Jean-Luc Fellahi
Marc Leone *Editors*

# Anesthesia in High-Risk Patients

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*Editors*
Jean-Luc Fellahi
Department of Anaesthesiology and
Critical Care Medicine
Louis Pradel Hosp, Hospices Civils Lyon
Lyon, Rhône
France

Marc Leone
Service d'Anesthésie-Réanimation
Hôpital Nord
Marseille cedex 20
France

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# Foreword

The practice of anaesthesiology (which in the definition of the European Society of Anaesthesiology includes anaesthesia, intensive care and perioperative medicine as well as pain therapy) has profoundly changed since the year 2000. Anaesthesiologists are not only those specialists who are in charge of providing analgesia and comfort to those patients who undergo surgery or invasive procedures. Anaesthesiologists are now those specialists who manage patients with comorbidities so that postoperative morbidity and mortality is as low as possible.

A recent European study [1] has revealed that postoperative mortality is slightly below 4%, orders of magnitude higher than the previously documented mortality associated with the practice of anaesthesia. It seems clear from this data that the practice of anaesthesiology has become the practice of perioperative medicine with new challenges: taking the patients and their comorbidities through the perioperative period so the intervention does not worsen the natural history of their comorbidities. In this context, the recent European Guidelines underline the role that anaesthesiologists play in decreasing postoperative morbidity and mortality [2, 3].

If the decrease of perioperative morbidity and mortality is the focus of anaesthesiologists, it becomes clear that identifying and managing the patient-related risk factors and their interaction with the intervention-related risk is mandatory. The group of experts who contributed to this book has reviewed many of the patient-related risk factors that are relevant for the contemporary practice of perioperative medicine. Some of the risks are frequent (atheroma and coronary artery disease); other risks have a lower incidence (e.g. pulmonary hypertension). Some "new" risk factors (frailty, drug addiction, severe obesity) are also discussed and their novelty reflects the recent social changes with consequences on the medical practice.

Each chapter provides anaesthesiologists with the necessary synthesis of data thus allowing them to manage risk factors in individual patients. The chapters are rich with the most recent publications and evidence, and the authors and the Editor should be commended for their efforts. The book, by gathering dispersed information, will facilitate the necessary integration of information and decision

making. This book arrives at a time when clinicians value the concentration of valuable information.

Dan Longrois
Département d'Anesthésie-Réanimation
Hôpital Bichat
Paris, France

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# Contents

# Part I

# Cardiac and Hemodynamic Risks

# The Patient with Acute Coronary Syndrome

# 1

Simon Hennink-Schadenberg and Benedikt Preckel

A growing number of patients with coronary artery diseases are subjected to surgery. Anaesthesia care providers will face patients with former or recent ACS. An ACS might also occur for the very first time during surgery or during the postoperative period. This chapter will highlight the relevant physiology and perioperative treatment options in this patient population.

Acute coronary syndrome (ACS) resembles different manifestations of coronary artery disease: unstable angina pectoris (UAP), non-ST-elevation myocardial infarction (non-STEMI) and ST-elevation myocardial infarction (STEMI; see Table 1.1) [1].

A differentiation is made on electrocardiogram (ECG) changes (STEMI versus non-STEMI/UAP) and release of cardiac-specific biomarkers (non-STEMI versus UAP). Constantly improvements of detection of very low concentrations of cardiac-specific biomarkers like troponin T or I, along with improved imaging techniques, nowadays allow detection of myocardial tissue necrosis also in the absence of

**Table 1.1** Classification of acute coronary syndrome [2]

| | |
|---|---|
| *STEMI* | ST segment elevation ≥2 leads *or* new LBBB on 12-lead ECG *and* release of cardiac-specific biomarkers |
| *NSTEMI* | ST depression, non-specific ST segment abnormalities, sometimes even normal ECG *and* release of cardiac-specific biomarkers |
| *UAP* | ST depression, non-specific ST segment abnormalities, sometimes even normal ECG *without* release of cardiac-specific biomarkers |

*ECG* electrocardiogram, *LBBB* left bundle branch block

S. Hennink-Schadenberg, M.D., M.Sc. • B. Preckel, M.D., Ph.D., D.E.A.A. (✉)
Department of Anaesthesiology, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands
e-mail: s.hennink@amc.uva.nl; b.preckel@amc.uva.nl



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**Table 1.2** Universal classification of myocardial infarction (MI) [2]

| |
|---|
| Type 1 MI: Spontaneous myocardial infarction (ACS) |
| Type 2 MI: Myocardial infarction secondary to an ischaemic imbalance |
| Type 3 MI: Myocardial infarction resulting in death when biomarker values are unavailable |
| Type 4 MI: Myocardial infarction related to either (a) percutaneous coronary interventions (PCIs) or (b) in-stent thrombosis |
| Type 5 MI: Myocardial infarction related to coronary artery bypass graft (CABG) surgery |

clinical symptoms or ECG changes. This will have influence on the perioperative treatment of the respective patients at cardiac risk in the future.

## 1.1 Definition of Myocardial Infarction (MI)

During the last decades, the definition of MI has been changed from 'any necrosis in the setting of myocardial ischaemia' to a more specific definition depending on the clinical situation of the respective patient (see Table 1.2) [1, 2]. In the current chapter, we will focus on type 1 and type 2 MI.

Myocardial infarction is likely if there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia by detection of rise and fall of cardiac biomarker values (preferentially cardiac troponin, with at least one value above the 99th percentile upper reference limit) with at least one of the following:

- Symptoms of ischaemia
- New significant ST-T wave changes or new left bundle branch block (LBBB) on ECG
- Development of pathological Q waves on the ECG
- Imaging evidence of new loss of previously viable myocardium or new regional wall motion abnormalities
- Identification of an intracoronary thrombus by angiography or autopsy

In some patients, cardiac death might occur after previous clinical symptoms suggestive of myocardial ischaemia and presumed new ECG changes or LBBB, but death occurred before biomarkers were obtained or before cardiac biomarkers would be increased (type 3 MI, Table 1.2).

## 1.2 Pathophysiology of Coronary Circulation

Risk factors for developing coronary artery disease include age, dyslipidaemia, hypertension, cigarette smoking, diabetes mellitus, cardiovascular and renal disease [3]. Often, ACS presents itself with acute onset of radiating chest pain, shortness of breath

and sweating, caused by ischaemia of the heart and subsequent myocardial dysfunction. Atypical presentations are seen in elderly, female and diabetic patients [1, 3–5].

The ACS is often caused by formation of an atheromatous plaque in the coronary circulation on the basis of inflammatory mechanisms and dyslipidaemia. Disruption of this 'vulnerable' plaque subsequently triggers local coagulation and formation of a local thrombus. Together with vasoconstriction—locally around the plaque or generalised due to sympathetic stimulation—this leads to partial or complete obstruction of the diseased coronary artery, with subsequent ischaemia in the dependent myocardium (type 1 MI, Table 1.2) [6].

Approximately 5% (250 mL/min) of cardiac output runs through the coronary circulation. At rest, the myocardium already extracts 75% of the delivered oxygen. When oxygen demand increases, for example during exercise, the myocardium cannot further increase oxygen extraction, but the coronary arteries have to dilate to increase blood flow and thereby oxygen delivery. If this increased demand cannot be met, ischaemia during the exercise will occur (type 2 MI, Table 1.2).

Two main coronary arteries with origin from the aortic route just behind the aortic valve are delivering blood to the heart. The right coronary artery (RCA) supplies the right atrium and ventricle, including the sinoatrial and atrioventricular node. It also supplies blood to part of the left atrium and one third of the interventricular septum. In approximately 80–90% of patients, the RCA supplies blood to the inferior wall of the left ventricle via the posterior descending artery (right dominant circulation). The left main coronary artery (LMCA or LM) branches into the left anterior descending (LAD) artery and the left circumflex artery (Cx, or ramus circumflexus (RCx)). The LAD artery supplies blood to two thirds of the interventricular septum and the anterolateral part of the left ventricle. The RCx supplies blood to the lateral part of the left ventricle, and in 10–20% of patients, it supplies the posterior descending artery (left dominant coronary circulation). All three main coronary arteries branch off smaller vessels. Depending on the involved coronary artery, ischaemia can result in dysrhythmias, heart failure, valve dysfunction, cardiogenic shock and even cardiac arrest. Table 1.3 gives an overview of ECG changes related to different parts of the coronary artery system and the supplied myocardial area.

The different types of ACS result from different degrees of obstruction of a coronary artery. Rarely, ACS is caused by vasospasms (Prinzmetal angina) or

**Table 1.3** Relation of ECG changes to coronary artery involved and areas of myocardial tissue involvement[a]

| ST elevation on ECG | Coronary artery | Areas of myocardial tissue |
|---|---|---|
| I, AvL, V5 V6 | RCx | Lateral left ventricle |
| II, III, AvF | RCA or RCx[b] | Posterior left ventricle |
| V1–V4 | LAD | Anterior left ventricle and septum |
| V1 and V4R[c] | RCA | Right ventricle |
| AvR | LMCA (LM) | Whole left ventricle |

[a]Only if reciprocal depressions are seen
[b]80% of people have a right dominant coronary circulation
[c]Right-sided placement of precordial lead V4 to indicate right ventricular infarction

**Table 1.4** Canadian Cardiovascular Society classification of angina severity [3]

| | |
|---|---|
| Class I | Ordinary activity does not cause angina (walking, climbing stairs) |
| Class II | Slight limitation of ordinary activity (i.e. angina when walking or climbing stairs) |
| Class III | Marked limitation of ordinary activity (i.e. angina when climbing stairs at a normal pace) |
| Class IV | Inability to carry on any activity without discomfort (angina at rest) |

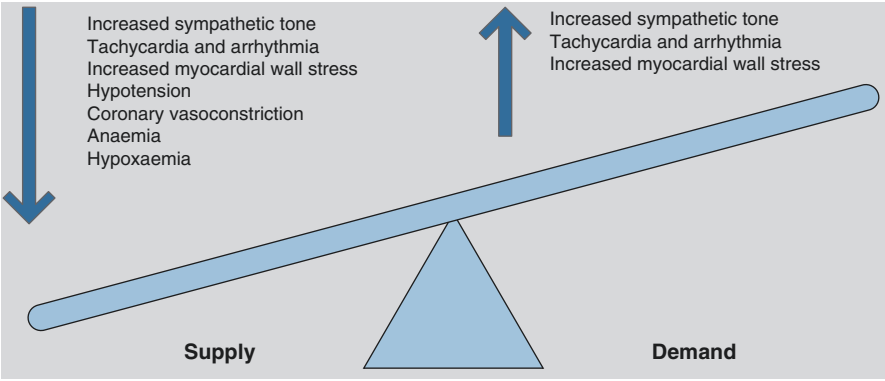


**Fig. 1.1** Balance of oxygen supply and demand; *arrows* indicate decrease in supply with its causes and increase in demand with its causes, respectively

embolisation into the coronary artery system. If a plaque rupture followed by thrombus formation leads to coronary artery obstruction, blood and oxygen supply distal to this obstruction will be hindered immediately, causing frequently STE-ACS (type 1 myocardial infarction, Table 1.2). In NSTE-ACS, there is often a partial occlusion of one of the coronary arteries. In patients with severe but stable coronary artery disease (SCAD), myocardial ischaemia is frequently caused by a reduced oxygen supply and/or increased oxygen demand (imbalance of oxygen supply-demand balance, type 2 MI). The severity of stable coronary artery disease can be classified according to the Canadian Cardiovascular Society classification of angina severity (CCS classification, Table 1.4) [3].

Type 2 ACS is the most common cause of perioperative MI. Oxygen *demand* of the heart can be *increased* by sympathetic nerve activity (stress, exercise, pain), tachycardia and arrhythmia (caused by, e.g. hypovolaemia, sympathetic nerve activity) and increased myocardial wall stress (due to hypertension, hypervolaemia). Oxygen *supply* can be *decreased* by changes of coronary artery anatomy, hypotension (cardiac decompensation, vasodilation), coronary vasoconstriction (stress, ischaemia), anaemia and hypoxaemia (pulmonary congestion, atelectasis, Fig. 1.1) [7].

## 1.3 Prevention of ACS

A distinction can be made between drug and nondrug therapy to prevent ACS. Most important nondrug therapies are lifestyle changes. Patients are encouraged to stop smoking, increase physical activity, reduce weight and change to a healthy diet. Patients who have been hospitalised for ACS should participate in a cardiac rehabilitation program to modify lifestyle habits and increase adherence to treatment. The goal of pharmacotherapy is to prevent formation of atherosclerosis, plaque rupture and subsequent thrombosis. This is namely achieved by prescribing statins and platelet aggregation inhibitors. Oxygen demand of the myocardium is reduced by β-blockers. If not tolerated, diltiazem or verapamil (calcium antagonists) can be an alternative. ACE inhibitors or angiotensin receptor blockers reduce myocardial wall stress and afterload. If left ventricular function is below 35% or symptoms persist during ACE inhibitor treatment, aldosterone receptor antagonists can be applied to the respective patients. In patients with hypertension, blood pressure should be kept below 140/90 mmHg; diabetic patients ideally should have an HbA1c of <7.0% to prevent microvascular disease [1, 3, 4, 8].

## 1.4 Treatment of Patients with ACS

Detailed treatment suggestions for different patient populations having ACS or MI are given in the respective guidelines [1, 3, 4].

### 1.4.1 Medical Therapy

Immediate medical therapy includes administration of nitrates, analgesics and oxygen. The symptoms of ACS, namely, radiating chest pain, shortness of breath, sweating as well as stress and anxiety, need immediate treatment not only due to human reasons but also to prevent/reduce sympathetic stimulation, which causes increased oxygen demand of the heart [1, 5].

Oxygen application is frequently recommended in clinical guidelines as the very first medical therapy, and it can be delivered via a nasal cannula, facemask or endotracheal tube. However, it is debatable whether additional oxygen is beneficial in all patients with MI [9]. In patients with ST-elevation myocardial infarction without hypoxaemia, application of oxygen increased myocardial injury and was associated with increased tissue necrosis 6 months after myocardial infarction [10]. In contrast, in patients with cardiac arrest undergoing cardiopulmonary resuscitation (CPR), hypoxia will quickly occur, and oxygen should be delivered in high concentrations as soon as possible. It is suggested to achieve an arterial oxygen saturation ($SaO_2$) of 94–98% (or 88–92% in case of chronic obstructive lung disease) in patients with return of spontaneous circulation (ROSC) after CPR for MI [5].

Chest pain due to myocardial ischaemia is effectively treated with glyceryl trinitrate, which induces dilation of venous capacitance vessels and coronary arteries.

Nitrates also reduce left ventricular failure and pulmonary congestion by diminishing ventricular afterload through arterial vasodilation. However, treatment with nitrates should not be initiated in severely hypotensive patients. In patients with inferior infarction and right ventricular involvement, nitrates might induce severe reduction of blood pressure and cardiac output. Whether nitrates can safely be used in patients taking phosphodiesterase-5 inhibitors (e.g. sildenafil) has not been determined definitely [11, 12]. When initiating nitrate therapy, one should keep in mind that nitrates might also redirect blood flow to non-diseased coronary arteries causing probably coronary steal phenomena.

Opioids are effective for pain relief and should be titrated on effect. Repeated doses may be required, and side effects like respiratory depression, nausea and vomiting, hypotension and bradycardia may need proper treatment [5].

Acetylsalicylic acid (ASA) is administered to all patients presenting with ACS, preventing (ongoing) thrombosis after rupture of an arteriosclerotic plaque. If the patient is not already on ASA therapy, a loading dose of 150–300 mg orally is administered in case of acute ACS. In some healthcare systems, intravenous instead of oral ASA is part of the first treatment algorithm. An oral dose of 75–100 mg ASA daily is continued indefinitely in patients experiencing an ACS. In patients intolerant to ASA, clopidogrel as single therapy is an alternative option [8]. Other important anticoagulation therapies for acute treatment of ACS include glycoprotein (GP) IIb/IIIa inhibitors (e.g. abciximab, eptifibatide, tirofiban) and antithrombins (e.g. unfractionated heparin, enoxaparin, fondaparinux) [1, 8].

### 1.4.2 Revascularisation

Revascularisation strategies after ACS include fibrinolysis, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). According to current guidelines, PCI is the treatment of choice [1, 4, 8].

Multiple studies have investigated the use of fibrinolysis for treatment of ACS. In STEMI patients, fibrinolysis remains a prehospital adjunct to PCI if the latter cannot be performed in due time. The benefit of PCI is diminished when performed more than 120 min after fibrinolysis. In approximately 1% of patients, fibrinolysis is complicated by intracranial bleeding with risk factors being age >75 years, lower body weight, female gender, prior cerebrovascular accident (CVA) and hypertension (systolic RR >180 mmHg). Non-intracranial bleeding occurs in 4–13% of patients undergoing fibrinolysis. Absolute contraindications for fibrinolysis are previous intracranial haemorrhage or stroke of unknown origin, ischaemic stroke in preceding 6 months, central nervous damage/neoplasms or atrioventricular malformations, major (head) trauma or surgery in preceding 3 weeks, gastrointestinal bleeding within the past month, known bleeding disorder, aortic dissection and noncompressible puncture in the past 24 h. Fibrinolysis is less effective in inferior wall infarctions and has a risk of incomplete revascularisation [4].

Primary PCI (PPCI) is considered the golden standard in current ACS care. Since the first development of coronary artery stents, most patients suffering ACS are treated

with stent implantation. Balloon angioplasty as single treatment has become rudimentary, except for specific cases. In acute STEMI patients, only the infarct-related artery should be treated in the acute situation, even if there is multivessel disease with stenoses in the other coronary arteries. Exceptions on this strategy are cardiogenic shock in the presence of multiple truly critical (>90% diameter) stenoses or highly unstable plaques or if there is still persistent ischaemia after PCI of the culprit lesion [4, 8]. Multivessel disease is estimated to be present in 40–80% of patients. In NSTE-ACS, incomplete revascularisation is associated with detrimental prognosis, and, therefore, complete revascularisation should be attempted in this patient population [1].

Coronary artery bypass grafting (CABG) can be performed in patients who are considered unsuitable for PCI because of complex coronary anatomy or in case of multivessel disease in NSTE-ACS. It should be considered in patients with STEMI and cardiogenic shock or in patients with severe complications after PCI. Mortality after 5.9 years of PCI and CABG seems to be similar (11.1% in PCI and 9.6% in CABG group) [13]. The most important advantage of CABG versus PCI is complete revascularisation in advanced multivessel coronary artery disease, thereby reducing unplanned revascularisation and major cardiac adverse events. Disadvantages of CABG versus PCI are higher rates of stroke (1.1% vs. 0%), major bleeds (45.5% vs. 9.1%) and renal injury (31.7% vs. 14.2%) [1].

## 1.5 The Patient with Recent ACS Needing (Emergency) Surgery

Every anaesthesiologist may be confronted with a patient who has suffered a recent ACS (within the previous 30 days). These patients are at a higher perioperative risk for death or cardiovascular complications.

While balloon angioplasty (PTCA) is able to overcome coronary artery stenosis, restenosis will occur very soon if no additional measures are taken. PTCA leads to endothelial denudation, which results in accumulation of platelets and fibrin. In addition, stretching, fracturing and disruption of atheromatous plaque can lead to intimal dissection and aneurysmal dilation. Elastic recoil and post-injury arterial shrinkage may also occur. Although balloon angioplasty is a controlled injury, it goes along with possible complications like acute vessel closure (4–8%). In 30–50% of patients, restenosis on the basis of mechanical, biochemical and histological factors will occur. To reduce the rate of restenosis, bare metal stents (BMS) were introduced and significantly improved patency of the coronary artery. However, in the beginning, a lot of stent thromboses were observed, leading to sudden coronary artery occlusion and MI, causing high mortality. After initiating routine anti-platelet aggregation therapy with a combination of aspirin together with a P2Y12 receptor antagonist (dual anti-platelet therapy—DAPT), this risk for thrombosis could be significantly reduced [14]. However, the BMS still showed early restenosis, making re-intervention in many patients necessary. Drug-eluting stents (DESs) were introduced to reduce this risk of restenosis by eluting anti-proliferative drugs from the stent struts [15]. Thereby, neointimal hyperplasia could be effectively reduced [16].

Because stent struts remain uncovered by endothelium for months, there is a prolonged need for anti-platelet therapy. While patients with BMS received DAPT for at least 30 days and preferably 3 months, DAPT was maintained for 3–6 months after DES implantation. First-generation DES contained sirolimus or paclitaxel [17] and showed to be very effective in reducing cardiovascular events [18]. However, a couple of years later, big registries showed an increased mortality for patients with DES compared to BMS [19]. This was most likely caused by (early) discontinuation of DAPT [20, 21] and led to guidelines suggesting DAPT after DES implantation for at least 1 year [22].

Hence, anaesthesiologists were confronted with patients on DAPT who might need emergence surgery within the first 12 months after ACS. In the meantime, newer generations of DES (e.g. second generation, everolimus-eluting stents; third generation, biolimus-eluting degradable stents) have been introduced, and first-generation DES are no longer used in developed countries. With these newer stents, a shorter time of DAPT seems to be reasonable: 6 months of DAPT was not inferior compared to 12 months of DAPT, and even shorter time periods might be suitable in special patient populations (like those undergoing surgery) [23]. The guidelines of the European Society of Cardiology (ESC) recommend that in patients with stable CAD and DES, DAPT should be maintained for 6 months or even shorter periods if the risk of bleeding is high (e.g. *perioperatively*). In contrast, in patients with high risk of ischaemia and low bleeding risk, DAPT might be continued for a longer period. For patients with ACS, DAPT should be maintained for 12 months regardless of stent type [8, 24]. We would like to stress out that interruption of DAPT is always an individualised, patient-specific decision, which should be taken after multidisciplinary patient conference. Some patients, e.g. those with high thrombotic risk due to numerous stents in one artery, bifurcation stents or with high thrombotic properties, may even profit from DAPT for more than 12 months [25]. All patients with previous ACS will remain on ASA lifelong.

Because the period for DAPT is reduced, nowadays anaesthesiologist will face less patients needing surgery while on DAPT after ACS. In all cases, it should be discussed whether aspirin and the P2Y12 inhibitor could be continued. If bleeding risk is high, the P2Y12 inhibitor should be discontinued and aspirin may be maintained. Different strategies to bridge DAPT have been proposed [26]. Following the ESC guidelines, 'for patients with a very high risk of stent thrombosis, bridging therapy with intravenous, reversible glycoprotein inhibitors, such as eptifibatide or tirofiban, should be considered' [27]. This has been investigated in several case series [28].

Some authors suggest bridging with heparin. However, arterial thrombosis depends on platelet function but not on coagulation cascade, and unfractionated heparin facilitates activation of platelets [29]. Heparin binds to the GP IIb/IIIa receptor, thereby possibly introducing a pro-thrombotic effect. Thus, the use of low-molecular-weight heparin (LMWH) for bridging in these patients should be avoided [27]. There is also an intravenous P2Y12 inhibitor, cangrelor, which has been shown to effectively inhibit platelet aggregation and has the advantage of

**Table 1.5** Lee revised cardiac risk index [49]

| |
|---|
| High-risk type of surgery |
| Ischaemic heart disease |
| Congestive heart failure |
| Cerebrovascular disease |
| Insulin-dependent diabetes |
| Preoperative serum creatinine >173 μmol/L (2.0 mg/dL) |

No risk factor, complication rate 0.4%; 1 risk factor, complication rate 1.0%; 2 risk factors, complication rate 7%; ≥3 factors, complication rate 11%

quick onset of action and a short half-life [30, 31]. In recent studies, cangrelor has been shown to be superior compared to clopidogrel during ACS and PCI [32, 33].

In all patients, DAPT should be resumed as soon as possible after surgery, preferably within 24–48 h [27].

Because emergency PCI is the only therapeutic option to improve patient outcome if stent thrombosis occurs, surgical procedures in these patients should be performed in hospitals where 24/7 catheterisation laboratories are available.

### 1.5.1 Preoperative Risk Assessment and Risk Adjustment

Like in every other patient, effort should be made to optimise the patient's clinical status. Functional capacity (metabolic equivalent of tasks, METs) and cardiac risk factors (see Table 1.5) should be determined. An estimation of surgical risk for cardiac complications should be made, depending on the surgical procedure to be performed (low risk <1%, intermediate risk 1–5% and high risk >5%) [27]. An ECG should be available for all patients with recent ACS. In high-risk patients, echocardiography helps to determine regional or global myocardial dysfunction.

Preoperative N-terminal pro-BNP plasma serum levels independently predict risk of perioperative cardiac events [27]. Assessment of cardiac troponins before and 48–72 h after surgery is currently a matter of debate [34]. Preoperative invasive strategies for cardiac evaluation (coronary angiography and possible interventions) have not been shown to be beneficial compared to noninvasive evaluation and medical therapy [35].

Preventive pharmacological therapy with β-adrenoceptor-blocking agents and statins should be continued. There is no evidence that β-adrenoceptor blockers, aspirin or α-2-adrenoceptor agonists should be initiated in all patients [36–38].

However, selected patients—with the correct indication for one of these agents—might substantially benefit from medical optimisation preoperatively if timely initiated.

In patients with heart failure or severe left ventricular dysfunction after ACS, angiotensin-converting inhibitors or angiotensin receptor blockers should be continued. In other patients, these agents should be withheld perioperatively to avoid intra- and postoperative hypotension [39, 40].

### 1.5.2 Choice of Anaesthesia

Optimisation of perioperative monitoring on cardiac events with 5-lead ECG is recommended, and 12-lead ECG monitoring might be suitable. Transoesophageal echocardiography may be considered in high-risk surgery and should be available if there is evidence of myocardial ischaemia. It seems to be of little importance which drugs are used for induction and maintenance of anaesthesia, as long as proper maintenance of organ perfusion is ensured. Effort should be made to prevent hypotension together with low levels of bispectral index [41–43].

For a long time, it has been suggested that volatile anaesthetics have myocardial protective effects and should be preferred over intravenous agents [44]. Although profound protection of these substances has been demonstrated in animal models as well as in cardiac surgery patients [45], today we do not have robust data that indicate superiority of volatile agents in patients with cardiac risk undergoing noncardiac surgery [46].

Superiority of neuraxial techniques can be questioned and evidence supporting reduction in cardiac events is lacking [47]. In patients on DAPT, there is no good reason to stop DAPT in order to use neuraxial anaesthesia techniques.

The main goal should be an optimisation of the balance between oxygen supply and demand throughout surgery; tachycardia should be avoided as it is the main reason for increased oxygen demand of the myocardium. Goal-directed fluid therapy might improve maintenance of haemodynamic stability [48]. Anaemia as well as hyperglycaemia should be treated adequately. During emerging from anaesthesia, sympathetic tone increases, and irritation of an airway device may induce enormous stress. Early extubation should therefore be considered, but hypoxaemia due to laryngeal spasms, coughing, mucus or other airway problems must be avoided. Pain should be treated adequately to avoid stress response, and non-steroidal anti-inflammatory drugs (especially COX-2 inhibitors) should be avoided. All these measures should be continued postoperatively; in addition, shivering significantly increases oxygen demand and has to be prevented and consequently treated.

## 1.6 Perioperative ACS

More than 200 million adults undergo major noncardiac surgery each year. Intraoperative mortality has been significantly reduced tenfold during the last three decades, but 30-day mortality is still a relevant problem with 2% of inpatients older than 45 years of age involved. The incidence of perioperative ACS varies from 0.4 to 11% depending on the patient's risk profile (Lee's Revised Cardiac Risk Index, Table 1.5) [49].

Early mortality of perioperative ACS ranges from 3.5 to 25%. Those who survive perioperative MI will have an increased amount of complications, longer hospital stay and increased medical costs [34].

If patients are awake, e.g. undergoing surgery with regional anaesthesia, symptomatology of perioperative MI might be similar to patients without anaesthesia. However, perioperative MI is a difficult diagnosis during general anaesthesia: it is silent and much more frequent than we imagine. Only 15% of patients with perioperative MI report chest pain, 65% of patients being asymptomatic. ECG changes may be transient and subtle, with more frequently ST depression instead of ST elevation. A period of 20–30 min of ST depression or a cumulative depression longer than 60 min was associated with adverse cardiac events [50]. In 60–90% of patients with perioperative MI, no Q waves are determined [7, 51]. If chest pain and ECG changes are not reliably detecting perioperative MI, we should focus on biomarker release. With the introduction of high-sensitivity troponin test, it is possible to detect very low levels of troponin. Even slight troponin elevations predict death, with a fourfold risk when troponin is increased up to 0.02 ng/mL and 17-fold risk when troponin is higher than 0.3 ng/mL [34, 52].

### 1.6.1 Intraoperative Management of Patients with Evident Perioperative MI

Management of patients with intraoperative myocardial ischaemia is challenging and depends on the clinical consequences. One challenge is to decide whether to continue or abort surgery. It is obvious to continue surgery if it is in an advanced stage and can be completed within reasonable time. If surgery has just commenced, it is probably best to abort immediately and go for revascularisation if necessary. Fibrinolysis and CABG are associated with significant bleeding complications in these patients. Therefore, reperfusion strategy of choice is emergency PCI; although there might be a therapeutic window of 24 h, PCI should be performed as soon as possible [53]. Whether a stent can be placed with the necessity of anti-platelet therapy should be discussed between surgeons, anaesthesiologists and cardiologists. In patients with a very high risk for bleeding complications, balloon angioplasty without stenting might be suitable at first. A second PCI might be necessary in the early postoperative period. In patients with low bleeding risk, stent implantation can possibly be performed immediately [54].

In patients developing perioperative MI, the anaesthesiologist should check whether currently installed monitoring is still adequate or should be extended (e.g. invasive blood pressure measurement, echocardiography). A cardiologist should be consulted, and transthoracic or transoesophageal echocardiography is very helpful to detect wall motion abnormalities and should be performed as soon as possible.

As mentioned earlier, perioperative MI is mostly due to imbalance of oxygen supply and demand, and not due to plaques rupture. Anaesthesiologists should optimise oxygen supply-demand balance by improving tissue oxygenation (increased

inspired oxygen fraction, use of positive end-expiratory pressure, treat anaemia to achieve haemoglobin levels of 8–10 mg/dL), reducing tachycardia to heart rates lower than 70/min (stress prevention with opioids, β-adrenoceptor blockers, normovolaemia) and treating possible arrhythmias. Glyceryl trinitrate may be used to induce coronary vasodilation, but significant systemic hypotension should be avoided. In some cases, cardiac output may only be maintained with inotropes (dobutamine, phosphodiesterase inhibitors, levosimendan). The concomitant vasodilation should consequently be treated with phenylephrine or norepinephrine to maintain coronary perfusion pressure. Other supportive measures include intraaortic balloon counterpulsation or implantation of a centrifugal pump (e.g. Impella®) allowing maintenance of cardiac output even in those patients with cardiogenic shock [55, 56].

## 1.7 Perspectives

Perioperative MI is most likely much more frequent than we thought up to now. Recently, the characteristics, diagnostic criteria, predictors and 30-day outcomes of patients with perioperative MI in over 15,000 patients have been described [57]. A new term—myocardial injury after noncardiac surgery, MINS—has been suggested. With the high-sensitivity biomarker test, detecting a higher incidence of ischaemia (8% of patients) is possible. Because patients with MINS had a higher 30-day mortality rate (9.8% vs. 1.1%) [57], detecting patients at risk at an early stage will help to initiate adequate treatment and further reduce 30-day morbidity and mortality.

In anaesthetised or sedated patients (e.g. postoperative pain management), clinical symptoms of coronary ischaemia (pain, discomfort) are frequently absent, and ECG changes might be very short and transient and might therefore be missed in a punctually performed 12-lead ECG. Therefore, in the future perioperative MI should namely focus on detection of rise and fall of cardiac-specific biomarkers in patients at increased cardiac risk, including those patients with coronary artery diseases and former ACS.

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# The Patient with Advanced Chronic Heart Failure

2

Patrick F. Wouters and Koen Lapage

## 2.1 Introduction

Heart failure has been announced as the "next frontier in perioperative medicine" [1]. Perioperative mortality in patients with HF is much higher than in patients with isolated ischemic heart disease. Ischemic heart disease was a subject of intensive outcome research over the past years, and this has led to clear evidence-based practice guidelines and improved perioperative survival. For HF patients, surgical outcome has not changed much. Nevertheless, the proportion of patients presenting for surgery with a diagnosis of HF is increasing. CHF is a disease of the elderly, and that segment of the population is growing rapidly.

It is a real challenge to develop clear guidelines for the perioperative management of CHF because there is not much scientific data available. In addition, CHF is a complex disease entity with heterogeneous etiology and distinct phenotypes, often accompanied by multiple comorbidities and organ system dysfunction(s). In this chapter, we will review the current knowledge on pathophysiology, diagnosis, and treatment of CHF. This will form the basis for a subsequent discussion on perioperative management including risk assessment and optimization strategies, as well as techniques for intraoperative monitoring and hemodynamic control.

## 2.2 Definition and Classification of HF

The European Society of Cardiology Task Force defines heart failure as "a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. pulmonary crackles, peripheral

P.F. Wouters (✉) • K. Lapage
Department of Anaesthesia and Perioperative Medicine, Ghent University and University Hospital, Ghent, Belgium
e-mail: Patrick.Wouters@UGent.be



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**Table 2.1** Classification of heart failure

| | ACCF/AHA stages of HF | NYHA functional classification | |
|---|---|---|---|
| A | At high risk for HF but without structural heart disease or symptoms of HF | None | |
| B | Structural heart disease but without signs or symptoms of HF | I | No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF |
| C | Structural heart disease with prior or current symptoms of HF | I | No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF |
| | | II | Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF |
| | | III | Marked limitation of physical activity. Comfortable at rest, but less-than-ordinary activity causes symptoms of HF |
| | | IV | Unable to carry on any physical activity without symptoms of HF or symptoms of HF at rest |
| D | Refractory HF requiring specialized interventions | IV | Unable to carry on any physical activity without symptoms of HF or symptoms of HF at rest |

edema) caused by a structural and/or functional cardiac abnormality, which result in a reduced cardiac output and/or elevated intracardiac pressures during rest or during stress" [2].

There are a number of ways to grade the severity of the syndrome (Table 2.1). The most popular is the NYHA Functional Classification, which relates patients' symptoms and signs to their level of activity. Patients move to a higher category (from I to IV) with progression of the disease but can return to a lower class, i.e., with less functional limitation, as a result of effective therapy. The ACCF/AHA classification of HF, in contrast, is unidirectional. It emphasizes the development and progression of the disease (from level A to D) and also includes preclinical stages [3].

Heart failure is also categorized into subgroups based on the quantification of ejection fraction: patients with reduced EF (<40%, HFrEF) are differentiated from those who have preserved EF (≥50%, HFpEF). These subgroups indeed appear to represent very distinct phenotypes with different etiologies, demographics, comorbidities, and therapeutic responses. The majority of outcome studies however show comparable short- and long-term mortality. In the most recent guidelines, the ESC Task Force distinguishes a third subgroup of HF patients with midrange EF (between 40 and 49%, HFmrEF) (Table 2.2). The ACCF/AHA considers patients with recovered HF as yet another distinct subgroup.

**Table 2.2** Different phenotypes of heart failure, classified according to ejection fraction (EF)

| Type of HF | HFrEF | | HFmrEF | HFpEF |
|---|---|---|---|---|
| Criteria | 1 | Symptoms ± signs | | |
| | 2 | LVEF <40% | LVEF 40–49% | LVEF ≥50% |
| | 3 | – | 1. Elevated levels of natriuretic peptide<br>2. At least one additional criterion:<br>(a) Relevant structural heart disease (left ventricular hypertrophy and/or left atrial enlargement)<br>(b) Diastolic dysfunction | |

## 2.3 Epidemiology

In developed countries, the overall prevalence of HF in the adult population is 1–2%, but it increases steeply with age and exceeds 10% in subjects older than 70 years [4]. Since HF is primarily a disorder of the elderly, the incidence and prevalence are expected to rise further over the next two decades as the population is aging rapidly [5].

HFrEF and HFpEF appear to be equally represented; although depending on the diagnostic criteria used, reported numbers vary between studies. Compared with HFrEF, patients with HFpEF are older, are more often female, and have a history of hypertension or atrial fibrillation [6].

Prognosis has improved over the past decade, but overall mortality rates remain high for patients with established HF. A new diagnosis of HF is associated with a 30-day mortality of 10%, and up to one third of older patients die within 1 year following initial hospitalization for HF [7, 8]. European data show a 5-year survival rate of 53% and 62% for HFrEF and HFpEF, respectively, while hospitalization rates are higher for HFpEF [9]. HF has a major impact on the quality of life for individuals and imposes a significant financial burden on society [10].

