 1974), who became a close friend and colleague, Dr. Carrel developed the first functional pump oxygenator 5 years later [5–7]. Together, Dr. Carrel and Lindbergh coauthored a book, *The Culture of Organs*, and they appeared on the cover of Time magazine (1938) (Fig. 25.3).

Early Description of Graft Rejection

In the 1930s, Frank Mann, MD (Sept. 11, 1887–Sept. 30, 1962), uncovered allograft rejection by examining failing heart transplants in animal models [8]. His seminal studies with heart transplantation examined implantation of the denervated heart of dogs. He found that the transplanted heart began to beat after coronary blood flow was established. The donor heart survived an average of 4 days [8]. The longest survival was 8 days. He noticed that every graft failure was caused by cardiac distention before a rhythm was established. Therefore, graft protection included avoidance of air embolism and ventricular distention. Once the donor heart was at the end of its lifespan, Dr. Mann examined the removed heart and found [5, 8]:

» *The surface of the heart was covered with mottled areas of ecchymosis; the heart was friable on section. Histologically the heart was completely infiltrated with lymphocytes, large mononuclears and polymorphonuclears… it is readily seen that the failure of the homotransplanted heart to survive is not due to the technique of transplantation but to some biologic factor which is probably identical to that which prevents survival of other homotransplanted tissues and organs.*

This observation would later prove valuable to our understanding of graft rejection and immunosuppressive therapy.

Parabiotic Perfusion

Twenty years later, at the Chicago Medical School, work on another piece of the puzzle started to progress: graft preservation [5, 9, 10]. Drs. Marcus, Wong, and Luisada tried using a third dog to support the donor heart until implantation [5]:

» *The method we have called interim parabiotic perfusion; it is a homologous extracorporeal pump.*

Unfortunately, the donor heart only survived 48 h. Another group from Hahnemann Medical College—Drs. Wilford Neptune, Charles Bailey, and Brian Cookson—also made strides in 1953 toward graft preservation [5, 7]. They used hypothermia of the donor heart, but only achieved a 6-h survival time when transplanting both the heart and lungs into dogs.

World's First Orthotopic Heart Transplant in an Animal

Although Dr. Vladimir Demikhov's work was not available in English until the early 1960s, Demikhov (July 18, 1916–Nov. 22, 1998) began making advances in heart transplantation in the late 1930s [5, 7, 10]. As a student in 1937, he engineered the first mechanical assist device and was able to support the circulation of an animal for 5.5 h with the heart excised. Due to WWII, there was a break in Demikhov's research, but in June 1946, he performed a heterotopic heart-lung transplant in an animal thorax. The animal survived 9.4 h. In 1951, he performed the first orthotopic heart transplant in an animal. Through the mid-1950s, he completed 22 orthotopic heart transplants without cardiopulmonary bypass by using sequential anastomoses to maintain perfusion throughout the procedure [5].

During one of his experiments in January 1955, he ligated the recipient's great vessels and closed the mitral valve so the recipient was exclusively dependent on the transplanted heart. The dog survived for 15.5 h. Death was secondary to thrombosis of the superior vena cava. From 1946 to 1958, Vladimir Demikhov performed 250 heart transplants in animal models, achieving survival up to 30 days [5]. Before his

death, Demikhov was awarded the Pioneer Award by the International Society for Heart and Lung Transplantation for his innovations in the field.

Cardiopulmonary Bypass

Thanks to the advancements of John Gibbon, MD (Sept. 29, 1903–Feb. 5, 1973), the device known as the cardiopulmonary bypass machine (CPB) was realized [5, 7, 9]. Early in his career, Dr. Gibbon witnessed the death of a patient from a massive pulmonary embolism. While at Massachusetts General Hospital, he began engineering a machine that would take over the work of the heart and lungs during surgery [5, 7]. He continued his work after moving to the University of Pennsylvania in the 1930s. In collaboration with engineers at IBM, including engineer and IBM chairman Thomas Watson, and after many successful experiments in animal models, the first machine for human use was developed [5]. This model was a failure. A second machine was developed in Dr. Gibbon's laboratory. This iteration minimized hemolysis and the formation of air bubbles and was operational (Fig. 25.4).

The first successful use of the cardiopulmonary bypass machine (May 6, 1953) was on an 18-year-old patient with an atrial septal defect [5]. The patient survived a 26-min bypass "run" without complication. Unfortunately, subsequent operations with the CPB machine resulted in mortalities, and Dr. Gibbon then placed a moratorium on the CPB machine. Gibbon's inventions earned him the Lasker Award in 1968. John Kirklin, MD (April 5, 1917–April 21, 2004), of the Mayo Clinic along with Richard A. DeWall, MD, and C. Walton Lillehei, MD (Oct. 23, 1918–July 5, 1999), of the University of Minnesota resumed Dr. Gibbon's work and refined the CPB machine (Fig. 25.5) [11]. Secondary to their work, cardiac surgery continued to mature in the late 1950s through 1960s.

In 1959, Drs. Henry Cass and Sir Russell Brock conducted several trials focused on canine heart transplantation. The technique left atrial cuffs instead of anastomosing the cava and pulmonary veins individually. These experiments met with limited success secondary to bleeding complications [5].

The Stanford Pioneers

Norman E. Shumway, MD (Feb. 9, 1923–Feb. 10, 2006), completed medical school at Vanderbilt Medical School, his residency training at the University of Minnesota, and then his PhD in cardiovascular surgery in 1956 under Owen Wangenstein, MD (Fig. 25.6) [5, 11]. During his research training, Dr. Shumway focused his efforts on total body hypothermia, pump oxygenators, prosthetic cardiovascular grafts, and arrhythmogenesis under the direction of F. John Lewis, MD (Fig. 25.7), and Dr. Lillehei [11]. Shumway left Minnesota for California where he ultimately accepted a position at Stanford Medical Center in 1958.

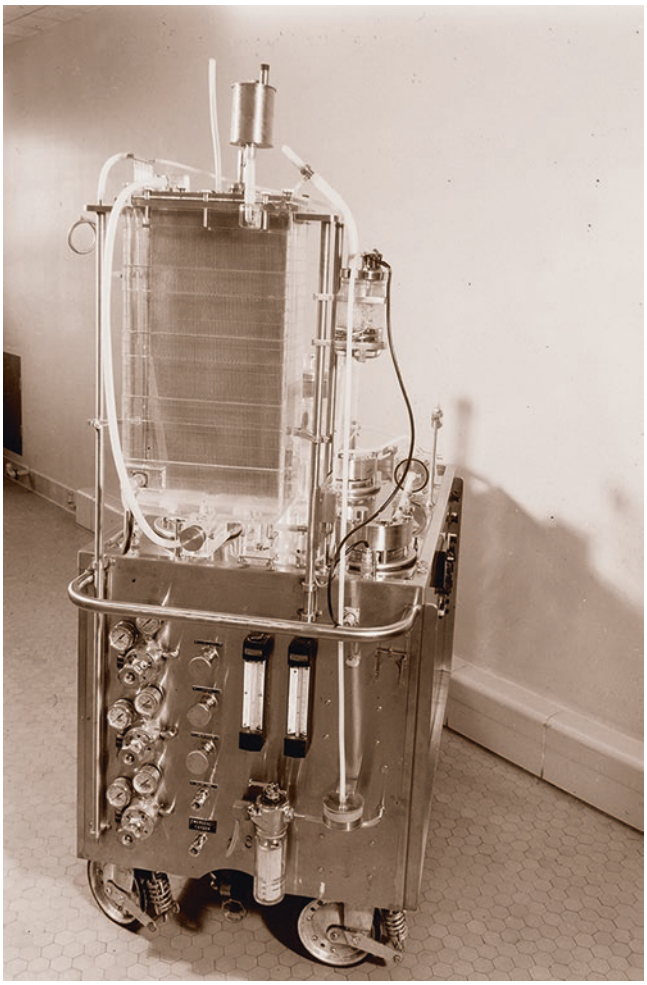

Fig. 25.4 World's first successful use of the heart-lung machine. On May 6, 1953, John H. Gibbon Jr., MD, used cardiopulmonary bypass for 26 min to close a large atrial septal defect in an adult female patient. Shown here is the Gibbon heart-lung machine (Model II), which consisted of a screen oxygenator

At Stanford, Drs. Shumway and Richard R. Lower, MD (Aug. 15, 1929–May 17, 2008), were able to optimize surgical techniques and organ preservation, and they performed the first fully successful animal model orthotopic cardiac transplant in 1959 [5]. Drs. Shumway and Lower used preservation techniques that included topical hypothermia to 4 °C with saline for graft protection and recipient protection using cardiopulmonary bypass and systemic cooling to 30 °C. Surgical techniques using atrial cuffs, previously used by Demikhov, Cass, and Brock, helped limit ischemic times to 1 h [5]. Of eight animals, five survived 6–21 days, but they quickly died from myocardial failure due to cell infiltration and interstitial hemorrhage from lack of immunosuppression [12].

» *Observation on these animals suggest that, if the immunologic mechanism of the host were prevented from destroying the graft, in all likelihood it would continue to function adequately for the normal life span of the animal.*

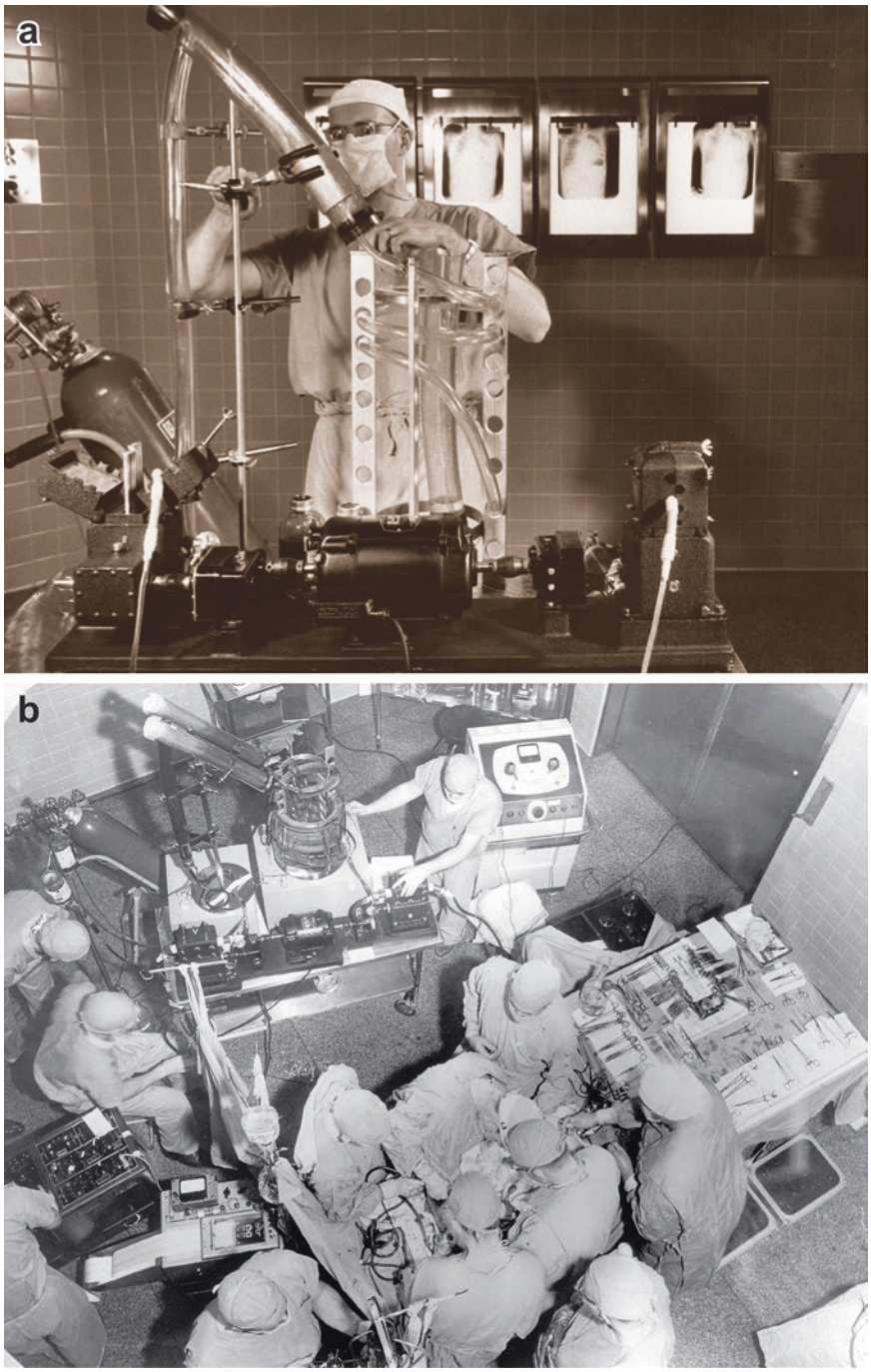

Fig. 25.5 The DeWall-Lillehei Bubble Oxygenator. (**a**) Richard A. DeWall, MD, working with C. Walton Lillehei, MD, developed an inexpensive ($15) bubble oxygenator that eliminated air bubbles. (**b**) Using the DeWall-Lillehei bubble oxygenator, Dr. Lillehei and his team performed open heart surgery to repair a patient's ventricular septal defect (May 13, 1955)

In 1961, Dr. Lower performed heart-lung transplant in canine models. Six recipients had spontaneous respirations post-implant and two were ambulatory [5]. The canine recipients died 5 days later and this was believed to be due to rejection. With continued research, it became apparent that immunologic responses were the limiting factor [12]. In 1965, Eugene Dong, MD, Dr. Lower, and Dr. Shumway found a relationship between EKG changes and rejection [5, 12]. They discovered that the EKG changes drastically improved with methylprednisolone and azathioprine, enabling one transplanted dog to survive 250 days [12].

The World's First Human Heart Transplant Using a Nonhuman Donor Organ

James D. Hardy, MD (May 14, 1918–Feb. 19, 2003), tried to promote heart transplantation in humans by way of nonhuman donors. During this time period, brain death was not accepted as end of life for a possible donor; only cardiorespiratory arrest could be used to constitute death [5, 11]. This created a conundrum in the advancement of transplantation [5, 7].

» *…The donor heart presumably would be derived from a relatively young patient dying of brain damage and the*

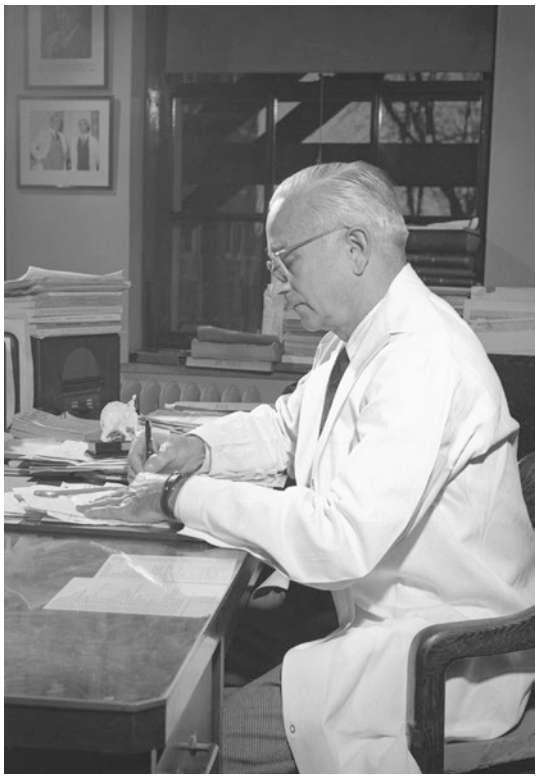

Fig. 25.6 Pioneering leadership transforms clinical practice. Owen H. Wangensteen, MD, PhD, referred to as "the Chief," served one of the longest tenures as chairman of the Surgery Department (1930–1967) and transformed the University of Minnesota surgical program, emphasizing the importance of research and its impact on clinical care of the patient

Fig. 25.7 Surgical pioneers and their impact on clinical care and the future generation of cardiovascular surgeons. F. John Lewis, MD (*right*), with Richard Varco, MD (*left*), utilized hypothermia in their open heart surgical procedures

> *recipient must be a patient dying of terminal myocardial failure… But how soon after "death" of the donor could the heart be removed?*
>
> Since we were not willing to stop the ventilator, we had concluded that a situation might arise in which the only heart available for transplantation would be that of a lower primate.

In 1964, the first human heart transplant using a nonhuman primate heart was undertaken. The first patient was a 68-year-old male with multiple medical problems, which led to a below-knee amputation, mechanical ventilation, vasopressors, and tracheostomy. At the time, there was no prospective human donor, but the dilemma with brain death again became a problem [5].

> *…for a homotransplant to succeed, the donor and the recipient must "die" at almost the same time; although this might occur, the chances that both simultaneously were very slim…Meanwhile, the condition of the prospective donor was not such that death appeared to be immediately imminent.*

Therefore, the team used a chimpanzee heart preserved by retrograde hypothermic oxygenated blood. Although the heart was implanted successfully, the cardiac output was not enough to maintain the flow needs of the patient. The patient expired in the operating room after 90 min of support by the transplanted heart. Dr. Lower performed one experiment that was similar to the experience of Dr. Hardy. He transplanted a cadaver heart into a baboon; the animal died due to elective termination of the experiment.

The World's First Successful Heart Transplant

Christiaan N. Barnard, MD (Nov. 8, 1922–Sept. 2, 2001), performed the first human-to-human heart transplant on Dec. 3, 1967, at Groote Schuur Hospital in Cape Town, South Africa (Figs. 25.8 and 25.9) [5–11]. Originally trained in renal transplantation under David Hume, MD, and Dr. Lower, MD, Dr. Barnard ultimately wanted to perform heart transplantation (Table 25.1).

The desire to pursue heart transplantation was primarily influenced during his 2-year research program at the University of Minnesota, where he interacted extensively with Dr. Shumway [11]. Having returned to Cape Town, South Africa, in 1958, Dr. Barnard resumed his research. He performed 48 transplants in dogs using techniques he learned in renal transplantation. Dr. Barnard is credited with the second successful renal transplant in South Africa in 1967. (The world's first renal transplant was performed in 1953.)

This research experience, the emergence of new surgical techniques by Drs. Shumway and Lower (then at Stanford), and renal transplant experience provided the platform for the world's first successful human cardiac transplant [5]. Louis Washkansky, age 53, a local grocer, was the first human recipient (Fig. 25.9). He suffered from ischemic heart disease; the donor was a brain-dead victim of a motor vehicle

accident the day before (Dec. 2, 1967). The donor was placed on cardiopulmonary bypass after the absence of EKG activity and spontaneous respirations were declared. Ischemic time was 21 min [5].

With a transplant team of more than 30 healthcare providers, the transplant was successfully performed (Fig. 25.8, Table 25.1). The immunosuppressive treatment at the time consisted of azathioprine, local irradiation, and prednisolone [12]. Unfortunately, the recipient was suffering from pseudomonas cellulitis at the time of transplant. Although he was given appropriate antibiotics, he died 18 days later due to pseudomonas and Klebsiella pneumonia [5]. Dr. Barnard had more success with his second attempt (Jan. 2, 1968) at heart transplantation with the recipient, Philip Blaiberg, MD, surviving 19 months. Further enthusiasm for cardiac transplantation was fueled by Dr. Blaiberg's book, *Looking at My heart*. Barnard would undertake an additional eight orthotopic heart transplants from 1967 to 1973, with the longest survivor living 23 years after transplant [5, 7].

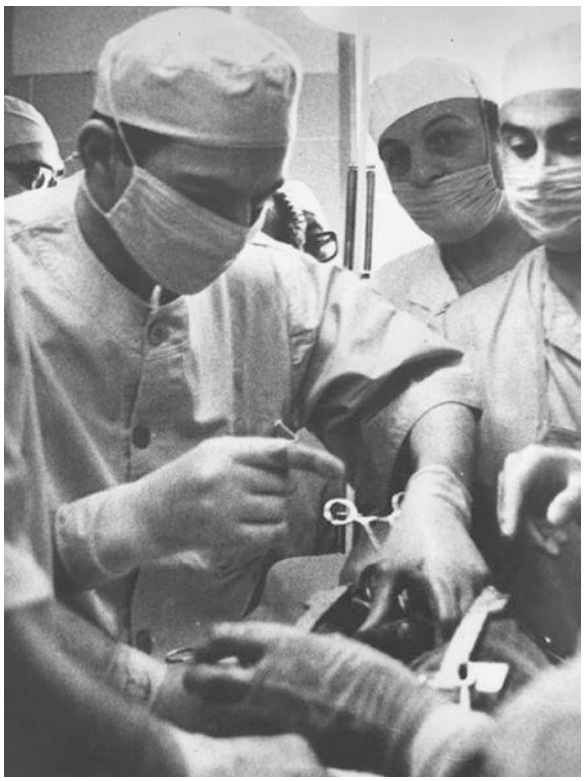

Fig. 25.8 World's first successful heart transplant. Christiaan N. Barnard, MD, performed the first human-to-human heart transplant on Dec. 3, 1967, at Groote Schuur Hospital in Cape Town, South Africa. Reprinted with permission from Central Press, Getty Images

Early Clinical Results for Human Cardiac Transplantation

Three days following the world's first successful heart transplant by Dr. Barnard, Adrian Kantrowitz, MD (Maimonides Medical Center, Brooklyn, NY), transplanted the heart of an anencephalic newborn into an 18-day-old infant with congenital heart disease [5, 7]. The recipient survived only 6.5 h after surgery.

By the late 1960s, more than 100 heart transplants had been performed. Due to dismal outcomes (mean survival of 29 days), a moratorium was placed on heart transplantation and only a few institutions continued to forge ahead. One of these institutions was Stanford University under the guidance of Dr. Shumway [5]. He and his team performed the fourth cardiac transplant on Jan. 6, 1968, with the recipient surviving 14 days (Fig. 25.10).

The 1-year survival of heart recipients improved to 65 % by 1978. Philip Caves, MD, developed a bioptome during this time that enabled endocardial biopsies to detect early organ rejection [5]. Research in rabbit antithymocyte globulin during this time also played a role in the treatment of rejection [12].

Fig. 25.9 The first successful heart transplants in the US Norman Shumway, MD, pioneered surgical techniques and performed one of the first successful heart transplants in the United States on Jan. 6, 1968, at Stanford Medical Center. Dr. Shumway is recognized as "the father of heart transplantation"

25

Table 25.1 History of Transplant Medicine

Date	Procedure	Physician(s)	Facility/location
1818	First successful blood transfusion	Dr. James Blundell	London, UK
12/23/1954	First successful renal transplant from living related kidney donor (identical twin)	Dr. Joseph E. Murray and Dr. David Hume	Brigham and Women's Hospital
04/05/1962	First successful renal transplant from deceased donor	Dr. Joseph E. Murray and Dr. David Hume	Brigham and Women's Hospital
03/01/1963	First successful human liver transplant	Dr. Thomas Starzl	University of Colorado Health Sciences Center
06/11/1963	First successful lung transplant	Dr. James Hardy	University of Mississippi Medical Center
12/17/1966	First successful pancreas/kidney transplant	Dr. Richard C. Lillehei and Dr. William Kelly	University of Minnesota
04/05/1967	First successful intestinal transplant	Dr. Richard C. Lillehei	University of Minnesota
12/03/1967	First successful human heart transplant	Dr. Christiaan Barnard	Groote Schuur Hospital (Cape Town, South Africa)
03/04/1968	First successful isolated pancreas transplant	Dr. Richard C. Lillehei	University of Minnesota
08/24/1968	First successful non-twin (allogeneic) bone marrow transplant	Dr. Robert A. Good	University of Minnesota
08/07/1968	Uniform Anatomical Gift Act established (Donor Card)		
10/30/1972	End-stage Renal Disease Program authorized by US Congress to promote Medicare coverage of renal dialysis and kidney transplant		
06/20/1979	First successful living related pancreas transplant	Dr. David E.R. Sutherland	University of Minnesota
03/09/1981	First successful heart-lung transplant	Dr. Bruce Reitz and Dr. Norman E. Shumway	Stanford Medical Center
11/1983	FDA Approval of CSA (Cyclosporin A)		
10/19/1984	National Organ Transplant Act (NOTA) establishes nationwide registry operated by UNOS, authorizes financial support for Organ Procurement Organizations (OPO), prohibits buying and selling of organs in the United States		
09/23/1998	First successful hand transplant	Dr. Earl Owen and Dr. Jean-Michel Dubernard	Lyon, France
11/27/2005	First successful partial face transplant	Dr. Bernard Devauchelle and Dr. Jean-Michel Dubernard	Amiens, France
03/20/2010	First successful full face transplant	Dr. Joan Pere Barret	Vall d'Hebron Hospital (Barcelona, Spain)

The research and continued operative success at Stanford showed promise for heart transplantation. Views on what constituted a donor remained in question [5]. Per Dr. Shumway [5]:

» *It should be underlined that no one can transplant a dead heart…Death of the donor is a diagnosis which must be made by the neurological and neurosurgical team.*

The donor pool was enhanced once the "Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death" was released. This enabled greater acceptance of brain death criteria and was pivotal in promoting organ donation [5].

The FDA's approval of the use of cyclosporine in 1983 rekindled national interest in heart transplantation [12]. This "miracle drug" boosted the 5-year survival to 60 %. Cyclosporine was developed from a fungus, *Tolypocladium inflatum*, that was initially extracted from soil samples obtained by Jean-Francois Borel, MD (1933–), while vacationing in Norway [7, 12]. Dr. Borel was originally studying this fungus for antibiotic properties. In the early 1970s, the immunosuppressive properties of 24–556, the extract from *Tolypocladium inflatum*, were identified. Unlike other immunosuppressants at the time, 24–556 was more selective in inhibiting lymphocytes compared to depressing the entire immune system [7, 12]. The active metabolite from

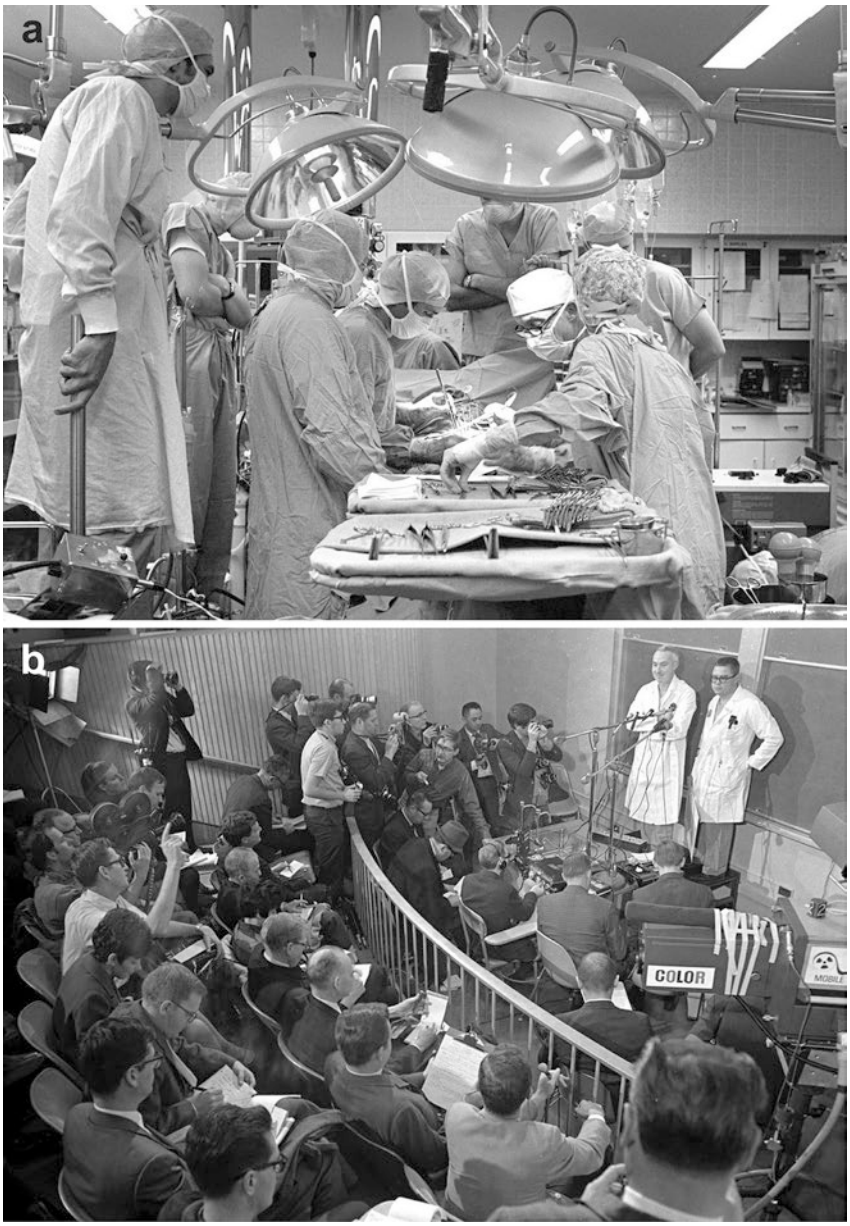

Fig. 25.10 The world's first successful heart-lung transplant. (**a**, **b**) Having implemented new immunotherapies, Drs. Reitz and Shumway performed the world's first heart-lung transplant in 1981 at Stanford University Medical Center

24 to 556 was purified and the compound CyA was discovered. This was eventually known as cyclosporin A.

Initially, due to the low interest in transplantation, the Pharmacology Department at Sandoz wanted to stop research on CyA unless Dr. Borel could offer more clinical proof of his discovery [12]. In 1976, Dr. Borel presented his findings at the British Society of Immunology. Two surgeons, Sir Roy Calne, MD, and David White, MD, approached Dr. Borel for samples of CyA. They used those samples in heart-transplanted mice. High doses were given and hepatic and nephrotoxicity ensued. Dog trials were undertaken but failed. Failure was later determined to be caused by low absorption.

Human trials were started but halted when it was found that the drug was not being absorbed. The preparation at this time consisted of pure cyclosporine in gelatin tablets. In 1977, three of the researchers—Dr. Borel; Hartmann Stähelin, MD; and B. von Graffen, MD—tested new preparations of the drug on themselves after determining proper laboratory tests that could accurately measure the serum drug levels [12]. The preparation found to have the most efficacy was an oral solution containing ethanol and detergent.

The next year, human trials led by Sir Roy Calne resumed on kidney transplant patients. Initial results were troubling as many patients developed hepatotoxicity, nephrotoxicity, and lymphoma. Through several more human trials using decreased dosage and the addition of steroids, morbidity from cyclosporine A was lowered to an acceptable level. The drug was approved for use in the United States 5 years later.

Cyclosporin A was later used and contributed to the success of the first heart-lung transplant performed by Bruce Reitz, MD, and Dr. Shumway (Fig. 25.11 and Table 25.1). An uncommon persistence, vision, and research depth separated Dr. Shumway and his team from the rest of the world of transplant clinicians. Shumway would oversee about 800 cardiac transplants from 1968 to 1993, coauthor more than 500 publications,

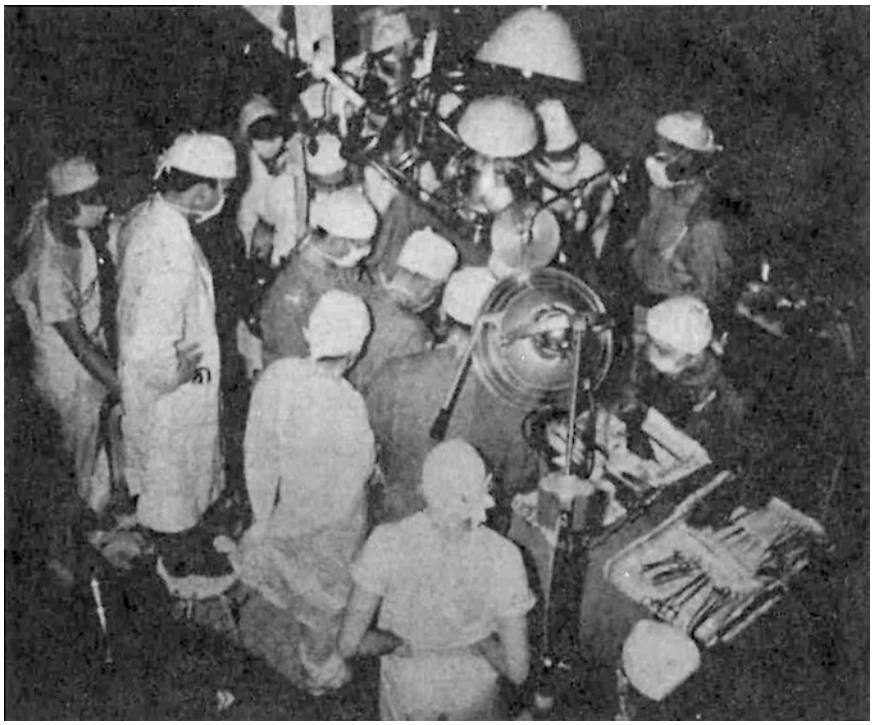

Fig. 25.11 World's first successful open heart surgical procedure. Using hypothermia, the world's first successful open-heart surgical procedure was performed on Sept. 2, 1952, at the University of Minnesota Medical Center. F. John Lewis, MD, was assisted by Dr. Richard Varco and Dr. C. Walton Lillehei, and used hypothermia to cool the five-year-old child's body to 28oC and close the atrial septal defect. *Source*: Unknown

and train scores of surgeons who, in turn, led cardiovascular surgical programs across the world. Today, Dr. Shumway is widely regarded as the "father of heart transplantation" [11].

Triple Drug Immunotherapy

The goal of immunosuppression is to (1) sufficiently suppress the recipient immune system to avoid damage to the transplanted organ, (2) not completely suppress the recipient so as to enable adequate response against infection, and (3) provide a complementary combination of medications that optimize immunosuppression while decreasing toxicity [12]. Early immunosuppression therapy consisted of radiation (1950s), azathioprine and/or corticosteroids (1960s), and antilymphocyte globulin/antithymocyte globulin (1960s–1970s).

The following section describes the development of the third goal of immunosuppressive therapy.

As previously stated, cyclosporin A revolutionized immunosuppression in organ transplantation. Secondary to toxicity, different drug combinations were introduced. Initially, cyclosporin A was used as monotherapy; however, because of nephrotoxicity, corticosteroids were added to the regimen. This allowed for lower dosing of cyclosporin A, decreases in nephrotoxicity, and improved graft survival. This regimen was further fine-tuned with the addition of azathioprine [12].

Azathioprine and corticosteroids were the mainstay immunosuppression therapy before the introduction of cyclosporin A. Azathioprine selectively downregulates T cell activity and suppresses cell-mediated rejection. In 1959, mercaptopurine (6-MP) was shown to suppress humoral immunity. Soon after this discovery, Sir Roy Calne determined prolonged renal graft survival in dogs with the use of 6-mercaptopurine (6-MP) [12, 13]. Azathioprine is 6-MP with an additional side chain, which provides a less toxic form of 6-MP.

Corticosteroids were introduced in renal transplantation in 1963 [12]. Steroids' main mechanism of action is lymphocyte depletion, mostly in T cells. B cell activity is not susceptible to steroids. Steroids clearly have many side effects, including hypertension, obesity, hyperglycemia, and osteoporosis. Theoretically, triple drug therapy enables lower doses of each of these drugs, thus maintaining efficacy while decreasing the toxic effects. The 1990s introduced another metabolite, mycophenolate mofetil, and the calcineurin inhibitor, tacrolimus, which are also used in triple drug regimens today [13].

A Recipe for Innovation and Discovery: The University of Minnesota

The innovations and discoveries that mark the field of heart transplantation, immunotherapies, and device support were only possible through the emphasis on research. The adage, "every failure brings success one step closer," underscores the importance of learning from every failed experiment. This philosophy requires a culture that emphasizes the essential role of research in clinical medicine. While the success of heart transplantation received worldwide attention, this accomplishment was only possible from decades of research.

Success does not emerge from a vacuum, but is built on the shoulders of many pioneering initiatives. Historically, one might ask why an inordinate number of cardiovascular surgical discoveries emerged from one program at one

Fig. 25.12 Surgical pioneer revolutionized cardiovascular medicine. Dr. C. Walton Lillehei, regarded as the "father of open heart surgery," impacted the field with surgical innovations and by training hundreds of surgeons across the world

institution. The short answer is leadership—institutional leadership that understands and values research and innovation. Leadership attracts faculty members and inspires them to take bold but calculated risks with their research—encouraging them to address big questions for their field (Table 25.1).

One such leader was Owen H. Wangensteen, MD, PhD [11, 14]. Dr. Wangensteen transformed the University of Minnesota Surgical Department and emphasized the essential role of basic science research and clinical medicine (Fig. 25.6). As department chair, Dr. Wangensteen required every faculty member to have a research laboratory and to pursue collaborative interactions with basic scientists [11]. He established a culture of intellectual risk taking, innovation, and discovery. For example, this culture yielded a number of "firsts," including Dr. Lewis performing the world's first successful open heart surgical procedure using hypothermia on Sept. 2, 1952 (Fig. 25.12) [11].

These innovations and bold initiatives were not only encouraged but they were demanded. Faculty members' rigor and creativity served as magnets for the recruitment of faculty and trainees alike. Dr. Wangensteen further required that all surgical trainees pursue PhD research training. Collectively, this culture and program produced an unprecedented array of trainees who would become academic leaders, discoverers, and industry leaders who would have a profound and lasting impact on clinical medicine [11]. These innovations and discoveries fueled visibility, reputation, and impact on the field and, ultimately, the lives of patients.

One of the emerging leaders at the University of Minnesota was Dr. Lillehei, "the father of open heart surgery" (Fig. 25.1) [11, 15]. Without his pioneering studies, cardiac surgery, let alone heart transplantation, would not have been possible (Fig. 25.13) [11, 15]. In 1954, Dr. Lillehei and associates performed a repair of a ventricular septal defect in a young boy using cross-circulation and the boy's father as the biological oxygenator (Fig. 25.14) [11]. Flow from the patient's cava was routed to the father's femoral vein, oxygenated, and returned to the patient via the carotid artery. This proved to be a major advance in cardiac surgery, although not widely used secondary to the risk to the parent. Through the continued research of Drs. Lillehei and Richard DeWall, the first effective bubble oxygenator was engineered and developed (Fig. 25.5) [11]. For 20 years, their invention was the standard for extracorporeal circulation.

The first heart transplant at the University of Minnesota Medical Center was performed in 1978 by Demetre Nicoloff, MD (August 2003), and William Lindsay, MD [14]. Although the first transplant in the world was performed in South Africa in 1967, Dr. Barnard trained under Dr. Wangensteen (Sept. 21, 1898–January 1981), Dr. Lewis, and Dr. Lillehei [11]. Newer immunosuppression medications were becoming available during this time and allowed for the first successful heart-lung transplant in 1986 at the university [14]. In 1987, the first heart-kidney transplant in the state of Minnesota was performed at the university. University of Minnesota physicians also performed the heart transplant on one of the longest-surviving recipients. As this text went to press, she continues to survive and lead a productive life more than 35 years after her heart transplant.

Mechanical Circulatory Support

Soon after the first use of the cardiopulmonary bypass machine, other uses for this technology became apparent with support for patients in postcardiotomy cardiogenic shock. The 1960s brought with it rudimentary cardiac assist devices to use in postoperative patients with shock. The initial use of an implantable cardiac assist device occurred in 1963 by Liotta [16]. This first design of an assist device consisted of a tubular displacement pump that was pneumatically driven. The device was connected to the left atrium and descending thoracic aorta. The left ventricular assist device supported the patient for 4 days, after which the patient died from multi-organ system failure. Although the patient did not survive, initial results were encouraging and, in 1964, the National Institutes of Health created the Artificial Heart Program [16].

In 1966, Michael Debakey, MD, used a pneumatic left ventricular device on a patient with postcardiotomy shock. After 10 days of support, the patient survived. With the first heart transplant performed in 1967, this new technology was explored as a bridge for patients until they could be transplanted. In 1969, Dr. Cooley used the first total artificial heart as a bridge to transplant [16]. While the early 1970s saw a moratorium on transplants due to poor outcomes and inadequate immunosuppression, this served as an inspiration to fine-tune mechanical support devices. The pneumatic devices available at this time could only support patients for a few days, caused significant hemolysis and thrombosis, and were cost-prohibitive.

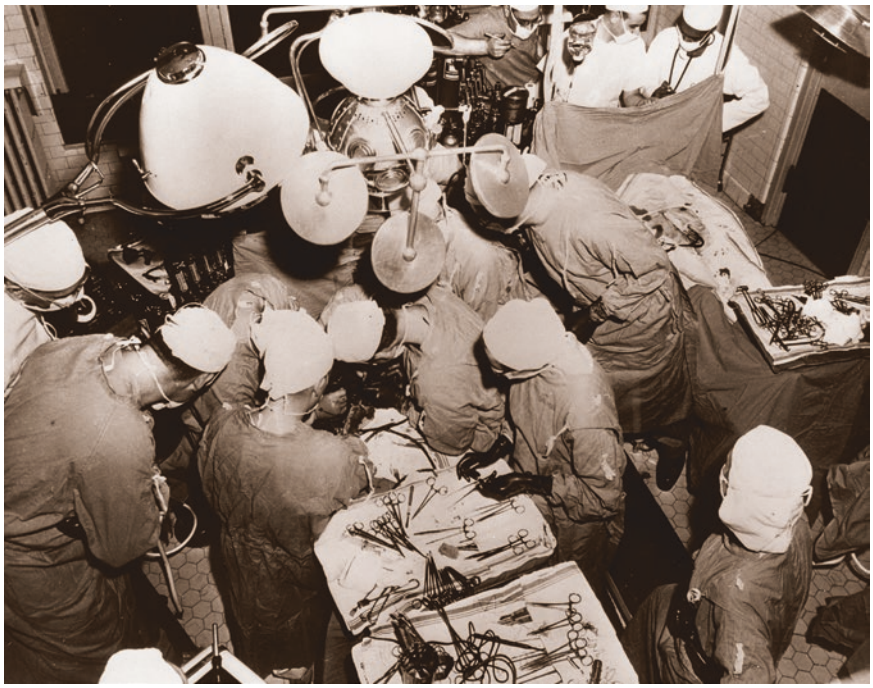

Fig. 25.13 Cross-circulation provided a platform that launched cardiac surgical procedures. Dr. C. Walton Lillehei used cross-circulation on March 26, 1954, to surgically repair a ventricular septal defect. Drs. C. Walton Lillehei, Richard Varco, Herbert Warden, and Morley Cohen received the Lasker Award in 1955 for cross-circulation and advances in cardiac surgery

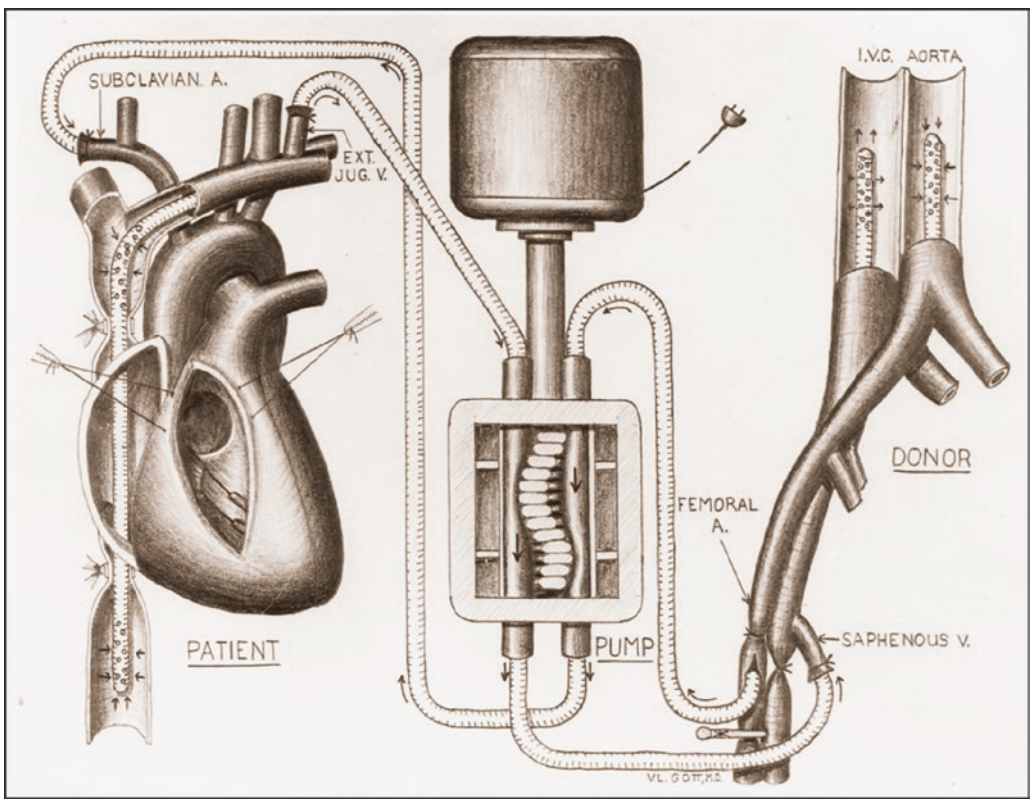

Fig. 25.14 Schematic representation of the cross-circulation procedure. Typically, children with congenital heart disease (patients) would have their blood pumped to an ABO-compatible relative (usually a parent) who would serve as the biological oxygenator. Between 1954 and 1955, 45 patients were supported using cross-circulation for their surgical procedure at the University of Minnesota Medical Center. When an ABO-compatible relative was unavailable, dog lungs were successfully used as the biological oxygenator in more than five patients at the University of Minnesota Medical Center

During this time, Novacor was refining the design of its ventricular assist device to make it more reliable and compact and to increase its efficiency [17]. Barney Clark, MD, became the recipient of the Jarvik-7 in 1982—a total artificial heart. He survived 112 days but eventually succumbed to infection. Total artificial heart development halted for a few years because of the high rates of complications: infection, stroke, and thrombosis.

In 1982, with persistence and ingenuity, Novacor developed a pulsatile left ventricular assist device to use as a bridge to transplant. It was first implanted in 1984 [17]. The patient's condition improved after implantation, and 9 days later, the patient successfully underwent a heart transplant. The FDA then approved multiple pulsatile devices in the mid-1990s; with fewer than 4000 donor hearts available, the devices were much needed.

In 2003, the FDA approved the Heartmate XVE for destination therapy. This supported treatment strategies for patients ineligible for transplant. Since then, many other assist devices have become available such as the Heartmate II (Thoratec), Heartmate III (Thoratec), CardioWest TAH-1 (Syncardia), and the Heartware. Survival at 1 year has been >80 % with current FDA-approved devices and the technology continues to improve.

Summary

The road to heart transplantation was an exercise in endurance and perseverance by many gifted individuals. From the basic building blocks of vascular anastomosis to the advent of cardiopulmonary bypass and the monumental discovery of cyclosporin A, all of these breakthroughs led to modern-day heart transplantation. Future improvements in treatments for heart failure and subsequent heart transplants will rely on improving mechanical circulatory devices, immunosuppression regimens, and ways to increase donor availability.

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Orthotopic Heart Transplantation

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_26

Introduction

Heart transplantation is a lifesaving therapy for patients with end-stage heart disease. Over the last 50 years, heart transplantation has emerged from animal experiments to the most effective therapy for end-stage congestive heart failure. Lower and Shumway first reported successful experiments of orthotopic heart transplantation in dogs in 1960 [1]. Barnard performed the first human-to-human heart transplant on December 3, 1967 [2]. Clinicians worldwide subsequently performed heart transplants between 1967 and the early 1970s with relatively poor outcomes; 5-year survival rates hovered around 40 %. In the late 1970s, Stanford University and the Medical College of Virginia were the only two programs still actively conducting heart transplants.

In December 1980, the immunosuppressant cyclosporine was first used for heart transplantation. In 1984, Bolman combined cyclosporine, corticosteroids, and azathioprine as "triple drug therapy" for heart transplant immunosuppression and proved it to be effective with less adverse effects than cyclosporine alone [3]. Since then, the triple therapy has been widely adopted. By the 1990s, it was clear that induction therapy could be added to triple drug therapy to delay early rejection [4]. Over the past 15 years, ventricular assist devices (VADs) have developed into effective bridges to transplantation or "destination therapy" for end-stage heart failure.

Today, heart transplantation is performed worldwide and has proven safe and reproducible. By June 2012, the International Society for Heart and Lung Transplantation (ISHLT) registry recorded the total number of heart transplants as 111,068 worldwide, with a mean survival of more than 11 years [5].

Recipient Selection

End-stage congestive heart failure patients appear in New York Heart Association (NYHA) class III or class IV heart failure. About 45 % of diagnoses are idiopathic and ischemic cardiomyopathies, and the remaining ones are valvular and congenital diseases. When these patients become refractory to maximal medical therapy, they are evaluated for heart transplant therapy.

Potential heart transplant recipients must undergo a battery of tests to determine whether or not they are appropriate transplant candidates. Initially, they undergo a thorough history and physical examination, standard lab tests, plain chest radiography, and pulmonary function tests. Cardiac-related tests include electrocardiography, echocardiography, left and right heart catheterization, endomyocardial biopsy, and peak exercise oxygen consumption measurements. Screening tests include stool guaiac, mammography for women, prostate-specific antigen for men, Papanicolaou smear for women, colonoscopy, bone densitometry, and a carotid duplex study. Occult infectious diseases are ruled out with serologies for hepatitis B and C, human immunodeficiency virus (HIV), human T-cell lymphotropic virus 1 (HTLV1) and HTLV2, cytomegalovirus, *Toxoplasma*, Epstein-Barr virus, syphilis, and tuberculosis. Recipient/donor match-related tests include blood type and antibody screening, human leukocyte antigen-antigen D related (HLA-DR) typing, and panel-reactive antibody (PRA) screening.

There are absolute and relative contraindications to heart transplantation (Tables 26.1 and 26.2). Once patients are listed for heart transplantation, they are followed by a cardiologist in a transplant center. Patients may require intravenous inotropic support (e.g., dobutamine or milrinone) if

Table 26.1 Absolute contraindications for heart transplantation

1. Positive prospective crossmatch
2. Irreversible pulmonary hypertension (PVR ≥ 5 Wood units)
3. Malignancy
4. Uncontrolled active systemic infection
5. Severe obstructive or restrictive lung disease
6. Coexisting systemic disease
7. Severe cerebral and peripheral vascular disease
8. Severe cachexia
9. Long-standing diabetes with end-organ damage
10. Noncompliance with medications
11. Ongoing tobacco use, alcohol abuse, or drug addiction
12. Inability to fully understand procedure and participate in follow-up care

PVR pulmonary vascular resistance

Table 26.2 Relative contraindications for heart transplantation

1. Age 70 or older
2. Active myocarditis
3. Graft failure due to acute rejection
4. Recent systemic or other organ system infection
5. Recent pulmonary/cerebral emboli
6. Active gastrointestinal disease
7. Obesity (BMI greater than 35)
8. Irreversible renal dysfunction (may have combined heart-kidney transplant)
9. Irreversible hepatic function (may have combined heart-liver transplant)

BMI body mass index

Table 26.3 UNOS medical urgency status categories for heart

1A. Patient has one of the following devices or conditions:
(a) Left and/or right ventricular assist device
(b) Total artificial heart
(c) Intra-aortic balloon pump
(d) Extracorporeal membrane oxygenation
(e) Mechanical circulatory support with evidence of significant device-related complications
(f) Mechanical ventilation
(g) Continuous infusion of a single high-dose intravenous inotrope
(h) Life expectancy <7 days
IB. One of the following devices or conditions:
(a) Left or right ventricular assist device
(b) Continuous infusion of intravenous inotropes
2. All other actively listed patients
3. Patient is temporarily removed from active waiting list

UNOS United Network for Organ Sharing

cardiac function further deteriorates. More advanced support such as intra-aortic balloon pumps or percutaneous, paracorporeal, or even implantable left and/or right ventricular assist devices may be needed if patients develop cardiogenic shock despite maximal medical therapy. Because of limited donor availability, the use of ventricular assist devices as a bridge to transplantation has been increasing.

Organ Allocation

In the United States, the United Network for Organ Sharing (UNOS) governs organ allocation. Heart allocation considers medical urgency, time on the waiting list, and the recipient's blood type. Medical urgency categories include statuses 1A, 1B, 2, and 7 (Table 26.3). The allocation algorithm is also modified by age so that adolescent donor hearts are preferentially used by pediatric recipients.

Donor Selection and Management

As with any organ donor assessment, the two most important goals are preventing disease transmission from the donor to the recipient and obtaining a graft that will adequately support the recipient's function. Before the donor heart is fully evaluated for transplantation, the following donor conditions should be evaluated, as listed in Table 26.4.

Table 26.4 Donor heart exclusion criteria

1. Malignancy with extracranial metastatic potential
2. Systemic sepsis or endocarditis
3. Significant coronary artery disease
4. Anatomic heart disease that will shorten the recipient's expected lifespan
5. Poor ventricular function

Ideally, the donor is younger than 55 years of age with no history of chest trauma or cardiac disease and no prolonged hypotension or hypoxemia. Hemodynamically, the mean arterial blood pressure should be maintained above 60 mmHg and the central venous pressure (CVP) less than 15 mmHg. Inotropic support requirements should be less than 10 μg/kg/min of dopamine or dobutamine. Normal electrocardiograms and echocardiograms should be verified.

Coronary angiography should be performed for donors with cardiac risk factors to rule out coronary artery disease. If donor myocardium insult is suspected, troponin should be measured and, occasionally, the left ventricular end diastolic pressure (LVEDP), to assess any underlying myocardium stiffness or diastolic impairment, despite a normal systolic function on the echocardiogram.

Most donors who have suffered acute brain injury will display some hemodynamic instability from neurologic shock, which may cause excessive fluid losses and bradycardia, or even transient depression of cardiac function. The donor may require intravenous vasopressin to keep up with excessive urine losses caused by diabetes insipidus. Hormonal therapy includes the use of thyroxine, cortisol, and antidiuretic hormone—and insulin may also be necessary. Sometimes, serial echocardiograms may be needed to show recovered cardiac function if the initial echocardiogram showed decreased ventricular function.

Due to a donor organ shortage, liberalizing certain donor selection criteria has been gaining favor. So-called marginal donor hearts, such as those from older donors, donor hearts with longer ischemic time, or donor hearts with mild left ventricular hypertrophy, mild valvular abnormalities, or mild coronary artery disease, have been successfully used. Concomitant coronary bypass grafting and valve repairs have been performed on donor hearts during the heart transplant procedure.

Certain strategies have been used to select the donor who best meets the recipient's functional demand. Typical acceptable donor weight ranges are between 70 and 130 % of the recipient's weight [6]. But for recipients with increased pulmonary vascular resistance (PVR) and with prior cardiac surgeries, it is often prudent to use a larger donor, preferably a male donor for a female recipient. Maximizing donor heart preservation during organ retrieval is also important. This includes the use of hypothermia, cardioplegia, and various preservation solutions that may contain antioxidant addi-

tives to help prevent reperfusion injury. More recently, an organ preservation device that provides continuous perfusion of myocardium with warm donor blood is used during transport of the heart. With this system, the donor heart remains beating during the transport. A completed multicenter clinical trial showed the system safe and efficient [7].

Preparation of the Recipient

The preparation of transplant patients should be started early—similar to the time needed to prepare patients for high-risk coronary artery bypass grafting (CABG), valve repair, or valve replacement surgery. Every single step of surgery should be well thought out and planned in anticipation of the impending heart transplant (Fig. 26.1). It is needed even more so than during ventricular assist device implantation procedure.

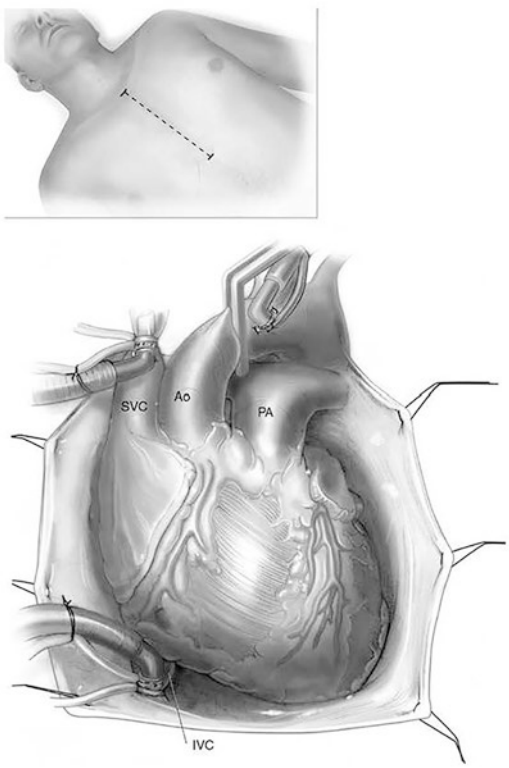

Fig. 26.1 Recipient operation setup. An overall setup similar for other open heart operations is adequate. Perioperative medications include the administration of antibiotics (usually first-generation cephalosporins) and immunosuppression agents. The recipient is usually intubated after confirmation that the donor heart is suitable for transplantation. A Foley urine catheter and a Swan-Ganz catheter are placed. Although all heart transplant patients on the waiting list would have had a right heart catheterization during their initial evaluation, determining their PA pressures following intubation might influence the need for peri- and postoperative pulmonary vasodilator therapy such as nitric oxide. Reprinted with permission from John R, Liao K. Orthotopic heart transplantation. Operative Techniques in Thoracic and Cardiovascular Surgery 2010; 15:138–146

The initial aortic cannulation site should be as distal as possible, allowing ample room between the aortic cannulation site and the proximal vein graft anastomosis or aortotomy incision. This provides room for the aortic cross-clamping and normal aortic tissue when sewing the anastomosis during the heart transplant. The use of suture pledgets on the aorta should be avoided, if possible, because dense tissue adhesions or scarring can occur around pledgets. Single-stage superior vena cava (SVC) and inferior vena cava (IVC) venous cannulation should be avoided, when possible, to preserve anatomy around the cava and to minimize scarring and stenosis of the SVC, especially when automatic implantable cardioverter-defibrillator (AICD) or pacemaker leads are present. In multiple redo patients, a colored elastic vessel loop is placed around the ascending aorta and left inside the mediastinum to be used as a landmark for easy dissection of the ascending aorta during transplant. With more and more transplant patients receiving left ventricular assist device (LVAD) support prior to transplant, the following strategies are used in our center to make chest reentry and LVAD explantation safe and expeditious: The LVAD outflow graft is kept relatively long and placed into the right pleural space to avoid reentry injury to the graft. A Gore-Tex mesh is placed behind the sternum to cover the right ventricle and LVAD outflow graft to avoid reentry injury to the right ventricle and/or the LVAD outflow graft. It is helpful to obtain a computed tomography (CT) scan of the chest to assess the proximity of the heart or other critical structures (e.g., the LVAD outflow graft) to the undersurface of the sternum.