The reported prevalence of HF in patients undergoing noncardiac surgery now varies between 2, 5, and 10% [11]. This number is expected to increase not only because the population ages but also because the number of less-invasive surgical and interventional options offered to high-risk patients continues to grow [12].

## 2.4 Pathophysiology

Heart failure is an end-stage syndrome that can evolve from a multitude of primary cardiovascular diseases. The diverse etiology is structured into three major categories: (1) diseases of the myocardium, (2) abnormal cardiac loading conditions, and (3) major arrhythmias (Table 2.3). An alternative approach to structure the heterogeneous etiology of HF is based on the pathophysiological mechanisms that drive the development of HF. There are mainly four categories: (1) traditional risk factors

**Table 2.3** Etiology of heart failure

| | |
|---|---|
| A. Diseases of the myocardium | |
| 1. Ischemic heart disease | Myocardial scar, stunning/hibernation, epicardial coronary artery disease, abnormal coronary microcirculation, endothelial dysfunction |
| 2. Toxic damage | Recreational substance abuse (e.g., alcohol, cocaine, amphetamines), heavy metals (e.g., copper, iron), radiation and medications (e.g., cytostatic drugs) |
| 3. Immune-mediated and inflammatory damage | Infection-related, autoimmune diseases, giant cell myocarditis, eosinophilic myocarditis (Churg-Strauss) |
| 4. Infiltration | Malignancy related (e.g., direct infiltration, metastasis), sarcoidosis, amyloidosis, hemochromatosis |
| 5. Metabolic derangements | Hormonal (e.g., thyroid diseases, acromegaly, diabetes, pregnancy-related pathology), nutritional deficiencies |
| 6. Genetic abnormalities | Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), LV non-compaction, arrhythmogenic right ventricular cardiomyopathy (AVRC), muscular dystrophy (e.g., Becker's disease) |
| B. Abnormal loading conditions | |
| 1. Hypertension | |
| 2. Valvular and myocardial structural defects | Acquired valvular diseases, congenital (e.g., atrial/ventricular septal defects) |
| 3. Pericardial and endomyocardial pathologies | Pericardial (constrictive endocarditis, pericardial effusion), endocardial fibroelastosis, hypereosinophilic syndrome (HES), endomyocardial fibrosis (EMF) |
| 4. High-output states | Sepsis, severe anemia, pregnancy, thyrotoxicosis, arteriovenous fistula, Paget's disease |
| 5. Volume overload | Renal failure, iatrogenic fluid overload |
| C. Arrhythmias | |
| 1. Tachyarrhythmias | Atrial/ventricular arrhythmias |
| 2. Bradyarrhythmias | Sinus node dysfunction, conduction disorders |

for cardiovascular disease including ischemic injury, hypertension, and metabolic syndrome (diabetes, hyperlipidemia, central obesity) representing the vast majority; (2) genetic factors linked to cardiomyopathy, e.g., hypertrophic obstructive cardiomyopathy; (3) mechanical factors, predominantly valve dysfunctions resulting in pressure and/or volume overload; and (4) immune-based factors, i.e., infectious diseases, both viral and bacterial, and autoimmune diseases [13].

Prevalence of the dominant cause varies within world regions. In developed countries, hypertension, ischemic heart disease, and valve dysfunction are the most important diseases leading to HF. Myocardial infarction is the main cause of HFrEF, while hypertension and atrial fibrillation are more often associated with HFpEF. Noncardiac comorbidities such as renal disease, diabetes, and obesity often add to the development and prognosis of HF. In Africa and Asia, rheumatic heart disease remains an important cause of HF, while in South America, still a significant proportion of patients develop HF from Chagas' disease [10].

The pathophysiology of HFrEF has been the focus of extensive study for decades. HFpEF, however, was only recently identified as a separate clinical entity. These two phenotypes differ primarily with regard to the underlying mechanism of cardiac dysfunction. Because a key feature of HFrEF is the limited capacity of the LV to eject blood, it is often referred to as systolic heart failure. In HFpEF (and HFmrEF), cardiac ejection appears normal, at least when quantified as the proportion of blood ejected during systole. Importantly, in HFpEF there is often a significant impairment of cardiac filling, hence the term diastolic heart failure. Diastolic heart failure has probably been underreported in the past because a diagnosis required invasive heart catheterization for the assessment LV filling pressures. Current guidelines accept diagnostic criteria based on noninvasive Doppler echocardiography and biomarkers (BNP and pro-BNP) [14] (Fig. 2.1).

The distinction between systolic and diastolic heart failure is somewhat arbitrary since patients with HFrEF often have diastolic abnormalities as well and, vice versa, patients with HFpEF may have subtle abnormalities in systolic function detected only with sensitive techniques such as myocardial deformation imaging. Nevertheless, this conceptual framework, distinguishing between primary systolic and primary diastolic dysfunction, provides a useful basis for the perioperative hemodynamic management of HF patients.

Patients with right ventricular heart failure may also present with a normal LVEF and theoretically this subgroup fits the HFpEF definition, but they have not been addressed in the available guidelines on HF today. The pathophysiology of PHT and primary RV failure is substantially different and will be discussed in a separate chapter.

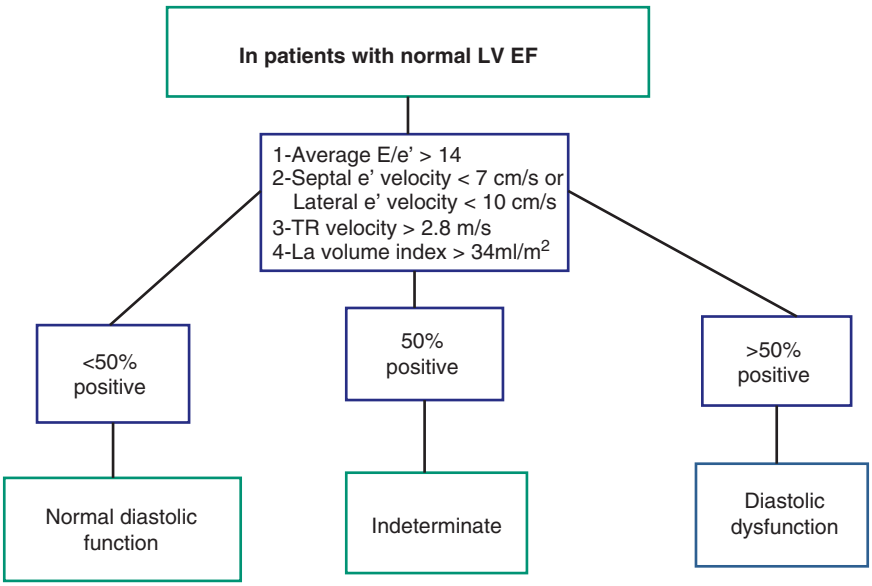


**Fig. 2.1** Noninvasive echocardiographic diagnosis of diastolic dysfunction

## 2.5 Treatment

For many years, the therapeutic strategy for heart failure focused mainly on mechanisms to increase cardiac inotropic state and restore pump performance (the failing pump model). A number of drugs were developed to enhance the availability of intracellular calcium at the myofilaments during systole. Whereas digoxin obtains this effect indirectly via inhibition of the sarcolemmal Na/K pump, the majority of current positive inotropic drugs operate by raising the intracellular levels of c-AMP, either through increased production of this second messenger (sympathomimetics) or by inhibition of its enzymatic breakdown (phosphodiesterase-III inhibitors). Such pharmacological agents were shown to have powerful and immediate positive inotropic effects; however, when used on a chronic basis for the treatment of heart failure, they invariably turned out to increase mortality [15]. Interestingly, only the less potent positive inotropic drugs, including digoxin and the more recently developed calcium sensitizer levosimendan, appear to have less or no detrimental effects on survival [16]. Levosimendan is the most recent clinically available drug in the category of positive inotropes with a unique mechanism of action. It operates primarily via sensitization of the myofilaments to calcium rather than by increasing intracellular calcium levels. This pharmacologic class of calcium sensitizers offers the theoretical advantage of a lower energetic demand as there is less need for reuptake of calcium in the SR during diastole [17].

Anyway, the pharmacological stimulation of contractile performance, while often effective in relieving symptoms and improving quality of life, appeared to concur no prognostic benefit or even to decrease survival in patients with chronic heart failure. The primary suspects for these increased mortality rates were life-threatening arrhythmias, due to increased c-AMP load and electrophysiological instability, and myocardial ischemia due to drug-induced increases in myocardial oxygen requirements [18]. Importantly, positive inotropic drugs do have an essential position in the management of acute heart failure and are indispensible to overcome acute decompensation in CHF, but this will be discussed later in the section on perioperative management.

A major breakthrough in the therapy came with evolving insights into the pathophysiology of CHF, when neurohumoral reflexes were targetted as key players in disease progression. Activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosteron system (RAAS) occurs in response to hypotension and reduced organ perfusion. These reflexes are homeostatic and beneficial in acute hypovolemia, when fluid retention and vasoconstriction serve to restore organ perfusion. In CHF, however, there is a persistent activation of neurohumoral reflexes causing vasoconstriction and fluid retention, a constant burden of increased cardiac pre- and afterload for the already dysfunctional pump. Sustained neurohumoral activation also promotes the development of myocardial fibrosis and adds further to the pathogenesis of cardiac remodeling.

The current therapeutic approach in CHF entirely focuses on blocking such maladaptive responses (neurohumoral antagonism model). The three pharmacological classes, with 1A recommendations, all involve inhibition of the RAAS or SNS. ACE inhibitors, angiotensin receptor blockers (ARBs), and beta-blockers are considered

first-line treatment in chronic HF. ARBs are a viable alternative for patients who are intolerant to ACE inhibitors. If symptoms remain despite optimal ACE inhibitor/ARB and beta-blocker therapy, a mineralocorticoid receptor antagonist (MRA) is added as the third component of neurohumoral antagonism.

The most recent addition to the armamentarium is an angiotensin receptor antagonist/neprilysin inhibitor (ARNI). Neprilysin is an endogenic enzyme that degrades natriuretic peptides and vasoactive peptides such as bradykinin and adrenomedullin. Blockade of neprilysin increases the level of vasodilatory peptides and natriuretic peptides causing favorable hemodynamic conditions. Because neprilysin also degrades angiotensin II, an angiotensin receptor blocker is associated to counteract increased levels of this vasoconstrictor, an unwanted effect of neprilysin inhibition. Initial studies have shown promising results, and ARNIs are now included as 1B recommendation to replace ACE inhibitors in patients with symptoms refractory to standard triple therapy (ACE inhibitor, beta-blocker, MRA) [19]. A specific indication is reserved for ivabradine, a drug that directly inhibits K-channels in the sinus node and reduces heart rate independently from sympathetic tone. ESC guidelines state that ivabradine should be considered in patients with elevated heart rate despite adequate beta-blocker treatment.

Other neurohumoral pathways have been explored as well, but attempts to intervene pharmacologically have not been successful yet. These interventions include the use of vaptans, antagonists of the arginine vasopressin receptor, endothelin A receptor antagonists, and renin inhibitors [20].

It is important to acknowledge that the above recommendations are based on strong evidence from large-scale studies, none of which included patients with preserved EF. Hence, the beneficial effects of neurohormonal and sympathetic modulation only pertain to patients with HFrEF. No treatment has been shown to reduce morbidity or mortality in patients with HFpEF (or HFmrEF) until today [2].

Along with, and in addition to, neuromodulation which is an outcome-oriented therapy, the therapeutic approach to CHF also consists of symptomatic therapy. Diuretics are a mainstay to correct and control symptoms of congestion, particularly in newly diagnosed or decompensated HF. This applies to HFrEF as well as to HFpEF and HFmrEF. In acute settings, symptoms relief can also be achieved rapidly by unloading the heart with venous and arterial vasodilators. Vasodilators are also effective in correcting volume overload in the perioperative phase, but chronic use of vasodilating agents, including recombinant BNP, has not been shown to affect outcome [21].

Current research focuses on the role of inflammation in the pathophysiology of CHF (the inflammation model). Inflammatory pathways contribute to the development of HF in the acute settings of myocardial injury and tissue repair. Patients with HF, both HFrEF and HFpEF, have a low-grade chronic inflammation with elevated levels of proinflammatory cytokines which correlate with adverse outcome. It is still not clear however whether inflammation is causative to disease progression or just a consequence [22]. The majority of clinical trials aiming at limiting inflammation in CHF have largely been negative. The scientific challenge probably resides in the distinction between physiological inflammation (repair) and pathological pathways. Immunomodulation by means of stem cell therapy is a promising extension of this strategy, for which some studies have demonstrated beneficial effects based on autocrine mechanisms. [13].

Both atrial and ventricular arrhythmia is common in HF patients. Increased atrial pressures predispose to atrial fibrillation and when atrial fibrillation occurs in CHF patients with a previously normal sinus rhythm, it is often the cause of an acute exacerbation. Cardiac remodeling and myocardial fibrosis form the substrate for micro-reentry circuits causing ventricular arrhythmia. Sudden death due to major ventricular arrhythmia is relatively common in HF patients, and many are treated with implantable cardiac defibrillators. ICDs are considered for primary prevention in symptomatic patients with EF > 35% if they are expected to have a life expectancy with good functional status longer than 1 year.

Ventricular remodeling also induces disruption of the normal conducting system of the heart, hence the sequential activation of atrial and ventricular myocytes via the fast His-Purkinje system. Uncoordinated cardiac contractions have a large impact on pump efficacy. There is strong evidence that, in addition to optimal medical therapy, cardiac resynchronization therapy (CRT) is of benefit to HF patients with a LVEF <35% and a left bundle branch block with a prolonged QRS (>130 ms) and should be considered preoperatively [2].

Surgical approaches to improve ventricular function in the severely dilated, remodeled heart, in particular after extensive myocardial infarction and scarring, include surgical ventricular reconstruction (SVR) and aneurysmectomy. The rationale for that procedure is to reduce LV wall tension by excluding the scarred myocardium and reshaping the heart to its original elliptical geometry. Encouraging results have been reported in a limited number of centers, but the procedure remains controversial and is not adapted widely [23].

Mechanical circulatory support is considered in CHF patients with acute deterioration when pharmacotherapy fails, or as a last resort for patients with end-stage disease. Temporary support can suffice to bridge a period of cardiogenic shock until hemodynamics and organ perfusion stabilize, but is mostly used to buy time for decision making with regard to heart transplantation—if patients are eligible—or to long-term installation of mechanical assist as destination therapy. Mechanical circulatory assist devices will be discussed in a separate chapter.

## 2.6 Perioperative Management of the Patient with Advanced Heart Failure

The prevalence of heart failure in the perioperative setting varies between 2, 5, and 10% in noncardiac surgery and is expected to rise due to the relative increase in elderly patients presenting for surgery [24]. Outcome studies invariably show a higher risk for MACE and an increased mortality in patients with a history of heart failure undergoing noncardiac surgery [25]. There is also a higher incidence of noncardiac complications such as pneumonia and sepsis in these patients [26]. Interestingly, patients with heart failure have substantially higher risk for operative mortality and hospital readmission than patients with coronary disease [27, 28]. While significant improvements were made in perioperative care for patients with IHD, this has clearly not been achieved for CHF yet [1].

## 2.7 Preoperative Risk Stratification and Optimization of HF Patients

Risk stratification is not a means by itself but an essential component in optimizing the perioperative strategy for individual patients. The ACC/AHA 2014 perioperative clinical practice guidelines promote the use of risk prediction tools such as the Revised Cardiac Risk Index (RCRI) and the NSQIP Surgical Risk Calculator. These models focus primarily on risk related to ischemic heart disease, however, and their validity in HF remains to be established.

Similar to IHD, red flags for HF are a "de novo" diagnosis and an unstable condition with worsening signs and symptoms. Indeed, the stability of HF appears a key determinant of hospital stay, hospital readmission, and long-term mortality rate [26, 29].

A complete history and clinical examination with focus on the typical signs and symptoms of HF is of primordial importance (Table 2.4). In patients with known or suspected HF, echocardiography is strongly recommended in the ESC/ESA 2014 guidelines (class I, level A) [30]. When integrated in a preoperative assessment, TTE is an excellent noninvasive and readily available tool to provide rapid and important prognostic information for patients undergoing noncardiac surgery [31].

**Table 2.4** Symptoms and signs typical of heart failure

| Symptoms | Signs |
|---|---|
| *Typical* | *More specific* |
| Breathlessness<br>Orthopnea<br>Paroxysmal nocturnal dyspnea<br>Reduced exercise tolerance<br>Fatigue, tiredness, increased time to recover after exercise<br>Ankle swelling | Elevated jugular venous pressure<br>Hepatojugular reflux<br>Third heart sound (gallop rhythm)<br>Laterally displaced apical impulse |
| *Less typical* | *Less specific* |
| Nocturnal cough<br>Wheezing<br>Bloated feeling<br>Loss of appetite<br>Confusion (especially in the elderly)<br>Depression<br>Palpitations<br>Dizziness<br>Syncope<br>Bendopnea | Weight gain (>2 kg/week)<br>Weight loss (in advanced HF)<br>Tissue wasting (cachexia)<br>Cardiac murmur<br>Peripheral edema (ankle, sacral, scrotal)<br>Pulmonary crepitations<br>Reduced air entry and dullness to percussion at lung bases (pleural effusion)<br>Tachycardia<br>Irregular pulse<br>Tachypnea<br>Cheyne-Stokes respiration<br>Hepatomegaly<br>Ascites<br>Cold extremities<br>Oliguria<br>Narrow pulse pressure |

European Heart Journal (2016) 37, 2129–2200 [2]

Elevated BNP and NT-pro-BNP levels in the preoperative setting have been associated with a higher odds ratio both for postoperative MACE and short-term mortality [32]. The predictive value of BNP in HF patients with chronically elevated levels with regard to perioperative risk is still subject to research. The wide cutoff ranges complicate interpretation of the results, and there is no evidence yet that a BNP-guided approach improves postoperative outcomes. Laboratory tests are required to assess potential electrolyte imbalances and signs of organ dysfunction. Screening for anemia is also recommended as this appears to be a particular risk factor in HF patients [33].

The goal of risk assessment is to identify patients who are not able to cope with the increased physiologic demands of surgery and anesthesia. As a rule of thumb, a minimum of four METs, which corresponds to an oxygen consumption of 12 mL $O_2$/kg/min, is considered a threshold value in moderate- to high-risk surgery. Clinical estimation of functional capacity by physicians is not very consistent however, particularly not in the lower ranges [34]. Cardiopulmonary exercise testing (CPET) provides an objective quantitative means to assess anaerobic threshold. Values <11 mL $O_2$/kg/min correlate with increased risk [35]. Although one meta-analysis reported peak oxygen consumption and anaerobic threshold as predictors of perioperative morbidity and mortality in thoracoabdominal surgery [36], CPET is not yet recommended as a standard in preoperative assessment.

## 2.8 Risk Reduction Strategies

It is unlikely that any single intervention will prove effective in reducing perioperative mortality in HF patients. Each step in the perioperative process should be considered and optimized as outcome will ultimately be determined by the weakest link in the chain of care. This can be best achieved in a multidisciplinary setting.

The physical condition of the HF patient ought to be stable and optimized, i.e., with proper therapy according to the recent guidelines. If this is not the case and the patient is still symptomatic, elective surgery should be postponed and the patient referred to a cardiologist. Particularly with a new diagnosis of HF, nonurgent surgery should be deferred at least 3 months to allow treatment to be effective. It is contraindicated to quickly institute new beta-blockade and/or ACE inhibitor therapy without the necessary time to allow optimal dose titration [30].

CHF patients often present with significant comorbidity, either causally related to heart failure, e.g., hypertension and diabetes, or as induced by the syndrome. Typical consequences of HF are renal dysfunction, anemia, cachexia, skeletal muscle wasting, and sleep-disordered breathing. Intravenous iron replacement is beneficial in ambulatory settings and should be considered before surgery. Metabolic abnormalities are also common due to renal dysfunction and the use of diuretics, and should be corrected as per standard [30]. Geriatricians should be consulted regarding the utility and possible implementation of muscle training and preoperative nutritional support. Sleep-disordered breathing can be due to obstructive sleep apnea but is mainly caused by central sleep apnea in patients with more severe heart

failure [10]. Although little is known about the subject, it seems important to screen for sleep apnea in HF patients as this may impact on the type and duration of postoperative surveillance.

Standard therapy for HF patient, i.e., beta-blockade, ACE inhibitors (or ARBs), and possibly MRAs, can be continued on the morning of the surgical intervention. For patients with low blood pressure, the administration of ACE inhibitors or ARBs can be given the evening before the scheduled surgical intervention. Heart failure medication should not be interrupted and needs to be resumed as soon as possible after surgery. Diuretics can also be continued perioperatively with careful attention to volume status and electrolyte status.

Patients with HF and atrial fibrillation should generally be anticoagulated. NOACs are recommended for non-valvular AF as they seem equally effective and safer in patients with HF than in subjects without HF, provided there is no renal failure. For patients who have mechanical heart valves or at least moderate mitral stenosis, oral vitamin K antagonists are recommended [2]. In the preoperative setting, these drugs need to be discontinued temporarily and replaced with shorter acting substitutes according to the most recent guidelines. The strategy needs to be clearly stated in the patient's records and communicated to all teams involved. There is no evidence on the benefit of antiplatelet drugs in HF patients without accompanying coronary artery disease.

HF patients may present with ICD and/or CRT devices. The preoperative and intraoperative optimization and management of such devices is important [37] but will be addressed in another chapter.

The surgical team will aim for the least invasive type of surgery. In abdominal surgery, urology, and gynecology, the laparoscopic approach causes less surgical trauma and less fluid shifts. However, the surgical conditions, including pneumoperitoneum and head-down position, cause increased afterload, altered venous return, and hypercapnia which is less well tolerated in CHF. The 2014 ESC/ESA guidelines therefore advocate to treat laparoscopic procedures in patients with heart failure as an open procedure as the cardiac risk is not diminished [30]. Video-assisted thoracic surgery (VATS) is also less invasive and is increasingly performed as an alternative to open thoracotomy. There are no large randomized controlled trials yet comparing outcome in VATS vs open thoracic surgery (Table 2.5).

An important part of the preoperative work-up is in planning of the postoperative follow-up. The early postoperative course should be conducted in a high care facility.

## 2.9 Selection of Anesthetic Drug and Technique

Most general anesthetics, intravenous as well as inhalational, are direct vasodilators and decrease sympathetic tone. The reduction in cardiac pre- and afterload due to anesthetics is usually well tolerated and even favorable for patients with HFrEF, promoting forward flow and organ perfusion—provided that there is no hypovolemia. Mechanical ventilation also has an unloading effect on the left heart and is

**Table 2.5** ESC/ESA recommendations on heart failure in noncardiac surgery

| Recommendations | Class | Level |
|---|---|---|
| It is recommended that patients with established or suspected heart failure, and who are scheduled for noncardiac intermediate- or high-risk surgery, undergo evaluation of LV function with transthoracic echocardiography and/or assessment of natriuretic peptides, unless they have recently been assessed for these | I | A |
| It is recommended that patients with established heart failure, who are scheduled for intermediate- or high-risk noncardiac surgery, be therapeutically optimized as necessary, using beta-blockers, ACEIs or ARBs, and mineralocorticoid antagonists and diuretics, according to ESC guidelines for heart failure treatment | I | A |
| In patients with newly diagnosed heart failure, it is recommended that intermediate- or high-risk surgery be deferred, preferably for at least 3 months after initiation of heart failure therapy, to allow time for therapy uptitration and possible improvement of LV function | I | C |
| It is recommended that beta-blockade be continued in heart failure patients throughout the perioperative period, whereas ACEIs/ARBs may be omitted on the morning of surgery, taking into consideration the patient's blood pressure. If ACEIs/ARBs are given, it is important to carefully monitor the patient's hemodynamic status and give appropriate volume replacement when necessary | I | C |
| Unless there is adequate time for dose titration, initiation of high-dose beta-blockade before noncardiac surgery in patients with heart failure is not recommended | III | B |

usually supportive for the HFrEF patient. Induction of anesthesia almost invariably decreases blood pressure. Even when cardiac output is usually preserved, this hypotensive effect raises concern on organ perfusion. There is no consensus on the definition of hypotension and no clear guide on what level of blood pressure is safe and acceptable [38]. Modern monitoring techniques such as NIRS of brain tissue oxygenation may be helpful for this purpose. During induction of anesthesia, the awake values can be used as a reference, and new algorithms may even assist in determining the individual limits of autoregulation [39].

While for the phenotype of HFrEF, vasodilation and mechanical ventilation promote forward flow and organ perfusion, HFpEF is far less tolerant to a reduction in preload because this compromises ventricular filling in the presence of diastolic dysfunction. In addition, many of these patients have hypertrophic ventricles, prone to develop ischemia when afterload decreases and perfusion pressures drop. In this subgroup, maintenance of blood pressure as close as possible to awake levels is an important target. For that purpose, etomidate or ketamine may be safer induction agents. Etomidate decreases sympathetic tone, but it does not have direct vasodilatory properties; hence, blood pressures are better preserved during induction. Ketamine is the only drug that does not reduce sympathetic tone and is the best guarantee to avoid hypotension, although direct cardiac depressant effects have been documented and its effects on diastolic function are also a matter of concern. In fact, the selection of a specific anesthetic drug is perhaps less important than the modalities of its use, i.e., the dose and speed of injection, and the timely administration of fluids and vasoactive drugs to counteract the known hemodynamic effects.

Peripheral nerve blocks are preferred over general anesthesia if they cover the surgical area of intervention and provided that the patient feels comfortable during the procedure. Neuraxial anesthetic techniques however are more controversial. Many CHF patients are treated with anticoagulants or antithrombotic agents, and the risk for epidural hematoma should be carefully weighed against any potential benefits. Several studies suggest that epidural analgesia significantly reduces the incidence of postoperative pulmonary complications in abdominal and thoracic surgery. Unstable heart failure patients are prone to develop pulmonary complications and pneumonia [26] and could therefore benefit from epidural analgesia. Thoracic epidural anesthesia causes cardiac sympathectomy, reducing inotropic and chronotropic state of the left ventricle and limiting the adaptive properties of the right ventricle, but this has not been reported to be a problem in clinical practice yet [40]. The effects of sympathectomy on cardiac loading conditions again differ with regard to the phenotype of HF. For HFrEF, the reduction in pre- and afterload due to venous and arterial dilatation is well tolerated. In HFpEF, this may cause significant decreases in cardiac output and compromise myocardial perfusion.

## 2.10 Monitoring

The threshold to install an invasive blood pressure line, in addition to standard ASA monitoring, in HF patients undergoing anesthesia should be kept low. The additional information from invasive pressure monitoring is considerable: besides online availability of blood pressure and pulse pressure values, it can provide a continuous estimate of cardiac output via pressure wave analysis and of the respiratory variation of pulse pressures. The latter has been shown to correlate with fluid responsiveness in mechanically ventilated HFrEF patients, at least in the absence of arrhythmias and tamponade [41]. Finally, an arterial line provides rapid access for blood gas and electrolyte analysis during and after surgery.

The decision to insert central venous lines is less obvious. The primary argument is not the need to monitor volume status, as central venous pressures are not a reliable indicator, but rather the need for port access to administer potent drugs such as inotropes and vasopressors. It is important to monitor volume status in major surgery where large fluid shifts and blood loss are expected, but volume-based parameters are generally considered superior to filling pressures for this purpose. It is not so evident in HFrEF patients though since absolute cardiac volumes (or dimensions) are difficult to interpret with optimal values mostly lying outside the normal range. In HFpEF patients, fluid management based solely on LV volumes may result in excessive preloading: due to reduced ventricular compliance and diastolic dysfunction, the administration of even small quantities of volume can result in LV high filling pressures and pulmonary hypertension. In general, measurements of cardiac volume/dimension and pulse pressure variation are useful to diagnose hypovolemia, while LV filling pressure measurements are essential to avoid hypervolemia and congestion. Assessment of pulmonary capillary wedge pressures (PCWP) via a thermodilution catheter however has been criticized over the last decades and is

considered too invasive, except for patients at risk for pulmonary hypertension and RV failure [42]. Echocardiography and Doppler assessment of mitral inflow velocities ($E_{max}$) and mitral annular tissue velocities ($E'$) offer a valid noninvasive alternative [43]. Although the use of intraoperative echocardiography is of superior value for hemodynamic monitoring of patients with CHF, it requires considerable training and proficiency [44]. For high-risk surgery in HF patients, it is advisable to have a cardiac anesthetist with advanced echocardiography training involved.

If a central venous line is in place, venous oxygen saturation is a valuable indicator for the ratio between oxygen supply and demand. A decrease in venous oxygen saturation is an early sign of increased oxygen extraction and calls for attention to all determinants of oxygen transport, i.e., low cardiac output, anemia, and hypoxemia, as well as increased oxygen consumption, i.e., inadequate levels of anesthesia and analgesia. Interestingly, changes in tissue brain oxygen saturation as measured noninvasively with cerebral NIRS appear to parallel the changes in SVO2 during anesthesia, and this may offer a convenient alternative [45].

Monitoring depth of anesthesia using algorithm-based EEG recording is recommended in CHF patients. Because of fragile hemodynamics, there is a tendency to use low doses of anesthetics in this population which increases the risk of awareness. On the other hand, altered pharmacokinetics predispose these patients to higher free drug concentrations and excessively deep levels of anesthesia. This has also been associated with an increased incidence of postoperative complications [46].

## 2.11 Fluid Management

CHF patients cannot rely on endogenous compensatory mechanisms to cope with fluid shifts because of the disease (reduced contractile reserve, diastolic dysfunction, renal failure) and its treatment (neurohumoral antagonism). Monitoring of fluid status is also more complex than in normal patients for reasons mentioned earlier. While goal-directed therapy is currently being recommended to manage patients undergoing intermediate to major surgery, such algorithms are not easily applicable and sometimes inappropriate for CHF patients. When cardiac output or surrogate markers thereof are used as target end points, application of the therapeutic algorithms often results in supranormal hemodynamic performance because they do not account for the reduced oxygen requirements during anesthesia. For CHF patients, the cardiac loading conditions required to obtain such goals are often excessive and easily result in volume overload. Volume management based on dynamic preload indices (e.g., SVV and PPV) showed promising results in terms of reduction of perioperative morbidity in high-risk patients or high-risk surgery, but the same restrictions mentioned above may apply [47]. Instead, therapeutic goals reflecting oxygen supply/demand ratio, such as SVO2 and lactate, kept optimal at the lowest possible cardiac load, would theoretically be more appropriate for this population. Particularly for HFpEF patients, careful volume administration, aiming at zero fluid balance, is recommended. Only when oxygen extraction increases or other signs suggestive of hypovolemia occur, additional fluid challenges should be given until normalization.

This is preferentially guided by echo-Doppler monitoring of mitral inflow and mitral annular motion velocities. When fluid administration is not effective, or results in high filling pressures (*E*/*E'* ratio), and when other determinants of oxygen supply (hemoglobin, oxygen saturation) and demand have been optimized, vasopressors (for HFpEF) and inotropes (for HFrEF) should be considered.

## 2.12 Inotropic Support and Vasoactive Drugs

Positive inotropic drugs have no beneficial effect on outcome in the long-term treatment of CHF but are extremely effective in providing temporary support, to bridge patients over a period of acute deterioration and to overcome hemodynamic challenges in the perioperative period [48]. There is an enormous practice variability regarding the type of drug, or drug combinations, and the doses of inotropes used [49]. Because there are no good comparative studies, the therapeutic choice is best based on clinical expertise, diagnostic skills, and comprehension of the underlying pathophysiology. From a practical point of view, inotropes can be classified into inodilators and inopressors depending on their additional effects on blood vessels. For sympathomimetics, the pharmacodynamic profile depends on which subtype of receptors they act on and at which potency (see Table 2.6). PDE inhibitors are obligatory inodilators because the intracellular increase of c-AMP in smooth muscles induces vasodilation. The effect of sympathomimetics is dependent on receptor density and function, while PDE inhibitors bypass these receptors and act intracellularly. Interestingly, dopamine and dobutamine in part derive their inotropic effect from indirect actions, i.e., by inhibiting reuptake of endogenous norepinephrine, and for dopamine via stimulation of norepinephrine release. Clearly, the efficacy of indirectly acting sympathomimetics is reduced in denervated transplanted hearts and in CHF where norepinephrine stores are reduced [50]. Drugs with a different mechanism of action can be combined to obtain synergy, but the combination of drugs with similar mechanisms of action may decrease efficacy due to competitive interaction at the receptor level [51].

Both sympathomimetics and PDE-III inhibitors increase myocardial oxygen consumption because they increase intracellular calcium, the reuptake of which in diastole is an energy demanding process, and because they raise heart rate. This is of particular concern in patients with ischemic heart disease and in patients with HFpEF as tachycardia may further compromise ventricular filling. Both drug types operate via an increase in c-AMP which has been linked to electrical instability and major arrhythmia. Levosimendan does not rely on intracellular calcium handling for its inotropic action, instead it increases the sensitivity of troponin to calcium. This has been shown to impact less on myocardial energetics. Levosimendan is a weak inotrope with an active metabolite that may explain its late onset of action. It is an inodilator because it activates K-ATP channels in blood vessels and has mild PDE-III activity. Both animal studies and clinical studies show promising results, particularly in RV failure [52].

**Table 2.6** Receptor specificity for sympathomimetic drugs

| | Receptor type | ß1 | ß2 | α1art | α1ven | α2 | DA1 | DA2 | Uptake 1 inhib | Tyramine-like effect |
|---|---|---|---|---|---|---|---|---|---|---|
| Inodilators | Isoprenaline | +++++ | ++++ | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Dopamine | ++ | +/− | +++ (dose) | +++ | + (dose) | +++ | ++ | ++ | ++ |
| | Dobutamine | +++ | ++ | ++ | 0? | 0 | 0 | 0 | + | 0 |
| | Dopexamine | +/− | +++ | 0 | 0 | 0 | ++ | + | +++ | 0 |
| Inoconstrictors | Adrenaline | +++ | + | +++ | 0 − ++++ (dose) | + | 0 | 0 | 0 | 0 |
| | Noradrenaline | +++ | 0 | ++++ | +++++ | + | 0 | 0 | 0 | 0 |

Because there are fundamental differences in the pathophysiology of HFrEF, typically a systolic type of pump failure, and HFpEF mainly characterized by diastolic dysfunction, it is reasonable to expect that the optimal pharmacological approach to support the cardiovascular system for these two phenotypes is not the same. In HFrEF, the failing heart benefits from pre- and afterload reduction, in addition to positive inotropy; hence, inodilators such as dobutamine and PDE-III inhibitors are first choice. In HFpEF, however, inotropic support is less needed, while vasodilation and tachycardia should be avoided; hence, inopressors such as norepinephrine are first choice. There are no drugs yet that improve diastolic performance although several approaches are currently being investigated.

There is a growing concern about the side effects of positive inotropic drugs even in acute settings such as the perioperative period where data suggest a negative correlation between the use of inotropes and outcome [53]. This may be related to the rather liberal and often routine use of these powerful drugs that have a high toxic-to-therapeutic ratio. Their indication should be limited to cardiogenic hemodynamic instability and infusions kept to the lowest possible dose and for the shortest time possible, i.e., until the critical phase is bridged or function returns. Strict and frequent monitoring is therefore mandatory. Levosimendan may be a safer option: it is a less potent inotrope, carries a lower risk of arrhythmia and myocardial ischemia, and in fact may have cardioprotective properties. Future studies are required to confirm these claims because recent data suggest that levosimendan may have severe arrhythmogenic potential as well [54]. Myosin activators, a new class of cardiotonic drugs, also have positive inotropic actions independently of intracellular calcium load and are currently under investigation [55].

## 2.13 Postoperative Care

Perhaps one of the most important measures to maximize outcome in patients with CHF is the continuation of high-level care outside the operating theater. The early postoperative course should be conducted at a high care facility with advanced hemodynamic monitoring and high nurse-to-patient ratio. Follow-up with cardiac biomarkers such as troponin and BNP is recommended.

**Conclusion**

Heart failure is an important risk factor in perioperative medicine with high mortality rates even for minor interventions. The number of patients with HF presenting for surgery is steadily increasing. Outcomes have not changed much over the past years, and there is little reason to expect improvement unless we make it a research priority. CHF is a complex disease entity with heterogeneous etiology and at least two very different phenotypes, characterized by predominant systolic (HFrEF) and predominant diastolic dysfunction, respectively. Advanced knowledge of the diagnosis and treatment of CHF and a fair understanding of its pathophysiology are a prerequisite to optimize care and develop a perioperative strategy for individual CHF patients.