Once donor availability is confirmed, the recipient is admitted to the hospital. Clinicians take a pertinent medical history, perform a physical examination, and order routine blood tests. Special attention is paid to double-checking donor and recipient blood types and crossmatching results. The patient's current status of infection and anticoagulation should be assessed and addressed with appropriate antibiotics and blood product transfusion, if time allows. If the patient had a mechanical ventricular assist device recently implanted for acute myocardial infarction, the heart may not have time to dilate and the pericardial space can be small due to decompression by the device. It is important to review the patient's current chest X-ray or CT scan to have a realistic estimation of the recipient's pericardial space to avoid donor and recipient heart size mismatch. Comparing the ratio of cardiac silhouette dimension to chest wall dimension, in addition to a height comparison between the donor and recipient, can be very useful objective measurements.

Intraoperative Monitoring

The recipient receives a radial artery line and a Swan-Ganz catheter. The catheter is usually placed via the left internal jugular vein. This approach is used to preserve the right internal jugular vein route for postoperative transvenous

endomyocardial biopsies. However, for a patient with AICD and pacemaker leads, a right internal jugular approach is used to avoid resistance. Pulmonary artery pressure is first measured and then the catheter tip is pulled back into the superior vena cava before the recipient cardiectomy is performed. A transesophageal echocardiography (TEE) probe is routinely placed only to be used later to assess the donor heart contractility and volume status and to help remove air from cardiac chambers.

In patients requiring redo sternotomy, external defibrillator pads are placed in case of ventricular fibrillation during early mediastinal dissection, and a femoral arterial catheter is placed for quick establishment of femoral-femoral cardiopulmonary bypass support should injury to the heart occur during entry to the mediastinum.

Timing of Donor and Recipient Operations

Most research data has shown that the donor heart will tolerate ex vivo cold preservation of 4–6 h. It is common practice that all measures are taken to limit the donor heart ischemic time to less than 6 h. Particularly when the recipient has an elevated pulmonary artery pressure or the donor heart is from a marginal donor, or there is a donor and recipient weight discrepancy, it is highly advantageous to achieve reperfusion in the shortest possible time to allow optimal right ventricular function. Coordination of the donor and recipient operations is key to shortening the donor ex vivo ischemic time.

The following factors must be considered when estimating the donor heart ex vivo ischemic time: (1) the time that other organ procurement teams need to complete their dissection before donor heart cross-clamping, especially when multiple organs are procured, (2) organ transportation time, (3) anticipated difficulty of monitoring line insertion and anesthetic induction, and (4) anticipated difficulty of accessing the heart in a recipient who had previous cardiac surgical procedures and, specifically, when he or she is supported by an intracorporeal LVAD. Within these confines, attempts are made to effectively coordinate every single step to minimize waiting periods in the recipient operating room and minimize time on cardiopulmonary bypass support. When the donor heart has safely arrived in the region of the recipient's hospital, cardiopulmonary bypass begins. Recipient cardiectomy is performed only when the donor heart arrives in the operating room and is inspected by the transplant surgeon. In recent years in our practice, we have seen increased numbers of recipients with multiple cardiac operations and with ventricular assist device support. Importantly, we'd rather have the recipient ready and wait for the donor heart to arrive than the other way around.

It should be noted that no incision is made in the recipient until the retrieving surgeon is satisfied with the donor heart, and no cardiectomy is performed until the donor heart arrives in the recipient's operating room.

Donor Heart Procurement

Donor heart procurement is performed through a median sternotomy. The pericardium is opened widely. The heart is inspected for any signs of trauma, infection, or congenital anomalies. Overall contractility of both the left and right ventricles is appreciated. The four chambers of the heart are palpated to detect any valve or vessel pathology-related thrills. The coronary arteries are palpated to rule out any evidence of coronary artery disease. The ascending aorta is separated from the pulmonary artery. The superior vena cava is mobilized circumferentially up to and beyond the level of the azygos vein and encircled with two heavy ties of 0 silk sutures. The inferior vena cava likewise is mobilized circumferentially and surrounded with a vessel loop.

At least 300 units of heparin/kg of donor weight are administered intravenously to the donor. A cardioplegia needle is inserted into the ascending aorta. Venous return to the heart is interrupted by dividing the SVC between the two silk ties. The IVC is divided flush with the diaphragm. The tip of the left atrial appendage is amputated. The ascending aorta is cross-clamped and about 2 L of cold cardioplegia is administered into the ascending aorta. Ice slush is immediately poured into the pericardial space and onto the heart to provide rapid topical cooling. Once cardiac arrest is achieved, the heart is excised in an expedient fashion. First, the pulmonary veins are divided flush with the pericardium. The aorta is divided as distal as possible, usually at the takeoff of the innominate artery, and the main pulmonary artery is divided at its bifurcation. If the recipient requires reconstruction of both pulmonary arteries, then the branch pulmonary arteries are divided at the level of the pulmonary hilum. Additional length of the ascending aorta may be required for recipients with hypoplastic left heart syndrome or with L-transposition of the great vessels.

Recipient Cardiectomy [8, 9]

Incision and Establishment of Cardiopulmonary Bypass

A median sternotomy is performed in all recipients. In patients who have had a previous cardiac surgical procedure, particularly if multiple ones, or if the hemodynamic status is precarious or the heart is severely dilated, it is wise to isolate both the femoral artery and vein so that rapid femoral-femoral bypass can be instituted should circulatory decompensation or uncontrollable bleeding occur. After the skin and subcutaneous tissue incision, the sternal wires are cut but not pulled. An oscillating saw is used to cut the sternum's anterior plate and stopped when the saw hits the wires. The wires are then pulled out and the sternum's posterior is cut with a pair of straight Mayo scissors while the sternum is lifted up with bone hooks and the ventilator is put on hold.

In patients with no previous cardiac surgical procedures, the pericardium is opened and secured to the sternotomy edges with sutures. The aorta and pulmonary artery are separated using electrocautery. After systemic heparin infusion, the purse-string sutures are placed in the ascending aorta and right atrium or vena cava. The ascending aorta is cannulated in routine fashion just proximal to the innominate artery. The cannula size varies from 20 French to 24 French, depending on the recipient's body weight. Venous cannulation differs depending on whether the patient has a previous AICD/pacemaker lead placement or scarring and whether the surgeon will use a biatrial or bicaval anastomosis. If the patient has no AICD/pacemaker leads or has a dilated superior vena cava or a bicaval anastomosis is to be performed, a right-angle 32 French cannula, if possible, is inserted directly into the SVC. Otherwise, a straight venous cannula is placed posteriorly in the right atrium near the orifice of the SVC and advanced into the SVC. The inferior vena cava cannula, preferably a 36 French size, is inserted posteriorly in the right atrium near the IVC orifice. The cavae are then encircled with Rommel tourniquets to allow institutions of total bypass. The choice of caval cannulation sites must allow a generous cuff of posterior atrium for biatrial anastomosis and a generous atrial cuff of both SVC and IVC for bicaval anastomosis (Fig. 26.2).

In patients with redo sternotomies, the aorta and right atrium are first isolated so that cardiopulmonary bypass support can be readily established in case of unstable hemodynamics during the cardiac dissection. Sometimes it is necessary to place the patient on the bypass to facilitate safe and expeditious dissection, especially in patients with previous coronary artery bypass grafting surgery and with patent grafts. The attempt is made in all cases to avoid systemic heparinization and the start of cardiopulmonary bypass for as long as reasonably possible—to lessen the period of bypass and attendant bleeding complications. A metal-tip aortic cannula is used for all the redo aortic cannulations to make penetration easy through scar tissues.

In patients with LVAD or Bi-VAD implantation, the entry to the mediastinum should be as cautious as with the other redo sternotomies, if not more. The injury to the LVAD outflow graft can result in a large amount of blood loss in a short period of time, and quick hemodynamic compromise because of its high intraluminal pressure. After starting the technique to place the LVAD outflow graft in the left pleural space, injury to the graft is completely avoided during reentry to the mediastinum. With the HeartMate LVAD, the Thoratec Company developed a Gore-Tex outer graft to protect the inner Dacron graft from being injured and to reduce adhesions around the Dacron graft so that its removal is easier. The Gore-Tex outer graft is also a useful landmark to trace to the proximal ascending aorta. Once the patient is placed on cardiopulmonary bypass support, both LVAD and right ventricular assist device (RVAD) can be turned off. Once the donor heart arrives at the hospital, the LVAD outflow graft can be divided and the RVAD inflow cannula and outflow graft can be removed and divided, respectively.

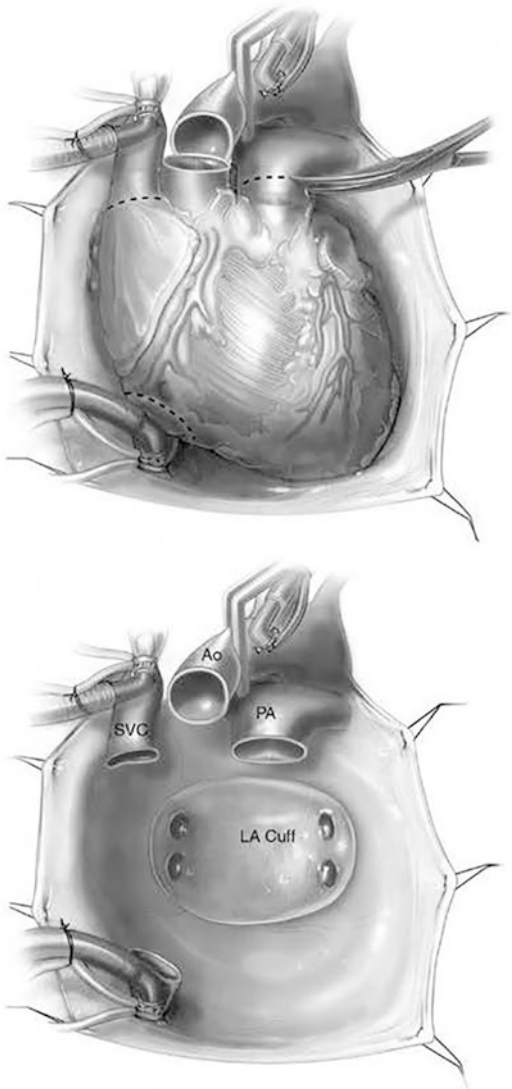

Fig. 26.2 Recipient cardiectomy. Recipient cardiectomy is usually performed such that it is completed at the same time that the donor heart arrives in the operating room. The patient is placed on cardiopulmonary bypass; the aorta is cross-clamped and the caval snares are tightened. The aorta and the pulmonary artery are separated and the interatrial groove is developed. The great vessels are divided just distal to their respective valves. The superior vena cava is transected at the cavo-atrial junction. A large cuff of IVC is prepared by transecting the right atrium adjacent to the IVC (this incision is ideally made by carrying it medially through the ostium of the coronary sinus and laterally through the floor of the fossa ovalis). The left atrial cuff is prepared by entering the roof of the left atrium (this is facilitated by the development of the interatrial groove); this incision is extended to leave behind a generous cuff of posterior left atrial tissue while observing the orifices of the four pulmonary veins. The left atrial appendage is also usually excised. Reprinted with permission from John R, Liao K. Orthotopic heart transplantation. Operative Techniques in Thoracic and Cardiovascular Surgery 2010; 15:138–146

Once the donor heart arrives on the grounds and is being returned to the recipient hospital by ambulance, the patient is placed on cardiopulmonary bypass, and the body temperature is cooled to 28 °C.

Excision of Recipient Heart (Fig. 26.2)

The distal aorta is cross-clamped. Excision of the diseased heart begins at the lateral right atrial wall. The right atrium is entered at the midpoint, 2–3 cm anterior to the caval cannulae. This excision is extended inferiorly toward the coronary sinus. Superiorly, this incision is extended around the superior aspect of the right atrium and to the aortic root at the level of the noncoronary sinus. The aorta and pulmonary artery are divided at the level of their respective semilunar valves. The interatrial septum is then entered at the anterior portion of the fossa ovale close to the tricuspid valve. The incision is extended superiorly to the left atrial roof and inferiorly, staying close to the atrioventricular groove. The heart is then pulled upward and toward the right side. The remaining attachments of the left atrial are divided close to the atrioventricular groove to leave a generous cuff of the posterior left atrium anterior to the pulmonary veins. The aorta and pulmonary artery are separated using electrocautery. Care must be taken to avoid injury to the right pulmonary artery during this maneuver. The recipient left atrial cuff may be trimmed appropriately based on the size of the donor left atrium to lessen their size discrepancy.

If a bicaval anastomosis technique is used, the SVC and IVC are cannulated as distally as possible. The heart is first excised in the standard fashion, leaving the posterior aspect of the left atrium and the posterolateral aspect of the right atrium. The right atrium is then excised so as to leave 2–3 cm of atrial cuff around each cava.

A small endotracheal suction catheter which insufflates continuous carbon dioxide (CO_2) is anchored to the pericardial sac. The gravity of CO_2 is heavier than that of the air, and it is used to expel air from the open cardiac chambers. CO_2 is readily absorbed by the blood and forms no air bubbles. The perfusionist should pay special attention to the blood PH and CO_2 level to adjust the CO_2 flow rate and prevent acidosis.

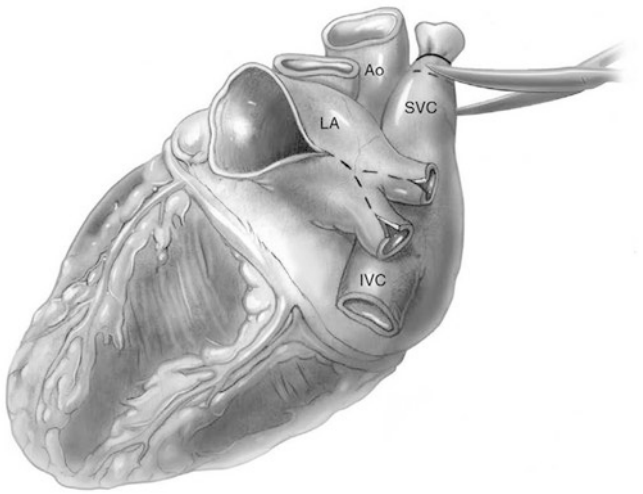

Fig. 26.3 Preparation of the donor heart. The aorta and pulmonary arteries are separated and the posterior pulmonary artery attachments to the left atrium are divided. The left atrial cuff is created by connecting incisions between each of the four pulmonary veins and trimming excess tissue to create a smooth continuous edge. The fossa ovalis is inspected and probed to identify a patent foramen ovale, which can be closed by a continuous 4-0 Prolene suture from the right atrial side. For the bicaval technique, the recipient cuff is present. For the biatrial technique, the SVC is doubly ligated, and the right atrium is opened from the lateral IVC toward the right atrial appendage, to avoid the sinus node. Ao = aorta, IVC = inferior vena cava, LA = left atrium, SVC = superior vena cava. Reprinted with permission from John R, Liao K. Orthotopic heart transplantation. Operative Techniques in Thoracic and Cardiovascular Surgery 2010; 15:138–146

Implantation of the Donor Heart [8–10]

Donor Heart Preparation

The donor heart is prepared as follows: Using electrocautery, the aorta and pulmonary arteries are separated and the posterior pulmonary artery attachments to the left atrium are divided. The left atrial cuff is created by connecting incisions between each of the four pulmonary veins and excising the posterior atrial wall. The fossa ovalis is inspected. If a patent foramen ovale or a septal defect is present, it is over-sewn with a 4-0 Prolene suture. If biatrial anastomoses are planned, the inferior vena cava is opened curvilinearly toward the right atrial appendage to avoid the sinoatrial node. The SVC is closed circumferentially (Fig. 26.3).

A retrograde cardioplegic catheter is inserted into the coronary sinus and a dose of 400 cm^3 cold blood cardioplegia is infused. The infusion of retrograde cardioplegia before implanting the donor heart has the following potential benefits: (1) it provides nutrients to the heart before it sustains an extra 30–60 min of ischemia; (2) it can expel the debris and air trapped inside the donor coronary arteries that occurred during harvesting and the transportation process; and (3) it may improve the initial recovery of transplanted hearts.

Left Atrial Anastomosis

Left atrial anastomosis is begun at the base of the left atrial appendage near the left superior pulmonary vein using a long 3-0 Prolene suture. The initial couple of sutures are placed with the donor heart resting on the left sternal edge. The heart is then lowered into the recipient pericardium. A dry 4 × 4 sponge is placed inside the left atrium cavity to prevent debris from falling into pulmonary veins during anastomosis. The two ends of suture are run inferiorly and superiorly and eventually joined in the middle of the interatrial septum. The sponge is then removed. The left atrium is filled with cold saline and the lungs are ventilated to expel the air before the sutures are tied. To minimize the chance of left atrial thrombosis formation, we use an everting suture technique to approximate smooth endocardial surfaces of the donor's and recipient's left atrium and avoid rough tissue surface exposure to blood.

Cava Anastomoses

Donor and recipient inferior vena cava are trimmed to the appropriate lengths to minimize any tension. A long 4-0 Prolene sutures is used to perform an end-to-end anastomosis starting from the posterior wall and then to the anterior wall. The donor and recipient superior vena cava ends were prepared to appropriate length and kept relatively straight to prevent SVC kinking. Two separate 4-0 Prolene sutures are used to perform an end-to-end anastomosis to prevent "purse-string effect" on the anastomosis (Fig. 26.4).

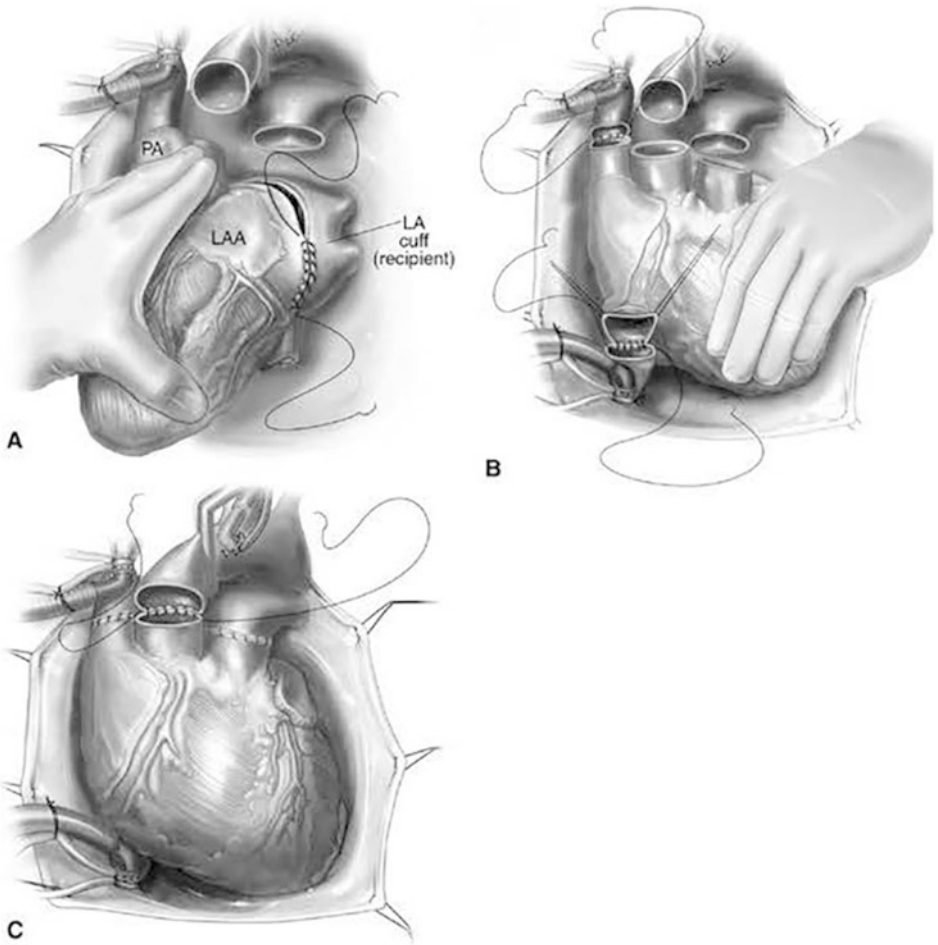

Fig. 26.4 Orthotopic heart transplantation: bicaval anastomosis technique. (**a**) Left atrial anastomosis. The left atrial anastomosis is always performed first by using a long 3-0 Prolene suture starting at the left atrial cuff adjacent to the left superior pulmonary vein and passing it through the donor left atrial cuff adjacent to the left superior pulmonary vein and passing it through the donor left atrial cuff adjacent to the left atrial appendage. The initial few sutures are completed with the donor heart positioned at the level of the sternal edge, and the heart is subsequently lowered into the pericardial space. The posterior left atrial suture line is first completed and then subsequently the anterior suture line (as shown in the figure, this is facilitated by the assistant retracting the donor aorta and PA to provide adequate exposure of the left atrium). To minimize the risk of left atrial thrombus formation, an everting suture technique should be done to facilitate approximation of the smooth endocardial surfaces of donor and recipient left atrial tissue. A left ventricular vent can be passed through an opening between the two untied left atrial sutures that can help with deairing. During all the anastomosis, a cold saline-soaked laparotomy pad can be placed on the heart. In addition, continuous carbon dioxide is also run into a pericardial well. (**b**) Superior and inferior vena caval anastomosis. Next, the inferior and superior vena caval anastomoses are usually performed with 3-0 and 4-0 Prolene sutures, respectively. During performance of the IVC anastomosis, care is taken to avoid deep sutures being placed in the region of the donor coronary sinus ostium to avoid potential injury. The donor right atrial appendage is medially oriented to facilitate proper orientation of the SVC anastomosis. This is important to avoid the SVC from being kinked or improperly aligned. Further, attention should be closely paid to avoid "purse-stringing" the SVC anastomosis to prevent inadvertent narrowing at the anastomotic level. (**c**) Pulmonary artery and aortic anastomosis. It is important to avoid excess length of pulmonary artery to avoid kinking at the level of the anastomosis. The median raphe on the PA may help orient the anastomosis, which is performed with 4-0 Prolene suture. Next, the aortic anastomosis is completed with 4-0 Prolene suture. If the recipient aortic tissue quality is suboptimal, a 2-layer technique, with an inner layer of horizontal mattress suture and outer layer of running suture, can be performed to ensure adequate hemostasis. LA = left atrium, LAA = left atrial appendage, PA = pulmonary artery. Reprinted with permission from John R, Liao K. Orthotopic heart transplantation. Operative Techniques in Thoracic and Cardiovascular Surgery 2010; 15:138–146

Pulmonary Artery Anastomosis

The pulmonary arteries of the donor and recipient are lined up and trimmed appropriately. The donor pulmonary artery is transected 2–3 cm distal to the pulmonary valve. Excessive length of pulmonary arteries should be avoided to prevent kinking of the pulmonary artery later when the right heart is filled. A 4-0 running Prolene suture creates the anastomosis, starting in the posterior wall and finishing in the anterior wall. If possible, an everting suture technique is used.

Aortic Anastomosis

Donor and recipient aortas are lined up and trimmed only slightly. Leaving the aorta long has the advantages of avoiding tension on the anastomosis and facilitating visualization of the left atrial and pulmonary artery anastomotic suture lines in case bleeding would occur following removal of the aortic cross-clamp. The two-layer technique completes the anastomosis—with an inner layer of horizontal mattress sutures and an outer layer of running sutures. Two 4-0 Prolene sutures reinforced with Teflon felt are placed as horizontal mattress sutures starting at the center of the posterior wall and carried up each side of the aorta as an inner horizontal mattress and an outer running layer. The sutures are tied in the middle anterior wall. The inner layer of the horizontal mattress suture enables smooth endothelial coaptation. A strip of bovine pericardium or Teflon strip is sometimes used to reinforce the aortic anastomosis if the aorta is poor quality.

Right Atrial Anastomosis

The right atrial anastomosis is begun at the superior end of the atrial incision. A long 3-0 Prolene suture is used in a running suture fashion. First, the suture ends are carried both inferiorly and superiorly to complete the septal anastomosis, and then they are joined at the lateral wall of the atrium. Rewarming of the heart is started during this anastomosis (Fig. 26.5).

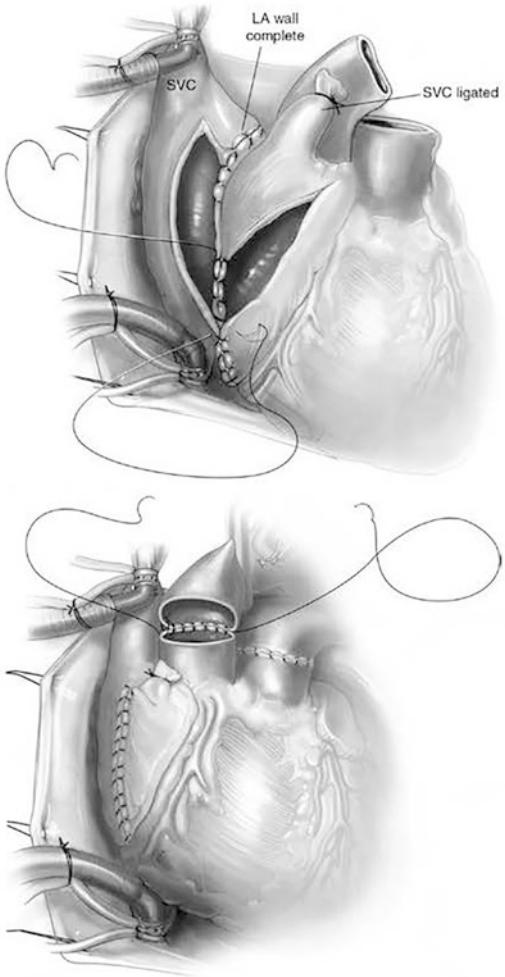

Fig. 26.5 Orthotopic heart transplantation: biatrial anastomosis technique. The left atrial anastomosis is initiated as mentioned earlier at the base of the left atrial appendage adjacent to the left superior pulmonary vein using a long 3-0 Prolene suture. The two ends of the suture line are run inferiorly and superiorly and are eventually joined in the middle of the interatrial septum. The right atrial anastomosis is initiated at the superior end of the atrial incision. A long 3-0 Prolene suture is used, and the suture ends are carried both inferiorly and superiorly to first complete and septal anastomosis, and then they are joined at the lateral wall of the septum. The PA and aortic anastomosis are performed as previously described. LA = left atrium, SVC = superior vena cava. Reprinted with permission from John R, Liao K. Orthotopic heart transplantation. Operative Techniques in Thoracic and Cardiovascular Surgery 2010; 15:138–146

Sequences of Implant Anastomosis

The left atrial anastomosis needs to be performed first, but the order of subsequent anastomoses is dictated by the ischemic time of the donor heart and the recipient's comorbidities, such as pulmonary vascular resistance. From a technical standpoint, it is desirable to complete the pulmonary artery anastomosis as well as the inner and inferior portions of the right atrial anastomosis before releasing the aortic cross-clamp. When patients have normal pulmonary vascular resistance and the donor ischemic time is within safe limits, the following sequences are used: (1) left atrium, pulmonary artery, right atrium, aorta, and release of cross-clamp or (2) left atrium, pulmonary artery, inner and inferior right atria, aorta, release of cross-clamp, and remainder of right atrium. The latter allows about 30 min of reperfusion for the donor heart, while the right atrial anastomosis is being completed and the suture lines are being checked and reinforced where necessary. When the donor heart ischemic time is a major concern, the following sequences can be used: (1) left atrium, posterior pulmonary artery, inner and inferior right atria, aorta, release of cross-clamp, remainder of pulmonary artery, and right atrium or (2) left atrium, aorta, release of cross-clamp, pulmonary artery, and right atrium (Fig. 26.4).

Completion of the Procedure (Fig. 26.6)

Before releasing the cross-clamp, the patient's temperature is rewarmed. Five hundred mg of Solu-Medrol and 100 mg of lidocaine are given to the patient. The patient is placed in the deep Trendelenburg position and a 16 French angiocatheter is placed in the most anterior portion of the ascending aorta to allow air to escape. The venous return is reduced and both lungs are ventilated. The heart is shaken and squeezed. The cardiopulmonary bypass flow is turned down and the cross-clamp is removed. The caval tourniquets are removed at this moment, and the superior vena cava cannula is pulled back and placed into the right atrium to prevent right heart distention. The CO_2 insufflation is turned off. A TEE is used to guide further deairing efforts. Since the introduction of CO_2 insufflation during heart transplantation, we have noticed significant reduction of residual air inside cardiac chambers.

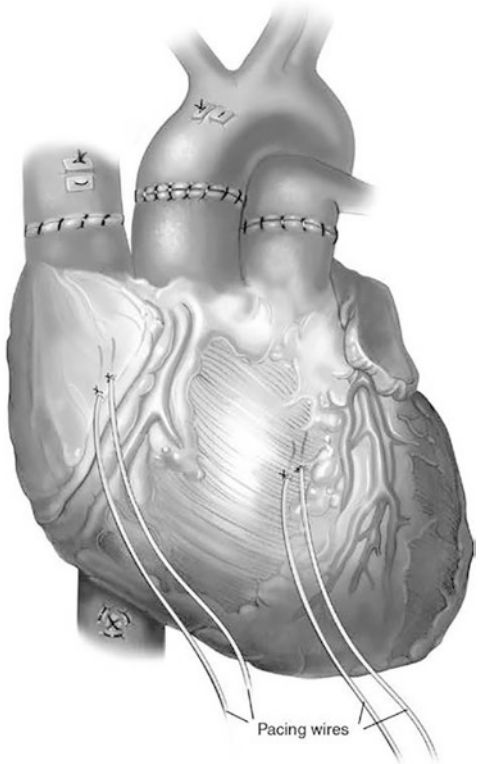

Fig. 26.6 Completed orthotopic heart transplantation. After completion of all the anastomosis, IV Solu-Medrol is administered; the patient is placed in a Trendelenburg position, and standard deairing maneuvers are performed. The aortic cross-clamp is removed with suction on the aortic root as well as the left ventricular vent cannula. Sufficient time is allowed for reperfusion. During this time, all suture lines are carefully inspected for hemostasis, especially areas such as the left atrial suture line that would be extremely difficult to inspect after cardiopulmonary bypass is terminated. Right atrial and right ventricular temporary pacing wires are placed. Appropriate inotropic support is also initiated during the period of reperfusion. The need for aggressive pulmonary vasodilator therapy including nitric oxide may be required for certain recipients. Standard deairing maneuvers are performed and confirmed by transesophageal echocardiography. The patient is subsequently weaned off cardiopulmonary bypass in the usual manner. Intraoperative transesophageal echocardiography is also utilized to confirm adequate functioning of the implanted heart and document ventricular function as well as valvar competence. Standard chest tubes are placed, including adequate drainage of the posterior pericardial space, as these patients are at increased risk of developing postoperative pericardial effusions because of the relative size mismatch between the donor heart and the relatively large pericardial space. Reprinted with permission from John R, Liao K. Orthotopic heart transplantation. Operative Techniques in Thoracic and Cardiovascular Surgery 2010; 15:138–146

At least 30 min should be allowed for thorough rewarming and for reperfusion of the heart to wash out the cardioplegia. The suture lines are inspected for hemostasis. Sometimes, in order to provoke certain hidden bleeders, especially in the left atrial and posterior pulmonary artery suture lines, the bypass flow is temporarily turned down to help find bleeders at "physiological pressure." Bleeders in these areas are very difficult to visualize once the bypass is discontinued.

When the patient is normothermic and hemostasis is secured, an infusion of isoproterenol is started at a dose of 0.02 μg/kg/min to achieve a heart rate of 100–120 beats per minute. A pair of atrial and ventricular pacing leads is placed to ensure a heart rate faster than 90 beats per minute. A gram of calcium is placed into the pump and the patient is slowly separated from bypass.

If the recipient has increased pulmonary artery pressure documented by a preoperative right heart catheterization study or by a Swan-Ganz catheter measurement during induction, aggressive measures are taken to lower the pulmonary artery pressure before the weaning from bypass is even attempted, thus minimizing the afterload stress on the right ventricle. The following steps are taken to lower the pulmonary artery pressure and support the right heart: (1) hyperventilation of the lungs to keep the patient's $CO_2 < 30$, PH > 7.4, (2) infusion of milrinone at a dose of 0.5 μg/kg/min, (3) infusion of epinephrine at a dose of 0.01–0.04 μg/kg/min, and (4) continuous inhaled nitric oxide via ventilator at a concentration of 20 ppm.

Bicaval Anastomosis Technique [11, 12]

The bicaval anastomosis technique requires a complete dissection of both the IVC and SVC and complete excision of the recipient's right atrium, in addition to the standard donor cardiectomy procedure. The left atrial anastomosis is begun first, followed by the pulmonary artery and aortic anastomoses. These three anastomoses are carried out similar to those previously described. A sucker is placed into the coronary sinus to remove blood and the IVC anastomosis is completed in a running end-to-end anastomosis fashion using a 4-0 Prolene suture. Air is removed from the heart and the aortic cross-clamp is released. The SVC anastomosis is performed with the heart beating, using a 4-0 Prolene running suture. Occasionally, in order to minimize donor ischemic time, the aortic cross-clamp can be removed before bicaval anastomosis is started (Fig. 26.4).

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Comparison of Biatrial and Bicaval Techniques [13–16]

The biatrial anastomosis technique has long enjoyed the reputation of being simple, safe, and reproducible. It consists of four anastomoses: left atrium, right atrium, pulmonary artery, and aorta. The majority of heart transplants were performed with this technique before the mid-1990s, and its long-term survival results are excellent.

The bicaval anastomosis technique was introduced in the early 1990s with the goal of reducing right atrium size, reducing distortion of the recipient heart, and preserving atrial conduction pathways. The technique has gained wider acceptance in the past decade. It is proven safe and reproducible and has demonstrated certain anatomical and physiological advantages over the biatrial technique. However, it consists of five anastomoses: left atrium, pulmonary artery, aorta, IVC, and SVC. It is slightly more time-consuming.

A series of prospective and retrospective studies was conducted to compare postoperative atrial geometry, arrhythmia, atrioventricular valvular function, hemodynamics, exercise ability and peak oxygen consumption, and survival between biatrial and bicaval techniques. These studies generated conflicting results and some differences were statistically insignificant. Most studies, however, showed improved atrial geometry and function, decreased incidence of atrioventricular valve dysfunction, and decreased incidence of atrial arrhythmia. Whether these improvements confer a better exercise capacity, survival, or morbidity advantage remains to be proven. A multicenter randomized clinical trial is needed to better answer these questions.

Postoperative Care [17]

ICU Care

The principles of posttransplant care are similar to that used in postoperative care of routine cardiac surgery patients. Hemodynamic monitoring is performed, including continuous arterial pressure, pulmonary artery pressure, central venous pressure, cardiac output and index, urine output, and mixed venous oxygen saturation (SVo2). Adequate oxygenation and normal pH are maintained. Special attention is paid to keeping carbon dioxide partial pressure (pCO2) relatively low and avoiding base deficit (a measurement of lactic acid and an indicator of perfusion), especially when the patient's pulmonary artery pressure is elevated. Chest tube output, coagulopathy parameters, and serial hemoglobins are closely monitored and blood loss replaced with packed red blood cell transfusions after the coagulopathy is corrected. Hemoglobin is kept above 9 g/dL to ensure adequate oxygen delivery to the tissues. Urine output is closely monitored and diuretics used if the central venous pressure is elevated and urine output decreased. Urine output is kept above 30 ml/h.

The following hemodynamic parameters are considered physiological and optimal: systemic blood pressure greater than 90 mmHg, mean arterial pressure greater than 60 mmHg, central venous pressure between 5 and 18 mmHg, pulmonary artery pressure one-third or less of systemic blood pressure, and cardiac index greater than 2 L/min/m^2 and SVo2 greater than 65. For many heart transplant patients, postoperative recovery is generally straightforward. Ventilation weaning is begun as soon as the patient is awake and hemodynamically stable, with no sign of mediastinal bleeding.

A few unique physiological features of a transplanted heart need to be considered in the early postoperative period [18]. One distinct characteristic is that the heart is totally denervated, which may result in reduction in heart rate. The transplanted heart is subject to heart rate change to maintain pump function and cardiac output. A chronotropic catecholamine agent is routinely used. Isoproterenol is infused at a dose of 0.01–0.03 μg/kg/min infusion. The goal heart rate is set over 90/min. If the heart rate fails to respond to an isoproterenol drip, epicardial pacing, preferably atrial pacing, is initiated at 90 beats per minute. Transplanted heart rhythm dysfunction typically resolves spontaneously within 48 h after surgery, and the isoproterenol drip is gradually weaned. Besides its chronotropic effect, isoproterenol has the benefit of improving cardiac output and reducing pulmonary vascular resistance. Cardiac output and SVo2 should be closely monitored during the weaning of isoproterenol because both parameters can drop despite an adequate intrinsic heart rate. Terbutaline is added to keep the heart rate over 60 beats per minute once the patient starts oral intake, and, occasionally, a permanent pacemaker may be necessary if heart rate remains slower than 60 [19].

A second beta-adrenergic agent such as an epinephrine drip is added if the patient's cardiac output is inadequate or the heart rate response to isoproterenol is too fast or becomes arrhythmogenic. If the patient's systemic blood pressure and peripheral vascular resistance are low, a vasoactive agent such as vasopressin is added. Vasopressin is preferred over other vasoconstrictors due to its limited effect on pulmonary vascular resistance. A milrinone drip is initiated if the patient had a history of pulmonary hypertension or has elevated pulmonary artery pressure and elevated central venous pressure after transplant or has signs of right heart failure.

The causes of low cardiac output after transplant can be multifactorial. Increased use of older, marginal donor hearts, prolonged donor heart ischemic time, and mismatch of donor and recipient weight all contribute to unstable postoperative hemodynamics. The treatment of low cardiac output is similar to that used in routine cardiac surgery patients. Maintaining adequate heart rate by isoproterenol infusion or atrial pacing is crucial in a transplanted heart, followed by volume expansion to maintain central venous pressure between 10 and 18 mmHg. Another beta-adrenergic agent is usually needed. Milrinone infusion is started if right heart dysfunction is suspected, and volume infusion is controlled by reducing central venous pressure lower than 20 mmHg. If low cardiac output persists despite these interventions, an echocardiogram needs to be performed to rule out cardiac tamponade and to assess left and right ventricular function.

Early graft failure is unusual, but it can occur secondary to poor myocardial protection or early acute rejection. Early acute rejection can occur in the setting of a preoperative 0 % reactive antibody titer. Early endomyocardial biopsy to look for cellular rejection or immunofluorescent staining to identify humoral rejection may be required. True hyperacute cardiac rejection is extremely rare in the modern era of transplantation. Progressive left ventricular dysfunction due to primary graft failure may require further support with an intra-aortic balloon pump. A left or biventricular assist device may be required if multi-organ failure and severe acidosis cannot be reversed by medical management. A short-term, extracorporeal ventricular assist device can be used to support the failed heart for up to 2 weeks to allow the myocardium to recover from ischemia or to allow antirejection treatment to work. The extracorporeal ventricular assist device is inserted in the standard manner with an inflow cannula inserted in the atrium and outflow cannula inserted in the appropriate great artery [20].

Recipients who had pulmonary vascular resistance above 3.0 Wood units also have an increased risk of developing elevated PVR after a heart transplant and resulting acute right heart failure. Many steps can be taken to prevent right heart failure, including obtaining a heart from a donor of a larger size or giving a heart from a male donor to a female recipient, minimizing donor heart ischemic time, avoiding excessive blood and blood product transfusion by giving recombinant activated coagulation factor VII (rFVIIa) to correct coagulopathy, correcting hypoxia and hypercapnia, initiating milrinone early and even nitric oxide, and electively leaving the chest open for delayed closure. Inserting a right ventricular assist device in the setting of high PVR has a very limited effect, and the clinical result is usually dismal [21].

Immunosuppressive Management

The goal of immunosuppression is to prevent or treat cardiac allograft rejection while minimizing both drug toxicities and the major sequelae of immune suppression, namely, infection and malignancy. Most clinically used immunosuppressive regimens consist of triple-therapy immunosuppression: corticosteroids, calcineurin inhibitors, and antiproliferative agents [3, 22, 23].

Corticosteroids are nonspecific anti-inflammatory agents. Lymphocyte depletion is the main antilymphocyte action of steroids. They reversibly block T-cell- and antigen-presenting cell (APC)-derived cytokine and cytokine receptor expression that otherwise would occur as a consequence of T-cell activation. The nonspecific action of steroids leads to many side effects such as weight gain, glucose intolerance, gastric distress, hyperlipidemia, and hypertension.

Calcineurin inhibitors, cyclosporine, a small fungal cyclic peptide, and tacrolimus, a macrolide antibiotic, have become the cornerstone of immunosuppressive therapy in solid organ transplantation. Tacrolimus, formerly known as FK506, is the active ingredient in Prograf. Cyclosporine binds to a group of immunophilins called cyclophilins that are important biologic molecules present in all tissues. Tacrolimus forms a complex with FK506 binding proteins (FKBPs). These complexes bind to calcineurin, a pivotal enzyme in T-cell IL-2 production, thereby inhibiting cytokine transcription by the CD4 cell. Blockade of cytokine production and cytokine receptor expression inhibits T-cell proliferation and differentiation so that the various effector arms of the immune response are not activated. Compared to cyclosporine, Prograf causes less nephrotoxicity [24].

The antiproliferative agent mycophenolate mofetil (MMF, CellCept) is a selective inhibitor of the de novo pathway of purine biosynthesis, thereby providing more specific and potent inhibition of T-cell and B-cell proliferation. MMF causes less bone marrow suppression compared to the other agents in its class.

Daclizumab (Zenapax) is a monoclonal antibody that is an IL-2 receptor antagonist that is typically reserved for preventing rejection in the setting of renal insufficiency or in a recipient who has gastrointestinal dysfunction for an extended time [25].

Dosing of Immunosuppression Drugs

Methylprednisolone 1000 mg IV is given preoperatively. Following implantation of the heart, another 500 mg IV is administered at the release of the aortic cross-clamp. Additional methylprednisolone 125 mg is given every 8 h for three doses after the patient has returned to the intensive care unit. Prednisone is initiated at 1 mg/kg/day in two divided doses and progressively tapered over a 4-week period by 5 mg/day to 20 mg BID. Patients must be free of rejection for 3 months before complete steroid withdrawal. The prednisone taper schedule is illustrated in Table 26.5.

Prograf is started postoperatively for 1–3 days if the patient's renal function is normal. The starting dose of Prograf is 0.5 mg twice a day and is increased to 2 mg twice a day depending on the blood level. The patient's renal function or creatinine is closely monitored when Prograf is given. The 12-h trough level of Prograf is maintained at about 10–15 mg/L immediately after transplant and tapered afterward (Table 26.6).

Mycophenolate mofetil (MMF), 1500 mg, is given PO preoperatively and then 2–3 g IV/PO per day in two divided doses after transplant. The target level of MMF is maintained at 2–4 and the dose is titrated to keep white blood cell count >4000/dl.

Table 26.5 Prednisone taper

Month 1	Prednisone 0.3 mg/kg/day
Month 2	Prednisone 0.2 mg/kg/day
Month 3	Prednisone 0.1 mg/kg/day
Month 4	Prednisone 0.05 mg/kg/day or 2.5 mg/day
Month 5	Prednisone discontinued

Table 26.6 Prograf blood level taper

0–3 months	10–15 mg/L
3–6 months	8–12 mg/L
6–9 months	6–12 mg/L
9–12 months	6–12 mg/L
After year 1	6–10 mg/L
Off prednisone	6–10 mg/L

Table 26.7 International Society for Heart Lung Transplantation (ISHLT) 1990 classification of acute cellular rejection in transplant endomyocardial biopsy specimens

Grade 1A: focal, mild acute rejection
Grade 1B: diffuse, mild acute rejection
Grade 2: focal, moderate acute rejection
Grade 3A: multifocal, moderate rejection
Grade 3B: diffuse, borderline severe acute rejection
Grade 4: severe acute rejection

Rejection

Rejection of the transplanted heart is a major cause of morbidity and mortality in the first year after heart transplantation. Rejection is classified as hyperacute, acute cellular, acute humoral (antibody-mediated), or chronic (allograft vasculopathy) [26].

Hyperacute rejection occurs within minutes to hours of the blood flow being reestablished and is caused by preformed antibodies to ABO blood group antigens, HLA, or endothelial antigens. With ABO matching of recipients to donors, and prospective or increasingly virtual crossmatching of patients who have been previously sensitized to HLA, hyperacute rejection is rare. When it does occur, it is catastrophic because preformed antibodies bind to endothelial antigens on the transplanted heart, resulting in activation of complement. This results in thrombosis of the grafted heart's vessels and complete loss of heart function. In the setting of hyperacute rejection, the transplanted heart has severely decreased function.

Acute cellular rejection may occur at any time after transplantation, but is most common in the first 3–6 months. It is a T-cell-mediated response with infiltration of lymphocytes and macrophages and resultant myocytolysis. The diagnosis is made by endomyocardial biopsy with a standardized grading scheme ranging from mild to moderate to severe acute rejection [26]. Moderate rejection indicated by endomyocardial biopsy is associated with mononuclear cell infiltrates and myocytolysis. A diagnosis of moderate rejection generally prompts antirejection therapy that varies according to histological severity (grade of rejection) and hemodynamic function. Patients with acute cellular rejection may have no signs or symptoms, but often notice mild symptoms of fatigue or shortness of breath. Signs of right ventricular dysfunction are often noted with elevated jugular venous pressure. More severe rejection may be associated with signs of left heart failure and left ventricular dysfunction. Therapy may include intravenous or oral steroids, monoclonal or polyclonal antilymphocyte agents, or an increase or change in oral therapy. The type of therapy generally depends on timing after transplantation, the severity (particularly the severity of hemodynamic compromise), and the protocols of individual centers.

Routine endomyocardial biopsy remains the gold standard for monitoring and grading such rejection. The first consensus statement on grading rejection in transplant endomyocardial biopsy specimens was published in 1990 [27]. It described the various histologic patterns of inflammation in biopsy specimens and is summarized in Table 26.7.

Antibody-mediated rejection (*AMR*) occurs when the recipient forms an antibody against the donor heart. Unlike acute cellular rejection, which is primarily a recipient T-lymphocyte-mediated response mounted against the allograft tissue, AMR refers to allograft injury resulting from activation of the complement system, typically by recipient-generated antibodies against the allograft tissue. Although AMR most commonly occurs months to years following transplantation, a rare subtype, hyperacute rejection, can occur within minutes to hours after transplantation. Risk factors for developing antibody-mediated rejection (AMR) include pregnancy, previous transplantation, blood transfusions, sensitization by OKT3 induction therapy, and use of ventricular assist devices [28, 29].

Diagnosing AMR can be difficult. Criteria for its diagnosis include complement deposition in capillaries, especially of CD4; capillary endothelial swelling; and inflammation involving the capillaries, most typically macrophage infiltrates in the vessel wall and lumen [28].

Treatment of Rejection

Endomyocardial biopsy is performed weekly for the first month after transplant, followed by biopsies at less frequent intervals. The clinical manifestations of cardiac transplant rejection are variable and may or may not correlate with the severity of rejection. During an episode of rejection, the clinical presentation can range from asymptomatic to profound heart failure. Arrhythmias and sudden death have also been reported following heart transplantation. Ischemia may be produced secondary to cardiac allograft vasculopathy (CAV); however, typical angina is usually absent because the donor heart is not innervated by the host.

Patients with endomyocardial biopsy evidence of 3A or worse are treated with prednisone 1000 mg per day for 3 days. If patients are within the first month of transplant or still in the hospital, intravenous methylprednisolone 10 mg/kg/day is given for three doses. Other maintenance immunosuppressive

agents are adjusted for optimal level. Patients with any positive grade of biopsy and hemodynamic compromise are admitted to the hospital and receive either intravenous thymoglobulin, a polyclonal antibody, or T3 monoclonal antibody (OKT3). If hemodynamically compromised patients have negative cellular rejection in endomyocardial biopsy, an immunofluorescence study should be performed; sometimes that may demonstrate humoral-mediated rejection. Plasmapheresis is initiated if humoral rejection is suspected. Occasionally, empiric antirejection therapy may be started for hemodynamically compromised patients without a definitive biopsy result or diagnosis. If the patient is sensitized to the donor (has a positive donor-specific crossmatch) or has clinical signs of early acute rejection, early immunosuppression is used to decrease humoral antibody load and B-lymphocyte proliferation. Plasmapheresis may also be performed to decrease antibody load [30–32].

Clinical Outcomes [5, 33, 34]

The median survival after orthotopic heart transplant is currently 10 years for the entire cohort of adult and pediatric heart recipients, with a median survival of 13 years for those surviving to 1 year. Median survival has steadily improved from 8.3 years during the 1980s to 10.4 years during the 1990s—and survival has further improved since 2000. The mortality risk is highest in the first 6 months after transplant, and the improvement in survival associated in recent years is mainly a result of lower mortality during this early posttransplant period. Following 1 year after transplant, the mortality rate is fairly constant, at about 3–4 % per year, which is higher than the mortality rate of the general population. In the last 20 years, long-term survival of those patients who are alive at 1 year has not significantly improved, and it is likely that the potential for further survival improvement now lies in approaches that could reduce this long-term mortality rate.

Graft failure is the leading cause of death in the first 30 days after transplant (39 % of deaths) and continues to remain prominent throughout the posttransplant period. Within the first 30 days, most cases are primary graft failure; later after transplant, graft failure is more likely due to chronic graft injury from antibody-mediated rejection or cardiac allograft vasculopathy (CAV). Acute rejection is now a fairly uncommon cause of death, being responsible for no more than 11 % of deaths.

Deaths related to CAV become prominent between 1 and 3 years after transplant and are responsible for 10–15 % of deaths thereafter. The rate of death from malignancy also increases in this period and is responsible for about 20 % of the deaths past 3 years after transplant. The risk of infection-related death is highest in the first year after transplant, as it causes 29 % of deaths between 2 and 12 months. After 1 year, the risk decreases, but not below 10 %. Renal failure as the primary cause of death becomes more prominent with time since transplant.

Within the first year of a heart transplant, patients bridged to heart transplantation with mechanical circulatory support devices appear to have a higher risk of death compared with patients without a mechanical circulatory support bridge. Congenital etiology of pretransplant heart disease results in increased risk, and patients with ischemic cardiomyopathy fare somewhat worse than those with nonischemic cardiomyopathy. Comorbidities that are significant risk factors include the need for hemodialysis, mechanical ventilation, prior need for blood transfusion, and recent infection. Recipient and donor age, allograft ischemic time, and serum markers of hepatic and renal dysfunction also affect survival.

Mortality at 5 years is affected to a great degree by factors similar to those affecting 1-year mortality. Additional risk factors include recipient history of pregnancy, female allograft allocation to a male recipient, and recipient history of stroke. The risk factors that affect the 10-year mortality are similar to those that affect the 1- and 5-year mortality. The additional significant predictor of risk at 10 years after transplant is gender—female recipients and male recipients receiving female allografts appear to have a higher risk of death than males receiving male allografts. A PRA level of more than 10 % is also a significant mortality risk factor, although the increased risk is modest.

Only a few factors are associated with 20-year mortality. Younger patient age at transplant favored a 20-year survival. Donor age and allograft ischemic time—consistent predictors of mortality at 1, 5, 10, and 15 years after transplant—are not associated with mortality at 20 years. The possible explanation is that during the 1980s, heart allografts from older donors were not routinely used and longer allograft ischemic times were avoided. Recipients who underwent a transplant for nonischemic cardiomyopathy did better than those with ischemic cardiomyopathy, and patients with congenital heart disease did even better than those who underwent transplant for nonischemic cardiomyopathy.

Future Directions

The last three decades have witnessed steady improvement in the field of heart transplantation, ranging from better management of heart failure patients on the waiting list, to introduction of new immunosuppression drugs, increased use of left ventricular assist devices as bridge support, improved donor organ preservation, and, ultimately, increased patient survival. However, many obstacles remain. Limited donor organ availability has remained constant for decades. The potential solutions for donor organ shortages reside in expanding the pools of alternative donors for alternative recipients who are excluded by conventional criteria and by increasing efforts in xenotransplantation research that, potentially, could solve the donor shortage. A portable organ perfusion device to continuously perfuse donor hearts, expanding the current preservation time limit of 6 h, will increase the number of available donor organs and better match the donors with ideal recipients. Advances in small,

durable, and implantable ventricular assist devices as destination therapy will ease the increasing demand for donor hearts and, ultimately, delay or avoid heart transplant in most end-stage heart failure patients.

Since deaths from infection, malignancy, and renal failure can be partly attributed to overaggressive immunosuppressive therapies, and deaths from rejection, CAV, and late graft failure often result from inadequate immunosuppression, there is a need to assess the individual patient's immune status and risks more accurately and tailor immunosuppressive therapy accordingly. Immune surveillance with noninvasive techniques enables clinicians to detect rejection early and treat it more efficiently. Finally, the continued search for new and improved immunosuppression drugs is needed to reduce the side effects of current immunosuppressive regimens.

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Cardiac Transplantation: Immunobiology and Immunotherapy

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_27

Introduction

In the early twentieth century, Paul Ehrlich, MD, published his thesis regarding the concept of "horror autotoxicus" and established the autoimmune response paradigm [1]. The horror autotoxicus concept focused on the "unwillingness" of an organism to endanger itself—so it forms toxic autoantibodies as a defense. This paradigm emerged from Dr Ehrlich's studies where he immunized animals with the blood of their own species [1]. These and other studies launched the field of immunobiology.

Initial efforts targeted the immune system and allowed for the world's first successful cardiac transplant by Christiaan Barnard, MD, in 1967 [2]. Following the initial successful transplant, a number of centers across the world developed heart transplant programs. While tremendous enthusiasm existed for this novel therapy, survival following heart transplantation was extremely limited, mainly due to acute rejection [3] or complications of immunosuppressive therapy [4]. Due to the limited survival, only several cardiac transplant programs persisted in the US, and they continued to pursue research focused on new immunosuppressive agents. The historical review emphasizes the importance of clinical research; the limited survival of patients with advanced heart failure, which provided a "burning platform" for new innovations; and the collaborative spirit of discovery science, which uncovered new small-molecule immunosuppression agents.

Over the next 20 years, (1967–1987), important advances in tissue typing and immunosuppressive agents reinvigorated the field and attracted more programs and centers to once again offer cardiac transplantation to patients with end-stage heart disease. The renewed interest was a result of advances in immunotherapy with improved graft outcomes and survival rates. In the latest report, the Organ Procurement and Transplantation Network reported a 5-year survival of 75.3 % following cardiac transplantation. The number of heart transplant survivors has continued to increase, and as of June 2013, 27,120 heart transplant recipients were alive with a functioning graft [5]. The number of patients who have received a heart transplant and their survival emphasize the successful approaches of matching donors and recipients and the strategic modulation of the recipient's immune system. This chapter introduces and highlights the key features related to transplant immunobiology and the immunosuppressive agents commonly used following cardiac transplantation.

Overview of the Immune System

An organism is an integrated group of cells with maintained "self"-identity. Purposefully, the immune system exists essentially to detect the entry of "nonself" into the "self" body, to serve as a protective barrier, and to promote elimination. In heart transplantation, the allograft constitutes nonself, and it promotes an immunological response once transplanted. This is first achieved by a rapid, nonspecific innate immune response that is followed by a more targeted adaptive immune response (Fig. 27.1).

The innate immune system includes more immediate and less specific responses not dependent on antigen recognition. It relies on the process of inflammation, humoral amplification, and phagocytosis to accomplish a rapid destructive reaction without a latent period required for lymphocytic activation and antibody production. When the circulation is restored in the transplanted heart, the innate immune system generates an inflammatory reaction induced by reperfusion of the transplanted heart. If left untreated, it will lead to allograft hyperacute rejection. The adaptive immune system, on the other hand, depends on responses mediated by T and B lymphocytes, requiring an interval following the first exposure of "nonself" before its destructive effects are manifested (Fig. 27.2). Lymphocytes express antigen receptors that can recognize "nonself" antigens, culminating in cellular activation and antibody production.

Within minutes following reperfusion, the blood carries the donor materials to the spleen and lymph nodes. The antigen-presenting cells (APCs) within the spleen are capable of trapping large amounts of antigens and processes them for presentation to the T lymphocytes (Fig. 27.3). The T lymphocytes migrate from the bone marrow (Fig. 27.4) and peripheral circulation to the lymph nodes and spleen, enter the para-cortical areas, bind the major histocompatibility

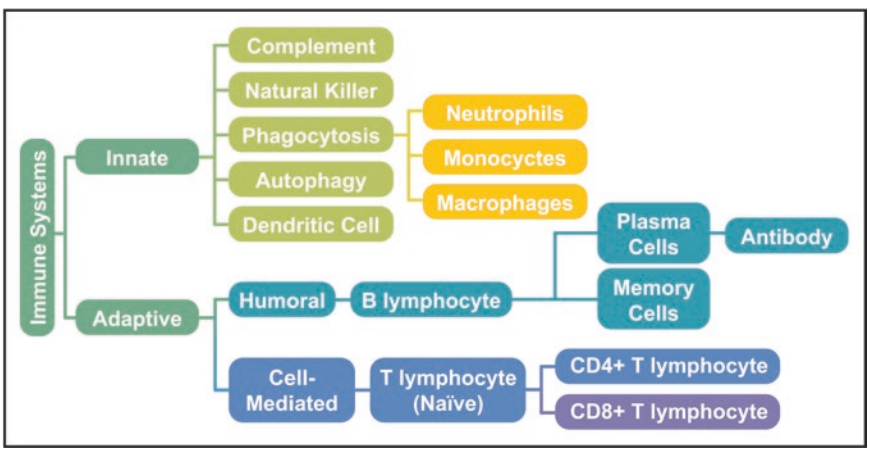

Fig. 27.1 Overview of the human immune system. Schematic highlighting the innate and adaptive immune system. Both arms play a major role in allograft survival and rejection. The innate immunity is the first-line nonspecific defense against nonself antigens. Its activation results in hyperacute rejection and can be generally avoided with ABO histocompatibility matching. The adaptive immunity is the dedicated and specific defense against nonself antigens. Activation of the adaptive immunity arm results in cellular and antibody-mediated rejection and is generally prevented or treated with chronic immunosuppression

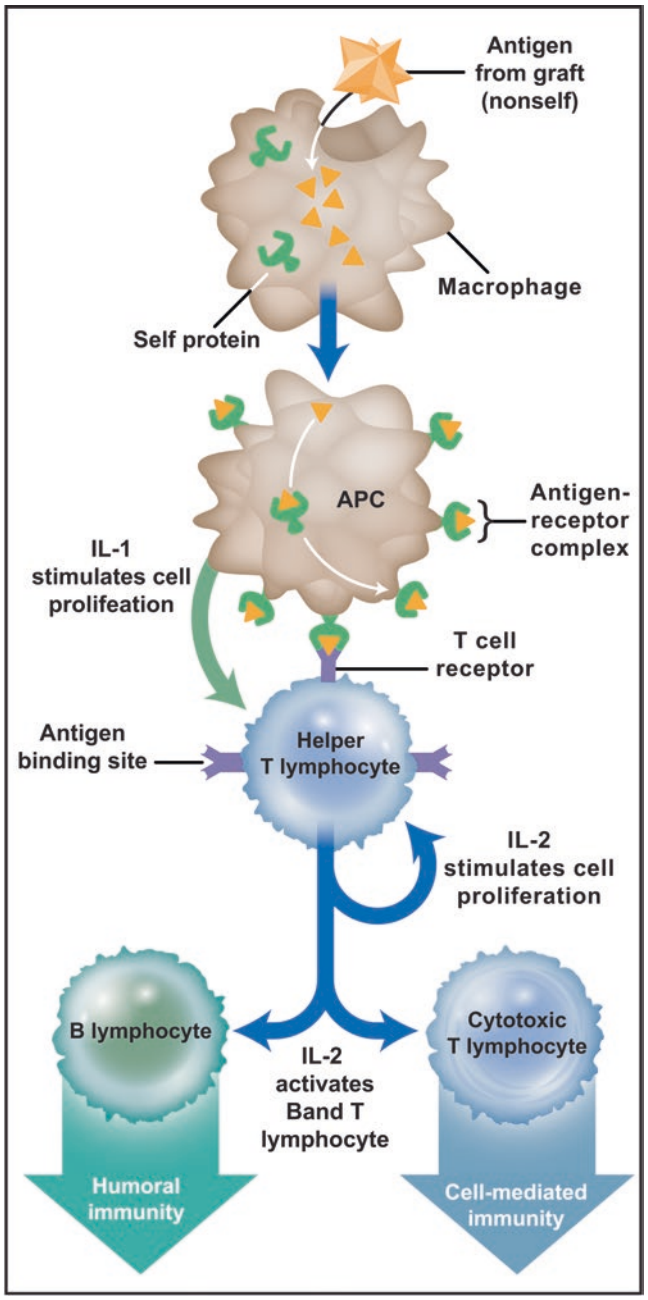

Fig. 27.2 Humoral and cell-mediated immune responses to an antigen. An antigen is phagocytosed by a macrophage. The macrophage recognizes the antigen as "nonself" and forms a self–nonself complex that is mobilized to the cell surface of the antigen-presenting cell (APC). The APC presents the complex to the T-helper lymphocyte via a receptor-mediated process. Chemokines stimulate cellular proliferation of the T-helper lymphocytes and activation of B lymphocytes and T lymphocytes

complex (MHC)-presenting antigens, and ignite the adaptive immune response and cellular-mediated rejection (CMR). In the process, T lymphocytes will interact with B lymphocytes. This interaction induces B-lymphocyte activation and differentiation into plasma cells that function in antibody production (Fig. 27.5). This B-lymphocyte–T-lymphocyte interaction is the basis for antibody-mediated rejection (AMR) (Figs. 27.1, 27.2, and 27.5).

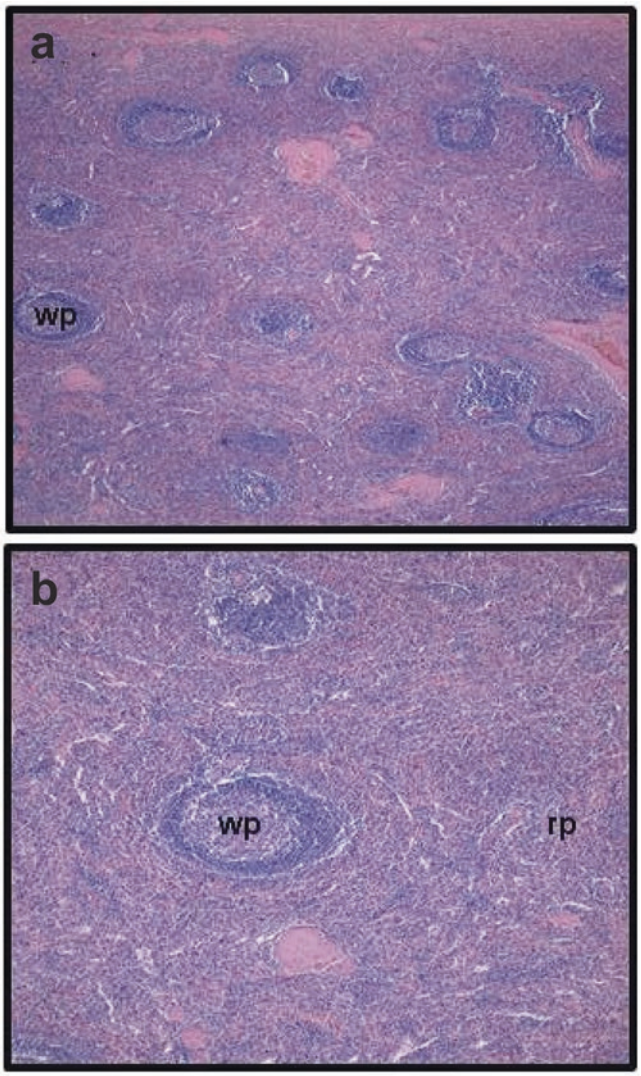

Fig. 27.3 Histology of the human spleen. Histological sections of the spleen at low magnification (**a**) and at higher magnification (**b**). The spleen is a major lymphoid organ that is divided into the red pulp (rp), representing the storage of blood and the white pulp (wp), which are the lymphocytes, macrophages, plasma cells, etc. Note that the white pulp has a nodule (primarily containing B lymphocytes) that consists of a central germinal center and a peripheral mantle zone and an adjacent periarterial lymphatic sheath, which is the primary site for T lymphocytes

Innate Immunity

Following the initial encounter with nonself, the nonspecific innate immunity is triggered (Fig. 27.2). It primarily consists of macrophages, natural killer (NK) cells, granulocytes, and the complement cascade [6]. Morphologically, NK cells strongly resemble B or T lymphocytes; however, they are not antigen-specific and do not express T-cell receptors or immunoglobulins. NK cells function by lysing target cells or antigens regardless of the presence or absence of any major MHC complexes. Thus, they are directly involved with the initial nonspecific inflammatory response against the donor allograft.

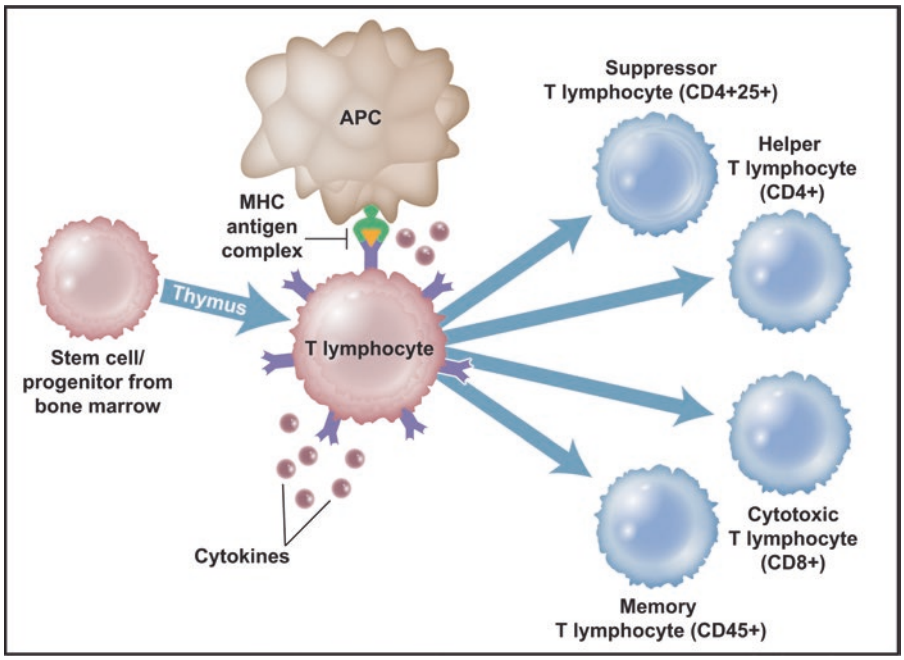

Fig. 27.4 Differentiation of the T lymphocytes. Schematic highlighting the maturation, activation, and the clonal expansion of the T lymphocytes. Hematopoietic stem cells and progenitors emerge from the bone marrow and populate the thymus. Subsequent maturity of the thymocytes ultimately produces cytotoxic, memory, suppressor, and T-helper lymphocytes

Cytokines, on the other hand, are secreted proteins that alter the immunologic response of nearby cells in an autocrine and paracrine fashion during both innate and humoral responses. The major cytokines in heart transplantation include interleukin-2 (IL-2), interleukin-6 (IL-6), interferon-γ, and tumor necrosis factor (TNF). IL-2 is a key growth factor that is required for the expansion of T lymphocytes during a T-lymphocyte-mediated response (Fig. 27.2). Stimulated cells begin to produce IL-2 and respond to IL-2 via an IL-2 receptor in an autocrine manner. IL-6 primarily induces B lymphocytes to differentiate into plasma cells. TNF is pro-inflammatory and cytotoxic and is primarily secreted by granulocytes. Interferon-γ mainly affects the differentiation of T lymphocytes into T-helper CD4 T cells. It also stimulates NK cells and CD8 T lymphocytes.

A critical step in the immune response pathway is the aggregation and transport of leukocytes into areas targeted for immunologic attack. The adhesion molecules play a key role in maintaining the structural integrity and promoting adhesion of leukocytes to surrounding structures. They include integrins, selectins, and immunoglobulin superfamily adhesion molecules. Adhesion molecules mediate the initial interaction of T lymphocytes with antigens, their migration, and retention within the transplanted organ. Likewise, the activation and migration of T lymphocytes in the lymph nodes and spleen are also dependent on adhesion molecules.

Generally, integrins act as cellular adhesive agents as they anchor cells to the extracellular matrix. Cell-to-cell adhesion is the role of selectins and immunoglobulin superfamily molecules. Although initial graft reperfusion following implantation causes host leukocytes to enter the graft, it also allows leukocytes and other cells in the donor organ to be "flushed" into the host. These cells travel through the blood to the peripheral lymphoid organs, including the thymus (Fig. 27.6), nodes, and spleen (Fig. 27.3), which are primary sites of the initiation of specific T-lymphocyte-mediated response (Fig. 27.4).

Another important arm of innate immunity is the complement system [7, 8]. As outlined in Fig. 27.7, the complement cascade can be activated through three different pathways: classical, lectin, and alternative. All three pathways of complement activation converge in the activation of complement component 3 (C3).

Activation of complement via the classical pathway is initiated by the first component of human complement (C1), which can bind to antibodies. When the classical pathway of complement is activated through an antibody-mediated process, the globular heads of a single C1 interact simultaneously with two or more Fc regions of IgM or IgG (Fig. 27.8). Once C1 binds, its protease function is activated, and it cleaves the fourth component of complement (C4), yielding two fragments—C4a and C4b. C4 can also be activated by a mannose-binding lectin (MBL). After binding, the lectin can cleave C4 through two associated serine proteases (MASP-1, 2, and 3). C4b continues the complement cascade by binding to C2, which is then cleaved by C1 or MASP to generate C2b that diffuses away and by the remaining C2a that is associated with C4b. C4b and C2a together form the classical pathway C3 convertase (Fig. 27.7). This complex is a protease that can cleave the central component of the complement system, C3.

C3 also can be directly activated by the alternative pathway of complement. Like C4, C3 contains an internal thioester group. In the alternative pathway, small numbers of C3 molecules sporadically undergo a spontaneous conformational change, and several of these C3 molecules covalently bind to nearby proteins. The microenvironment in which C3 binds determines whether this pathway continues through activation of factor B or whether factor H inactivates C3b.

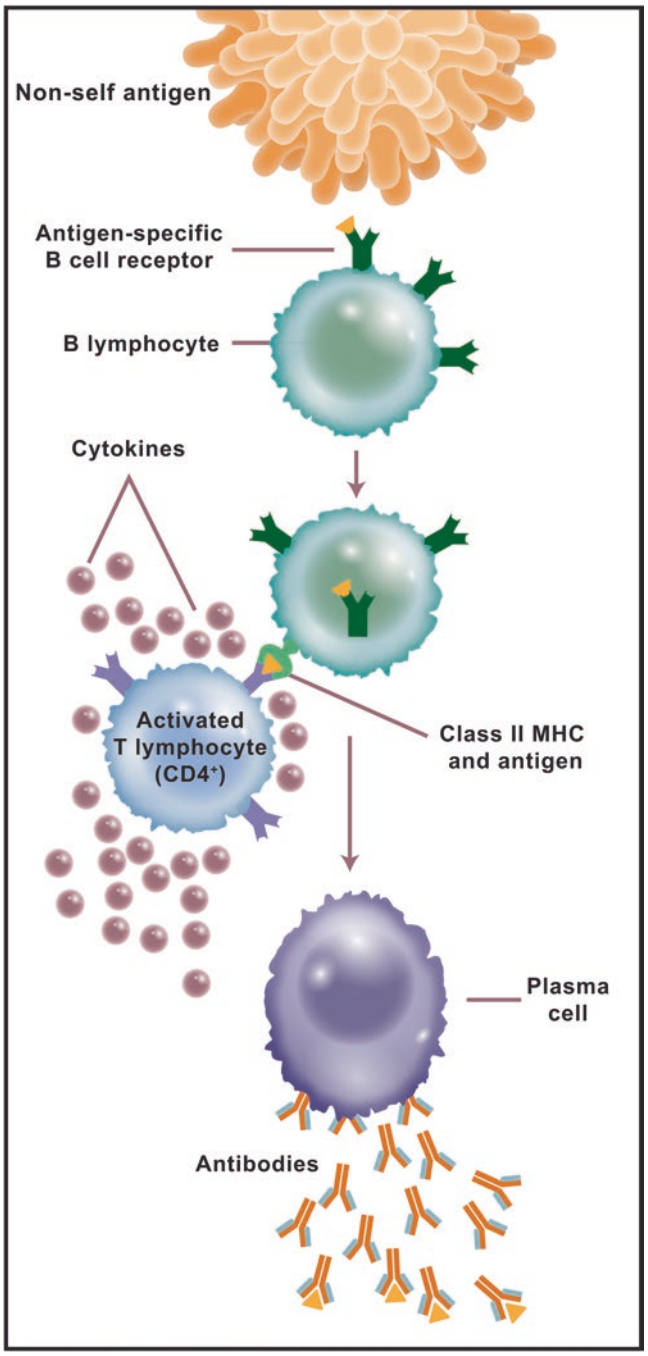

Fig. 27.5 B-lymphocyte-mediated production of antibodies. Nonself antigens are recognized by B lymphocytes and subsequently activate T-helper lymphocytes (via class II MHC-binding mechanism) or generate plasma cells that produce and release specific antibodies

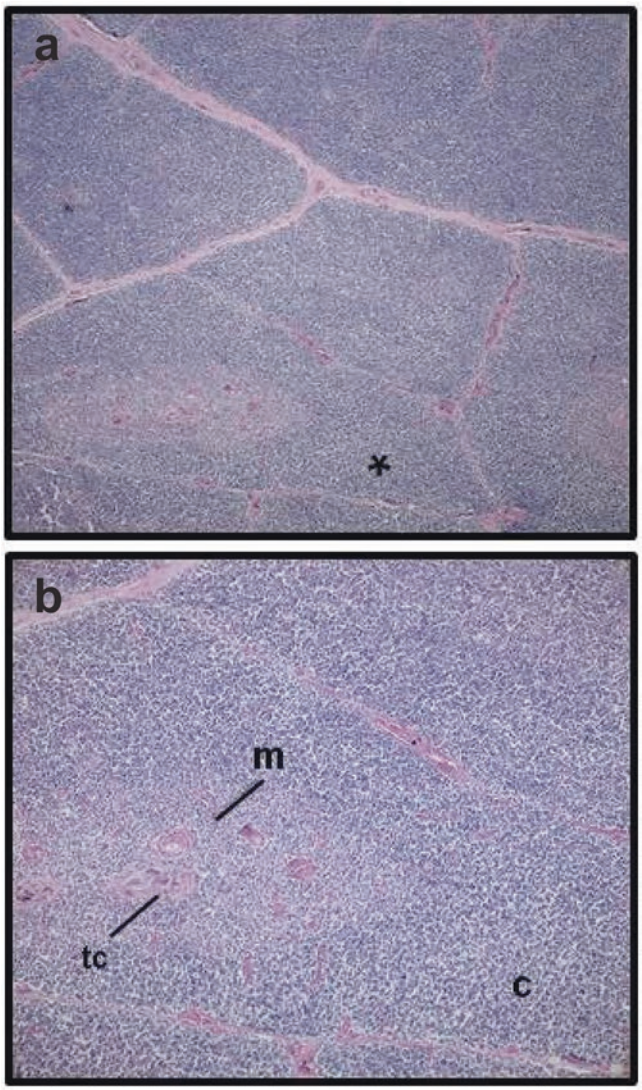

Fig. 27.6 Histology of the neonatal human thymus. The histological structure of the neonatal thymus is shown at low magnification (**a**) and higher magnification (**b**). The thymus is dived into lobes and lobules (*) by septa. Each lobule is divided into the cortex (c), which is rich in T lymphocytes, and a central medulla (m), which contains epithelial cells and thymic corpuscles (tc). The thymus is fully developed prenatally and begins to atrophy following puberty

When factor B is bound to C3, it is a substrate for the serum protease factor D. Cleavage of factor B results in a soluble fragment Ba and a larger fragment Bb that remains complexed with C3. Properdin stabilizes the activity of the C3Bb complex, and this complex is the alternative pathway C3 convertase.

The classical and alternative pathways converge at C3. Either convertase can cleave C3 into two fragments, C3a and C3b. The smaller C3a fragment can bind to C3a receptors (C3aR) on nearby tissue mast cells, basophils, or eosinophils. The larger fragment, C3b, is deposited together with components of either the classical or alternative C3 convertase pathway forming a complex, the C5 convertase, which is capable of cleaving C5. The small fragment, C5a, is quantitatively much more potent as a chemotactic agent than C3a and affects a wider range of cells, including neutrophils, monocytes, basophils, and eosinophils. The larger fragment, C5b, initiates assembly of the terminal components of complement (C5b-C9) into a pore-forming structure, the membrane-attack complex (MAC). The MAC forms a hole in the membrane of the foreign allograft cells that disrupts membrane integrity and causes cell lysis. Hyperacute rejection is one of

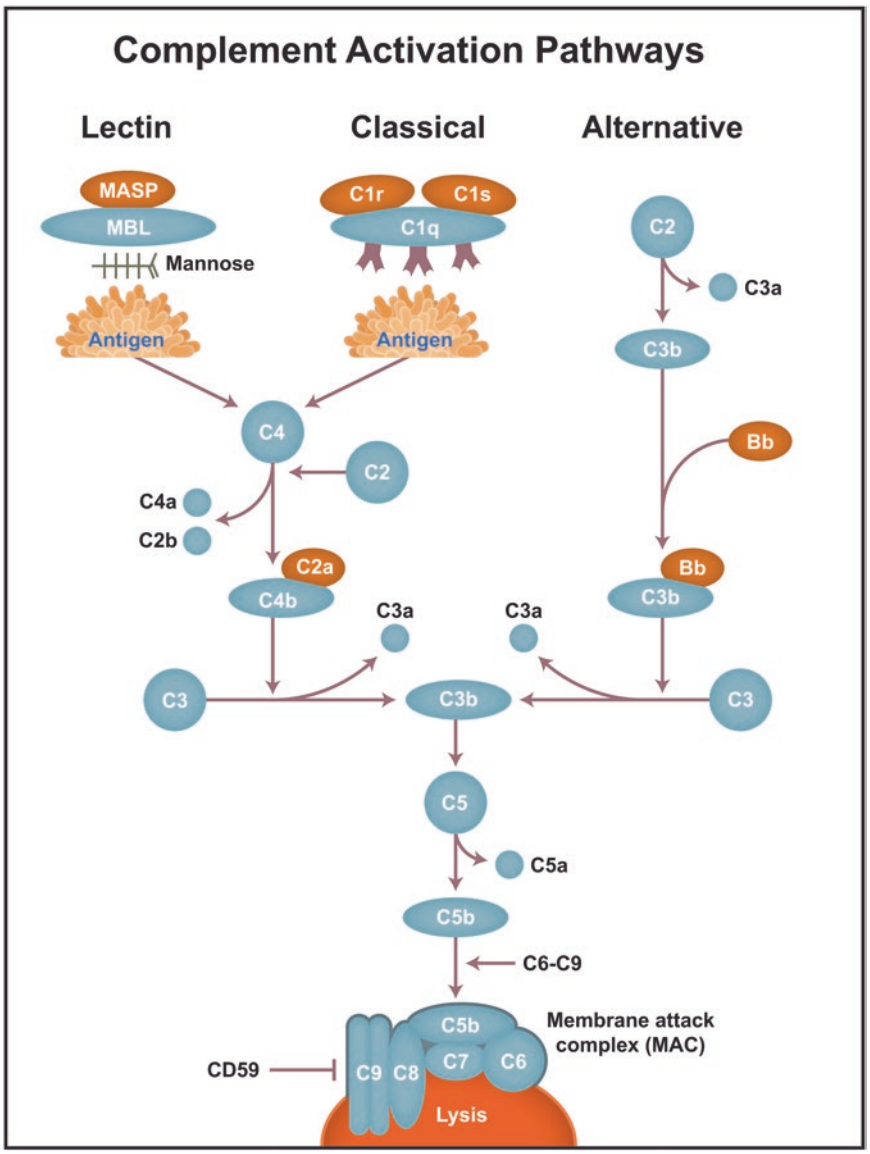

Fig. 27.7 Overview of the human complement system. Schematic highlighting the lectin, classical, and alternative complement activation pathways. The membrane-attack complex (MAC) is responsible for cellular lysis in the nonspecific innate immune response and hyperacute rejection

the manifestations of the speed and potency of complement activation by preformed antibodies directed against the transplanted allograft [9].

Adaptive Immunity

The specific adaptive response is primarily mediated by T lymphocytes, B lymphocytes, and APCs [10]. The cell surface proteins primarily responsible for the immune response in heart transplantation are called MHC or human leukocyte antigens (HLA). T lymphocytes only recognize antigenic peptides that are contained within the MHC-binding domain on the surface of APCs. The MHCs are highly polymorphic, which establishes the basis for graft rejection. The function of MHC molecules is closely related to their three-dimensional structure, which is composed of two α-helices on top of a β-pleated sheet.

The proteins of the MHC complex are subdivided into class I, class II, and class III. Class I and class II directly relate to transplantation but differ in the composition of the polypeptide chains that constitute them and in their distribution on different cells and tissues.

Class I molecules are expressed on all nucleated cells, with subtypes A, B, and C. The *HLA-A* gene includes more than 50 alleles, the *HLA-B* gene includes more than 75 alleles, and the *HLA-C* gene includes more than 30 alleles. These genes are composed of two chains—a larger, highly polymorphic, heavy α-chain encoded on chromosome 6 and a smaller, non-polymorphic β-chain termed β-2 microglobulin encoded on chromosome 15. Antigens originating from inside the cell are processed via the endogenous pathways; they are complexed with MHC class I molecules and presented to T lymphocytes (Fig. 27.2).

Class II molecules are expressed on a limited subset of cells, such as macrophages, dendritic cells, and B lympho-

cytes. The MHC complex classes that are relevant to transplantation are HLA-DR, HLA-DP, and HLA-DQ. These molecules are composed of an α-chain and a β-chain. Unlike class I molecules, which interact primarily with CD8 T lymphocytes, class II molecules interact primarily with CD4 T lymphocytes. Antigens originating from outside the cells are processed via the exogenous pathway and presented with the MHC class II molecules, which is the principal mechanism for processing and presenting the alloantigens following heart transplantation [11]. Figure 27.9 demonstrates the three-dimensional structure of the class I and class II molecules.

T lymphocytes represent the cornerstone of the immune system that mediates the rejection response to the alloantigens that are expressed in the transplanted heart. The CD4 helper T lymphocytes function primarily to detect foreign antigens. Once activated, the CD4 helper T lymphocytes facilitate other cell types, such as CD8 cytolytic T lymphocytes, B lymphocytes, and neutrophils, to participate in the immune response (Fig. 27.1). The CD8 cytolytic T lymphocytes function primarily as effector cells, which kill targeted cells expressing foreign antigens. During their development, the precursor T lymphocytes originate from the bone marrow (Fig. 27.10) and then migrate to the thymus (Fig. 27.6) where they first appear in the subcapsular cortex. Subsequently, they begin to express CD3, CD4, and CD8 molecules resulting in distinct T lymphocytes, and they acquire specific T-cell receptors needed to detect presented foreign antigens. During the selection process, the cells migrate from the thymic cortex to the medulla and then to the periphery (Fig. 27.6).

In the context of the immunologic response, the T-cell antigen receptor on the surface of T lymphocytes must first bind to the antigen presented by the MHC molecule. This binding then transmits a signal to the interior of the cell along the designated transduction pathways. This recognition process is very specific, despite the presence of many diverse antigens. This process recognizes antigens only in the presence of self-MHC molecules.

In the case of CD4 T lymphocytes, which initiate the cellular response to transplant antigens, the antigen must first be associated with an MHC complex on the cell surface through a process called antigen presentation. This presentation is performed by APCs (Fig. 27.4). The antigen first must be internalized within the APC, where it is broken down into small polypeptides. The peptides are then physically associated with MHC molecules and exported to the cell surface as a complex. Cells that serve as APCs are dendritic cells, macrophages, and B lymphocytes. Dendritic cells are the most efficient in presentation and can be found scattered throughout the lymphoid and nonlymphoid tissues. After the recognition phase, the CD4 T lymphocytes progress through a series of activations that culminate in the induction of the rejection response. Specifically in cellular rejection, CD8 cytolytic T lymphocytes are jointly activated and programmed for nonself-destruction through exocytosis-mediated cytolysis and ligand-mediated triggering of apoptosis. Figure 27.11 shows the various transduction pathways involved (calcineurin and mTOR) that provide the basis for the immunosuppression agents being used.

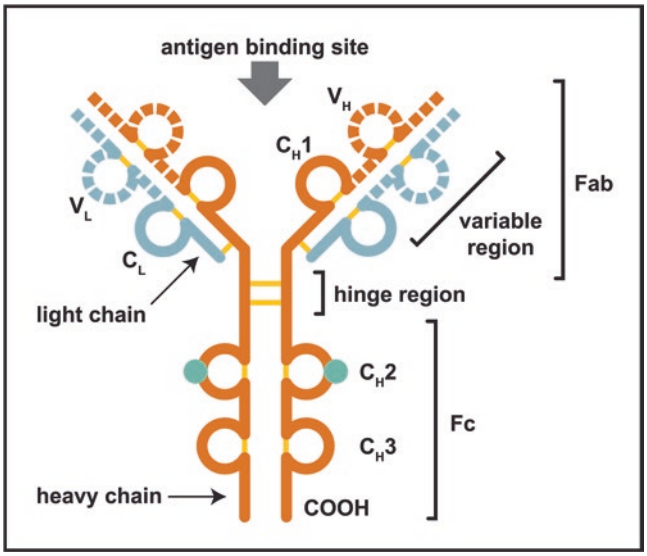

Fig. 27.8 Schematic of the human antibody. Antibodies include the Fab arms that recognize antigens (light chain) and the Fc (heavy chain) components

Similar to the T lymphocytes, the B lymphocytes originate or are produced in the bone marrow (Fig. 27.10). However, they act via immunoglobulins, and the end products of differentiation for the B lymphocytes are plasma cells and memory B cells. B lymphocytes depend on surface immunoglobulins for the binding of antigens. Plasma cells produce immunoglobulins (antibodies) (Fig. 27.5), that consist of four polypeptide chains in two pairs (Fig. 27.8). Each pair of chains is identical to the other, consisting of a heavy chain and a shorter light chain. Figure 27.8 depicts the basic configuration of an antibody molecule.

In order for the immune system to contend with the vastly differing antigens, the antigen-binding portion of the antibody must be extremely heterogeneous (Fig. 27.8). The heavy-chain regions form the basis of the classification of immunoglobulins into isotypes: IgG, IgA, IgM, IgD, IgE, and IgG [12]. The initial production of IgM and, later, IgG are the main isotypes involved in transplant rejection. The term humoral (or antibody-mediated) rejection refers to the production of antibodies against the nonself allograft cells, primarily mediated by the activation of B lymphocytes. The main effector mechanisms described in the humoral responses are neutralization, opsonization, and complement activation.

The discovery and characterization of such immune responses and their biological targets, as well as emerging classes of immunosuppressive therapies, have contributed to enhanced preservation of the transplanted allografts. Alteration of these biological mechanisms using agents such as steroids, antimetabolites, calcineurin inhibitors, mTOR pathway inhibitors and others have revolutionized the field of transplantation.

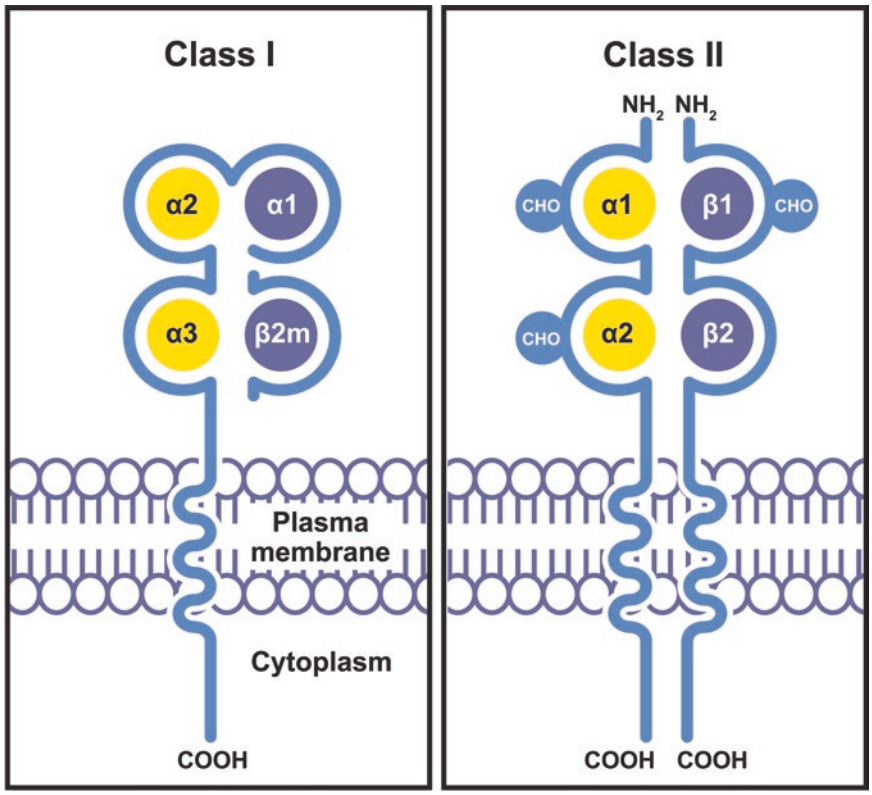

Fig. 27.9 Structure of MHC I and MHC II proteins

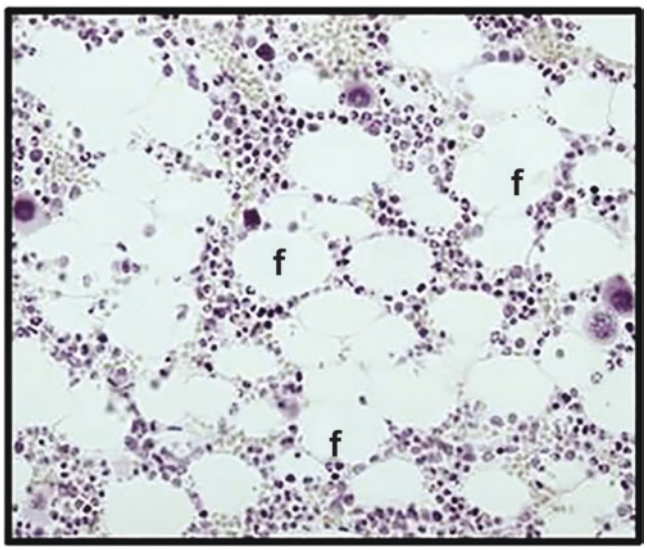

Fig. 27.10 Histology of the human bone marrow. Low magnification demonstrating the fatty component (f) and erythroid and myeloid components

The History of Immunosuppressive Agents

Successful human transplants have a relatively long history that preceded the use of immunosuppression agents for postoperative survival and graft preservation. After decades of failed solid organ transplantation, in 1951, Medawar from the British National Institute for Medical Research suggested that immunosuppressive agents could be used to mitigate the effects of rejection [13]. Corticosteroids had been traditionally used, and the more effective azathioprine (AZA) was identified in 1959, but it was not until the discovery of cyclosporine A (CsA) in 1970 that transplant surgery found a sufficiently powerful immunosuppressive (Fig. 27.11).

In 1968, surgical pioneer Denton Cooley, MD, performed more than 15 transplants. Fourteen of these recipients did not survive more than 6 months [14, 15]. By 1984, two-thirds of all heart transplant recipients survived for 5 years or more. In 1981, the first successful heart–lung transplant took place at the Stanford University Hospital. The lead surgeon, Bruce Reitz, MD, credited the patient's recovery to CsA [16]. Since then, many other drugs have been developed, such as the various calcineurin inhibitors, mammalian target of rapamycin (mTOR) inhibitors, and mycophenolate mofetil (Figs. 27.11 and 27.12).

Prospectively, the emerging field of regenerative medicine promises to solve the problem of organ transplant rejection by regrowing organs in vitro using allogeneic stem cells. Until then, the reliance on current pharmaceutical agents and the development of new agents remain vital for the continuation of transplant medicine.

Immunosuppressive Agents

Calcineurin Inhibitors: Cyclosporin A (CsA)

CsA is an immunosuppression drug widely used in organ transplantation for rejection prophylaxis. It interferes with the activity or expansion of T lymphocytes (Figs. 27.11 and 27.12). CsA was initially isolated from the fungus

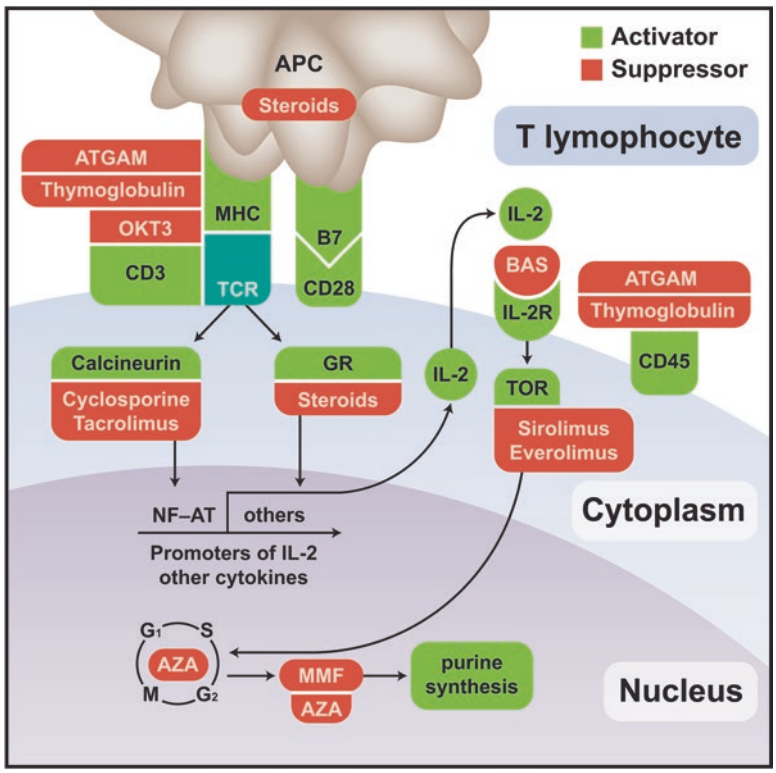

Fig. 27.11 Overview of the functional impact of immunosuppression agents on the T lymphocytes. Note the impact of corticosteroids on the APCs: calcineurin inhibitors decrease the production of IL-2, MMF decreases purine synthesis, and sirolimus inhibits the mTOR pathway (*ATGAM* antithymocyte globulin, *OKT3* antihuman CD3 antibody, *MHC* major histocompatibility complex, *TCR* T-cell receptor, *IL-2* interleukin-2, *IL-2R* IL-2 receptor, *NFAT* nuclear factor of activated T cells, *AP-1* activator protein-1, *TOR/mTOR* mammalian target of rapamycin, *AZA* azathioprine, *MMF* mycophenolate mofetil)

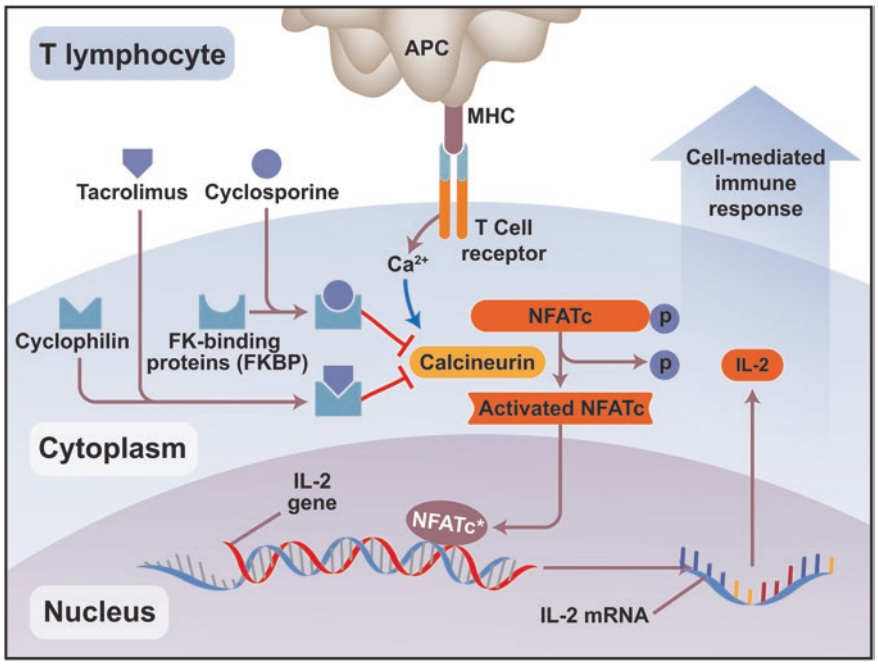

Fig. 27.12 Calcineurin inhibition by cyclosporine and tacrolimus. Cyclosporine and tacrolimus inhibit the phosphatase activity of calcineurin. This inhibition prevents the activation of NFATs and their translocation to the nucleus to activate IL-2 and other cytokines in the T lymphocytes (*MHC* major histocompatibility complex, *FKBP* FK-binding protein, *IL-2* interleukin-2, *NFAT* nuclear factor of activated T cells)

Tolypocladium inflatum in 1969 [17]. It is a cyclic nonribosomal peptide of 11 amino acids and contains a single D-amino acid that is rarely encountered in nature.

The success of CsA in preventing organ rejection was initially demonstrated in kidney transplant recipients by Calne at the University of Cambridge [18] and in liver transplants by Starzl at the University of Pittsburgh [19]. It was then approved by the Food and Drug Administration (FDA) to prevent rejection of kidney, heart, and liver transplants. Mechanistically, CsA binds to the cytosolic protein cyclophilin (immunophilin) of T lymphocytes. This complex of cyclosporin–cyclophilin inhibits calcineurin which, under normal circumstances, is responsible for activating the transcription of IL-2 via dephosphorylation of nuclear factor of activated T cells (NFAT) transcription factors (Fig. 27.12).

In T lymphocytes, the activation of the T-cell receptor normally increases intracellular calcium, which acts via

calmodulin to activate calcineurin. Calcineurin then dephosphorylates the transcription factor, nuclear factor of activated T lymphocytes (NFATc), which translocates to the nucleus and increases the activity of genes encoding IL-2 and related cytokines (Fig. 27.12). It also inhibits lymphokine production and interleukin release and, therefore, leads to a reduced function of effector T lymphocytes [20, 21].

CsA was first used in human cardiac transplantation in 1980 and then became the standard immunosuppressant in heart transplant recipients. No randomized prospective trials comparing the efficacy of CsA with conventional immunosuppressive regimens have been reported, and the rationale for its use emerged from preclinical animal models and kidney transplantation trials. However, the results of retrospective comparisons showed a marked improvement in outcome when patients were treated with CsA. For example, the 1- and 2-year survival rates were approximately 80 % and 70 %, respectively, in a single-center Stanford experience. These results represented a significant improvement in survival compared with the 60 % and 55 % 1-year and 2-year survival, respectively, formerly noted with AZA. Results reported by the University of Pittsburgh and the United Kingdom Trial were comparable, with 79 % and 76 % overall survival noted, respectively [22].

More recently, CsA has been used less frequently due to its extensive side effect profile and the presence of more effective immunosuppressive agents, such as tacrolimus and sirolimus (Figs. 27.11 and 27.12). Nephrotoxicity represents the most frequent and clinically important complication associated with CsA use and may ultimately define the limits of clinical utility of the drug for long-term immunosuppression. CsA is primarily metabolized by the liver and excreted via the biliary system (Table 27.1). It has a half-life of 8.4 h (Table 27.1) [22].

Tacrolimus (Tac)

Tac (FK 506) is a lipophilic 23-member macrolide lactone discovered in 1984 from the fermentation of the bacterium *Streptomyces tsukubaensis*. It was first approved by the Food and Drug Administration in 1994 for use in liver transplantation, and, since then, its use has been extended to kidney, heart, small bowel, pancreas, lung, skin, cornea, bone marrow, and limb transplants. Tac is a calcineurin inhibitor (via binding to FK 506-binding protein) with a similar mechanism of action as CsA, thus inhibiting both T-lymphocyte signal transduction and IL-2 transcription (Fig. 27.12) [23]. It has been prospectively compared with CsA in three randomized trials, with no difference in 1-year survival or in the incidence of significant rejection [24–26].

Although the short-term impact of Tac and CsA are comparable regarding patient and graft survival, Tac has a more favorable lipid profile, increased potency, and is associated with a significantly lower rate of acute rejection compared with CsA-based immunosuppression [27]. This characteristic is unique, for it is well known that CsA will not reverse

Table 27.1 Current immunosuppressive agents used for cardiac transplantation

Drug	Therapeutic level	Major side effects
Steroids/ prednisone	None—follow clinical response	Hypertension
		Diabetes
		Obesity
		Hyperlipidemia
		Osteoporosis
		Avascular necrosis
		Poor wound healing
		Cushingoid features
AZA	None—follow clinical response	Anemia
		Thrombocytopenia
		Neutropenia
		GI toxicity
		Hepatic toxicity
MMF	Controversial, trough levels of 2.5–5.0 g/mL	GI distress
		Anemia
		Thrombocytopenia
		Neutropenia
CsA	Trough levels 300–350 ng/mL early, decreasing to ~200 ng/mL 1 year posttransplant	Hypertension
		Hyperlipidemia
		Renal insufficiency
		Tremor
		Hirsutism
		Gingival hyperplasia
		GI distress
		Hypomagnesemia
		Hyperuricemia
		Anemia
Tac	Trough levels 10–15 ng/mL early, decreasing to 5–10 ng/mL posttransplant	Hypertension
		Diabetes
		Hyperlipidemia
		Renal insufficiency
		Osteoporosis
		GI distress
		Hepatic toxicity
		Hypomagnesemia
		Hyperuricemia
		Thrombocytopenia

(continued)

Table 27.1 (continued)

Drug	Therapeutic level	Major side effects
Sirolimus	Trough levels 5–15 ng/mL	Hyperlipidemia
		Poor wound healing
		GI distress
		Tremor
		Hyperuricemia
		Anemia
		Thrombocytopenia
		Neutropenia

established ongoing immune responses. Tac is normally prescribed (Table 27.1) as part of a triple posttransplant regimen including steroids and mycophenolate mofetil (MMF). It is extensively metabolized in the liver by the CYP450 enzyme complex and is mainly excreted in feces (92 %) and urine (2 %) (Table 27.1). Tac has a half-life of 4–40 h depending on the hepatic function (Table 27.1).

One of the first major clinical trials that examined the efficacy of Tac in heart transplant recipients was performed at the University of Pittsburgh in 1992. At that time, it was used as the primary immunotherapy in conjunction with low-dose steroids and AZA. Overall 1-year patient survival was 92 %, with a low incidence of cardiac rejection episodes (grade III) within 90 days of transplantation (0.95/patient). Achieving this level of immunosuppression was comparable to that of CsA-based triple-drug therapy. Renal dysfunction occurred during the perioperative period in most patients in this trial. However, the incidence of hypertension was 54 % compared with 70 % during the CsA era. Ten adults underwent successful rescue therapy with Tac after cardiac rejection refractory to conventional immunotherapy [28]. Tac is now considered the standard of care for initiation and maintenance of immunosuppression for the cardiac transplant recipient.

Azathioprine (AZA)

AZA is a purine analogue synthesized originally as a cancer drug and a prodrug for mercaptopurine (6-MP) in 1957. Since then, it has been widely used as an immunosuppressive agent [29]. Following the studies performed by Medawar and Elion who discovered the immunological basis of rejection of transplanted tissues, Calne, the British pioneer in transplantation, introduced 6-MP as an experimental immunosuppressive agent for kidney and heart transplantation [30]. For many years, dual therapy with AZA and steroids was the standard immunosuppressive regimen, until CsA was introduced into clinical practice in 1978.

AZA functions as a prodrug for 6-MP, inhibiting an enzyme required for the synthesis of DNA. Its active metabolite, methyl-thioinosine monophosphate (meTIMP), is a purine synthesis inhibitor that blocks the enzyme amidophosphoribosyl transferase. Thioguanosine triphosphate (TGTP) is incorporated into RNA, compromising its functionality. It also interacts with the GTP-binding protein Rac1, blocking the induction of the protein Bcl-xL and thus promoting apoptosis of activated T lymphocytes. The closely related thio-deoxyguanosine triphosphate (TdGTP) is incorporated into DNA.

Thioinosinic acid impedes the later steps of DNA synthesis via adenylosuccinate synthase and IMP dehydrogenase. Moreover, it blocks the downstream effects of CD28 costimulation, a process required for T-lymphocyte activation [31]. AZA is absorbed from the gastrointestinal tract with 88 % bioavailability, which varies greatly between individual patients (30–90 %), as it is incompletely inactivated in the liver (Table 27.1). AZA is metabolized extensively in the liver and erythrocytes, with an average plasma half-life of 25–80 min for AZA and 3–5 h for the drug metabolites (Table 27.1). Since the first heart transplant, the combination of steroids and AZA was the standard immunosuppressive regimen until the introduction of CsA (Fig. 27.11). This combination lost popularity due to its increased side effect profile and the introduction of more efficacious medications.

Mycophenolate Mofetil (MMF)

Mycophenolate is derived from the fungus *Penicillium stoloniferum* [32]. Mycophenolate mofetil (MMF) is metabolized in the liver to the active entity, mycophenolic acid. It reversibly inhibits inosine monophosphate dehydrogenase, the enzyme that regulates the synthesis of guanine monophosphate in the de novo pathway of purine synthesis used in the proliferation of B and T lymphocytes [33]. It is typically used as part of a three-drug immunosuppressive regimen in cardiac transplantation that also includes a calcineurin inhibitor (CsA or Tac) and prednisone. More recently, the salt mycophenolate sodium (Myfortic) has also been introduced. This salt is primarily metabolized in the liver and converted to the active metabolite mycophenolic acid. MMF, with a half-life of 18 h, is primarily excreted in the urine (Table 27.1).

Since its introduction in clinical practice, multiple prospective clinical trials have provided the basis for MMF use in heart transplant recipients. Initial human clinical trials in heart transplant recipients suggested that MMF was as effective as AZA [34]. A subsequent large, prospective, multicenter, randomized trial compared AZA and MMF in combination with CsA/steroids. In an intention-to-treat analysis, there was no difference in survival or rejection, but in an analysis of treated patients, there was a reduction in mortality at 1 year (6.2 % versus 11.4 %; $P = 0.031$) and a reduction in rejection requiring treatment (65.7 % versus

73.7 %; $P = 0.026$) in the MMF patients [35]. Data from the International Society of Heart and Lung Transplantation Registry have been analyzed for the differences in the effects of MMF and AZA in patients on a CSA-based regimen. Patients treated with MMF had an actuarial survival benefit (1 year, 96 % versus 93 %; 3 year, 91 % versus 86 %; $P = 0.0012$) [36]. MMF is effective in reversing recurrent rejection when used in place of AZA [37].

mTOR Inhibitors

Sirolimus

Sirolimus (Rapamycin) is a natural product of the actinomycete *Streptomyces hygroscopicus* discovered in Easter Island [38]. The US FDA approved it for clinical use in 1999 as an antifungal agent. However, this use was abandoned when it was discovered to have potent immunosuppressive and antiproliferative properties (Fig. 27.13). Unlike the similarly named tacrolimus, sirolimus is not a calcineurin inhibitor, but it has a similar suppressive effect on the immune system (Figs. 27.11 and 27.13). Sirolimus inhibits IL-2 and other cytokine receptor-dependent signal transduction mechanisms via action on mTOR, thereby blocking the activation of T and B lymphocytes. It binds the cytosolic protein FK-binding protein 12 (FKBP12) in a manner similar to Tac. Unlike the Tac-FKBP12 complex, which inhibits calcineurin, the sirolimus-FKBP12 complex inhibits the mTOR pathway by directly binding to mTOR Complex 1 (mTORC1) (Fig. 27.13) [39]. Clinically, sirolimus can also be used alone or in conjunction with calcineurin inhibitors, such as Tac and/or MMF, to provide steroid-free immunosuppression regimens.

Impaired wound healing and thrombocytopenia are the main side effects of sirolimus; therefore, some transplant centers prefer not to use it immediately after the transplant operation but, instead, administer it only after a specified period (i.e., months) following transplantation. Its optimal role in immunosuppression has not yet been determined, and it remains the subject of a number of ongoing clinical trials. However, it is extensively used in treating coronary allograft vasculopathy (CAV), a form of allograft rejection. The rationale for this use emerges from sirolimus' ability to repress the TOR molecule and the proliferation of smooth muscle cells and endothelial cells in response to growth factors. This latter mechanism may explain why sirolimus inhibits arterial smooth muscle cell and endothelial cell proliferation and has been shown to prevent graft atherosclerosis in rat cardiac allografts [40]. It is extensively metabolized by the liver and the gastrointestinal tract, and is mainly excreted in feces (Table 27.1). It has a long half-life of 62 h (Table 27.1).

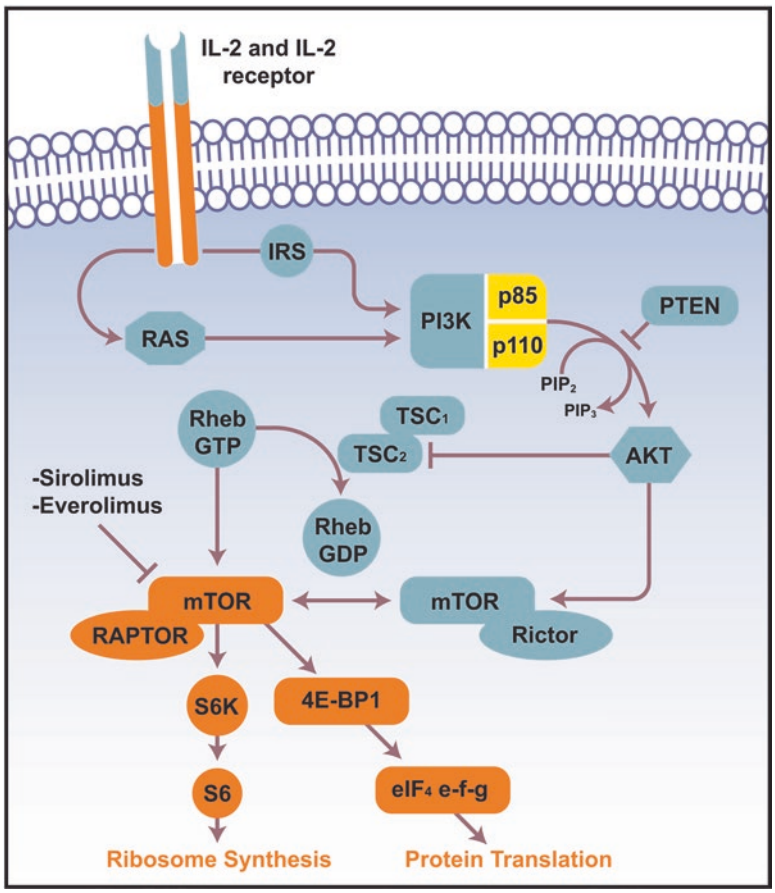

Fig. 27.13 Sirolimus inhibits the mTOR pathway in T lymphocytes. Schematic highlighting the mechanistic role of sirolimus and everolimus as inhibitors of the mTOR pathway in T lymphocytes. IL-2 binding to the IL-2 receptor results in mTOR protein activation which, via S6K, results in ribosomal synthesis and assembly and via elf4, results in protein synthesis. The mTOR pathway is particularly important in smooth muscle cell activation and coronary allograft vasculopathy

Two major randomized, open-label clinical trials have evaluated sirolimus as part of the immunosuppressive therapy in de novo heart transplant recipients. Keogh and coworkers randomly assigned 136 patients undergoing heart transplantation to receive sirolimus or AZA with CsA/prednisone as adjunctive therapy. After 6 months, the primary end point of significant rejection had occurred in 33 % of patients treated with sirolimus versus 57 % of patients in the AZA group [41]. Kobashigawa et al. randomly assigned 343 de novo cardiac transplant recipients to receive steroids and a combination of either Tac/sirolimus, Tac/MMF, or CsA/MMF. After a 1-year follow-up, there was no difference between the Tac/sirolimus and the Tac/MMF groups, but there were fewer treated rejection episodes in the Tac/sirolimus group versus the CsA/MMF group [42].

Everolimus

Everolimus is the 40-O-(2-hydroxyethyl) derivative of sirolimus and works in a comparable fashion as an inhibitor of the mTOR pathway. Thus, it solely affects the mTORC1 protein complex. This can result in a hyperactivation of the kinase AKT via inhibition on the mTORC1 negative feedback loop while not inhibiting the mTORC2 positive feedback on AKT. This increase in AKT can lead to longer survival in some cell types. Hence, everolimus plays an important role in cell growth, proliferation, and survival [43]. Its role in heart transplantation has been evolving due to its efficacy, especially in the prevention and treatment of CAV as well.

Everolimus is metabolized in the liver and mainly excreted in feces (Table 27.1). Although it has not yet been approved for clinical use, one major trial assessing everolimus in de novo heart transplant recipients showed its efficacy. This study randomly assigned 634 patients to everolimus or AZA/CsA/steroids. The primary end point was a composite of death, graft loss, or significant rejection. At 6 months, significantly fewer primary end points had occurred in the everolimus groups than in the AZA group (27–36 % for everolimus versus 47 % for AZA) [44]. It is metabolized by the liver via the CYP450 3A4 substrate, and 80 % of it is excreted through feces. It has a half-life of 30 h.