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# Pulmonary Hypertension in Cardiac Surgery

3

Bastien Olivier

## 3.1 Definition

Pulmonary hypertension (PH) is defined as an elevated level of pulmonary pressure above the normal range, and several hemodynamic parameters are used in defining pulmonary hypertension [1]. A systolic pulmonary pressure (PP) >30 mmg Hg, a mean PP >25 mmHg, or a pulmonary vascular resistance >200–300 dyn.s.cm$^{-5}$ are the most common used definition. Pulmonary arterial hypertension (PAH) is a disease of the small pulmonary arteries that is, in part, due to vasoconstriction and remodeling of the vascular wall. These processes contribute to a characteristic progressive increase in pulmonary vascular resistance (PVR) and subsequent effects on the right ventricle that will eventually lead to death. Several of these definitions have been used in cardiac surgery, but information are obtained before the procedure and usually from an awake patient. For these reasons, the severity could be underestimated. This preoperative information could be acquired through preoperative catheterization or, more frequently, estimated *via* transthoracic echocardiography by using the Bernoulli's equation. Right ventricular function is described by pressure-volume relationships and is a major parameter of risk during PH. Acute PH expose to right ventricular (RV) failure after a short period of inotropic adaptation by the Anrep's law [2]. The RV chronically exposed to pulmonary hypertension undergoes hypertrophic changes and an increase in contractility, allowing for preserved flow output until decompensation.

B. Olivier, M.D., Ph.D.
Department of Anesthesia and Critical Care, University Lyon I, Lyon, France

National Agency of Biomedicine, 1 av Stade de France, 93212, Saint Denis la plaine, France
e-mail: olivier.bastien@biomedecine.fr



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## 3.2 Etiology

PAH is typically classified as capillary, precapillary, or postcapillary, depending on the site where the cause of PAH is present. The 2003 World Symposium on PAH proposed a classification based on five groups, and this classification has been modified in Nice [3] in 2013 (Table 3.1).

Pulmonary hypertension related to left heart disease (LHD) by far represents the most common form of PAH, accounting for 65–80% of cases. The distinction between pulmonary arterial hypertension and PH-LHD may be challenging, and it has direct therapeutic consequences [4].

Regardless of the origin, PH is defined by a mean pulmonary artery pressure (PAP) ≥25 mmHg. Based on the left-sided filling pressure determined either as LV end-diastolic pressure (LVEDP), left atrial pressure (LAP), or pulmonary arterial wedge pressure (PAWP), the hemodynamic definition further distinguishes pre- (≤15 mmHg) and postcapillary PH (>15 mmHg). In postcapillary PH, the elevation of PAWP leads to a proportionate increase of the mean PAP, maintaining a normal transpulmonary pressure gradient (TPG = mPAP–PAWP) <12 mmHg and low pulmonary vascular resistance (PVR) <3 Wood units (WU) or <240 dynes s $cm^{-5}$. However, chronic elevation of the left-sided filling pressure associated with neurohormonal and mediator activation may cause excess vasoconstriction with or without vascular remodeling leading to a "disproportionate" increase of the PAP and thus resulting in an elevated TPG and PVR, which has been described as "reactive," "out-of-proportion," or "combined" post- and precapillary PH (Cpc-PH) [5].

Heart failure (HF) is now separated between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), with similar clinical syndrome of "heart failure," but distinct entities regarding pathophysiology, cardiopulmonary interaction, and response to therapy. In HFrEF, the prevalence of PH was reported to be between 40 and 75% [6]. In patients with HFpEF, recent studies indicated a PH prevalence in a range between 36 and 83%. The prevalence of Cpc-PH in patients with HF is 12–38%. All the data indicate that PH and RV dysfunction are frequent and associated with a poor outcome in patients with LV HF.

During many years, the heterogeneity of PH was not understood and the reasons why some patients develop severe PH and RV dysfunction, whereas others do not, unclear. Two factors are now well described: the susceptibility for pulmonary vascular disease (due to genetic factors and/or environmental stressors and/or comorbidities) and the factor "time." Genetic factors as gene BMPR2, which was the first discovered, can be researched now by many laboratories (see Table 3.1). For the Eisenmenger syndrome, time factor is determinant. Prolonged overcirculation-induced pulmonary arterial hypertension is a cause of right ventricular failure.

**Table 3.1** Updated clinical classification of PH (Nice 2013)

| |
|---|
| 1. Pulmonary arterial hypertension (PAH) |
| 1.1. Idiopathic |
| 1.2. Heritable |
| 1.2.1. BMPR2 |
| 1.2.2. ALK1, ENG, SMAD9, CAV1, KCNK3 |
| 1.2.3. Unknown |
| 1.3. Drug and toxin induced |
| 1.4. Associated with: |
| 1.4.1. Connective tissue diseases |
| 1.4.2. HIV infection |
| 1.4.3. Portal hypertension |
| 1.4.4. Congenital heart diseases |
| 1.4.5. Schistosomiasis |
| 1′. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH) |
| 1″. Persistent pulmonary hypertension of the newborn (PPHN) |
| 2. Pulmonary hypertension due to left heart disease |
| 2.1. Left ventricular systolic dysfunction |
| 2.2. Left ventricular diastolic dysfunction |
| 2.3. Valvular disease |
| 2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies |
| 3. Pulmonary hypertension due to lung disease and/or hypoxia |
| 3.1. Chronic obstructive pulmonary disease |
| 3.2. Interstitial lung disease |
| 3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern |
| 3.4. Sleep-disordered breathing |
| 3.5. Alveolar hypoventilation disorders |
| 3.6. Chronic exposure to high altitude |
| 3.7. Developmental abnormalities |
| 4. Chronic thromboembolic pulmonary hypertension (CTEPH) |
| 5. Pulmonary hypertension with unclear multifactorial mechanisms |
| 5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy |
| 5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleimoyomatosis |
| 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders |
| 5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis, segmental PH |

## 3.3 Treatment Available

Standard medical therapies include oxygen, anticoagulant, prevention of fluid overload, and cardiac support. Calcium channel blockers decrease blood pressure and are appropriate for a small minority of patients (<10%) demonstrating a favorable response to vasodilator testing at the time of heart catheterization. But specific treatments have been progressively discovered over the past two decades and have changed the prognosis of these severe patients. Three major pathways (the prostacyclin, endothelin, and nitric oxide (NO) pathways) have been established as being key to the development and progression of PAH [7]. These pathways have been targeted by PAH-specific therapies (Table 3.2) that fall into three main drug classes in practice: prostacyclin analogues, endothelin receptor antagonists (ERAs), and phosphodiesterase-5 inhibitors (PDE-5i). As for antibiotics, it is not recommended to associate two drugs of the same class, but can be switched.

Whereas targeted therapies are available for pulmonary arterial hypertension (PAH), these treatments have not been adequately evaluated or are not indicated and may even be harmful in patients with PH related to LHD [8]. All of these treatments

**Table 3.2** Specific treatments of PAH

| |
|---|
| Endothelin receptor antagonists (ERAs) |
| • Ambrisentan (Letairis®) |
| • Bosentan (Tracleer®) |
| • Macitentan (Opsumit®) |
| NO pathway |
| • Nitric oxide (NO) |
| Phosphodiesterase inhibitors (PDE-5 inhibitors) |
| • Sildenafil (Revatio™) |
| • Sildenafil (Revatio™) for pediatric use |
| • Tadalafil (Adcirca®) |
| Soluble guanylate cyclase stimulators |
| • Riociguat (Adempas®) |
| Prostacyclin pathway |
| Oral |
| • Oral Treprostinil (Orenitram®) |
| • Oral IP prostacyclin receptor agonists selexipag (Uptravi®) |
| Inhaled treatment options |
| • Iloprost (Ventavis®) |
| • Inhaled Treprostinil (Tyvaso™) |
| Intravenous treatment options |
| • Intravenous Treprostinil (Remodulin®) |
| • Epoprostenol (Flolan®) |
| • Room Temperature Stable Epoprostenol (Veletri®) |
| Subcutaneous treatment options |
| • Subcutaneous Treprostinil (Remodulin®) |

**Table 3.3** Drugs trial and results

| Drugs | Study | Hemodynamics | Combined test | Survival |
|---|---|---|---|---|
| *Endothelin pathway* | | | | |
| Bosentan | BREATHE-1 | ++ | + | |
| Ambrisentan | ARIES-1 and 2 | + | + | |
| *NO pathway* | | | | |
| Sildenafil | SUPER-1 | + | + | |
| Tadalafil | PHIRST | + | – | |
| *Prostacyclin pathway* | | | | |
| Intravenous epoprostenol | | + | | + |
| Inhaled iloprost | AIR | + | + | |
| Subcutaneous treprostinil | | + | + | |
| Inhaled treprostinil | TRIUMPH | | – | |
| Oral beraprost | ALPHABET | – | + | |

Analyse inspired by Galiè [9]
*NO* nitric oxide, *Hemodynamics* PH or vascular resistance, *Combined* combination of 10% improvement in 6 min walking distance combined with an absence of clinical deterioration, +/– parameter improved or not

are not available in all countries, depending of national health authority. Some of them are prescribed only by reference centers, and differences are observed between clinical effects during trial [9] (Table 3.3). All these treatments should be known preoperatively by the anesthetist in order to continue them during perioperative period without any rupture or additive to intravenous or inhaled treatment. Nitric oxide [10, 11], prostacyclin [12], and PDE-5i [13, 14] like sildenafil or similar are the most common drugs used in ICU after cardiac surgery or during cardiac transplantation. Side effects are frequent and specific of each product (flush, hypotension, biological effects like transaminase increase or platelets effects) and should be monitored. The endothelin receptor antagonist bosentan has been reported to improve overcirculation-induced pulmonary hypertension [15].

During acute PH, norepinephrine restored arterial pressure, increased RV contractility, and increased but did not normalize RV-PA coupling and cardiac output. Dobutamine restored arterial pressure, markedly increased RV contractility, and normalized RV-PA coupling and cardiac output. Compared with norepinephrine, dobutamine decreased PA resistance and elastance and increased RV contractility and RV-PA coupling. In case of right ventricular failure due to PH, norepinephrine added to a pulmonary vasodilator is the most common choice, but levosimendan restores right ventricular-pulmonary arterial coupling, because of combined pulmonary vasodilation and increased right ventricular contractility, and has been tested [16].

Early appropriate treatment is necessary to reverse acute PH and RV failure. If not appropriate, a persistent right ventricular failure appears, and it is now demonstrated that this organ damage is related to an early activation of apoptotic pathways and to a local overexpression of tumor necrosis factor-alpha, a proinflammatory cytokine [17]. New drugs like riociguat are under evaluation or appropriate in some countries. Riociguat is a stimulator of soluble guanylate cyclase (sGC) that targets the NO pathway. Riociguat also sensitizes sGC to NO and promote vasorelaxation [18].

## 3.4 Risk Factors and Hemodynamic Parameters

For research trial or cath lab, the gold standard of RV systolic function is maximum elastance (E max), which is the maximal value of the pressure/volume ratio. This value is few sensitive to changes in loading conditions. The gold standard of afterload is arterial elastance (Ea), defined by the ratio of pressure at E max to stroke volume. The optimal coupling of ventricular function to the arterial circulation occurs at an E max/E a ratio between 1.5 and 2 [2]. Patients with severe pulmonary hypertension often present an increased E max, a decreased E max/E a, and increased RV dimensions. The normal subject had an Emax/Ea ratio of 2. The Emax/Ea ratio was decreased to 1 in the PAH patient.

In clinical practice, pulmonary artery systolic pressure (PASP) estimated by echocardiography strongly predicted all-cause and cardiovascular mortality independently of known predictors of outcome. While the TPG is influenced by volume load and cardiac function and does not prognosticate outcome in PH-LHD, the diastolic pressure gradient (DPG), defined by the difference between diastolic PAP and PAWP, is assumed to be less dependent of stroke volume and loading conditions and was shown to correlate with pulmonary vascular remodeling in PH-LHD [19]. These findings led to the current terminology and classification of postcapillary PH [5] as either isolated postcapillary PH (Ipc-PH), if the DPG is <7 mmHg and/or PVR ≤3WU, or combined post- and precapillary PH (Cpc-PH), if the DPG is ≥7 mmHg and/ or PVR >3 WU. A combination of elevated PAP and reduced RV systolic function was particularly associated with an unfavorable outcome in HFrEF. Furthermore, HFpEF patients commonly display RV dysfunction, but elevated PAP occurs at more advanced stages and represents a strong predictor of death. The prognostic value of the DPG in PH-LHD is not yet conclusive.

A TAPSE of less than 1.8 cm is associated with greater RV systolic dysfunction, right heart remodeling (right atrial area index, 17.0 vs. 12.1 cm/m$^2$), and RV-left ventricular (LV) disproportion (RV/LV diastolic area, 1.7 vs. 1.2), versus a TAPSE of 1.8 cm or greater. In patients with pulmonary arterial hypertension, the one-year survival rate was 94% vs. 60%, in groups with TAPSE > or <1.8 cm. Reduced RV free wall peak longitudinal strain was associated with an increased risk for RV failure among patients undergoing LVAD implantation [20].

During surgery for mechanical assistance, emergency situation, creatinine clearance, and bilirubin levels were more important risk factors of right ventricular failure than pulmonary pressure [21]. Many scoring systems have been proposed.

## 3.5 PAH in Practice: Anesthesia

During general anesthesia, risk factors for major complications in a PAH population of 114 patients [22] are reported as an elevated right atrial pressure (OR 1.1), a 6-min walking distance <399 m at the last preoperative assessment (OR 2.2), the perioperative use of vasopressors (OR 1.5) and the need for emergency surgery (OR 2.4). Although there is consensus among anesthesiologists that regional anesthesia

is preferred over general anesthesia in patients with PAH, this is not possible in cardiac surgery. Hemodynamic monitoring is essential to detect the onset of an acute PAH crisis [23] but also to give direct information on the efficacy of treatment. The care of PAH patients for cardiac catheterization performed at a pulmonary hypertension center with expertise [24] is associated with low complication rates (1.2%) and mortality (0.2%). During valvular surgery, PH may be challenging, and the incidence of postcardiotomy acute refractory right ventricular failure ranges from 0.04 to 0.1%. But PAP returns to near-normal values in patients with severe preoperative PH and to normal values in patients with mild preoperative PH immediately after mitral valve replacement [25]. The outcome after surgery in patients with severe PH is comparable to those with mild PH and depends mainly on the right ventricular function.

Acute pulmonary hypertension may induce a series of mechanically triggered biologic events, which include an activation of proapoptotic pathways and local TNF overexpression that could contribute to persistently depressed RV function and ventriculo-arterial decoupling. So a particularly strict adaptation of pulmonary circulation and ventilation is needed to prevent a prolonged complication and death.

Inhales but not IV anesthetics are reported to decrease pulmonary vascular resistance. Different animal models (hypoxic, overflow, or pulmonary banding) could have conflicting results. Isoflurane and desflurane markedly impair RV-PA coupling efficiency in dogs, during hyperoxia and hypoxia, both by increasing RV afterload and by decreasing RV contractility [26]. But isoflurane compared to propofol impaired RV vascular coupling caused by the decrease of RV contractility, while afterload may be unchanged [27]. Sevoflurane causes significant depression of global RV function associated with a qualitatively different effect on inflow and outflow tracts, without any modification of PVR [28].

PH is frequent in pediatric cardiac surgery [29]. Incidence of cardiac arrest was 0.78% for cardiac catheterization procedures, 10% for major surgical procedures, and 1.6% for all procedures. Ketamine administration was not associated with increased complications [30]. No differences were found between dexmedetomidine/fentanyl and midazolam/fentanyl in terms of the duration of sedation, mechanical ventilator use, and CICU stay in children with PAH [31], but a lower incidence of delirium than patients in the midazolam group.

## 3.6 PAH in Practice: Intensive Care

### 3.6.1 PH and Transplantation or LVAD

Acute refractory right ventricular failure has also been reported in 2–3% patients after a heart transplant and in almost 20–30% patients who receive a left ventricular assist device (LVAD) support. PH is not considered now as a contraindication for heart transplantation, but a risk factor [32]. Nevertheless adaptation of the right ventricle after the end of CPB should be considered as a difficult period for the anesthetist. Pulmonary vascular resistance over 450 dynes s $cm^{-5}$ is the cutoff

for risk factor. Reversibility during pharmacological test could be tested before transplantation. All cofactors increasing pulmonary pressure like hypoxia, bleeding, and pain should be avoided. Monitoring pulmonary pressure is recommended.

During LVAD procedure, right ventricular failure increases the risk of death. Due to low cardiac output evaluation of pulmonary pressure and resistance could be difficult, so the level of pulmonary pressure is not directly the main risk factor. The need for right ventricular assistance is so far difficult. Nevertheless clinical experience during prolonged LVAD has proved the reversibility of disproportioned vascular resistance during the first 6 months [33]. But if measurement of right ventricular load (effective arterial elastance, pulmonary vascular compliance, and pulmonary vascular resistance) improves between the pre- and early post-LVAD time periods, the early phase could be different. Despite decreasing load and pulmonary artery wedge pressure (PAWP), RAP could be unchanged and the RAP/PAWP ratio worsened early post-LVAD (0.44 vs. 0.77 $p < 0.001$), suggesting a worsening of RV adaptation to load [34]. For that reason most patients are treated by NO or sildenafil in the early postoperative period. One of the most challenging period is the beginning of the left assistance, when PH acts as a barrier from right to left filling of the LVAD.

### 3.6.2 Mechanical Ventilation

The normal RV wall is thin and is able to accommodate to large changes in venous return, but unable to maintain flow output during sudden increase in pulmonary artery pressure or intrathoracic pressure. Patients with PAH who undergo invasive mechanical ventilation have an in-hospital mortality of 39% [35]. The types of patients who benefit most from advanced respiratory support in a critical care setting is not clearly defined. Peak pressure and plateau pressure should be monitored and right ventricular effect assessed by echocardiography after intubation.

**Conclusion**

Pulmonary hypertension is a high-risk situation for anesthesia, specifically during cardiac surgery. Significant progresses in specific medical treatments have changed the prognosis, but PH associated with left heart failure need more evaluation.

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# The Patient with Severe Aortic Valve Stenosis

4

Priscilla de Medeiros Teixeira, Rémi Schweizer, and Jean-Luc Fellahi

## 4.1 Introduction

The prevalence of aortic valve stenosis in adults over 65 years is between 2% and 9% [1]. Valve diseases are poorly represented in the international classification of diseases. It might be ignored without echocardiography. Several facts suggest that the role of valve disease as a public health problem contributes to morbidity and mortality [2]. Aortic valve stenosis is associated with an increased risk of myocardial infarction, stroke, and death, even after adjustment on traditional cardiovascular risk factors [3].

The incidence of noncardiac surgeries in patients with preexisting aortic valve stenosis has significantly increased over the past few decades [4]. Thus, it is mandatory to know the severity rating and its main implications in morbidity and mortality within the perioperative period, in order to define the best anesthetic management.

## 4.2 Epidemiology and Main Causes of Aortic Valve Stenosis

Aortic valve stenosis is the most prevalent valvular heart disease encountered in cardiology and perioperative medicine (Table 4.1) [5]. The Tromsø study reported an exponential increase of the prevalence of aortic valve stenosis with age: 0.2% in the 50–59 year group, 1.3% in the 60–69 year group, 3.9% in of the

P. de Medeiros Teixeira
Service d'Anesthésie-Réanimation, Hôpital Cardiovasculaire et Pneumologique Louis Pradel, Hospices Civils de Lyon, 59 boulevard Pinel, 69394, Lyon Cedex, France

R. Schweizer • J.-L. Fellahi (✉)
Service d'Anesthésie-Réanimation, Hôpital Cardiovasculaire et Pneumologique Louis Pradel, Hospices Civils de Lyon, 59 boulevard Pinel, 69394, Lyon Cedex, France

Faculté de Médecine Lyon Est, Université Lyon 1 Claude Bernard, Lyon, France
e-mail: jean-luc.fellahi@chu-lyon.fr



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**Table 4.1** The aortic valve stenosis is both the most frequent and the most serious cardiac valvular disease in noncardiac surgery in Europe countries [5]

| Valvular diseases | Prevalence (%) |
|---|---|
| Aortic stenosis | 43 |
| Mitral regurgitation | 32 |
| Aortic regurgitation | 13 |
| Mitral stenosis | 12 |

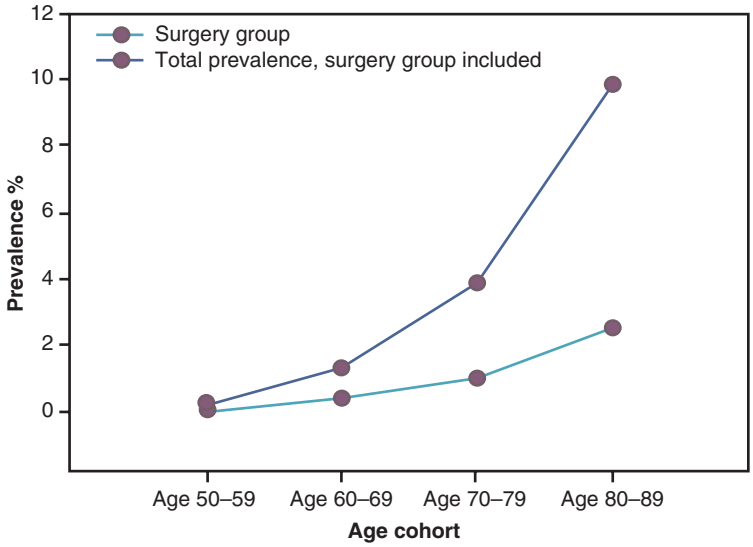


**Fig. 4.1** Prevalence of aortic valve stenosis according to age in the surgical and in the whole population. Adapted from [6]

70–79 year group, and 9.8% of those aged 80–89 years (Fig. 4.1). In the same study, when evaluating the causes of death, an age-adjusted logistic regression analysis disclosed an increased risk of cardiovascular death in the aortic valve stenosis group (57.4%) when compared to the population without aortic valve stenosis (37.1%) [6].

Causes of aortic valve stenosis other than degenerative are predominantly due to bicuspid aortic valve disease in younger groups [7]. The incidence of rheumatism heart disease has decreased dramatically in high-income countries [8].

## 4.3 Diagnosis of Aortic Valve Stenosis

### 4.3.1 Clinical Diagnosis

Clinical examination remains the primary method for initial evaluation of patients with a suspected valvular disease [9, 10]. Aortic valve stenosis may cause nonspecific symptoms as angina, dyspnea, dizziness, or syncope. Careful questioning is critical and must take into account the possibility that patients deny symptoms as

they subconsciously reduce their activities [11]. The characteristic systolic aortic murmur may occasionally be faint in case of low cardiac output. Primary presentation of aortic valve disease may be heart failure of unknown cause.

### 4.3.2 Doppler Echocardiography

Doppler echocardiography is the key tool for diagnosis. It can confirm the presence of aortic valve stenosis, assess the degree of stenosis, and evaluate both left ventricular function and wall thickness. Doppler echocardiography also detects the presence of other associated valve diseases or aortic pathologies and provides useful prognosis information. Typical findings are both a reduced valve area and an increase in trans-valvular flow gradients [11].

Preoperative Doppler echocardiography should be performed when there is a reasonable suspicion of valvular or structural heart disease. It should also be conducted for re-evaluation of known aortic valve stenosis or for prosthetic aortic valve with a change in clinical status or cardiac exam. Routine preoperative Doppler echocardiography is considered appropriate for surveillance of known aortic valve stenosis (every year, in case of moderate to severe aortic stenosis, and every 3 years in case of mild aortic stenosis) and surveillance of prosthetic aortic valve (every 3 years) [12].

### 4.3.3 Severity Criteria

The disappearance of the second aortic sound is specific to severe aortic valve stenosis, although it is not a very sensitive sign [11]. Delayed or diminished carotid upstroke is characteristic of severe aortic valve stenosis [13]. The main echocardiographic criteria of severity in aortic valve stenosis are summarized in Table 4.2. However, cautious interpretation should be made for trans-aortic pressure gradient. Indeed, this gradient is strongly dependent of cardiac output, so that a pseudo-normal trans-aortic pressure gradient can be observed in case of severe aortic valve stenosis with low cardiac output, as depicted in Fig. 4.2 [14].

**Table 4.2** Classification of aortic valve stenosis severity [echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice]

| Echocardiographic data | Mild | Moderate | Severe |
|---|---|---|---|
| Valve area ($cm^2$) | >1.5 | 1–1.5 | <1 |
| Indexed valve area ($cm^2/m^2$)[a] | >0.85 | 0.6–0.85 | <0.6 |
| Trans-valvular mean gradient (mmHg)[b] | <20 | 20–40 | >40 |
| Trans-valvular maximum jet velocity (m/s)[b] | 2.6–2.9 | 3–4 | >4 |
| Velocity ratio[c] | >0.5 | 0.25–0.5 | <0.25 |

[a]Valve area indexed on body surface area; this variable is particularly useful in patients with small body mass indexes

[b]In patients with normal cardiac output and/or trans-valvular flow

[c]Ratio between mean and maximum trans-valvular jet velocity

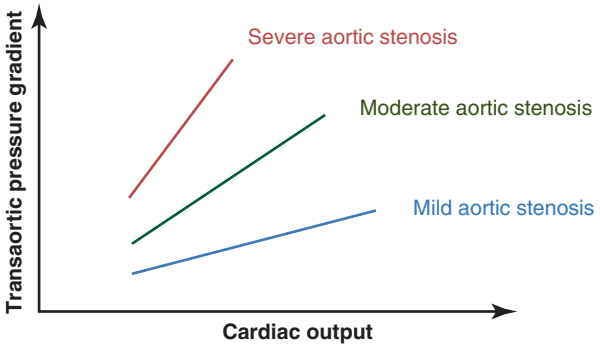


**Fig. 4.2** Relationship between trans-aortic pressure gradient and cardiac output in severe, moderate, and mild aortic valve stenosis. The pressure gradient can be low in case of low cardiac output, even in severe aortic valve stenosis. Adapted from [14]

## 4.4 Preoperative Evaluation and Principles of Decision in Noncardiac Surgery

### 4.4.1 Perioperative Risk Associated with Aortic Valve Stenosis in Noncardiac Surgery

Aortic valve stenosis is considered to be an independent risk factor for cardiac complications in patients undergoing noncardiac surgery [15]. In the Original Cardiac Risk Index, severe aortic valve stenosis was associated with a perioperative mortality rate of 13%, compared with 1.6% in patients without aortic valve stenosis [16]. In a single tertiary-center study, patients with moderate or severe aortic valve stenosis (aortic valve area <1.0 $cm^2$) undergoing elective noncardiac surgery had a 30-day mortality rate of 2.1%, compared with 1.0% in propensity score-matched patients without aortic valve stenosis ($p = 0.036$) [17].

### 4.4.2 Decision Tree

#### 4.4.2.1 General Considerations

Figure 4.3 represents an algorithm based on last guidelines of noncardiac surgery [18]. As represented in that diagram, firstly noncardiac surgery should be considered. Then, physicians are not exempted of seeing the patient in the preoperative period for a careful evaluation and medical care optimization, as recommended by those guidelines. The Heart Team, associating cardiologists, cardiac surgeons, and cardiac anesthesiologists, should ideally be implicated in any discussion concerning a patient with aortic valve stenosis scheduled for noncardiac surgery. Making the distinction between elective and urgent surgery is sometimes difficult, particularly

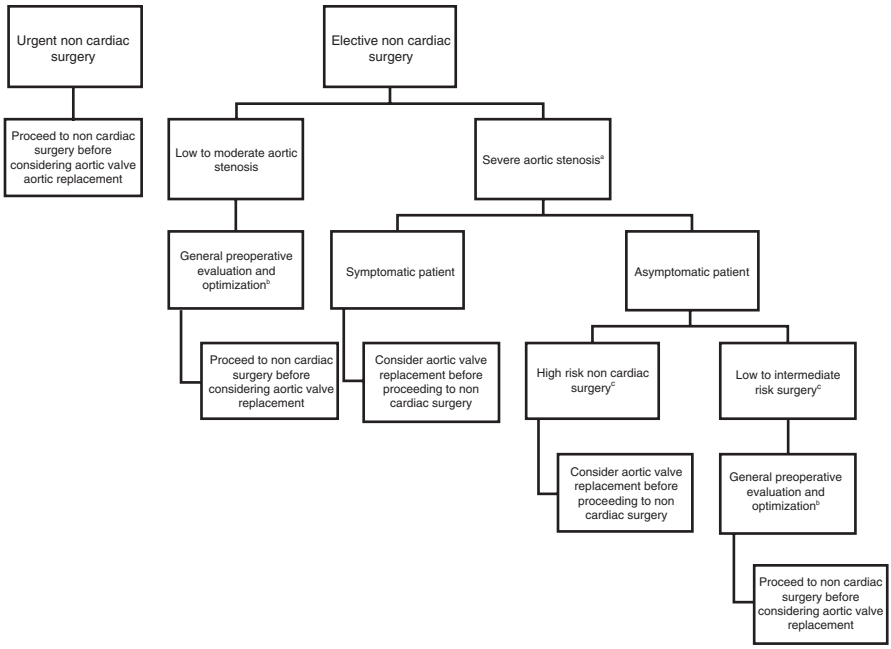


**Fig. 4.3** A stepwise approach for patient with aortic valve stenosis scheduled for noncardiac surgery. Adapted from the ESC/ESA guidelines on noncardiac surgery [18]. [a]As defined in EAE/ASE guidelines for echocardiographic assessment of valve stenosis: recommendations for clinical practice; [b]As recommended by the joint Task Force on the management of valvular heart disease of the ESC and the EACTS [11]; [c]As defined in ESC/ESA guidelines on noncardiac surgery [18]

in case of oncological diseases or obstetrical purposes. A multidisciplinary discussion (noncardiac surgeons, noncardiac anesthesiologists, the Heart Team, etc.) is crucial to determine the optimal strategy.

#### 4.4.2.2 Type of Aortic Valve Replacement

If an aortic valve replacement is considered, it can be done either by surgical way or transcatheter way, depending on the preoperative cardiac surgical risk. Transcatheter aortic valve replacement should be preferred to surgical aortic valve replacement for high-cardiac-surgical-risk patients [11, 18]. Moreover, it is very likely that transcatheter aortic valve replacement will be in the next future recommended for an increasing number of patients with an intermediate surgical risk, according to the last published studies [19].

Another strategy is the balloon aortic valvuloplasty. However, the recurrence of aortic stenosis is frequent (nearly 80% after 6–12 months) and requires an additional treatment, while no improvement in survival has been reported [20].

## 4.5 Intraoperative Management of a Patient with Severe Aortic Valve Stenosis

### 4.5.1 Hemodynamic Considerations

#### 4.5.1.1 Myocardial and Hemodynamic Consequences of Aortic Valve Stenosis

The fixed obstruction of the left ventricular outflow tract impedes the increase in cardiac output. Subsequently, a decrease in systemic arterial resistance can result in severe hypotension. The left ventricular hypertrophy secondary to chronic elevation in afterload has two major consequences:

- A left ventricular diastolic dysfunction: ventricular filling becomes more dependent upon the blood volume brought by the atrial contraction. Thus, the loss of sinus cardiac rhythm often results in a dramatic decrease of cardiac output in patients with severe aortic stenosis. Besides, if the correct ventricular filling requires the preload must be maintained, an abnormal elevation of preload can rapidly result in pulmonary edema.
- A myocardial fragility: even in the absence of significant coronary artery stenosis, myocardial ischemia can occur because of the unbalance between the increase in myocardial mass and the growth in neo-angiogenesis of the left ventricle. Thus, an increase by 50% of left ventricular mass will be experimentally associated with an increase of the neovasculature by 36% only. Subsequently, any clinical situation generating an increase in myocardial oxygen demand (tachycardia, hypoxia, anemia, inflammatory state, shivering, etc.) will potentially induce significant myocardial ischemia.

#### 4.5.1.2 Hemodynamic Goals in the Intraoperative Period

Hemodynamic goals in the intraoperative period are pretty simple. They aim to maintain stability for heart rate, preload, afterload, and rhythm, as summarized in Table 4.3.

#### 4.5.1.3 Hemodynamic Monitoring

No large-scale prospective studies have validated the clinical utility of any type of intraoperative hemodynamic monitoring in patients with aortic valve stenosis. Although not clearly recommended, the invasive and continuous blood pressure

**Table 4.3** Clinical intraoperative hemodynamic goals in severe aortic valve stenosis

| Hemodynamic | Objectives in severe aortic stenosis |
|---|---|
| Preload | Keep constant (mind the pulmonary edema) |
| Afterload | Avoid hypotension |
| Contractility | Keep constant |
| Rhythm | Avoid arrhythmias |
| Heart rate | Avoid both bradycardia and tachycardia |

monitoring should be encouraged to allow rapid and reliable detection of systemic blood pressure variation. Electrocardiographic monitoring with a selected lead combination, or 12-lead electrocardiography when feasible, should be considered for better detection of ischemia in the operating room [18]. In high-risk surgical patients, it is recommended to titrate intraoperative volume administration by measuring beat-to-beat stroke volume or cardiac output, in order to reduce postoperative morbidity, length of hospital stay, and the recovery time of oral feeding in patients undergoing abdominal surgery [21]. Stroke volume measured by means of calibrated arterial pulse contour analysis seems to be a reliable technique in severe aortic valve stenosis [22]. To date, other continuous cardiac output monitoring devices are not validated [23]. Routine pulmonary artery catheter or transesophageal echocardiography cannot be recommended, but they can be useful in some situations [18]. The pulmonary artery catheter can however provoke significant arrhythmias.

### 4.5.2 The Choice of Anesthetic Procedure

Local or regional anesthesia without deleterious hemodynamic consequences should be preferred whenever possible. If neuraxial anesthesia is classically contraindicated for patients with severe aortic stenosis, no large-scale clinical study has compared general anesthesia and neuraxial anesthesia [24]. Some case reports describing successful neuraxial anesthesia in patients with severe aortic valve stenosis have however been published [25, 26]. More than the type of anesthesia, anesthesiologists should focus on major hemodynamic goals. It is probably preferable to conduct a carefully titrated spinal anesthesia with a tight hemodynamic monitoring than "standard" general anesthesia. In the same way, it seems hazardous to contraindicate some anesthesia drugs. Any modern anesthesia drug could be used if carefully titrated by using a tight hemodynamic monitoring.

Drugs offering a good hemodynamic stability are usually preferred, as intravenous etomidate or ketamine. However, propofol can be used safely when using target-controlled infusion.

### 4.5.3 Hemostatic Considerations: Acquired Von Willebrand Syndrome

Von Willebrand factor abnormalities are directly related to the severity of aortic valve stenosis and are improved by valve replacement in the absence of mismatch between patient and prosthesis (Fig. 4.4) [27]. Vicentelli et al. reported that patients with severe aortic valve stenosis commonly present a type 2A von Willebrand syndrome, as a consequence of the mechanical obstruction of blood flow [27]. Two recent studies showed that patients with von Willebrand abnormalities may commonly present severe aortic stenosis, but loss of the largest multimers does not seem to generate clinical bleeding in most patients [28, 29].

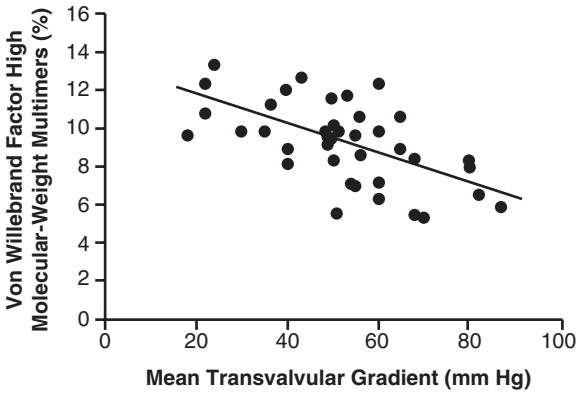


**Fig. 4.4** Relationship between von Willebrand factor abnormalities and the severity of aortic valve stenosis illustrated by the value of mean transvalvular gradient. Adapted from [27]

### 4.5.4 Infectious Considerations: Endocarditis Prophylaxis

The most recent guidelines recommend to limit endocarditis prophylaxis to high-risk patients (prosthetic valve, previous infective endocarditis, untreated congenital cyanotic heart disease) undergoing high-risk dental procedures (manipulation of gingival tissue or periapical region or perforation of oral mucosa) [30].

## 4.6 Postoperative Management

Ambulatory hospitalization is not recommended in patients with severe aortic valve stenosis. The decision to admit (or not) a given patient in the intensive care unit during the postoperative period is not an easy one. The Surgical Apgar Score represents an interesting and convenient approach to help physicians to predict postoperative outcome according to intraoperative events [31]. Using an estimated blood loss, the lowest heart rate, and the lowest mean arterial blood pressure during the intraoperative period, this 10-point score is discriminant to identify patients at risk of major postoperative complications [31]. In addition, the measurement of high-sensitive troponins following surgery may be helpful to improve risk stratification [18, 32]. Another strong predictor of adverse outcome in patients with severe aortic stenosis is the occurrence of atrial fibrillation. Several previous studies demonstrated an increased risk of mortality in patients with atrial fibrillation undergoing open-chest valve surgery [33, 34].

The management of myocardial injury in noncardiac surgery remains a matter of debate and a real challenge for the anesthesiologist. Even in the absence of intraoperative and/or postoperative complications, patients with severe aortic valve stenosis should be evaluated by a cardiologist after noncardiac surgery, in order to plan valvular management. Hemodynamic optimization during the perioperative period is an important goal that should be achieved in any case.

**Conclusion**

The presence of a severe aortic valve stenosis represents an important risk factor in patients undergoing noncardiac surgery. The discussion regarding the necessity of prior aortic valve replacement can be requested in elective nonurgent surgery. In any case, the preoperative cardiac evaluation (meticulous clinical examination and Doppler echocardiography) is crucial to stratify the patient's risk. A multidisciplinary approach, including both the cardiac anesthesiologist and the cardiac surgeon, is highly recommended.

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# The Patient with Congenital Cardiac Disease

5

Philippe Mauriat and Jana Assy

## 5.1 Introduction

Until a few decades ago, congenital heart disease (CHD) caregivers focused on pediatrics. Due to the medical and surgical improvements in the treatment of these children, a growing number of patients are surviving into adulthood.

Thus, the proportion of adults with congenital heart disease (ACHD) is increasing rapidly and exceeds now the proportion of children with CHD. Therefore, it seems more appropriate to talk about management and medical care of both adult and pediatric congenital heart diseases.

After close evaluation, the majority of CHD patients are not completely cured, despite primary surgical repair. They definitely require long-term and specific follow-up throughout life.

As these patients grow older, the risk of complications increases. It is important to know that arrhythmia, heart failure, pulmonary hypertension (PHT), endocarditis, and thromboembolism may complicate the progression of these adults. Women represent half of these patients, and pregnancy in this context constitutes a major challenge for the multidisciplinary staff and sometimes a significant risk for the mother. It is thus necessary for the anesthesiologist to fully understand the pathophysiology of these anomalies and their inherent risks during the different stages of the perioperative care, whether it is for cardiac or noncardiac interventions.

P. Mauriat (✉)
Pediatric and Adult Congenital Heart disease Intensive Care, Haut-Lévèque Hospital, Avenue Magellan, 33604, Pessac, France
e-mail: philippe.mauriat@chu-bordeaux.fr

J. Assy
Department of Pediatrics and Adolescent Medicine, American University of Beirut Medical Centre, PO Box: 11-0236, Riad El Solh, Beirut, 1107 2020, Lebanon



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## 5.2 Adult Congenital Heart Diseases

### 5.2.1 Growing Population

The incidence of CHD varies from 7/1000 to 10/1000 live births. Moderate and severe defects represent 3/1000 live births. There are almost 138 million live births each year with approximately one million babies born with a CHD. From 1950 to 1980, death rates for moderate and severe CHD were high, and almost all the patients died before adulthood. The majority of CDH-related deaths occurred during the first week of life (Fig. 5.1).

Demographic changes in this population could be explained by the major and continuous improvements in different areas, starting with prenatal screening for CHD during pregnancy and at birth, alongside with advances in the medical and interventional management of these babies. Tremendous progress has been also achieved in surgical repair, especially in cardiopulmonary bypass techniques, anesthesia, and postoperative management. Currently, there are more adults living with CHD than children. Recent demographic analysis demonstrated that CHD-related death in pediatrics has decreased by 30% between two time periods: 1987–1988 and

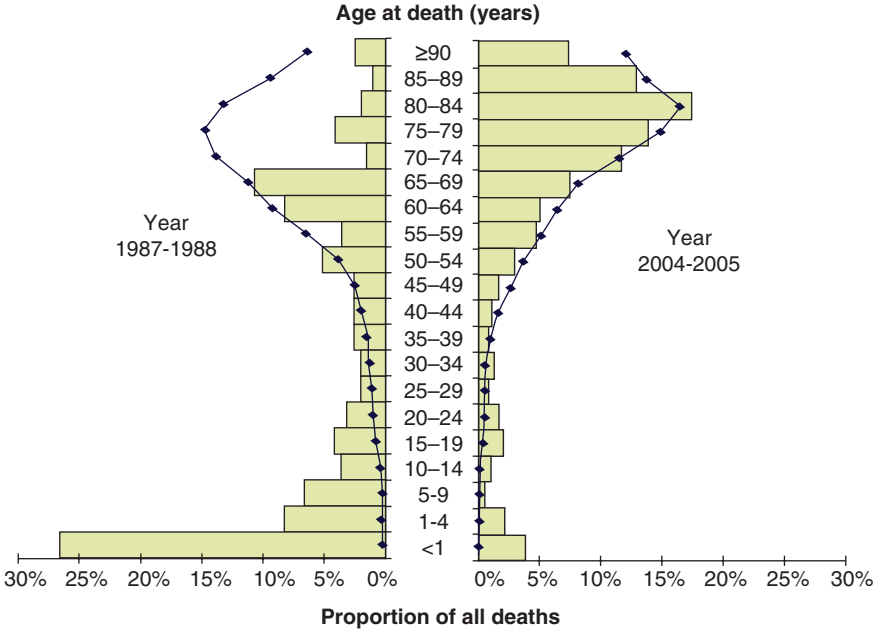


**Fig. 5.1** Distribution of age at death in patients with congenital heart disease in 1987–1988 and 2004–2005. Histogram bars depict the proportion of all deaths (*x*-axis) according to age at death (*y*-axis) in our cohort of patients with congenital heart disease in the first (1987–1988; *left graph*) and final (2004–2005; *right graph*) years of observation. *Bold black curves with diamonds* represent the corresponding age at death distribution in the general Quebec population during the same periods of observation (Reproduced from Avila et al. [1])

2004–2005. It also showed that the decrease was much more noticeable in severe CHD: 67% less mortality [1].

More than 85% of the children born with CHD survive now to adulthood. This phenomenon explains why this cohort tends to grow old. In approximately 20 years, the median age at death increased from 2 to 23 years for complex CHD. For adults with CHD, the median age at death has also shifted from 60 to 75 years. Children with CHD reaching adulthood are estimated to be approximately one million in the United States, 1.8 million in Europe, and around 100,000 in Canada [2, 3].

In a recent study published in 2016, Agarwal assessed the burden of ACHD presenting to US emergency departments [4]. Numbers increased significantly between 2006 and 2012, with a striking increase in patients presenting with PHT. There was an increase in the prevalence of cardiovascular risks among these patients, including smoking, obesity, hypertension, diabetes, and vascular disease, as well as respiratory disorders and chronic kidney disease. Ultimately, adults with CHD undergo the pathological progression of their heart disease, in addition to the common cardiovascular risk factors and consequent organ injury. This certainly explains the difficulty and complexity in the management of these patients by non-specialized medical teams.

Patients admitted to the emergency departments had simple as well as complex ACHD. Primary reasons for presentation to the emergency department differed among these patients but were mainly described as "nonspecific chest pain and respiratory disorders." Some reasons were more specific like arrhythmias, acute myocardial infarction, PHT, and endocarditis (Fig. 5.2). Pregnancy was often considered as an "illness" in these patients, and in cases of complex CHD, it was managed like a life-threatening condition [4].

## 5.2.2 Common Issues

### 5.2.2.1 Mortality

The reported mortality associated with CHD has decreased during the last 3 years, and survival rates have significantly improved for simple heart defects, as well as for more complex forms, like tetralogy of Fallot and transposition of the great arteries. Nevertheless, the mortality rate for adult patients with Eisenmenger syndrome remained high [5–7].

A recent single-center retrospective study identified the leading causes of death among 7000 adult patients with CHD: chronic heart failure (42%), pneumonia (10%), sudden cardiac death (7%), cancer (6%), hemorrhage (5%), and perioperative mortality [8].

In a literature review, Drenthen demonstrated that almost 11% of women with CHD suffered from cardiac complications during pregnancy. Arrhythmias were identified in 4.5% of the cases. Pregnant women with Eisenmenger syndrome presented frequently with a stroke and died from cardiovascular complications [6, 9].

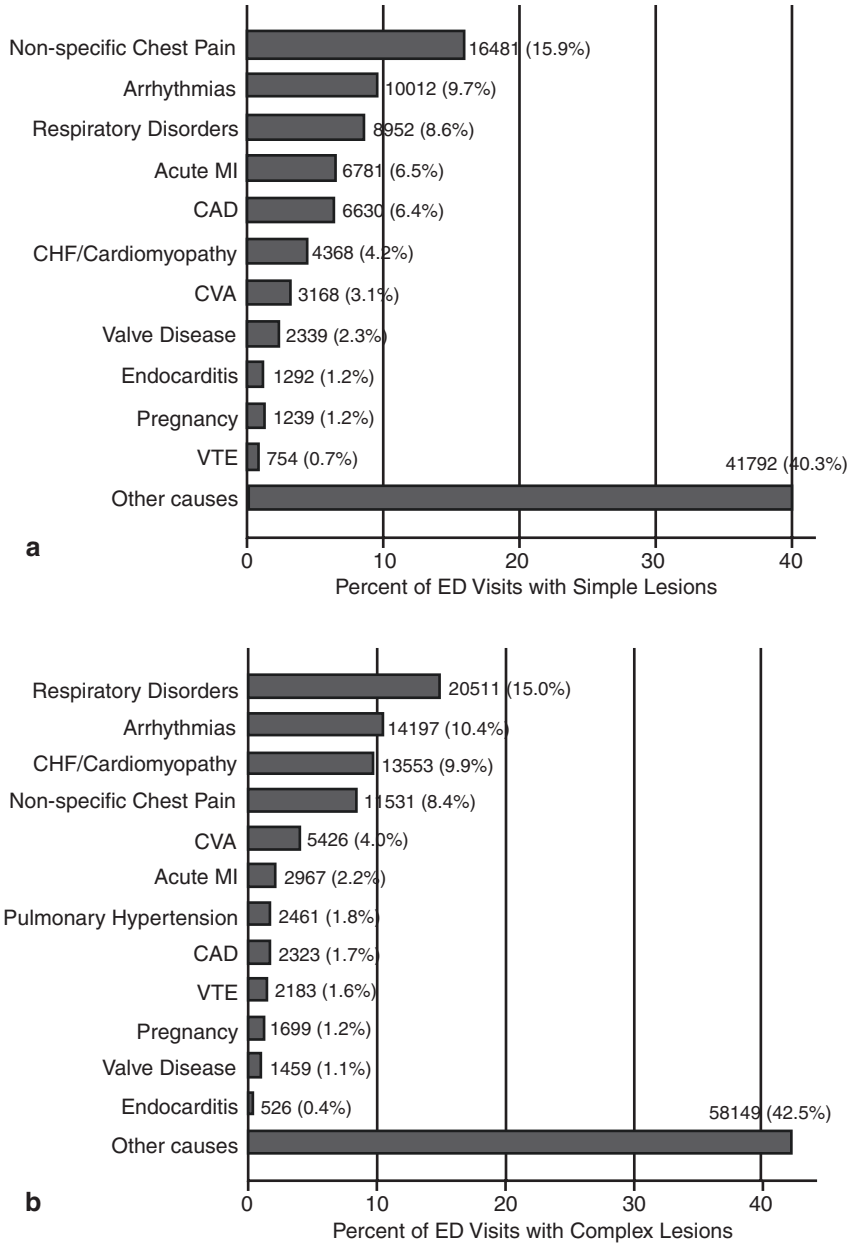


**Fig. 5.2** This figure demonstrates the primary reasons for presentation to the ED among patients with (**a**) simple ACHD and (**b**) complex ACHD. Abbreviations: *ACHD* adult congenital heart disease, *CAD* coronary artery disease, *CHF* congestive heart failure, *CVA* cerebrovascular accident, *ED* emergency department, *MI* myocardial infarction, *VTE* venous thromboembolism (Reproduced from Agarwal S et al. [4])

#### 5.2.2.2 Morbidity

Comorbidities and complications like arrhythmias, heart failure, or endocarditis are common in adult patients with CHD. Pulmonary arterial hypertension is also a serious burden and might progress to Eisenmenger syndrome.

Pregnancy represents a major challenge in the care of female patients with ACHD. The risks of mortality and morbidity, as well as the impact of possible surgeries or interventions, complicate the delicate management of these patients.

Cardiac catheterization and surgery are also increasing; this is mainly due to residual heart defects, the need for valve replacement, and in some cases palliating anomalies when complete repair is not possible.

Holst KA et al. demonstrated that arrhythmias, low cardiac output syndrome, strokes, hemorrhages, ventilation disorders, and kidney injuries may complicate surgery in 15–25% of the patients. Furthermore, perioperative mortality is also estimated to range between 3% and 8% [11].

#### 5.2.2.3 Arrhythmias

Arrhythmias are the most common long-term complication and represent the leading cause of morbidity and death as well as the primary reason for hospital admission. Walsh EP has shown that sudden death is significantly more frequent in ACHD patients than in the general population, with an incidence of 0.09% per year. The prevalence of tachyarrhythmias or bradyarrhythmias is correlated with age and complexity of the heart disease [10].

Sinus node dysfunction and atrioventricular (AV) block are common in the postoperative period. In some cases, AV block will need an implantable permanent pacemaker [12]. Congenital AV block can occur in 3–5% of congenitally corrected transposition of the great arteries, with an increase of 2% each year [10, 12].

Almost 20% of patients with Ebstein's anomaly develop associated arrhythmias, related to the structural defect itself, like Wolff-Parkinson-White. Surgical repair for Fontan, ASD, tetralogy of Fallot, and Mustard and Senning procedures are frequently complicated with flutter and atrial arrhythmias (tachycardia or bradycardia) [12]. Medical management of supraventricular tachycardia (SVT) is rarely efficient and will require catheter ablation in most cases, although associated with recurrent episodes of SVT [13, 14].

In congenital mitral and aortic valve disease and in single ventricle, atrial fibrillation is frequent (20–30%) [15].

Patients with repaired tetralogy of Fallot are at high risk (2%) of sudden death secondary to SVT, 20 years following surgical repair [16]. These particular patients must undergo meticulous investigations to determine the risk factors that require an implantable defibrillator.

The Heart Rhythm Society, with the collaboration of the American College of Cardiology, the American Heart Association, the European Heart Rhythm Association, and the Canadian Heart Rhythm Society, has suggested recommendations for the management of arrhythmias in patients with ACHD [17].

#### 5.2.2.4 Heart Failure

The pathophysiology of heart failure associated with ACHD is complicated: it is attributed to a number of interrelated mechanisms. The ventricles (especially the right ventricle) suffer from volume overload in an atrial septal defect (ASD) and from volume and pressure overload in a ventricular septal defect (VSD). A single ventricle, in its various forms, might not be capable of responding to long-term metabolic demands. Pulmonary blood flow and lung perfusion are impaired in cases of anomalies in the pulmonary outflow tract. The AV conduction system can be compromised in these patients.

ACHD-associated heart failure is the most common reason for hospitalization in ACHD patients. Hence, this condition should be considered carefully and managed differently from heart failure associated with acquired heart disease.

ACHD patients with cyanotic single ventricle physiology suffer mostly from systolic dysfunction [18]. In these particular patients, mortality and arrhythmias are associated with diastolic dysfunction.

Aggravating factors in ACHD-associated heart failure may be related to many complex parameters: arduous diagnosis, tedious medical and surgical care, and challenging and specialized lifelong follow-up. However, difficulties associated with activities of daily living and with moderate to intense exercise should alarm the specialized medical team. These patients have characteristic lower physical capacity [19].

#### 5.2.2.5 Pulmonary Arterial Hypertension

PAH is associated with ACHD in 4–10% of the cases. Delayed management of left-to-right shunts (VSD, patent ductus arteriosus, truncus arteriosus, aortopulmonary window, and even ASD in some cases) could be responsible for PAH, especially with underlying genetic predisposition to PHT.

Pulmonary endothelial dysfunction and remodeling, worsened by inflammation and infection, will lead to an increase in pulmonary vascular resistance (PVR). With an adequate and maintained right ventricle function, PHT will develop secondary to increased PVR. However, high PVR can lead to right ventricle dilation and dysfunction [20].

Eventually, PVR and PHT become fixed and progress to Eisenmenger syndrome. Multi-organ involvement is usually present, and mortality rate is highly increased when ACHD patients develop Eisenmenger syndrome. Major advances in pulmonary vasodilator drugs may improve survival [21]. CHD with left-to-right shunt are currently being repaired as soon as possible, practically always before the age of 9 months, an approach that has decreased the incidence of Eisenmenger syndrome. However, there are cases of PAH in ACHD, not related to the initial heart defect.

#### 5.2.2.6 Infective Endocarditis

The complexity of surgical repair and the implantation of foreign material or grafts favor the development of infection. Endocarditis in ACHD patients is 20 times more frequent than in the general population [21, 22, 47]. Management of these patients has also improved, decreasing the mortality rate by 10%. However, surgery remains necessary in more than 30% of the cases.

Because of the growing crisis of antibiotic-resistant infections, antibiotic prophylaxis prior to dental procedures is indicated only for ACHD patients with foreign material (i.e., prosthesis) or patients with partially repaired CHD. Moreover, prophylaxis has been limited to 6 months following surgical intervention. Antibiotic prophylaxis is not recommended anymore before pulmonary or respiratory track procedures, neither for digestive nor genital and urinary track interventions. Tattoos and piercings should be avoided in ACHD patients [23].

#### 5.2.2.7 Pregnancy

Fetal mortality and premature birth represent almost 4% of all births from ACHD, making it four times higher than in the general population. Maternal and fetal risks are both increased in pregnant women with ACHD. Eleven percent of these women present cardiac complications, particularly in those with PAH and in some complex situations like outflow tract stenosis (pulmonary and aortic), pulmonary atresia, left AV valve stenosis, residual coarctation of the aorta, bicuspid aortic valve with dilated aortic root, and Marfan and Turner syndromes [9, 24]. In women with an arterial oxygen saturation of less than 85%, only few pregnancies are successful [25]. The most common maternal risks are heart failure (4.8%) and arrhythmias (4.5%). Women with ACHD and PAH can present with acute cardiac decompensation during pregnancy, especially around 25 weeks of gestation. This risk is increased with inflow obstructive lesions of the systemic ventricle. Preeclampsia, eclampsia, and thromboembolic events are also more frequent in women with ACHD.

ZAHARA study identified risk factors during pregnancy in women with ACHD: cyanotic heart disease, mechanical valve replacement, and systemic or pulmonary AV valve regurgitation (Table 5.1) [9].

Neonatal complications were frequently encountered, the most common being prematurity, respiratory distress syndrome, intraventricular hemorrhage, low birth weight, and growth retardation. Pregnant women with ACHD should be carefully followed in specialized multidisciplinary units [26, 48].

**Table 5.1** Scores predicting maternal cardiovascular complications during pregnancy (Reproduced from Ntiloudi [6])

| ZAHARA | |
|---|---|
| • Prior arrhythmia | 1.50 |
| • NYHA functional class III/IV | 0.75 |
| • Left heart obstruction (peak LVOT gradient >50 mmHg or aortic valve area <1.0 $cm^2$) | 2.50 |
| • Mechanical valve prosthesis | 4.25 |
| • Systemic AV valve regurgitation (moderate/severe) | 0.75 |
| • Pulmonary AV valve regurgitation (moderate/severe) | 0.75 |
| • Cardiac medication before pregnancy | 1.50 |
| • Cyanotic heart disease (corrected and uncorrected) | 1.00 |

In ZAHARA score the risk is: 2.9% with <0.5 points, 7.5% with 0.5–1.5 points, 17.5% with 1.51–2.50 points, 43.1% with 2.51–3.5 points and 70% with >3.5 points

#### 5.2.2.8 Hemostatic Disorders

Thromboembolic events are 10–100 times more frequent in patients with ACHD. A study on 23,150 patients with ACHD demonstrated that 2% suffered one or more strokes (0.05% event per year per patient). Patients with cyanotic heart disease and reduced systemic arterial oxygen saturation are the most exposed to cerebral thrombotic events [26, 48].

There are currently no absolute guidelines or recommendations for anticoagulation strategies in these patients. Individualized approach and management should be considered to prevent thromboembolic events [27].

### 5.2.3 Anesthesia and Postoperative Care

The management of ACHD patients following surgical interventions is complex and challenging. Specialized teams of anesthesiologists and intensivists are imperative. A scrupulous understanding of the patient's structural heart defect and his functional status following the surgical repair or the cardiac catheterization is one of the most important aspects in the management of these particular patients.

Careful acknowledgment of the cardiac output, the systemic vascular resistances, and the heart-lung interaction is fundamental for the majority of congenital heart diseases, at all times.

Vascular access might be problematic due to the previous numerous surgical procedures in many of these patients. Moreover, reoperation is associated with increased mortality [28]. Management strategies should be well established in order to prevent and avoid complications and to provide patients with rapid and correct medical care and treatment.

### 5.2.4 Physiology

Patients with decreased pulmonary blood flow secondary to right ventricular outflow tract and pulmonary valve obstruction (i.e., patients with tetralogy of Fallot) are dependent upon preload conditions. Thus, maintaining relatively high blood pressure and cardiac output and avoiding increased PVR and oxygen consumption are very important during the perioperative period.

An opposite situation is that of a patient with increased pulmonary blood flow (i.e., patients with VSD); this patient has a compromised systemic perfusion that might lead to left heart failure.

In these two situations, pulmonary-to-systemic blood flow ratio should be maintained constant at all time, by optimizing the cardiac output, volemia, and the pulmonary and systemic vascular resistances.

#### 5.2.4.1 Preoperative Assessment

Thorough and meticulous understanding of the initial cardiac defect and its progression is a must for the anesthesiologist. He should also well identify previous

surgeries and interventions. Complete clinical and biological evaluation should be performed prior to cardiac, as well as noncardiac surgery. Identifying comorbidities, in particular performing pulmonary function test to detect respiratory problems or stress test in some cases, has an impact on the management of these patients. ACDH patients have limited physical capacities, which could compromise the weaning from mechanical ventilation. Ultrasound evaluation of vascular access should be performed to rule out thrombosis due to frequent catheterizations and surgeries and to decide upon the sites for central and arterial lines.

#### 5.2.4.2 Anesthetic Management

Sedative premedication is necessary. Nevertheless, it should be administered with caution in case of hypoxemia. Selection of the sedative agent should be individualized.

Inhaled anesthetic agents used for induction may have a delayed result in case of decreased pulmonary blood flow. Increasing the agent's concentration should be avoided because of its toxicity. Patience and more time are needed for these patients with congenital heart disease.

In addition, the majority of anesthetic agents produces systemic vasodilation and has negative inotropic effect on the heart, compromising the delicate balance of pulmonary-to-systemic blood flow ratio in case of intracardiac shunts.

Intravenous induction should also be performed with caution and should be associated with volume and fluid expansion.

Ventilation with high FiO2 will decrease PVR, thus increasing pulmonary blood flow while decreasing systemic blood flow. In such cases, resultant hypotension should not be managed by adding inotropes, because it will also increase the pulmonary blood flow. Once again here, each case should be managed individually.

Limited FiO2 should always be considered in case of left-to-right shunt and increased FiO2 in case of low pulmonary blood flow. Systematic high oxygenation should be avoided in the anesthetic management of patients with congenital cardiac disease.

It is recognizable that the choice of the anesthetic agent for this particular population should be based upon its hemodynamic consequences in order to preserve the cardiac output and the pulmonary-to-systemic blood flow ratio [23].

#### 5.2.4.3 Monitoring

Pulmonary and cardiac dysfunction and destabilization during the perioperative period can be detected early with the appropriate use of hemodynamic and oxygenation-monitoring devices, especially in complex ACHD patients. Thus, the insertion of a pulmonary artery catheter or Swan-Ganz catheter allows for the continuous monitoring of mixed venous oxygen saturation (SvO2) and accurately measures the pulmonary artery pressure. This approach can be very useful for the perioperative management despite the potential risk of ventricle arrhythmias that may occur during Swan-Ganz insertion. Central venous catheters with continuous SvO2 measurement may be a safer alternative.

Left atrial pressure (LAP), measured by a transthoracic catheter inserted during surgery into the left atrium, is rarely used for acquired heart disease. However, LAP measurement remains a powerful tool for the continuous assessment of the preload of the systemic ventricle in complex ACHD patients.

Near-infrared spectroscopy (NIRS) is also an effective noninvasive technique used for monitoring regional oxygenation and tissue perfusion. It is of particular interest in compromised cerebral and somatic oxygenation during cardiopulmonary bypass, when the only measurement of SpO2 is not enough to determine regional oxygenation.

The use of transesophageal echocardiography (TEE) is now widely spread for perioperative hemodynamic and cardiac assessment. In most centers, TEE is routinely used in the operating room for the evaluation of surgical repair and cardiac function, in order to guide the therapeutic strategies [29, 30].

#### 5.2.4.4 Intensive Care

Postoperative complications are more frequent in this complex and challenging ACHD population; this emphasizes the need for close and vigilant postoperative care in order to prevent the complications and minimize their impact. Complications include mainly arrhythmias, heart failure, pulmonary arterial hypertension, kidney injury, and respiratory disorders. Bleeding is also important to monitor because of the higher risk associated with reoperation and cyanotic heart disease [11].

For more complex ACHD, multimodal monitoring is mandatory; invasive blood pressure, continuous SvO2, PAP, NIRS, and transthoracic or TEE allow for the early detection of complications and their prevention in some of the cases.

Weaning from inotropic support and from invasive mechanical ventilation should follow strict criteria including improvement in hemodynamic and oxygenation parameters and decreased cardiac biomarker levels (troponin, brain natriuretic peptide), which vary according to the cardiac anomaly and type of repair. This strategy aims to prevent secondary complications, associated with higher morbidity and mortality rates.

Early and dedicated respiratory and physical therapy is fundamental while weaning from invasive mechanical ventilation. Commonly, ACHD patients with limited physical capacities will require prolonged noninvasive ventilation following extubation. Moreover, rehabilitation can be necessary for months.

Prolonged cardiopulmonary bypass and aortic cross clamp times are sometimes necessary in complex ACHD, but it may compromise cardiopulmonary function. Thus, mechanical support may be required in some cases: extracorporeal membrane oxygenation (ECMO), as a short-term mechanical support, sometimes associated with intra-aortic balloon pumping, allows the heart and the lungs to better recover.

For severe respiratory failure (i.e., acute respiratory distress syndrome) in Fontan patients, ECMO should be considered to allow for correct gas exchange while the lungs recover. In addition, ECMO may be used for malignant arrhythmias, maintaining adequate tissue perfusion, while the arrhythmia is treated [31].

#### 5.2.4.5 Patients with Pulmonary Arterial Hypertension

In these high-risk surgical patients, PHT crisis can be critically severe and is related to pulmonary endothelial hyperactivity mediated by sympathetic stimuli (pain or surgical stress). Other factors may also contribute to PHT including acidosis, hypoxia, hypercapnia, pulmonary infection, and the inflammatory response produced by the cardiopulmonary bypass. To prevent and treat PHT, FiO2 should be kept high and normocapnia targeted, with a pH of 7.4. General anesthetic agents and opioids (i.e., sufentanil, remifentanil, etc.) will minimize sympathetic stimuli. Inotropic support should also be considered in case of right ventricle failure and elevated PVR. In this context, the combination of milrinone-epinephrine is advantageous [32]. Systemic vasoconstriction with norepinephrine might also be necessary in order to maintain adequate coronary perfusion pressure. Inhaled nitric oxide will minimize the vasoconstrictor effect of norepinephrine. In this particular situation, vasopressin seems to be preferable [33].

PHT can sometimes be very severe and difficult to manage. Barnett demonstrated that combining various pulmonary vasodilators (prostacyclin, sildenafil, endothelin antagonists) with inhaled nitric oxide is a more efficient way to treat these patients [34].

#### 5.2.4.6 Fontan Patients

Patients that underwent Fontan operation present around 30 years later with multiple organ failure. This is largely due to progressive and irreversible single ventricle dysfunction; cardiac output at rest in these patients is 70% below normal.

In most cases, the direct connection between both vena cava and pulmonary arteries are responsible for the "right heart failure" symptoms, despite the absence of a right ventricle. It is attributed to the continuous rise in PVR [35] with identical symptoms: ascites, peripheral edema, liver failure, and, more specifically, protein-losing enteropathy. Another particularity is the production of obstructive viscous bronchial secretions leading to atelectasis and decreased pulmonary blood flow, with consequent desaturation [36].

More than 50% of Fontan patients suffer from supraventricular arrhythmias such as atrial flutter and reentrant supraventricular tachycardia. However, ventricular arrhythmias are rare. Tachycardia and non-sinus rhythm are not well tolerated by these patients and should be treated as soon as possible to prevent thromboembolic events [37].

During the last two decades, the survival rates of Fontan patients have improved, reaching 85% at 10 years and 80% at 20 years. Leading causes of death are arrhythmia, heart failure, and thromboembolic events. Worse outcome is associated with protein-losing enteropathy with only 50% survival rate at 5 years [38].

#### 5.2.4.7 Patients with Tetralogy of Fallot

Within the last 50 years, surgical repair of the tetralogy of Fallot (TOF) progressed considerably. This explains the differences seen among these patients throughout the years. The initial approach was to perform a palliative procedure by creating a shunt between the subclavian artery and the pulmonary artery, also called the Blalock-Taussig shunt. A few years later, the shunt was closed and the VSD repaired, along with the

enlargement of the right ventricular outflow tract. At that time, "the heart is cured" was the message delivered to the family. However, long-term progression showed to be less optimistic: progressive pulmonary regurgitation in repaired TOF patients using a transannular patch is responsible for right ventricle dilation and failure with consequent tricuspid regurgitation. These patients have decreased exercise capacity and are predisposed to ventricular and supraventricular arrhythmias, with a high risk of sudden cardiac death when QRS duration exceeds 180 ms [39]. Pulmonary valve replacement is indicated when the right ventricular end-diastolic volume is greater than 150 ml/m$^2$ on magnetic resonance imaging, with a pulmonary regurgitant fraction greater than 35%. Beyond these values, normalization of right ventricular function following pulmonary valve replacement becomes less likely [40, 41].

A promising novel approach, with valve-sparing total repair performed very early in life (during the first few months), may prevent the progression into right ventricular failure.

#### 5.2.4.8 Transplantation

For some ACHD patients, transplantation is the only possible therapeutic strategy, whether heart, heart-lung, or single- or double-lung transplantation. For these patients, mechanical support could be considered as a bridge to transplantation when indicated. However, transplantation is technically complex in these patients, due to the multiple previous interventions and surgeries.

Transplantation in patients with single ventricle physiology and Fontan repair is considered to be the final palliation [42].

Adult patients with transposition of the great arteries and Mustard or Senning procedure may also benefit from heart transplantation [43].

Heart-lung or double-lung transplantation may be offered to ACHD patients with Eisenmenger syndrome. In these particularly severe patients, transplantation outcomes are worse than those of the general population [44].

#### 5.2.4.9 Noncardiac Surgery

Noncardiac surgery for ACHD patients represents a challenge for non-experienced medical team. A full understanding of the cardiac anomaly and its physiopathology is critical. Identifying special risk factors related to surgery is also essential, like digestive system surgery or labor and delivery in a Fontan patient [45] or respiratory system surgery in a patient with low pulmonary blood flow or a failing right ventricle. Careful planning and communication with cardiology and anesthesia are crucial to organize the anesthetic management and anticipate the possible complications. Perioperative risks should be well understood by both surgeon and anesthesiologist. These patients are extremely sensitive to hemodynamic instability and bleeding. Management of postoperative bleeding complications can be difficult because of the continuous need for anticoagulation. Blood product transfusion and inotropic support should be considered early. For ACDH patients with PHT, inhaled nitric oxide must be available.

Perioperative monitoring is much more important in ACHD patients, compared to noncardiac patients. The use of invasive monitoring, like invasive arterial blood pressure or invasive central venous pressure, is advisable. In addition, TEE should be considered for hemodynamic and cardiac function evaluation throughout the procedure [46].

#### 5.2.4.10 Management of ACHD Patient in a Referent Specialist Center

In a study performed on Quebec ACHD patients, Darren Mylotte suggested the following clinical perspectives:

> There are expected to be over a million adults living with congenital heart disease (CHD) in the United States. Clinical guidelines recommend specialized care for this complex patient population burdened with life-long morbidity. Despite the growing need to bring quality to CHD care, there are no data demonstrating that specialized adult CHD (ACHD) care can improve outcomes. In this population-based analysis, we examined the impact of specialized care on ACHD mortality. We examined referral rates to specialized ACHD centers and ACHD patient mortality rates between 1990 and 2005 by using the population-based Quebec Congenital Heart Disease database that includes 71,467 patients. Concurrent with the guideline publication recommending specialized care for ACHD patients, we showed a significant increase in referral rates to specialized ACHD centers associated with a parallel significant reduction in ACHD patient mortality. Independent of age, sex, and comorbidity, specialized ACHD care was associated with reduced odds of death, an effect predominantly driven by patients with severe CHD. To our knowledge, this is the first study to analyze the relationship between specialized ACHD care and mortality. Our findings support the guidelines recommending specialized care for all ACHD patents as a means of improving quality of care and outcomes for this growing patient population. [2]

The survival rate of ACHD patients is highly dependent on the expertise of the center where these patients are treated (Fig. 5.3). This statement highlights the importance of transferring these patients to referent, specialized hospital centers, whether it is for the management of a complication related to the initial cardiac disease or another pathology.

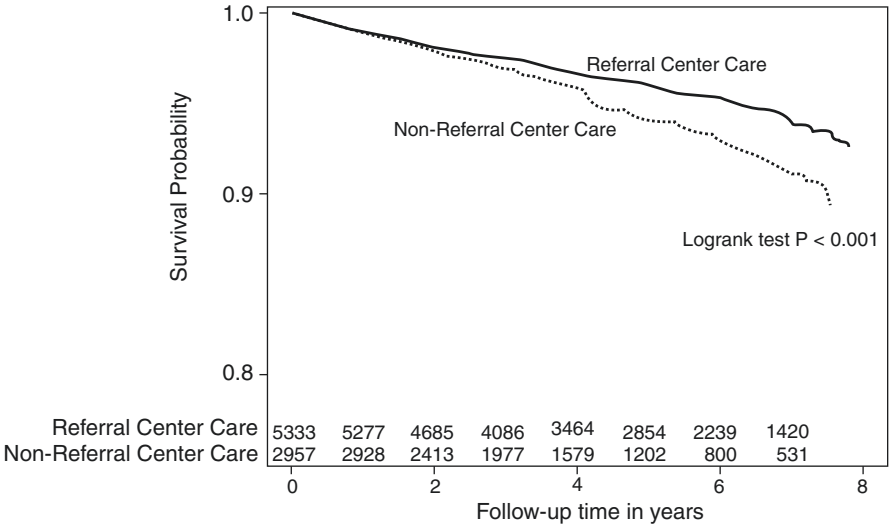


**Fig. 5.3** Cohort study: adjusted Kaplan-Meier survival curves. Adjusted Kaplan-Meier survival curves in patients with ACHD referral center care (*solid line*) and those with nonreferral care (*dashed line*). ACHD indicates adult congenital heart disease (Reproduced from Mylotte et al. [2])

## Conclusion

As a result of medical and surgical advances in the management of children born with heart disease, there are an increasing number of adults with CHD surviving into adulthood. Thus, there is an increasing need for specialized care for this challenging population.

In addition, some of these congenital heart diseases are uncorrectable despite the primary surgical repair and will require lifelong and specialized follow-up and medical care.

ACDH patients can undergo cardiac and noncardiac surgeries. And they will have to be managed and approached differently from the normal population. For simple and complex heart defects, in-charge physicians should be well informed about the initial pathology, the type of surgical repair or cardiac catheterization, and the associated functional modifications. In particular, for cardiac surgeries that are particularly complex, anesthesiologists and intensivists have a specific training for the management of these challenging but rewarding patients.

Outside of this specialized context, the medical advice and consultation of referent cardiologists and anesthesiologists are necessary for a noncardiac intervention, for a stable ACHD patient. On the other hand, when the CHD is complex and not well tolerated, it is essential to transfer the patient to a multidisciplinary specialized referent center, especially ACHD pregnant women with Fontan procedure or severe PHT [46].