Collectively, the mTOR inhibitors are effective in preventing coronary restenosis by inhibiting vascular smooth muscle cell proliferation when used in coronary stents [45]. Consequently, when used in heart transplantation, these agents might be expected to reduce or prevent the incidence of CAV. Recently, an open-label prospective study of 46 patients with CAV randomized to the addition of sirolimus compared with continued current immunosuppression. Over a follow-up of 2 years, three patients in the sirolimus group compared with 14 in the placebo group developed clinically significant adverse events (death, need for angioplasty or bypass surgery, myocardial infarction, or a 25 % worsening of the catheterization score), supporting its role in management of CAV [46]. In the study by Keogh et al., serial angiograms and intravascular ultrasounds were performed in a subgroup of de novo transplant patients. While intimal and medial thickening occurred rapidly after transplantation in the AZA group, the treatment with sirolimus significantly reduced the development of CAV [41]. Similarly, Eisen et al. showed that everolimus used in de novo heart transplant patients was associated with a significantly lower incidence of CAV after 12 months of therapy [47].

Glucocorticosteroids

Prednisone

Prednisone is a synthetic corticosteroid drug first isolated and identified in 1950 [48]. It has effects similar to other corticosteroids such as methylprednisolone. These synthetic corticosteroids mimic the action of cortisol, the naturally occurring corticosteroid produced in the body by the adrenal glands. Corticosteroids have many effects on the body, but most often, they are used for their potent anti-inflammatory effects, particularly in those conditions in which the immune system plays an important role, such as heart transplantation (Fig. 27.11).

Steroids remain an important arm of immunosuppressive regimens used for induction and maintenance therapy (Fig. 27.11). They have been previously used in combination with AZA and, later, CsA, for maintenance therapy, but they have been replaced with the newer agents due to their significant side effects.

Induction Immunosuppression

IVIG

Intravenous immunoglobulin (IVIG) is a blood product administered intravenously. It contains the polyvalent IgG antibodies extracted from the plasma of donor blood. A wide variety of immunoglobulins are present in the IVIG preparation. Therefore, an extended spectrum of activities may arise including immunomodulation and anti-inflammation. IVIG has cytokine-neutralizing and cytokine-stabilizing effects and may decrease the synthesis of other cytokines. It inhibits apoptosis, chemokine production, and leukocyte adhesion. The mechanism by which IVIG reduces apoptosis is unknown but is assumed to be, in part, attributed to the impairment of Fas-mediated apoptosis [49].

The effect of IVIG on the complement system is somewhat controversial. Both complement activation and complement inhibition (membrane-attack complex, C3b, and C4b) have been reported [50]. Antibodies found in IVIG may also decrease de novo synthesis of anti-nonself antibodies by B and T lymphocytes. The effect is achieved, in part, by balancing Th1 and Th2 activities and their cytokine production. IVIG saturates the IgG transport receptor and therefore shortens the half-life of pathogenic antibodies [51]. Other mechanisms that contribute to immunomodulation include

saturation of Fcγ receptors on macrophages, which may inhibit cell-mediated cytotoxicity. The downregulation of dendritic cell differentiation decreases antigen presentation and contributes to the immunoregulation and decreased T-lymphocyte activation [51].

IVIG has been primarily used in induction and treatment of AMR in cardiac transplantation. It is particularly important in allo-sensitized recipients. The presence of high panel-reactive antibodies (PRAs) against HLA-1 increases the risk of early graft rejection, and mortality—which may be avoided by selecting a crossmatched donor.

IVIG decreases sensitization and enables patients awaiting renal transplantation to undergo the procedure. Left ventricular assist devices may serve as a bridge for cardiac transplantation but also cause patient sensitization by B-lymphocyte activation. Sensitization is also encountered following the use of allograft tissue in congenital cardiac surgical procedures. Thus, IVIG may reduce sensitization by its anti-idiotypic properties, as well as by containing HLA molecules [52]. In a study of 16 sensitized patients receiving IVIG treatment over a period of 1–3 months, researchers observed a 33 % reduction in antibody reactivity within 1 week of treatment, while an additional 20 % reduction could be achieved in resistant patients by using a high-dose regimen [52]. A reduction of up to 100 % of panel-reactive antibodies may be encountered in some case reports. Low-dose IVIG prophylaxis therapy following cardiac transplantation had no significant effect on the risk of developing reactive antibodies.

Plasmapheresis serves as an alternative for IVIG treatment in order to decrease the PRA, but achieving the required effect takes more time and is associated with more infections and complications. A combined treatment of both plasmapheresis and IVIG is considered more effective than IVIG monotherapy and has shown promising results in positive crossmatch patients [53]. The use of IVIG in acute AMR has reversed the graft rejection process in ten patients following cardiac transplantation and postponed rejection relapse following 5 years of follow-up [54]. It has a half-life of 30–40 days (Table 27.1). IVIG effects last between 2 and 10 weeks.

Rituximab

Rituximab is a chimeric monoclonal antibody that recognizes the protein CD20, which is primarily found on the surface of B lymphocytes. Rituximab is cytolytic for B lymphocytes and is therefore used to treat diseases characterized by excessive numbers of or dysfunctional B lymphocytes. These diseases include lymphoproliferative malignancies, autoimmune diseases, and transplant rejection.

CD20 is widely expressed on B lymphocytes, from early pre-B cells and differentiating B lymphocytes, but it is absent on terminally differentiated plasma cells. The interaction between rituximab and CD20 promotes cellular destruction by NK cells [55]. Since it does not affect mature plasma cells, few studies have shown that rituximab can be particularly effective in desensitizing patient pre-transplantation [56] and/or in cardiac transplant recipients with AMR [57, 58]. For example, in a single-center experience, Ravichandran et al. reported improved survival for heart transplant recipients treated with rituximab for AMR compared to the non-rituximab group ($P=0.0089$). There were no differences in secondary outcomes of infection, changes in ejection fraction, or re-hospitalization [59].

The first clinical trial involving heart transplant recipients started recruiting patients in 2015 who will be randomized in the first few weeks after transplant to receive four doses of rituximab versus placebo in addition to standard posttransplant immunosuppression to determine whether the development of CAV can be reduced. Rituximab is metabolized in the liver via the CYP450 system, with a half-life of 18–32 days.

Antithymocyte Globulin (ATG)

ATG is an infusion of horse- or rabbit-derived antibodies against human T lymphocytes, which is used to prevent and treat acute rejection in heart transplantation. The first report of immunizing an animal of one species against the immune cells of another species was described by Metchnikoff in 1873 [60]. He reported injecting cells recovered from mouse lymph nodes into guinea pigs and waiting for the immunization to result in the accumulation of anti-mouse antibodies in the guinea pig's blood. When he subsequently collected the serum from these guinea pigs and injected it into normal mice, he observed a marked depletion in the number of circulating lymphocytes. Thus, ATG administration substantially reduces immune competence in patients with a normal immune system through a combination of actions.

Rabbit ATG (rATG), in particular, displays specificity toward a wide variety of surface antigens on both immune system and endothelial cells. The precise mechanism(s) of action underlying its immunosuppressive efficacy is unclear, although T-cell depletion is considered to play a key role. Other mechanisms include lymphocyte surface antigen modulation, transcription factor activation, and interference with processes of immune system cells, such as cytokine production, chemotaxis, endocytosis, stimulation, and proliferation. rATG may also induce apoptosis, antibody-dependent lysis or complement-mediated lysis of various immune system cells and negate leukocyte-endothelial cell adhesion [61]. Today, it is mainly used for immunosuppression induction and the treatment of acute CMR [62]. However, medical opinion remains divided as to when the benefit of this profound reduction in T lymphocytes outweighs the concomitant increased risks of infection and malignancy.

Interleukin-2 Receptor Antagonists

Basiliximab

Basiliximab is a chimeric mouse–human monoclonal antibody that recognizes the α-chain of the IL-2 receptor (CD25) on T lymphocytes. It competes with IL-2 to bind to the IL-2

receptor on activated T lymphocytes, thus preventing its signaling (Fig. 27.11). This monoclonal antibody prevents T lymphocytes from replicating and activating B lymphocytes. It is used in the induction phase of immunosuppression and in the treatment of acute rejection [63]. In a study by Rosenberg et al., early administration of basiliximab as a renal-sparing CsA-free induction regimen enabled delayed initiation of CsA after cardiac transplantation to postoperative day 4. This occurred without an increase in rejection and reduced the risk of postoperative renal dysfunction [64]. Basiliximab has a half-life of 7 days.

Alemtuzumab

Alemtuzumab is a monoclonal antibody that recognizes CD52, a protein present on the surface of developed B lymphocytes but not on the stem cells from which these lymphocytes are derived. After treatment with alemtuzumab, these CD52-bearing lymphocytes are targeted for destruction [65]. This monoclonal antibody is currently used for induction immunosuppression. Early results from retrospective studies and a randomized trial were promising, with similar survival, but fewer rejections, in heart transplants [66]. Further studies on alemtuzumab are needed before its routine use can be considered.

Novel Agents in Early Stages of Development

Bortezomib is the first proteasome inhibitor used in humans [67]. It is typically used in hematological malignancies such as multiple myeloma, but emerging evidence suggests that bortezomib may be of benefit in sensitized patients pretransplant and in the management of refractory AMR [68, 69]. A new randomized clinical trial of bortezomib versus placebo in highly sensitized patients awaiting cardiac transplantation began in 2015 to determine whether this agent can enable cardiac transplantation in that patient population.

Tofacitinib is an inhibitor of Janus kinase (JAK). The JAK-signal transducer and activator of transcription (JAK-STAT) transmembrane signaling pathway is involved in the modulation of gene expression for immune activation. JAK inhibition results in the modulation of tofacitinib-mediated inhibition of T lymphocytes and NK cells [70]. This inhibitor has been studied in renal transplant recipients and was found to be as effective as Tac [71].

Belatacept is a T-lymphocyte inhibitor, that is generated from the fusion of the Fc portion of human IgG-1 and the extracellular portion of cytotoxic T-lymphocyte-associated 4 (CTLA-4), which is involved in T-lymphocyte activation through co-stimulation. In an open-label, randomized clinical trial of belatacept regimens compared with CsA in renal transplant recipients, belatacept showed promising results. Results are promising [72]. This agent is approved for use in calcineurin inhibitor-free regimens in conjunction with basiliximab and MMF. Unfortunately, belatacept is not approved for cardiac transplantation and has not been used even for off-label uses in these patients; however, it has the potential as an important and effective agent in cardiac transplantation.

Eculizumab is an IgG2/4 monoclonal antibody that is an inhibitor of complement component C5. It blocks the assembly of the membrane-attack complex, thus preventing inflammation and cell necrosis while preserving other functions of the complement cascade. Eculizumab has been reported to prevent AMR in renal transplant recipients. It has also been shown to reverse severe AMR in lung and kidney transplant recipients [73, 74]. It is extremely expensive and has not yet been studied in cardiac transplant recipients.

Sotrastaurin is a protein C kinase inhibitor, which has a functional role as an inhibitor of T lymphocytes. Sotrastaurin has been shown in preclinical cardiac transplant experiments to be effective in prolonging graft survival [75]. However, it is less effective in calcineurin inhibitor-free regimens, with higher rates of AMR [76, 77].

Summary

The fields of immunobiology and immunosuppression therapies have evolved tremendously and have resulted in improved survival and quality of life following cardiac transplantation. Despite this improved survival, side effects (i.e., organ toxicity, infection, allograft vasculopathy, malignancy, etc.) continue to limit graft and patient survival. While efforts have focused on reducing the conventional three-drug regimen (steroids, mycophenolate mofetil, and calcineurin inhibition) to a two-drug regimen, continued research focused on effective treatment of the sensitized patient, and the development of an immunosuppression protocol that is customized for each patient will increase graft and patient survival.

In addition, new therapies will emerge that target and promote the induction of regulatory T cells, decrease inflammation, inhibit reactive oxygen species/injury, induce tolerogenic antigen-presenting cell-mediated regulatory T cells all aimed at inducing allotolerance in the transplant recipient. Furthermore, strategies to limit ischemia-reperfusion of the newly transplanted graft will limit the inflammatory and immunoreactive response by the recipient. Targeted strategies focused on establishing the transplantation tolerance paradigm will address the distortion of MHC recognition of antigen-reactive cells, the production of anergy, and the deletion of antigen-reactive cells. The deletion of antigen-reactive cells in the donor organ prior to transplantation may require the implementation of a donor immunosuppression protocol in order to further improve graft survival.

In summary, the future of cardiac transplantation has always been impacted by our knowledge and tools aimed at modulating the patient's immune response. The future continues to brighten with all the emerging therapies and strategies that will have a tremendous impact on this field.

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Cardiac Transplantation Pathology

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_28

Introduction

The only definitive therapy for end-stage heart failure is cardiac transplant. About 2000 cardiac transplants are performed each year in the United States. This number, however, has reached a plateau due to a lack of donors.

The major indications for cardiac transplants are coronary artery disease and dilated cardiomyopathy. Survival rates have improved tremendously not only due to advancements in immunosuppressive therapy but also to advancements in our ability to recognize transplant rejection. Data from the Scientific Registry of Transplant Recipients reveal an 88 % 1-year survival rate, 75 % 5-year survival rate, and about a 56 % 10-year survival rate. While advancements in immunosuppressive therapy have lowered the rate of acute cellular rejection (ACR), the incidence of antibody-mediated rejection (AMR) remains relatively unaffected [1, 2]. AMR continues to appear in about 10–20 % of heart transplant patients, correlating with poor outcomes such as hemodynamic instability and greater development of cardiac allograft vasculopathy (CAV). Cardiac biopsies remain the mainstay for the diagnosis of both ACR as well as AMR. Gene expression tests that measure the up- or downregulation of specific molecular and cell pathways are being developed as an alternative to the standard biopsy-based diagnosis of rejection. Currently, however, cardiac biopsy remains the gold standard in monitoring rejection.

Endomyocardial Biopsy

Endomyocardial biopsies (EMBs) remain the preferred means for surveillance of rejection and management of cardiac transplant patients [3]. Currently, no other modalities—radiologic or serological—have the high sensitivity and specificity of EMB [4, 5] for diagnosing acute cellular rejection.

The frequency with which EMB is performed after transplantation varies from institution to institution. Ideally, a "time zero biopsy" of the donor heart should be performed at transplantation. This biopsy provides baseline status of the donor heart including myocyte hypertrophy, ischemia, or the presence of other pathologic processes such as myocarditis. The first posttransplant biopsy is generally performed a week or 10 days after transplant. Subsequent biopsies are performed once a week for the first month, every 2 weeks for the second month, and every 6–8 weeks from the third through 12th months. After the first year, the frequency of biopsies can be decreased to quarterly, biannually, or annually. If the patient remains stable after 1 year, EMBs are needed only when clinical suspicion of rejection exists. If a rejection is diagnosed, the patient can then benefit from closer surveillance, with repeat biopsies performed after 1–2 weeks.

EMBs are procured from the right ventricle via a bioptome introduced through the jugular or femoral vein. Immediate fixation in 10 % formalin at room temperature is important to prevent artifacts. Pieces procured for immunofluorescence studies should be snap frozen in OCT compound embedding medium (Miles Inc, Diagnostic Division, Elkhart, IN). All pieces should be submitted to the pathology department without triage at the cardiac catheterization suite, as pieces that may look hemorrhagic or grossly appear white, suggesting the sampling of endocardium may harbor valuable myocardial tissue.

To adequately assess rejection, current guidelines require a minimum of three biopsy pieces, each containing at least 50 % myocardium, excluding regions of previous biopsy site changes [6]. Specimens that do not reach this criterion should be labeled as "inadequate biopsy." If rejection is noted in a biopsy with fewer than three adequate pieces, however, the rejection grade may be indicated with emphasis that a higher-grade rejection cannot be ruled out.

Pathophysiology of Acute Cellular and Antibody-Mediated Rejection

Allograft placement results in the activation of several components of the recipient's immune system. The plethora of nonself, major histocompatibility complex (MHC) molecules on the graft cells are recognized by the recipient's T cells, B cells, and natural killer cells.

Activated B cells produce specific antibodies that bind to alloantigens, including the MHC antigens. In the classic complement pathway, activation of complement subsequent to its binding to antibodies results in vascular injury. Activated macrophages may also bind to antibodies, leading to antibody-mediated target cell lysis. The detection of complement and the presence of macrophages in the graft thus provide evidence of antibody-mediated rejection and form the basis for the diagnosis of AMR on EMB.

T cells recognize alloantigens either via direct or indirect pathway. In the direct pathway, the T helper cells recognize antigen on the graft cells, which are often associated with the MHC of the donor's antigen-presenting cells (APCs). In the indirect pathway, the foreign antigen is first broken down into small peptides by the recipient's own APCs such as dendritic cells. These antigens are presented to the naïve T cells in a complex with the recipient's MHC antigens. In response, activated T helper cells (CD4+) proliferate and produce cytokines that stimulate the production of cytotoxic T cells (CD8+), B cells, and macrophages that, in turn, cause destruction of the graft by direct lysis of target cells.

Morphologic Aspects of Cardiac Allograft Rejection

Hyperacute Rejection

Hyperacute rejection results from the presence of preformed antibodies and occurs within minutes to hours of allograft implantation. Factors associated with hyperacute rejection include preformed antibodies to epitopes of the ABO blood

group and HLA genetic systems, previous pregnancies, multiple surgeries with use of transfused blood, and other organ transplantations.

The preformed antibodies activate the complement cascade, producing severe damage to the endothelial cells as well as activating platelets, resulting in clotting and thrombosis. The heart appears grossly edematous. Diffuse histopathologic changes include prominent interstitial edema, endothelial cell swelling, extravasation of red blood cells, vascular thrombosis, necrosis, and inflammatory infiltrate composed of polymorphonuclear cells.

Acute Cellular Rejection (ACR)

While ACR is primarily a T cell-mediated process, substantial numbers of activated B lymphocytes and natural killer cells are seen in moderate-grade rejection [7]. Increasing numbers of antigen-presenting cells, including macrophages and dendritic cells [7–10], are also seen with a higher grade of rejection.

Historically, ACR was graded using many different schemata. In 1990, the International Society for Heart and Lung Transplantation (ISHLT) proposed a standardized grading system to effectively communicate outcomes in multicenter drug trials. This grading system was mainly based on the amount of inflammatory infiltrate and the presence of myocyte damage [11] (Table 28.1, Fig. 28.1) and quickly became the standard for reporting rejection.

Despite this attempt to standardize reporting of ACR, variability occurred in the interpretation of histologic grading among pathologists. In 2001, the Banff Allograft Pathology Group invited pathologists, cardiologists, and cardiac surgeons to discuss their experiences after a decade of using the 1990 ISHLT system. In 2004, under the direction of the ISHLT, a working group composed of an international multidisciplinary team of subspecialists in cardiac transplantation met to review the ISHLT 1990 definitions.

A major controversy of the 1990 schema was the diagnosis and treatment of grade 2 rejection [12, 13]. While many transplant centers used grade 2 rejection as the tipping point for treatment, others observed that, in the majority of cases, grade 2 lesions resolved without treatment. This and other considerations led the working group to propose a revised schema (Table 28.2, Figs. 28.1, 28.2, and 28.3) designated by the suffix "R." In the revised classification system, the 1990 grade 2 rejection was categorized as mild rejection (ISHLT 2004 grade 1R). Additionally, 1990 grades 3A and 3B were combined into grade 2R which represents moderate-/intermediate-grade ACR.

Despite the revised grading system, several pitfalls remain in the diagnosis of ACR. One challenge is accurate recognition of myocyte damage. The morphologic spectrum of myocyte damage is wide. These lesions may be subtle and represented by vacuolization of myocytes, perinuclear halo, ruffling of the cytoplasmic membrane, and irregular myocyte border. Other changes are more easily recognizable, such as outright splitting or branching of myocytes and myocyte encroachment with partial disruption by inflammatory infiltrate [4, 14]. In the revised ISHLT scheme, myocyte damage is described as "clearing of sarcoplasm and nuclei with nuclear enlargement and occasionally prominent nucleoli" [6]. Architectural distortions and myocyte dropout also frequently indicate myocyte damage. These changes are subtle, open to interpretation, and account for major interobserver variability in grading ACR.

Another pitfall in accurately diagnosing ACR is the difficulty in distinguishing histological features of Quilty lesions from true ACR lesions. Quilty lesions are dense endocardial lymphocytic infiltrates composed of predominantly T lymphocytes with admixed B cells, occasional macrophage, and plasma cells that can also be seen in the endocardium of transplanted hearts. Quilty infiltrates can either be confined to the subendocardial regions (previously known as Quilty A) or infiltrate deeply into the myocardium (previously known as Quilty B). Infiltrating Quilty lesions can be big. A biopsy without overlaying the subendocardial component of

Table 28.1 1990 grading system of the International Society for Heart and Lung Transplantation for acute cellular rejection

Grade 0	No acute rejection
Grade 1A	Focal, mild acute rejection
Grade 1B	Diffuse, mild acute rejection
Grade 2	Focal, moderate acute rejection
Grade 3A	Multifocal moderate rejection
Grade 3B	Diffuse, borderline severe acute refection
Grade 4	Severe acute rejection

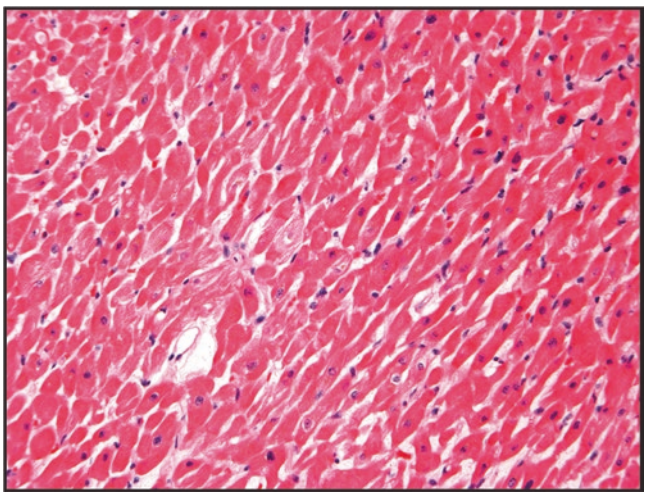

Fig. 28.1 Cardiac transplant biopsy, H&E section at 20× magnification. The biopsy reveals myocardium with no evidence of interstitial lymphocytes; no acute cellular rejection is noted (classified as ISHLT 0R)

Table 28.2 Comparison of the 1990 and 2004 ISHLT grading systems for ACR (acute cellular rejection)

1998 ISHLT		2004 ISHLT	
Grade 0	No acute rejection	Grade 0R	No acute rejection
Grade 1A	Focal, mild acute rejection	Grade 1R	Mild low-grade ACR interstitial and/or perivascular infiltrate with up to a sing to focus of damage
Grade 1B	Diffuse, mild acute rejection		
Grade 2	Focal, moderate acute rejection		
Grade 3A	Multifocal moderate rejection	Grade 2R	Moderate, intermediate-grade ACR; two or more foci of Infiltrate with myocyte damage
Grade 3B	Diffuse, borderline severe acute rejection		
Grade 4	Severe acute rejection	Grade 3R	Severe, high-grade ACR; diffuse infiltrate with multifocal myocyte damage with or without edema, hemorrhage and vasculitis

Quilty can be easily mistaken for moderate rejection. In such instances, it's helpful to examine multiple levels and carefully assess the biopsies to identify the continuity of the lesion from the myocardium to the overlying subendocardial component. Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES)-positive cells are abundant in acute cellular rejection [15], and an immunohistochemical stain for RANTES may help differentiate true rejection lesions from Quilty infiltrates.

Ischemic lesions can be associated with severe rejection or can be secondary to a prolonged ischemia time [16]. In the revised grading system, ischemia is divided into early ischemia, which occurs within 6 weeks of transplantation, and late ischemic injury. Late ischemic injury may explain cardiac allograft dysfunction secondary to severe allograft atherosclerosis and should be reported. Early posttransplant ischemia is subendocardial with foci of myocyte necrosis with or without associated macrophages and polymorphonuclear leukocytes. Distinguishing the healing phase of ischemic injury from moderate rejection may be difficult. In such situations, clinical correlation and communication among the cardiologists are helpful in management of the patient and in determining the patient's status and best treatment options.

Previous biopsy sites are very commonly found during transplant surveillance biopsies [17]. Due to inherent anatomic configuration of the allograft, the bioptome is guided to the same general region at the interventricular septum, leading to sampling of previous biopsy sites. Healing biopsy sites, especially when cut tangentially, may have entrapped myocytes with associated inflammation and are sometimes difficult to distinguish from ACR.

Because of improved immunosuppressive regimens, posttransplant lymphoproliferative disease (PTLD) is rare in contemporary transplant centers. In the rare cases where PTLD does occur, it can be seen on routine surveillance EMB. Distinguishing PTLD from ACR is very important as the former is managed by decreasing immunosuppressants and the latter by increasing them. Decreasing immunosuppression may lead to complete regression of PTLD [18, 19]. The majority of PTLD cases seen today are large B-cell lymphomas. Immunohistochemical stains for T and B cells and in situ hybridization for detection of Epstein-Barr virus (EBV) are performed for making the diagnosis. T-cell lymphomas can also occur, but usually present in the extranodal sites [20].

Additional rare findings on EMB that should be carefully assessed include the presence of chordae tendineae, valvular tissue, adipose tissue, dystrophic calcifications, and intussusception of small arteries. Chordal rupture may or may not result in clinically significant tricuspid regurgitation [21–23]. The presence of chordae should be described in the report and correlated with clinical findings. Adipose tissue is mostly seen in the epicardial region. Microscopic foci of fat, however, may be present within the myocardium in all four chambers, especially in obese patients, older patients, and patients taking steroid hormones. On the rare occasion that the bioptome may actually sample the right ventricular free wall, a finding of adipose tissue may suggest perforation. The presence of mesothelial cells associated with adipose tissue suggests an epicardial sampling. Tamponade is rare after such events because organized pericarditis usually forms a dense, fibrous, protective layer around the myocardium, but the findings should be reported to the clinical team.

Antibody-Mediated Rejection

Herskowitz et al. [24] first described AMR as a type of rejection that was physiologically characterized by arteriolar vasculitis and clinically associated with poor outcomes in heart transplant recipients. Two years later, in 1989, Hammond et al. [25] provided initial immunohistochemical evidence that AMR involved antibody deposition followed by complement activation, which resulted in tissue injury and coagulation.

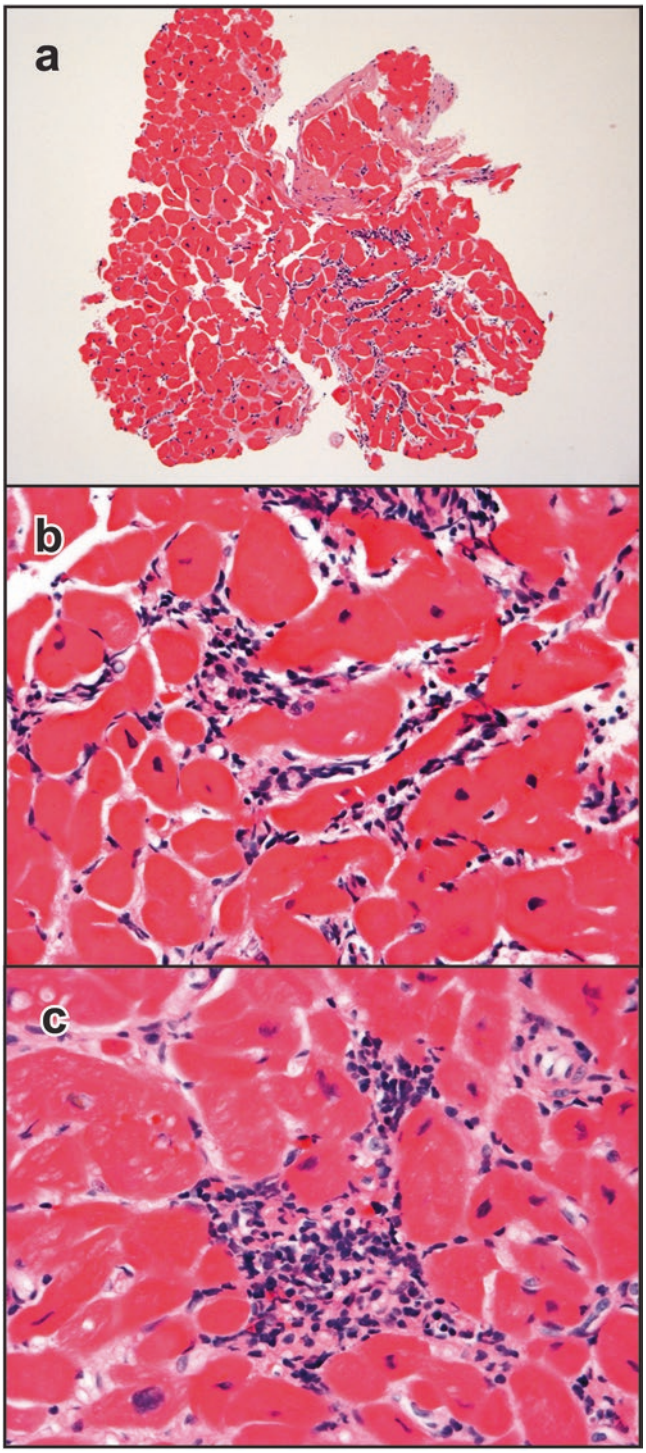

Fig. 28.2 (**a**) Low power view (10×) H&E section of a myocardial biopsy with interstitial infiltrate. (**b**) Medium power view (20×) H&E section with interstitial infiltrate without evidence of myocardial damage. Mild acute cellular rejection classified as 1R under the current classification and 1A as per the 1990 ISHLT system. (**c**) High power view (40×) H&E section of myocardium with a single focus of myocyte damage. This will be classified as mild acute cellular rejection 1R in the current classification system. Under 1990 ISHLT classification system, this focus would suggest a moderate-grade rejection

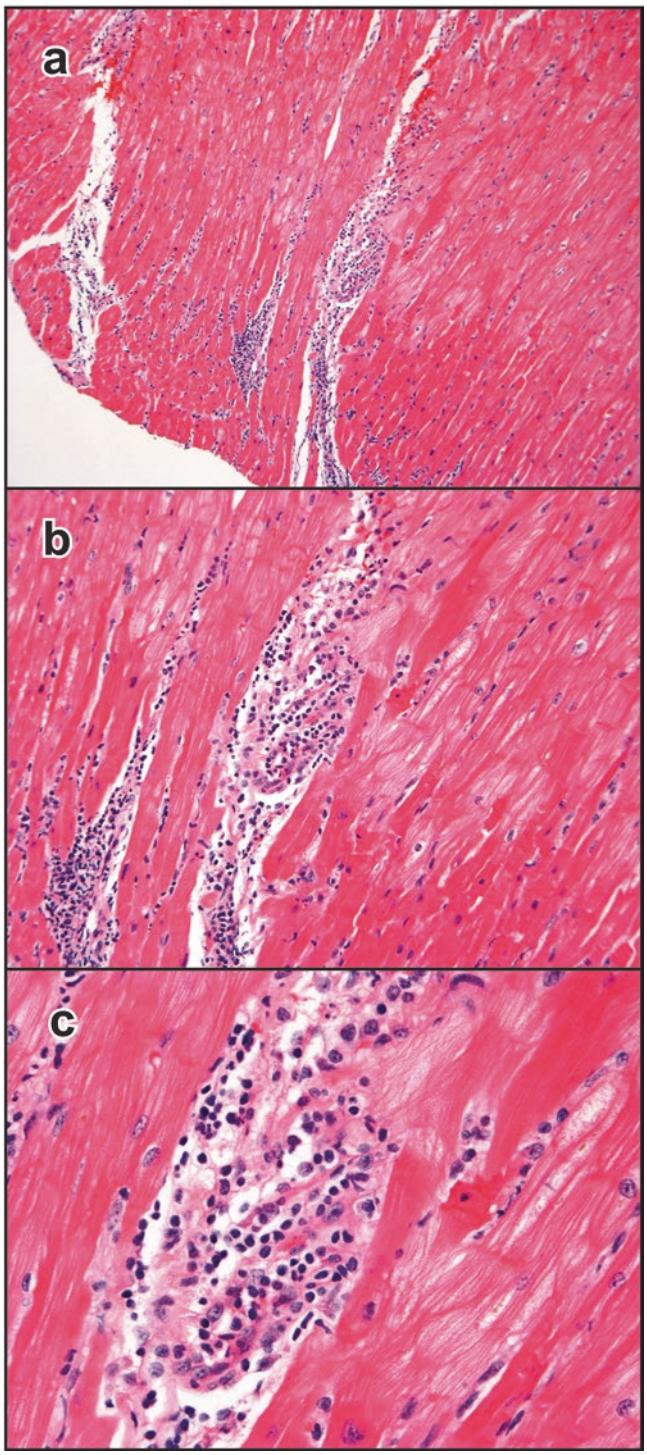

Fig. 28.3 (**a**) Low power view of a myocardial biopsy with patchy moderate infiltration. (**b**, **c**) Medium and high power view of foci of myocyte damage. This case has two separate pieces with myocardial damage. The current ISHLT classification of 2R is associated with moderate acute cellular rejection. Under the 1990 ISHLT classification, this case would represent severe acute cellular rejection

Activation of complement cascade generates biologically active complement split products such as C3a, C4a, and C5a, which initiates vasoactive responses in addition to mediating chemotaxis of neutrophils, monocytes, and macrophages [26]. The vascular responses to C5a and membrane attack complex include release of von Willebrand factor, P-selectin, and CD63 from the Weibel-Palade storage granules present in the platelets [26]. The interaction between P-selectin receptors on platelets and the vascular cell adhesion molecules expressed by activated endothelial cells leads to the release of inflammatory molecules, thereby further enhancing leukocyte localization and activation [27].

A number of risk factors are known to be associated with increased incidence of AMR. These include female gender, elevated pretransplant panel-reactive antibodies (PRAs), development of de novo donor-specific antibodies, positive donor-specific crossmatch, seropositivity for cytomegalovirus (CMV), retransplantation, and prior implantation of a ventricular assist device [28–32]. Thus, AMR can occur early as a result of preformed antibodies or can occur late in the life of an allograft as a result of de novo donor-specific antibodies (DSAs). Accurate recognition of AMR during the life of an allograft therefore is important to reduce morbidity and increase allograft survival.

Despite the recognition of AMR as a distinct phenomenon, criteria for its accurate pathologic and clinical diagnosis and specific treatment have been lagging behind. The majority of available treatment regimens are largely intended to interfere with T-cell signaling pathways [33]; as a result, the incidence of ACR has drastically decreased, while that of AMR remains unchanged.

In 2010, ISHLT organized a consensus conference to assess the status of AMR. A preconference survey revealed that most (56 %) centers diagnosed AMR on the basis of cardiac dysfunction accompanied by a negative endomyocardial biopsy specimen. Others used various combinations of factors including cardiac dysfunction, pathologic findings of endomyocardial biopsy specimens, and circulating antibodies [34]. The "heart session" of the 10th Banff Conference on Allograft Pathology (2009) attempted to standardize the pathologic and immunologic criteria for the diagnosis of AMR. Attendees agreed that the diagnosis of AMR requires input from biopsy findings along with concurrent serological status, and clinical parameters of graft function. That is, there should be a team approach to evaluating a patient suspected of developing AMR.

Evaluation of Cardiac Biopsy for AMR

Immunologic Evaluation of EMB

Cardiac biopsies are evaluated for deposition of C4d with or without additional staining with C3d. The presence of C4d and C3d can be studied on fresh frozen biopsy tissue using immunofluorescence (IF) techniques or on formalin-fixed, paraffin-embedded tissue using immunohistochemical (IHC) assays.

Table 28.3 Proposed ISHLT-WF 2004 AMR grading system

pAMR 0	Negative for pathology AMR; histologic and immunologic studies are both negative
pAMR 1	Suspicious for pathologic AMR, divided into two subcategories as follows
	pAMR 1 h: histology findings positive, immunologic findings negative
	pAMR 1-I: histology findings negative, immunologic findings positive
pAMR 2	Positive pathologic AMR; histologic and immunopathologic findings are both present
pAMR 3	Severe pathologic AMR; interstitial hemorrhage, capillary fragmentation mixed inflammatory infiltrates endothelial cell pyknosis and/or karyorrhexis and marked edema

Only interstitial capillaries are evaluated for the presence of these complement breakdown products. Arterioles, veins, arteries, endocardium, and blood vessels in Quilty lesions should not be considered in evaluating AMR. A summary of the ISHLT consensus conference indicated a good equivalence between immunofluorescence detection of C4d and C3d and immunohistochemical detection of these two markers. Additionally, an ISHLT consensus reported a very good reproducibility between centers in North America and Europe in evaluating these markers—believing that, with minor technical adjustments to the immunohistochemical techniques, pathologists can achieve almost 100 % reproducibility.

Histopathology Parameters on EMB

Endothelial cell activation and intravascular macrophages, capillary destruction, interstitial edema and hemorrhage, neutrophilic infiltrates, capillary fragmentation, and endothelial cell pyknosis are associated with AMR. The proposed schema for pathologic diagnosis of AMR combines histopathologic and immunopathologic findings. These findings are designated as pathological diagnosis of AMR, denoted as pAMR, and are summarized in Table 28.3 and Fig. 28.4.

The Current Recommendation for Monitoring for AMR Includes the Following

When AMR is clinically suspected, a blood draw at biopsy is recommended for concurrent evaluation of donor-specific HLA class I and II antibodies. The clinician should use these test results along with DSAs to assist in the diagnosis and specific management of the AMR episode. When anti-HLA

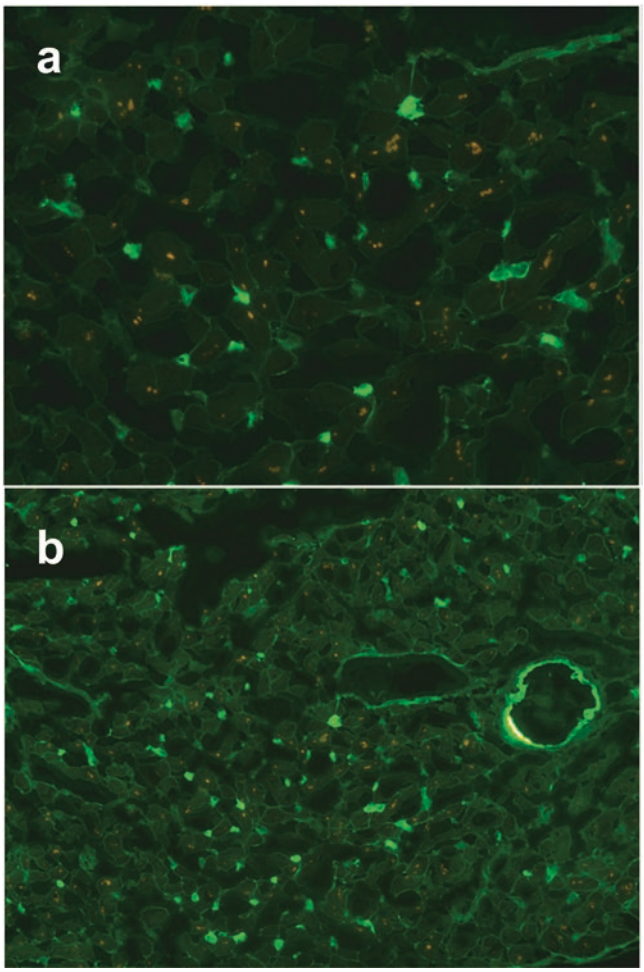

Fig. 28.4 Immunofluorescence studies for C4d. (**a**) Only interstitial capillary staining is considered positive. (**b**) Demonstrates larger capillary revealing intimal staining for C4d which is not included in the evaluation

antibodies are not detected, the assessment of non-HLA antibodies may be indicated.

The current recommendation for detecting circulating antibodies is to use a solid phase assay and/or cell-based assays to assess for DSA. In the past, cardiac dysfunction or the presence of DSA or both have been included as criteria for the diagnosis for AMR. These criteria only accounted for symptomatic AMR. Subclinical, asymptomatic, biopsy-proven AMR is important to recognize as it is associated with greater incidence of cardiac allograft vasculopathy [35] (CAV) and a higher mortality rate [36].

Every EMB specimen should be reviewed at regular intervals for histologic features of AMR and immunopathologic staining for C4d. Evaluation for AMR should be performed at 2 weeks and at 1, 3, 6, and 12 months after transplant. Similarly, DSA quantification of antibodies, if present, should be performed at 2 weeks and at 1, 3, 6, and 12 months after transplantation, and then annually thereafter or whenever AMR is clinically suspected. A positive result for C4d at any time after 12 months should trigger routine staining of subsequent specimens for that patient.

A positive C4d and/or C3d is not always accompanied by dysfunction of the graft. Apart from physiologic explanations for this phenomenon, artifactual staining also plays an important role. Autofluorescent lipofuscin deposits, nonspecific binding to collagen in the interstitium and to the internal elastic lamina of arteries, may lead to false-positive interpretation of the results. Necrotic myocytes also bind to complement.

Cardiac Allograft Vasculopathy

The ISHLT registry reports that only 47 % of adults are free of CAV at 9.5 years posttransplant. CAV develops as early as 3 years in a majority of patients. No overt clinical presentation is seen in most of these patients due to denervation of the donor heart, and patients often present for the first time with arrhythmias, congestive heart failure, or cardiac arrest. CAV is therefore a challenging problem in the long-term survival of the allograft.

Allograft vasculopathy involves the entire length of the coronary arteries [37]. While larger blood vessel vasculopathy can be picked up on angiography or intravascular sonography, early diagnosis is limited by the inability to assess the distal intramural lesions.

Some of the common risk factors associated with the development of early CAV [38–40] are donor hypertension, history of rejection within the first year of transplantation, or infection within 2 weeks requiring IV antibiotics.

Both immunogenic and nonimmunogenic factors are associated with the development of CAV. The primary target for cell and antibody-mediated response is directed toward MHC class I and II antigens located on the endothelial cells. Secretion of cytokines by activated T lymphocytes promotes proliferation of alloreactive T cells, activates monocytes and macrophages, and stimulates expression of adhesion molecules by endothelial cells [41]. Macrophages are then recruited to the intima where they elaborate cytokines and growth factors, leading to smooth muscle proliferation and synthesis of extracellular matrix [42]. Numerous excellent reviews of the pathobiology of vasculopathy are available in the literature [43–46].

Nonimmune factors associated with CAV include immunosuppressive therapy [47–49], donor-transmitted coronary atherosclerosis [50, 51], CMV infections [52–55], and myocardial ischemia [56–60].

The histology of CAV varies with the caliber of the arteriolar vasculature. Larger epicardial blood vessels show concentric intimal proliferation composed of smooth muscle and myointimal cells. Allograft vasculopathy reveals abundant deposition of proteoglycans in a pattern distinct from atherosclerosis, but similar to that seen in angioplasty-related restenotic lesions [61]. Early lesions reveal extensive proliferation, hence appear more cellular. Inflammatory infiltrate associated with early CAV is a mix of T cells, macrophages, and foam cells. The periadventitial region and the outer half of media may reveal fibrosis associated with lymphocyte-

mediated injury of the vasa vasorum. Late lesions show a decrease in smooth muscle cells and a fibrotic intima. When present in CAV, atheromatous plaques are indistinguishable from conventional atherosclerosis, but only involve the proximal to middle segments of large epicardial arteries.

Small intramural branches reveal concentric thickening of intima, but foam cells are not prominent. Endothelialitis of small branches is frequently observed in autopsy material. The myocardium often reveals chronic ischemic changes in the form of bilateral, patchy, microscopic acute, and healing ischemic lesions [62].

Posttransplant Morbidity

Immunosuppression is the mainstay in maintaining allograft health and, paradoxically, also a significant cause of morbidity and mortality in the first year posttransplantation. Complications of chronic immunosuppression include drug toxicity, increased risk of infection, and development of malignancy and posttransplant lymphoproliferative disease. The majority of patients eventually develop hyperlipidemia, hypertension, diabetes mellitus, and renal insufficiency. Infections are most common about 2 months after transplantation. Rejection, CAV, and malignancy are the most common morbidities in the first 4 years, and, subsequently, CAV and malignancies remain the main causes of morbidity. The ISHLT registry reports a 26 % incidence of malignancy based on 8-year cumulative data (2005 ISHLT adult transplant report). Lymphoproliferative disorders; squamous cell carcinoma of the skin; sarcoma, including Kaposi sarcoma; renal cell carcinoma; carcinoma of the vulva and perineum; and hepatobiliary tumors have been reported most often [63]. Many mechanisms of developing posttransplant malignancies have been proposed including oncogenic viral infection, defective immune surveillance, and transmission of cancer from donor to recipient. The most common causes of sudden death include arrhythmias and diffuse involvement of coronary arteries by CAV.

Future Directions

Over the last few decades, cellular rejection of cardiac allografts has been well studied, and immense progress has been made toward its accurate recognition and management. AMR and CAV remain major sources of morbidity and mortality from cardiac allografts. EMB remains the gold standard for diagnosis but is associated with a finite risk of complications. The probability of complications is especially high in patients who require closer monitoring.

Better tools to recognize and treat early signs of CAV and episodes of AMR are urgently needed. Proteomic and genomic markers to predict cardiac transplant rejection and risk of graft failure are under investigation. Quantitative assessment of mononuclear cell gene expression in peripheral blood specimens has been explored as a method to monitor cardiac allografts [64, 65]. Based on these studies, a commercially available test was developed and validated for clinical use and was shown to correlate well with the results of EMB [65].

The IMAGE (Invasive Monitoring Attenuation through Gene Expression) trial performed at Stanford University Medical Center [66] randomized 602 patients to the gene expression profiling or EMB arm, with both groups receiving additional clinical and echocardiographic assessment of graft function. During a median follow-up period of 19 months, similar 2-year cumulative outcome rates were noted in the two groups. The gene expression profiling group, however, had a statistically significantly lower rate of treatment of asymptomatic rejection as compared to the EMB group. This occurred because the gene expression method did not pick up asymptomatic rejection. While the cumulative risk of graft dysfunction, death, or retransplantation was similar in the two groups at 2 years, the difference in long-term complications is not known. Undetected rejection in the gene expression arm may lead to long-term graft dysfunction through such mechanisms as progressive myocardial fibrosis or CAV. While the current gene expression profiling test from peripheral blood specimens may offer a reasonable alternative to routine biopsies, it has its limitations. In summary, the ultimate long-term success of cardiac allografts will probably involve a combination of modalities and a close working relationship among pathologists and the cardiac transplant team before and after the transplant.

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Management of the Posttransplant Cardiac Patient

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_29

Introduction

The incidence and prevalence of heart failure is increasing at epidemic proportions. The only curative therapy for end-stage heart failure is orthotopic heart transplantation (OHT). Each year, more than 2000 Americans receive cardiac transplantation and this therapy is limited by donor organ supply. With a limited number of organs, donor and recipient are carefully matched, and attention is focused on limiting any complications during the posttransplant period in order to preserve graft function.

This chapter addresses issues pertaining to early graft function, periprocedural immunosuppression, infection prophylaxis, and allograft-related right ventricular dysfunction. These issues that occur during the early period following transplantation are managed by a highly trained and collaborative multidisciplinary health-care transplant team. The key to a successful outcome is measured in all the details surrounding the cardiac transplantation procedure.

The Multispecialist Health-Care Team

Every successful cardiac transplant program offers a highly coordinated team of health-care workers all focused on one common goal. This team includes the cardiac transplant surgeon, transplant cardiologist, the patient's nurse, transplant coordinator, social worker, pharmacist, psychologist, subspecialists (pulmonologist, neurologist, infectious disease specialist, gastroenterologist, etc.), a financial coordinator, dietician, chaplain, and a physical therapist (Fig. 29.1). All of the clinicians and members of the health-care team have tremendous expertise in the care of the transplant patient and the immunosuppressed patient. Everyone involved has important duties that span the pretransplant phase, the transplant procedure, and the posttransplant phase. Collectively, this health-care team provides a high standard of quality care that is required for optimal outcomes.

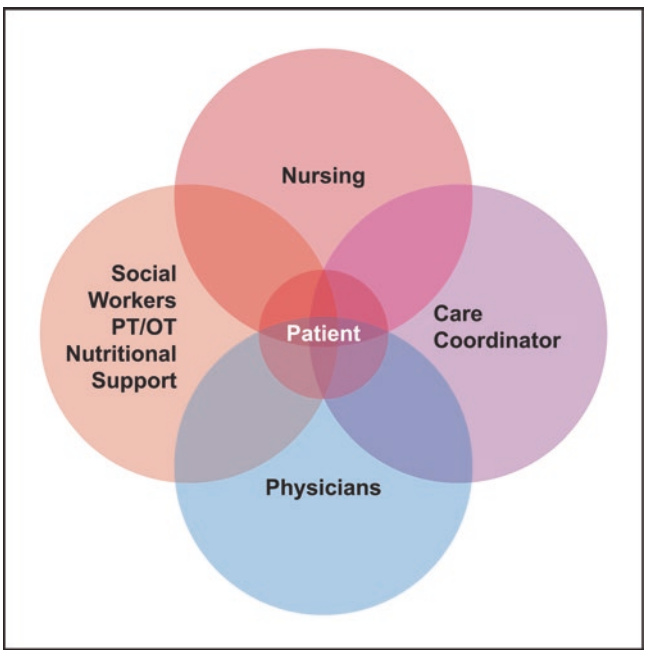


Fig. 29.1 A successful cardiac transplant program requires an integrated team of experts. Venn diagram highlighting the interaction of a multidisciplinary team to deliver care to posttransplant patients

Donor Organ Availability

Each year, about 2200 cardiac transplant procedures are performed in adult US patients. This limited number of transplants is due to a limited number of donor organs. Despite campaigns to increase donor volume, supply has remained flat. A recent study suggests there may be a larger number of organs available for transplant. Data from the US Organ Procurement and Transplantation Network of all potential adult heart donors from 1995 to 2010 revealed more than 82,000 potential donor hearts [1, 2]. About 34% of these donor hearts were accepted, 48% were rejected, and 18% were used for research purposes [3].

The large number of rejected "marginal" hearts is an opportunity for new technologies to boost availability of viable organs. For example, new organ preservation technologies such as "heart in a box" (TransMedics, Inc.) have recently emerged as options that may increase donor organ numbers. TransMedics' Organ Care System is a warm preservation device that provides a clinical platform for ex vivo human heart perfusion and may help preserve function and decrease the ischemic period, resulting in the use of a greater number of donor organs [4]. The PROCEED II (Randomized Study of Organ Care System Cardiac for Preservation of Donated Hearts for Eventual Transplantation) trial demonstrated non-inferiority of ex vivo preservation to cold ischemia. Further, three heart transplant cases in Australian hospitals used organs after cardiac death due to benefits offered by the Organ Care System [5]. Developing new technologies should ultimately facilitate the use of every viable donor organ.

Recipient Issues Affecting Early Postoperative Care

The transplant recipient may present factors that will impact the success of the cardiac transplant procedure. These factors include comorbid conditions such as diabetes mellitus, peripheral vascular disease, chronic kidney disease, pulmonary dysfunction, pulmonary hypertension, obesity, and cachexia. Additional issues include the urgency of transplantation, such as from hemodynamic instability requiring an intra-aortic balloon pump or the need for parenteral inotropic therapy, or presence of ventricular arrhythmias or need for ventilatory support, prior cardiothoracic surgical procedures, and the overall nutritional, emotional, and physical status, (such as frailty) at the time of transplant [6, 7].

In recent years, an increased number of patients with advanced heart failure (and awaiting cardiac transplantation) were supported by mechanical circulatory support devices. The International Society for Heart and Lung Transplantation reported that 19.1 % of cardiac transplant recipients were bridged with mechanical circulatory support in 2000. This number increased to 41.2 % in 2012 [8]. While this field is rapidly evolving with the introduction of new generations of devices, it has also been marked by increased waiting periods for transplant candidates. Moreover, patients supported by mechanical circulatory support typically have longer ischemic periods during the cardiac transplant procedure and have higher panel-reactive antibodies (PRAs) due to a history of blood transfusions, typically at the time of left ventricular assist device (LVAD) implantation [9, 10].

Donor Issues Affecting Early Postoperative Care

Donor biological factors also have a significant impact on the immediate postoperative care of a transplant recipient. Donor-recipient matching in heart transplantation is a multifaceted process. Factors such as age, donor-recipient size matching, cardiac function, preexisting cardiac abnormalities, infection, tissue histocompatibility, and ischemic time for the graft can all affect surgical outcomes. In an era where donor availability is scarce, with increased wait list times, waiting for the "perfect" donor is not a viable strategy. Matching the donor to recipient needs to be individualized on a case-to-case basis.

Donor-Recipient Size Matching

Donor-recipient size matching has resulted in an inconsistent impact on posttransplant survival [11–14]. Sizing considerations for organ allocation currently focuses mainly on body weight, assuming a direct correlation between body weight and cardiac size [15–18]. In one of the largest analyses to date, Patel and colleagues evaluated heart size matching for more than 15,000 recipients and did not demonstrate a 5-year mortality benefit from body weight size matching [16].

Despite these results, guidelines have recommended the following:

1. A heart from a donor whose body weight is less than 30 % of the recipient is acceptable.
2. A male donor with an average weight of 70 kg can be considered for any recipient size regardless of weight [19].
3. Heart size varies by sex. Reduced survival has been shown with donor organ sex mismatch, particularly for male recipients of female organs [15, 18, 20, 21]. As such, caution is advised with female donors whose weight is 20 % lower than that of a male. (4) Undersizing of donor hearts appears to correlate with increased filling pressures [22].

Data suggest that cardiac output in undersized hearts is maintained by elevated filling pressures and tachycardia [22]. Although undersized hearts appear to adapt following transplantation, they frequently are associated with significantly elevated filling pressures in the early postoperative period, which increases the risk of right ventricular and renal failure [23]. Monitoring the use of an undersized donor organ is predicated on the maintenance of optimal filling pressures via the management of volume and the use of inotropes and vasodilators. Depending on the hemodynamic profile, milrinone, nitroprusside, and epinephrine may be useful in alleviating congestion and improving cardiac output.

Severe pulmonary artery hypertension (PAH) is a contraindication for orthotopic heart transplantation. PAH is defined as irreversible pulmonary vascular resistance (PVR) >5 or transpulmonary gradient (TPG) exceeding 15 mmHg [24–26]. PAH in the OHT patient is associated with postoperative right ventricular failure and high morbidity and mortality in the postoperative period. In the setting of mild-moderate preoperative PAH, oversizing is believed to be beneficial in recipients, but this concept is controversial and not universally supported [26, 27]. Patel et al. reported on the association of higher mortality rates with undersized hearts as compared with oversized hearts in the setting of high PVR (>4 Wood units) in the postoperative setting [16]. Costanzo-Nordin and colleagues observed that oversizing was negatively associated with survival irrespective of transpulmonary gradient [27]. Oversizing can delay chest closure and can lead to increased filling pressures and right ventricular failure. Unlike undersized hearts, which adapt, the oversized heart has anatomic constriction, which in the worst cases can only be alleviated with retransplantation or mechanical circulatory support.

The current method of matching size is frequently debated since weight does not represent an accurate and universal assessment of appropriate heart size [20]. Echocardiographic assessment of dimensions, volume, and mass may provide a more accurate assessment of donor-recipient matching.

Donor Age

No set criteria define an age cutoff for donor heart selection. However, older donor age has been identified as a risk factor for all-cause mortality and early graft failure [19]. Advanced donor age is likely associated with a decline in myocardial reserve and the reduced ability to withstand an episode of primary graft failure or acute rejection. Guidelines suggest a donor less than 45 years of age as ideal. Donors between ages 45 and 55 can be used when the ischemic time is less than 4 h, and the use of donor hearts older than 55 years are reserved for recipients whose survival benefit of heart transplantation exceeds the up-front increase in early mortality (extended donor criteria) [19].

Cause of Death

The cause of death of the donor can confer increased risks of mortality for the recipient. For example, donors with brain death commonly have left ventricular (LV) dysfunction, which may or may not improve during the posttransplant period. This LV dysfunction associated with brain death resembles stress-mediated cardiomyopathy. Moreover, left ventricular hypertrophy (especially in the setting of a longer allograft ischemic period) and obstructive coronary artery disease (CAD) of the donor heart can contribute to a worse outcome during and after the transplant. In addition, a donor history of diabetes mellitus is associated with a worse recipient outcome.

Donor Infection

While chronic infections such as human immunodeficiency virus (HIV) and hepatitis C result in a worse recipient outcome, overall, the risk of donor-to-recipient infection transmission is low. However, potential transmission of mediators of endotoxins and infection resulting in donor sepsis may contribute to myocardial dysfunction. Donor hearts deemed low risk for infection transmission are based on the following: (1) donor infection is community acquired, (2) repeat blood cultures prior to procurement are negative, (3) the donor had received pathogen-directed antimicrobial therapy, (4) the donor's myocardial function is normal, and (5) no evidence of endocarditis is present by direct inspection [19, 29].

Drug Toxicities in Donor Hearts

Cocaine: The cardiotoxic effects of cocaine include endothelial dysfunction, vasoconstriction, and direct toxicity resulting in a cardiomyopathy [30]. Intravenous cocaine has an increased incidence of cardiotoxicity and the use of hearts in this scenario is not advised. Based on data from the United Network for Organ Sharing (UNOS), remote cocaine use (less than 6 months) appears to have limited cardiotoxicity, and the donor organ is relatively safe with respect to early postoperative cardiac function. Donor hearts with past or current nonintravenous cocaine abuse can be used for cardiac transplantation, provided cardiac function is normal and left ventricular hypertrophy is absent [30].

Ethanol Abuse: The impact of a donor's alcohol abuse on graft function following transplantation is controversial. Direct toxic effects may result in changes in energy stores—reducing the efficiency of calcium uptake by the sarcoplasmic reticulum, the impairment of sodium-potassium ATPase, and interference with calcium-troponin binding [19, 31]. Therefore, transplantation of a heart with a donor history of alcohol abuse may unmask myocardial biochemical abnormalities and present as early graft failure. The transplant team will have to weigh the potential benefit to the recipient with a heart from a donor who had a history of alcohol abuse.