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# Perioperative Management of the Patient with an Implantable Cardioverter Defibrillator

6

Julien Amour

Patients suffering from arrhythmic, ischemic, or dilated cardiomyopathy are particularly exposed to the risk of sudden death from ventricular fibrillation [1–3]. In 2015 [2], guidelines for the indications of ICD implantation were update from 2005 [2], in the light of the publication of two large studies [2, 3]. In this context, early defibrillation by electric shock offers the best chance of survival [2–5]. With over 500,000 sudden deaths a year in the North American continent alone, the number of cardiac defibrillators implanted has increased exponentially since 2005, especially after publication of different studies and meta-analyses showing the benefit of this treatment in terms of survival [5–7]. Thus 270,000 defibrillators were implanted worldwide in the year 2005 alone, of which 30% were in the USA.

In addition, these figures are in perpetual progression with more than 100,000 implantations per year in the USA [1]. Consequently the anesthesiologist encounters these patients more and more frequently in his practice. In this context, it would appear crucial for the physician to understand how this device works and to know how to prevent and treat perioperative dysfunctional complications.

## 6.1 Principal Characteristics and Modes of Function of Implantable Cardioverter Defibrillators (ICD)

ICD is a device detecting episodes of life-threatening arrhythmias such as ventricular tachycardia or ventricular fibrillation by means of specific intracardiac leads. Once detected, these arrhythmias can be interrupted immediately. In the case of a

J. Amour
Sorbonne Universités, UPMC Univ Paris 06,
UMR INSERM 1166, IHU ICAN, Paris, France

Department of Anesthesiology and Critical Care Medicine, Hôpital Pitié-Salpêtrière,
Assistance Publique-Hôpitaux de Paris (APHP), Paris, France
e-mail: julien.amour@aphp.fr



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ventricular tachycardia, the ICD delivers a high-frequency stimulation corresponding to the "overdrive pacing" functionality. In the case of ventricular fibrillation, the ICD delivers an internal electric shock corresponding to the "cardioversion" functionality. The first ICD was developed by Dr. Michel Mirowski in the 1980s while working at NASA. The device was implanted in association with a pacemaker and necessitated a thoracotomy for placement of the epicardial electrodes with the generator being implanted in the abdominal cavity for reasons of size. Present-day technology has allowed miniaturization of the ICD permitting subpectoral implantation of devices measuring only 3.5 $cm^2$ and 1.2 cm wide. The most sophisticated devices may combine double or triple intracardiac leads to associate defibrillator, pacemaker and cardiac resynchronization therapy.

ICD leads are inserted into the right heart chambers via the superior vena cava. For a single-chamber device, the lead tip is positioned in the right ventricle. For a dual-chamber device, the additional tip is positioned in the right atrium. In the case of resynchronization therapy, the third lead is introduced into the coronary sinus and onward to the left ventricle leading to simultaneous pacing of the right and left ventricles. The device is powered by a small voltage battery amplified by a transformer which allows delivery of a 30–36 J shock. Modern devices also provide overdrive pacing to electrically convert a sustained ventricular tachycardia and a pacemaker function for backup pacing in case of bradycardia. The pulse generator acts as the cathode for the defibrillation, the shock being delivered from the right ventricular lead, called "coil," toward the generator in order to place the ventricles in the middle of the electric field for an effective cardioversion. The ICD is also able to detect and analyze arrhythmias, storing this information in the device for analysis. Modern ICD has multiple programmable features, but essentially it measures each cardiac R-R interval and categorizes the rate as normal, too fast (short R-R interval), or too slow. When the device detects a sufficient number of short R-R intervals within a period of time, it will declare a tachycardia episode. The internal computer will decide between antitachycardia pacing and shock based on its programmed algorithm. The defibrillator is programmed to detect different types of malignant arrhythmias according to the heart rate and the morphology of the QRS whose characteristics will have previously been defined for each individual patient. Thus the cardiac electrophysiologist will establish frequency intervals specific to each patient defining a ventricular tachycardia or ventricular fibrillation. The appearance of an episode of arrhythmia corresponding to one of these threshold zones previously determined will lead to the appropriate response of the ICD. Thus the highest frequencies correspond to the ventricular fibrillation threshold which will activate the cardioversion function triggering a shock of up to 36 J. In the case of a ventricular tachycardia of a lower frequency corresponding to the threshold previously defined for a ventricular tachycardia, the anti-tachyarrhythmia function will be activated. This activation will result in the delivery of a series of trigger impulses at a high synchronized frequency with the object of pacing the heart at a higher rate than the intrinsic arrhythmia in order to force the conduction network into a refractory period, thus blocking the spontaneous arrhythmia. In the majority of case, this therapy is painless, well tolerated, and often successful and thus can be considered to be

**Table 6.1** Generic defibrillator code

| 1st letter | 2nd letter | 3rd letter | 4th letter |
|---|---|---|---|
| Shock chamber | Antitachycardia pacing chamber | Tachycardia detection | Antibradycardia acing pacing chamber |
| O: none<br>A: atrium<br>V: ventricle<br>D: dual (A + V) | O: none<br>A: atrium<br>V: ventricle<br>D: dual (A + V) | E: electrocardiogram<br>H: hemodynamic | O: none<br>A: atrium<br>V: ventricle<br>D: dual (A + V) |

an important therapeutic progress. In the case where this mode is unsuccessful, an internal shock can be delivered. However, when the rate of a sinus tachycardia or a supraventricular arrhythmia overlaps the zone calibrated for ventricular rate, the risk of provoking the anti-tachyarrhythmia function or even an electric shock exists. To avoid this problem, the majority of modern ICDs can be programmed to increase the diagnostic specificity notably by considering the widening of the QRS. This does not totally solve the problem for the supraventricular tachycardia with a bundle branch bloc, a consideration which the cardiac electrophysiologist must take into account when programming. Thus the modern 3rd and 4th ICD generations have been shown to be effective in 98% of episodes of arrhythmias [8].

Finally, the anti-bradycardia function is available on all recent ICD and consists of a pacemaker able to compensate a bradycardia or an asystole post-defibrillation. It may consist of simple ventricular pacemaker, but a dual- or even triple-chamber pacemaker is possible especially when a ventricular resynchronization is required.

Like pacemakers, ICDs have a generic code to indicate lead placement and function (Table 6.1).

When venous access is difficult, subcutaneous defibrillator may be helpful [2]. An electrode system is placed entirely subcutaneously, outside the thoracic cavity. A distal electrode on the defibrillator lead is associated to a proximal electrode located 8 cm from the tip of the lead. A coil is located between the tip and proximal electrode for defibrillation. The distal part of the lead is located at the left parasternal edge, and the device is placed over the fifth intercostal space between the left anterior and mid-axillary line. The device is capable of defibrillating with an output of 80 J [2]. Limits of this device are patients who require bradycardia pacing >30 s, antitachycardia pacing, or patients needing cardiac resynchronization therapy [2].

## 6.2 Intraoperative Dysfunction

The most frequent source of ICD dysfunction in the intraoperative period is electromagnetic interference (EMI) stemming from electric devices such as monopolar electrocautery or electric shaving occurring in proximity to the ICD generator. Radiofrequency waves between 0 and $10^9$ Hz can generate EMI and thus cause ICD or pacemaker malfunction. Figure 6.1 summarizes the most frequent sources of EMI encountered during the intraoperative period. In contrast, X-rays, infrared, or

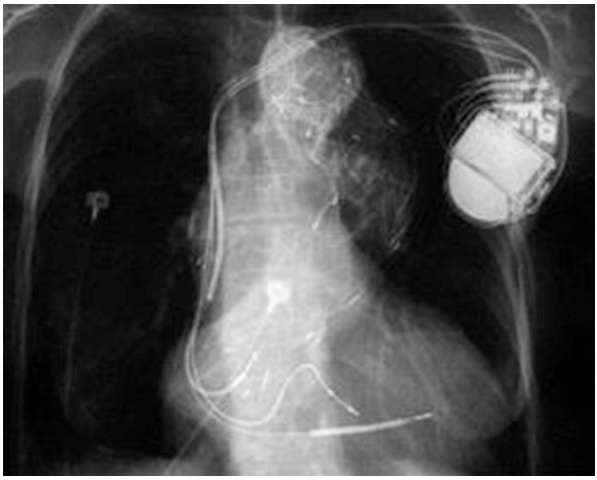

**Fig. 6.1** ICD associated with a dual-chamber pacemaker

ultraviolet does not interfere with ICD..; In the specific case of radiotherapy, repeated exposures can damage the electric circuits in the generator but do not produce EMI of itself [5]. Thus, despite progress for enhancing protection against EMI risk, ICD remains still highly sensitive to interference in the intraoperative period. The manufacturers now incorporate filters and circuit shields that insulate the internal components. Moreover, for pacemakers, a shift toward bipolar leads (since 2000), which minimize the physical distance of the circuit with the anode and cathode incorporated in the lead tip, reduces the potential for EMI.

In contrast, the EMI risk is still high in ICD as the anode (lead tip) and cathode (generator) remain inevitably separated. During the intraoperative period, EMI can lead to the activation of the anti-tachyarrhythmia function and/or to delivery of an

**Table 6.2** Most frequent sources of EMI with ICD during the intraoperative period

| Sources of EMI with ICD during intraoperative period |
|---|
| • Electrocautery (monopolar > > bipolar) |
| • Nerve stimulators |
| • Evoked potential monitors |
| • Fasciculations (succinylcholine) |
| • Electric shaving |
| • High tidal volumes |
| • Radiofrequency ablation |
| • Magnetic resonance imaging |
| • External defibrillation |
| • Lithotripsy |
| • Electroconvulsive therapy |

inappropriate electric shock. Total or partial inhibition of the pacemaker may occur, leading to cardiac arrest if the patient is pacemaker dependent (Table 6.2).

## 6.3 Indications and Benefits of ICD

The ICD has proven its efficiency in preventing sudden death: both in primary prevention, as in the case of sudden death post-myocardial infarction or consecutive to a nonischemic dilated cardiomyopathy, and in secondary prevention, for patients having already presented episodes of malignant arrhythmias [2–5].

### 6.3.1 Primary Prevention of Sudden Cardiac Death

In 2006 [4], update in 2015 [2], guidelines for the indications of ICD implantation were update from 2006, in the light of the publication of two large studies MADITII [9] and DINAMIT [10] in addition to one meta-analysis [11] considering all the ten studies published in the domain: MADIT I [12], CABG-Patch, MUSTT [13], MADIT II [9], CAT [14], AMIOVIRT [15], COMPANION [16], DEFINITE [17], SCD-HeFT [18], and DINAMIT [10].

A complete analysis of these data has allowed to define the indications for these devices [2–5]. Thus the patients who reaped the biggest benefit from the ICD in primary prevention are those who present a chronic left ventricular dysfunction at distance from an acute myocardial infarction or those within the context of a nonischemic dilated cardiomyopathy. Only four studies did not demonstrate the beneficial character of the ICD. The aforementioned studies, however [10, 14, 15], were carried out on a limited number of patients (CAT [14] and AMIOVIRT [15]) or in a context of recent myocardial infarction (between the 6th and the 40th day for DINAMIT [10]) or concerned implantations following coronary bypass surgery (CABG-Patch), a treatment which decreases considerably the relative risk of sudden death in the control groups.

On the other hand, the MADIT I [12] study carried out on a group of 196 patients in a context of ischemic heart disease and prior infarct with a left ventricular ejection fraction ≤35% highlighted a reduction in the annual mortality of 54% compared to the control group [12]. Coming from the same team, the MADIT II study concerning a larger sample size of 1232 patients, in a context of ischemic heart disorder with left ventricular ejection fraction ≤30% estimated at least 1 month after an infarct, reinforced these results with a reduction in annual mortality of 31% compared to the control group [9]. The MUSTT study, regarding a group of 704 patients, showed a reduction in mortality of 51% in the patients implanted in comparison to the control group which consisted of coronary patients for whom a ventricular hyper excitability could be medically treated without resort to a ICD [13]. The study COMPANION, concerning 1520 patients with ejection fraction ≤35%, 59% of whom were coronary, confirmed the advantage of the ICD with a reduction of 36% in the annual mortality when it was associated with a biventricular pacemaker compared to the patients

treated medically or by a biventricular resynchronization only [17]. Regarding the group with nonischemic dilated cardiomyopathy and a left ventricular ejection fraction ≤35%, the DEFINITE study concluded a decrease in the annual mortality of 35% [17]. The largest sample size came from the SCD-HeFT study with 2521 cases with cardiac insufficiency and a left ventricular ejection fraction ≤35% of ischemic etiology for 52% of the cases [18]. In this study, the reduction in the annual mortality with regard to the control group was 23%.

Finally, a meta-analysis which ensues from the analysis of these ten randomized studies concluded a relative reduction of 25% and an absolute reduction of 7.9% in the global mortality on a 2- to 4-year follow-up of the patients with a ICD [11].

In consequence, the recommendations concerning the implantation of ICD in primary prevention of sudden cardiac death put forward are: [2–5]

- The coronary patient with or without symptoms of cardiac insufficiency (NYHA II or III) with a left ventricular ejection fraction ≤30% estimated at least 40 days after an IDM and 3 months after surgical revascularization or angioplasty
- The coronary patient with left ventricular dysfunction (LVEF ≤35%) estimated at least 40 days after an infarct and 3 months after surgical revascularization or angioplasty presenting a triggerable ventricular arrhythmia (VT or VF)
- The patient presenting a seemingly primitive dilated heart disorder with left ventricular dysfunction (LVEF ≤30%) and symptomatic (NYHA II or III)
- The patients with documented ventricular fibrillation or hemodynamically not tolerated ventricular tachycardia in the absence of reversible causes or within 48 h after myocardial infarction who are receiving chronic optimal medical therapy and have a reasonable expectation of survival with a good functional status >1 year
- The patient with hypertrophic cardiomyopathy with an estimated 5-year risk of sudden death ≥6% and a life expectancy >1 year following detailed clinical assessment that takes into account the lifelong risk of complications and the impact of an ICD on lifestyle, socioeconomic status, and psychological health
- Cardiac amyloidosis, restrictive cardiomyopathy, and genetic disease at high risk of sudden death by ventricular fibrillation without any other known effective treatment

In patients with cardiac failure who remains symptomatic (NYHA III or IV) under optimal medical treatment, with left ventricular dysfunction (LVEF ≤35%) and duration of the QRS >120 ms, a biventricular pacemaker is recommended in association with the ICD for cardiac resynchronization.

### 6.3.2 Secondary Prevention of Sudden Cardiac Death

Secondary prevention by the ICD allowed a 27% reduction in the global mortality of the patients concerned [19]. Moreover, in the AVID study relating to 1016 patients having presented a cardiac arrest during a ventricular tachycardia or fibrillation, the

ICD resulted in a decrease in mortality, respectively, of 39, 27, and 31% at 12, 24, and 36 months, in comparison to the control group treated by amiodarone alone [20]. In the CIDS study, including 658 cardiac arrest survivors due to a ventricular tachycardia or fibrillation, the ICD tended to decrease, in a not significant way, the relative risk of mortality of 33% after 5 years in comparison to the control group benefiting from an anti-arrhythmic treatment by amiodarone alone [21]. The CASH study including also a limited group of 288 patients and realized according to the same protocol as the two previous studies concluded to a nonsignificant decrease in the mortality of 23% at 9 years in comparison to the groups treated medically by amiodarone or metoprolol alone [19]. Due to the restrained sample size, these two studies were not significant. A meta-analysis merging these three studies allowed to conclude significantly in a reduction of 27% in the global mortality of the ICD group and more particularly when left ventricular ejection fraction is ≤35%. The recommendations concerning the indications ICD implantation in secondary prevention of sudden death are as follows: [ 2–5]

- Cardiac arrest because of ventricular tachycardia or fibrillation without any acute or reversible cause such as a drug intoxication or an ischemic heart disorder with the possibility of revascularization
- Symptomatic spontaneous steady ventricular tachycardia, with or without a detectable cardiac anomaly, for which a medical treatment or an ablation cannot be realized or has failed
- Syncope of unknown cause with ventricular tachycardia or triggerable ventricular tachycardia, in the presence of an underlying cardiac anomaly (especially if the left ventricular ejection fraction is ≤35%)

## 6.4 Perioperative Management of the ICD

The objective of the active management of a patient with an ICD is to promote optimal conditions of safety and security by limiting the complications such as the inappropriate activation of the ICD or its incorrect deactivation in the event of ventricular arrhythmias.

The events specifically related to the ICD intraoperatively are the following: [4, 22]

- Damage to the generator or the leads
- Failure of defibrillation or an inappropriate shock
- Deregulation of the pacemaker associated with the ICD or of the defibrillator itself with electrical reset and default to a particular setting depending on the manufacturer and device with cancelation of the parameters specific to the patient

These events may obviously aggravate the morbidity and the mortality of such patients and furthermore may result in cancelation or delay of the surgery with resulting prolongation of the hospitalization and additional cost [5].

### 6.4.1 Preoperative Period

During the preoperative consultation, it is fundamental to appreciate any incident which may be connected to the malfunction of the ICD by noting the indication for device implantation, the device type, manufacturer and model, device response to magnet placement (mode of inhibition), and whether the patient is pacemaker dependent.

If no prospective study estimated the impact of an inadequate preoperative evaluation of an ICD, there are nevertheless a number of published case reports in which a deficient evaluation has resulted in intraoperative problems [4, 22]. During the preoperative consultation, it is thus essential to question the patient concerning the information on his ICD information card, device type and manufacturer, the current programming, and whether the patient is pacemaker dependent. If the patient is not capable of supplying the required informations, it is essential to contact the cardiac electrophysiologist in charge for adding this information clearly in the medical record.

Examination of the electrocardiogram may indicate the presence of a pacemaker and whether it is functional. The presence of a pacing spike preceding every complex would suggest that the patient is pacemaker dependent. A Valsalva maneuver can unmask the activity of a silent pacemaker during the bradycardia inferred by this operation. The response to magnet placement will allow distinction between a pacemaker and ICD. After application of a magnet, an asynchronous mode of pacing is manifest with a pacemaker (typically VOO), whereas the magnet will suspend arrhythmia detection in the ICD while leaving the pacemaker function intact. The chest X-ray may also be useful to demonstrate the presence of an ICD which is characterized by a right ventricular lead with thick radiopaque sections representing the high voltage coils. The lead configuration may distinguish between a single-chamber pacemaker and double-chamber pacemaker depending on the presence of leads in the right atrium and ventricle simultaneously, while a lead passing through the coronary sinus toward the left ventricular border will indicate a biventricular device for resynchronization.

### 6.4.2 Prevention of Electromagnetic Interferences (EMI)

Although much progress has made in terms of isolation, EMI can be interpreted by a pacemaker as intrinsic cardiac activity, especially when monopolar electrocautery is used in close proximity to ICD. To limit the EMI nuisance, it is recommended to use preferentially a bipolar cautery. Nevertheless, when unipolar electrocautery is used, it is recommended to place the dispersal patch so as to direct the current away from the pulse generator without passing through it. It is also recommended to use the electrocautery in a sequenced, irregular way and with the lowest possible intensity to limit the EMI. Whatever, the ICD anti-tachyarrhythmia or defibrillation functions should be turned off for the intraoperative period. There are two possibilities for this: first, preoperative ICD reprogramming by the electrophysiologist and, second, inhibition by a magnet applied to the ICD during

intraoperative period. In the case of reprogramming by the cardiac electrophysiologist, the patient must be equipped with an external defibrillator positioned in anterior-posterior configuration on the chest, as far as possible from the ICD generator. External defibrillator patches have to be positioned perpendicular to the ICD leads, for decreasing the risk of high voltage current in ICD leads, what would have the consequence of burning the myocardium due to the intensity of the shock—300 J as opposed to the usual 36 J delivered by ICD. The external defibrillator must be positioned before the reprogramming takes place and maintained until reactivation.

In the case of inhibition by application of a magnet, a safe and recognized method [5], the anti-tachyarrhythmia and cardioversion functions are suspended. When the magnet is applied in a continuous way, a tone coupled with the wave R testifies the inactivation of the device. On withdrawal of the magnet, these activities are restored. In case of intraoperative ventricular tachycardia or fibrillation episodes, the magnet can be removed from the case to obtain an internal electric shock. In parallel, as a safety precaution however, external defibrillator must always be set up as described above and prepared for immediate use. In addition, it is important to remember that if the application of the magnet inhibits of the ICD, associated pacemaker is not affected and will not pass to an asynchronous mode (VOO or AOO) as is the case for a patient with an isolated pacemaker. Thus if the patient is pacemaker dependent, this reprogramming must be carried out by an appropriate specialist with a device programmer before the beginning of the procedure [5, 22].

### 6.4.3 Intraoperative Management

Strict monitoring of the heart rate and rhythm of the patient with an ICD is crucial during the inoperative period. As the ECG may potentially be perturbed by EMI as well, supervision of the heart rhythm may be usefully carried out by the pulse oximeter or the arterial waveform if invasive arterial pressure monitoring is present [4, 5, 22]. The presence of EMI may lead to over sensing by the pacemaker with consequent inhibition of pacing. Limiting the duration of the applications of EMI may be effective; otherwise, magnet placement is imperative. In the case of ventricular fibrillation or tachycardia, the ICD may be reactivated rapidly by removal of the magnet. Otherwise external cardioversion may be used.

For anesthesia protocol by itself, anesthetic agents do not interfere with ICD. Apart from the electrocautery, other potential sources of EMI include fasciculation (suxamethonium), electric shaving in the proximity of the ICD generator, and high tidal volumes [5]. These elements should be avoided if possible.

### 6.4.4 Postoperative Management

The American recommendations suggest that all ICD should be verified by a electrophysiologist following a surgical operation [4]. By considering the increasing

number of patient implanted with this device (plan), it seems unreasonable to verify every ICD after the surgery, this especially as 77% of cardiac electrophysiologists consider that it is inequitable [4, 5]. Thus, ESC/ESA recommends to control the device only when there has been a nonadapted anti-tachyarrhythmia or defibrillation episodes or in case of evident dysfunction [5, 22]. In the case of administration of an external electric shock, the device will be systematically interrogated [5, 22].

Moreover certain consider as crucial to check the ICD after cardio-thoracic surgery when there is a risk of mobilisation of the lead tips [2].

### 6.4.5 Specific Conditions

In the case of radiofrequency, ICD should be inhibited, likewise for lithotripsy. Of course, magnetic resonance imaging is formally contraindicated.

## 6.5 Key Points in the Perioperative Management of the Patient with a CIED

### 6.5.1 Preoperative Period

The anesthetic consultation must determine systematically:

- Indication (primary or secondary prevention, associated cardiac insufficiency)
- Device type, manufacturer (Medtronic ®, Biotronik ®, Sorin ®, St Jude ®, Medico ®)
- Presence of a pacemaker with unipolar or bipolar leads
- Current programming mode of ICD and the pacemaker DDD, DDI, VVI, AAI
- Patient pacemaker dependent or not
- Systematic ECG

### 6.5.2 Intraoperative Period

- Preferably bipolar electrocautery or otherwise, if unipolar electrocautery is used, it is recommended to place the dispersal patch so as to direct the current away from the pulse generator without passing through it.
- Inhibition of the ICD by apposition of a magnet. The anti-tachyarrhythmia and fibrillation detection will be inactivated by magnet whereas the pacemaker function is not affected. Then, the pacemaker will not change to an asynchronous mode, and patient is exposed to low cardiac output in the case of EMI. Therefore, in case of pacemaker dependent, reprogramming must be performed by a cardiologist with a specific device programmer before performing the surgery.
- External defibrillator in position and functional
- Continuous monitoring of the pulse oximetry or blood pressure curve throughout the period of inhibition of the ICD, in the operating theater and ICU

- Prompt removal of the magnet or an external shock in the case of ventricular arrhythmias or fibrillation with cessation EMI
- Postoperative interrogation by the cardiologist in case nonadapted ICD activity, external defibrillation, or device dysfunction has occurred during intraoperative period.

**Conclusion**

Because of the exponential increase of the number of patients with ICD, the anesthesiologist is required to undertake the perioperative management of this population more and more frequently. Then, it is imperative for the physician to know the indications, the functioning, and, in addition, the means of preventing and treating the problems usually related to the presence of perioperative EMI. It must be understood that the management of the underlying cardiac pathology remains the main concern, with most of patients having left ventricular function less than 35%. A preoperative evaluation of the patient is crucial, the physician making the decision of reprogramming the device or to use a magnet application to inhibit it as appropriate. Then, the dependence or not to pacemaker function is crucial point to make the decision. Thus the patient can be managed in the conditions of security required.

**Key Points**

- With the exponential increase in the number of cardiac defibrillators implanted (ICD) in the last decade, the anesthesiologist is confronted more and more frequently with the management of these patients in the perioperative period.
- It is therefore imperative to understand the indications and the functioning of these devices in addition to predicting potential problems which may occur and their treatment and implications.
- In addition to the problems related to the defibrillator, it must be remembered that these patients require a thorough cardiac evaluation due to their underlying pathology.
- The defibrillator, like the pacemaker with which it is associated, is sensible to electromagnetic interferences (EMI) which should be limited as far as possible by the use of bipolar electrocautery.
- If unipolar electrocautery is used, it is recommended to place the dispersal patch at a distance from the ICD and in such a way as to prevent the electric arc passing through the generator.
- The anti-tachyarrhythmia and defibrillation functions of the ICD can be inactivated by application of a magnet on the device. Nevertheless, in the case of an associated pacemaker, the ICD will be inhibited by the magnet whereas the pacemaker function remains unchanged. It means the pacemaker will not change to an asynchronous mode. If the patient is pacemaker dependent, reprogramming must be carried out by a cardiac electrophysiologist with a device programmer.
- The defibrillator should be interrogated in the case of a nonadapted anti-tachyarrhythmia or defibrillation episode during intraoperative period or following an external choc or in case of any evident dysfunction.

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# What Every Anaesthetist Needs to Know About Respiratory and Cardiovascular Dynamics in Patients with Obesity or Intra-abdominal Hypertension

7

Manu LNG Malbrain, Claudia Olvera, and Adrian Regli

## 7.1 Introduction

Worldwide, the incidence of intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) is still underestimated by clinicians working in the emergency department (ED), operating room (OR) or intensive care unit (ICU). Increased intra-abdominal pressure (IAP) can have an immense impact on organ function, not only within but also outside the abdominal cavity including the brain, the cardiovascular system, and the lungs as summarised in Fig. 7.1. We will focus on cardiovascular and respiratory function as these are the closest monitored functions during surgery and anaesthesia. Respiratory failure can be defined as an imbalance between ventilatory capacity and ventilatory load. Whilst ventilatory capacity is mainly determined by respiratory drive, neuromuscular transmission and muscle strength, ventilatory load depends on minute volume, airway resistance and lung and chest wall compliance. Table 7.1 summarises the factors that affect chest wall compliance, IAP being one of the most important ones. In particular, because increased IAP affects the mechanical properties of the chest wall, it will

M.L. Malbrain, M.D., Ph.D. (✉)
Ziekenhuis Netwerk Antwerpen, ZNA Stuivenberg,
Lange Beeldekensstraat 267, B-2060 Antwerpen, Belgium

ICU Director, University Hospital Brussels (UZB), Jette, Belgium and Professor at Vrije Universiteit Brussel (VUB), Faculty of Medicine,
Brussels, Belgium
e-mail: manu.malbrain@telenet.be

C. Olvera, M.D.
The American British Cowdray Medical Center, Universidad Anahuac, Mexico City, Mexico
e-mail: claudia_olvera@me.com

A. Regli, M.D
Intensive Care Unit, Fiona Stanley Hospital, Murdoch Drive Murdoch, 6152, WA, Australia
e-mail: adrian.regli@gmail.com



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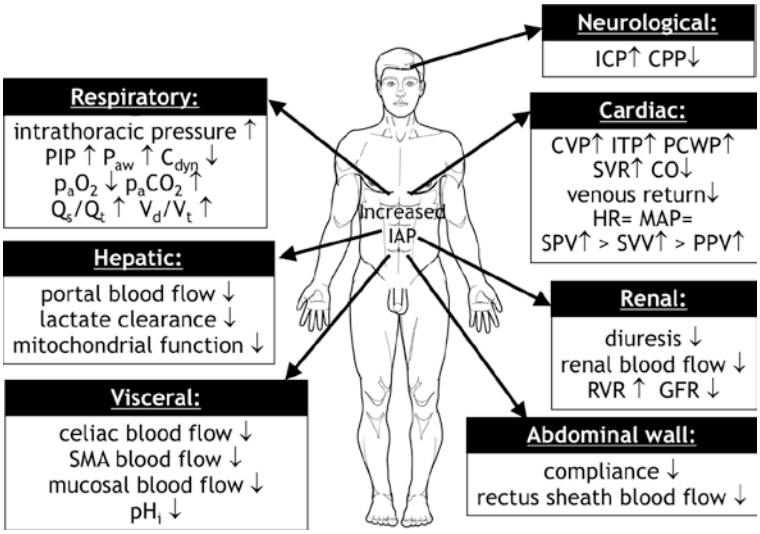


**Fig. 7.1** Summary of the most important pathophysiologic effects of increased intra-abdominal pressure on end-organ function within and outside the abdominal cavity. Figure legend: *Cdyn* Dynamic respiratory compliance, *CO* Cardiac output, *CPP* Cerebral perfusion pressure, *CVP* Central venous pressure, *GFR* Glomerular filtration rate, *HR* Heart rate, *ICP* Intracranial pressure, *ITP* Intrathoracic pressure, *MAP* Mean arterial pressure, *PIP* Peak inspiratory pressure, *Paw* Airway pressures, *PCWP* Pulmonary capillary wedge pressure, *pHi* Intramucosal gastric pH, *Qs/Qt* Shunt fraction, *RVR* Renal vascular resistance, *SMA* Superior mesenteric artery, *SVR* Systemic vascular resistance, *Vd/Vt* Dead space ventilation

**Table 7.1** Factors that affect chest wall compliance

| |
|---|
| • Pleural effusion |
| • Lung transplant |
| • Sternotomy (post-CABG) |
| • Obesity |
| • Ascites |
| • Fluid overload |
| • Rib fractures |
| • Abdominal distension |
| • Intra-abdominal hypertension (IAH) |
| • Abdominal compartment syndrome (ACS) |

consequently also affect the respiratory function in different conditions [1]. In this chapter, we will start by listing the consensus definitions on IAH and ACS, followed by the different effects of IAH and ACS on ventilator-induced lung injury (VILI), respiratory mechanics, lung recruitment manoeuvre, lung oedema and lymphatic function. Table 7.2 summarises the respiratory effects induced by IAH and ACS. Afterwards, we will discuss what every anaesthetist needs to know about the cardiovascular effects of IAH and ACS (Table 7.3). Finally, we will translate these findings into clinical management suggestions. After reading this chapter, the way you will look at and treat your patients in the ED, OR and ICU especially those with obesity and IAH will never be the same, but it will save lives.

**Table 7.2** Pulmonary effects of intra-abdominal hypertension and abdominal compartment syndrome. Adapted from Pelosi et al. [1]

| Pulmonary effects related to increased IAP |
|---|
| Diaphragm elevation ↑ |
| Intrathoracic pressure ↑ |
| Pleural pressure ↑ |
| Peak airway pressure ↑ (volume-controlled MV) |
| Mean airway pressure ↑ |
| Plateau airway pressure ↑ |
| Functional residual capacity (FRC) ↓ |
| All lung volumes (TLC, TV, etc.) ↓ (~restrictive disease) |
| Extrinsic compression lung parenchyma ↑ |
| Auto-PEEP ↑ |
| Compression atelectasis ↑ |
| Pulmonary vascular resistance ↑ |
| Alveolar baro−/volutrauma = ↑ |
| Compliance ↓ |
| Respiratory system compliance ↓ |
| Chest wall compliance ↓↓ |
| Lung compliance = |
| Upper inflection point on PV curve ↓ |
| Lower inflection point on PV curve ↑ |
| Hypercarbia—$pCO_2$ retention ↑ |
| $PaO_2$ ↓ and $PaO_2/FiO_2$ ↓ |
| Alveolar oxygen tension ↓ |
| Oxygen transport ↓ |
| Dead space ventilation ↑ |
| Intrapulmonary shunt ↑ |
| Ventilation perfusion mismatch ↑ |
| Ventilation diffusion mismatch ↑↑ |
| Oxygen consumption ↑ |
| Metabolic cost and work of breathing ↑ |
| Alveolar oedema ↑ |
| Extravascular lung water (EVLW) = ↗ |
| Pulmonary vascular permeability index (PVPI) = ↗ |
| Prolonged ventilation |
| Difficult weaning |
| Activated lung neutrophils (experimental) ↑ |
| Pulmonary inflammatory infiltration (experimental) ↑ |
| Pulmonary infection rate (experimental) ↑ |

**Table 7.3** Cardiovascular effects of intra-abdominal hypertension and abdominal compartment syndrome. Adapted from Malbrain et al. [2]

| Cardiovascular effects related to increased IAP[a] |
|---|
| Diaphragm elevation and cardiac compression ↑ |
| Pleural and intrathoracic pressure (ITP) ↑ |
| Difficult preload assessment |
| Pulmonary capillary wedge pressure (PCWP) ↑ |
| Central venous pressure (CVP) ↑ |
| Mean systemic filling pressure ↑ |
| Transmural filling pressure = ↘ |
| Intrathoracic blood volume (ITBV) = ↘ |
| Global end-diastolic volume (GEDV) = ↘ |
| Right ventricular end-diastolic volume (RVEDV) = ↘ |
| Right, global and left ventricular ejection fraction = ↘ |
| Extravascular lung water (EVLW) = ↗ |
| Stroke volume variation (SVV) ↗ |
| Pulse pressure variation (PPV) ↗ |
| Systolic pressure variation (SPV) ↗ (Δdown =, Δup ↑) |
| Inferior vena caval flow ↓ |
| Venous return ↓ |
| Left ventricular compliance and contractility ↓ |
| Downward and rightward shift of Frank-Starling curve |
| Cardiac output ↓ |
| Systemic vascular resistance (SVR) ↑ |
| Mean arterial pressure (MAP) ↗ = ↘ |
| Pulmonary artery pressure (PAP) ↑ |
| Pulmonary vascular resistance (PVR) ↑ |
| Heart rate ↗ = |
| Lower extremity hydrostatic venous pressure ↑ |
| Venous stasis, oedema, ulcers ↑ |
| Venous thrombosis ↑ |
| Pulmonary embolism[b] ↑ |
| Mixed venous oxygen saturation ↓ |
| Central venous oxygen saturation ↓ |
| False negative passive leg raising test ↑ |
| Functional haemodynamic thresholds for fluid responsiveness ↑ |

[a]Cardiovascular effects are exacerbated in case of hypovolaemia, haemorrhage, ischaemia, auto-PEEP or high PEEP ventilation
[b]Upon decompression

## 7.2 Epidemiology

Around one in four patients will have signs and symptoms of IAH on ICU admission, whilst around one out of two will develop IAH within the first week of ICU stay [3]. Moreover, 1 in 20 patients will develop overt ACS, a lethal syndrome with a mortality rate above 75% when left untreated [4]. To this day, patients may have unrecognised IAH. The major risk factors of IAH include abdominal surgery, surgery performed in the emergency setting, severe poly-trauma, abdominal trauma, severe haemorrhagic shock, severe burns, severe acute pancreatitis, large volume fluid resuscitation (especially crystalloid) resulting in fluid overload, ileus and liver dysfunction [5].

## 7.3 Consensus Definitions

Recently the World Society of the Abdominal Compartment Syndrome (WSACS) changed its name into the Abdominal Compartment Society (www.wsacs.org) [6]. As the focus concerning ACS becomes less paramount as it becomes less frequent, it became even more apparent that the actual name of the Society was limiting in terms of reflecting the true breadth and depth of the Society's mission. The ACS emphasises the most dramatic condition to be addressed, but it does not reflect upon the full scope of the Society's interests and activities [6]. In order to reflect the evolving science and to embrace important concepts related to abdominal wall anatomy and function, the focus was broadened from ACS to formally appreciating the abdominal compartment as a whole within all the body's interrelated compartments [6]. Hereby follows a short list of the latest consensus definitions as formulated by the WSACS, the Abdominal Compartment Society [7].

*Definition 1: Intra-abdominal pressure* IAP is the steady-state pressure concealed within the abdominal cavity.

*Definition 2: Abdominal perfusion pressure* In analogy to cerebral perfusion pressure, abdominal perfusion pressure (APP) is defined as mean arterial pressure (MAP) minus IAP.

*Definition 3: IAP measurement* IAP should be expressed in mmHg and measured at end expiration in the complete supine position after ensuring that abdominal muscle contractions are absent and with the transducer zeroed at the level where the mid-axillary line crosses the iliac crest.

*Definition 4: Gold standard IAP measurement method* The reference standard for intermittent IAP measurements is via the bladder with a maximal instillation volume of 25 mL of sterile saline.

- Paediatric-specific definition: The reference standard for intermittent IAP measurement in children is via the bladder using 1 mL/kg as an instillation volume, with a minimal instillation volume of 3 mL and a maximum installation volume of 25 mL of sterile saline.

*Definition 5: Normal IAP* Normal IAP is approximately 5–7 mmHg and around 10 mmHg in critically ill adults.

- Paediatric-specific definition: IAP in critically ill children is approximately 4–10 mmHg.

*Definition 6: Intra-abdominal hypertension* IAH is defined by a sustained or repeated pathologic elevation of IAP ≥12 mmHg.

- Paediatric-specific definition: IAH in children is defined by a sustained or repeated pathological elevation in IAP >10 mmHg.

*Definition 7: IAH grading* IAH is graded as follows:

- Grade I: IAP 12–15 mmHg
- Grade II: IAP 16–20 mmHg
- Grade III: IAP 21–25 mmHg
- Grade IV: IAP >25 mmHg

*Definition 8: Abdominal compartment syndrome* ACS is defined as a sustained increased IAP ≥20 mmHg (with or without an APP <60 mmHg) that is associated with new organ dysfunction or failure.

- Paediatric-specific definition: ACS in children is defined as a sustained elevation in IAP of greater than 10 mmHg associated with new or worsening organ dysfunction that can be attributed to elevated IAP.

*Definition 9: Primary IAH/ACS* Primary IAH/ACS (formerly also known as surgical or abdominal) is a condition associated with injury or disease in the abdomino-pelvic region that frequently requires early surgical or interventional radiological intervention.

*Definition 10: Secondary IAH/ACS* Secondary IAH/ACS (formerly also known as medical or extra-abdominal) refers to conditions that do not originate from the abdomino-pelvic region.

*Definition 11: Recurrent IAH/ACS* Recurrent IAH/ACS (formerly also known as tertiary) refers to the condition in which IAH/ACS redevelops following previous surgical or medical treatment of primary or secondary IAH/ACS.

*Definition 12: Polycompartment syndrome* A polycompartment syndrome is a condition where two or more anatomical compartments have elevated compartmental pressures. This will be discussed further.

*Definition 13: Abdominal compliance* Abdominal compliance ($C_{ab}$) quantifies the ease of abdominal expansion and is determined by the elasticity of the abdominal wall and diaphragm. $C_{ab}$ is expressed as the change in intra-abdominal volume per change in intra-abdominal pressure in L/mmHg.

*Definition 14: Open abdomen* An open abdomen (OA) is any abdomen requiring a temporary abdominal closure (TAC) due to the skin and fascia not being closed after laparotomy. The technique of temporary abdominal closure should be explicitly described.

*Definition 15: Open abdomen classification* The open abdomen is classified with the following grading system:

1—No fixation.
- 1A: Clean, no fixation.
- 1B: Contaminated, no fixation.
- 1C: Enteric leak, no fixation.

2—Developing fixation.
- 2A: Clean, developing fixation.
- 2B: Contaminated, developing fixation.
- 2C: Entero-atmospheric/cutaneous fistula, developing fixation.

3 and 4—Frozen abdomen.
- 3: Frozen abdomen, no fistula.
- 4: Frozen abdomen with entero-atmospheric/cutaneous fistula.

*Definition 16: Lateralization* Lateralization of the abdominal wall refers to the phenomenon whereby the musculature and fascia of the abdominal wall, most well seen by the rectus abdominis muscles and their enveloping fascia, move laterally away from the midline with time.

## 7.4 Effects of Intra-abdominal Hypertension on Respiratory Mechanics

### 7.4.1 Intra-abdominal Hypertension and Ventilator-Induced Lung Injury (VILI)

Animal studies have shown that increasing IAP during mechanical ventilation may result in cytokine release and subsequent lung injury. Rezende-Neto et al. showed in a study of 50 rats that 60–90 min of IAH (IAP of 20 mmHg via insufflated

intraperitoneal air) resulted in increased plasma levels of IL-6, increased polymorphonuclear leucocyte activity in the lungs as evaluated by myeloperoxidase (MPO) assay [8].and intense pulmonary inflammatory infiltration including atelectasis and alveolar oedema on lung histology. Schachtrupp et al. showed in a study of 12 pigs that 24 hours of IAH (IAP of 30 mmHg) also resulted in histological findings similar to those found in VILI (interstitial and alveolar leucocytes and fibrin) but also proximal tubular necrosis in the kidneys and paracentral necrosis in the liver [9]. Since the strain on lung structures leading to VILI depends on transpulmonary pressure, it is not unreasonable to imagine that the frequently used relative too low transpulmonary pressures in the context of IAH will cause shear stress with increased repetitive opening and closing of alveoli units.

### 7.4.2 Effect of Intra-abdominal Hypertension on Respiratory Mechanics

As stated above lung distension is in part regulated by chest wall mechanics. The stiffer the chest wall, the less lung distension will occur during mechanical ventilation for a given airway pressure. In a Chinese study of 16 patients undergoing decompressive laparotomy (DL), different lung volumes were calculated with computed tomography (CT) at baseline, before and after DL. Compared to controls ($n$ = 6), patients ($n$ = 16) had lower total lung and higher non-aerated lung volumes [10]. This is illustrated in Fig. 7.2. Whereas chest wall elastance accounts in normal conditions for only 15% of the total respiratory system elastance, this number may increase up to 50% during IAH with IAP above 20 mmHg (due to the stiffening of the chest

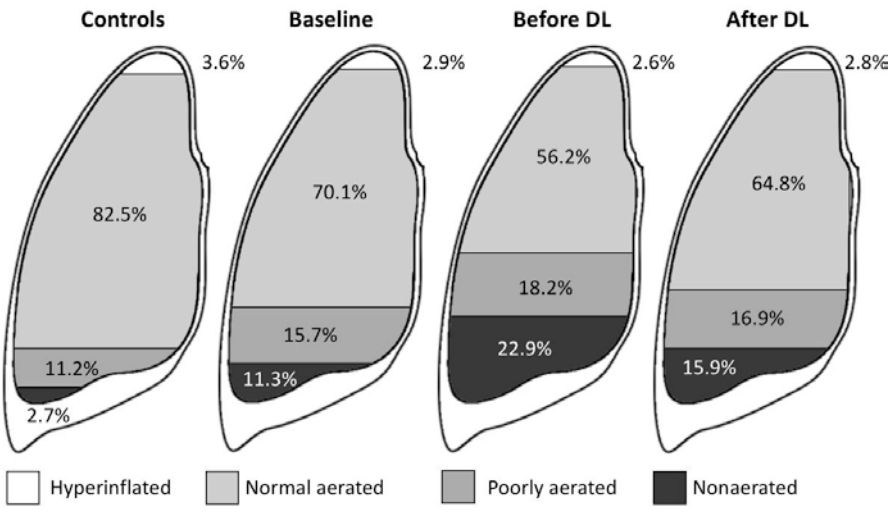


**Fig. 7.2** Effect of abdominal hypertension and decompressive laparotomy on total lung volumes expressed percentages of different aerated lung volumes. Adapted from Zhou et al. [10]

wall). According to the polycompartment model (as will be discussed further down), IAH can increase intrathoracic pressure (ITP) and subsequently increase alveolar pressures [11]. We previously showed in a pig study ($n = 11$) that IAH up to 30 mmHg (with abdominal saline infusion intraperitoneally) resulted in an abdomino-thoracic transmission index (ATI) between 17% and 62% when looking at end-expiratory vs end-inspiratory oesophageal pressures, respectively [12]. With increasing IAP, both total respiratory system ($C_{RS}$) and chest wall ($C_{CW}$) compliance decreased significantly. The decrease was more pronounced for the chest wall and showed a strong inverse correlation with IAP ($r = -0.84$, $p < 0.0001$). A pilot study in 14 mechanically ventilated patients with acute lung injury (ALI) showed that the application of an abdominal Velcro belt increased IAP from 8.6 to 15.4 mmHg with a concomitant increase in alveolar plateau pressures (Pplat) from 18 to 23.3 $cmH_2O$ (data on file). These changes were paralleled by a decrease in dynamic respiratory compliance from 37 to 28 $mL/cmH_2O$. This probably explains why the suggested lung-protective ventilation strategies are difficult to apply in patients with IAH or those with diminished chest wall compliance like in morbid obesity. Previous animal and human 'PV curve' studies focusing on the importance of IAH showed that abdominal and subsequently chest wall compliance improves after abdominal decompression [13, 14].

Acute respiratory distress syndrome (ARDS) is a syndrome and not a disease, and as a consequence, not all ARDS patients are the same which may be a possible explanation why there are conflicting results in previous ARDS studies. Ranieri et al. found that patients with ARDS had different respiratory mechanics depending upon the underlying aetiology and the presence of IAH. He found that surgical patients had stiffer chest walls compared to medical patients, probably due to the increased presence of abdominal distension [13]. Respiratory system and chest wall compliance improved after DL in these patients. Unfortunately, the effect of positive end-expiratory pressure (PEEP), forced residual capacity (FRC) and IAP was not measured. Mergoni and colleagues studied respiratory system mechanics partitioned between the lung and chest wall and showed that in a subgroup of ARDS patients in which the lower inflection point (LIP) was mainly determined by chest wall ($C_{CW}$) PEEP was not as effective in improving $pO_2$ [15]. In contrast, in ARDS patients in which LIP was determined by the lung compliance ($C_L$), PEEP was effective.

These findings are somewhat in contradiction with those found by Gattinoni and co-workers, and this can in part be explained by the difference in measurement manoeuvres and techniques as well as the assumptions used [16]. Gattinoni showed that the localised character of parenchymal involvement in primary ARDS (with primary lung involvement, e.g. pneumonia) resulted in decreased lung but normal chest wall compliance, whilst secondary ARDS (mainly as a result of abdominal sepsis) presented with preserved lung but decreased chest wall compliance, and PEEP allows to recruit lung units markedly only in secondary but not in primary ARDS [16]. The results imply that the application of PEEP in pulmonary ARDS may cause over-distension of already open lung units, making these patients more prone to ventilator-induced lung injury (VILI) than patients with extrapulmonary ARDS and IAH. The same phenomenon may be responsible for the change in respiratory mechanics seen in morbidly obese patients [17]. Measuring IAP may therefore provide an easy bedside method to

estimate altered chest wall mechanics and avert the need to measure oesophageal pressure (as surrogate for ITP). Measuring oesophageal pressure is not easy due to some practical problems at the bedside [1]. IAP also influences the shape of the PV curve (with downward flattening and rightward shifting) of the total respiratory system and the chest wall, whilst the lung mechanics basically remain unaffected [18].

### 7.4.3 Effect of Intra-abdominal Hypertension on Lung Recruitment

The most frequent performed recruitment manoeuvre is a 40-by-40 manoeuvre (40 s holding 40 cmH2O inspiratory pressure). It is estimated that transpulmonary opening pressure equal to 30 $cmH_2O$ is required to open atelectasis. In the setting of IAH with altered $C_L/C_{RS}$ ratio from 0.85 to 0.5, the resulting transpulmonary pressure during a 40-by-40 recruitment manoeuvre may only be 20 $cmH_2O$; hence, the alveolar units with long-time constants would remain collapsed [19]. Therefore in the setting of IAH, higher opening pressures closer to 40 $cmH_2O$ + IAP/2 may be required [20]. Lung-protective ventilation implies opening the lungs (with a recruitment manoeuvre or thus peak alveolar pressures) and keeping the lungs open (with appropriate PEEP setting) [21]. The altered lung mechanics and the different recruitment manoeuvres needed in IAH have also an impact on lung-protective ventilation (limiting Pplat below 30 $cmH_2O$) as this will result in very low tidal volumes (TV) in the setting of IAH or ACS. Therefore, Pplat should be limited towards a maximal peak alveolar pressure of '30 $cmH_2O$ + IAP/2', or stated otherwise, transpulmonary Pplat calculated as Pplat—IAP/2 should be kept below 30 (to 35) $cmH_2O$. This statement is supported by the fact that Talmor and co-workers found that IAP (e.g. measured via the stomach) and oesophageal pressure (e.g. measured via an oesophageal balloon) are closely correlated [22]. Therefore, not only opening pressures but also closing pressures are increased during IAH and ACS and as such higher PEEP levels are required to prevent end-expiratory lung collapse. Keeping the lungs open is equally important after a recruitment manoeuvre to avoid shear stress of opening and closing lung units that may induce VILI. As a rule of thumb, PEEP (in $cmH_2O$) can be set equal to IAP (in mmHg). This assumption takes into account the fact that the ATI is not 100% as the conversion factor from mmHg to $cmH_2O$ is 1.36. Some experimental data suggested the use of higher TVs around 10 mL/kg (as compared to 6 mL/kg) in IAH/ACS, but this strategy cannot be recommended yet in patients [23].

### 7.4.4 Effect of Intra-abdominal Hypertension on Lung Oedema and Lymphatic Drainage

A landmark paper by Quintel and co-workers showed that IAH causes an increase in lung oedema in a pig model of acute lung injury (induced by oleic acid) [18]. When IAP was increased from 0 to 20 $cmH_2O$, lung oedema distribution changed from the dorsobasal regions to the complete lung. In keeping with this, Schachtrupp showed an increase in extravascular lung water (EVLW) in and histological lung alterations

at IAP levels of 30 $cmH_2O$ [24, 25]. An epidemiologic study in humans also found a correlation between IAP, fluid balance and EVLW in patients with acute lung injury, suggesting a link between sepsis, capillary leak, fluid overload, abdominal hypertension and lung oedema [26]. This may explain why active fluid removal or so-called de-resuscitation with PAL treatment (PEEP in $cmH_2O$ set at the level of IAP in mmHg, followed by hyperoncotic albumin 20% and Lasix®) was able to reduce IAP and EVLWI in a pilot study of 57 patients matched with historical controls [27, 28].

Fluid drainage from the lungs can take place via three mechanisms: transpleural, via the lung hilum or transabdominal [29]. The effects of different ventilatory settings and increasing IAP on thoracic and abdominal lymph flow were studied in a porcine endotoxin sepsis model [30]. The study was performed in three parts and data were collected from a total of 32 pigs. In summary the authors found that lipopolysaccharide infusion increased IAP and lymphatic flow, that PEEP increased IAP and lymph production but impeded lymphatic drainage across the diaphragm, that spontaneous breathing improved transdiaphragmatic lymph drainage and finally that increased IAP diminished lymphatic flow. Although often overlooked, the role of lymphatic flow is complex but very important to determine not only the fluid balance in the lung but also in the peripheral organs [31]. Different pathologies and treatments can markedly influence the pathophysiology of the lymphatics with dramatic effects on end-organ function.

## 7.5 Effects of Intra-abdominal Hypertension on Cardiovascular Dynamics

### 7.5.1 Effect of Intra-abdominal Hypertension on Cardiac Contractility

Diaphragmatic elevation and increased ITP exert direct mechanic effects on cardiac contractility. This will be accompanied by an increase in pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) with a simultaneous decrease in left ventricular preload, finally leading to a decrease in cardiac output (CO). Animal studies have demonstrated a rightward and downward shift of the Frank-Starling curve in a dog model of IAH up to 40 mmHg created with fluid infusion in the peritoneal cavity [32]. Left ventricle wall motion assessment with trans-oesophageal echocardiography showed a significant decrease at the level of the anteroseptal wall in eight children during laparoscopic herniorraphy (with IAP levels of only 12 mmHg) [33]. Increases in central venous pressure (CVP) and IAP have also been observed in patients with congestive heart failure developing acute renal failure [34]. Whilst initially responsive to fluid loading and inotropic (dobutamine but not dopamine) support at lower levels of IAH, the deleterious cardiovascular effects in patients with ACS can only be effectively treated by nonoperative measures to reduce IAP or abdominal decompression. The APP seems a promising target to guide resuscitation in combination with less invasive haemodynamic monitoring like the transpulmonary thermodilution technique. After induction of IAH via pneumoperitoneum in ten pigs, an increase in CO following fluid loading was only indicated by calibrated CO but not by uncalibrated continuous CO methods using arterial waveform analysis [35].

### 7.5.2 Effect of Intra-abdominal Hypertension on Cardiac Preload

As described above, increased IAP causes a concomitant increase in ITP (via the ATI) and diaphragm elevation. This will result in direct compression of the heart and the vascular structures within the thorax. Vascular compression reduces the flow in the inferior vena cava (IVC) limiting blood return from below the diaphragm in a pressure-dependent manner (Fig. 7.3). When IAP increases, the cranial deviation of the diaphragm compresses and narrows the IVC where it enters the diaphragm, further reducing venous return (already at IAP levels of 10 mmHg) [2]. The resulting reduced venous return has an immediate effect on CO through decreased stroke volume. Since barometric filling pressures are zeroed against atmospheric pressure, they will be erroneously increased in patients with IAH and ACS because the elevated ITP is directly transmitted to the intravascular pressures like the central venous (CVP) and pulmonary capillary wedge pressure (PCWP), making (barometric) preload assessment difficult [36]. Mean systemic filling pressure may also increase during IAH explaining the marked susceptibility to pulmonary oedema, even minimal volume administration [37]. Finally, mixed venous and central venous oxygen saturation may fall.

### 7.5.3 Effect of Intra-abdominal Hypertension on Cardiac Afterload

As explained above (and as illustrated in Fig. 7.3), IAP can increase systemic and pulmonary vascular resistance via compression of the aorta, systemic and pulmonary vasculature, mesenteric splanchnic pool and pulmonary parenchyma. Accompanying

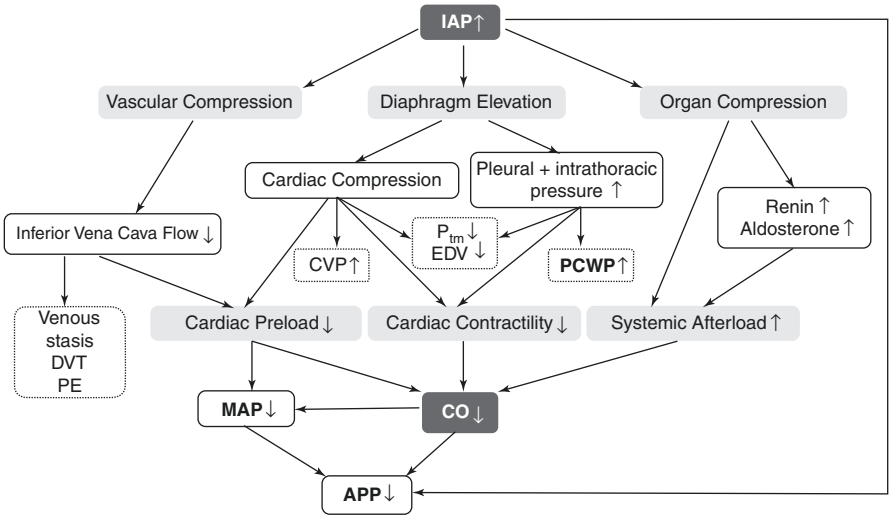


**Fig. 7.3** Cardiovascular effects on preload, afterload and contractility related to increased intra-abdominal pressure. Adapted from Malbrain et al. [2]. Figure legend: *APP* Abdominal perfusion pressure, *CO* Cardiac output, *CVP* Central venous pressure, *DVT* Deep vein thrombosis, *EDV* End-diastolic volume, *IAP* Intra-abdominal pressure, *MAP* Mean arterial pressure, *PCWP* Pulmonary capillary wedge pressure, *PE* Pulmonary embolism, $P_{tm}$ Transmural pressure

alterations in the renin-angiotensin-aldosterone mechanism have also been described [38]. The increased afterload also compensates for the reduced venous return. As a result of this physiologic compensation, MAP typically remains stable in the early stages of IAH and ACS. The cardiovascular effects are poorly tolerated in patients with impaired contractility, systemic underfilling or mechanical ventilation with high PEEP levels.

### 7.5.4 Effect of Intra-abdominal Hypertension on Functional Haemodynamics

Experimental data has shown that increased IAP resulting in increased ITP (ATI around 50%) will also increase functional haemodynamic parameters like stroke volume variation (SVV), pulse pressure variation (PPV) or systolic pressure variation (SPV) by exerting pressure on the thoracic vessels. This means that our usual thresholds (of 12–15%) defining fluid responsiveness may need to be changed in the setting of IAH or ACS. In fact, a summary of previous animal reports concludes that an increase in IAP up to 20 mmHg almost doubles the values of SVV and PPV suggesting thresholds around 24–30% to identify a fluid responder [39]. The increase in SPV seen during IAH is most likely a $\Delta_{up}$ phenomenon rather than a $\Delta_{down}$ phenomenon (Fig. 7.4), only the latter being correlated with fluid responsiveness [40].

## 7.6 Practical Implications at the Bedside

### 7.6.1 ARDS Definitions

In view of the above-cited clear differences between pulmonary and extrapulmonary ARDS, the current Berlin definition is inappropriate at the bedside for several reasons [41]. First, chest radiography has several limitations in mechanically ventilated patients in supine position as it lacks sensitivity and specificity to detect

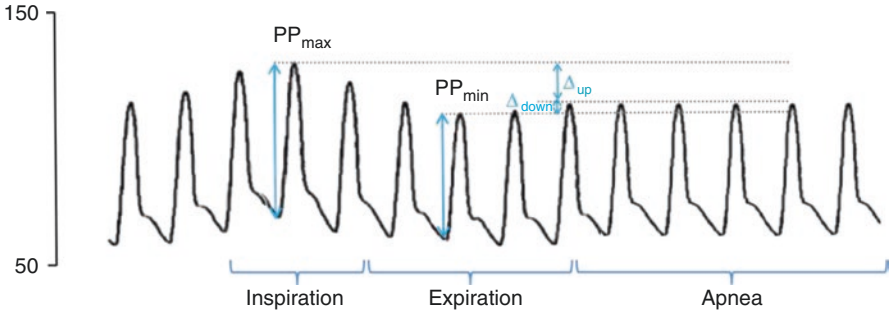


**Fig. 7.4** Effects of abdominal hypertension on pulse and systolic pressure variations. Increased pulse (PPV) and systolic pressure variations (*SPV*) in a patient with IAP of 18 mmHg. The PPV can be calculated as $[(PP_{max} - PP_{min})/PP_{mean}] \times 100$ (%). After an apnoea test, it becomes clear that the increased SPV and PPV seen on the monitor are mainly related to a $\Delta_{up}$ phenomenon as only a smaller portion is caused by $\Delta_{down}$. This means that the increased PPV and SPV are not necessarily correlated to fluid responsiveness and higher thresholds are probably needed

**Table 7.4** A new definition for acute lung injury and ARDS, adapted from Michard et al. [45]

| |
|---|
| 1. A pulmonary disease process known to increase pulmonary vascular permeability (normal IAP) |
| (a) Viral or bacterial pneumonia |
| (b) Gastric or smoke inhalation |
| (c) Etc. |
| Or |
| 2. An extrapulmonary disease process known to increase pulmonary vascular permeability (increased IAP >12 mmHg) |
| (a) Chest trauma and/or poly-trauma and/or polytransfusion |
| (b) Pancreatitis or severe burns or severe sepsis or septic shock |
| (c) Etc. |
| With |
| 3. Evidence for lung oedema |
| (a) Bilateral pulmonary infiltrates on chest radiography (with exclusion of pleural effusion or atelectasis) |
| (b) EVLWI >10 ml/kg PBW |
| (c) PVPI >2.5 |
| (d) Bilateral consolidations on chest CT scan |
| And |
| 4. The need for: |
| (a) FiO2 between 0.4 and 0.6 to maintain $S_aO_2 > 95\%$ (ALI) |
| (b) FiO2 > 0.6 to maintain $S_aO_2 > 95\%$ (ARDS) |
| (c) Regardless of PEEP level |

pulmonary oedema [42] and may be mistaken with pleural effusions that are not necessarily related to increased EVLW [43]. Second, it is well established that the $PaO_2/F_iO_2$ ratio depends on $F_iO_2$, the relationship between the numerator and the denominator being non-linear. Moreover, this ratio also depends on the level of PEEP used. Third, as mentioned above, the definition also does not take into account the differences that may exist between primary and secondary ALI/ARDS and the role of IAP [26]. Finally, the evidence for cardiac dysfunction does not imply causality as patients with chronic cardiac diseases have an abnormal cardiac function on echocardiography also when they develop lung injury [44]. Therefore, the existence of a disease known to increase pulmonary vascular permeability seems more important than the lack of left ventricular dysfunction in order to accurately diagnose ALI/ARDS. Table 7.4 suggests a possible new ARDS definition [45].

### 7.6.2 Polycompartment Syndrome (PCS)

The abdominal compartment has unique effects because it is geographically situated ‘upstream’ from the extremities and ‘downstream’ from the thorax and the cranium [11]. Therefore, IAH and ACS may influence the physiology and pathophysiology of each of these other compartments. The presence of a compartment syndrome often plays a role when we are dealing with a therapeutic conflict, which is a dilemma

where each of the possible therapeutic decisions carries potential harm, e.g. the decision about fluid administration in particular should be done within this context in patients with ACS and haemodynamic instability accompanied with increased EVLW. Because the abdomen plays a major role in the interactions between different compartments, IAP affects portal and hepatic vein pressure hence facilitating blood shunting away from the lungs. This can be referred to as hepato-abdominal-pulmonary syndrome (HAPS) [11]. Similarly, IAP has also recently been identified as the missing link triggering renal failure (via increased renal vein pressures) in patients with chronic congestive heart disease, referred to as CARS or cardio-abdominal-renal syndrome [46]. Likewise deteriorating kidney function in patients with liver cirrhosis may be referred to as HARS or hepato-abdominal-renal syndrome.

### 7.6.3 Obese Patients

Studies have shown that obese patients with a body mass index higher than 35–40 kg/m$^2$ have higher IAP values compared to nonobese patients [47, 48]. Similarly to patients with IAH and ACS, the increased IAP values seen in obese patients will equally result in impairment in respiratory mechanics and gas exchange and decreased lung volumes particularly during sedation, paralysis and mechanical ventilation. As a consequence, the mechanical load exerted on the diaphragm is increased, especially in the supine position both during spontaneous breathing and general anaesthesia [1].

## 7.7 Respiratory Management in Intra-abdominal Hypertension: Hints and Tips

### 7.7.1 Recruitment

As stated above, in order to recruit the lung in IAH/ACS, higher than usual opening pressures are needed. As a rule of thumb, a 40 plus IAP/2-by-40 manoeuvre may be required. In fact, the transpulmonary peak pressure will open the lungs, and the higher the IAP, the lower the chest wall compliance and thus the higher the opening pressure (whilst transpulmonary opening pressure will remain unaffected).

### 7.7.2 Ventilator Settings During Lung-Protective Ventilation

Lung-protective ventilation is ideally set below Pplat 30 cm$H_2O$. In the context of IAH, higher Pplat may be required. When using an oesophageal balloon, lung-protective ventilation can be set targeting transpulmonary Pplat below <30 (to 35) cm$H_2O$. The application of PEEP by itself may increase IAP at the level of the diaphragm but only if PEEP is significantly higher than IAP. In a study of 30 patients with ALI/ARDS, the application of moderate PEEP of 12 cm$H_2O$ resulted in a 3 mmHg increase in IAP [49], the effects being more pronounced in patients with underlying IAH. A recent review summarising different studies looking at the effects of PEEP on IAP found an average increase in IAP with 1.5 mmHg for a PEEP setting of 15 cm$H_2O$ [47]. As

discussed previously, recent experimental data suggests the possibility for using a higher TV in IAH/ACS; however, to date, there is no hard human data to support this statement, and moreover this may be potentially dangerous [23].

### 7.7.3 Best PEEP

To date, the best PEEP in the setting of patients with IAH is largely unknown. As stated above, in IAH/ACS, the lung will collapse at higher closing pressures during expiration. As a rule of thumb, PEEP ($cmH_2O$) can be set at the level of IAP (mmHg) to prevent end-expiratory lung collapse. Different animal and scarce human data have looked into this hypothesis. A first study was conducted in 13 pigs with healthy lungs, and IAH was created with an inflatable balloon; the PEEP levels (5, 8, 12 and 15 $cmH_2O$) were unmatched to the level of IAP [50]. The conclusions were that commonly applied PEEP levels, set below the IAP level, cannot prevent FRC decline. Noteworthy was that IAP reached 18 mmHg or thus 25 $cmH_2O$, whilst PEEP was only set up to a maximum of 15 $cmH_2O$. In a second study, conducted in nine pigs with healthy lungs, IAH was again created with an inflatable balloon, and the PEEP levels were now matched for IAP [51]. The authors found a preservation of end-expiratory lung volume (EELV) without improvement in arterial oxygen tension but with a reduction in CO. In a third study, conducted in eight pigs with ALI induced by saline lavage and IAH created with $CO_2$ insufflation up to 20 mmHg, the PEEP levels (27 $cmH_2O$) were matched for IAP [52]. The major findings during PEEP application were lower LIP (reversal of shifting of PV curve to right with flattening), improved compliance and decreased $D(A\text{-}a)O_2$ (less shunt). In a fourth animal study in nine pigs, IAH induced by an inflatable balloon was combined with oleic acid-induced lung injury, and PEEP levels were matched to IAP [53]. The authors found better EELV, lower shunt fraction, lower dead space and a better P/F ratio. So far only one human study looked at 20 patients with ALI/ARDS with normal IAP or grade II IAH treated in the surgical ICU. There was no difference in oxygenation; however, EVLW was decreased in ALI/ARDS patients with IAH and high PEEP. The authors observed a decreased elastance of the respiratory system and the lung at PEEP of 15 $cmH_2O$. There were however many limitations: the numbers were small as only two times ten patients were included (underpowered), the values of IAP were relatively low (16 vs 8 mmHg) and there was no real matching between PEEP and IAP.

### 7.7.4 Prone and Other Positioning

Placing ARDS patients in the prone or upright position does not result in univocal beneficial effects on respiratory mechanics and oxygenation parameters [54]. Mure and co-workers demonstrated in an interesting animal model that the prone position improves pulmonary gas exchange to a greater degree in the presence of IAH as shown by increases in $PaO_2$ and decreases in $D(A\text{-}a)O_2$ and V/Q heterogeneity [55]. The observed decrease in IAP (estimated via gastric pressure), resulting in a concomitant decrease in pleural pressure (ITP) in the prone position, may be a possible

explanation for these observations, hence facilitating regional ventilation in the dependent lung zones near the diaphragm. The 45° head-of-bed or upright position can also affect respiratory mechanics. We previously published a case of ACS in an obese patient on non-invasive ventilation via face mask (with aerophagia) resulting in cardiovascular collapse after being put in the upright position [56]. Return of spontaneous circulation was only achieved after abdominal decompression via placement of a nasogastric tube and evacuation of the stomach contents. There seems to be a merit for unloading the abdomen (with suspensions) during prone ventilation. The pressure exerted by the chest suspension will result in a decreased $C_{CW}$, whilst the suspension at the level of the symphysis pubis will make sure that the abdomen can hang freely, hence exerting a 'gravity' effect limiting transmission of IAP towards the dorsobasal lung regions and diaphragm. This decreases IAP and improves $C_{ab}$ avoiding atelectasis via dorsobasal recruitment. The theoretical benefits of proning a patient with IAH/ACS need to be outweighed against the practical risks (e.g. especially in case of an open abdomen). Further studies are required in patients with IAH although weightlessness appears to be beneficial for patients with ARDS [57]. Instead of proning, the combination of a weight placed on the chest with a vacuum shell placed on the abdomen may have similar effects to that of weightlessness with reducing $C_{CW}$ and improving $C_{ab}$ (Fig. 7.5) [58].

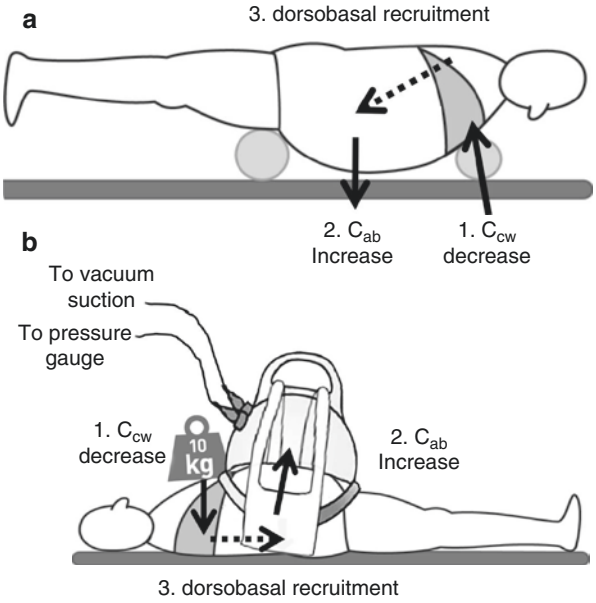


**Fig. 7.5** Effects of positioning on chest and abdominal wall compliance. *Panel A:* Effects of prone positioning with abdominal suspension on chest and abdominal wall compliance. The suspension placed under the chest will reduce chest wall compliance, whilst the abdominal suspension placed at the level of the symphysis will exert a gravitational effect that will increase abdominal wall compliance. This will result in recruitment of dorsobasal lung regions. *Panel B*: Effects of supine positioning in combination with weight placed on the chest and vacuum bell on the abdomen. The weight placed on the chest will reduce chest wall compliance, whilst the abdominal vacuum bell will increase abdominal wall compliance. This will result in recruitment of dorsobasal lung regions

## 7.8 Cardiovascular Management in Intra-abdominal Hypertension: Hints and Tips

### 7.8.1 Improvement of Barometric Preload Indices (Calculation Transmural Cardiac Filling Pressures)

Because of the impact of IAP and ITP on the validity of intracardiac filling pressures like CVP and PCWP, a quick estimation of the transmural PCWP ($PCWP_{tm}$) or CVP ($CVP_{tm}$) at the bedside may improve the accuracy of barometric preload indicators as resuscitation endpoints [2, 12]. Theoretically, transmural ($_{tm}$) filling pressures are calculated as the end-expiratory value ($_{ee}$) minus the ITP or thus $CVP_{tm}$ calculated as $CVP_{ee}$—ITP and $PCWP_{tm}$ calculated as $PCWP_{ee}$—ITP.

The ITP is usually estimated from the pleural pressure which in turn is typically determined by measuring lower oesophageal pressure using a balloon-tipped catheter and is closely correlated to IAP [22]. As discussed previously, the ATI is around 20–80%, so that on average 50% of IAP is transmitted to the thorax [59]. As a rule of thumb, a quick estimate of transmural filling pressures can be obtained by subtracting half of the IAP from the measured filling pressure at end expiration or thus $CVP_{tm}$ calculated as $CVP_{ee}$—IAP/2 and $PCWP_{tm}$ calculated as $PCWP_{ee}$—IAP/2. The calculation of transmural pressures is a better way to estimate true preload in patients with IAH or ACS for a number of reasons. First, since both PCWP and CVP are measured relatively to atmospheric pressure and are in fact actually the sum of intravascular pressure and ITP, the transmural pressures will more closely reflect true intracardiac pressures. Second, ventricular compliance is dynamic and changes from beat to beat in the critically ill, resulting in a variable relationship between pressure and volume, and as a result, changes in intravascular pressure will no longer reflect changes in intravascular volume, further reducing the accuracy of absolute intracardiac filling pressures.

### 7.8.2 Volumetric Preload Indices Better Reflect the True Preload Status in Intra-abdominal Hypertension

The value of volumetric preload indices like right ventricular end-diastolic volume (RVEDV) or global end-diastolic volume (GEDV) over traditional intracardiac filling pressures is especially notable in patients with elevated ITP or IAP where, as stated above, PCWP and CVP are at greatest risk for providing erroneous information regarding preload status [60]. Elevated ITP and IAP result in marked decrease in GEDV despite paradoxical increases in PCWP and CVP [61]. As IAH significantly depletes intravascular volume, it becomes clear that these changes are most appropriately detected by volumetric and not by pressure-based measurements of intravascular volume. Volumetric preload indicators can be further ‘improved’, as IAH also commonly results in cardiac dysfunction and decreased ejection fraction (EF). As a result of this constantly changing ventricular compliance, there cannot be a single value of GEDV that can be considered the goal of resuscitation for all patients with IAH [2]. Therefore, each patient must be resuscitated to the GEDV that optimises cardiac preload and systemic perfusion at any given moment. By ‘correction’ of the GEDV for the underlying EF, the predictive power improves [62].

### 7.8.3 Importance of Abdominal Perfusion Pressure

To improve the sensitivity of a single threshold value of IAP (that cannot be globally applied to the decision-making in all critically ill patients), one could include it in an assessment of APP. Similar to the widely accepted concept of cerebral perfusion pressure (CPP), APP, calculated as MAP minus IAP, has been proposed as a more accurate endpoint for resuscitation in patients with IAH or ACS. Reaching an APP of 50–60 mmHg appears to be superior over other macro- and microcirculatory parameters [63]. However, in order to achieve the target APP, the ICU physician needs to find a judicious balance between fluid resuscitation and the use of vasoactive medication. So far, studies with regard to APP are scarce, often retrospective and including only small numbers of patients [2].