Carbon Monoxide Poisoning: Carbon monoxide poisoning causes a leftward shift in the oxygen-hemoglobin dissociation curve, reduced oxygen delivery to the tissues, and dysfunction of the mitochondrial cellular respiration [32]. The myocardium becomes particularly susceptible to oxygen deprivation and may manifest as primary graft failure in the postoperative period [32]. Reports of outcomes linked to donors with carbon monoxide poisoning are variable with mixed results [33, 34]. Clinicians should be aware that, despite donors with carbon monoxide poisoning having normal cardiac function based on ejection fraction, there may be a higher incidence of primary graft failure [35, 36]. In cases of carbon monoxide poisoning, the acceptability of donor hearts should be based on all of the following: a normal electrocardiogram and echocardiogram, minimal elevation of cardiac enzymes, minimal inotropic support, short ischemic time, a favorable donor-to-recipient weight ratio, and a recipient with normal pulmonary vascular resistance.

Extended Criteria of Donor Heart

Ongoing debates occur about offering a "marginal donor" heart to a patient who may be a borderline heart transplant candidate, such as an elderly patient or a younger patient with significant comorbidities [37]. Table 29.1 lists the extended donor criteria. Survival outcomes are mixed regarding the use of marginal donor hearts, with some reports of similar outcomes and others reporting worse outcomes—up to 20 % worse than non-marginal heart recipients at 5 years [38–41]. In a retrospective analysis, Schumer and colleagues examined the differences in wait list survival of patients with continuous-flow left ventricular assist devices (CF-LVADs) and posttransplant survival of patients receiving marginal donor hearts. No significant difference in survival was shown up to 2 years follow-up between the two groups [42]. However, survival is worse when comparing recipients of marginal donors' organs to optimal donor organ recipients [42].

Table 29.1 Proposed extended donor criteria for borderline heart transplant recipients

Extended donor criteria
• Donor age > 55
• Hepatitis C positive
• Ejection fraction <45 %
• Requirement for high inotropic support
• Undersized organ mismatch >30 %
• Single vessel coronary artery disease
• Substance abuse (long-term alcohol or cocaine abuse)
• Death by poisoning (carbon monoxide, cyanide)
• Malignant brain tumor
• Long-standing diabetes mellitus
• Prolonged ischemic time

Perioperative Immunosuppression

Protocols for immunosuppression in the perioperative period vary from institution to institution. Preoperative regimens typically include preoperative glucocorticoids and a cell cycle inhibitor. Data from the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) show that the most common regimen in the early postoperative period includes a glucocorticoid, tacrolimus, and mycophenolate mofetil [43]. The benefit of induction therapy remains debated, but about half of US cardiac transplant centers continue to use it [19, 43]. The protocol at the University of Minnesota for cardiac transplantation is outlined as follows. Preoperative steroids in preparation for cardiac transplant are a standard part of the perioperative immunosuppression protocol. The University of Minnesota's protocol for methylprednisolone is 1000 mg IV preoperatively, then 500 mg IV at the release of cross clamp, and then 125 mg intravenous every 8 h (3 doses) starting 12 h postoperatively. Prednisone therapy (1 mg/kg, given in two divided doses) is initiated after completion of the methylprednisolone, tapered (5 mg total per day) until 20 mg po BID, and then tapered by 5 mg after each normal biopsy to 5 mg daily.

In the event of preexisting renal dysfunction, induction therapy with basiliximab may be used to delay initiating a calcineurin inhibitor (CNI). At the University of Minnesota, we use a CNI-delaying protocol for patients with impaired renal function (i.e., creatinine $\geq$1.6 or glomerular filtration rate (GFR) < 30) at the time of transplant and/or posttransplant renal dysfunction. Commonly used agents include thymoglobulin and basiliximab. Thymoglobulin is a polyclonal immunoglobulin mixture raised in rabbits against T lymphocytes (dosing 0.5–1.5 mg/kg IV daily). Dose adjustment is based on CD3 counts, platelet count, and absolute lymphocyte numbers. Thymoglobulin may be used as induction therapy, particularly in sensitized patients and those with a positive B-cell crossmatch, or if renal dysfunction occurs after transplant. Thymoglobulin may be used daily until there is an improvement in renal function. Basiliximab is a chimeric anti-interleukin-2 (IL-2) receptor monoclonal antibody with an initial dose 20 mg given IV day 0 followed by a second dose 20 mg IV on post-op day 4 [44].

Currently, tacrolimus is the most commonly used calcineurin inhibitor during the first posttransplant year [43, 45]. At the University of Minnesota, tacrolimus is the most commonly used CNI and it is typically initiated on postoperative day 1, pending normal renal function. If the renal function is normal and there are no infectious complications, then the target 12-h trough level is approximately 10–15 mg/l immediately posttransplant. Cyclosporine, the alternative CNI, has a target trough level of about 250 ng/ml [43]. Mycophenolate mofetil (MMF) is the preferred cell cycle inhibitor and has been previously shown to be superior to azathioprine in reducing mortality and rejection, although infections were shown to be more common [46]. MMF is given preoperatively at the University of Minnesota (1500 mg po as a single dose) and is subsequently initiated immediately following surgery at 2–3 g IV/PO QD in two divided doses [43].

Bacterial Infection Prophylaxis

Bacterial infections remain a major cause of morbidity and mortality within the first 2 months following cardiac transplantation, with the highest risk in the first week after transplantation [19]. Preventing infection is critical for optimal outcomes and increased patient survival. Strict handwashing before and after patient examination is essential and is the cornerstone of prevention.

Perioperative prophylactic antibiotics include intravenous cefazolin (2 g IV 1 h prior to incision and then 1 g IV every 2 h while patient is in surgery for patient's weight less than 120 kg) or vancomycin (1 g IV 1 h prior to surgical incision then 1 g IV every 8 h while patient is in the operating room with the first dose 8 h after the preoperative dose; the vancomycin should not be given if the creatinine clearance is less than 50 ml/min). Vancomycin is administered in place of cefazolin if the patient is allergic to cephalosporins, has a history of MRSA, or has a history of an anaphylactic reaction to penicillin. Postoperatively, cefazolin (1 g IV every 6 h) is administered for 48 h. For those patients unable to receive cefazolin, vancomycin (1 g every 12 h) is administered for 48 h.

Viral, Fungal Infection Prophylaxis

Cytomegalovirus (CMV) infection, even subclinical, is associated with cardiac allograft vasculopathy and poor outcomes. Prophylaxis has been associated with decreased risk of vasculopathy [47, 48]. For this reason, CMV monitoring and prophylaxis are essential components of posttransplant management. CMV prophylaxis should be initiated within 24–48 h posttransplant. Donor-positive and recipient-negative CMV serology represents the highest risk for the development of CMV-related infections and requires prophylaxis. In addition, at the University of Minnesota, prophylaxis is provided for either donor- or recipient-positive serology (Tables 29.2 and 29.3).

The management of recipients who have negative CMV serology and donor-negative serology is unclear, with some centers electing to administer acyclovir. ISHLT guidelines suggest intravenous ganciclovir postoperatively for high-risk patients [19]. Valganciclovir is an acceptable alternative as its bioavailability is comparable to intravenous ganciclovir and is tenfold higher than that of oral ganciclovir, although it is associated with a greater incidence of leukopenia [49]. It is comparable to oral ganciclovir in preventing CMV infection [50]. Low-risk patients may be considered for preemptive therapy, as they are monitored for nucleic acid or CMV antigenemia assay, and only receive acyclovir for anti-herpes simplex prophylaxis [19] (Table 29.4).

Table 29.2 Recommendations for the prevention of cytomegalovirus in heart transplant recipients (CMV, cytomegalovirus)

Donor serostatus (CMV IgG)	Recipient serostatus (CMV IgG)	CMV risk category	Viral prophylaxis
Neg	Neg	Low risk	Acyclovir 400 mg PO BID ×3 months
Neg	Pos	Moderate risk	Valganciclovir 900 mg PO daily ×3 months
Pos	Pos		
Pos	Neg	High risk	Valganciclovir 900 mg PO daily ×6 months

Table 29.3 Recommended dose adjustments for valganciclovir therapy based on creatinine clearance for cytomegalovirus prophylaxis

Creatinine clearance (ml/min)	Valganciclovir maintenance dose
≥ 60	900 mg QD
40–59	450 mg QD
25–39	450 mg every 2 days
10–24	450 mg twice weekly
Dialysis	Consider IV ganciclovir

Table 29.4 Garding criteria for cellular rejection in heart transplant recipients

Grade		
2004	1990	Histopathological findings
OR	0	No rejection
1R	1A	Focal perivascular and/or interstitial infiltration without myocyte damage
	1B	Multifocal infiltrate with myocyte damage
	2	Diffuse infiltration without necrosis
2R	3A	One focus of infiltrate with associated myocyte damage
3R	3B	Diffuse infiltrate with myocyte damage
	4	Diffuse, polymorphous infiltrate with extensive myocyte damage ±edema, ±hemorrhage, +vasculitis

Antifungal prophylaxis to prevent mucocutaneous candidiasis should be initiated with nystatin or clotrimazole lozenges post extubation. *Pneumocystis jirovecii* pneumonia and *Toxoplasmosis gondii* prophylaxis should also be initiated. Trimethoprim (TMP)/sulfamethoxazole (800–160 mg, one tablet twice weekly) is the standard prophylactic therapy. In the setting of sulfa allergy or glucose-6-phosphate dehydrogenase deficiency, alternative regimens include aerosolized pentamidine, dapsone with or without TMP or pyrimethamine, atovaquone, or clindamycin and pyrimethamine.

Evaluation and Treatment of Early Coagulopathies

Patients with multiple sternotomies, congestive hepatopathy, and those on warfarin therapy are at increased risk for bleeding complications. Platelets and fresh frozen plasma, as directed by the surgical team, are administered as needed. Vitamin K (IV) should be considered preoperatively in high-risk patients—with lower doses preferred compared to higher doses secondary to increased risk of anaphylaxis [19, 51]. Aprotinin, a bovine serine protease inhibitor with antifibrinolytic and anti-inflammatory properties, can reduce bleeding during heart transplantation [52, 53]. However, an observational study showed an increased incidence of end-organ dysfunction, including myocardial infarction, stroke, and renal failure leading to recommendations against its routine use [54].

Tranexamic acid and epsilon-aminocaproic acid also have antifibrinolytic activity that may be considered in high-risk patients to reduce the risk of bleeding before cardiopulmonary bypass. Neither agent has been found to be associated with increased end-organ dysfunction [19, 52, 55]. Recombinant factor VIIa interacts with tissue factor and activates the coagulation cascade. In situations of life-threatening bleeding, recombinant factor VIIa can also be considered [19, 56, 57]. Overall, increased intraoperative use of blood products has been associated with decreased recipient survival at 1 and 5 years posttransplant.

Right Ventricular Dysfunction and Pulmonary Vascular Hypertension Following Heart Transplantation

Despite significant improvements in heart transplant outcomes, right ventricular (RV) failure or dysfunction remains a challenge during the postoperative period. Typically, RV failure after transplant occurs in the setting of preexisting pulmonary hypertension. An increased transpulmonary gradient (greater than 15 mmHg) or a fixed pulmonary vascular resistance greater than 5 Wood units has been associated with an increased 30-day mortality post cardiac transplantation. Moreover, a linear relationship exists between PVR and mortality [58]. Early recognition and preemptive use of pulmonary vasodilators may be beneficial.

In the setting of RV failure due to pulmonary hypertension, pulmonary vasodilators such as sildenafil, nitric oxide, and epoprostenol may improve RV afterload [59–63]. Inotropic support may also be useful as preload optimization, maintenance of sinus rhythm, atrioventricular synchrony, and optimization of ventilator support [19, 64]. Inotropic support agents that augment right ventricular performance include isoproterenol, milrinone, dobutamine, and epinephrine [65]. Atrial and ventricular temporary epicardial pacing support should be used to maintain heart rates greater than 90 beats/min postoperatively [19, 64]. If there is no response to inotropic and pulmonary vasodilator therapy, or if progressive end-organ dysfunction occurs, consideration should be given to mechanical circulatory support.

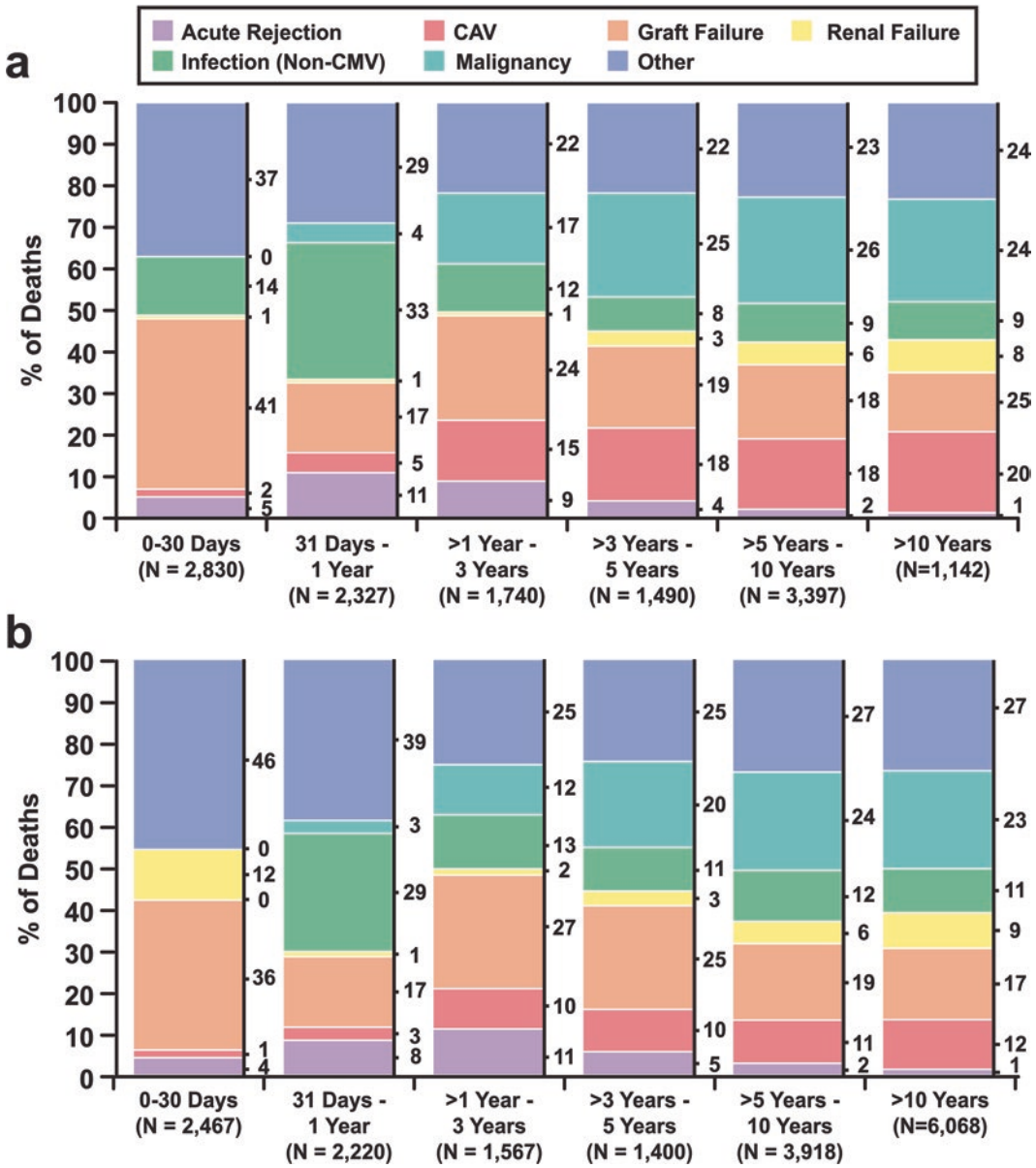
Immune and Rejection Monitoring

The challenge of finding the delicate balance between rejection and infection begins immediately after transplant. The risk of cellular rejection is highest in the first year following a

heart transplant. Heart transplant recipients with preexisting antibodies are particularly challenging due to their increased risk of rejection and mortality after transplant [66]. Furthermore, de novo antibodies can develop, placing a patient at increased risk for rejection in the early posttransplant period.

Monitoring for rejection should include the measurement of donor-specific antibodies and early biopsy for cellular and antibody-mediated rejection (AMR) (i.e., within 10 days following cardiac transplantation). The criteria for pathologic AMR were recently defined and suggestions made for monitoring intervals [19, 67, 68]. AMR should be evaluated using either immunohistochemical assays for C4d and C3d immunofluorescence.

Measurement and interpretation of donor-specific antibodies have been limited due to the lack of standardization. In addition, the management of donor-specific antibodies (DSAs) in the absence of graft dysfunction or evidence of rejection on biopsy is unclear. However, DSAs are associated with poor survival and cardiac allograft vasculopathy [68–70]. The majority of de novo DSAs appear to be anti-HLA-DR and anti-HLA-DQ [68–70]. The use of solid-phase assays has enabled the identification of HLA antibodies and their strength. New techniques, such as the C1q assay provide assessment of complement fixation, which will further define the antibodies that are clinically relevant, at least in the short term. ◘ Figures 29.2 and 29.3 illustrate the leading causes of death stratified by era and time of death.



◘ **Fig. 29.2** Causes of death for cardiac transplant recipients. (**a**) Highlights causes of death for adult cardiac transplant recipients from 1994 to 2001. (**b**) Highlights causes of death for adult cardiac transplant recipients from 2002 to 2012 (Data adapted from J Heart Lung Transplant. 2014;(32)10. Thirtieth Official Adult Heart Transplant Report—2013)

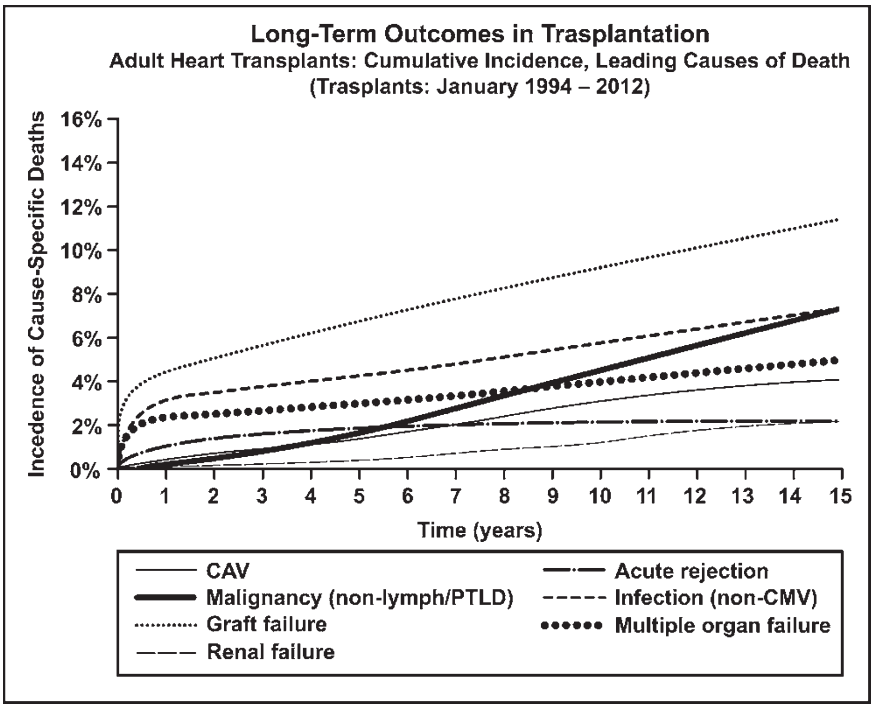


Fig. 29.3 Graft failure is the leading cause of death following heart transplantation. Data highlighting the leading causes of death following cardiac transplantation from 1994 to 2012 (Data adapted from J Heart Lung Transplant. 2014;33(10))

29

Managing Sensitization and Positive Crossmatch

As previously emphasized, sensitization is associated with poor outcomes following heart transplantation [66]. Prior to transplantation, desensitization could be performed to reduce the number of HLA antibodies. Desensitization strategies in cardiac transplantation have typically emerged from data based on the management of kidney transplants. A few small, single-center studies have been conducted with heart transplant recipients, and results have been difficult to interpret due to lack of standardization and controls.

Strategies that have incorporated IVIg and plasmapheresis appear to be successful in decreasing antibodies [71]. There are data suggesting rituximab and bortezomib as viable strategies [72, 73]. In our experience at the University of Minnesota, few patients actually respond to these therapies, and a decision has to be made whether to pursue transplantation in this setting. Figure 29.4 outlines our initial algorithm for desensitization. Several strategies may be undertaken in this scenario. Pre-, intra-, and postoperative plasmapheresis may be used to remove circulating antibodies, and the addition of IVIg, thymoglobulin, and/or rituximab may decrease the production of antibodies. Campath has been used in highly sensitized patients undergoing transplant, but it is associated with a high rate of rejection [74]. Close monitoring for rejection after transplant is required.

A positive crossmatch is associated with increased risk of mortality and hyperacute rejection [75, 76]. In a retrospective analysis of recipients who had a positive crossmatch, those who received plasmapheresis had improved survival compared to those who did not receive plasmapheresis [77]. IVIg may abrogate a positive crossmatch and may be considered in this setting. It is typically combined with plasmapheresis [78].

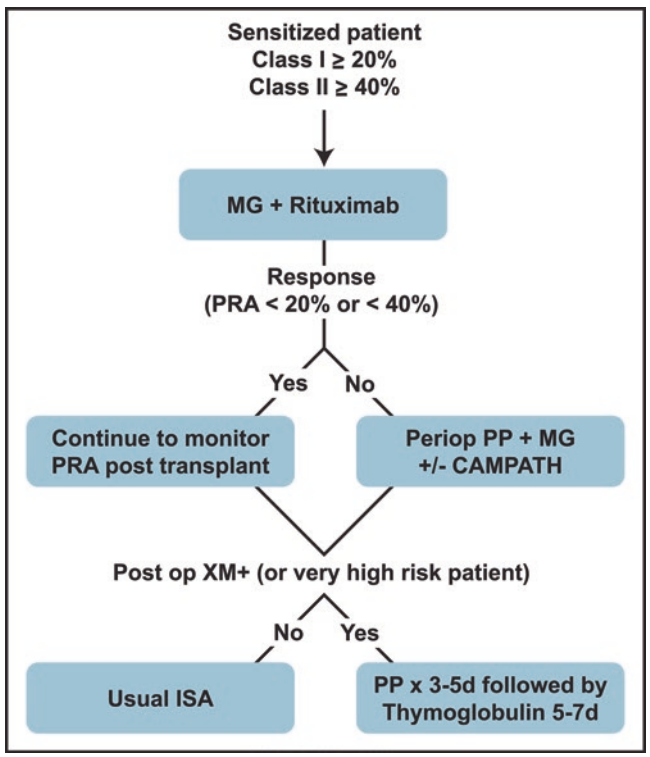


Fig. 29.4 Proposed algorithm for desensitization therapy. Note that desensitization therapies include intravenous immunoglobulin (IVIG) infusion, rituximab, plasmapheresis (PP), Campath (alemtuzumab), and thymoglobulin [postoperative (post op) and crossmatch (XM)]

Summary and Future Initiatives

Survival following cardiac transplantation has improved tremendously over the past several decades. The sustained function of the allograft is multifactorial. The use of a coordinated

health-care team, infection prophylaxis, renal-sparing immunosuppression protocols, and matching strategies to pair the best donor and recipient has collectively impacted the quality of life of the cardiac transplant recipient and their survival. Future initiatives that will further impact survival and graft function following cardiac transplantation will include personalized immunosuppression modifications, the development and use of donor risk scores, the development of new immunosuppressive agents that have limited organ toxicity profiles, and improved organ preservation systems (e.g., heart-in-a-box technology). The ability to use all available donor organs for cardiac transplantation will have an enormous impact on the field and save lives.

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Adult Orthotopic Heart Transplantation: Early Complications

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_30

Introduction

The combination of cardiac surgery, frequent perioperative hemodynamic instability, and an immunosuppressed state places heart transplant recipients at an extremely high risk of neurologic, hemodynamic, and immunologic complications in the early postoperative period. These, along with infection, are the most common causes of early mortality following heart transplant (Fig. 30.1). The early complications of orthotopic heart transplantation will be reviewed.

30

Perioperative Technical Considerations

Orthotopic heart transplantation (OHT) requires a full (often repeat) sternotomy, cardiopulmonary bypass, explantation of the diseased heart, along with any previously placed ventricular assist device(s), and allograft implantation, which may be performed using a bicaval or biatrial technique. The biatrial technique involves excision of the division of the donor left atrium anterior to the pulmonary vein ostia, incision of the right atrium from the inferior vena cava toward the right atrial appendage, and biatrial anastomosis [1, 2]. The bicaval technique is a more popular technique characterized by one left atrial and two caval anastomoses, preserving the right atrium and leaving only a small posterior portion of the recipient left atrium between the pulmonary veins [3, 4].

Intraoperative factors such as mediastinal adhesiolysis (which can be tedious and time-consuming), length of aortic cross clamping and cardiopulmonary bypass, cardiac manipulation, anesthetic factors, and other issues play an important role in the early postoperative course following reoperative cardiac surgery and OHT is no exception [5]. Great care must be taken to minimize the insults associated with each of these factors to prevent significant intraoperative and postoperative bleeding. Failure to do so may result in stroke (ischemic or hemorrhagic), renal failure, liver failure, and other systemic sequelae. A thorough discussion of the evaluation and management of postoperative stroke is beyond the scope of this chapter. Bleeding also leads to hemodynamic instability, need for massive transfusion, re-exploration, and prolonged intubation and ICU stay. Furthermore, the combination of these factors increases the risk of deep sternal wound infection (DSWI) with or without mediastinitis, discussed later [6].

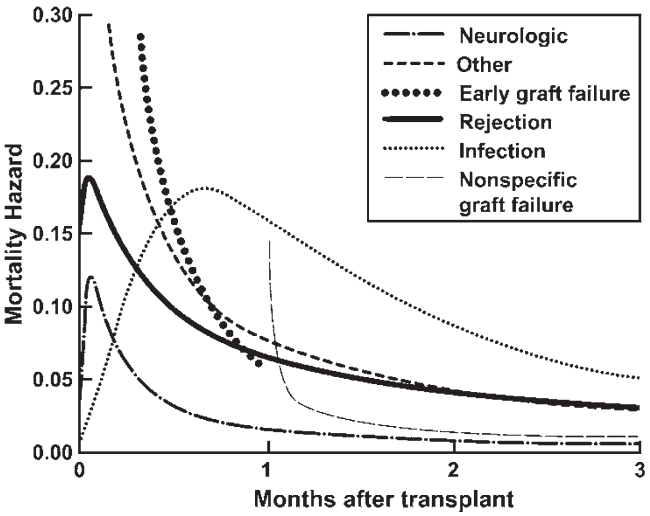

Fig. 30.1 Most common causes of early mortality after heart transplant. The most common causes of death in the first month after transplant are graft failure, neurologic events, and rejection. Infection is also a common cause of early mortality (Adapted from Kouchoukos NT et al. Kirklin/Barratt-Boyes Cardiac Surgery, 2013)

Hemodynamic Complications

Allograft Dysfunction

Primary Graft Dysfunction

Primary graft dysfunction (PGD) is a phenomenon of circulatory insufficiency following orthotopic heart transplantation (OHT) caused by single ventricular or biventricular systolic graft dysfunction in the absence of rejection or other obvious etiology in the first 24–48 h postoperatively, causing hemodynamic instability requiring aggressive pharmacologic and/or mechanical circulatory support (MCS). Long considered a diagnosis of exclusion, a 2013 International Society of Heart and Lung Transplantation (ISHLT) conference created the first consensus definitions of primary and secondary graft dysfunction. Secondary graft dysfunction occurs in the context of a known cause of graft dysfunction, such as acute/hyperacute rejection, surgical complications, or pulmonary hypertension [7]. The consensus definitions and severity scale (Table 30.1) of PGD are listed below:

1. Severe left, right, or biventricular systolic dysfunction detected by direct intraoperative visualization or by measurement of left ventricular ejection fraction (LVEF) of <45 % by transthoracic (TTE) or transesophageal (TEE) echocardiography performed during or immediately after surgery
2. Hemodynamic instability lasting longer than 1 h characterized by systolic blood pressure (SBP) < 90 mmHg or cardiac index (CI) < 2.2 L/min/m [2] requiring two or more inotropes or MCS with extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump (IABP), or temporary ventricular assist device (VAD) support with or without an inability to wean from cardiopulmonary bypass (CPB) despite adequate cardiac filling pressures (CVP > 15 mmHg and/or PAWP < 20 mmHg)
3. Occurs within 24–48 h following implantation
4. The absence of other likely causes of graft dysfunction, including hyperacute/acute rejection, cardiac tamponade, anastomotic kinking, pulmonary hypertension, hypoxemia, and acidosis [8–11]

Retrospective analysis of PGD is challenging because a consensus definition was created only recently, but factors predictive of PGD can be grouped into three main groups: those related to the donor, to the recipient, or to the technical aspects of the procurement and implantation.

Table 30.1 Definition and severity scale in primary graft dysfunction (PGD)

PGD-left ventricle (PGD-LV)	Mild PGD-LV: one of the following criteria must be met	LVEF < 40 % by echocardiography
		Hemodynamics with RAP > 15 mmHg, PCWP > 20 mmHg, CI < 2.0 L/min/m^2 (lasting more than 1 h) requiring low-dose inotropes
	Moderate PGD-LV: must meet one criterion from I and another criterion from II	I. One criteria from the following
		LVEF < 40 % by echocardiography
		Hemodynamics with RAP > 15 mmHg, PCWP > 20 mmHg, CI < 2.0 L/min/m^2 (lasting more than 1 h) requiring low-dose inotropes
		II. One criteria from the following
		(a) High-dose inotropes—inotrope score > 10[a]
		(b) Newly placed IABP (regardless of inotropes)
	Severe PGD-LV	Dependence on left or biventricular mechanical support including ECMO, LVAD, BiVAD, or percutaneous LVAD. Excludes requirement for IABP
PGD-right ventricle (PGD-RV)	Diagnosis requires either both a and 2 or 3 alone	(a) Hemodynamics with RAP > 15 mmHg, PCWP > 15 mmHg, CI < 2.0 L/min/m^2
		(b) TPG < 15 mmHg and/or PASP < 50 mmHg
		(c) Need for RVAD

PGD following heart transplant is marked by progressive hemodynamic dysfunction and graded based on the required level of support (Adapted from Kobashigawa J et al. *J Heart Lung Transplant* 33: 327)
BiVAD biventricular assist device, *CI* cardiac index, *ECMO* extracorporeal membrane oxygenation, *IABP* intra-aortic balloon pump, *LVAD* left ventricular assist device, *PCWP* pulmonary capillary wedge pressure, *RAP* right atrial pressure, *RVAD* right ventricular assist device, *TPG* transpulmonary pressure gradient, *PASP* pulmonary artery systolic pressure
[a]Inotrope score = dopamine (1) + dobutamine (1) + amrinone (1) + milrinone (15) + epinephrine (100) + norepinephrine (100) with each drug dosed in μg/kg/min

Donor risk factors include female sex, diabetes, head trauma, abnormal echocardiography (reduced LVEF and/or wall motion abnormality), and high-dose inotrope/vasopressor therapy prior to donation [10, 12–15]. Increased donor age is also considered a risk factor, although this is somewhat controversial [10, 12, 16, 17]. Other donor risk factors include substance abuse, preexisting myocardial or valvular dysfunction, sepsis, and hypernatremia [7].

Recipient risk factors for PGD include advanced age, need for preoperative mechanical circulatory support, heart failure due to congenital heart disease, redo sternotomy, associated left ventricular assist device (LVAD) explant, and acute and chronic medical comorbidities, including multisystem organ failure or dysfunction [7, 12, 14, 18]. Procedural risk factors include prolonged (>2–4 h) graft ischemic time, limited institutional experience, type of preservation solution, and emergent transplantation [18–22].

Allograft myocardial injury can occur as early as the onset of donor brain death or as late as reperfusion at the time of implantation. The most frequent cause of PGD is myocardial stunning secondary to inadequate myocardial protection, which can occur during the pre-procurement, transport, and implantation phases of OHT. Stunned myocardium is characterized by a period of prolonged but reversible postischemic ventricular dysfunction. The major mechanisms implicated in the etiology of stunning are intracellular calcium (Ca^{2+}), reperfusion injury, and oxidative stress induced by reactive oxygen species, cellular swelling, extracellular edema, cellular acidosis, depletion of metabolic substrate, and endothelial injury [23]. Although stunned myocardium is viable, it is hypocontractile despite normal or near-normal coronary blood flow. Recovery may take as long as 1–2 weeks, depending on the severity and length of the ischemic insult. Currently, heart preservation after procurement is limited to 4–6 h of cold ischemic storage; longer periods of ischemia are known to adversely affect survival [24].

The current standard of care for allograft preservation in OHT is static cold storage in a slush of ice and specialized preservation solution, which is preceded by a cold flush at the time of procurement. Several such solutions, including University of Wisconsin (UW) and Celsior, are currently in use. Major features of these include high concentration of potassium and oncotic, antioxidant, and buffer additives intended to mitigate allograft edema, reperfusion injury, and acidosis. Studies examining the comparative effects of different preservation solutions on allograft function have not demonstrated one to be clearly superior [21, 24–26].

Cooling alone reduces glucose utilization, adversely alters intracellular pH regulation, and slows tissue oxygen uptake.

Mitochondrial respiration and membrane integrity is reduced as well, which may cause a decline in levels of mitochondrial ATP and subsequent cellular electrochemical derangement through impaired function of ion transport channels. Although cold storage causes a dramatic decrease in myocardial energy consumption, the residual metabolic activity (~10 % of warm activity) in the absence of oxygen and glucose supply promotes anaerobic metabolism and subsequent lactic acidosis, which can be deleterious to allograft function following implantation [24].

Segovia et al. have described the RADIAL score, the first and only validated predictive scoring system for PGD based on donor, recipient, and procedural factors. Elements of the score are recipient Right atrial pressure ≥10 mmHg, recipient Age ≥60 years, recipient Diabetes mellitus, recipient Inotrope dependence, donor Age ≥30 years, and Length of ischemic time ≥240 min. Each donor-recipient pair receives a single point for each element present. Further work demonstrated that the RADIAL score can be used to create three risk strata, low (RADIAL < 2, PGD risk 12.1 %), intermediate (RADIAL = 2, PGF risk 19.1 %), and high (RADIAL > 2, PGD risk 27.5 %).

The cornerstone of management of PGD is mechanical circulatory support (MCS). MCS in patients with PGD can be provided using intra-aortic balloon pumps (IABP), extracorporeal membrane oxygenation (ECMO), and temporary ventricular assist devices (VADs). Most data regarding the use of these devices for PGD is retrospective in nature [9, 19, 27, 28]. Algorithms for the use of MCS, and its concomitant use with pharmacologic support for PGD, are generally individualized between high-volume centers [29]. There is a trend toward early initiation of MCS, frequently prior to leaving the operating room, with the goal of mitigating the systemic insult of a period of prolonged cardiac dysfunction [11].

Inotropes, vasodilators, and inhaled nitric oxide serve as valuable adjuncts in this setting, although no universal protocol exists for their use. Levosimendan, one of the only agents for which dedicated data exists in this setting, is a calcium channel sensitizer that acts as a positive inotrope and peripheral vasodilator without increasing myocardial oxygen demand and has been specifically studied for use in PGD. A small descriptive case series of heart transplant patients with PGD treated with levosimendan demonstrated expeditious weaning from other pharmacologic support and 93 % survival at 30 days after surgery, with only one patient requiring MCS [30]. However, these benefits were not appreciated at 3 years of follow-up [31].

Heart transplantation carries a 30-day mortality of approximately 8 %, during which time PGD is responsible for 35–40 % of deaths, making it the leading cause of early mortality following heart transplant [32]. The mortality risk of PGD managed exclusively with pharmacologic means is 40–50 % [33]. In some series the use of ECMO for PGD is associated with 30-day and 1-year survival as high as ~80 % and 70 %, although the need for VAD support portended worse overall outcomes [33].

Right Ventricular Failure

Risk Factors

Defined as a failure of the right ventricle (RV) to maintain adequate flow through the pulmonary circulation to allow adequate LV filling, right ventricular failure remains a significant and vexing problem after cardiac transplantation and a source of major morbidity and mortality in the perioperative period [34]. Severe RV failure is defined by ballooning of the RV with corresponding end-organ dysfunction or the need for mechanical circulatory support with a right ventricular assist device (RVAD) [35].

The most common risk factor for RV failure following OHT is ischemia-reperfusion injury, which is caused by the process of organ procurement, cold ischemic transport, and implantation/reperfusion. Other risk factors include mechanical trauma during transport and implantation, warm ischemia in the operating room, coronary air embolus, and any extrinsic factor that would raise pulmonary vascular resistance, such as mechanical ventilation with high PEEP and acute and/or chronic recipient pulmonary hypertension [35]. Common causes of posttransplant RV failure are summarized in Fig. 30.2.

The complicated geometry of the RV makes it difficult to measure its function directly. Jugular venous distention, peripheral edema, a split second heart sound, and a tricuspid regurgitation murmur are clinical data suggestive of elevated right-sided filling pressures, especially in the absence of left-sided dysfunction. A number of echocardiographic adjuncts, such as RV size, tricuspid annular plane systolic excursion (longitudinal displacement of the RV base relative to the RV apex), and estimated RV systolic pressure, are helpful in the diagnosis of RV failure, although each of these can be affected by factors extrinsic to RV function [34]. Pulmonary artery (PA) catheters are routinely left in place following OHT and data such as central venous pressure (CVP) and PA pressure are crucial in making this diagnosis.

Management of Right Ventricular Preload and Contractility

Elements of the management of RV failure can be grouped into those modifying preload, afterload, and the intrinsic contractility of the ventricle (Fig. 30.3). The RV is a thin-walled and highly compliant chamber that responds poorly to acute increases in preload. Acute distention of the RV can induce a level of wall tension beyond which it is unable to pump effectively. Furthermore, ventricular interdependence, a phenomenon in which massive RV distention can cause the ventricular septum, which forms the posterior wall of the RV, to invert its curvature and impede LV filling. Poor LV filling has a negative impact on its function, which can exacerbate right heart failure. Conversely, inadequate filling of the RV, most commonly caused by systemic hypovolemia, can also impair RV output [36]. The great sensitivity of the RV to fluid overload mandates careful management of volume status in these patients, often with the aggressive use of diuretics and, in some cases, hemofiltration [34, 36].

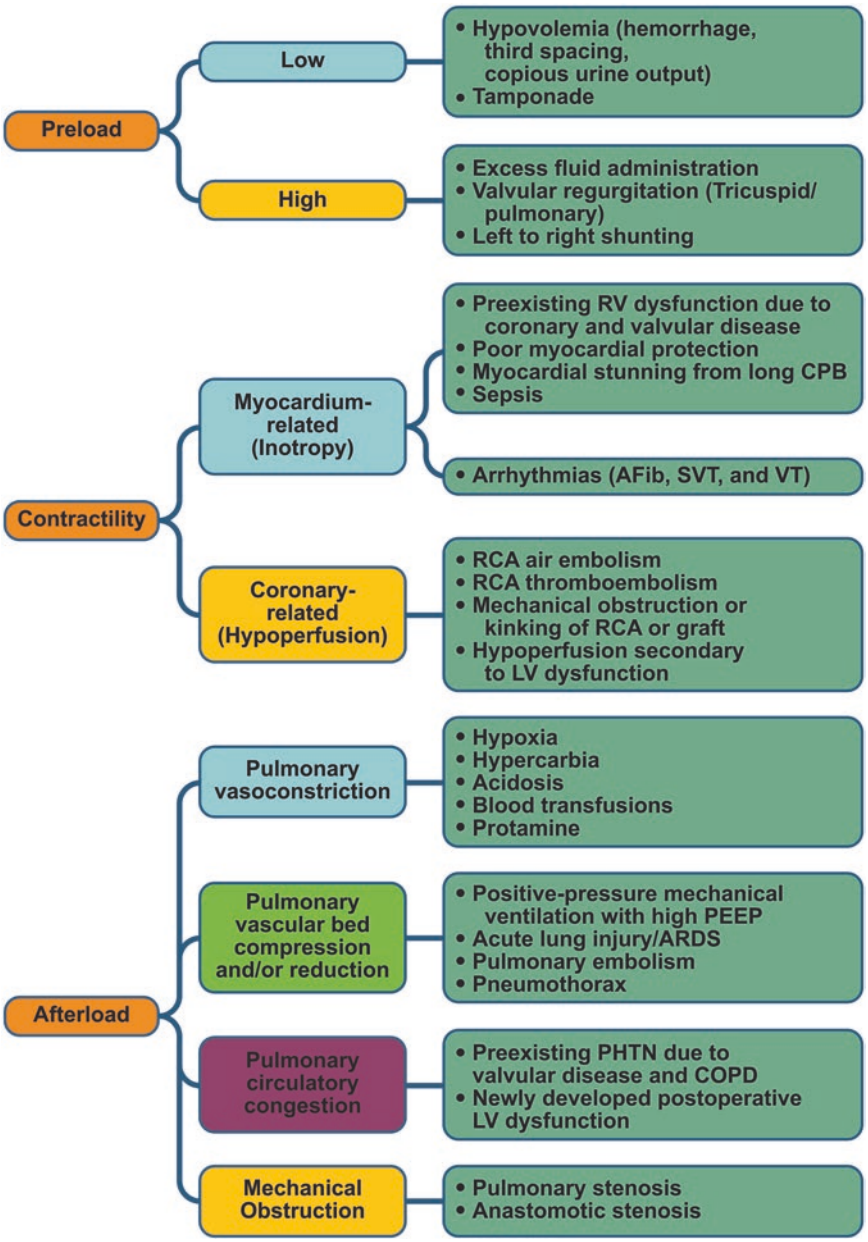

Fig. 30.2 Etiologies of posttransplant right ventricular (RV) failure. RV failure following transplant is generally related either to dysregulation of preload, impaired contractility due to intrinsic myocardial dysfunction or insufficient coronary flow, or excess afterload causes by left ventricular dysfunction, pulmonary vasoconstriction/hypertension, or valvular/anastomotic narrowing (Adapted from Itagaki S et al. Semin Cardiothorac Surg 24:188)

Decreased contractility in RV failure is considered to be due either to impaired inotropy or impaired myocardial perfusion. Impaired inotropy can be due to myocardial stunning from ischemia-reperfusion injury, mechanical trauma, and donor or recipient sepsis [35, 36]. Perfusion to the myocardium of the right ventricle can be compromised by impaired inflow to the right coronary system, which can be caused by air embolism or thromboembolism of the right coronary artery (RCA), kinking of the RCA due to extrinsic compression or problems with allograft positioning at implantation, and impaired global coronary perfusion due to LV dysfunction. Impaired RV contractility is managed primarily with inotropes, such as dobutamine, milrinone, and isoproterenol. Isoproterenol is customarily used for several days after OHT for its positive chronotropic effects, although there are no prospective studies comparing its effectiveness in this regard to other inotropes [37, 38].

Right Ventricular Afterload and Pulmonary Hypertension

Right ventricular afterload is dictated by the pulmonic valve and the resistance of the pulmonary vascular bed. Pulmonary vasoconstriction, which can elevate pulmonary vascular resistance (PVR) can be caused by hypoxia, hypercarbia, acidosis, massive transfusion, and protamine administration, all of which can be common at the time of OHT [36]. Extrinsic compression or other compromise of pulmonary inflow caused by pneumothorax, massive pleural effusion, pulmonary embolus, and elevated intrathoracic pressures caused by positive-pressure ventilation with high PEEP can also increase PVR [36]. Complications associated with the PA anastomosis, such as narrowing or kinking, can create a fixed mechanical impediment to RV unloading and must be, along with the other factors listed above, avoided or corrected at the time of implantation.

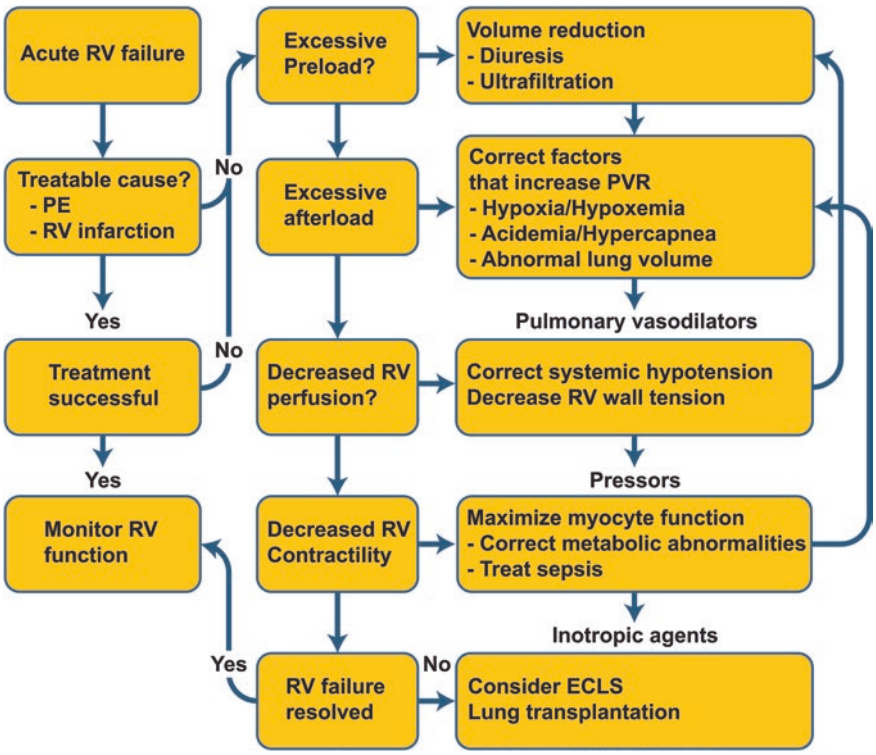

Fig. 30.3 Management of posttransplant RV failure. A suggested algorithm for the correction of RV dysfunction following transplant. In the absence of an obvious cause of RV failure that may or may not be immediately correctable, optimization of RV function should be considered in a stepwise manner, although simultaneous correction of multiple issues may be appropriate based on a particular clinical situation (Adapted from Ventetuolo CE et al. Ann Amer Thorac Soc 11: 811)

Recipient pulmonary hypertension (PH), defined as invasively measured mean pulmonary artery pressure ≥25 mmHg, is associated with high morbidity and mortality in the acute postoperative period after OHT [35]. Chronic elevation of left-sided filling pressures resulting from LV systolic dysfunction is the most common cause of pulmonary hypertension in OHT recipients [39]. Other common causes of pulmonary hypertension include chronic hypoxia (e.g., COPD, sleep apnea, and developmental/interstitial lung disease), chronic pulmonary thromboembolic disease, and secondary effects of many systemic illnesses, such as chronic kidney disease, sarcoidosis, and hemolytic anemias. Pulmonary arterial hypertension, which can be idiopathic or associated with other comorbid conditions such as scleroderma or portal hypertension, is rare in OHT recipients.

Parameters such as transpulmonary gradient (TPG, mean PA pressure-mean pulmonary capillary wedge pressure, mmHg) and pulmonary vascular resistance (PVR, $\frac{80 \cdot \text{TPG}}{\text{Cardiac Output}}$, $\frac{\text{dyn} \cdot \text{sec}}{\text{cm}^5}$), which is frequently described in Wood units ($\frac{\text{PVR}}{80}$), are generally obtained with the use of a PA catheter and are useful in characterizing the severity of pulmonary hypertension [40]. At the time of measurement, patients are treated with short-acting pulmonary vasodilators to determine the reversibility of their PH. Nonreversible PH is predictive of early and late mortality after OHT because of the attendant risk of RV failure. It is generally agreed upon that a resting PVR > 5 Wood units is a contraindication to OHT, although, while mortality in this setting is strongly linked to increasing severity of PH, no threshold level of PVR is absolutely predictive of RV failure [40, 41]. Patients with PH in whom PVR can be reduced to ≤2–3 Wood units with the use of inhaled or intravenous pulmonary vasodilators prior to OHT demonstrate a mortality risk essentially equivalent to heart recipients without preexisting PH [42–45]. There may, however, be an elevated risk of post-op RV failure, and patients who have residual PH after transplant may have decreased long-term survival [42, 43].

Implantable long-term left ventricular assist device (LVAD) therapy has been used to ameliorate fixed pulmonary hypertension in patients with end-stage heart failure being considered for OHT [46–48]. Maximum benefit appears to be reached by 6 months of therapy, with decreases in TPG and PVR predicting the greatest mortality benefit after OHT compared to patients who did not receive pretransplant MCS [46, 47].

Postimplantation RV failure is commonly recognized in the operating room based on the presence of a distended and hypokinetic RV, underfilling of the LV, and/or elevated PA pressures; these can be detected by transesophageal echocardiography, direct visualization, and data from the PA catheter [49]. A low threshold should be held for the initiation of pulmonary vasodilator therapy, either with the use of either inhaled nitric oxide or prostacyclin, which are equally efficacious in this setting [50]. Both of these medications require gradual weaning because of the potential for rebound PH with rapid withdrawal of therapy. Sildenafil, commonly started either before or in the days following transplant, is also effective in combating recipient PH [51]. Slow (days to weeks) weaning of inotropic medications such as milrinone and/or dobutamine and efforts to minimize PEEP in the postoperative period can also be important adjuncts following transplantation in patients with pulmonary hypertension and/or any evidence of RV failure [36].

Mechanical Circulatory Support

Frequently, mechanical circulatory support (MCS) is required in the management of posttransplant RV failure that is refractory to maximal medical therapy. IABP can be useful in the setting, with one series demonstrating near-immediate improvement in systemic and right-sided hemodynamics following IABP insertion with durable response and pump removal after an average of ~44 h of therapy [52]. More severe cases of posttransplant RV failure have required the use of right ventricular assist devices (RVADs) or biventricular assist devices (BiVADs).

Multiple case reports and series from the late 1980s through 2000 report the use of extracorporeal RVAD support immediately following OHT in a total of 20 patients [53–59]. The most common indication for MCS in this aggregate cohort was recipient pulmonary hypertension. Outcomes in these studies were almost universally poor; only three studies reported a total of four patients who survived to discharge [53–55]. Of the patients that died, nine were able to be weaned from RVAD support (56 %) before death. The most common causes of death among all non-survivors were sepsis, multisystem organ failure, and hemorrhagic complications [53, 54, 56–59].

In 2003 Kavarana et al. described a series of 20 heart recipients who received postoperative MCS, of whom 14 required either RVAD or BiVADs. Consistent with prior studies, the most common indication for support was recipient pulmonary hypertension. Of all RVAD/BiVAD recipients in this study, only six (43 %) could be weaned from support, and two of those patients went on to die of multisystem organ failure. Of those who did not wean, the most common causes of death were intraoperative arrest, refractory heart failure, and sepsis [9]. More recently, Klima et al. reported in 2005 a series of 35 patients who met criteria for severe RV failure following OHT and 15 of these patients received some combination of RVAD, ECMO, and IABP; no mortality benefit was realized from the use of MCS in this cohort [35].

Overall, the need for MCS for RV failure following heart transplantation portends extremely high mortality. Although recovery to discharge is possible, including after as long as 80 days of RVAD therapy in one case report, the incidence of fatal complications is extremely high in this cohort, and a frank and thoughtful discussion should occur between all involved providers and loved ones before this level of support is initiated [60].

Heart Size Mismatch

Donor-recipient size matching is an established component of the organ allocation process. Traditionally, a weight difference of <20 % has been sought in pairing donors and recipients for OHT, but outcome data over the last two decades have undermined this practice. It has been demonstrated previously that weight and heart size are not meaningfully correlated [61, 62]. A retrospective, single-center study in the early 1990s demonstrated no increase in mortality with a weight differential up to 30 % and another such study demonstrated increased mortality from undersized donors only in recipients who were listed United Network for Organ Sharing (UNOS) status I for transplant [63, 64].

A multicenter retrospective analysis of UNOS data in 2008, the largest study of this question to date, demonstrated that donor-recipient weight differentials of >20 % did not affect survival, except in a few special circumstances. The implantation of undersized hearts in recipients with significant pulmonary hypertension negatively affected survival, particularly when a female donor was paired with a male recipient. Interestingly, no survival advantage was conferred by the use of oversized allografts in recipients with PH [65]. Recent data from the Multi-Ethnic Study of Atherosclerosis (MESA) study have shown that heart size does not depend only on weight but also on height, age, and sex, suggesting that it may be more appropriate to size match donors and recipients on these data in lieu of weight alone [66, 67].

Rejection

Hyperacute Rejection

Immediate allograft failure caused by binding of preexisting recipient antibodies to donor vascular endothelium by preexisting recipient antibodies is known as hyperacute rejection. This immunologic reaction occurs within minutes to hours after restoration of allograft perfusion and results in complement activation and intravascular thrombosis. Lysis of capillary endothelial cells leads to disruption of vessel integrity, loss of vascular contents, and exposure of platelets to the underlying matrix resulting in platelet adhesion, aggregation, and local vasoconstriction due to loss of nitric oxide. This is ultimately followed by interstitial hemorrhage without lymphocytic infiltrate [68, 69]. Largely prevented by ABO and human leukocyte antigen (HLA) matching, the only therapy for this catastrophic diagnosis is emergent MCS therapy and retransplantation, although outcomes are extremely poor even if a suitable organ can be found [70].

Acute Cellular Rejection

Prior to the development of cyclosporine in the 1970s, inability to manage rejection safely and reproducibly was the primary barrier to the growth of heart transplantation following its early development [71]. Although rejection rates continue to decline, the risk of rejection remains significant, particularly in the early period following transplantation, necessitating routine surveillance for both acute cellular (ACR) and antibody-mediated rejection (AMR).

ACR is characterized by a predominantly T-cell-mediated response with infiltration of lymphocytes and macrophages into the interstitium of the allograft, which may lead to myocyte necrosis [70]. Although it can occur at any time after OHT, it occurs most commonly in the first 3–12 months after transplant. Nearly 40 % of adult heart transplant patients have one or more ACR episodes to some degree within the

Table 30.2 ISHLT biopsy grading for acute cellular rejection (ACR)

Grade 1R (mild)	Interstitial and/perivascular infiltrate with up to 1 focus of myocyte damage
Grade 2R (moderate)	Two or more foci of infiltrate with associated myocyte damage
Grade 3R (severe)	Diffuse infiltrate with multifocal myocyte damage ± edema ± hemorrhage ± vasculitis

Severity of rejection is determined by the level of cellular infiltration and myocyte damage/edema/hemorrhage
Adapted from Stewart S et al. *J Heart Lung Transplant* 24: 1710

first month, and over 60 % experience one or more ACR within 6 months. At 1 year only one third of patients remain free of ACR. Within the first year, about 30 % of patients will have rejection which will require adjustment of immunosuppressive therapy. Risk of ACR beyond 1 year is low and does not appear to change over time [72, 73].

Donor risk factors for ACR within 1 year of transplant include female sex, positive CMV serology, brain death, and ischemia-reperfusion injury. Brain death and ischemia-reperfusion are thought to increase donor antigen expression, which may promote ACR. Recipient risk factors include female sex, young age, African-American race, increased HLA mismatching, prior infection following transplant, and recent (separate) episodes of rejection [74]. The development of acute rejection requiring treatment predicts a higher incidence of cardiac allograft vasculopathy and long-term mortality [75, 76].

In part because of the allograft denervation inherent to the transplant process, the presentation of ACR can be protean in nature, manifesting as any combination of fever, leukocytosis, mild hypotension, or other vague systemic symptoms [77]. In rare cases, the presentation is much more dramatic, with patients demonstrating severe heart failure, refractory hypotension, or circulatory collapse [69]. The inconsistent presentation of ACR makes endomyocardial biopsy (EMB) the gold standard for diagnosis. The biopsies are obtained percutaneously, usually from the interventricular septum, with a dedicated bioptome passed through the internal jugular or femoral vein [69]. Pathologic analysis of the biopsy specimens is used to grade the severity of ACR in accordance with ISHLT guidelines, which were most recently updated in 2004. ACR is graded on a scale from 0R (no evidence of ACR) to 3R (severe ACR) based on the level of cellular infiltrate and tissue destruction (myocyte damage, edema, hemorrhage, and vasculitis) (Table 30.2) [78].

OHT recipients undergo routine surveillance endomyocardial biopsy to identify early rejection. The timing of biopsies following transplant varies by institution, but they are generally performed weekly for the first month after surgery, biweekly for the second month, monthly until 6 months post-OHT, and then quarterly until the end of the first year. There are no data to support the efficacy of a particular biopsy regimen in all recipients, although more aggressive screening, particularly in years 2–5 after transplant, in certain high-risk groups has been demonstrated to have some mortality benefit. There does not appear to be benefit from screening biopsy beyond 5 years after transplant in any population [79]. Noninvasive screening for ACR based on genetic screening is being increasingly used; however, it is not recommended for routine clinical use by the guidelines.

The treatment of ACR is guided by the acuity and timing of clinical presentation and grade of rejection observed in biopsy specimens (Fig. 30.4). Pulse-dose corticosteroid therapy, either oral or intravenous, is recommended in all patients with ACR confirmed by biopsy, regardless of grade [80]. In asymptomatic patients, additional therapy may consist only of augmentation of the current immunosuppression regimen. For patients presenting with allograft dysfunction (ranging from mild heart failure to cardiogenic shock) related to rejection, the addition of cytolytic immunosuppressive therapy with antithymocyte globulin (ATG) may be considered. Supportive hemodynamic measures, including inotropes, IABP, or mechanical circulatory support with ventricular assist devices or ECMO, should be initiated as appropriate depending on the severity of cardiac dysfunction [80]. Other adjunctive immunosuppressive measures, including plasmapheresis, intravenous immune globulin, and antimetabolite and/or radiation therapy, may be required in severe cases. Repeat EMB is commonly employed to monitor resolution. Mortality in this cohort can be high despite aggressive therapy [81].

Acute Antibody-Mediated Rejection (AMR)

Promoted by recipient HLA sensitization prior to transplant, AMR is a process in which preexisting donor antibodies target the endothelium of allograft arterioles and capillaries, leading to a small-vessel vasculitis [68, 81]. Commonly (~70 %) presenting within a month after transplant as allograft dysfunction in the absence of evidence of acute cellular rejection, AMR is a significant risk factor for chronic allograft vasculopathy (CAV) and increased short-term and long-term mortality [68, 82, 83]. Management is based on the severity of presentation. Asymptomatic AMR does not affect long-term survival following heart transplant but does confer a greater risk of CAV [81, 84]. Patients presenting with hemodynamic compromise and biopsy evidence of AMR, however, require more aggressive treatment, often involving inotropes and/or mechanical circulatory support and mitigation of the antibody-mediated injury to the allograft, including high-dose corticosteroid or cytolytic pharmacotherapy, plasmapheresis, immune apheresis, or IVIg [69, 80]. Rituximab, bortezomib, or anticomplement antibodies are also potentially useful as secondary therapy [29].

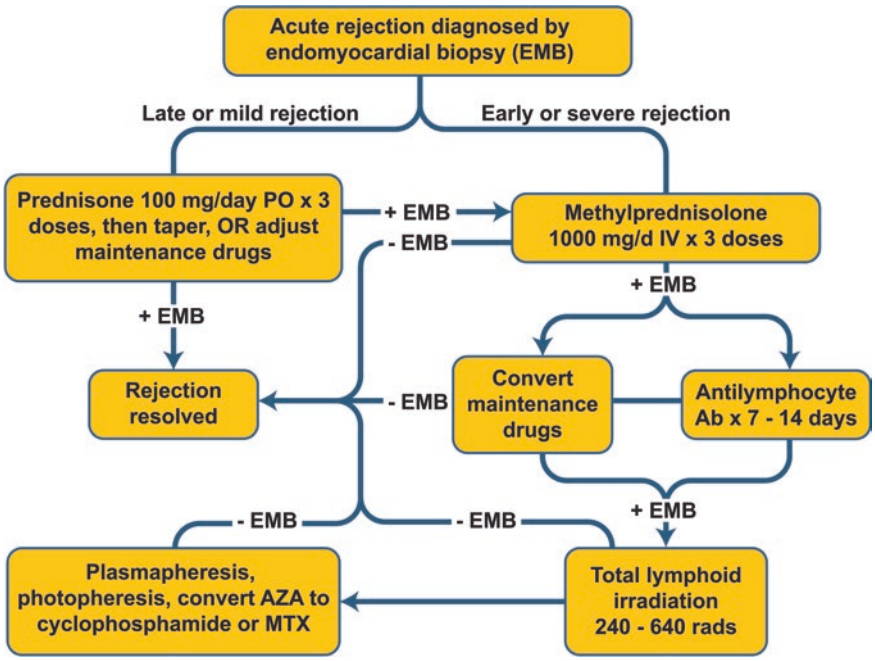

Fig. 30.4 Management of acute rejection (ACR) following heart transplantation. A suggested algorithm for the management of ACR. Management varies by institution but generally varies by acuity and timing of presentation. *Ab* antibody, *AZA* azathioprine, *MTX* methotrexate (Adapted from Chiu P et al. Sabiston and Spencer Surgery of the Chest, 2015)

Infection

As is the case with all solid organ transplant recipients on chronic immunosuppression, infectious complications are a major cause of morbidity and mortality in OHT recipients. Although the overall mortality from infection in the first year following transplantation is <5 %, it accounts for approximately 20 % of deaths in the first year following transplant. The risk of infection is greatest in the first 3–4 months after transplant; bacterial infections are the most common, followed by viral and fungal (Fig. 30.5) [85]. The immunosuppressed state of heart transplant recipients can obscure the presentation of even severe infections, so the timely and aggressive evaluation of even mild fever, leukocytosis, tachycardia, or vague patient complaints is mandatory. A low threshold should be held for the initiation of parenteral antibiotic/antiviral/antifungal therapy. The risk of infection of all types is increased in OHT recipients, but mortality is highest in patients with fungal and protozoal infections [85, 86]. The most critical transplant-specific risk factors for post-transplant infection include advanced recipient age, the need for mechanical ventilation or a VAD at the time of transplantation, induction therapy with OKT3, and donor CMV seropositivity [85].

The most common infections in the first month after transplantation are bacterial, with the most common being pneumonia (35 %) and urinary tract infections (24.4 %), followed by bloodstream (7.7 %) and subcutaneous (7.3 %) infections [87]. Bloodstream and subcutaneous infections are dominated by *Staphylococcus* and *Streptococcus* species. Most pneumonias in this setting are caused by Gram-negative bacteria, with *Legionella pneumophila* (24 %) and *Pseudomonas aeruginosa* (19 %) being the most common; *E. coli* is the offending pathogen in ~8 % of cases. Urinary tract infections

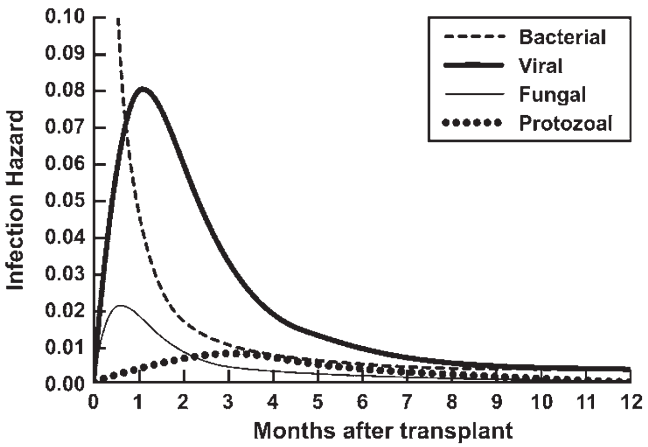

Fig. 30.5 Time-dependent hazard of infection after heart transplant by type. Infection risk is greatest in the first 3–4 months after transplant. The most common etiologies are bacterial and viral, followed by fungal, which also has a low overall incidence but an early peak (Adapted from Kouchoukos NT et al. Kirklin/Barratt-Boyes Cardiac Surgery, 2013)

are usually Gram-negative (*E. coli*, 63 %), but Gram-positive (*Enterococcus* spp., 17 %) infections are also common [87].

Although it is less common than those listed above, heart transplant patients are at significant risk for surgical site infection (SSI), a category that includes both superficial infection and deep sternal wound infection (DSWI), a devastating complication exacerbated by the immunosuppressed state of the recipient [88]. Risk factors for SSI in all cardiac surgery patients (diabetes, reoperation, increased BMI) apply to heart transplant recipients as well, but these patients may also suffer malnutrition of chronic illness, renal insufficiency,

and preoperative implantable VAD therapy, all of which increase the risk of SSI [85, 88]. Other reported risk factors include nonwhite recipients and prolonged time on cardiopulmonary bypass. There is also evidence to suggest that the use of mTOR inhibitors such as sirolimus and everolimus increases the risk of SSI because of their detrimental effects on cells participating in angiogenesis, proliferation of myofibroblasts, and other wound healing processes [88].

SSIs of all types are present in 8–15 % of recipients. Superficial wound infection affects between 4 and 16 % of recipients, while DSWI is present in anywhere from 2.4 to 35 %, with sternal dehiscence occurring in 12.5–25 % of patients [88, 89]. A variety of Gram-positive (*Staphylococcus* spp., *Enterococcus* spp.), Gram-negative (*Escherichia coli*, *Acinetobacter* spp.), and fungal (*Candida* spp., *Nocardia* spp., *Legionella* spp., and *Aspergillus* spp.) organisms have been implicated in superficial and deep sternal wound infections [85, 87, 90]. In series of 149 consecutive heart transplants, recipients with DSWI (8.7 %) suffered a hospital mortality of 31 %, compared to only 8 % in recipients without DSWI [89]. Any concern for SSI should prompt an immediate pursuit of source control, either by local debridement and wound care or, in the case of DSWI with mediastinitis, operative re-exploration and debridement with cultures, drainage with or without an open chest, and chronic targeted antimicrobial therapy [85, 88].

Invasive fungal infection also occurs most commonly in the first month after surgery, although they can occur at any time following OHT and carry a mortality in excess of 30 % [85]. The most common types are pneumonia (41 %), and disseminated infections (30 %), with *Aspergillus* and *Candida* species being the main pathogens in both cases. *Candida* can also be isolated from sternal wound and bloodstream infections, as described earlier. Infection with *Cryptococcus neoformans* has also been observed both in the CNS and in disseminated forms [85]. Finally, *Pneumocystis carinii* is a common cause of pneumonia in all immunocompromised patients, but it is not known whether or not these infections are primary or reactivation phenomena. For this reason pharmacologic prophylaxis against *Pneumocystis* infection with chronic oral sulfamethoxazole-trimethoprim therapy is standard in all heart transplant recipients [85].

The chief viral pathogen affecting all transplant recipients, including heart recipients, is cytomegalovirus (CMV), particularly in the first 3 months following transplant. CMV infection occurs in between 36 and 100 % of all transplant recipients and is symptomatic in 11–72 % of patients if preventative therapy is not administered [90]. Risk factors for posttransplant CMV infection include the pairing of an allograft from a donor with CMV seropositivity with a CMV-negative recipient and the use of induction immunosuppressive therapy with monoclonal antibodies or antithymocyte globulin (ATG). Disseminated infection is most common and may present as a systemic febrile illness or an asymptomatic rise in CMV titers. Tissue-invasive infections may also be localized in 30 % of patients with CMV infection and present with appropriate symptomatology in the lungs (radiographic abnormalities, hypoxia, and shortness of breath), gastrointestinal tract (diarrhea, ulceration, GI bleeding), liver (hepatitis), or eyes (chorioretinitis with or without eventual blindness) [85, 88, 90].

CMV infection has been demonstrated to increase the long-term risk of allograft vasculopathy and can be deleterious to systemic vascular endothelial and renal function in heart transplant recipients [91]. Heart transplant recipients at high risk for CMV infection (donor positive/recipient negative or recipient positive) will initiate a course of prophylactic antiviral therapy with ganciclovir or valganciclovir starting within 24–48 h after transplant and lasting for a minimum of 3 months [80].

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Late Complications Following Heart Transplant

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_31

Abbreviations

HT - Heart transplantation
CAV - Cardiac allograft vasculopathy
IST - Immunosuppressive therapy
ECMO - Extra corporal membrane oxygenation
TAH - Total artificial heart
DSA - Donor-specific antibodies
IVUS - Intravascular ultrasound

Introduction

Late complications following heart transplantation (HT) have been a significant barrier to improvement in longevity of HT recipients. While improvement in surgical techniques has reduced perioperative morbidity and mortality and adoption of virtual donor-recipient cross-matching and new strategies for identifying and treating the hypersensitized recipients have reduced the incidence of hyperacute rejection, late complications of HT, including allograft rejection and vasculopathy, infection, and malignancy, have remained the major cause of morbidity and mortality among HT recipients (Fig. 31.1). Most late complications following HT are somehow linked to the lack of ideal immunosuppressive balance. Treatment remains rudimentary with little guidance from the literature regarding tailoring therapy except in the case of an adverse event. From this perspective, late complications following HT can be divided into three major categories:

1. Complications related to the lack of effective immunosuppressive therapy (IST), including acute and chronic rejection, as well as cardiac allograft vasculopathy (CAV), a condition that is often regarded as a manifestation of chronic rejection.
2. Complications related to the lack of ideal immunosuppressive balance, including susceptibility to infection and malignancy. These complications result from nonspecific effects of IST on the immune system beyond allograft protection. This is compounded by the inability to adequately monitor response to therapy.
3. Complications related to side effects of IST, including a wide range of adverse effects of individual drugs routinely used in IST such as renal dysfunction, neuropathy, osteoporosis, hypertension, diabetes mellitus, and anemia.

In this chapter, we will review common late complications after transplant and their management.

Allograft Rejection

Despite advances in IST, rejection continues to be a major challenge in HT recipients, associated with increased morbidity, mortality, and cost. It is estimated that 25 % of HT recipients experience at least one episode of rejection during the first posttransplant year and 5 % of these rejections are severe and associated with hemodynamic compromise [1]. Rejection can be antibody-mediated, including hyperacute rejection and delayed antibody-mediated rejection (AMR), or cell-mediated. The cumulative effect of repeated episodes of rejection, if recovered, ultimately results in graft failure or re-transplantation.

Although allograft rejection is typically a relatively early phenomenon occurring in the first year of transplant, it is becoming increasingly recognized later after transplant, possibly due to improved monitoring surveillance strategies. In the pediatric HT population, 25 % of those who survive the first year experience rejection greater than 1 year after transplant [2]. Late recurrent rejection in adults appeared to be related to the number of episodes of rejection during the first year and history of cytomegalovirus (CMV) infections [3]. The true incidence of late rejection is unclear since definitions have evolved over time and earlier studies described mainly cellular rejection. Nevertheless, late rejection appears to occur infrequently, in 3.5–5 % of surveillance endomyocardial biopsies (EMBs) after during years 2–7 [4]. In a more contemporary study, Loupy reported that very late rejection,

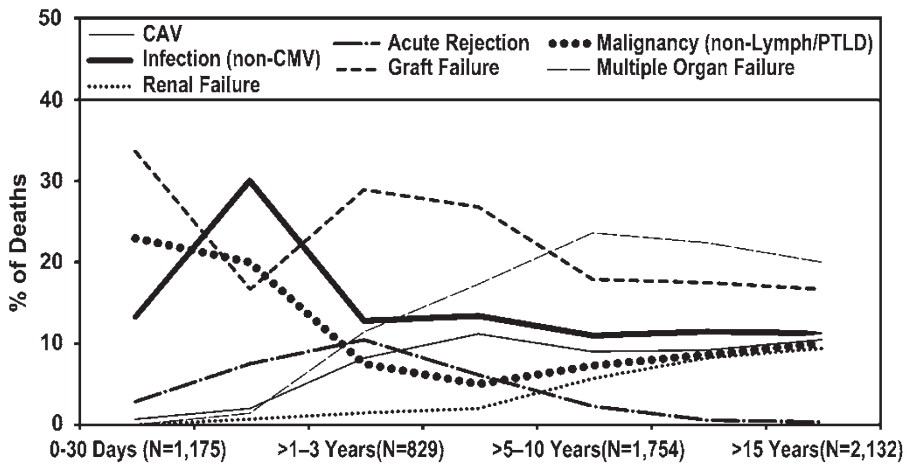

Fig. 31.1 Trends in immunosuppression after heart transplantation. Modified from the *American Journal of Transplantation*, 1998–2012, Volume 14, Issue S1, pages 113–38, 28 DEC 2013

defined as occurring >7 years after transplant, was associated with significant microvascular injury, complement deposition, and CAV [5].

Cardiac allograft rejection is often initially asymptomatic until it presents with graft dysfunction. Therefore, early diagnosis relies on screening and surveillance testing. EMB remains the mainstay for the diagnosis of allograft rejection. Most transplant centers perform frequent scheduled EMBs during the first posttransplant year (weekly during the first month, biweekly at 2–3 months, monthly at 3–6 months, and bimonthly at 6–12 months). While most centers continue annual EMBs at 2–5 years posttransplant, the benefit of continuing surveillance EMBs beyond the first year in asymptomatic patients with no prior history of rejection remains unclear [4, 6]. Noninvasive testing is promising and may prove to be a useful first-line screening tool, reducing the need for repeated EMBs. Gene expression profiling test has been shown to have high negative predictive value for acute cellular rejection and could be used to rule out rejection in low-risk patients with no prior history of rejection [7]. Evaluation of donor-specific antibodies may be useful in evaluating for AMR; however, the significance of asymptomatic elevation of DSAs in the absence of graft dysfunction is unclear.

Treatment is warranted for any degree of AMR or acute cellular rejection associated with graft dysfunction. Treatment should be initiated in acute graft dysfunction when rejection is clinically suspected even before histological diagnosis is established. However, it is unclear whether treating asymptomatic AMR is beneficial despite the evidence linking asymptomatic AMR with the development of CAV and with poor outcome [8, 9]. Treatment of asymptomatic AMR is advised in the presence of positive DSA or CAV [10]. Treatment is recommended for moderate and severe asymptomatic cellular rejection. Protocols used for the treatment of allograft rejection vary across transplant centers and will not be discussed here.

Cardiac Allograft Vasculopathy

CAV is perhaps one of the most vexing medical complications facing transplant recipients. This is in large part due to the fact that there are no reliable means to determine which patients develop clinically significant CAV and the lack of effective treatments for the most malignant forms of CAV. CAV is a distinct entity seen in HT recipients and differs from atherosclerotic coronary artery disease in several aspects. CAV is characterized by diffuse intimal proliferation manifesting in lesions that are diffuse and circumferential and involve distal portions of the coronary artery [11, 12]. CAV is very common in HT recipients. It is estimated that 7.1 % of HT survivors at 1 year and 52.7 % of HT survivors at 10 years have CAV and/or late graft failure [13]. CAV and late graft failure are responsible for one third of death of HT recipients after the fifth transplant year [13].

There are multiple theories regarding the etiology and pathophysiology of CAV. The *response-to-injury* theory proposes that CAV is a result of an ill response to endothelial injury of the transplanted heart caused by both immunologic and non-immunologic insults [14]. Exposure of foreign major histocompatibility antigens of donor endothelial cells to recipient dendritic cells results in T cell activation, triggering a cascade of inflammatory cytokines and growth factor release and activating macrophages and lymphocytes, which in turn secretes various growth factors leading to vascular smooth muscle cell proliferation and intimal hyperplasia seen in CAV [14]. Non-immunologic insults include, but not limited to, ischemia, reperfusion injury, donor age, donor brain death, cytomegalovirus infection, and recipient traditional risk factors such as diabetes, hypertension, and dyslipidemia [15]. Modifications of these non-immunological factors have shown benefit in reducing the incidence and progression of CAV.

Diagnosis of CAV is challenging. Due to allograft denervation, most patients with CAV do not experience angina. Clinically evident acute myocardial infarction rarely occurs, as CAV preferentially affect medium- and small-size vessels. The first clinical manifestation of CAV is often graft dysfunction and graft failure presenting with congestive heart failure, arrhythmia, or sudden cardiac death [15]. Therefore, it is imperative to establish early diagnosis of CAV before it is clinically evident. Coronary angiography, the gold-standard test for the diagnosis of CAV, is routinely performed in transplant recipients (usually at baseline and annually thereafter). The sensitivity of coronary angiography is limited in detecting CAV lesions due to their diffuse, circumferential nature and their involvement of distal and small vessels [16]. The adjunctive use of intravascular ultrasound (IVUS) to measure the maximum intimal thickness (MIT) significantly improves the sensitivity of coronary angiography in detecting CAV during its early stages [17]. Both coronary angiography and IVUS provide significant prognostic information in HT recipients. The absence of angiographically significant lesions on coronary angiogram is a significant predictor of cardiac event-free survival [18]. IVUS findings that predict poor outcome include MIT > 0.5 mm and mean intimal thickness >0.3 mm, and change in MIT by more than 0.5 mm at 1 year is associated with adverse cardiovascular events even with normal coronary angiogram [19–21]. Other adjunctive measures that have been used during coronary angiography include the fractional flow reserve (FFR), the thrombolysis in myocardial infarction frame count (TFC), and the index of microcirculatory resistance (IMR). All these measures are shown to predict the development of CAV and to convey poor outcome [22].

Noninvasive tests with various sensitivities and specificities are often used for screening and surveillance of CAV when contraindications to coronary angiogram are present. Dobutamine stress echocardiography and myocardial perfusion imaging can detect obstructive CAV, and its positivity predicts adverse outcome [23, 24]. Cardiac magnetic resonance

(CMR) has evolved in the past decade as a promising tool in detecting myocardial ischemia (stress CMR) as well as myocardial scarring (late gadolinium enhancement (LGE)) and extracellular fibrosis (T1 mapping). LGE in cardiac allograft is frequently seen in patients with CAV and indicates subclinical myocardial infarctions [25]. Studies are ongoing to determine the prognostic values of LGE on CMR of HT recipients. Multi-slice computed tomography (CT) is evolving as a noninvasive imaging modality for evaluating the presence of obstructive CAV. One study of 102 patients reported a negative predictive value for angiographically significant CAV (lesions with >50 % stenosis) of 96.6–99.7 %. However, the positive predictive value was low (<45 %) when compared to invasive coronary angiography [26].

Several blood markers and tissue markers, reflecting endothelial and vascular injury, are elevated in HT recipients with CAV and those at an increased risk of developing CAV [27]. Among these markers are C-reactive protein (CRP), triglycerides to HDL ratio, brain natriuretic peptide (BNP), high-sensitivity troponin T, circulating micro-ribonucleic acid (micro-RNA) particles, von Willebrand factor (VWF), circulating apoptotic endothelial cells and endothelial microparticles, and high gene expression profile (AlloMap) analysis.

The mainstay in managing CAV is primary and secondary prevention. Several interventions targeting risk factors known to be involved in the pathophysiology of CAV have shown to reduce the incidence and progression of CAV. These interventions must be applied early posttransplant as the majority of intimal thickness occurs in the first year. Optimal management of traditional cardiovascular risk factors including diabetes mellitus, hypertension, and dyslipidemia is associated with survival benefit and is recommended by the ISHLT guidelines [28]. The use of hydroxymethylglutaryl-CoA reductase enzyme inhibitors (statins) provides benefits beyond cholesterol lowering, including anti-inflammatory effects, and inhibition of DNA synthesis and, hence, the replication of CMV [29]. Statins have been shown to reduce the incidence of CAV and to improve long-term outcome of HT recipients [30, 31]. Both treatment of established CMV infection and CMV prophylaxis have been shown to improve endothelial function and reduce the progression incidence and progression of CAV [32, 33]. The use of mammalian target of rapamycin (mTOR) inhibitors (both sirolimus and everolimus) has been shown to reduce the incidence of CMV infection, improve endothelial function (as measured by brachial artery flow-mediated dilation), and reduce the progression of CAV [34, 35]. In addition to above, measures to minimize ischemic and operative injury of the allograft have been shown to improve survival and reduce the incidence of CAV [36].

Revascularization for CAV has not shown any mortality benefit and is done largely on a palliative basis [37]. Percutaneous coronary intervention (PCI) is the mainstay of revascularization. In-stent restenosis rate is significantly higher than what is seen in native coronary artery disease, up to 53 % at 1 year and 69 % at 5 years [38]. This is attributed to the diffuse nature of the disease requiring the use of longer and narrower stents as compared with native coronary artery disease (CAD). Contrary to the evidence in native CAD, it is not clear if the use of drug-eluting stents (DES) reduces the incidence of in-stent restenosis or target lesion revascularization [39]. Surgical revascularization is rarely done due to technical challenges (diffuse disease, prior sternotomies) and prohibitively high operative morality (up to 80 %) [40]. Cardiac re-transplantation remains the only definitive therapy for patients with severe CAV resulting in graft failure.

Posttransplant Malignancy

Malignancy is typically a late manifestation after HT occurring in 2.7 % at 1 year and 28.7 % at 10 years posttransplantation [41]. The incidence of new malignancy among solid organ transplant recipients is increased by two- to fourfold, with cancers of the lymphoid system and skin and cancers linked to viral etiology having the highest excess absolute risk [42]. Overall incidence of new malignancy among HT recipients is reported to be 14.3 per 1000 persons/year, with lung cancer being the most common, followed by prostate cancer, posttransplant lymphoproliferative disorder (PTLD), and skin cancer [43]. Malignancy occurs late posttransplant, with mean time to diagnosis of 1267 days. Age older than 39 years, male sex, hepatitis B virus (HBV)-positive recipient status, and non-Hispanic race were associated with increased risk of posttransplant malignancy [43]. Recipients using cyclosporine A (CsA) also have an increased risk of posttransplant malignancy, while switching to or adding an mTOR inhibitor to their immunosuppression regimen reduces the risk of malignancy [44]. The use of statin in HT recipients lowers the incidence of malignancy based on retrospective data of a single center study of 255 patients (cumulative incidence of malignancy over 8 years (34 % vs. 13 %)) [45]. Cancer is a major cause of late mortality in HT recipients surviving the first year posttransplantation. It accounts for 25 % of all deaths at 5 years [46, 47].

Recurrence of pretransplant malignancy after HT is also common. While patients with active cancer are typically excluded from transplantation, there is no clear consensus on the optimal cancer-free waiting period before a patient with prior history of cancer can be listed and may depend on the type of malignancy. A recent study showed that the rate of posttransplant recurrence of pretransplant malignancy was 63 %, 26 %, and 6 % for patients who were cancer-free for less than 12 months, 12–60 months, and more than 60 months, respectively [48].

Skin Cancer

The incidence of all types of skin cancer is drastically increased in HT recipients. Population studies have shown 84-fold, 65-fold, tenfold, and 3.4-fold increase in the incidence of Kaposi sarcoma, squamous cell carcinoma, basal

cell carcinoma, and malignant melanoma, respectively, among all solid organ transplant recipients [49]. The higher incidence of skin cancer among transplant recipients is largely attributed to IST, which results in reduced tumor surveillance by the immune system [49, 50]. In addition, individual immunosuppressants contribute directly to the incidence of skin cancer. Calcineurin inhibitors (CNIs), such as cyclosporine and tacrolimus, increase the incidence of squamous cell carcinoma by increasing the levels of growth factors such as transforming growth factor beta (TGF-beta) and vascular endothelial growth factor (VEGF) [44, 51]. Studies have shown that using mTOR inhibitors, such as sirolimus and everolimus, reduces the incidence of SCC in HT recipients [52]. Azathioprine increases photosensitization to UVA, which causes direct DNA damage [53]. Azathioprine is also associated with increase in the incidence of tumor-suppressor gene p53 mutations [54]. The ISHLT guidelines for the care of HT recipients recommend close surveillance, patient education on preventive measures, and annual dermatological examination (level 1C) [28].

PTLD

PTLD is a wide spectrum of lymphoid disorders, ranging from indolent polyclonal lymphoid hyperplasia to aggressive lymphomas [55]. PTLD occurs in up to 5 % of solid organ transplant recipients and in 0.5–1 % of hematopoietic stem cell transplant recipients [56]. Multiple risk factors of PTLD have been identified, including viral infections and recipient-specific characteristics. Epstein-Barr virus (EBV)-seronegative recipients who seroconvert after transplant due to acute exposure or as a result of receiving allograft from an EBV-seropositive donor have sixfold increase in the risk of developing PTLD [57]. Likewise, CMV-seronegative recipients who seroconvert after transplant have sevenfold increase in the risk of developing PTLD [58]. Hepatitis C virus and human herpes virus-8 infection are also associated with increased risk of PTLD, especially in hosts who have EBV infection [58]. The risk of PTLD is also increased in patients with extreme age (<10 and >60 years), patients with history of pretransplant malignancy, and patients with various genetic variations such as polymorphisms in certain cytokine genes, including interleukin-10 (IL-10), interleukin-6 (IL-6), and interferon-gamma (IFN-γ), and polymorphism in certain donor and recipient human leukocyte antigens (HLAs) [59, 60]. More than 90 % of PTLDs are B cell type. Two thirds of B cell PTLDs are EBV-related, while only 10–15 % of T cell PTLDs are EBV-related. EBV-negative PTLDs tend to be monomorphic, diagnosed late, and less responsive to therapy [55].

Clinical manifestation of PTLD is often nonspecific. In addition to the classic B symptoms, lymphadenopathy can be present in nodal disease, while symptoms related to the organ involved are present in extra-nodal disease. Extra-nodal disease often involves the gastrointestinal tract, lungs, skin, bone marrow, and central nervous system [61].

Reduction in immunosuppression (RI) has remained the first-line therapy for PTLD for the past four decades [62]. However, response to reduction in immunosuppression alone varies, ranging between 0 and 73 %, and sustained response is only seen in 10–20 % of cases [63, 64]. Older age, late posttransplant onset of disease, the presence of B symptoms, multi-organ involvement, and EBV seronegativity are predictors of poor response to RI. Furthermore, 40 % of patients treated with RI alone developed acute graft rejection [60]. Therefore, adjunct therapy is often used in addition to RI, including rituximab, chemotherapy, radiation therapy, antiviral therapy, and immunotherapy [56]. Other therapies have also been tried, including IL-6 and IL-10 monoclonal antibodies and autologous stem cell transplant [65, 66]. Since treatment of PTLD differs from that of de novo lymphomas, the ISHLT guidelines recommend referral to a transplant center with expertise in posttransplant malignancies for the initial evaluation and therapeutic plan of patients with new diagnosis of PTLD.

Posttransplant Infection

Infection is a leading cause of death after HT, second to graft failure [67]. Although the incidence of death due to infection peaks during the first transplant year, afterward, infection accounts for approximately 10 % of deaths up to 15 years after transplant. Much attention is given to viral infections, particularly cytomegalovirus (CMV) and Epstein-Barr virus (EBV), due to the association with CAV and PTLD; however, bacterial infections remain more common than viral infections in solid organ transplant recipients [68]. In a series of 620 HT recipients, bacterial infections caused 43.6 % of infectious episodes, followed by viruses, fungus, *Pneumocystis carinii*, and protozoa. The most common site of infection was the respiratory tract [68]. Prophylaxis is routinely performed for opportunistic infections.

CMV is a major cause of morbidity and mortality in solid organ transplant. The highest risk of infection occurs when a CMV-seronegative recipient receives an organ from a seropositive donor. CMV may cause a wide spectrum of morbidity including bone marrow suppression and cytopenias, pneumonia, hepatitis, and nephritis, but perhaps most commonly seen is CMV gastrointestinal disease [69]. Furthermore, CMV may contribute to graft failure by its association with CAV [15]. Cytomegalovirus infection is associated with cardiac allograft rejection and atherosclerosis [70]. CMV promotes a pro-inflammatory environment and causes dysregulation of the NO synthase pathway. CMV typically occurs during the first 3 months if prophylaxis is not given. Both valganciclovir and oral ganciclovir have been shown to be efficacious in preventing CMV infection in high-risk seronegative recipients of organs from seropositive donors [71]. Subclinical CMV antigenemia may increase the risk of allograft rejection and CAV, and providing CMV prophylaxis has been shown to reduce the risk of both entities [33, 72].

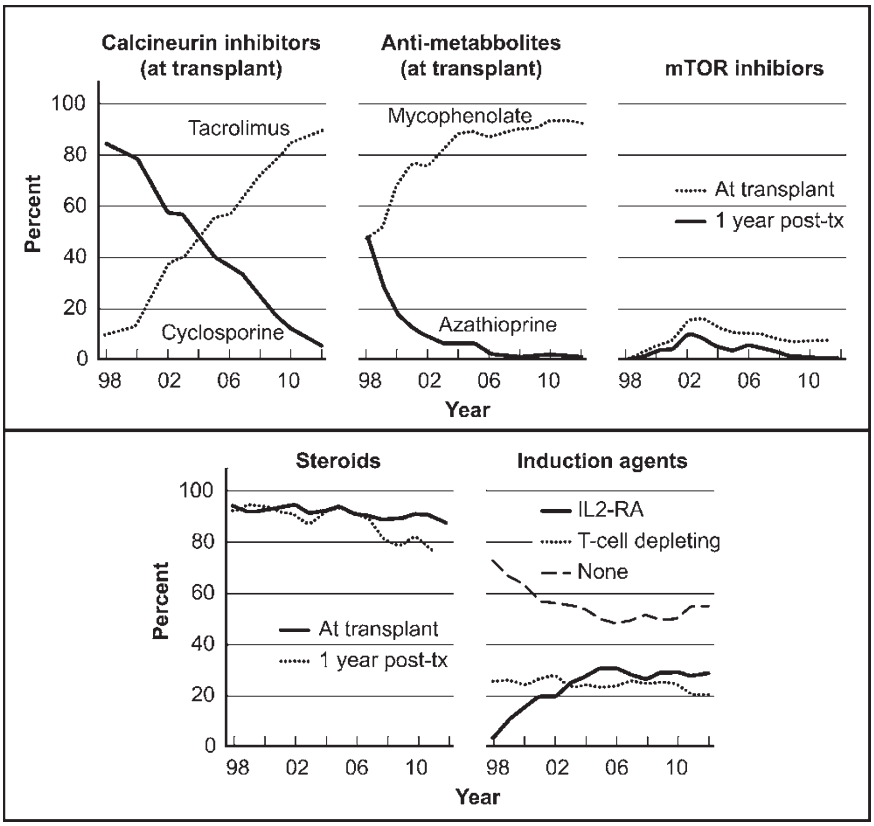

Fig. 31.2 Relative incidence of leading causes of death for adult heart transplant recipients, January 2009–June 2014. International Society for Heart and Lung Transplantation Registry. Since only leading causes of death are shown, the sum of percentages for each time period is less than 100 %. *CAV* cardiac allograft vasculopathy, *CMV* cytomegalovirus, *PTLD* posttransplant lymphoproliferative disorder. Modified from JHLT. 2015; 34(10): 1244–54

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Adverse Effects of Immunosuppressive Drugs and Comorbid Conditions After Transplant

There are four major classes of immunosuppressive drugs that are routinely used in IST: glucocorticosteroids (GCS); calcineurin inhibitors (CNIs), including cyclosporine A (CsA) and tacrolimus; antiproliferative drugs, including azathioprine and mycophenolate mofetil (MMF); and mammalian target of rapamycin (mTOR) inhibitors, including sirolimus and everolimus. Over the past 15 years, there has been significant change in the trend of use of these drugs worldwide (Fig. 31.2). These drugs are used in combination according to standardized IST regimens, which vary across transplant centers, and often modified according to patient-specific circumstances.

GCS were used indefinitely in older immunosuppression regimens consisting of CsA, azathioprine, and GCS. However, many centers now discontinue GCS within 6 months after transplantation in the absence of rejection. CNIs remain the backbone of most IST regimens. Tacrolimus-based regimens may be associated with lower rejection rates than a CsA-based regimen, with no difference in overall survival, although tacrolimus is associated with greater incidence of diabetes and hyperlipidemia [73, 74]. MMF has largely replaced azathioprine as first-line antiproliferative drug due to its superiority in allowing GCS taper and its association with better survival and fewer rejection episodes [75]. Immunosuppression regimens containing mTOR inhibitors have not shown any survival or antirejection benefit over MMF-containing regimens. However, mTOR inhibitors inhibit endothelial cell proliferations and have been shown to reduce progression of CAV [34, 35]. In addition, patients treated with mTOR inhibitors are shown to have lower incidence of CMV infections and other opportunistic infections [76].

Renal Dysfunction

The prevalence of renal dysfunction drastically increases after HT. The prevalence of chronic kidney disease (CKD) stages 4 and 5 in HT recipients increases from 3 % at the time of transplant to 11 % at 1 year and to 15 % at 6 years posttransplantation [77]. According to data from the ISHLT registry, renal dysfunction is present in 36.7 % of HT recipients at 1 year and 68.2 % at 10 years posttransplant. By posttransplant year 10, 6.1 % of HT recipients are on chronic dialysis and 3.6 % have had a kidney transplant [78]. Mortality risk is significantly higher in HT recipients with renal dysfunction (hazard ratio 1.66 for CKD stage 4 and 4.07 for CKD stage 5 on dialysis) [78]. The incidence and progression of renal dysfunction are higher in HT recipients receiving CNI (both CsA and tacrolimus) for immunosuppression and correlate with the dose of CNI used [79]. Recent biopsy-based study revealed that the etiology of renal dysfunction in the majority

of HT recipients is hypertensive and diabetic nephropathy rather than merely the effect of CNIs, although the latter is shown to accelerate the progression of hypertensive and diabetic nephropathy [80]. This underscores the importance of optimal management of underlying hypertension and diabetes in transplant recipients with renal dysfunction in addition to minimizing exposure to CNI.

CNI-mediated nephrotoxicity is thought to be the end result of CNI-mediated altered glomerular hemodynamics and tubular function and CNI-mediated direct tubular injury [81]. Altered glomerular hemodynamics result from vasoconstriction of the afferent arterioles caused by decrease in nitric oxide and prostaglandin E2 and increase in thromboxane, endothelin, and the renin-angiotensin system [82]. CNI use may also alter tubular function by causing electrolyte disturbances such as hypomagnesemia, hyperkalemia, hyperuricemia, and hyperchloremic metabolic acidosis [83, 84]. Direct CNI toxicity is characterized by arteriolar hyalinosis and nodular hyaline deposits in the media of afferent arterioles, resulting in arteriolar narrowing and leading to the development of interstitial fibrosis, tubular atrophy, and glomerular sclerosis. Interstitial fibrosis and glomerulosclerosis can also result from activation of the renin-angiotensin-aldosterone (RAS) system and upregulation of TGF-B, leading to irreversible renal injury [85].

The use of mTOR inhibitor has allowed for CNI-eliminating or CNI-minimizing immunosuppression regimens that are often adopted in HT recipients who develop renal dysfunction on full-dose CNIs. Significant improvement in renal function with both CNI elimination (conversion from full-dose tacrolimus plus MMF to everolimus plus MMF for HT recipients >1 year posttransplant) and CNI minimization (conversion from full-dose tacrolimus plus MMF to reduced-dose tacrolimus plus everolimus for HT recipients <1 year posttransplant) has been demonstrated [86]. Conversion from tacrolimus or CsA to the mTOR inhibitor, sirolimus, in HT recipients with mild to moderate renal dysfunction (GFR 40–90 ml/min/1.73 m^2) is associated with significant improvement in GFR at 1 year, however, with the trade-off of more rejection and discontinuation of sirloins due to side effects [87]. While CNI-minimizing regimens are beneficial in patients with established renal dysfunction, using these regimens in HT recipients with normal renal function did not lower the incidence of CNI-induced renal dysfunction [88].

Neurological Adverse Effects

Approximately one third of solid organ transplant recipients present with neurologic symptoms related to a wide spectrum of pathology including CNS infections, tumors, encephalopathy, stroke, and peripheral neuropathy [89]. These conditions are often related to immunosuppression in general or adverse effect of the specific immunosuppressive medications.

Neurotoxic adverse effects are experienced by 10–28 % of patients receiving CNI and are more severe with tacrolimus than with CsA [90]. Symptoms include tremor, insomnia, nightmares, headaches, vertigo, dysesthesia, photophobia, mood disturbances, akinetic mutism, seizures, cortical blindness, focal neurological deficits, psychosis, and encephalopathy. Treatment often includes switching from tacrolimus to CsA or vice versa, decreasing the dose of CNI by switching to an everolimus-based regimen or, when feasible, eliminating CNI, especially when symptoms are severe and risk of rejection is low.

Other immunosuppressive drugs are also associated with neurological complications. Progressive multifocal leukoencephalopathy has been reported in patients receiving MMF and attributed to the activation of the JC virus [91]. Aseptic meningitis is seen in 5–10 % of patients receiving monoclonal antibodies (such as OKT3 and daclizumab) and polyclonal antibodies (such as antithymocyte globulin (ATG)) for induction therapy and rescue therapy of rejection. This is attributed to the rapid release of pro-inflammatory cytokines, lymphocyte activation, and cell lysis [92, 93]. The use of GCS is often associated with behavioral changes such as confusion, mood disturbance, and manic states and psychosis, especially at higher doses. These effects usually resolve after lowering the dose or discontinuing GCS when feasible.

Non-immunosuppressive drugs often used in HT recipients can also cause neurological complications, either directly or as a result of their interaction with immunosuppressive drugs. For instance, antifungal medications, macrolide antibiotics, and calcium channel blockers interfere with the metabolisms of CNIs affecting their blood level and may precipitate neurological adverse effects.

Finally, neurological symptoms in HT recipients can be manifestations of an underlying central nervous system opportunistic infection or malignancy, especially PTLD. Vigilance must be applied to evaluate for these conditions before attributing symptoms to drugs adverse effects.

Hypertension

Hypertension is common among HT recipients. According to the ISHLT registry 2014 adult HT report, 71.8 % of recipients have hypertension at 1 year and 91.7 % at 5 years posttransplant, largely attributed to aging and the use of IST, especially CNI [67]. The predominant theory for the development of CNI-related hypertension is via dysregulation of renal and systemic vascular tone, either due to increased vasoconstriction or decreased vasodilatation. Tacrolimus may be associated with less systemic hypertension than CsA due to a lesser effect on systemic vascular resistance and is associated with improved cardiovascular risk profile [94, 95]. Treatment goals for HTN after HT are the same as those in the general population. Calcium channel blockers have commonly been used. Diltiazem and verapamil may increase levels of cyclosporine.

Osteoporosis

Osteoporosis is commonly seen in transplant recipients due to prolonged period of inactivity, heparin use, and systemic steroids. Significant bone loss is documented during the first 3–6 months after HT, as shown by the drop in bone mineral density at the femoral neck and lumbar spine. This has been attributed to the use of high-dose glucocorticoids and increased bone turnover due to renal disease [96, 97]. Preexisting bone disease is common due to lifestyle factors such as smoking, alcohol use, and immobilization and comorbid conditions such as chronic kidney disease and medications. Therefore, all transplant candidates should be screened and treated prior to transplantation [98]. The spine and ribs are common sites of fractures after cardiac transplantation. In a small series, the incidence of vertebral fractures in HT recipients was 21 % during the first year, increasing to 27 % during the second, 31 % in the third, and 32 % in the fourth year [99]. It is recommended that all HT recipients and candidates receive the recommended daily allowance for calcium depending on age and menopausal status as well as vitamin D to maintain serum 25-hydroxyvitamin D levels above 30 ng/ml. Antiresorptive therapy with bisphosphonates is also recommended.

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Heart Transplantation and Antibody-Mediated Rejection

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_32

Incidence of AMR

AMR is likely underreported and, therefore, the true incidence is not known. This is largely due to the lack of routine screening and standardized diagnostic criteria, which in published studies have included pathological and clinical findings. Consequently, the published incidence of AMR has varied significantly (between 3 and 85 %). When histological and immunofluorescence (IF) techniques were used, the reported incidence was 85 % [1]. Alternatively, when C4d deposition and graft dysfunction were used to diagnose AMR, the incidence was <3 % [2]. One study defined AMR based on ISHLT 2004 and 2006 criteria (i.e., allograft dysfunction, serologic evidence of donor specific antibodies (DSA), and biopsy evidence of complement deposition) and found an incidence of 3 % and 5 %, respectively [3, 4]. Clearly, the variation in definition impacts the reported incidence, but more importantly, it has implications for treatment.

Risk Factors for AMR

Typical risk factors for AMR include elevated panel reactive antibodies (PRA), prior mechanical circulatory support (MCS), female sex, cytomegalovirus (CMV) seropositivity, prior treatment with OKT3 with the development of antibodies against OKT3, multiparity, and a history of retransplantation and a positive crossmatch [5–7]. The risk of AMR in women is disproportionately higher compared to men. Women comprise about 50 % of the heart transplant recipients with AMR, yet they only account for approximately 25 % of the cardiac transplant recipients [3, 6]. The presence of circulating anti-HLA antibody following transplantation has been also shown to be associated with AMR [3, 8].

Pathogenesis of AMR

The endothelium is the first immunological cellular layer that the recipient immune cells encounter. When the transplant recipient produces antibodies against the donor human antileukocyte antigens (HLA) that reside on the surface of the endothelium of the transplanted heart, the patients develop AMR. This antibody mediated response results in the activation of the complement cascade resulting in tissue injury. Complement activation stimulates the innate and adaptive immune responses, leading to complement and immunoglobulin deposition within the microvasculature of the transplanted heart. These depositions are detected using immunofluorescence techniques. Complement deposition stimulates and amplifies the inflammatory reaction. This process is marked by the activation of endothelial cells, an induction of cytokines, the activation of macrophages, increased permeability of the vasculature, and thrombotic events in the microvasculature [9]. Ultimately, allograft dysfunction may occur.

AMR may occur during the acute period (1 week) following transplantation in patients who are pre-sensitized to donor HLA antigens (hyperacute rejection), within the first month of transplant due to DSA, and years following transplantation [6, 10–13]. Although AMR may occur concomitantly with ACR in up to 24 % of reported cases, the incidence of AMR increases to almost 50 % of heart transplant recipients who develop rejection more than 7 years after transplant [1, 14]. The definition of cardiac AMR is undergoing evolution and methodology for diagnosis is improving, providing even more pathologic and immunologic information. These studies support the notion that AMR may represent a range of immunological injury from subclinical (characterized by histological findings or serological markers) to overt AMR with hemodynamic compromise.

Histopathological Characteristics of AMR

The primary focus of immunologic injury associated with AMR is the endothelium associated with the microvasculature of the transplanted heart. Progression of AMR ultimately involves the epicardial coronary arteries. The most consistent histological findings associated with AMR include enlarged or swollen endothelial cells as a result of endothelial activation, interstitial edema, and hemorrhage; however, bioptome trauma may obscure these findings [15–18]. Intravascular thrombi can also be seen in severe cases.

Immunopathological Characteristics of AMR

Activation of the complement cascade is the key initiator of AMR and evidence of complement and immunoglobulin deposition have been used to diagnose AMR (Fig. 32.1). Detection of tissue-bound immunoglobulins (IgG and IgM) and immune complexes, used for decades in kidney biopsies for the detection of glomerulonephritis, was among the first assays used to detect AMR in the cardiac transplanted allograft [19–21]. Due to limited sensitivity and specificity, these are no longer the sole determinants of AMR. Rather, the deposition of the classic complement pathway degradation products, C4d and C3d, has become a routine assay in the assessment of AMR in the kidney transplant allograft and has been recently proposed as a diagnostic criterion for cardiac transplant AMR. C4d binds to the endothelium and is deposited in capillaries (Table 32.2). Deposition in other structures may also be observed, but does not indicate AMR. The activation of the complement cascade is further marked by C3d cleavage and indicates progression of the complement cascade (Table 32.2). The incidence of AMR using C4d alone appears to range from 35 to 71 % and when it is combined with clinical graft dysfunction, the incidence is approximately 27 %. C3d is typically found in conjunction with C4d, and the combination is a better predictor of graft dysfunction and mortality than C4d alone [4]. Complement

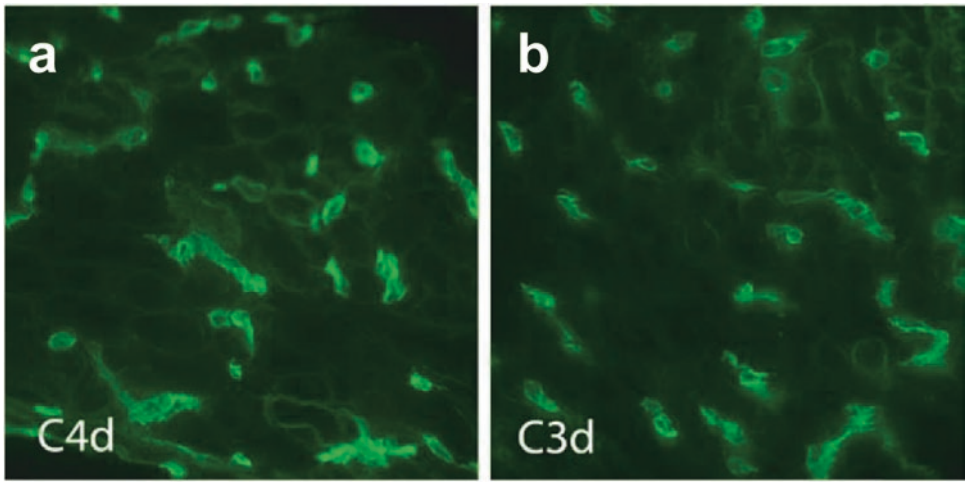

Fig. 32.1 Deposition of C4d and C3d in biopsy sections of the cardiac allograft with AMR. (**a**) Immunofluorescence techniques reveal C4d deposition in capillaries of biopsy sections of the cardiac allograft. (**b**) Immunofluorescence techniques reveal C3d deposition in capillaries of biopsy sections of the cardiac allograft (**a**)

regulators (CD59 and CD55) may be used with complement split products to indicate aborted complement activation, but these assays are impractical for routine use. In addition, the capillary integrity may be examined using HLA-DR staining. A disrupted pattern indicates endothelial damage [23].

Intravascular macrophages are pathognomonic for AMR, and the macrophage antigen CD68 can be used to distinguish AMR from cellular rejection by the demonstration of intravascular/perivascular macrophages and differentiation from lymphocytes. Further, the endothelial cell markers, CD34 and CD31, can delineate endothelial damage and intravascular location of macrophages [24].

Antibodies

Both HLA and non-HLA antibodies have been implicated in immune-mediated injury following heart transplantation. The development of HLA antibodies, particularly Class II antibodies, after transplantation has been shown to be associated with cardiac allograft vasculopathy, cellular rejection, and mortality. Furthermore, HLA antibodies directed against the donor appear to be associated with AMR in addition to cellular rejection and CAV. Non-HLA antibodies may also cause immune injury and can be present in the absence of HLA antibodies.

Clinical Features Associated with Symptomatic AMR

Patients with AMR typically present with signs and symptoms of heart failure due to right and/or left systolic or diastolic dysfunction (Fig. 32.2). These clinical symptoms include: shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, elevated neck veins, ascites, and peripheral edema. Acute AMR may result in hemodynamic compromise and is observed in more than 40 % of the patients [6, 15, 24–26]. Even the definition of hemodynamic compromise can be unclear and may range from a decrease in left ventricular ejection fraction to an unexplained elevation in intracardiac pressures with reduced cardiac output and the need for inotropic therapy.

Clinical Features Associated with Subclinical AMR

Although the definition of AMR has included clinical evidence of graft dysfunction in addition to histological and immunological derangements, it has been demonstrated that complement activation may be observed in the absence of kidney or heart allograft dysfunction (Fig. 32.2). Thus, the term subclinical AMR may be used to characterize these patients [27–29]. Moreover, complement deposition without graft dysfunction may be observed in accommodation, a state believed to be achieved after complement regulatory proteins successfully terminate the activated complement cascade in an attempt to achieve a state of accommodation [5]. Therefore, in a subpopulation of heart transplant recipients, complement deposition without perturbed allograft organ function represents accommodation. The induction of regulators of complement activation within the tissue concomitant with C4d deposition supports this concept [30]. Whether subclinical AMR should be treated remains unclear. There are data, however, that support the association of subclinical AMR with adverse outcomes. Wu et al. examined heart transplant recipients with subclinical AMR, heart transplant recipients that were treated for AMR and had LV dysfunction and a control group of heart transplant patients without AMR [31, 32]. Using a rigorous definition for AMR that included histology and immunohistochemistry, the 5-year survival for the subclinical AMR group, the treated AMR group and control group demonstrated no significant difference. The patients with subclinical AMR had significantly less freedom from cardiac allograft vasculopathy than the control group and similar outcomes to patients with treated symptomatic AMR. Patients with subclinical AMR have been reported to have a worse cardiovascular mortality compared to patients with acute cellular rejection and

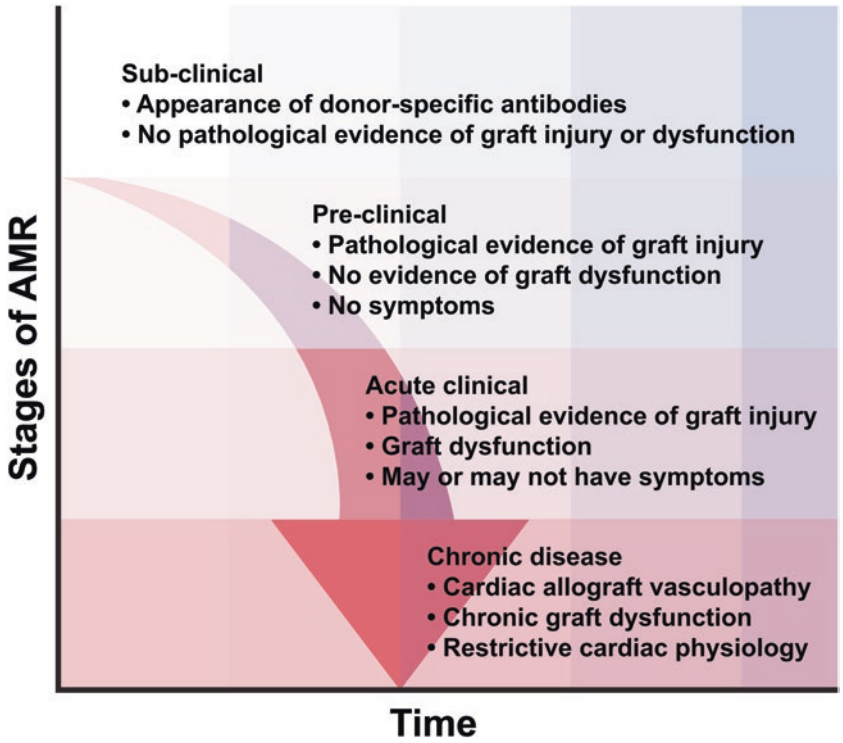

Fig. 32.2 Progression of AMR ultimately results in graft failure. Schematic highlighting subclinical, clinical, and chronic disease associated with AMR (adapted from [22])

comparable mortality to those with mixed (ACR and AMR) rejection [33]. Therefore, this study supports the notion that subclinical AMR is associated with a poor outcome.

Diagnosis of AMR

In 2010, a committee and conference sponsored by the ISHLT was assembled to further the understanding of AMR. The committee and conference included transplant cardiologists, surgeons, pathologists, and immunologists. The conference discussed and defined AMR, the significance of subclinical AMR, and the contribution of donor specific antibodies (HLA and non-HLA antibodies). Although previous revisions to the definition of rejection have not recommended screening for AMR, the screening for AMR and antibodies were recommended by this committee and conference. The criteria for the diagnosis of AMR were outlined in a published scientific statement [34]. The proposed scoring system encompassed histopathology, immunohistochemistry, and immunofluorescence techniques and established the nomenclature for the diagnosis of pathologic AMR. This scoring system was based on the fact that although clinical features were taken into account, there was a definition for pathologic cellular rejection but none existed for AMR. The classification of AMR was published in 2011 and more recently in 2013 (Tables 32.3 and 32.4).

While the field has advanced by the refinement of the definition of pathologic AMR, it is important to take into account the clinical presentation: symptoms, hemodynamics, and graft function. In areas where there is little information regarding treatment, the clinical presentation may be the determining factor. Finally, DSAs may also influence the decision to treat AMR. There are multiple classifications of AMR that will require decision-making by the clinician.

Imaging Modalities

Although the gold standard for diagnosing AMR is the endomyocardial biopsy, imaging may provide important clues as to the status of graft function and a potential immunological cause. Unfortunately, most imaging studies have focused on cellular rejection and there are limited data regarding their use for AMR. Left ventricular diastolic dysfunction can be one of the earliest features of acute rejection [35–38]. In order to increase the sensitivity of the imaging modality, cardiac magnetic resonance imaging (CMR) is increasingly used for the diagnosis of AMR as it is able to assay myocardial edema and increases in LV mass [39]. For example, T2 quantification is an important modality in CMR. As T2 relaxation time is the decay time constant of the magnetic signal following an excitatory pulse studies demonstrate that T2 relaxation time lengthens with the degree of myocardial edema. Of all the CMR parameters, T2 quantification correlates best with biopsy proven AMR. T2 quantification remains investigational, and future studies will be necessary to determine the role of non-invasive imaging studies for the diagnosis of AMR [40].

Serologic Markers of Rejection

B-type natriuretic peptide (BNP) has been shown to be associated with acute rejection in heart transplant recipients. Changes in BNP over time are correlated with acute rejection as opposed to specific levels. In a series of 146 patients, there was only a marginal association between nt-BNP and rejection; for every 100 pg/ml increase in nt-BNP, there was only a 1% increase in the risk of rejection; however, a twofold increase in nt-BNP was associated with an odds of 2.4, a fivefold increase associated with odds of 6.8, and a tenfold increase associated with an odds of 21.6, after adjusting for decrease in EF and rise in PCWP [41]. Wu and colleagues demonstrated that the log BNP was associated with a greater than fivefold increase in the risk of vascular rejection [42]. Another commonly used serological marker for rejection and the detection of cardiac injury is troponin. Routinely, cardiac troponin I (cTnI) is monitored during the early stages of rejection and the response to treatment. Finally, the gene expression profile (AlloMap) has been shown to reliably exclude acute cellular rejection; however, it has not been demonstrated to be useful in excluding AMR [43].