### 7.8.4 Validity of the Passive Leg Raising Test in Intra-abdominal Hypertension

Since about 25% of critically ill patients with a PPV above 12% are not fluid responsive, this suggests different thresholds for different conditions [64]. Within this respect, it is important for the ED, OR and ICU physician to realise that the PLR test can be false negative in responders to fluid administration, and this can be related to increased IAP and diminished venous return from the legs and mesenteric veins. Therefore, care should be taken and IAP should be measured whilst interpreting the result of a PLR test.

## 7.9 Medical Management

Medical management strategies for raised IAP may be divided into five categories according to their proposed mechanism of action:

First, improvement of abdominal wall compliance (sedation and analgesia, neuromuscular blockade, epidural anaesthesia and body positioning changes)
Second, evacuation of intra-luminal contents (nasogastric or rectal decompression and use of prokinetic agents)
Third, drainage of intra-abdominal fluid collections (paracentesis or percutaneous catheter drainage)
Fourth, avoidance of excessive fluid resuscitation and correction of a positive patient fluid balance (with judicious use of fluids, e.g. rather hypertonic solutions instead of crystalloids)
Fifth, organ support (respiratory and cardiovascular monitoring as outlined above)

It would be beyond the scope of this chapter to discuss the different medical management strategies into detail. An overview of the WSACS IAH/ACS medical management algorithm (and the associated grades of recommendations) is shown in Fig. 7.6.

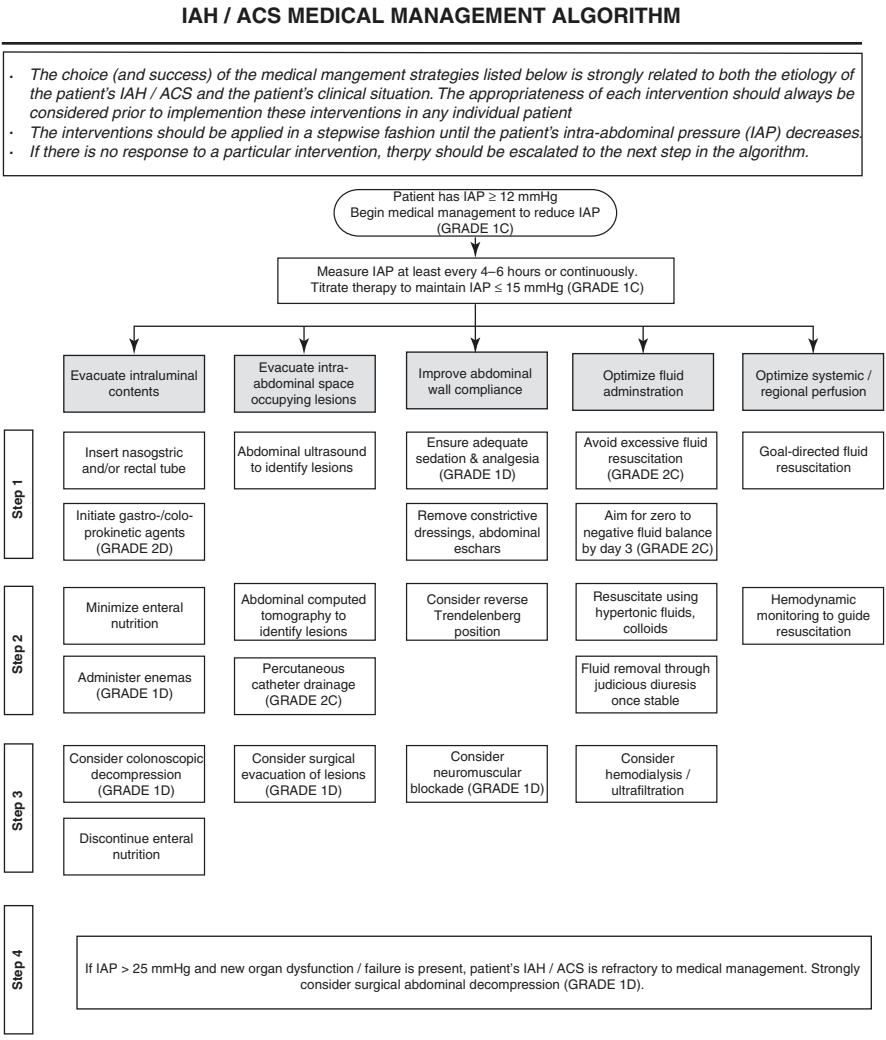


**Fig. 7.6** WSACS 2013 intra-abdominal hypertension/abdominal compartment syndrome medical management algorithm. *IAP* intra-abdominal pressure. Figure reproduced with permission from Kirkpatrick et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated guidelines and consensus definitions from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med* 2013;39 [8]:1190–1206 [7]

## 7.10 Take-Home Messages

With regard to ventilator setting in patients with ALI/ARDS and abdominal hypertension, it is important to measure IAP and if possible also oesophageal pressure as surrogate for ITP [65]. Of note IAH can lead to the polycompartment syndrome with the associated interactions between different compartmental pressures [11].

Within this respect, one should avoid HOB above 45° in patients with high BMI. The ICU physician should get an idea of the ATI and TAI by looking at changes in IAP vs changes in airway ($P_{aw}$), intrathoracic (ITP) and filling pressures (CVP). During lung recruitment, higher opening pressures need to be used in patients with IAH or ACS. This cannot be done with a standard 40-by-40 manoeuvre, but rather a (40 + IAP/2)-by-40 manoeuvre should be used instead. In addition, higher PEEP settings are required in order to prevent end-expiratory lung collapse. The best PEEP (in $cmH_2O$) can be calculated by performing a low-flow PV loop (with best PEEP equal to LIP +2 $cmH_2O$), but as a rule of thumb, best PEEP ($cmH_2O$) can be set equal to IAP (mmHg). During recruitment manoeuvres, haemodynamic status (CO) needs to be monitored. And in view of the exponential deleterious effects, it is worthwhile monitoring EVLW and pulmonary vascular permeability (calculated with transpulmonary thermodilution and defined as EVLW divided by pulmonary blood volume). Deep sedation with a short course of neuromuscular blocking agents may be used in selected patients or as a bridge towards decompressive laparotomy. Body positioning is important, and the anti-Trendelenburg position or proning with abdominal suspension may have beneficial effects on respiratory mechanics. During lung-protective ventilation, transmural or transpulmonary airway pressures are preferred, and as a rule of thumb, transpulmonary pressures, calculated as Pplat minus IAP/2, should be kept below 30–35 $cmH_2O$.

With regard to cardiovascular optimisation, the ED, OR and ICU physician must realise that cardiovascular dysfunction and failure (low CO, low contractility, high SVR) are common in IAH and ACS. Clinical evaluation of the patient is important when interpreting the haemodynamic parameters. Before administering fluids to patients with IAH or ACS, one should carefully check whether the patient is truly intravascular fluid depleted and fluid responsive. Accurate assessment and optimization of preload, contractility and afterload are essential to restore end-organ perfusion and function. Traditional haemodynamic monitoring techniques must be re-evaluated in IAH/ACS since pressure-based estimates of intravascular volume as PCWP and CVP can be erroneously increased. Mean systemic filling pressure may also be increased in IAH. The clinician must be aware of the interactions between ITP, IAP, PEEP and intracardiac filling pressures as misinterpretation of the patient's minute-to-minute cardiac status may result in the institution of inappropriate and potentially dangerous treatment. Transmural filling pressures may better reflect the true preload status in the setting of increased IAP, and resuscitation towards an APP >60 mmHg may be a good alternative resuscitation endpoint. Volumetric estimates of preload status such as global end-diastolic volume (GEDV) can be very useful because of the changing ventricular compliance with elevated ITP. Functional haemodynamic parameters such as PPV (rather than SVV or SPV) should be used to assess volume responsiveness, but the traditional thresholds need to be revised as around 25–35% of patients with IAH and a PPV >12% are nonresponders. The best threshold to predict fluid responsiveness in grade II IAH (15–20 mmHg) is a PPV >20–25%. One also needs to bear in mind that IAH can be a cause for a false negative passive leg raising test. Finally, the cardiovascular effects are aggravated by hypovolaemia and the application of PEEP, whereas hypervolaemia may have a temporary protective effect.

## Conclusions

Although considerable progress has been made over the past decades with regard to the identification and understanding of IAH and ACS, a number of important questions remain relating to the consequences and the optimal management of these conditions. Still, every day, patients may be exposed to the risks of unrecognised pathological increases in IAP. Every ED, OR and ICU physician should therefore learn to understand these pathophysiological mechanisms in order to positively impact organ function during IAH and ACS. IAP measurement is a first step, followed by prevention and medical management to lower the IAP. Monitoring of the respiratory and cardiovascular function during anaesthesia and surgery is of great importance. With our improved understanding of the pathophysiology and epidemiology, future randomised studies should be focused on defining whether targeted or multifaceted medical (and minimally invasive surgical) interventions aimed at reducing IAP and improving $C_{ab}$ will ultimately improve outcomes in patients with IAH and ACS.

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# Part II

# Respiratory Risks

# Obstructive Sleep Apnea (OSA) and Anesthesia

8

Silvia Martin and César Aldecoa

## 8.1 Introduction

Obstructive sleep apnea (OSA) is a highly prevalent disease, characterized by upper airway collapse during sleep; its prevalence is increasing at time obesity does. It causes loud snoring, frequent awakenings, disrupted sleep, and daytime sleepiness. When obstruction of the airway occurs, inspiratory airflow can be reduced (hypopnea) or completely absent (apnea). OSA syndrome is defined as five or more episodes of apnea or hypopnea per hour of sleep with associated symptoms as excessive daytime sleepiness, fatigue, or cognitive impairments. The disease severity is measured using the apnea-hypopnea index (AHI), the mean number of apneas and hypopneas per hour of sleep. OSA is defined when the AHI is ≥5 and OSA syndrome when AHI ≥5 is accompanied with symptoms [1–3] (Fig. 8.1).

It is well known that OSA is often associated with severe complications, major cardiovascular disorders (there is a strong correlation between the disease and hypertension, coronary artery disease, heart failure, arrhythmias, and stroke), neurocognitive impairments (attention and concentration changes, executive function and fine motor coordination), and mood disorders as depression [4].

The amount of patients diagnosed with OSA has increased drastically and is becoming a public health issue with potential social consequences [2]. The recognition of this syndrome is essential in patients undergoing elective surgery in whom prevalence of sleep apnea is much higher. Indeed, sedation and anesthesia have been shown to increase the upper airway collapsibility and therefore increase the risk of having postoperative complications in these patients. It is important to identify these patients preoperatively so that appropriate actions can be taken [3, 5, 6].

S. Martin • C. Aldecoa (✉)
Department of Anesthesiology and Surgical Intensive Care Unit, Rio Hortega University Hospital, Valladolid, Spain
e-mail: caldecoaal@saludcastillayleon.es



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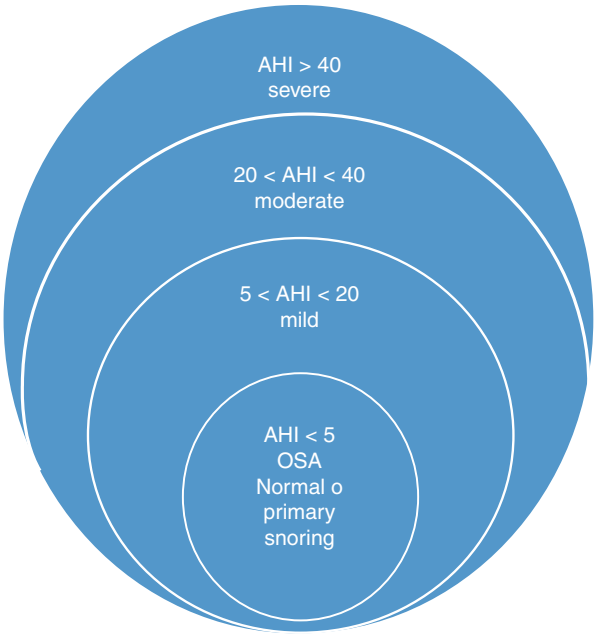


**Fig. 8.1** Severity of OSA based on AHI

## 8.2 Epidemiology

The prevalence of OSA has increased in epidemiological studies over time. Differences and the increase in prevalence of sleep apnea are probably due to different diagnostic equipment, definitions, study design, and characteristics of included subjects including effects of the obesity epidemic [2]. The estimated prevalence of OSA syndrome (AHI ≥5 and excessive daytime sleepiness) has been reported between 6 and 22% in men and 4 and 17% in women. This disease is often asymptomatic, and the prevalence of patients with OSA, who do not present clinical syndrome, has increased in the last studies. It was reported in 37% of men and in 50% of women in the middle-aged population [1, 2, 7].

### 8.2.1 Risk Factors Associated with OSA

Surgical patients are at higher risk of having complications for a variety of reasons, which are essential comorbidities, especially chronic obstructive pulmonary disease, coronary artery disease, and renal failure. Considering this, it is extremely important to identify correctly patients preoperatively. Patients with OSA are more frequently male, obese, and 65 years old or more. OSA is also related to race. African-Americans are more frequently affected and develop the disease at a younger age than other races [4].

The most important factors associated with OSA observed in studies over time are related with obesity, gender, age, smoking and alcohol abuse, and cardiovascular disease (Fig. 8.1).

#### 8.2.1.1 Obesity

Obesity is the most important risk factor for snoring and sleep apnea and a majority of patients with OSA are overweight. A body mass index (BMI) of ≥25 kg/m2 is associated with moderate-to-severe OSA in more than 50% cases. Fat distribution, in particular, deposition around the trunk and neck, predisposes to upper airway obstruction and OSA because of mass loading. Neck or waist circumferences are better predictors of OSA breathing as compared with BMI alone. Neck circumference seems to be the most important risk factor for snoring in recent studies between populations [1].

In addition, it has been shown that caloric restriction or bariatric surgery in combination with positive airway pressure (CPAP) therapy obtains better results, reducing the severity of OSA than CPAP alone in overweight people.

Nevertheless, not only subjects with obesity and fat necks suffer from sleep apnea but also lean subject, and about one-third of OSA syndrome patients are non-obese [2].

#### 8.2.1.2 Gender

OSA is more common in men than women with an estimated ratio about 2:1. The prevalence of snoring shows similar gender differences. Possible explanations for the male predominance include hormonal effects in the upper airway, gender differences in body fat distribution, and differences in pharyngeal anatomy and function. Hormonal influences could play an important role in the pathogenesis of OSA; indeed, postmenopausal women are also at higher risk, but the pathophysiological roles of hormones are, however, unclear [2, 7].

In recent studies, it has been reported that sleep apnea occurs in as much as 50% of females aged 20–70 years old in the population. OSA symptom differs between males and females; daytime sleepiness is rare in females; instead, hypertension, obesity, and age were associated with sleep apnea in females. Moreover an epidemiologic study reported that 39% of normal-weighted women had OSA, but only 0.1% of them had severe sleep apnea [1, 2, 8].

#### 8.2.1.3 Age

The risk of OSA increases as well with increasing age. Snoring frequency increases with age up to 50–60 years old and then decreases after. Recent studies reported an increase in OSA after 65 years; in contrast, the frequency of OSA syndrome declined. An association between sleep-disordered breathing and morbidity and mortality at older ages has been observed, so that sleep apnea in seniors represents a specific entity compared with middle-aged adults [2].

Obstructive sleep apnea (OSA) is a common pediatric health problem, and children at risk need to be identified, investigated, and treated in a timely manner because

the resultant activation of inflammatory cascades can impose wide-ranging effects, impacting the neurocognitive, cardiovascular, and metabolic systems [2]. Although the etiologies of pediatric OSA are multiple, they can be broadly classified into conditions which result in intrinsic upper airway narrowing and those that result in increased upper airway collapsibility. Adenotonsillar hypertrophy is currently the most common example of the former. Other anatomical features resulting in upper airway narrowing such as micrognathia, macroglossia, and midface hypoplasia are often found in children with craniofacial syndromes (e.g., Treacher Collins syndrome, Crouzon syndrome, Apert syndrome, Pierre Robin sequence), achondroplasia, trisomy 21, Beckwith-Wiedemann syndrome, and mucopolysaccharidoses [9].

#### 8.2.1.4 Smoking

Several epidemiological studies observed significant associations between cigarette smoking and snoring or sleep apnea. Moreover there is a dose-response relationship between smoking and the severity of OSA. Heavy smokers have greatest risk to snoring and sleep disorders. The main reasons possible include airway inflammation and sleep instability from overnight nicotine withdrawal. Never-smokers who have been exposed to passive smoking on a daily basis display an increase in the odds of being a habitual snorer after adjusting for age and BMI.

However, some doubts about smoking as a risk factor for OSA emerges. In an epidemiologic studies, smokers displayed less sleep apnea than nonsmokers, and data on the impact of smoking on the incidence and remission of sleep apnea are scarce [2, 7].

#### 8.2.1.5 Alcohol

Alcohol produces hypotonia of the oropharyngeal muscles as a result of reducing motor output to the upper airway. It also increases both the number of apneas and the duration of them. However, when we study the relationship between chronic alcohol and snoring or OSA, we found an association in some of the patients but not in others, so it is not clear [1, 2].

In other studies, it is observed that alcohol is related to snoring in lean women, in whom there was no compromised upper airway because of fat deposits or overweight.

#### 8.2.1.6 Cardiovascular Disease

Hypertension and OSA are both prevalent and many people suffer from them together. Compared with subjects with no OSA, the odds ratio for the prevalence of hypertension is >2 for both mild and moderate-to-severe OSA. A causal relationship between OSA and hypertension has been indicated in observational studies but however has also observed not get such as effective results in reducing hypertension when we treat OSA with CPAP [2].

Another positive association is founded between coronary artery disease and OSA. They frequently coexist, but OSA is usually being undiagnosed. Patients with OSA had a higher incidence of coronary artery disease (16.2%) compared with snorers without OSA (5.4%) in a prospective studies [1].

Clinical studies suggest an important link between sleep apnea and stroke, which are the only two risk factors that negatively affected mortality. Studies concluded that OSA syndrome significantly increases the risk of stroke or death, and it is independent of other risk factors, including hypertension [4].

Different types of arrhythmias have been described in patients with OSA. Atrial fibrillation and various degrees of heart block seem to be the more common. Many observational studies report an increase in vagal tone during apneic events, being the possible mechanism in the development of bradyarrhythmias [2, 4].

OSA and diabetes mellitus share several risk factors. These factors usually coexist with snoring, and in general population studies, they are observed as independent of obesity and other factors. There is an association reported between snoring and diabetes in both males and females. Studies also concluded that OSA as a risk factor for future diabetes development is not conclusive [2, 4].

## 8.3 Pathogenesis

OSA is characterized by recurrent periods of upper airway occlusion during sleep. When the pharynx collapses, airflow obstruction elicits neuromuscular responses that can mitigate the obstruction and restore airway patency and ventilation [7]. If these neuromuscular mechanisms are inadequate, additional factors contribute to the development of recurrent periods of airway obstruction and arousals from sleep.

We consider that the upper airway collapses dynamically during sleep and reopens during wakefulness. Investigators have previously modeled dynamic alterations in patency as a function of transmural pressure across collapsible segments in biologic conduits in the cardiovascular, gastrointestinal, and genitourinary systems. The human pharynx is considered as a collapsible tube whose purposes are speech, swallowing, and respiration. There is not provided with a rigid structure as a skeletal support and during inhalation collapse [1, 7].

In the upper airway, the collapsible segment is bordered by two rigid segments: upstream, the nasal passages, and downstream, like the trachea. The segments upstream and downstream to the collapsible site have fixed diameters and resistances, $R_{US}$ and $R_{DS}$, respectively, and the pressures upstream and downstream are $P_{US}$ and $P_{DS}$, respectively. When $P_{US}$ and $P_{DS}$ are less than the critical pressure surrounding the collapsible segment ($P_{CRIT}$), the transmural pressure is negative, the airway closes, and the airflow ceases. Flow can be reestablished by raising $P_{US}$ above $P_{CRIT}$. Taking into account this model, flow through the upper airway is proportional to the pressure gradient across the entire airway. Moreover, when $P_{US}$ is greater than $P_{CRIT}$ and $P_{DS}$ is less than $P_{CRIT}$, however, the airway enters a flow-limited condition, and flow would cease transiently. As the upper airway occludes, the pressure immediately upstream of the occlusion would equilibrate with $P_{US}$ and rise above $P_{CRIT}$. This increase in pressure would inevitably lead to reopening of the airway (Fig. 8.2).

Current evidence suggests that disturbances in $P_{CRIT}$ play a primary role in OSA pathogenesis. Elevations in $P_{CRIT}$ have been demonstrated in OSA patients compared to age, sex, and body mass index (BMI)-matched controls under general

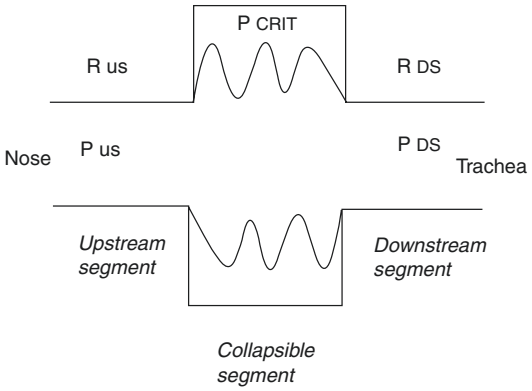


**Fig. 8.2** Starling resistor model of the upper airway

anesthesia and neuromuscular blockade as well as during sleep. Additional evidence for the primacy of upper airway collapse in OSA pathogenesis is provided by studies demonstrating a dose-response relationship between pharyngeal collapsibility and severity of OSA. As $P_{CRIT}$ rises progressively, increases in severity of upper airway obstruction during sleep have also been observed clinically [3, 7].

In addition, evidence shows that treatments that decrease $P_{CRIT}$ (e.g., weight loss or uvulopalatopharyngoplasty) lead to improvements in OSA and to resolution of disease. Similarly, a positive transmural pressure can be induced by increasing $P_{US}$, leading to resolution of upper airway obstruction. With application of progressively increasing nasal pressure during CPAP titration, upper airway obstruction and recurrent obstructive apneas and hypopneas are reversed [3, 7, 10].

Many conditions such as negative pressure, soft tissues, and bony structures predispose the pharynx to collapse. However, the tonic and phasic contractile activity of the dilator muscles produces the opposite effect. When an imbalance between these forces is developed, the upper airway obstruction is produced and recurs in patients with sleep-disordered breathing [1].

In fact, both anatomic and neuromuscular factors are involved and the development of OSA. The findings suggest that elevations in pressure in the collapsible segment of the pharynx of OSA patients are due to defects in both upper airway structural and neuromuscular controls, and both play a pivotal role in OSA pathogenesis. OSA can only develop when neuromuscular responses do not adequately mitigate the obstruction caused [2, 7].

Anatomic alterations have been identified such as a variety of factors that contribute to increased collapsibility. In a narrow upper airway, according to the Venturi effect, while airflow velocity increases, pressure on the lateral wall of the pharynx decreases, and the collapsibility does it as well. Excessive fat deposits, particularly parapharyngeal ones, also contribute to OSA development. In addition, lung volumes are decreased in obese persons, leading to decreased caudal traction on the

upper airway and an increased critical closing pressure. Another anatomic factor associated with OSA is the presence of tonsillar and tongue hypertrophy, retrognathia, or inferior displacement of the hyoid bone [2, 7].

An impairment in neuromuscular control responses account for much of the balance of the OSA variability. This kind of patients depends on neuromuscular activity to maintain airway patency and ventilation during sleep. Reductions in neuromuscular tone, especially with reduction in pharyngeal dilator tone at sleep onset, are suspected to contribute to increased OSA severity during REM compared to NREM sleep in selected patients and particularly in women and children. Current studies also suggest that endogenous neurohumoral agents can contribute to modulation of neuromuscular responses. Neurohormonal modulation of pharyngeal neuromuscular activation may take part in prevalence and severity of OSA and differences between men and women. It could be explained because of elevations in circulating leptin levels in women compared to men [1, 7].

Neuromuscular responses are also influenced by pharmacologic modulators of sleep-wake state. Alcohol, sedative medications, and hypnotics could decrease responses to upper airway occlusion and promote upper airway obstruction during sleep. Benzodiazepines are known to prolong obstructive apneas and hypopneas. Opiates have not been well studied in association with upper airway collapsibility. Nevertheless, blockade of opioid receptors has been demonstrated to decrease pressure in the airway, which suggests that it may increase susceptibility to pharyngeal occlusion [5, 7].

Pharyngeal neuromuscular activity is also controlled by chemical and mechanical reflexes. Hypercapnia is also a potent stimulator of upper airway neuromuscular activity.

Hypocapnia, on the other hand, produces a relatively passive state and is associated with elevations in pressure. Pharyngeal sensory inhibition has been demonstrated to decrease neuromuscular responses to upper airway obstruction [7].

## 8.4 Clinical Manifestations

OSA manifestations develop in a variety of ways from unrecognized symptoms to classic findings. However, the most common presentation is not the recognizable one, and usually OSA progresses over years, delaying diagnosis and producing adverse effects.

As epidemiologic studies are observed, OSA is underdiagnosed, and it is necessary that clinicians are familiar with both the subtle and overt clinical manifestations of OSA to accurately identify patients at risk for the disease and order appropriate testing, to decrease the risk of postoperative mortality in patients with a known diagnosis of sleep apnea [2, 4]. Perioperatively identification of patients is mandatory in order to optimal management [5].

Many classic symptom and exam findings are shown in OSA patients (Table 8.1). The association between OSA and different disorders has been shown in several studies, especially cardiovascular and neurocognitive impairments but also metabolic and endocrine disturbances [4, 11].

**Table 8.1** Classic symptoms and exam findings in OSA

| Classic symptoms | Exam findings |
|---|---|
| Snoring | Obesity |
| Excessive daytime sleepiness | Enlarged neck circumference |
| Choking or gasping at night | Crowded upper airway |
| Night sweats | Hypertension |
| Neurocognitive impairments | Pulmonary HTN |
| Heartburn | Retrognathia/overjet |
| Morning headaches | Nasal obstruction |
| Maintenance insomnia | Decreased oxygen saturation |
| Erectile dysfunction | S3 heart sound(congestive heart failure) |
| Nocturia | Lower extremity edema |

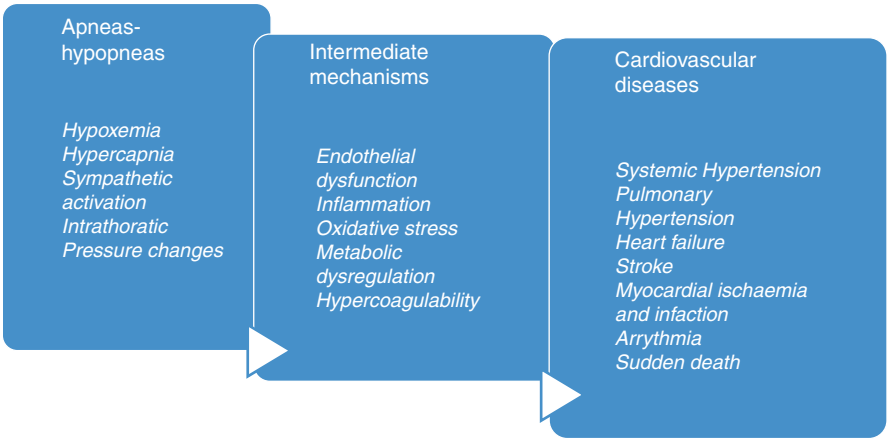


**Fig. 8.3** Pathological association between OSA and cardiovascular diseases

## 8.5 Cardiovascular

From the cardiovascular point of view, the consequences of OSA, hypoxemia, and intrathoracic pressure changes produce intermediate mechanisms as sympathetic activation, endothelial dysfunction, hypercoagulability, inflammation, oxidative stress, and metabolic dysregulation, which finally develop into cardiovascular diseases, systemic hypertension, heart failure, arrhythmia, stroke, myocardial ischemia, and even sudden death (Fig. 8.3).

## 8.6 Neurocognitive

OSA is associated with variable degrees of neurocognitive impairment. Traffic accidents and work performance deficits are surrogate markers of these neurocognitive impairments in the OSA population that may be reported in clinic. OSA produces

negative effects on inductive and deductive reasoning, attention, vigilance, learning, and memory. OSA usually is manifested by impaired judgment, slowed reaction time, impaired learning, and poor working memory, compromised driving, and poor performance at work. Patients with OSA often complain of difficulty staying on task at work, falling asleep inappropriately at their work space, and memory trouble causing professional difficulties [12].

There also seems to be an association between sleep health and mood disorders. Studies relate risk for the development of depression in patients with OSA and also found a dose-response association. However, other studies have not found a relationship between depression and OSA, particularly in men [1, 11].

## 8.7 Metabolic and Endocrine

OSA also affects the metabolic profile, particularly in moderate-to-severe disease. The adverse impact of the OSA on glucose homeostasis, lipid metabolism, and fatty liver disease suggests that OSA should be considered as a potential component of metabolic syndrome [1, 11, 12].

Among the causes of metabolic syndrome in OSA patients, alterations in the hypothalamic-pituitary-adrenal axis, aberrant sympathetic activation, induction of certain adipokines, an increased inflammation/oxidative stress and altered glucose metabolism has been described. Investigators found a significant reduction in insulin sensitivity in patients with OSA, and this reduction in insulin sensitivity correlated with severity of the disease, and the correct treatment of apneic events improves glycemic control [7, 11].

OSA appears to have an impact on lipid metabolism with studies suggesting functional abnormalities in high-density lipoproteins (HDL) and elevations in total cholesterol, low-density lipoproteins (LDL), and triglyceride levels. Studies observe decreased lipoprotein clearance, increased lipolysis, and enhanced hepatic lipid output. Finally, these metabolic impairments contribute to the development of hepatic steatosis [11].

### 8.7.1 Pediatric OSA

Pediatric OSA manifestations differ from OSA in adults and also the definition does. The most common cause of OSA in children is adenotonsillar hypertrophy, and surgery is the primary treatment for this condition, curing the disease in 70% of children. OSA is also associated with obesity and inflammatory disorders as sinusitis, allergic rhinitis, and asthma. In children, neurological alterations often present as learning difficulties, behavioral problems, and hyperactivity. In severe OSA, cardiovascular disease can develop as hypertension, cardiac dysfunction, and cardiac failure. Snoring is a common sign; as many as 40% of snoring children who are referred for evaluation by an otolaryngologist or sleep specialist prove to have OSA [1, 9, 12].

## 8.8 Diagnosis and Preoperative Screening

Although polysomnography is the gold standard for the diagnosis of OSA, it is costly and time-consuming. It is essential for clinicians to identify patients at greater risk for major invasive procedures, and for this reason, effective screening strategies are required [3]. At present, there is limited scientific literature on the preoperative preparation of patients with suspected OSA (Fig. 8.2).

During polysomnographic studies, several physiological variables are measured and recorded while the patient sleeps including pulse oximetry, electroencephalogram, electrooculogram, nasal and oral airflow measurements, chest wall movements, electromyogram, and electrocardiogram [12]. An obstructive apnea is defined as a cessation of airflow for at least 10 s despite ongoing inspiratory effort; a hypopnea is defined by one of the following three features: more than 50% airflow reduction, moderate airflow reduction (50%) associated with oxyhemoglobin desaturation, and moderate airflow reduction with electroencephalographic evidence of awakening. The apnea-hypopnea index (AHI), calculated by dividing the number of events by the number of hours of sleep, is the most useful and objective way of classifying the severity of the disease [3, 12]. Using the AHI, OSA can be classified as "mild" (AHI 5–14), "moderate" (AHI 15–29), or "severe" (AHI $\geq$ 30) (Fig. 8.1) [1]. The diagnostic criteria and classification of OSA syndrome are summarized in Table 8.2.

Patients should undergo thorough history and physical examination preoperatively, so adults should be asked about symptoms associated with OSA, including snoring, witnessed apneas, and daytime drowsiness, and focus on physical examination to evaluate neck circumference, body mass index, modified Mallampati score, tongue volume, tonsillar size, and nasopharyngeal characteristics [3, 13] (Table 8.1).

Blood gas analysis is not typically included in the standard preoperative setting, but venous serum bicarbonate concentration might be a helpful screening tool for an occult, chronic, respiratory acidosis. A serum bicarbonate level greater than 27 mmol/l has been shown to be highly sensitive (92%) for an elevated arterial partial pressure of carbon dioxide [7, 12].

Questionnaires used for screening in OSA are the Berlin questionnaire, the ASA checklist, the STOP questionnaire, and the STOP-Bang questionnaire. These

**Table 8.2** Diagnostic criteria of OSA syndrome

| |
|---|
| A. Excessive daytime sleepiness that is not better explained by other factors |
| B. Two or more of the following that are not better explained by other factors: |
| Choking or gasping during sleep |
| Recurrent awakenings from sleep |
| Unrefreshing sleep |
| Daytime fatigue |
| Impaired concentration |
| C. Overnight monitoring demonstrates ≥5 obstructed breathing events per hour during sleep |
| Diagnosis: confirmed by the presence of criterion A or B plus criterion C or by the presence of 15 or more obstructed breathing events per hour of sleep regardless of symptoms |

questionnaires are simple and easy to administer preoperatively and have been validated in the surgical population [13, 14].

The STOP questionnaire seems to be the easiest to use, and the STOP-Bang modification (Table 8.3) improves the sensitivity and negative predictive value of the first one and shows better accuracy at predicting moderate-to-severe OSA in surgical patients. The sensitivity of STOP-Bang score of 3 or greater is 84%, 93%, and 100% to predict all OSA (AHI > 5), moderate-to-severe OSA (AHI > 15), and severe OSA (AHI > 30), respectively. Due to its moderate specificity (37–56%), the STOP-Bang questionnaire may result in false positives leading to unnecessary referrals for sleep studies [14]. As we mentioned before, the specificity can be improved combining a STOP-Bang score with an elevated serum bicarbonate. Recently some studies have shown that adding specific constellations of predictive factors improved the specificity of STOP-Bang questionnaire. For patients, a STOP

**Table 8.3** STOP and STOP-Bang questionnaires for adult obstructive sleep apnea screening

| | | |
|---|---|---|
| *STOP questionnaire* | | |
| 1. Snoring? Do you Snore Loudly (loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night)? | Yes | No |
| 2. Tired? Do you often feel Tired, Fatigued, or Sleepy during the daytime (such as falling asleep during driving or talking to someone) | Yes | No |
| 3. Observed? Has anyone Observed you Stop Breathing or Choking/Gasping during your sleep? | Yes | No |
| 4. Pressure? Do you have or are you being treated for High Blood Pressure? | Yes | No |
| High risk of OSA: answering yes to > or 2 questions; Low risk of OSA: answering yes to <2 questions | | |
| *STOP-Bang questionnaire* | | |
| 1. Snoring? Do you Snore Loudly (loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night) | Yes | No |
| 2. Tired? Do you often feel Tired, Fatigued, or Sleepy during the daytime (such as falling asleep during driving or talking to someone)? | Yes | No |
| 3. Observed? Has anyone Observed you Stop Breathing or Choking/Gasping during your sleep? | Yes | No |
| 4. Pressure? Do you have or are being treated for High Blood Pressure? | Yes | No |
| 5. Body Mass Index more than 35 kg/m$^2$? | Yes | No |
| 6. Age older than 50 years? | Yes | No |
| 7. Neck size large? For male, is your shirt collar 17 in./43 cm or larger? For female, is your shirt collar 16 in./41 cm or larger? | Yes | No |
| 8. Gender: male? | Yes | No |
| Low risk of OSA: Yes to 0–2 questions | | |
| Intermediate risk of OSA: Yes to 3–4 questions | | |
| High Risk of OSA: Yes to 5–8 questions | | |
| or Yes to 2 or more of 4 STOP questions + male gender | | |
| or Yes to 2 or more of 4 STOP questions + BMI 35 kg/m2 | | |
| or Yes to 2 or more of 4 STOP questions + neck circumference (17 in./43 cm in male, 16 in./41 cm in female) | | |

**Table 8.4** Pediatric obstructive sleep apnea screening: "I'M SLEEPY" questionnaire (Parent Version)

| | |
|---|---|
| I: Is your child often irritated or angry during the day? | Y/N |
| M: Body mass index >85%? | Y/N |
| S: Does your child usually snore? | Y/N |
| L: Does your child sometimes have labored breathing at night? | Y/N |
| E: Ever noticed a stop in your child's breathing at night? | Y/N |
| E: Does your child have enlarged tonsils and/or adenoids? | Y/N |
| P: Does your child have problems with concentration? | Y/N |
| Y: Does your child often yawn or is he or she often tired/sleepy during the day? | Y/N |
| Score of 0 to 2 indicates low risk of OSA; high risk isindicated by a score of 3 or more | |

score of ≥2, male gender, and BMI of >35 kg/m2 are more predictive of obstructive sleep apnea than age ≥50 and neck circumference of >40 cm [13].