Pathology

The diagnosis of acute cellular rejection is made solely on the basis of pathologic findings. AMR, however, has typically relied mainly on clinical findings due to the lack of pathologic criteria. The definition of AMR published in 2009 required the presence of graft dysfunction and/or circulating donor specific antibodies in addition to the histological and immunopathological findings. These criteria were removed during the Consensus Conference in 2010. Thus a pathological definition of AMR was established. In this definition, the criteria for establishing a positive diagnosis was established (Table 32.1). C4d and C3d staining are scored based on distribution of staining within the capillaries (negative, focal, or multifocal/diffuse) and the intensity of staining (negative, trace, strong) (Table 32.3). In addition, HLA staining is recommended for assessment by immunofluorescence and CD68 with immunohistochemical techniques. Other markers are considered optional. Although immunofluorescence is considered the gold standard, immunohistochemistry is used by 80% of US and European centers. During the consensus conference, both methods were evaluated. There appeared to be good reproducibility between centers using immunohistochemistry and also good correlation between immunofluorescence and immunohistochemical techniques. Immunopathology assays rely on processed tissue (fresh frozen or paraffin infiltrated and embedded) and the detection of specific antigens by using specific antibodies. Tissue (endomyocardial biopsy specimens) that is fresh frozen and sectioned typically uses immunofluorescence protocols and primary antisera directed against C4d, C3d, immunoglobulin heavy chains, fibrin, HLA-DR, and CD55. These primary antibodies are then detected using a fluorophore conjugated secondary antibody. In contrast, the detection of more stable antigens (that can withstand the paraffin processing) use an immunoperoxidase detection system to examine for the expression of C4d, CD68, C3d, CD34, CD31, CD3, and CD20. Each mode of processing (frozen vs. paraffin processing) has advantages and disadvantages. For example, the immunoperoxidase protocol uses paraffin processing which

Table 32.1 Criteria for acute antibody mediated rejection of the cardiac allograft [22]

	Required findings	Optional
1. Clinical evidence of acute graft dysfunction		Recommended in combination with other evidence to support diagnosis of AMR
2. Histological evidence of acute capillary injury (a and b required)	(a) Capillary endothelial changes	(c) Neutrophils in capillaries (severe)
	(b) Macrophages in capillaries	(d) Interstitial edema/hemorrhage (severe)
3. Immunopathologic evidence for antibody- mediated injury (a or b or c required)	(a) IgG, IgM, and/or IgA + C3d and/or C4d or C1q (2–3+) by IF	
	(b) CD 68 for macrophages in capillaries (CD31 or CD34) and/or C4d (2–3+ intensity) in capillaries by paraffin IH	
	(c) Fibrin in vessels (severe)	
4. Serological evidence of anti-HLA or anti-donor antibodies		Anti-HLA class I and/or class II or other anti-donor antibody at time of biopsy (supportive of clinical and/or morphological findings)

AMR antibody-mediated rejection, *HLA* human leukocyte antigen, *IF* immunofluorescence, *IH* immunohistochemistry
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Table 32.2 Immunopathological features of AMR [22]

	Endomyocardial biopsy	Circulating antibody
Methodology	Histological evaluation	Solid-phase assay and/or cell-based assays to assess for presence of DSA (and quantification if antibody present)
	Immunoperoxidase: C4d	
	Immunofluorescent staining: C4d and C3d	
Intervals	Histological evaluation of every protocol biopsy	2 weeks and 1, 3, 6, and 12 months, and then annually after transplantation
	Immunoperoxidase/immunofluorescent staining:	When AMR is clinically suspected
	2 weeks and 1, 3, 6, and 12 months after transplantation	
	When AMR is suspected on the basis of histological, serological, or clinical findings routine C4d (C3d) staining on subsequent biopsy specimens after a positive result until clearance	

AMR antibody-mediated rejection, *DSA* donor-specific antibody, *ISHLT* International Society for Heart and Lung Transplantation
Modified from Kobashigawa et al. [2] with permission from the International Society for Heart and Lung Transplantation. Copyright © 2011, International Society for Heart and Lung Transplantation

Table 32.3 Proposed scoring system for pathological AMR [22]

Positive biopsy	Immunohistochemistry	Immunofluorescence
Capillary distribution and intensity	Multifocal/diffuse weak or strong staining of C4d	Multifocal/diffuse weak or strong staining of C4d/C3d
Intravascular CD68 distribution	>10% Focal/multifocal/diffuse Intravascular macrophages	–
HLA-DR distribution and intensity	–	Multifocal/diffuse weak or strong staining
Caveats	Focal strong C4d staining is classified as negative but warrants close follow-up	Focal strong C4d staining is classified as negative but warrants close follow-up

AMR antibody-mediated rejection, *HLA* human leukocyte antigen
Modified from Berry et al. [3] with permission from the International Society for Heart and Lung Transplantation. Copyright © 2011, International Society for Heart and Lung Transplantation

is commonly available in pathology laboratories and yields superior morphology for the analysis of both complement deposition and the surrounding tissue (i.e., analysis of the endothelium and the myocardium). In addition, the immunoperoxidase-stained sections/slides provide a permanent archival slide record that can be stored at room temperature for long periods of time. In contrast, the immunofluorescence detection method relies on the freezing of the tissue which has the advantage of rapid processing and improved antigen preservation with decreased nonspecific signal. Moreover, residual frozen tissue can also be a valuable resource for viral polymerase chain reaction or other molecular tests. The challenges with the immunofluorescence technique are the need for technical expertise to obtain high-quality frozen sections and the inability to have a permanent archival slide record as the immunofluorescent signal fades over time.

Comparison of the results using both the immunofluorescence and the immunoperoxidase staining techniques is important for the diagnosis of AMR. For example, C4d expression from endomyocardial fragments obtained at the same biopsy procedure can equally detect C4d expression using either the immunofluorescence of the immunoperoxidase technique [29, 44, 45] (Fig. 32.1). Using the immunoperoxidase technique, Fedrigo and colleagues observed that C4d capillary staining was present in about 35% of heart transplant recipients, and AMR (using the 2005 ISHLT criteria) was present in 7% of heart transplant recipients [27]. Over a median follow-up period of approximately 2 years, cardiac transplant recipients who were C4d-positive experienced higher mortality than those that were C4d-negative, regardless of graft function. In contrast, C4d positivity that is detected only by immunofluorescence is of unclear significance. The immunofluorescent coexpression of C3d and C4d

Table 32.4 Proposed nomenclature for pathological AMR [22]

Category	Description
pAMR 0: Negative for pathological AMR	Both histological and immunopathologic studies are negative
pAMR 1 (H+): Histopathologic AMR alone	Histological findings present immunopathologic findings negative
pAMR 1 (I+): Immunopathologic AMR alone	Histological findings negative and immunopathologic findings positive
pAMR 2: Pathological AMR	Both histological and immunopathologic findings are present
pAMR 3: Severe pathological AMR	Severe AMR with histopathologic findings of interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis and/or karyorrhexis, and marked edema

AMR antibody-mediated rejection, *pAMR* pathological antibody-mediated rejection category

significantly enhances the diagnosis of AMR. For example, Tan et al. [4] demonstrated that endomyocardial biopsy specimens from cardiac transplant recipients having linear capillary deposition of C4d with C3d deposition was associated with allograft dysfunction (in more than 80 % of the patients) and the incidence of allograft dysfunction was more than 90 % with the presence of DSA. Only one patient with C4d staining alone (C3d negative) had concurrent allograft dysfunction. This result supports the notion that the immunofluorescent detection of C4d alone is not a specific indicator of AMR. In addition, reperfusion injury and viral infections have been shown to cause C4d deposition, but may not be associated with AMR or a poor prognosis. In summary, the diagnosis of AMR using the immunofluorescence technique should include both C3d and C4d deposition, whereas the use of the immunoperoxidase protocol requires only the expression of C4d. Importantly, it is essential to have the expertise of a dedicated cardiac pathologist to ensure timely and consistent reporting of the results to the transplant team. Areas that still require clarification include the transition to AMR, appropriate monitoring strategies, the role of serial biopsies, and the significance of late appearing DSAs.

The working formulation for pathologic criteria for AMR range from pAMR 0 to pAMR 3 based on the presence or absence of histological and immunopathological features (Table 32.4 and Fig. 32.3). Routine surveillance is recommended. Evaluation during the first 2 weeks after transplant may be confounded by preoperative changes; however, two samples (2 and 4 weeks) are recommended during the first month after transplant. Monitoring following a positive result should continue until clearance although it is not clear when clearance occurs. One study using immunofluorescence techniques suggested that the clearance of capillary staining of C3d occurs within 2 weeks to 1 month and C4d within 1–2 months, although anecdotally, staining can persist for several months, although the clinical significance is not clear. Although it is recommended that AMR surveillance using immunofluorescence or histological techniques be performed, it has been acknowledged that this may represent a challenge for some centers. For those centers, it was recommended that immunostaining be guided by histological features. To be considered positive, staining for C4d and C3d may be either weak or strong in intensity but must be multifocal or diffuse in distribution. The clinical significance of lesser degrees of staining is unclear and consideration should be given to monitoring.

Histological features should also be considered. Morphological findings suggestive of AMR include the presence of intravascular activated macrophages or endothelial cells, hemorrhage, interstitial edema, myocyte necrosis, capillary damage, and evidence of inflammation [46].

Supporting features of AMR include donor specific antibodies and clinical presentation. The topic of DSAs exceeds the scope of this chapter. Currently, there is no consensus on what constitutes significant levels of DSA and how they should be managed in the absence of clinical or pathological findings. It is recommended, however, that they are monitored routinely after transplant or when rejection is suspected (Table 32.5) and that solid phase or cell-based assays be used. Clinical features may include signs and symptoms of heart failure, restrictive physiology, hemodynamic and/or echocardiographic parameters, and requirement for circulatory support. It is not yet clear whether the diagnosis of pAMR alone, without clinical or supporting features is enough to warrant treatment except in the case of severe pAMR or pAMR 3. If there is clinical evidence of AMR, then treatment should be initiated regardless of the level of pAMR (Tables 32.6 and 32.7). There is less clarity with intermediate degrees of pAMR and an absence of clinical findings. The decision to treat the patient should be considered carefully with collaboration between the pathologist, immunologist, and cardiologist.

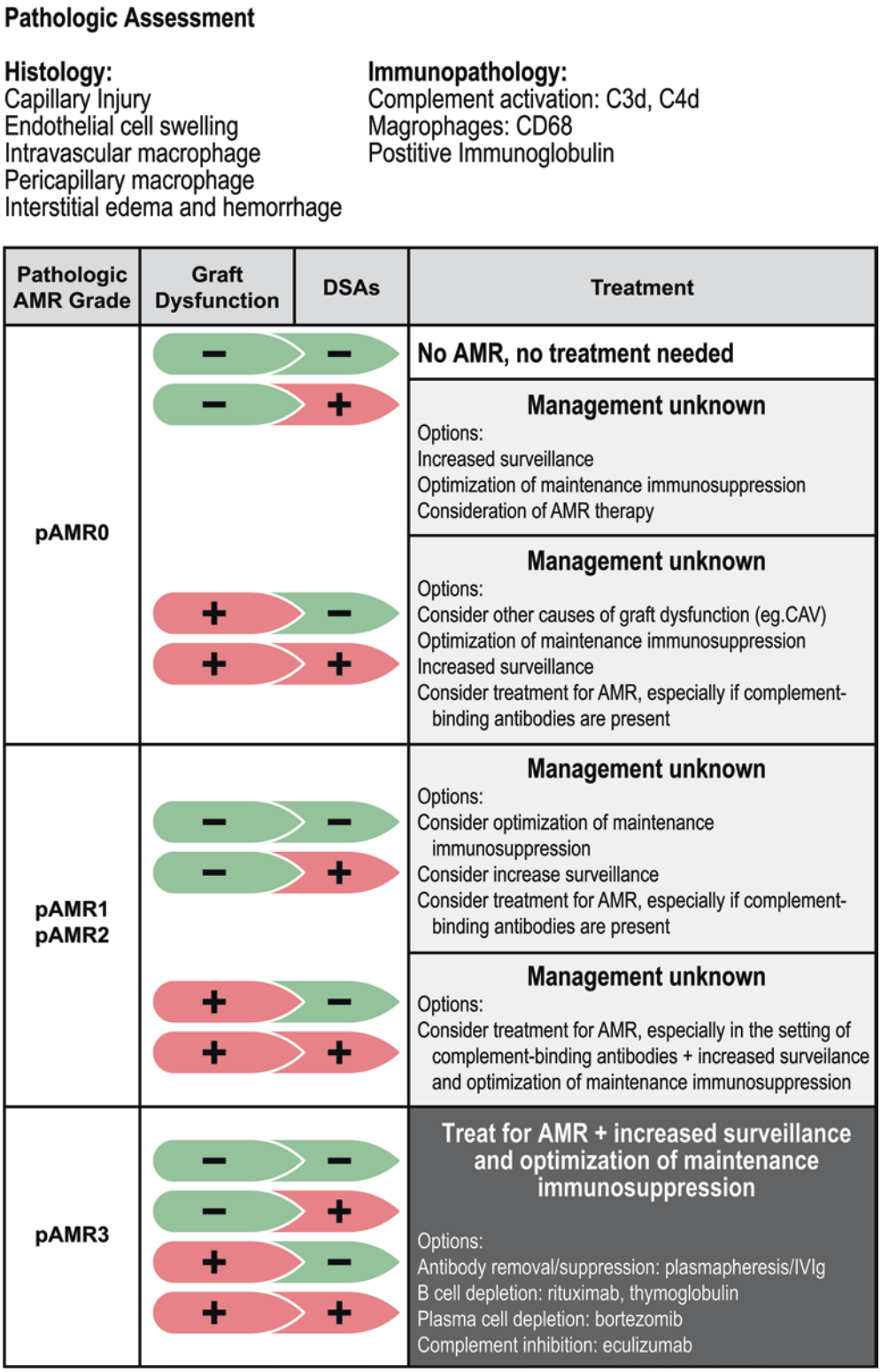

Fig. 32.3 Categories of AMR and possible therapeutic interventions (adapted from [22])

Management of AMR

As the number of cardiac transplants is limited, there are no large studies that examine treatments for AMR. ISHLT treatment guidelines have been established, but all recommendations are based on consensus (level of evidence C) [47]. Due to the limited number of heart transplants each year, transplant management typically follows the treatment protocols for the kidney transplant program (Fig. 32.3). Therapies for AMR have usually been based on agents that

Table 32.5 ISHLT recommendations for AMR monitoring [22]

	Interpretation	AMR	Limitations
IgG/IgM	Immunoglobulin binding	+	Easily dissociated
			Short half-life
			Interobserver variability
C3, C1q	Complement activation	+	Short half-life
C3d/C4d	Complement activation	+	Combination more predictive of AMR than C4d alone, long half-life
HLA-DR	Endothelial integrity	+	Staining always present, but "frayed" pattern indicates capillary injury
Fibrin	Thrombotic environment	+	Interstitial extravasation suggests more severe AMR episode
CD55, CD59	Complement inhibitor	–	Long incubation and granular staining pattern
			Difficult to interpret
CD31, CD34, CD68	Intravascular macrophages	+	CD68 confirms macrophage lineage of mononuclear cells
			CD31/34 are endothelial markers which differentiate macrophages from endothelial cells and delineates intravascular location

AMR antibody-mediated rejection, *HLA* human leukocyte antigen

were originally used to treat cancer, blood diseases, and autoimmune diseases [34]. The goals for managing or treating AMR include the following: (1) suppression of the T-cell mediated response (corticosteroids, mycophenolate mofetil (MMF), anti-lymphocyte antibodies, photopheresis, etc.), (2) elimination of circulating antibodies (e.g., plasmapheresis), (3) inhibition of remaining antibodies (e.g., intravenous immunoglobulins), (4) suppression or depletion of B cells (e.g., corticosteroids, rituximab, or splenectomy), (5) suppression or depletion of plasma cells (e.g., bortezomib), and (6) inhibition of complement (e.g., eculizumab, intravenous gamma globulin [IVIg]). Additional information for using these therapies for AMR is outlined in Table 32.6.

Corticosteroids

Corticosteroids were first used in clinical renal transplantation in 1963 and ultimately have become a standard immunotherapy for induction, maintenance, and antirejection in heart transplantation [48, 49]. Both corticosteroid pulse and taper regimens have been considered important components of standard therapy for acute cellular rejection for decades and have been adapted as baseline therapy for AMR [47]. Corticosteroids are potent specific and nonspecific immunosuppressive and anti-inflammatory agents with a plethora of physiologic and cellular effects by impacting the number and function of leukocytes and endothelial cells [50]. A single dose of corticosteroids has been shown to cause a transient 90 % decrease in circulating monocytes and a 70 % decrease in circulating lymphocytes ([51]). This effect appears to occur within 4–6 h and normalizes within 24 h. T cells appear to be more sensitive to suppression than B cells. The effects on immunoglobulin production appear to be variable, with low doses of corticosteroids having little to no effect, while high dose appears to suppress immunoglobulin production 2–4 weeks after treatment. The transcription factors nuclear factor-kB and activator protein-1 are the downstream effectors that mediate the cellular response to corticosteroids [52, 53]. Corticosteroids also exert their effect via suppression of IL-1 and decrease in Fc and C3 receptor expression and function [51]. The lone impact of corticosteroids for the treatment of AMR is difficult to define as essentially every treatment protocol includes corticosteroids in combination with other immunotherapies. Nevertheless, corticosteroids are a commonly used component for the treatment of AMR.

Intravenous Gamma Globulin

Intravenous gamma globulin or IVIg is pooled IgG antibodies obtained from plasma of numerous donors. IVIg contains anti-idiotypic antibodies that inhibit Class I and II HLA-specific alloantibodies, constimulatory molecules, complement, cytokine and cytokine receptors, and T-cell and B-cell receptors in vitro and in vivo [54–57].

IVIg has been used to treat the highly sensitized patient prior to cardiac transplantation but its efficacy for prevention

Table 32.6 Summary of agents used to treat AMR [22]

Theraputic modality	Mechanism of action	Adverse events
Corticosteroids Mg	Upregulation of anti-inflammatory gene expression, mediated by activated protein-1 and NF-kB, Blockade of Fc-q receptor, Complement inhibition, Downregulates B-cell receptor, Neutralizes circulating antibody and cytokines	Dyslipidemia, hyperglycemia, osteoporosis, leukocytosis
		Headache, Chills, Rigors, Fever, Myalgia, Volume overload
Tissue plasma exchange (plasmapheresis)	Nonselective removal of circulating alloantibody, proteins, cytokines; IAP removes only immunoglobulins	Rebound antibodies, Bleeding diathesis, Hypotension, Allergic reaction, Transmission of blood-borne pathogens
Photophoresis	Upregulation of costimulatory molecules, downregulation of T cells, immunoregulation via T-regulatory cells	Vascular access complications, skin erythema, pruritus, nausea, rare drug-induced lupus or scleroderma-like syndrome
Monomurab (OKT3)	Binds CD3 antigen on T lymphocytes, leading to early activation of T cells, cytokine release, and blockade of T-cell function	Cytokine release syndrome, anti-murine antibodies, anaphylaxis, hypersensitivity, infection (viral, fungal, bacterial), increased incidence of PTLD and lymphoma
Rabbit ATG (thymoglobulin)	Decrease circulating T lymphocytes	GI (diarrhea, abdominal pain, nausea, vomiting) myalgias, headache, dizziness, dyspnea, hypertension peripheral edema, tachyarrhythmia, hypokalemia, leukopenia, thrombocytopenia, fever, infection (viral, fungal, bacterial), increased incidence of PTLD and lymphoma
Equine antithymocyte globulin (ATGAM)	Binds CD3 antigen on T lymphocytes	GI (diarrhea, abdominal pain, nausea vomiting) myalgias, headache, dizziness, dyspnea, hypertension peripheral edema, tachyarrhythmia, hypokalemia, leukopenia, thrombocytopenia, fever, infection (viral, fungal, bacterial), increased incidence of PTLD and lymphoma
Rituximab	B lymphocyte depletion, antibody depletion, complement-induced cell lysis, Induction of apoptosis	Fever, chills, nausea, headache, myalgia, rash
Alemtuzumab	Monoclonal antibody against CD52 on surface of all B and T lymphocytes, absent on platelets, hematopoietic stem cells, and lymphoid progenitors; transient depletion of mature lymphocytes without myeloablation	Lymphopenia, pancytopenia, infusion-related effects[a]; increased CMV viremia, coagulopathy, cardiac toxicity (heart failure, arrhythmias) in patients receiving chemotherapy
Bortezomib	Reversible 26S proteasome inhibitor present on plasma cells	Diarrhea, sensory neuropathy, fatigue, thrombocytopenia, conjunctivitis
Eculizumab	Terminal complement (C5) inhibitor	Flu-like symptoms, sore throat, headache, pack pain, nausea, neutropenia, extravascular hemolysis, increased risk of meningococcal infection
Mycophenolate	Reversible inosine monophosphatase dehydrogenase blocker that inhibits de novo guanosine synthesis, inhibits T- and B-cell proliferation	Diarrhea, esophagitis, increased lymphomas and other malignancies, leukopenia, anemia, thrombocytopenia, increased CMV infection, hypogammaglobulinemia
Cyclophosphamide	Nitrogen mustard alkylating antineoplastic agent, targets B cells, inhibition of cholinesterase activity	Bone marrow toxicity, hemorrhagic cystitis, gonadal failure, malignancies, nausea, diarrhea, vomiting, stomatitis, mucositis, anorexia, pacytopenia, cardiotoxicity, interstitial pneumonitis, pulmonary fibrosis, hepatoxicity, toxic epidermal necrolysis, teratogenic
Total lymphoid irradiation	Suppression of activated T cells and interleukin-2 pathway, eliminates circulating T and B cells	Bone marrow suppression, pancytopenia, nausea, PTLD, myelodysplasia, opportunistic infection, PTLD
Splenectomy	Diminishes antibody production by debulking plasma cells activated B cells	Increased risk of sepsis and/or death (kidney transplant)

[a]Infusion-related effects: nausea, vomiting, diarrhea, headache, fatigue, dyspnea, rash, pruritus, fever, rigors, bronchospasm, and hypotension

Table 32.7 Clinical indicators for diagnosis of pathological AMR in the heart [22]

Immunopathologic indicators	Required	Supporting features	Recommended clinical indicators
Histology	Capillary endothelial changes and intracapillary macrophages	–	Clinical heart failure based on symptoms and signs of heart failure Hemodynamics: PCWP >20 mmHg and CI < 2.0 L min^{-1} m^{-2}
Frozen section: immunofluorescence	C4d, C3d (2–3+ intensity) anti-HLA-DR	C1q (2–3+), Ig, fibrin, IgG, and IgM HLA for cellular integrity	Requirement for inotropes or mechanical support during hospital stay
Paraffin section: Immunohistochemistry	C4d (2–3+ intensity), CD68	Pan-T-cell Cd3, pan-B-cell CD20, complement C3d, endothelial cell CD31 or CD34, complement regulatory proteins	Systolic dysfunction: EF < 50 % or ≥25 % decrease from baseline
Other	–	Presence of circulating donor-specific HLA antibodies, especially those that fix complement	Restrictive physiology characterized by the following: EF > 50 %, E/A > 2 IVRT < 60 ms, and DT < 150 ms and/or RAP > 12, PCWP > 25 mmHg, and CI < 2.0 L min^{-1} m^{-2}

AMR antibody-mediated rejection, *CI* cardiac index, *DT* deceleration time, *E/A* ratio of early to late mitral inflow velocities, *EF* ejection fraction, *HLA* human leukocyte antigen, *IVRT* isovolumic relaxation time, *PCWP* pulmonary capillary wedge pressure, *RAP* right atrial pressure
Modified from Berry et al. [4] with permission from the International Society for Heart and Lung Transplantation. Copyright © 2013, International Society for Heart and Lung Transplantation

of AMR is unknown [58]. IVIg is frequently used in combination with other immunomodulating therapies for the treatment of desensitization or AMR so the functional impact of IVIg alone is unclear. In limited studies of kidney and heart transplant recipients who developed AMR, IVIg administered with cyclophosphamide or tacrolimus was shown to successfully reverse rejection but had a high rate of recurrence [3, 59]. IVIg is less expensive and probably has a relatively more favorable side effect profile when compared to other immunomodulating agents.

Plasmapheresis

Using therapeutic plasma exchange, double-filtration plasmapheresis, and immunoadsorption pheresis, plasmapheresis removes circulating antibodies. Plasma exchange uses membrane filtration or centrifugation to separate plasma from the cellular components of blood. Exogenous albumin and/or fresh-frozen plasma or crystalloid are added back to the cellular components of the patient's blood and reinfused to the patient. Consequently, plasmapheresis nonselectively removes all proteins. In contrast, immunoadsorption plasmapheresis removes only immunoglobulins and less efficiently removes soluble cytokines. However, immunoadsorption plasmapheresis does not require the replacement of fluids to the patient.

Plasma exchange is more widely used in the USA due to its relatively lower cost, usability, and availability [57]. The most common method used for the decrease of soluble alloantibody levels in transplantation patients with plasmapheresis is the use of plasma exchange [58]. Although plasma exchange is commonly used for the treatment and management of AMR, there have been no randomized trials using plasma exchange in cardiac transplant recipients [57]. There have been a number of case series reports that used plasmapheresis for the initial treatment and refractory AMR in cardiac transplantation in addition to several case reports describing the use of plasma exchange for the reduction of alloantibodies in highly sensitized patients awaiting heart transplant and in facilitating transplant across a positive crossmatch [60–62].

There are limited data to support the use of plasma exchange as monotherapy as its reported use is typically in combination with other therapies. Wang et al. [62] reported the use of plasma exchange in patients with cardiac allograft dysfunction, hemodynamic compromise, and biopsy-proven AMR. These cardiac transplant recipients with AMR were treated using a protocol that included 5 days of plasma exchange and 3 days of intravenous corticosteroids (methylprednisolone 1 g/day). In a number of cases, tacrolimus was substituted for cyclosporine. Although the overall survival was decreased in the patients with AMR, this treatment protocol resulted in 1- and 5-year survival rates of 75 % and 51 %, respectively.

In a similar retrospective study, 11 of 12 patients with hemodynamic compromise and biopsy proven AMR, had recovery of allograft function after treatment for 3 days with

methylprednisolone 1 g/day and a 1 week protocol of daily plasma exchange [2]. In this series, baseline immunosuppression was modified with the substitution of MMF or cyclophosphamide for azathioprine and tacrolimus for cyclosporine.

Grauhan and colleagues [35] compared the outcomes of patients treated for AMR. These patients had hemodynamic instability or allograft dysfunction and no evidence of cellular rejection. These investigators examined the treatment and survival of this patient population with AMR from 1986 to 1990 and 1991–1999. The cardiac transplant recipients from 1986 to 1990 were managed with methylprednisolone (500 mg) and cytolytic antibodies (muromonab-CD3 or antithymocyte globulin) for at least a 3 day period. In contrast, patients from 1991 to 1999 were also treated with plasma exchange (plasma exchange of 5% of body weight). Cyclophosphamide was substituted for azathioprine in both eras. Compared with subjects in the earlier era who were treated with cytolytic antibodies, those treated with plasma exchange had better survival.

Photopheresis

Photopheresis, or PUVA (extracorporeal psoralen (P) and high intensity, long wavelength ultraviolet A irradiation (UVA)), is an apheresis technique whereby a patient's plasma is treated with a photosensitizing agent (8-methoxypsoralen), and exposed to high intensity, long wavelength ultraviolet A radiation. Following this treatment, the patient's plasma is reinfused in order to modify the immune response [63]. The peripheral blood lymphocytes that were exposed to UVA radiation are damaged and are subsequently phagocytosed by activated monocytes. The internalized apoptotic cells prevent the upregulation of costimulatory molecules. The irradiated leukocytes also release more HLA-G molecules which modulates the number of circulating T cells by increasing the regulatory T cells. In addition, these leukocytes enhance the pro-tolerogenic function of dormant dendritic cells.

The efficacy of using photopheresis to prevent or treat transplant AMR is unclear. In contrast to the use of immunosuppressive drugs, photopheresis does not result in generalized immunosuppression [63–66]. Although no studies have examined the efficacy of photopheresis for the treatment of biopsy-proven AMR, photopheresis has been successfully used to treat recurrent AMR and acute cellular rejection, with and without hemodynamic compromise [67–71]. Kirklin et al. [72] studied 36 adult heart transplant recipients with recurrent AMR ($n=20$), rejection with hemodynamic compromise ($n=12$), and anti-DSA ($n=4$) who received a 3 month course of photopheresis. In this study, the absence of hemodynamic compromise and death due to rejection were significantly reduced in the patients who received photopheresis. Subsequent clinical trials supported the notion of us using photopheresis prophylactically in transplant recipients [73, 74]. In a pilot study of 23 heart transplant recipients, Barr et al. [73] used a protocol that included prophylactic photopheresis beginning 1 month following transplant and for two consecutive days every month during the first year, every 6 weeks during the first 6 months of year 2, and every 8 weeks during the second 6 month period of year 2. In the photopheresis group, PRA levels were significantly reduced during the first 6 postoperative months, and coronary artery intimal thickness was significantly reduced in the photopheresis group at 1 year and at 2 years compared to the control group. As photopheresis has a relatively favorable risk profile and has been shown to be efficacious in the treatment of acute cellular rejection, further studies are warranted to define its role and impact on refractory AMR.

Anti-lymphocyte Globulins

Anti-lymphocyte globulins are monoclonal (muromonab-CD3 also known as OKT3) or polyclonal (lymphocyte immune globulin or anti-thymocyte globulin or ATG) antibodies directed against T-cell lymphocytes. There are two different formulations of ATG that include: rabbit antithymocyte globulin (RATG or Thymoglobulin) and equine anti-thymocyte globulin (ATGAM). ATG has been used for AMR. Muromonab-CD3 is included for historical purposes as it is no longer marketed. There is limited data to support the use of polyclonal antibodies in AMR, as most studies have focused on acute cellular rejection or induction [75, 76]. RATG has been used in combination for induction therapy. In these studies, RATG was used with IVIg, plasmapheresis, and rituximab in sensitized patients [77]. Direct comparisons between both formulations of polyclonal ATG and muromonab-CD3 demonstrated that they have a comparable efficacy in decreasing acute cellular rejection; however, polyclonal ATG has fewer side effects [78, 79]. Emerging concerns focus on whether muromonab-CD3 prophylactic treatment may cause sensitization and AMR in heart transplant recipients [80]. The efficacy of the various polyclonal ATG regimens appear to be similar [81, 82]. Similarly prophylactic equine ATG has been associated with C4d and horse IgG capillary deposition of heart transplant recipients in the absence of clinical AMR [83]. ATG (RATG and equine ATG) induction therapy has been reported to induce acute and hyperacute AMR in nonsensitized kidney transplant recipients [84]. Despite the limited data regarding the use of polyclonal antibodies in cardiac AMR, they remain a cornerstone of many AMR treatment strategies.

Monoclonal Antibodies: Rituximab

Rituximab is an engineered, chimeric murine–human monoclonal antibody that detects CD20 which is expressed on all B lymphocytes. Rituximab was first used by oncologists as

treatment for B-cell non-Hodgkin lymphoma. Subsequently, rituximab has also been used for myasthenia gravis and post-transplantation lymphoproliferative disorder [85].

Rituximab is generally used in combination with other therapies when used to treat AMR or sensitization. The impact of rituximab was demonstrated in cardiac transplant recipients with biopsy-proven AMR and LV dysfunction who were treated with rituximab 375 mg/m^2 per week for 4 weeks as monotherapy. All the patients in this study had normalization of LV function with complete histological resolution of AMR without significant infections or drug-related complications [86]. There are also reports of the successful use of rituximab for desensitization as well as salvage therapy for refractory AMR [87, 88]. These studies emphasize the importance of targeting the B-lymphocyte population in order to decrease the antibody production for the successful treatment of AMR in the transplant recipient.

Monoclonal Antibodies: Alemtuzumab (Campath)

Alemtuzumab is a humanized, lymphocyte-depleting rat monoclonal antibody that detects and binds to CD52 which is expressed on the surface of all T and B lymphocytes, natural killer cells, monocytes, and macrophages. As CD52 is not expressed on most granulocytes, erythrocytes, platelets, hematopoietic stem cells, and lymphoid progenitors, transient and effective depletion of mature lymphocytes is observed without impacting the cellular reconstitution capability of the bone marrow [89]. As a subpopulation of CD34+ cells may have transient or variable expression of CD52, alemtuzumab has been used for the treatment for lymphoma and leukemia, particularly chronic lymphocytic leukemia. Alemtuzumab has been used as induction therapy and desensitization in solid organ transplantation such as abdominal and lung transplantation. Relatively few reports highlight the use of alemtuzumab for the treatment of rejection. In a limited number of lung transplant recipients with rejection refractory to steroids and ATG, alemtuzumab appeared to be effective in reversing rejection [90]. Similarly the treatment of AMR appears similarly effective in kidney transplant recipients but this treatment therapy may have an increased incidence of infection-related deaths [91–93]. Woodside and Lick [94] demonstrated the successful reversal of AMR in a cardiac transplant recipient with recurrent and refractory hemodynamically significant rejection. Currently in 2016, there are no prospective studies that examine the efficacy of alemtuzumab as treatment for AMR in the cardiac recipient. When used as induction therapy in a steroid-free protocol and compared to a standard regiment, alemtuzumab appears to be associated with similar survival up to 5 years and less rejection [95, 96].

Monoclonal Antibodies: Bortezomib

Antibodies and B cells are important potentiators of AMR; however, plasma cells are the major alloantibody-producing cells. AMR protocols generally have not included agents that target plasma cells. Thus, it is possible that an essential target for AMR is not being treated with current protocols. Bortezomib, a reversible 26S proteasome inhibitor, depletes plasma cells in addition to exhibiting other pleiotropic immunomodulatory effects [97]. Bortezomib was initially used for the treatment of multiple myeloma. While bortezomib has been used for desensitization and AMR in the renal transplant recipient with variable results, it has been used as a rescue therapy for refractory AMR [98–101]. In these studies, kidney transplant recipients with refractory AMR and acute cellular rejection were treated with a single cycle of bortezomib (1.3–1.5 mg/m^2 × 4 doses over 11 days (days 1, 4, 8, and 11)) combined with cytolytic antibodies, corticosteroids, rituximab, plasma exchange, and IVIg [102]. All patients demonstrated improved allograft function with decreased levels of DSA after bortezomib treatment. Similarly, Perry et al. [101] reported that two kidney transplant recipients that were treated with bortezomib, plasma exchange, and IVIg had a transient decrease in bone marrow plasma cells and alterations in alloantibody specificities. In contrast, Sberro-Soussan et al. [103] observed that a single cycle of bortezomib (1.3 mg/m^2 × 4 doses) as monotherapy for AMR had limited impact on DSA levels in sensitized kidney transplant recipients. Therefore it is possible that the success of bortezomib in the treatment of AMR may be due to the combination therapy that has been utilized to impact the immune system. Little data exists regarding the use of bortezomib in heart transplantation. Bortezomib use following failure of therapy with plasmapheresis alone or in combination with IVIg and rituximab (one case), has been reported in pediatric heart transplant recipients with AMR. There was resolution of graft dysfunction, clearing of C4D and IgG, and reduction in DSAs in all patients, although two died from complications [104]. Eckman and colleagues reported successful use of bortezomib in a patient with refractory AMR [105]. Finally, Patel and colleagues reported successful desensitization in 6 of 7 heart transplant candidates, resulting in successful transplantation in four patients. These limited successes and supporting evidence from the renal literature suggest that additional studies of bortezomib in heart transplant are warranted.

Eculizumab (Complement Inhibitor)

Complement activation is necessary for AMR to occur. It is the predominant effector pathway of AMR, thus making complement activation an attractive target for AMR therapies. Eculizumab, a C5 inhibitor approved for use in paroxysmal nocturnal hemoglobinuria, blocks serum complement-

mediated hemolytic activity [106, 107]. Preclinical studies are supportive of the potential for eculizumab as treatment for AMR. In a mouse presensitized kidney transplant model, Rother et al. [108] observed that despite the continued presence of DSA, there was complete inhibition of intragraft terminal complement deposition, AMR and ACR. Similar observations have been reported in rat and murine heart transplant models [109].

Stegall and colleagues [110] demonstrated that induction therapy with eculizumab in highly sensitized kidney transplant recipients reduced the incidence of AMR. Complete resolution of biopsy-proven AMR with restoration of graft function has been reported in a single case of a kidney transplant recipient who received eculizumab as rescue therapy in combination with IVIg, plasma exchange, and rituximab. The use of eculizumab remains experimental and off-label. Cost and lack of coverage by most insurers for the indication of AMR limit its use; however, due to its targeting of one of the most essential links in the pathophysiology of AMR, eculizumab could represent an effective therapy for AMR.

Mycophenolate Mofetil

Myocophenolate Mofetil is an essential component of the immunotherapy for the cardiac transplant recipient. Despite clinical and scientific data documenting the impact of MMF on B-cell proliferation and antibody production, it has not been systematically studied in the prevention or treatment of AMR [111]. MMF effectively reduces posttransplantation HLA and no-HLA antibodies and B-cell counts when compared to azathioprine in healthy controls and in heart transplant recipients [112].

Cyclophosphamide (Cytoxan)

Cyclophosphamide targets B lymphocytes and is a nitrogen mustard alkylating antineoplastic agent. Although no longer used by most heart transplant centers, cyclophosphamide, has been used for decades for refractory rejection and desensitization. In general, cyclophosphamide has been combined with other therapies such as plasmapheresis and rituximab when treating AMR [113]. In the early years following the first heart transplant, cyclophosphamide was substituted for azathioprine as maintenance immunosuppression in patients with AMR. Almuti et al. [114] undertook a retrospective study of 37 patients with biopsy-proven AMR treated with plasmapheresis (5–6 cycles) and intravenous cyclophosphamide (0.5–1 g/m^2 every 3 weeks for 4–6 months) and reported that the 1-year survival in this series was 78 %. Cyclophosphamide has been rarely used due to its failure to prevent AMR recurrence and its potential serious and long-term side effects [22].

Total Lymphoid Irradiation

Total lymphoid irradiation (TLI) delivers targeted irradiation to lymphoid tissue. TLI was first described in clinical transplantation approximately 50 years ago as a nonmyeloablative treatment for Hodgkins disease. It was used as adjuvant therapy to prolong renal allograft survival in humans [115]. TLI has also been reported to induce cardiac allograft tolerance. The first report (1978) of cardiac allograft tolerance following transplantation was in rodents. Induction of tolerance with TLI was reported in humans in 1984 [116, 117]. In the late 1980s and early 1990s, TLI was more commonly used for recurrent or refractory cardiac allograft rejection [118, 119]. Since then, TLI has rarely been used for heart transplant recipients due to potential long-term radiation-related side effects, such as myelodysplasia and leukemia [120].

TLI has been successfully used in heart transplant recipients with biopsy-negative cardiac allograft dysfunction [121, 122], although most studies in heart transplantation have focused on ACR [123]. The University of Alabama at Birmingham program has examined the impact of TLI. In their series, 73 adult recipients were treated with TLI during the first 6 months following transplantation for rejection with vasculitis (4 %), rejection with perturbed hemodynamics (25 %) and recurrent rejection (71 %). TLI resulted in decreased rejection episodes, but this therapy was complicated by myelodysplasia or acute myelogenous leukemia which was observed in seven patients [124]. Considering the potential for serious and potentially fatal side effects, TLI is not recommended for the treatment of AMR.

Splenectomy

Plasma cells produce antibodies and therefore this cellular population represents an attractive target for intervention. The B lymphocytes and the plasma cells that produce the antibodies, which contribute to AMR, reside in the spleen. Plasma cells do not express CD20 antigen and therefore they are unaffected by rituximab [85]. Splenectomy is a method of removing plasma cells and activated B cells, thereby diminishing antibody production to a level that can be managed with other therapies [125]. Splenectomy, however, does not affect the plasma cells and B cells that reside outside of the spleen in the lymph nodes and bone marrow. Therefore, the inability to remove all the activated B lymphocytes and antibody producing plasma cells may limit the role of splenectomy in the management of AMR. Splenectomy has been used in desensitization protocols in kidney transplantation [126, 127], as rescue therapy in patients with refractory kidney AMR [125, 128, 129], and in ABO-incompatible kidney transplant, although splenectomy in ABO-incompatible kidney transplant was later deemed to be unnecessary [130].

Currently, in 2016, the use of splenectomy as treatment for AMR in heart transplant recipients has not been reported. In part, this is due to the reports of death and infectious complications following splenectomy in kidney transplant recipients [125, 131]. If used at all, splenectomy should be considered rescue therapy for patients with refractory AMR.

Combination Therapies and Emerging Therapies

As outlined above, most of the therapies for AMR are typically used in combination, in an attempt to affect multiple pathways of the immune response. AMR has frequently been treated with modification of the baseline maintenance immunosuppression protocol, corticosteroids, anti-lymphocyte globulin, plasmapheresis, IVIg and rituximab. Refractory AMR has been treated with the emerging agents, such as eculizumab, bortezomib, alemtuzumab, and photophoresis. Older modalities, such as TLI and splenectomy, while holding theoretical benefits are not used due to their adverse side effect profiles. Therapies used in hematology and oncology continue to stimulate interest in transplant medicine. One example used in hematological malignancies includes carfilzomib, an irreversible proteasome inhibitor. Belimumab and atacicept are newer engineered monoclonal antibodies directed at B lymphocyte activation and survival.

Mechanical Circulatory Support and AMR

Mechanical circulatory support has been increasingly used in hemodynamically compromised patients. It has been also been used in heart transplant recipients with primary graft failure [132, 133]. Extracorporeal membrane oxygenation (ECMO) has also been used in primary graft failure and long-term survival (of patients treated with ECMO) appears to be comparable to that in recipients without primary graft failure [134, 135]. Successful use of other nondurable devices has been used for primary graft failure [135, 136], and specifically for AMR [137–140]. Kittleson and colleagues [137] observed that heart transplant recipients undergoing AMR and treated with mechanical circulatory support had improved hemodynamics after support with ECMO. Preemptive use of ECMO conferred a significant survival benefit when compared to salvage therapy. 26 % of the patients preemptively treated with ECMO, compared to only 7 % of the salvage patients were alive at 1 year. Cardiac transplant recipients with primary graft failure due to acute rejection constitute a high-risk group. Thus, ECMO or other temporary mechanical support can be considered as salvage therapy in those patients with AMR and hemodynamic compromise refractory to medical therapy.

Maintenance Immunosuppression

Although cytolytic or antibody-directed therapies generally tend to be the focus in treating AMR, opportunities should be sought to optimize background regimens. There is little supporting literature in this regard. In cases of non-adherence, drug interactions that lead to reduced immunosuppression drug levels, or iatrogenic reasons for subtherapeutic levels, modifying baseline therapy is an obvious strategy. In other cases, there may be more subtle considerations, particularly in regards to B lymphocytic agents. MMF and sirolimus inhibit B-cell proliferation, immunoglobulin production and induce significant B-cell apoptosis [141–144]. Other B-cell specific drugs that have been previously used for AMR but are no longer used include cyclophosphamide [145–148] and methotrexate [149, 150]. Based on limited available data, the following strategy is recommended: cardiac transplant recipients with AMR who are taking azathioprine can be switched to MMF, those patients taking MMF can be switched to sirolimus and patients taking cyclosporine should be transitioned to tacrolimus. Additionally increasing the MMF dose or adding corticosteroids may be beneficial [47]. In patients with refractory or persistent AMR immunotherapy, doses can be increased and/or addition of one of the emerging therapies can be considered.

Summary

The only curative therapy for end-stage heart failure is orthotopic heart transplantation. Survival following cardiac transplantation is limited, in part, by AMR. The establishment of pathologic criteria for cardiac AMR has propelled the field further although large knowledge gaps remain. Recommendations established by the AHA and ISHLT provide guidance in some areas and it is anticipated that they will serve as a springboard for additional research. Data sharing and molecular analyses will further uncover new mechanisms to limit or arrest AMR in the future.

Diagnostic, Surveillance, and Management of AMR Recommendations (Adapted from [34])

Diagnosis (see Tables 32.1 and 32.4)
1. The diagnosis of AMR should include immunopathological and histological features and clinical symptoms and results (i.e., LV graft dysfunction). Histological evidence of AMR, should be considered diagnostic of rejection (Class I; Level of Evidence C).
2. C4d and C3d expression using immunofluorescent techniques or C4d and CD68 (or C3d) immunoperoxidase staining techniques should be undertaking for the diagnosis of AMR (Class I; Level of Evidence B).
3. Determination of antiendothelial, antivimentin, and anti-MICA and anti-MICB antibodies (i.e., non-HLA antibodies), may be considered when anti-HLA antibodies are absent and AMR is suspected (Class IIb; Level of Evidence C).
Surveillance (see Table 32.5)
1. Immunofluorescent and immunoperoxidase staining techniques should be performed to assess for C4d and/or C3d expression during the first 90 days after transplantation or when AMR is suspected (Class I; Level of Evidence C).
2. Assay for DSA and quantification of antibody should be undertaken during the first 3 months after transplantation or when AMR is suspected (Class I; Level of Evidence C).
3. Examine an endomyocardial biopsy specimen for histological evidence of AMR. This is particularly important if there is a high clinical suspicion for AMR and no evidence of cellular rejection (Class IIa; Level of Evidence C).
4. Perform immunofluorescent and immunoperoxidase staining techniques for C4d and/or C3d expression at least 3, 6, and 12 months after transplantation or with the center's routine surveillance protocol (Class IIa; Level of Evidence C).
5. Perform assays to assess for DSA and quantification of antibody for surveillance at 3, 6, and 12 months after transplantation and annually thereafter or in accordance with the center's routine surveillance protocol (Class IIa; Level of Evidence C).
6. Perform immunofluorescent and immunoperoxidase staining techniques (for C4d and C3d) after a positive result until clearance (Class IIa; Level of Evidence C).
Management (see Table 32.6)
1. Primary therapy for AMR may include IVIg, plasmapheresis, anti-lymphocyte antibodies, and high-dose corticosteroids (Class IIa; Level of Evidence B).
2. Secondary therapy for AMR to include rituximab, bortezomib, and anti-complement antibodies (Class IIa; Level of Evidence C).
3. Consider optimizing maintenance therapy by switching from cyclosporine-based immunosuppression to tacrolimus or by increasing the dose of MMF. Substituting MMF with sirolimus may also be considered (Class IIb; Level of Evidence C).
4. Consider the treatment of rising DSAs in the early posttransplantation period as this may represent a rapid anamnestic antibody response. Supporting evidence that the antibodies fix complement may be useful (Class IIb; Level of Evidence C).
5. The appearance or increase in DSA more than 30 days after transplantation without clinical signs or symptoms or pathological evidence of AMR is unclear, and treatment may be considered by the clinician (Class IIb; Level of Evidence C).
Colvin MM, et al. (2015) Antibody-mediated rejection in cardiac transplantation: emerging knowledge in diagnosis and management a scientific statement from the American Heart Association. *Circulation* 131(18): 1608–39

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Heart and Heart–Lung Transplantation in Adults with Congenital Heart Disease

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_33

Introduction

Since the first intracardiac operations in the early 1950s, the survival of children born with congenital heart disease (CHD) has continually increased. At least 85 % now live into adulthood. With this increased survival, the estimated more than one million adults with CHD now surpass the number of children with such a malformation.

Many of the early operations, such as those for atrial septal defect or patent ductus arteriosus, had and continue to have excellent outcomes and leave patients with few symptoms or cardiac problems as they age. Patients with more complicated anomalies or who had operations that were palliative may experience hemodynamic problems as adults.

Adults with CHD are also living longer, but, unfortunately, even today, the mean age of death of individuals with CHD remains greatly reduced. The median age at death was 57 years in 2007 [1]. The Dutch CONCOR national registry revealed that 77 % of deaths in patients with CHD had a cardiovascular origin, with chronic heart failure being the most common cardiac diagnosis [2]. A recent study showed a 26 % incidence of heart failure in a mixed cohort of patients with simple, moderate, and complex CHD [3]. However, like CHD itself, the true incidence of heart failure in CHD remains unknown.

For many CHD patients, cardiac failure becomes progressively resistant to medical management. One approach to these individuals is heart or heart–lung transplantation. Studies suggest that as many as 10–20 % of children being treated for CHD may eventually need a heart transplant [4].

Heart Transplant Statistics

More than 100,000 heart and heart–lung transplants have been reported to the Scientific Registry of the International Society for Heart and Lung Transplantation (ISHLT) since the first heart transplant in 1967 [5]. From 1987 through 2006, 35,334 adults were reported to the United Network for Organ Sharing (UNOS) and the Organ Procurement and Transplantation Network for cardiac transplantation. Of these adult patients, 689 (1.9 %) underwent transplantation for CHD.

The total number of heart transplants performed worldwide has remained relatively stable over the past several decades, but the prevalence of heart transplantation for CHD has increased by 41 %, from 1.8 to 2.5 % of the total transplant population. This increase in the CHD transplant population contrasts with the 28 % decrease in transplants performed in adult recipients for all other indications. The adult cardiac transplant population will probably increase further as more patients with CHD reach adulthood. A similar trend has occurred with combined heart–lung transplantation, which has a prevalence among adult CHD patients ranging from 1.8 to 2.4 %.

As reported by ISHLT [6], this increase in CHD patients across the transplant population is likely a combination of both effective medical therapy and the use of mechanical support for the more "conventional" forms of heart failure. Little data exist to guide effective medical therapy for most congenital heart lesions. Furthermore, mechanical support options are limited in CHD patients because of anatomical and hemodynamic factors. Thus, heart failure may progress in adult CHD patients, with transplantation being the only suitable advanced treatment option.

The number of adults with CHD needing transplantation will likely increase and present new challenges [7]. Elevated pulmonary vascular resistance (PVR), challenges in measuring PVR accurately, elevated antibody levels, complications following a Fontan procedure, technical surgical challenges, and more complicated postoperative care are issues that complicate transplantation in these patients.

Not surprisingly, the outcome for transplantation differs for patients with CHD or other conditions. Comparing 41,849 adults listed for cardiac transplantation between 1995 and 2009, the 1035 with CHD had a higher early, 1-year, and 5-year mortality following the operation [8]. The higher early mortality may be partly related to the complexity of the transplant surgery itself.

CHD patients often had prior complex cardiac operations. In a study of 24 adults with CHD, 22 had a mean of two previous operations and, at transplantation, 18 of the 24 patients had an additional procedure performed on an extracardiac lesion [9]. Complications from a prior sternotomy and additional reconstructive procedures result in significantly longer mean ischemic and bypass times compared to adults without CHD [10]. This is a well-recognized risk factor for both poor short- and long-term outcomes. The unique surgical challenges pose increased reoperative risk for CHD patients, with a mortality of 18.9 % compared to 9.6 % for non-CHD patients. The early mortality in CHD patients was still higher (16.6 %), even in those without a previous cardiac operation, compared to 6.3 % for those without CHD.

Additional factors affecting survival include cytomegalovirus (CMV) mismatch, previous right heart bypass procedures, high levels of human leukocyte antigens (HLA), and elevated PVR or transpulmonary pressure gradient. In over half of CHD patients, PVR exceeds 4 Wood units, an established risk factor for operative mortality. Finally, heart failure before transplantation contributes to a higher early mortality. Conventional "bridging" therapies, such as mechanical support devices or inotropes, may be unavailable or less effective, resulting in CHD patients being more ill at transplantation. Thus, a CHD patient is often sicker at the time of transplantation than a non-CHD patient.

Knowledge and experience gained over the past decades likely contribute to the decreasing posttransplant mortality among the CHD population. A recent study [11] compared survival in 19 adults with CHD aged 39 ± 13 years with 428 adults aged 54.7 ± 12 years who received transplants for other conditions. No difference in posttransplant survival was found for any period through 5-year posttransplant, with survival being 70 % and 72 %, respectively. No correlation was found for a number of factors including failed Fontan

procedure, end-stage liver disease, or percent of reactive antibodies. The authors were encouraged that, with proper donor and recipient selection, the results for adults with CHD resembled those for other patients undergoing transplantation. Greutmann and associates [12] compared 13 adults and adolescents with CHD to 322 patients without CHD. The survival of the 13 was 85 % at 30 days, 1 year, 5 years, and 10 years and 77 % at 20 years. This survival was no different from that of either the entire group or the age-matched patients with dilated cardiomyopathy.

Finally, recent data from ISHLT confirms that adult CHD patients at the time of transplant tend to be younger and have fewer comorbidities. These statistics, combined with improved patient selection, surgical techniques, and postoperative management, have resulted in an overall median survival for CHD patients of 13 years compared to 10 years for the remaining populations. In fact, the conditional median survival (survival of patients who live the first year following transplant) is even more favorable for the CHD population: 18 years versus 13 for non-CHD patients [13]. These data further support transplantation as a viable option in carefully selected CHD patients.

Indications for Heart Transplantation

With a relatively small number of adults with CHD, experience and information about adults with acquired cardiac disease are used to direct transplantation care. Because CHD patients are younger at time of transplant and posttransplant survival is limited, the operation should not be performed prematurely nor prolonged by palliative or other operations, which may decrease the success of transplantation. One group [14] suggested that transplantation be delayed, if possible, until a child with CHD has reached at least late adolescence. None of the author's 14 patients had an early or late death, suggesting that a larger body size makes it easier to perform the transplant and provide postoperative care. Determining optimal transplant timing for a CHD patient is complicated by the lack of data about outcomes of medical therapy and the risk of developing irreversible complications in other organ systems.

In adults with acquired heart disease, the VO2 max has been used to define severe congestive heart failure (CHF) and is associated with 1-year posttransplant mortality. A <14 ml O_2kg^{-1}/min^{-1} (or <12 ml O_2kg^{-1}/min^{-1} if treated with beta-blockade) or <50 % predicted VO2 max has been considered an indication for heart transplantation [15, 16]. These guidelines have been extrapolated to CHD patients despite the lack of supporting data. Given the known reduction in exercise capacity in a large percentage of CHD patients [17, 18], the results of such cardiopulmonary stress testing should be complemented by other factors including functional classification, hospitalization requirements, ventricular function, abnormal laboratory results (low serum sodium, renal dysfunction, elevated brain natriuretic peptide, etc.), and underlying etiology.

Elevated pulmonary artery pressure and/or vascular resistance are contraindications for transplantation. Specifically, a pulmonary vascular resistance >5 Wood units and a transpulmonary pressure gradient >15 mmHg are considered contraindications. If initial testing reveals elevated pulmonary vascular resistance, pulmonary vasodilators are administered to assess patients. If pulmonary vascular resistance falls to normal levels, transplantation can be considered, but with an increased risk. If levels are unresponsive to vasodilators, transplantation should not be performed.

Data about patients needing transplantation are submitted to UNOS and classified according to body size, blood group, and clinical status (see below). An encouraging fact is that the survival of patients listed with UNOS has improved from 49.5 to 69.0 % between 1990–1994 and 2000–2005 [19].

UNOS Classifications

1A.
- Inpatient + mechanical circulatory support <30 days
- Mechanical circulatory support >30 days with significant device-related complications
- Mechanical ventilation
- Continuous infusion of high-dose inotropes
- Life expectancy <7 days without transplantation

1B.
- VAD [ventricular assist device] >30 days
- Continuous infusions of inotropes (not high dose)
- Justified exceptional case

2.
- Does not meet status 1A or 1B.

Ongoing inotrope infusion, mechanical ventilation, or circulatory support may not be used as often in CHD patients compared to other adults listed for transplantation because of CHD patients' unique anatomy and physiology. Consequently, many patients with CHD are not classified as 1A or 1B for transplantation because they fail to meet traditional UNOS criteria. To be considered for transplantation, CHD patients must be listed as an exception. For instance, patients who develop significant PLE following a Fontan procedure do not meet class 1A or 1B criteria, even though this serious complication improves following transplantation. Therefore, patients with significant protein-losing enteropathy (PLE) should be submitted to UNOS as an exceptional case for a higher priority listing for transplantation. Review of The Organ Procurement and Transplantation Network and United Network for Organ Sharing database from 2005 to 2009 showed that adult patients with CHD are less likely to be listed at higher urgency status and to have a higher cardiovascular mortality compared to individuals without CHD awaiting heart transplantation. Compared to non-CHD individuals, those with CHD were less likely to receive a transplant at any time after listing [20].

In evaluating adults with CHD, two factors limit the ability to classify patients or find appropriate donors. One factor

is the difficulty determining the pulmonary artery pressure and vascular resistance in patients with vascular abnormalities or more than one source of pulmonary blood flow. These abnormalities, which make it difficult to access the pulmonary vascular bed, may either be congenital or caused by an operation.

The second limiting factor is the level of HLA antibodies. Many patients who underwent a previous cardiac operation had a blood transfusion or a procedure that used homograft tissue. Each enhances the risk for increased HLA antibody development. Prior pregnancies or ventricular assist device use further increases the risk. The presence of antibodies makes it more difficult to find an appropriate donor heart. Panel-reactive antibody (PRA) values exceeding 10% increases the chance of acute rejection and death [21, 22]. For these patients, a donor-recipient crossmatch (virtual or prospective) should be performed before transplantation to reduce chances of rejection.

Patients with a high antibody level often have a longer waitlist time before a suitable donor heart becomes available. Immune system alteration in patients with significant PLE does make it difficult to accurately measure anti-HLA antibodies. This places patients at higher risk of rejection and a poor posttransplant outcome.

If medically indicated, an adult congenital heart disease (ACHD) specialist should be aggressive in encouraging appropriate patients to consider transplantation. As they reach middle age, many adults with CHD believe they have reached the point in life when they would probably die. That prediction was often made when information about CHD was limited and heart transplantation was in its infancy. Times and capabilities change. Transplantation should be encouraged in appropriate patients. The expectations of patients with CHD and those with an acquired condition differ. This highlights the need for discussion between ACHD specialists and members of the transplantation team for proper evaluation and referral of ACHD patients.

Posttransplant Considerations

While adults with CHD have a higher initial mortality following transplantation, their 10-year survival is favorable [23]. The relative risk for death during the first year compared to those with a cardiomyopathy was 2.46 for those aged 18–30 years and 2.18 for those aged 31–60 years [23]. In part, this relates to unique issues faced by adults with CHD following transplantation:

- Increased bleeding because of coagulation abnormalities may complicate the operative and immediate postoperative period.
- Coagulation abnormalities may be related to more complicated surgery and longer bypass time, but often are exacerbated by preoperative liver disease. If the liver disease is advanced, concomitant vasodilation may necessitate higher dosages of vasoactive medications to maintain appropriate blood pressure.
- Aortopulmonary collateral vessels can cause a significant left-right shunt leading postoperatively to high-output heart failure. If significant, the shunt(s) may be closed by interventional catheter techniques.
- Patients with protein-losing enteropathy have a tendency for infections; that tendency is worsened by posttransplant immunosuppression. Depending on the severity of immunoglobulin loss in these patients, the immunosuppression regimen may need to be altered. This step, however, increases rejection risk.
- Patients have a higher risk of developing tricuspid regurgitation posttransplant because of their underlying pretransplant hemodynamics. Factors causing tricuspid regurgitation were assessed in a study of transplanted patients ages 12–64 years [24]. Early regurgitation was related to rejection of grade 2 or greater severity and elevated pulmonary vascular resistance. Late regurgitation was related to standard, rather than bicaval, transplant technique, the number of episodes of rejection, and the number of biopsies and elevated right-sided pressures.
- Finally, complex vascular anatomy may make routine surveillance biopsies difficult.

Because of these unique challenges facing CHD patients, it is important for a team of physicians and nurses, including those with advanced knowledge and experience with CHD, to participate in posttransplant care.

Common transplant comorbidities are also present in CHD patients, but their incidence is unknown. These include the well-identified factors of hypertension, hypercholesterolemia, renal dysfunction, and diabetes, all of which can result from immunosuppression protocols. Allograft rejection is most common during the first year posttransplant. A higher rejection risk exists because of underlying anti-HLA antibodies. Patients with rejection during the first postoperative year have a lower survival (88% compared to 94% at 3 years) [25]. Additionally, rejection increases the risk of developing cardiac allograft vasculopathy. Vasculopathy, which may be a form of chronic rejection, is an important contributor to long-term mortality. Other contributing factors are hypertension, hypercholesterolemia, diabetes in the heart donor, male gender, large body size, and HLA mismatch. Although malignancies are usually a late complication of immunosuppression, lymphoma, specifically posttransplant lymphoproliferative disease (PTLD), occurs more commonly during the first years after transplantation. PTLD is closely associated with Epstein–Barr infection. Because of the younger average age at time of transplant, CHD recipients are more frequently EBV naïve. This increases the risk of developing primary EBV infection and subsequent PTLD. Therefore, heightened EBV monitoring is indicated in all posttransplant recipients who are EBV naïve.

The fact that a younger age is usually associated with fewer comorbidities suggests that long-term transplant survival would be greater. Younger adults (aged 18–35 years), however, may have a higher death rate than older patients following heart transplantation. Data from the Cardiac

Transplant Research Database showed 5-year survival rates at 67 % (aged 18–35 years), 78 % (35–59 years), and 76 % (>60 years) [25]. Furthermore, compared to those over age 35, the younger age group had a higher risk of death from rejection, but a low risk of death from infection. Younger patients' tendency to not comply with treatment regimens was of significant magnitude; however, this did not solely account for the difference. George et al. [25] considered current immunosuppression regimens suboptimal for young adults and believed they should be changed, but did not suggest specific modifications.

Specific CHD Conditions and Transplantation

Congenital heart disease encompasses a variety of anatomic and hemodynamic anomalies. Ideally, survival could be determined for each individual condition, but that data are unavailable. The next three sections address issues related to and results of heart transplantation for different hemodynamic lesions.

Conditions Treated with a Right Ventricular Bypass Procedure

This group includes patients with a double-inlet left ventricle, tricuspid atresia, or a form of hypoplastic left ventricle. Patients with the hypoplastic left ventricle had undergone the Norwood sequence of operations. Ultimately, each has been treated by a Fontan procedure in which the right side of the heart is bypassed. Therefore, the systemic venous return is delivered directly to the pulmonary arterial system without an intervening ventricle.

The primary indications for cardiac transplantation following a Fontan procedure include protein-losing enteropathy, arrhythmia with ventricular dysfunction, or ventricular heart failure [26]. PLE is a serious complication, with about half of patients dying, whether treated medically or surgically [27]. Its cause is unknown, but could relate to systemic venous congestion and disturbed lymphatic drainage. These changes leading to protein loss do not occur in all patients with elevated venous pressure, and individuals with normal venous pressure may develop this syndrome. Furthermore, PLE resolves in most patients following transplantation, but occasionally persists [28], suggesting that a permanent intestinal change has occurred.

After a well-performed Fontan procedure that leaves no anatomic abnormality, 10-year survival is between 60 and 81 %. The late mortality and morbidity are affected by a number of pre- and postoperative issues. These include ventricular failure, PLE, atrioventricular valve regurgitation, obstruction of the venous pathways, hepatic dysfunction, aortopulmonary collaterals, and thromboembolism. The physiologic features of the Fontan circulation, the often complex cardiac anatomy, and the patient's status all affect a transplant's outcome, which is often the only treatment option.

Issues making transplantation challenging following a Fontan operation include pulmonary vascular abnormalities, the complex anatomy of the cardiac anomaly, bleeding risks, and adhesions from previous operations [29]. Changes in the pulmonary vascular bed are often present from early life—before the Fontan circulation was established. These pulmonary vascular changes include abnormalities of size or distribution of pulmonary arteries; increased pulmonary blood flow; pulmonary venous obstruction, even if mild; and pulmonary thromboembolism. Obtaining reliable data to calculate pulmonary vascular resistance is difficult. Potential barriers include collateral circulation, pulmonary arteriovenous malformations, low cardiac output, unequal distribution of pulmonary flow, and pulmonary venous obstruction. Certainly, elevated pulmonary vascular resistance affects the posttransplant status, and it is uncertain whether the pulmonary changes will subsequently resolve.

Among children and adults undergoing transplantation for a failed Fontan procedure, the survival rate was lower (77 % and 70 %, respectively, for 1- and 5-year survival) than for non-Fontan patients (88 % and 81 %, respectively, for 1- and 5-year survival) [30]. Davies and coworkers [31] reviewed the records of 43 patients with a Fontan connection whose ages ranged from 1 to 47 years. They compared their features with 129 patients with other forms of cardiac malformations. Among the Fontan patients' indications for transplantation were PLE in 17, chronic heart failure in 18, and acute post-Fontan failure in 4 patients. These patients were more likely to need pulmonary artery reconstruction (85 %) and had longer cardiopulmonary bypass times (278 min). The 90-day mortality rate was 35 % compared to the 20 % for the other group.

Of 35 patients [32], 24 with a Fontan and 11 with a Glenn procedure but no Fontan operation 10 (28.5 %) died within 6 weeks following heart transplantation. The early deaths were primarily from postoperative hemorrhage or infection. Six of 15 patients who had PLE prior to transplantation died early. Of the 25 patients discharged following transplantation, 10-year survival was 92 %. The survivors, however, were not free of morbidity. There were 21 episodes of rejection, nine patients had hypertension, three others had functional renal abnormality, and another developed PTLD.

In another study, the early posttransplant mortality for adults with a single ventricle was higher (23 %) than for those with two functioning ventricles (8 %) [33]. The operative mortality, however, decreased over time in both groups of patients. Patients with a Fontan, or those with an alteration in the usual transplant procedure, such as reconstructing proximal pulmonary arteries, seem to have a higher operative mortality.

Experienced clinicians at Washington University, St. Louis [34], identified 34 patients with a failed Fontan procedure. The patients were divided into two groups: 17 with preserved ventricular function and 17 with impaired ventricular function. The posttransplant mortality at 1 year was

significantly greater in the group with preserved ventricular function (42 %) compared to those with impaired ventricular function (24 %). Those with preserved function also had a greater incidence of PLE, more aortopulmonary collaterals, and higher pulmonary vascular resistance. Since the risk in these patients is significant, pretransplant treatment of the collaterals and elevated pulmonary vascular resistance may improve the hemodynamics and outcome. The deaths were often from severe infection, thus underscoring the multisystem involvement in these complex patients.

In addition to sepsis, many deaths in patients with a Fontan occur from multisystem failure and hemorrhage in the first week posttransplant. An important contributing factor is hepatic cirrhosis from chronic elevation of venous pressure. Resultant coagulation abnormalities and hepatic decompensation after transplantation are complications that adversely affect the outcome. Advanced hepatic dysfunction is also accompanied by significant vasodilation. When combined with the coagulation deficits, vasodilation can greatly increase peri-transplant complications, even in the absence of frank hepatic failure.

Unfortunately, accurately evaluating the degree of liver dysfunction is difficult in this population. Routine liver function testing and imaging can significantly underestimate the degree of liver dysfunction. Many centers obtain hepatic biopsies during the transplantation evaluation to more accurately assess hepatic pathology. With knowledge of hepatic abnormalities, more aggressive approaches can be applied and, in certain instances, combined hepatic and cardiac transplantation performed [35]. The absence of prognostic data makes decisions difficult concerning when the liver dysfunction is too advanced to proceed with heart transplantation alone. The regenerative capacity of the liver must be considered in relation to the increased perioperative complications from its dysfunction.

Conditions with the Right Ventricle Sustaining Systemic Circulation

The right ventricle may be unable to maintain systemic circulation over a long time, leading to right ventricular enlargement and development of heart failure. The underlying conditions where this occurs are primarily complete transposition of the great arteries following an atrial switch (baffle) operation and congenitally corrected transposition of the great arteries. Systemic atrioventricular (AV) valve regurgitation is quite common as well in these patients. The severity of regurgitation may be overlooked and, when left untreated, leads to progressive dilation and further deterioration of RV function.

Even without significant valvular disease, right ventricular systolic function often progressively decreases in patients with a systemic right ventricle. In 61 % of patients with an atrial switch, right ventricular function decreased from normal to moderate or severe dysfunction after 14 years postoperatively [36]. Although congestive heart failure from systemic RV dysfunction appears to activate the same signaling cascades as with systemic left ventricular dysfunction [37], trials consistently fail to show an improvement with conventional heart failure therapy (i.e., beta blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, etc.) [38]. Thus, in patients with a systemic right ventricle, heart failure often progresses, leading to consideration of heart transplantation.

During the transplant procedure, the abnormal position of the aorta and pulmonary artery requires that the recipient arteries be extensively mobilized. The donor heart must have adequate length of the aorta and pulmonary artery so that connections will not be obstructed. In patients with an atrial baffle, reconstruction of the recipient atria with excess donor tissue is often needed, as well. Messner et al. [39] carefully describe the transplant procedure in complete transposition.

Compared to the outcome of patients with a Fontan, less information is available about heart transplantation in patients with systemic RV dysfunction. One study reported 113 patients who underwent a Mustard atrial baffle operation for complete transposition. When restudied 28 years later, the survival was 80 %, and 75 % were New York Heart Association class 1 [40]. The Spanish Heart Transplant Registry [41] reported ten adults with either congenitally corrected transposition or complete transposition following an atrial switch. No deaths occurred during the first 5 years posttransplant. Two deaths occurred at about 5 years and then no more until around 10 years. After 10 years, survival was similar to patients with single ventricle and pulmonary stenosis, those following a Fontan procedure, and those in right ventricular volume overload. Their 20-year survival was 50 % [41]. Other reports of adults from ages 37–56 years with either complete or corrected transposition are reported with details of their operation [39, 42, 43]. Reports describe the use of a left ventricular assist device to treat severe right ventricular failure in adults with an atrial baffle procedure as a bridge to transplantation [44, 45] and the reversal of marked pulmonary hypertension in another patient [46].

Other Conditions

For some patients with tetralogy of Fallot or other anomalies following repair, the long-term effects of pulmonary regurgitation on right ventricular volume and the development of heart failure prompt transplantation. Heart transplantation is also used for patients with complex, unrepairable, or incompletely repaired anomalies with persistent heart failure, but normal pulmonary vascular resistance.

Heart–Lung Transplantation and Lung Transplantation

During the past 20 years, the number of heart–lung transplants for all patients (both CHD and non-CHD) has decreased, in favor of bilateral lung transplantation. Issues

impacting this shift are well discussed in a recent review [47]. Two significant issues prompting the shift to lung transplantation are eliminating the need for cardiopulmonary bypass and having access to improved medications for treating pulmonary hypertension.

Both approaches can help adults with CHD and pulmonary vascular disease. Their number may increase as more of these patients live into adulthood.

Indications and Outcomes

One-third of heart–lung transplantations are performed in adults with Eisenmenger syndrome. Heart–lung transplantation is also used in patients with complex cardiac anomalies, previous unsuccessful operations, uncorrectable conditions, and severe left ventricular dysfunction. Operative mortality is high because of bleeding, infection, and graft failure. After the first year following transplantation, the survival rate is similar to patients with other indications for transplantation. In some patients, such as those with a ventricular septal defect and pulmonary vascular disease, defect repair and bilateral lung transplantation should be considered. Other patients with congenital anomalies of the pulmonary vascular bed, pulmonary venous obstruction, and significant peripheral pulmonary artery stenosis could certainly benefit from this procedure.

One study showed only an 8 % occurrence of cardiac vascular changes following heart–lung transplantation. Rejection changes in one organ do not predict rejection in the other organ. Disadvantages for heart–lung transplantation include increased waiting time for donor organs, the need for cardiopulmonary bypass, anticoagulation and rejection, and other cardiac complications.

Data reported in 2001 [48] covered a retrospective review of 69 adults with CHD. Thirty-one received heart–lung transplantation, 30 a lung transplant, and eight a heart transplant. For those with a heart–lung transplant, the survival through 3 years was comparable to those with other cardiac conditions. Survival was 74 %, 58 %, and 47 % at 1 month, 1 year, and 3 years, respectively. The early deaths were related to hemorrhage in five patients, presumably from bronchial collaterals, graft failure, pulmonary embolism, and tracheal dehiscence in one each. Late deaths were from infection and graft failure (three each), cerebrovascular accident (CVA) in two, and one from an unknown cause. In the 30 patients undergoing lung transplantation, seven had had a previous corrective cardiac operation and 23 underwent a simultaneous repair with the transplant. Survival was similar to heart–lung transplantation and to lung transplantation for other conditions: 73 % at 1 month, 60 % at 1 year, and 60 % at 3 years. Early causes of death were graft failure (4) and one each of infection or CVA. Late deaths were from rejection (5), graft failure (1), and perforated ulcer (1).

Certainly, lung transplantation with repair of the cardiac malformation increases the heart donor pool. Either double or single lung transplantation can be performed with similar survival.

To use either approach, clinicians must be certain that their patient has good cardiac function.

Other considerations include the degree of right ventricular hypertrophy from pulmonary hypertension and any problems reducing pulmonary artery pressure in patients with a left-to-right shunt lesion. Likewise, a dilated right ventricle and associated tricuspid regurgitation may require repair of the valve or placement of a transannular ring. Overall posttransplantation survival for lung transplantation has improved. For two time periods, 1984–1991 and 1992–1999, the 5-year survival was 40 % for the former and 60 % for the latter.

In another single-center study [49], 51 patients were transplanted, 46 by heart–lung, and five by lung allograft. There were six early and 13 late deaths.

Survival was 80, 69, and 53 % at 1, 5, and 10 years, respectively. There were no differences following these two operations compared to the same operations for patients with other underlying conditions. For both, early deaths were usually from graft failure or sepsis, while late deaths were from pneumonia or bronchiolitis obliterans.

Waitlist Classification for Lung Transplants

Referring patients for heart–lung or lung transplantation should be considered earlier than for heart alone. Difficulties predicting a patient's course can make the timing of an operation difficult.

Patients are usually listed in both lung and heart allocation systems. UNOS uses a lung allocation scoring system (LAS) that considers the severity of the disease and likelihood of survival after transplantation. Patients with pulmonary hypertension are not well classified in the LAS system. They may be more accurately classed by cardiac criteria.

Both cardiologists and pulmonary specialists monitor patients posttransplant. Pulmonologists perform bronchoscopy and transbronchial biopsies, more frequently in the first year after transplantation. Myocardial biopsies are performed more frequently during the first 4–6 months.

Summary

Advances in surgical techniques, medical management, and invasive and noninvasive diagnostic modalities have dramatically increased the survival of individuals born with CHD the past 50 years. These advances lead to an ever-increasing population of adults with CHD, including a significant percentage that will require specialized medical care. Data from the Nationwide Inpatient Sample indicates that the number of hospital admissions for adults with CHD increased 101.9 % from 1998 to 2005, with heart failure among the leading indications for hospitalization [50]. Unfortunately, data are lacking to guide diagnosis and treatment of heart failure in patients with CHD; thus, the proportion of cardiac transplantation in adults for CHD will likely continue to increase.

This is especially true for those with right heart bypass procedures, as with a Fontan/Kreutzer. In a carefully selected patient population, heart and heart–lung transplantations can be performed with an acceptable risk and a 50 % 10-year survival. However, the procedures are associated with technical problems, issues about wait list classifications, and risk for unique postoperative complications. Due to the procedures' complexity, CHD patients require multi- and interdisciplinary evaluation and care both pre- and posttransplant.

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Cardiac Xenotransplantation

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D.J. Garry et al. (eds.), *Congestive Heart Failure and Cardiac Transplantation*, DOI 10.1007/978-3-319-44577-9_34

The scarcity of human donor hearts limits cardiac transplantation to a small fraction of potential recipients. This scarcity will probably increase during the next several decades. While mechanical and bioengineered hearts might, in principle, supplant cardiac transplantation, the related cost and technical sophistication required may limit their use. Using hearts from animals (called xenotransplantation), especially from swine, could potentially address the scarcity of human hearts and the limitations of devices and bioengineered organs. However, the immune response of the recipient against the graft, and the potential for transferring zoonoses and physiologic incompatibilities, appears to pose barriers to clinical cardiac xenotransplantation today.

What makes these barriers seem less daunting is that swine has been genetically engineered to suppress expression of at least one key antigen and to produce multiple human proteins that constrain inflammation and immunity. Investigation of humans exposed to swine tissues and organs has decreased concerns about zoonoses. And physiological incompatibilities can potentially be addressed by genetic engineering and use of therapeutics to control inflammation, coagulation, and immunity. Therefore, cardiac xenotransplantation might soon be feasible as a bridge procedure, enabling clinicians to gain the knowledge required for cardiac replacement.

Xenotransplantation's Potential for Treating End-Stage Cardiac Disease

Failure of the heart causes more chronic disease and death in modern and modernizing societies than any other condition [1–3]. During the last 30 years, ischemic heart disease rose from fourth to first among causes of disability in global populations [2].

Transplantation remains the preferred treatment for many patients with severe cardiac disease not amenable to corrective surgery or other medical therapies [4]. However, the number of heart transplants performed in modern and modernizing countries has scarcely increased during the past decade and has probably declined in relation to the size of the population and prevalence of cardiac failure [5]. Even more telling is that only about 5 % of potential heart transplant recipients actually undergo the procedure.

This chapter considers whether the need or demand for heart transplantation is likely to change during the next three decades and whether and how the use of animals in lieu of humans as a source of hearts might allow transplantation to achieve a greater impact on human health.

Development and application of new technologies in transplantation and other complex fields of practice often spans decades. Thus, research aimed at using xenotransplantation or any new technology may start with a consideration of whether demand for treatment is likely to increase or decrease over time. The recent doubling of the number of patients waiting for cardiac transplantation [6] would seem to predict a further increase in demand during the next decades [5]. Moreover, extrapolation from past changes in the size of the waiting list would underestimate future need if individuals who might benefit from transplantation were not listed (e.g., they were deemed "low priority" for medical reasons or resided far from an active transplant center).

Changes in demographics, epidemiology of disease, and health care delivery might profoundly accentuate these trends. For example, the Pew Research Center projects that by 2030, the "elderly," defined as those over age 65, will comprise nearly 20 % of the population in the United States compared to about 12 % today [7]. If the next decades bring no other changes, the demand for organ transplantation, which we assume to be cumulative with age, will certainly increase because the incidence and prevalence of heart failure increases with age. Heidenreich et al. [8] estimate that by 2030, more than 40 % of adults in the United States will have cardiovascular disease, including 9.3 % with coronary artery disease and 3.5 % with heart failure, assuming no change in demographics or prevalence. Increasing rates of obesity and diabetes should further increase these rates.

Yet another demographic factor could profoundly change the demand for transplantation and the supply of organs. Immigration will account for most if not all of the US population growth during the next 30 years [7]. Most immigrants will be Hispanic, some Asian. Immigration could well impact the types of diseases people experience, the demand for organ transplants, and the frequency of organ donation. Changes in immigration law and extension of health benefits should also increase demand.

On the other hand, extrapolation from recent trends could overestimate future demand if medical advances decrease prevalence of cardiac failure or if implantable devices improve to the point where they can equal or exceed the outcome of transplantation. But experience in Europe and the United States suggests otherwise. Greater appreciation of the importance of controlling hypertension and hypercholesterolemia and the availability of new drugs and devices are believed to have dramatically decreased morbidity and mortality of cardiovascular disease in Europe and the United States [9], yet the number of subjects listed for heart transplants has increased [4]. Nor will changes in epidemiology of disease likely decrease demand. As mortality of cardiac disease in the United States decreased from ~300 per 100,000 population to ~150 per 100,000, the prevalence of diabetes and hypertension increased [10].

Approaches to Replacing Cardiac Function

Any means to replace cardiac function, including xenotransplantation, should be considered in the context of alternative approaches [5, 11, 12]. Detailed discussions of some other approaches, particularly allotransplantation, are found elsewhere in this volume (Chaps. 22 and 23). Here we describe how xenotransplantation emerged as one approach and why it remains a consideration today among existing and potential alternatives.

Interest in xenotransplantation originated more than 100 years ago. Development of the vascular anastomosis made organ transplantation surgically feasible, but concerns about the ethics dissuaded use of deceased human donors [13, 14]. This aversion to using human organs appeared to wane by 1912 when the first human kidney allograft was performed [15]. However, clinical application of organ transplantation had to wait decades until immunosuppressive and antimicrobial drugs became available, and extracorporeal support such as dialysis and cardiopulmonary bypass made it medically and surgically feasible.

By the early 1960s, advances in cardiopulmonary bypass and experimental surgery appeared to have made cardiac transplantation technically feasible. However, ethical concerns about whether a human heart could be harvested before beating had ceased and questions about whether such a cadaver heart would have suffered irreparable damage discouraged use of human hearts. Hence, the first clinical cardiac transplant was performed in 1964 using a heart harvested from a chimpanzee. The human subject was nearing death from cardiac failure [16]. This xenograft functioned for a few hours but ultimately failed because of a size mismatch.

At the same time, increasing success of clinical kidney allografts in the 1970s and 1980s eclipsed ethical concerns and shifted interest from xenotransplantation to allotransplantation. Still, some cardiac xenografts continued to be performed. Hearts from a baboon and a chimpanzee were transplanted heterotopically into subjects failing extracorporeal support [17]. These xenogeneic hearts helped support the subjects for ~5 h and ~4 days, respectively, but ultimately failed. These failures occurred, at least in part, because of dysrhythmia of the native hearts and rejection of the transplants.

In 1984, a baboon heart was transplanted orthotopically into a 2-week-old infant, "Baby Fae," with severe and worsening cardiac failure caused by a hypoplastic left heart [18]. Although a cardiac allograft might have been preferred, small hearts from infant "donors" were rarely available. Therefore, as a temporizing measure, clinicians performed a xenograft rather than palliative surgery, hoping a human might become available as a permanent replacement. The orthotopic xenograft functioned well for ~5 days, but function was progressively impaired by rejection. The xenograft ceased to function on the 20th postoperative day.

Increasing success over the years made allotransplantation the preferred therapy for cardiac failure. But this success generated a severe shortage of human organs, reigniting interest in xenotransplantation [19]. Interest grew with the belief that genetic engineering of animal sources may address the most challenging barriers to xenotransplantation [20, 21].

Research during the past several decades has shed new light on the barriers to xenotransplantation and has taught that new therapeutic strategies must be combined with genetic engineering if xenotransplantation of the heart will become a regular part of medical practice [22, 23]. This research has led to advances in genetic engineering of swine and immune modulation of recipients. Both of these developments have enabled swine hearts transplanted heterotopically into baboons to survive and function for more than 1 year [24] and orthotopic transplants to function up to several months [25].

Types of Xenografts for Treating Cardiac Disease

Cardiac Xenotransplantation. Animals may provide a functionally adaptive, plentiful, readily available, and inexpensive source of hearts for cardiac replacement (◘ Table 34.1). However, various barriers, detailed below, exclude cardiac xenotransplantation from current practice. These barriers include the immunological reaction of the recipient to graft, biochemical incompatibilities between humans and animals, and the possibility that the graft might convey an infectious organism to the recipient.

These barriers, with the exception of infection, would seem to be minimized if nonhuman primates were used as sources of hearts. However, despite this logic, nonhuman primates are no longer considered for such use because the number of hearts of suitable size would be too small to address the shortage of human hearts and because nonhuman primates might convey and their organs propagate novel infectious agents. Instead, swine are considered the most suitable species to use as a source of organ xenografts. Swine are favored because (1) hearts of suitable size can be obtained in large numbers, (2) they can be bred and genetically engineered to lower biological barriers, (3) breeding (and cloning) can generate genetically uniform transplants with definable properties, and (4) use of swine organs could be planned and might engender lower costs than alternatives.

While swine might harbor some microorganisms capable of transfer to humans, these organisms are better known and "less threatening" than those found in nonhuman primates. And in contrast to the use of human hearts, the use of swine as a source of hearts enables exclusion of known pathogens by breeding in a controlled environment, testing, and, if necessary, pretreating either the recipient or the animal source.

Xenogeneic Cell and Tissue Transplants. Cellular transplants of various types are being explored for treatment of cardiac disease [26–29], although the benefits and mechanisms underlying these benefits remain subjects of debate [26, 27, 30]. One question is whether cell transplants, and particularly stem cell transplants, regenerate myocardium directly or establish a microenvironment that facilitates regeneration. This question has practical implications because allogeneic cells, even without immunosuppression, have exhibited benefit, implying that the benefit reflects a transient impact on the microenvironment [26, 31].

If cell transplants need only deliver temporary impact, and if immunity to the transplant is not detrimental, then xenogeneic sources of cell transplants might merit consideration. As discussed below, xenogeneic cell and tissue transplants are usually not susceptible to the most explosive types

Table 34.1 Comparison of approaches to replacement of cardiac function, rated on a scale of 1–4 stars

Approach	Availability[a]	Cost[b]	Immune barrier[c]	Infectious barrier[d]	Global availability[e]
Allotransplant	*	**	***	****	***
Assist device	***	**	**	**	**
Artificial heart	**	**	**	***	**
Engineering[f]	*	****	*	*	*
Organogenesis[g]	*	****	*	*	*
Xenotransplant	****	*	****	*	****

[a]"Availability" presumes approaches are biologically feasible (some presently are not) and that availability is a function of the time and technical sophistication needed to provide the approach
[b]Cost of left ventricular assist device (LVAD) approximates cost of allograft [106] and will bridge to allograft; cost of engineered heart assumed to include cost of generating stem cells and organogenesis; relative cost of artificial heart and xenotransplant could vary
[c]The immune barrier is assumed to include inflammation generated by a device
[d]The infectious barrier refers to infection conveyed by the transplant and operative procedure
[e]Feasibility of application in developing regions and locations with limited technological base
[f]"Engineering" refers to use of a xenogeneic decellularized heart as a scaffold for engineering a living heart
[g]Organogenesis refers to a "reverse transplant" or other approach in which a heart is "grown" de novo

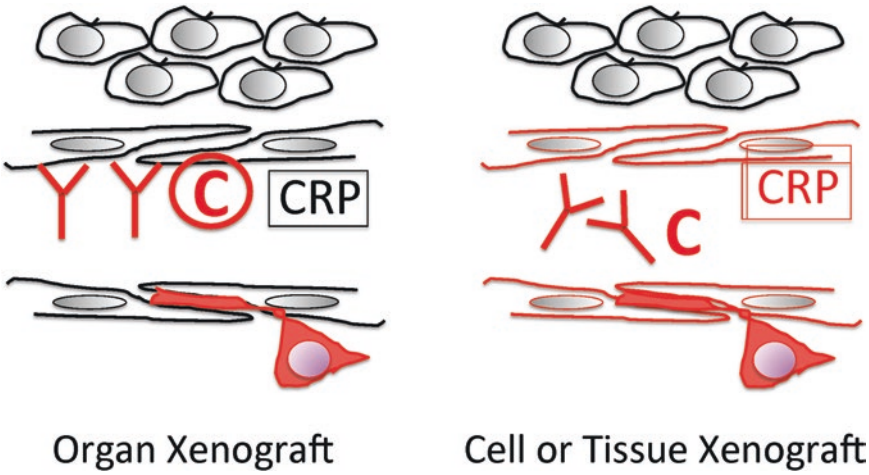

Fig. 34.1 Susceptibility of organ xenografts and cell and tissue xenografts to humoral and cellular immunity. Organ xenografts have a vascular system full of animal origin (black); therefore, the blood vessels are readily attacked by antibodies of the recipient (red). Bound antibodies activate complement of the recipient because heterologous complement regulatory proteins (CRPs) fail to control the complement cascade. Cell and tissue xenografts have blood vessels formed by ingrowth of the recipient's blood vessels. These recipient blood vessels are not targeted by recipient antibodies. Complement of the recipient is effectively controlled by the recipient's CRP. Both organ xenografts and cell and tissue xenografts are susceptible cell-mediated immunity because the recipient's lymphocytes and monocytes actively migrate between adjacent endothelial cells

of rejection (hyperacute and acute vascular rejection) seen in organ transplants (Fig. 34.1). Besides the ready availability and potentially uniform properties of xenogeneic cells, the cells could be obtained from animals genetically engineered to increase production of beneficial substances. Unlike allogeneic cells, the potential for oncogenicity is probably nil.

Tissue Engineering Using Xenogeneic Organ as Scaffold. Beyond the established uses of decellularized xenogeneic valves, decellularized xenogeneic organs have been envisioned as scaffolds for seeding with cells and engineering whole organs [32–34]. Besides availability, xenogeneic tissue and organs might be preferred for this purpose because the properties of the biological source can be controlled, potentially made uniform, and genetically engineered. Acellular organ scaffolds, like acellular valve tissue, would probably evoke less immunity and suffer less injury than living tissues. (Acellular tissue is not a true xenograft.) However, the extent of engineering and costs needed to generate a full-size, fully functioning "hybrid heart" for clinical use might still pose daunting hurdles to clinical application.

Reverse Xenotransplants. In what might be called a reverse xenotransplant, animals might also be used to generate human tissue or organs (i.e., organogenesis) from stem cells or primordia (Fig. 34.2). As one example, stem cells from an individual needing treatment might be engrafted into fetal animals to coax differentiation of an embryonic organ. At a suitable stage of development, the organ rudiment would be engrafted in a heterotopic site and development completed in the individual to be treated [5, 11, 35]. The developed tissues could be used to repair or replace the diseased organ.

Although the overall model is theoretical, each of the steps in this approach has been carried out successfully in one or another system. Besides complexity, the major limits to this approach include the need to assure that the new organ is vascularized by the human recipient rather than the temporary host animal (to avoid vascular rejection), the time required for the organ to develop and mature, and the extraordinary costs for each of the steps.

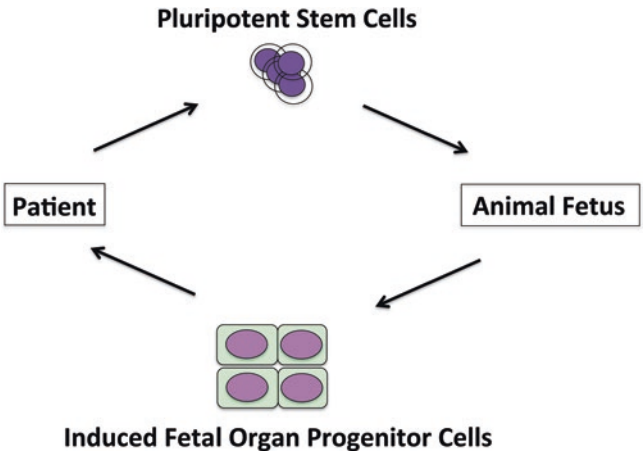

Fig. 34.2 Organogenesis by "reverse xenotransplantation." Limitations to using stem cells for generating whole organs may be addressed by reverse xenotransplantation. A patient's cells are harvested and used to generate pluripotent stem cells. The cells are introduced into a fetal animal where they can be induced and coaxed to generate an organ primordium. The human organ primordium is harvested and cells are introduced into the patient where an organ can form, mature, and become vascularized. Each of these steps has been taken successfully in one or another experimental system, but whether it can succeed as a strategy and at what cost are unknown

Immunological Barriers to Xenotransplantation

Natural Immunity. The initial barrier to xenotransplantation is called "natural" because it engages effector components of the immune system that are fully active at the time of transplantation and are not evoked by exposure to a foreign antigen. These effector systems include "natural antibodies," natural killer (NK) cells, phagocytes, and complement.

Individuals of the same species inherit many distinct gene variants and, therefore, produce many allotypic molecules.

Despite these differences, only natural immunity poses a significant barrier to organ allotransplantation. Individuals of different species differ at every genetic locus and have detectable, functionally significant differences in many macromolecules. Yet the natural immune barrier to organ xenotransplantation appears to reflect differences at only a few genetic loci, mentioned below. For this reason, genetic engineering of animals can potentially lower or eliminate the innate immune barrier to xenotransplantation, a possibility that has aroused much interest.

Xenoreactive natural antibodies that recognize cells of other species can be found in the blood of all immune-competent individuals [36]. These antibodies have the same properties as the natural antibodies that recognize blood group saccharides [37].

Xenoreactive natural antibodies in humans, apes, and old-world monkeys predominantly recognize a disaccharide—galactose-α-1,3-galactose (Galα1-3Gal)—that terminates complex carbohydrate substitutions on glycoproteins and glycolipids of nonhuman primates, such as pigs, and also new-world monkeys [38–42]. While other natural antibody-antigen combinations exist, Galα1-3Gal and anti-Galα1-3Gal constitute the main initial barrier to cardiac xenotransplantation, since removal of the antibodies against this sugar prevents hyperacute rejection of cardiac xenografts [43]. Exposure to Galα1-3Gal and inflammation attendant to transplantation causes increased production of the antibodies and isotype switching [44]; however, "affinity maturation" of these antibodies probably reflects selection of existing clones more than somatic hypermutation. Genetic engineering of swine solved the problem of natural anti-Galα1-3Gal antibodies by eliminating the enzyme α1,3-galactosyltransferase, which catalyzes production of Galα1-3Gal (45). Organs from the animals that cannot produce Galα1-3Gal (sometimes inaptly called "αGal-KO" animals) do not undergo hyperacute rejection after transplantation into nonhuman primates [46, 47].

The immune barrier posed by natural antibodies depends absolutely on the activation of complement, as the complement system presents the most daunting natural immune barrier to cardiac xenotransplantation. Complement recognizes foreign and/or damaged cells and causes the cells to be further injured, killed, engulfed, and/or used to stimulate inflammation and immunity.

Human complement recognizes swine cells via three potential mechanisms. First, the binding of xenoreactive natural antibodies (or elicited antibodies) to swine cells engages C1q, C1r, and C1s, triggering the classical complement pathway by cleaving C4 and C2. Fragments of C4 attach to cell membranes and associate with fragments of C2, generating an enzyme complex that cleaves C3, continuing and amplifying the activation of complement. Recruitment of the classical complement pathway to swine xenografts in primates depends on binding of xenoreactive natural antibodies [48]. Thus, the pathway does not proceed for the most part in "αGal-KO" organs transplanted into swine.

Second, complement is also activated on foreign cells via the "alternative pathway." This pathway begins with spontaneous hydrolysis of C3, leading sequentially to formation of C3b, attachment to cells, and formation of an enzyme complex with factor B and factor P, which further activates the complement cascade. Unlike the classical complement pathway, which remains inactive unless triggered, the alternative complement pathway is continuously activated, but full activation is blocked by inhibitors such as decay-accelerating factor (DAF). DAF is expressed on cell surfaces in the graft and factor H, which circulates in the blood. Decay-accelerating factor is so named because it promotes the decay, i.e., dissociation of the classical pathway and alternative pathway enzyme complexes. It dissociates homologous complexes much more efficiently than heterologous complexes. Factor H also dissociates C3b-factor B complexes and promotes cleavage of C3b by factor I. It does so much more effectively on homologous than on heterologous polyanionic surfaces. Factor H functions poorly or not at all on microbial, some xenogeneic, and damaged cell surfaces and on surfaces where the polyanions are blocked (e.g., by bound antibody) or shed. If factor H fails to control C3b-factor B complexes on xenogeneic cell surfaces, the alternative pathway will be activated without restraint, whether or not antibodies are bound [49, 50].

In most swine to human xenografts, factor H effectively regulates C3b-factor B complexes. Therefore, complement activation requires activation of the classical by antibodies (or by the lectin pathway as described below). However, the activity of factor H probably varies enough, with differences in cell surface chemistry, charge, and damage, that increased contribution of the alternative pathway cannot be dismissed without evidence.

Third, complement might be activated on xenogeneic cells through the lectin pathway. Association of mannose-binding lectin (MBL) and/or ficolins with damaged or dying cells (or to microorganisms) triggers the lectin pathway. MBL and ficolins recruit one or more MBL-associated serine proteases (MASPs), especially MASP-1 and MASP-2, to form a complex that cleaves C4 and C2, leading to activation of the rest of the complement cascade as described above. IgM bound to Galα1-3Gal or other targets can recruit MBL and MASP-2, leading to complement activation independent of C1q [51–53]. Given the breadth of potential targets for MBL and ficolins, it seems likely that regulation of the pathway by polyanions and antiproteases determines whether or not that pathway contributes to tissue injury in xenografts.

Natural killer cells and macrophages can also interact with and injure xenogeneic cells, causing researchers recently to question whether they contribute to the pathogenesis of xenograft rejection [54–59]. NK cells can be stimulated when UL16-binding protein or related proteins of swine interact with natural killer group 2, member D (NKG2D), and/or when swine major histocompatibility complex (MHC) class I fails to interact with human killer inhibitory receptors [60–62]. Interactions of human macrophages with

swine cells can be promoted by complement fragments and bound IgG and suppressed by failed interaction of swine CD47 with signal-regulatory protein-α (SIRP-α) [63].

NK cells and macrophages are both important in forming an innate immune barrier to cell and tissue transplants. But whether they initiate injury to organ grafts, and to what extent, is not clear. Thus, NK cells and macrophages rapidly (within minutes) injure or kill xenogeneic cells in culture. However, xenogeneic cells are found in xenogeneic heart transplants after periods of weeks or months and accompany other features of graft rejection [64].

Elicited/Adaptive Immunity. With few exceptions, transplants of foreign cell tissues or organs elicit "adaptive" immune responses in the recipient [65]. Unlike innate immunity, adaptive immunity requires activation and proliferation of B and/or T lymphocytes. The first step in activation of B cells and T cells involves the recognition of a foreign antigen (intact antigen in the case of B cells, antigen fragments associated with recipient MHC, or intact foreign MHC itself in the case of T cells) by antigen receptors. Because the repertoires of lymphocyte antigen receptors and, hence, of distinct lymphocyte clones is so vast (approximately 10^9), each T cell and B cell clone consists of as few as ten cells. Therefore, activation of B cells and T cells must be followed immediately by proliferation to expand by orders of magnitude the number of effector cells.

The bringing together of the few naive lymphocytes bearing receptors for a foreign antigen with that antigen, and expansion of these cells, usually requires 2–6 weeks—sooner if the antigen recruits an unusually large fraction of cells, such as alloreactive T cells. Therefore, the impact of adaptive immunity usually follows that of innate immunity. Nevertheless, antibodies and helper T cells use components of innate immunity, such as complement and macrophages, to exert effector functions.

Several factors might hasten and expand the adaptive immune response to xenografts. Practically every protein in xenografts can elicit an immune response. Some proteins, such as MHC proteins, are highly immunogenic and elicit immunity in practically all individuals. Other proteins are less immunogenic and elicit immunity in some individuals but not in others.

Besides whatever early damage it inflicts on grafts, the powerful innate immune response to xenografts accelerates adaptive immunity. For example, complement-induced tissue injury liberates antigen and activates antigen-presenting cells, increasing antigen processing, association with MHC, and migration to regional lymphoid organs. Heightened inflammation also speeds the migration of T cells to lymphoid organs, accelerating the relatively rare interactions with MHC-antigen complexes.

Activation of complement enables and amplifies B cell responses to an antigen. Even B cell responses thought to be "T cell independent" are hastened because of the availability of polymeric (i.e., carbohydrate) antigen. While the "direct" T cell response to xenogeneic cells might be impeded by incompatibility between CD4 and CD8 of T cells and xenogeneic MHC [66], this incompatibility has little impact on the dimensions of the cellular immune response to xenografts in vivo.

The Impact of Immunity on Xenografts

The intensity of immune responses does not necessarily determine the intensity of tissue injury observed in xenografts (or allografts). The dissociation between immunity and impact pathology reflects two factors—one related to the source of blood vessels feeding the graft and the other to the intrinsic susceptibility of the graft to injury.

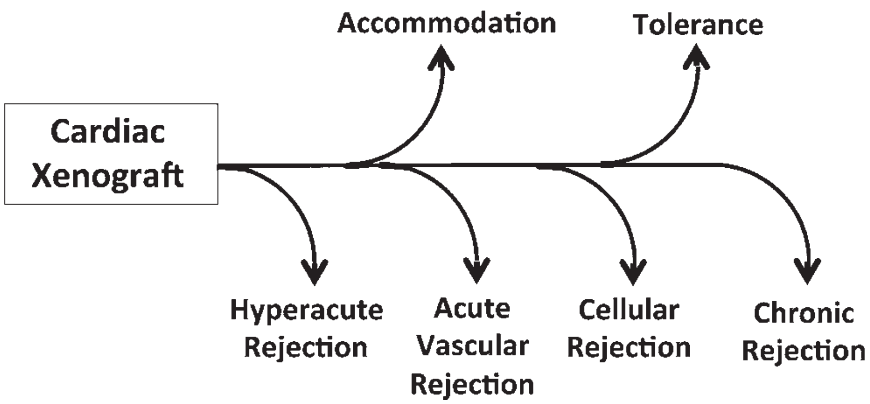

Fig. 34.3 Impact of immunity on cardiac xenografts. Cardiac xenografts are susceptible to hyperacute rejection over hours, acute vascular rejection and cellular rejection over days to weeks, and chronic rejection over months after transplantation. Hyperacute and acute vascular rejection can be countered by accommodation, the acquired resistance of the graft to immune and inflammatory injury. Rejection of every type might be countered by tolerance. In contrast to organ xenografts, cell and tissue xenografts are mainly susceptible to cellular rejection and to injury caused by natural killer cells and macrophages independent of immunity [not shown]

Origin of Blood Vessels in the Graft. The impact of immunity on xenografts depends to a considerable extent on the origin of blood vessels in the graft (Figs. 34.1 and 34.3) [11, 67]. Organs such as the heart are transplanted by primary anastomosis of the recipient's blood vessels with the large blood vessels of the graft (Fig. 34.1). Because of this anastomosis, the endothelial lining of the graft consists entirely of donor cells. With reperfusion, xenoreactive antibodies of the recipient circulating at the time of transplantation and those produced later can bind directly to graft blood vessels, activating complement and recruiting inflammatory cells (Fig. 34.3).

Hyperacute Rejection. The binding of xenoreactive antibodies to blood vessel lining cells and the rapid activation of complement (or direct activation of complement independent of antibodies) can cause hyperacute rejection. As in allografts, hyperacute rejection of xenografts is characterized by platelet thrombi, focal hemorrhage, infarction, and attachment of neutrophils to vessel walls. The pathogenesis of hyperacute rejection of cardiac xenografts depends absolutely on activation of the full complement cascade [68] and probably on the rate that full activation proceeds, since a low level of expression of human DAF, which slows but does not necessarily prevent complement activation in a swine organ, averts the condition [21]. Consistent with that concept, ABO-incompatible organ transplants, in which complement regulators such as DAF, of the donor are compatible with the recipient, do not usually undergo hyperacute rejection. The dramatic difference between the fate of cardiac xenografts and ABO-incompatible allografts exemplifies the importance of susceptibility of a graft to injury.

Acute Vascular Rejection. When hyperacute rejection does not occur or is prevented, a xenogeneic organ becomes subject to acute vascular or antibody-mediated rejection (sometimes called delayed xenograft rejection). Characterized by focal ischemia, swelling of endothelium, and fibrin thrombi, with or without fixation of antibodies and complement to vessel walls, acute vascular rejection typically begins days or weeks after transplantation, but, as seen in allografts, it can occur at later times.

In its earliest manifestation, acute vascular rejection is caused by natural antibodies directed against Galα1-3Gal [69, 70]. Later, acute vascular rejection is caused by antibodies elicited de novo after transplantation [71], although some of the targets might be the same as those recognized by natural antibodies [72]. Acute vascular rejection is associated with endothelial cell activation caused by small amounts of complement that escape control by complement inhibitory agents or expression of human complement regulatory proteins [73–76].

Endothelial cell activation and acute vascular rejection may also be caused by interactions of inflammatory cells or platelets with endothelium [77, 78]. However, activation of complement in small amounts, owing to incompatibilities of complement regulatory proteins or binding of small amounts of anti-swine antibodies, would probably activate the inflammatory cells and the endothelium, facilitating interactions.

Acute vascular rejection is the main biological barrier to clinical application of cardiac xenotransplantation.

Cellular Rejection. Xenografts, like allografts, are subject to cellular rejection and, presumably, to chronic rejection or coronary vasculopathy. While cellular rejection might be more aggressive, for reasons discussed above, its control by available immunosuppressive drugs makes it unlikely to cause loss of xenografts. An important question, however, is whether the recipient of a cardiac xenograft would be broadly sensitized to human leukocyte antigen (HLA). Broad sensitization to HLA and associated ineligibility for receiving most allografts might be considered a serious hindrance to using a xenograft as a "bridge" to allotransplantation. Investigation of a limited number of human subjects and nonhuman primates exposed to swine tissues and organs has not revealed consistent evidence of such "cross sensitization"; however, the risk has not been excluded.

Chronic Rejection. Whether chronic rejection would impair function and limit survival of cardiac xenografts has been a matter of conjecture because experimental cardiac xenografts succumbed to acute vascular rejection before chronic coronary vasculopathy could develop. Still, chronic rejection of heterotopic cardiac xenografts has been described [64], but whether this condition is more likely to arise, as suspected, or not is unknown.

Cell and Tissue Xenografts. Cell and tissue grafts derive their vascular supply from the ingrowth of the recipient's blood vessels. The full capillary network of cellular grafts is of recipient origin. The capillary network of tissue grafts is partly or fully of recipient origin. Hence, xenoreactive antibodies and complement do not bind directly to blood vessels of cell and tissue grafts and penetrate the vessels slowly, if at all (Fig. 34.1). Small amounts of heterologous complement produced in the graft are presumably controlled by the complement regulatory proteins of the graft. The limited availability of antibodies and complement of the recipient thus prevents antibody-mediated rejection of cell and tissue grafts [23, 67, 79]. On the other hand, cell and tissue xenografts are fully susceptible to cellular rejection because the recipient's activated T cells and phagocytes migrate actively through blood vessel walls.

Accommodation. Binding of xenoreactive antibodies and fixation of complement in transplanted organs sometimes induce resistance to injury by these or other components of the immune system. Acquired resistance to immune and inflammatory injury has been called accommodation [20, 80, 81]. What exactly induces accommodation in xeno- and allotransplantation is not completely known. But investigation of cells in culture indicates that exposure to subtoxic levels of xenoreactive antibodies and complement induces changes that enable the cells to resist subsequent exposure to higher, toxic levels [82–84].

The resistance described in cultured cells probably occurs in accommodated organs, as well [73, 82, 85, 86]. However,

systemic and regional factors such as availability of hormones and vasoactive substances also determine the well-being of organs [87–89]. In any case, accommodation is another example of how the susceptibility of a transplant to injury determines the impact of immunity on a graft.

Overcoming Immune Barriers to Xenotransplantation

Genetic Engineering, Cloning, and Breeding. Xenotransplantation makes it possible to use several approaches to "designing" and optimizing the source organs and tissues used for transplantation into humans. These approaches include adding genes, i.e., transgenesis; cloning, which enables targeting as well as adding of genes; and breeding to optimize existing sets of genes and to generate more uniform lines of animals [20, 90–92].

Genes encoding human complement regulatory proteins have been introduced in swine to overcome the incompatibility of swine complement regulatory proteins with human complement [21, 93]. Expression of even low levels of human decay-accelerating factor (CD55) or CD46 in transgenic pigs prevents hyperacute rejection when the organs of these pigs are transplanted into nonhuman primates (as a model for humans). Similar approaches are being used to express regulators of coagulation because coagulation is often seen in rejecting xenografts. However, the benefit has yet to be proven.

Several approaches to reproductive cloning have been used in conjunction with gene targeting in stem cells to generate swine with nonfunctional or absent α1,3-galactosyltransferase genes. These swine do not produce Galα1-3Gal [45, 94], the main antigen recognized by human xenoreactive natural antibodies. As might be expected, recipients of organs from these "Gal-KO" animals do not undergo hyperacute rejection. Treatment of recipients with maximum amounts of immunosuppressive drugs has enabled survival of heterotopic cardiac xenografts in nonhuman primates for 6 months and with other genetic manipulations for more than a year [24, 46].

While these results were achieved in nonfunctioning (heterotopic) model systems, it is entirely possible that equal or better results could be obtained in clinical trials because the transgenes introduced in swine were partially incompatible with nonhuman primates and because the level of monitoring and medical care available for experimental systems cannot approach those used in clinical practice.

Immune Therapeutics. All or nearly all immunosuppressive drugs and biologics used in allotransplantation have been tested in xenotransplantation models. Immunosuppressive drugs appear to effectively prevent early cellular rejection of most swine to primate cardiac xenografts. However, the drugs do not appear to avert T cell-dependent B cell responses. Nor do they necessarily do so in allotransplantation [95]. Their ability to effectively suppress cellular rejection over periods of months and years has not been explored. While the drugs and biologics routinely used in clinical practice do not reliably prolong survival of cardiac xenografts, these drugs and biologics were developed and optimized for use in humans, so they will likely prove more effective in human subjects than in nonhuman primates.

Induction of Tolerance. The failure of existing immune therapeutics to control the immune response to xenotransplantation has led some to conclude that clinical application of xenotransplantation might depend on induction of tolerance to swine antigens [96]. Induction of tolerance to antigens in xenografts would seem to pose a substantially greater hurdle than induction of tolerance to antigens in allografts because all xenogeneic proteins and some carbohydrates are potential targets of immunity and because innate immunity aggravates responses to these antigens.

On the other hand, tolerance to a xenograft might be induced more readily or at least with no greater difficulty than tolerance to an allograft for several reasons. First, if cloned or highly inbred swine are used as sources of xenografts, key antigens, once identified, might be suppressed, modified, or masked by genetic engineering or pretreatment of swine.

Second, because xenotransplantation can be scheduled in advance and the recipient is treated to induce tolerance before the transplant procedure, activation and expansion of xenoreactive lymphocytes are potentially preempted.

Third, planning makes it possible to test potential recipients for responses to key antigens and for efficacy of tolerance induction before initial exposure to the graft. Recent dramatic successes in experimental cardiac xenotransplantation were achieved using approaches such as costimulatory blockers (anti-CD154 or anti-CD40) that may be part of a tolerance regimen [24, 46].

Induction of Accommodation. The idea that a graft could acquire resistance to antibody-mediated rejection originated with observations made in ABO-incompatible kidney transplants and swine-to-nonhuman cardiac primate xenografts [20, 97]. The mechanisms that induce and maintain accommodation in transplants are not fully known, but nearly every pathway known to inflict injury on xenografts exhibits decreased toxicity over time [80].

So one key question may be whether acquired resistance to injury by these pathways is centrally coordinated or reflects the sum of many resistance pathways [98]. If accommodation is centrally coordinated, then a drug or biologic might be used to evoke accommodation and avoid exposure of the graft to subtoxic conditions. However, efforts to induce accommodation by expression of "survival proteins" that protect cells in culture do not prevent immunological damage. It seems more likely that while cell or tissue survival depends on invoking more than one survival pathway, the requisite set of survival genes might be recruited by one or a limited number of stress-sensing genes. Regardless of how accommodation is induced, one can imagine manipulating the animal source of cardiac xenografts to increase resistance to injury by antibodies, complement, and inflammatory cells.

Physiological Barriers to Xenotransplantation

Differences in physiology at the molecular, cellular, or organ levels between the source and the recipient of a xenograft have long been considered a potential barrier to xenotransplantation [99]. As already discussed, incompatibilities between the complement system of the recipient and complement regulatory proteins increase the rate of complement activation. Incompatibility between thrombin of the recipient and thrombomodulin in xenogeneic blood vessels slows activation of protein C, allowing accelerated coagulation.

However, despite these and what are probably many other relative incompatibilities, hearts and kidneys transplanted between disparate species, particularly between swine and nonhuman primates, function well enough to support life. In fact, the major impediment to the function of cardiac and renal xenografts appears to be the immune responses discussed above, rather than intrinsic incompatibilities, at least over periods of months.

What enables xenografts to overcome multiple molecular and physiologic incompatibilities are, in part, the compensatory pathways that increase cellular resistance to complement, ischemic injury, and thrombosis. The impact of compensatory pathways is especially apparent if one considers the kinetics of the pathways. For example, while incompatibility of coagulation and regulation causes thrombosis in vitro within minutes [100], widespread thrombosis is not observed over minutes or even days in vivo in the absence of immunological responses [64, 101]. The limited and delayed impact of molecular incompatibilities in vivo might allow the use of therapeutic agents to reverse or minimize the consequences over time.

Xenotransplantation and Infection

Successful cardiac allotransplantation requires balancing the need to avoid rejection with the risk of infection. This consideration enters into evaluation of donors, who might harbor microorganisms that could infect the recipient, and into decisions about the type and dosage of immunosuppressive drugs.

Although infection is commonly considered a barrier to xenotransplantation, a swine cardiac xenograft is probably far less likely to convey an infection to the recipient than a human cardiac allograft. Because many of the microorganisms that infect swine cannot infect humans, the diversity of potential zoonoses is smaller. And since humans and swine are in frequent contact on farms and in meat processing facilities, zoonotic pathogens are largely known. Many can be systematically excluded from the sources of xenografts by isolation, treatment, or genetic engineering of animal sources.

Nevertheless, some concerns about infectious risks of xenotransplantation remain. The recipient of a xenograft might be treated with a relatively severe immunosuppression regimen or a regimen that blocks key limbs of host defense, such as complement or leukocyte migration. Immune therapeutics and incompatibility of graft and host might hinder immune surveillance in the xenotransplant, exposing the recipient over a long period of time. A xenograft also might harbor an agent, such as an endogenous retrovirus that is not infectious or pathogenic in swine, but could be for a xenotransplant recipient.

The porcine endogenous retrovirus (PERV) has been thought to pose a potential risk for xenotransplant recipients [102]. A C-type retrovirus, PERV can be activated in cultured pig cells, releasing particles capable of infecting human cell lines. PERV cannot be fully eliminated by breeding or genetic engineering. However, investigation of human subjects who received skin xenografts and whose blood was perfused through porcine livers has failed to reveal any evidence that PERV was transmitted to treated subjects [103, 104]. Still, potentially infectious PERV has been found in human-swine hybrids that formed in human-swine hematopoietic chimeras [105]. These hybrids would have escaped detection in prior surveys of human subjects. Therefore, rigorous follow-up of xenotransplantation trials is warranted.

Ethical Considerations

Cardiac xenotransplantation could address some of the most vexing ethical challenges posed by human-to-human cardiac transplantation, but it raises some others.

Its use would reduce or eliminate the shortage of human hearts for transplantation, thus the need to allocate a scarce supply. Cardiac xenotransplantation might address the challenge posed by the high cost of harvesting human organs and purchasing devices, although the costs of immunosuppression to some extent offset the lower cost of organs. Cardiac xenotransplantation might also address disparity in health care resources since less technologic sophistication is needed to maintain a transplant than some devices.

But xenotransplantation also *raises* some ethical challenges. If both human and animal hearts are available, deciding which patient receives still-scarce human hearts versus plentiful animal hearts might equal the ethical challenge of today's allocation policies. And questions about the use of human subjects in experimental procedures, consent, etc., will challenge the field until procedures and treatments are optimized and outcomes known.

The most difficult ethical challenges stem from questions about whether xenotransplantation would enable unusual microorganisms to infect the recipient and spread from that recipient more broadly in the population. PERV has been considered one such unusual organism, but others might remain to be discovered. And even if no new organisms can be found, ongoing uncertainty might cause public health authorities to isolate recipients and subject them to obligatory screening. Only widespread experience with xenotransplantation will likely reduce the ethical considerations to the point where they will not pose an obstacle.

Concluding Remarks

Enthusiasm for xenotransplantation as an approach to replacing cardiac function has been kindled by each advance that appeared to address a difficult barrier to application. Enthusiasm waned when each advance failed to enable permanent engraftment in experimental models. If anything, this waxing and waning of enthusiasm mirrors the history of cardiac allotransplantation.

At least four factors might shorten the pathway to clinical application of cardiac xenotransplantation. First, a clear role and need for cardiac replacement have been established. Second, the cellular and molecular hurdles to cardiac xenotransplantation, such as Galα1-3Gal, complement regulation, and coagulation, have been defined at least in past, allowing rational development of specific therapeutics and genetic engineering. Third, this knowledge also provides reason to believe that results observed in swine-to-nonhuman primate models probably overestimate barriers to success. Fourth, cardiac xenotransplantation might be tested as a bridge to permanent cardiac replacement before it is applied as a final therapy.

Given the dimensions of the problem of cardiac failure, the preference for transplantation over alternative therapies, the decades needed to develop novel and effective alternatives such as organogenesis, engineered patches, and better mechanical devices, and the high cost of therapeutic approaches in current use [106], it seems prudent to consider xenotransplantation as one of the potential alternatives.

We can say with reasonable confidence today that vascular or antibody-mediated rejection, more than anything else, blocks the use of xenotransplantation of the heart and other organs. Antibody-mediated rejection of allografts is incompletely understood and existing treatments often fail. Given current interest in that problem and resources devoted to it, one can expect that better therapeutics will be forthcoming. These therapeutics might also address the corresponding problem in xenotransplantation.

To the extent that the greater severity of vascular rejection of xenografts reflects incompatibility of the complement, coagulation, or other systems between swine and human, one should also consider that genetic differences between nonhuman primates and humans might cause swine-to-primate transplantation models to underestimate the efficacy of therapeutic and genetic engineering applied to these problems. Thus, we may have made more progress than is apparent.

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