Nevertheless, OSA disease has a huge heterogeneity in presentation. In a recent study based in a sleep apnea French registry, authors found six distinct clusters of obstructive sleep apnea regarding clinical presentation, risk factors, and consequences which pointed out the need for more research in diagnosis, and the relationship between different clusters found long-term prognostic implications [12].

Pediatric questionnaires have not yet been fully validated. A pediatric screening questionnaire called I'M SLEEPY was recently developed (Table 8.4). Despite promising, the initial testing population was small, 150 children, so further validation is needed to confirm its usefulness as a reliable tool [9, 13].

In summary, preoperative management for OSA should consist of full history and physical examination, also a validated screening questionnaire should be made as a routine part of standard preoperative examination, and if it is necessary, consider a formal sleep evaluation in very high-risk group of patient [3, 12]. We propose the STOP or STOP-Bang questionnaire so it is user-friendly, accurate, and generalizable to different target populations.

## 8.9 Preoperative, Intraoperative, and Postoperative Care

Patients having a high probability of OSA should be managed according to ASA guidelines [3]. Surgeons and anesthesiologist need to be notified perioperatively, so preoperative management can be considered (Fig. 8.4).

When it is possible, high-risk patients should have a consultation with a sleep specialist and a home screening sleep study or complete polysomnography ordered. For patients not previously diagnosed with OSA, clinical management should be performed based on risk stratification. The sleep specialist can help determine the role of a sleep study and evaluate starting therapy with positive airway pressure [3, 5, 13].

In patients with known OSA who have been prescribed with CPAP, the use of CPAP is continued during the perioperative period. CPAP helps in opening the collapsed upper airway, improves functional residual capacity (FRC) and oxygenation

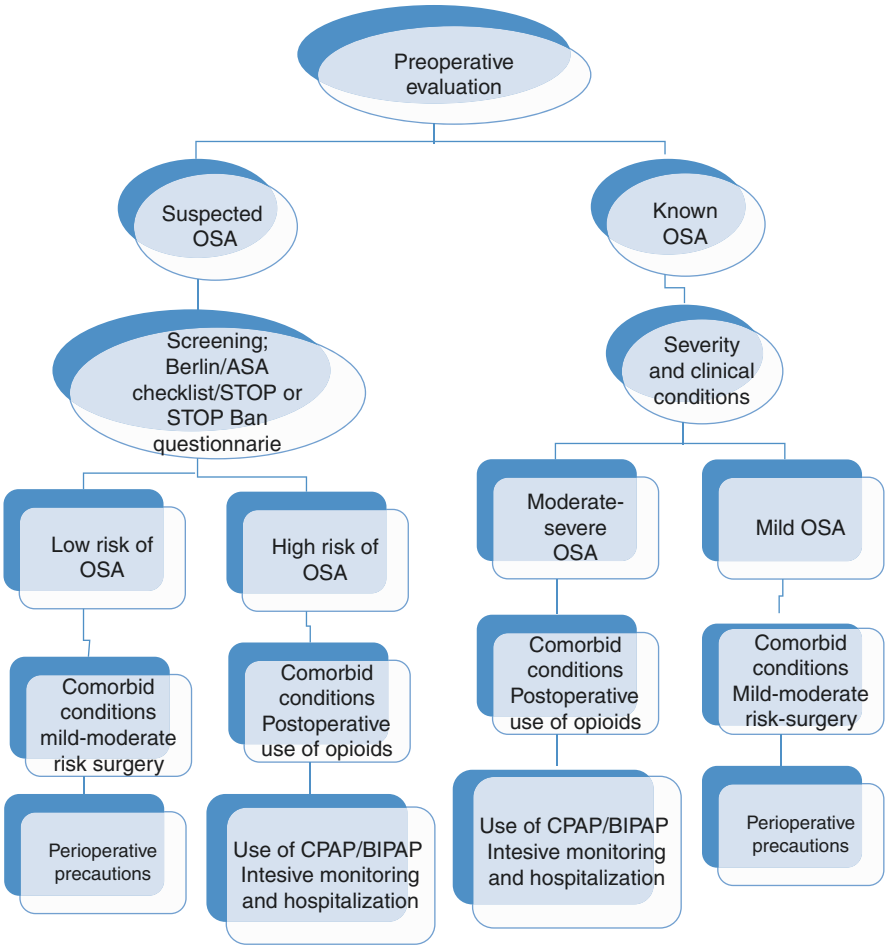


**Fig. 8.4** Perioperative evaluation in OSA patients (modified of Anesthetic considerations of parturients with obesity and obstructive sleep apnea. J Anaesthesiol Clin Pharmacol. 2012;28:436–4)

with reduction in work of breathing, and also improves excessive daytime sleepiness in patients with OSA [5, 15]. Recent evidence results show that CPAP reduced the rate of postoperative complications and decreased the hospital length of stay. Investigators also observed that the use of CPAP leads to reduction in the incidence of endotracheal intubation and other severe complications in patients who develop hypoxemia after elective major abdominal and cardiovascular surgery. Randomized controlled trials in the abdominal surgical population reported reduction in the rate of atelectasis, postoperative pulmonary complications, and pneumonia with the perioperative use of CPAP [10, 16].

In these patients, confirmed with OSA, or high-risk ones, specific methods should be used during intubation, intraoperatively, during and early after extubation, and in the postanesthesia care unit as well. Special attention must be paid in

fluid management, patient positioning, neuromuscular blockade, protective ventilation, pain management, and choice of anesthesia type and anesthetic [5, 6, 15].

The most important precautions to be considered during induction and intraoperative period are:

- Whenever possible, consider using regional or local anesthesia instead of general anesthesia.
- Minimize the surgical stress and reduce the duration of surgery.
- Anticipate difficult intubation and consider awake extubation preferably in semi-upright position.
- Monitoring of capnogram and tidal volume and protective ventilation with PEEP.
- Lung recruitment maneuvers immediately after intubation, and apply positive end-expiratory pressure (PEEP) for maintaining lung volume during surgery.
- Short-acting anesthetics and narcotics are preferred, and if possible, the use of sedatives and narcotics should be reduced.
- Avoid high-dose non-depolarizing neuromuscular blocking agent (NMBA), use neuromuscular transmission monitoring, and residual neuromuscular blockade should be reversed.
- Agents with reduced impairing effect on upper airway patency might be considered (e.g., ketamine).

Concerning pharmacological agents and their effects on breathing, it has been shown for all GABAergic drugs a dose-dependent increase in collapsibility of the upper airway through a depressed respiratory drive (propofol) or a reduced responsiveness of upper airway dilator muscles to negative pressure (isoflurane). Ketamine, and other N-methyl-D-aspartate (NMDA) antagonistic drugs, can be particularly useful for pain control during short procedures and small surgical interventions, and even low-dose ketamine preserves airway reflexes and maintains respiratory drive [1, 5–7].

Opioids are commonly used for surgical pain control during and after anesthesia. This is of special importance in OSA patients who have been observed to need higher doses of them. While pain management may improve respiratory settings, these analgesics induce a dose-dependent impairment of pharyngeal dilator muscle activity. Regional anesthesia with local anesthetics or nonsteroidal anti-inflammatory drugs should also be considered [5, 7, 13].

It is also important to focus on the complete and rapid reversal of neuromuscular blockade, so that it will decrease both the frequency of complications and costs in patients with high risk for postoperative respiratory system complications as in OSA patients. Sugammadex superiority over neostigmine is well known in terms of the reversal of neuromuscular blockade activity. According to recent studies, the use of sugammadex in OSA operations helps neuromuscular function to improve earlier and shortens the time spent in the operating theater and PACU [17]. Sugammadex in OSA patients contributes to the decrease frequency of respiratory system complications, and despite the increased reversal cost, the cost of complication treatment and thus total costs are decreased.

We should consider another useful drugs as dexmedetomidine as well. Some recent trials have been confirmed for its efficacy and safety in sedation, analgesia,

**Table 8.5** More frequent postoperative complications of OSA

| | |
|---|---|
| Hypoxemia | 5–20% |
| Cardiac ischaemia | 0–10% |
| Hypercapnic encephalopathy | 0–10% |
| Pulmonary tromboembolism | 1–6% |
| Cardiac arrhytmias | 2–6% |
| Pulmonary atelectasis | 3–5% |
| Pneumonia | 1% |

and prevention of emergency agitation in children with OSA after tonsillectomy and adenoidectomy [18]. Providing satisfactory postoperative analgesia should be expected to be not complicated by sedative-induced upper airway obstruction. In OSA patients undergoing airway reconstruction surgery, the use of dexmedetomidine maintained stable hemodynamics. This drug stimulates receptors in the locus coeruleus causing sedation and analgesia by stimulating spinal cord receptors and causes a mild decrease in minute ventilation and an increase in $PaCO_2$ but less pronounced than with opioids. The use of dexmedetomidine reduces the propofol and morphine requirements during bispectral index-guided sedation and also decreases the requirement of midazolam [19].

Postoperatively, patients with OSA or high-risk screening should be very closely monitored in the postanesthesia care unit (PACU), and postoperative complications should be considered (Table 8.5). They should have continuous monitoring of oxygenation with the help of pulse oximetry in order to avoid hypoxemia or other complications. Supplemental oxygen should have a stop order set at 2 L/min. A higher inspiratory fraction of oxygen administration is not recommended, because it could induce hypoventilation/hypercapnia by suppressing the central hypoxia response and by raising oxygen concentrations [5, 13]. As soon as possible, place the patients in the non-supine position after the surgery to improve respiratory function.

We should minimize the use of opioids and benzodiazepines in the perioperative period. Consider using nonsteroidal anti-inflammatory drugs, acetaminophen, tramadol, and regional analgesia for pain control or other options such as dexmedetomidine that can be very useful for sedation [5, 6, 19].

Another important issue in the postoperative period is the relationship between sleep fragmentation, poor-quality sleep, and OSA. Following sleep deprivation and fragmentation, a rebound effect with increased amount of REM sleep can be seen a few nights after surgery. REM sleep is associated with muscle atonia and impaired respiratory arousal. In addition sleep deprivation may also contribute to the development of delirium, further disrupting sleep patterns and cortical arousals [6, 13].

Recent studies observed that treatment of OSA patients with CPAP early after surgery improves sleep apnea and mitigates negative effects of opioid. Another trials demonstrate beneficial effects of early postoperative CPAP treatment across the continuum of wakefulness and non-REM sleep and on the respiratory depressant effects of opioids used for pain management. It was observed that CPAP improves opioid-induced worsening of OSA and ventilation early after bariatric surgery. Supervised CPAP treatment immediately after surgery in the PACU seems to improve postoperative respiratory safety [15, 16].

Clinical studies suggest that patients with OSA syndrome have a higher mortality risk and that treatment with tracheostomy or CPAP decreases this risk. The lack of randomized, controlled interventional trials clearly limits the evidence [16].

The impact of OSA on mortality in population has recently been analyzed in the Wisconsin Study and in the Sleep Heart Health Study. Both reported high mortality rate with increasing severity of sleep apnea (AHI ≥30), and also similar results were obtained for cardiovascular mortality [2, 7].

## 8.10 Treatment of OSA and Future Directions

Many options are now available for an effective management of OSA [20]. Continuous positive airway pressure (CPAP) is still recognized as the gold standard treatment. Other treatments could include, other positive airway pressure ventilation modalities for patients intolerant to CPAP, minimally invasive procedures or devices such as mandibular advancement splints or weight loss. Different surgeries are also effective treatments but candidate selection is essential [3].

CPAP therapy is indicated in all patients with an AHI greater than 15, independently from the presence of comorbidities or severity of symptoms. When AHÍ is between 5 and 15, CPAP is considered in the presence of symptoms, hypertension, coronary disease, or stroke. Studies observed that CPAP reduces the number of nocturnal obstructive events and improves sleep parameters and nocturnal $SaO_2$ from the first night of treatment. Daytime symptoms also reversed, especially sleepiness, after a short period of constant use. Neurocognitive impairment decreases after constant treatment improving memory, attention, and executive function. CPAP has a positive impact on cardiovascular outcomes. Patients with untreated severe OSA had a higher incidence of fatal and nonfatal cardiovascular events. However, the effect of CPAP on metabolic alterations is still inconclusive [21, 22].

In summary, data show us CPAP is extremely effective in controlling symptoms and consequences of OSA, and very few side effects have been documented. The efficacy of CPAP strictly depends on its constant use, and if no other treatment is used, CPAP represent a lifetime treatment [10, 22].

Nevertheless, no all patients tolerate CPAP. Other newer modalities of positive airway pressure ventilation such as bilevel PAP or autotitrating CPAP are more sophisticated but also effective [21].

Alternatives to positive air pressure are positional therapy, oral devices, weight loss, and surgery [21, 22].

### 8.10.1 Positional Therapy

Body position during sleep influences the frequency and the severity of the obstructive events. The supine position, mainly due to the effect of the gravity on the tongue and soft palate position, increases the number of apneas/hypopneas. So positional therapy prevents OSA patients from sleeping in supine posture.

### 8.10.2 Oral Devices

Oral appliances increase development and recognition in the last years. They are an alternative treatment of CPAP in mild-to-moderate OSA. The most common oral devices are mandibular advancement splints (MAS). These devices recolocate laterally the pharyngeal fat pads from the airway, and the tongue base will move forward, decreasing apneic events. However, many side effects have been observed such as excessive salivation, dry mouth, gingival irritation, arthralgia, teeth pain, and occlusal changes. Another newer group of oral appliances includes the tongue-retaining devices. They produce an anterior suction of the tongue and move it forward, to increase the upper airway dimension during sleep. They have demonstrated a reduction in AHI and have shown similar efficacy compared with MAS. Although promising, there is still insufficient evidence to recommend the use of these oral appliances in clinical practice [21].

### 8.10.3 Weight Loss

Weight loss in OSA patient is really necessary and important so obesity is a high-risk factor to develop the disease. This recommendation is a main goal in the management of OSA, and all patients should be encouraged to control their weight [3].

### 8.10.4 Surgery

Surgery treatment in the management of OSA has been widely explored in order to find a definitive option. However, its role remains extremely controversial. The aim of the surgery is to remove the cause of upper airway obstruction, and as these can occur at different sites, diverse levels of surgery are possible: nose, oropharynx tract, tongue, and craniofacial structures (5, 14). Tonsillectomy and adenoidectomy are the most commonly used surgical procedures to treat OSA in children and are highly effective. Uvulopalatopharyngoplasty, either conventional or laser, is an established surgical procedure for the treatment of OSA in selected patients. This kind of surgery will improve snoring, but there is no significant evidence for improving OSA. Maxillomandibular advancement (MMA) is obtained by osteotomy of the maxilla and mandible, advancing the skeleton structures passively. This technique is highly effective, the most after tracheotomy, but also extremely invasive treatment, often associated with complications and aesthetic sequelae [21, 22]. Therefore, the treatment should be reserved for selected patients when all other approaches and first-level surgery have failed. Finally, tracheotomy is the most effective surgical treatment and the last technique which must be reserved exclusively for patients with severe OSA whose life is at risk.

**Conclusions**

Obstructive sleep apnea (OSA) is a highly prevalent disease, characterized by upper airway collapse during sleep. Prevalence of OSA has risen with obesity, a major risk factor for developing the disease, and is much higher in patients undergoing elective surgery. OSA has significant clinical consequences such as daytime hypersomnolence, neurocognitive dysfunction, cardiovascular disease, metabolic dysfunction, respiratory failure, and cor pulmonale.

Sedation and anesthesia have been shown to increase the upper airway collapsibility, therefore increasing the risk of having perioperative complications in these patients, with the majority of them undiagnosed. Proper history, screening, and diagnostic test should be used in order to identify patients with OSA syndrome and consider an adequate perioperative management. CPAP is the most common and effective first-line treatment in mild-to-moderate OSA, but also other alternatives such as oral devices or surgery could be used.

OSA patients undergoing a surgical process should be managed perioperatively developing an individual plan focusing on preoperative screening procedures, an optimized anesthesia and sedation regimen in which high-risk group of patients avoid the use of respiratory depressant drugs, and intraoperative neuromuscular monitoring with goal-directed reversal of blockade and consider the use of CPAP therapy perioperatively, optimal opioid titration for postoperative pain control, and adequate monitoring in the PACU.

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# Anesthesia for End-Stage Respiratory Disease

9

Morgan Le Guen and Sofian Faiz

Providing anesthesia in case of end-stage respiratory disease represents a challenge for anesthesiologist as soon as the preoperative visit till the postoperative period. It includes two different situations: lung surgery with a specific intraoperative management and a major risk of postoperative respiratory complications and any other surgery. Minimizing the risk begins in the preoperative period with tobacco withdrawal, pulmonary rehabilitation, and patients' education.

Optimal management of these patients required multidisciplinary medical team with concertation and a common strategy to limit the occurrence of postoperative complications.

## 9.1 Definition of End-Stage Respiratory Disease

End-stage respiratory failure includes a wide range of different diseases with some common characteristics. Usually this end-stage occurs progressively when mechanisms of compensation are altered. The prominent symptom is impairment in patient's capability with dyspnea at rest and the constant feeling of limited breath during activity. Moreover, other symptoms as morning headaches, acidosis, and severe hypoxemia complete the schema [1]. Systemic signs included pulmonary hypertension in some cases with iso-systemic profile and heart failure. Classification and severity levels are described in Table 9.1.

M. Le Guen, M.D., Ph.D. (✉) • S. Faiz, M.D.
Department of Anesthesia, 40 rue Worth, 92150 Suresnes, France
e-mail: m.leguen@hopital-foch.org



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**Table 9.1** From chronic respiratory symptoms to the end-stage respiratory failure

| | Severe | Very severe impairment = end-stage respiratory disease | Inscription to a list of lung transplantation |
|---|---|---|---|
| FEV1 test | 30 < FEV1 <49% | FEV1 <30% | FEV1 <20% |
| 6-MWT | <200 m<br>Stable $SpO_2$ | < 100 m<br>Drop in $SpO_2$ <4% | Drop in $SpO_2$ >4% |
| Arterial gas | Normal pH with normocapnia | Hyperbaric | Hyperbaric<br>Eventual acidosis |
| Clinical symptoms | None or minor (cough, shortness of breath) | Shortness of breath during exercise or at rest<br>Need of oxygen during the day | Constant shortness of breath<br>Need of oxygen |

*FEV1* forced expiratory volume in 1 s, *6-MWT* 6-min walk test, *$SpO_2$* saturation in oxygen

Origins of end-stage respiratory failure concern many respiratory pathologies as in a decreasing order of occurrence:

- Post-tobacco emphysema
- Severe COPD
- Fibrosis or cystic fibrosis
- Interstitial lung disease
- Obliterative bronchiolitis after immunosuppressive treatments or after transplantation
- Chronic ARDS but this entity will not be affordable in this article

## 9.2 Preoperative Assessment

### 9.2.1 General Health

The most important way of assessment remains clinical with an estimation of patient's autonomy in his daily life. This could be measured by the (I)ADL scale which explored different common actions as the ability to wear, to eat, etc. Impairment in autonomy is strongly associated with a poor outcome [2].

Then objective criteria can stratify the severity of the disease. One of the most important is advanced age (>60 years old) with the presence of any other comorbidity (systemic hypertension, neurological ischemic event, etc.). As described in Table 9.1, clinical symptoms of acute core pulmonary or right ventricle failure mean poor prognosis. In this circumstance a complete and current cardiac exam is required because in case of right ventricle hypertrophy, cardiac output is only on the dependency of its function and tolerance. Any source of ischemia (uncompleted stenosis of the right coronary artery) may quickly impair cardiac output with a rapid organ ischemia and lactic acidosis. Morphologic heart exam is required and should be completed by a coronarography to ensure the absence of coronary lesion. If a major

repair is scheduled, tolerance during an effort should be measured through stress echocardiography or stress RMI. This complete assessment aims to decide the best anesthesia and analgesia strategy before surgery. At last, respiratory function is assessed. Shunt level and severity of hypoxemia are strong predictors of the functional "reserve" of lungs. Moreover, loss in the control of the pH is a sign of a quick decompensation, and it may indicate a delay in the surgery [3].

As every preoperative visit, the main aim is to perform a complete exam of comorbidities (Charlson score) with an accurate pre-anesthetic strategy. Risk of anemia or unexpected bleeding is crucial due to the linked risk of ischemia. In the other hand, any alternative to avoid a depression of the respiratory function should be counseling: local or regional anesthesia, limitation of mechanical stretch, non invasive ventilation support. In case of a scheduled lung surgery, a respiratory functional test should demonstrate a postoperative VEMS above 30%. A lower value is associated with a very high risk of complication with difficulty to wean the patient from the mechanical ventilation [3].

In some conditions, discussion about lung transplantation is open. In an attempt to balance the scarcity of donors and maximize societal benefit of lung transplantation, the indications for lung transplant have been updated to denote greater attention paid to the potential life years gained. It is now recommended that lung transplant only be considered in patients with >50% risk of death from lung disease within 2 years without transplant, >80% chance of a 90-day survival after transplant, and >80% expected a 5-year survival with transplant from general medical perspective, provided adequate graft function.

## 9.2.2 Preoperative Optimization

### 9.2.2.1 Breath or Pulmonary Rehabilitation

Rehabilitation can improve overall functional status acting primary on the muscle mass which is decreased due to a poor nutritional status with severe catabolism and decreased in the daily activity. In this situation, production of lactic acid and of carbon dioxide and ventilator demand are decreased for a similar effort. This benefit is particular for end-stage COPD, and this program includes smoking cessation, better detection of pulmonary exacerbation, and compliance to treatment.

In COPD, pulmonary rehabilitation program have been shown to significantly improve exercise capacity and health-related quality of life while reducing the severity of dyspnea. In a study led by Cesario et al., rehabilitation was able to change the status of patients with an improvement in respiratory function and allow them to be operated without complications in comparison to a control group [4]. This program is less well studied for other causes of end-stage respiratory disease. A clinical trial (NCT 1893008) still under recruiting status specifically studies the preoperative inspiratory muscle training through a tapered flow resistive inspiratory loading device. This program is tailored individually. Starting inspiratory load is aimed at 60% of the measured maximal inspiratory pressure. The load is incrementally increased based on the rate of perceived exertion, and patients have to complete 30 dynamic inspiratory efforts twice a day [5].

#### 9.2.2.2 Concept of Prehabilitation

Prehabilitation includes the whole care pathway in the preoperative period whose aim is the health improvement of the "future" surgical or oncologic patient. In this meaningful, the increase in muscle mass and muscle tolerance should compensate the expected loss of muscle during the hospital length of stay. This concept precedes rehabilitation program supported by the ERAS society around the world and includes at the minimum three components: repeated series of aerobic and anaerobic exercises during the week (three times at most) with a devoted coach (physiotherapist or sport doctor), a diet optimization (reduction of sarcopenia, daily protein intake of 1–1.5 g/kg), and a psychological support. This interest in the preoperative period was promoted by Carli et al. at McGill University with a minimal duration of 4 weeks before the surgery [6].

Feasibility of such a multidimensional program was previously demonstrated in colorectal cancer. Therefore, an increase in the functional capabilities was observed with a gain of 10% in $VO_2$ peak and in the 6-min walk test (6-MWT) as reference [7]. For responders, two consequences were described. First, this gain was related to a significant decrease in the postoperative complications (2% vs. 18%) and a specific shape in their performance. Indeed, the improvement disappears during hospital stay and secondly re-ups within 2 months. Finally, patients recover similar performances than preoperatively. At the opposite, control patients have a progressive impairment in their physical performances in the preoperative period and continuously alter their functional status in the postoperative period with a long and uncomplete recovery. They never reach their basal status. Compliance in the program seems really important as demonstrated by Coats et al. on patients scheduled for lung surgery [8]. A recent interesting report was performed after neoadjuvant radiotherapy for rectal cancer by West et al. and showed similarity with a significant decrease in the functional status during radiotherapy but a real improvement during the preoperative period in the prehabilitation group [9]. This concept needs further randomized controlled trial to achieve an undebatable demonstration even if many pilot studies give a common trend. Implementation of such a pathway in the surgical patient may encounter some barrier but we can imagine that the "temporal" window is not the same for end-stage respiratory patients. A previous study in which a partial program was proposed to severe COPD patients demonstrated a change in their functional status, and in this small cohort, patients were initially rejected from surgery and finally undergone it without any major complication or death in the postoperative period [4].

## 9.3 Conduct of Anesthesia

### 9.3.1 Preoxygenation

Preoxygenation should be used in any patient to anticipate difficult ventilation or intubation, and this recommendation especially concerns a patient who is hypoxic on air before induction. This time is essential to reduce the occurrence of hypoxemic event during induction related to an impaired passive oxygen delivery in case

of thickening in the alveolar-capillary membrane. Some alternatives to improve oxygenation should be proposed to increase efficiency of preoxygenation.

First, a simple way to improve quality of preoxygenation is proclive position with recruitment of alveolar territories and more efficient diaphragmatic course. In patients with severe COPD and hypoxia, CPAP (continuous positive alveolar pressure) or pressure support ventilation (PSV) with PEEP during induction may be used to improve the efficacy of preoxygenation and reduce the development of atelectasis. This therapy was supported by some studies of emergent induction by Baillard et al. [10]. Therefore, NIV was associated with a low occurrence of drop in $SpO_2$ compared to standard care: 93 ± 8% vs. 81 ± 15%, $p < 0.001$. Current studies suggest high flow of oxygen as a new way to optimize oxygenation during spontaneous ventilation while introducing a low PEEP and during apnea through passive transfer of oxygen to the alveolar. A great multicenter trial demonstrated that high flow of oxygen had a place in severe ill patients to optimize alveolar oxygenation [11]. This study confirmed the previous one comparing non-rebreather reservoir bag mask and high-flow nasal oxygen during intubation with a significant lower incidence of desaturation: 2% vs. 14%, $p = 0.03$ [12].

### 9.3.2 Regional Anesthesia

It is accepted that general anesthesia through tracheal intubation and intermittent positive pressure ventilation (IPPV) is associated with adverse outcomes in patients with COPD, fibrosis, or bronchiolitis. Such patients are prone to bronchial and tracheal hyper-responsiveness, cardiovascular instability, barotraumas, hypoxemia, and high rate of postoperative pulmonary complications. There is now increasing evidence to support the use of regional techniques in cases traditionally thought possible only under general anesthesia. One study found a 50% reduction in the risk of postoperative pneumonia in COPD patients when surgery was conducted with epidural anesthesia alone. The use of noninvasive ventilation (NIV) intraoperatively may also be used to ameliorate the respiratory exchanges [4]. Controversy remains over the use of interscalene brachial plexus block in patients with end-respiratory disease with a risk of diminished respiratory function resulting to phrenic nerve palsy. It is possible that better use of ultrasound guidance will minimize the volume of local anesthetic required and so may reduce the incidence of phrenic nerve involvement. To improve NIV and control pain in the postoperative course, use of epidural analgesia may be recommended.

### 9.3.3 Choice of Anesthetics for General Anesthesia

In a similar manner than the brain in extreme ages, some data suggest differences among anesthetics on postoperative lung complications (pneumoniae, atelectasis, etc.). Indeed, ischemia-reperfusion (IR) process may increase a primary inflammatory response which is different according to the anesthetic agents: halogenated volatile

agents (Sevorane or desflurane) or intravenous agent—propofol [13]. Concerning volatile, their interests come from a direct infusion in the alveolar compartment before crossing the alveolar-capillary membrane to reach plasma, thanks to their high lipophilic profile. On the other hand, propofol has an optimal bioavailability especially in a high-risk situation of gas lack during one-lung ventilation because liver metabolism is controlled. Some studies have demonstrated a benefit for halogenated anesthesia with a reduction in the production of pro-inflammatory mediators in experimental or clinical studies. In clinical practice no direct relationship with postoperative outcome was found between anesthetics except in one. The role of volatile anesthetics inhibiting inflammatory response was firstly suggested by Schilling et al. who compared propofol administration and halogenated volatile in clinical setting of OLV. In these experiments bronchoalveolar lavage and blood analysis were performed and showed a compartmentalized response with a predominant ipsilateral response to ischemia. Therefore pro-inflammatory cytokines increased in the ventilated lung after OLV whatever the agents. But mediator release was about twofold more enhanced during propofol anesthesia compared with desflurane or sevoflurane administration [14]. As it concerns propofol, some studies suggest a positive impact on lipid peroxidation reactions caused by release of oxygen free radicals and inhibit the release of inflammatory mediator IL-8 and decrease the respiratory index. Therefore, results are still controversial, and one large review currently published drew a more favorable balance for halogenated agents. This review was based on eight studies on 350 patients undergoing OLV for thoracic surgery with protective effects via attenuating inflammatory responses [15].

### 9.3.4 Decision of Extubation

Before extubation, it is important to optimize the patient's condition. The neuromuscular blocking agent should be fully reversed and the patient warm, well oxygenated, and with a $PaCO_2$ close to the normal preoperative value for the patient. Peri-extubation bronchodilator treatment may be helpful. Extubation of the high-risk patient directly to noninvasive ventilation may reduce the work of breathing and air trapping and has been shown to reduce the need for reintubation in the postoperative period after major surgery.

### 9.3.5 Protective Ventilation During Anesthesia

#### 9.3.5.1 Common Rules

In case of surgery, concept of protective ventilation remains true: low volume and low airway pressure are required. Concerning the first proposition, there is no influence of the etiology of the respiratory disease, and recommendations are still 6–7 mL/kg of ideal weight. About the second aspect (airway pressure), some etiologies may interact with pressure, and setting of the mechanical ventilation may be accurate and difficult. This is especially the case for severe COPD with a risk of auto-PEEP and with (cystic) fibrosis with increased peak pressure and sometimes of plateau pressure. This pathology is generally managed with really small tidal volume (5 mL/kg) and relative

prolonged expiratory time (1:1 ratio and sometimes inverted). Concerning the level of PEEP, literature remains controversial because current trials did not show superiority of high PEEP during general anesthesia. The actual recommendation suggests rather low tidal volume (6–8 mL/kg) with low PEEP (5–8 mmHg) [16].

A particular caution should be mentioned for alveolar recruitment maneuver despite demonstration of its positive effect in many studies. Indeed the occurrence of a pneumothorax or, even worse, a bilateral pneumothorax is a major risk during end-stage respiratory disease especially in emphysema. Every anesthesia participant should be alert concerning this risk and should closely monitor airway pressure and limit any dynamic hyperinflation: to reduce respiratory rate and allow expiration (increasing expiration time) are the both preferred settings.

#### 9.3.5.2 One-Lung Ventilation

This procedure for severely ill patients can occur in case of lung surgery like videothoracoscopy, and the management of one-lung ventilation can be difficult with association of high airway pressures and a high risk of hypoxemia (arterial shunt + inefficient hypoxic pulmonary vasoconstriction). Strategy about ventilation is not clear in such a situation. Most literature support a low tidal ventilation without clear reduction during OLV. But 6–7 mL/kg applied in one lung is equivalent to 12 mL/kg especially in the left lung. But in some description, lungs are non-injured, and this is probably not the case in end-stage respiratory disease. The last Cochrane analysis about intraoperative management of ventilation supports low volume as a way to decrease postoperative mortality, mechanical ventilation, and lung injury [17]. There is a greater consensus about PEEP and RM with low PEEP and no RM during OLV. In the first situation, alteration of hemodynamic conditions and decreasing the postoperative respiratory complications are the main arguments. About RM, the risk of severe increase in plateau or peak pressure in the ventilated lung may increase the risk of barotrauma, and this event could be difficult to diagnose and treat during OLV in lateral decubitus. Therefore, a recent randomized trial has tested low tidal volume with high or low PEEP and RM during bi-pulmonary ventilation or not. One hundred twenty patients were included in four different groups, and if PEEP improves the $PaO_2/FiO_2$ ratio, the best association about respiratory compliance and postoperative recovery was triple: low tidal volume + Low PEEP + RM. In patients with altered parenchyma, this recommendation should be also applied.

At last, the occurrence of hypoxemic event is an expected risk in such patients and a planned strategy is recommended. Among possibilities, the most easier and efficient action is to perform a transient bi-pulmonary ventilation after according with the surgeon. This bilateral ventilation will shortly cancel the inequality in VA/Q ratio and correct immediately low $PvO_2$. In some situation, this technique can disturb the surgeon and cannot be performed. Maintenance of an open nondependent lung by CPAP (continuous positive alveolar pressure) and administration of almitrine (bolus + continuous infusion) if no pulmonary hypertension is present are both alternatives.

#### 9.3.5.3 ECMO

ECMO (extracorporeal membranous oxygenation) in high-volume centers is now an interesting support for severe patients during non-cardiac and non-lung surgery. Indeed, it can support severe or refractory hypoxemic situations and limit hypercapnic

acidosis through an eventual veno-venous cannulation [18]. In these situations it is a real strategy to preserve oxygenation on end-stage lungs without increasing anaerobic catabolism. At the opposite side, ECMO can allow a very protective ventilation (3–5 mL/kg) in case of cystic fibrosis with exacerbation of bronchorrhea or in case of lung overdistension with a common risk of pneumothorax. Usually the choice is rather a veno-venous ECMO in jugular vein. A double-lumen tube (Avalon™) by percutaneous way is possible because there is no expected reason to add a partial cardiac support. Control of the good position of the cannula is recommended through transesophageal exam (bicaval view) to optimize blood aspiration. In our experience during lung transplantation, an ECMO limited to the perioperative period is not related with an increase in morbid events. Another indication of ECMO in end-stage respiratory disease could be the anticipated difficulty to manage patient's airway: antecedent of difficulty, limited mouth opening, and motionless cervical spine. A preemptive ECMO in such situation allowed usual management without risk of hypoxic event.

## 9.4 Postoperative Course

### 9.4.1 Noninvasive Ventilation

Noninvasive ventilation (NIV) in the postoperative care has demonstrated no clear interest in prevention of pulmonary complications and especially in the case of lung resection for cancer [19]. At the opposite, providing NIV or more recently high-flow oxygen when an acute failure occurs is interesting to limit risk of reintubation and prolonged hospital stay. A large current randomized European trial demonstrated on patients undergoing major abdominal surgery that use of NIV significantly reduces the risk of reintubation within 7 days in case of occurrence of acute respiratory failure: 33.1% vs. 45.5% in the standard oxygen group ($p = 0.03$). There was no difference in the mortality rate [20].

Concerning high-flow nasal oxygen, literature is still poor because this technique is really novel. Nevertheless, first randomized trials suggested this technique as an alternative to NIV in intensive care unit. It delivers high flow (till 60 L/min) with a high inspired fraction in oxygen and maintained in the same way as PEEP around 5. Therefore, Stefan et al. demonstrated non-inferiority in using high-flow nasal oxygen compared to BIPAP ventilation in 830 cardiothoracic patients with or at risk for respiratory failure: 87/414 failure vs. 91/416, $p = 0.003$ [21].

### 9.4.2 Rehabilitation

Postoperative rehabilitation was largely promoted through ERAS recommendations following Kehlet's principles [22]. The aim of this program is to restore the surgical patient's autonomy as soon as the recovery room, limiting drainage, enhancing mobilization, and early alimentation. Cooperation of the patient and relatives is essential. In the case of lung surgery, Cerfolio et al. has described a specific pathway with a significant reduction in the length of stay (3 days for a lobectomy) [23]. Chest drain is limited at one

with a large threshold before removing it. Rate of complications and readmission was low in this strategy. The surgical culture is probably the main barrier to large implantation of this program as demonstrated by other teams [24]. The risk of developing postoperative complications during the first 2 weeks after surgery has been reported to be dependent on different factors as preoperative cardiorespiratory capacity measured as $VO_2$ peak. A systematic review from 2011 concluded that postoperative exercise is safe and feasible for patients with lung cancer and is associated with improvement of fitness and self-reported outcome such as quality of life and fatigue. Finally, PROLUCA randomized clinical trial is to date in its recruiting phase to demonstrate the interest of association in pre- and postoperative exercise to decrease complications. The postoperative rehabilitation is started either at 2 weeks or at 6 weeks and is associated with preoperative home-based exercises whose ultimate goal was to ensure moderate-vigorous intensity (60–80% of maximum heart rate) for at least 30 min per day [25].

There is no a priori contraindication to rehabilitation whoever the patient (elderly, obese, etc.) or whatever the surgery, but this program should be adapted in its objectives. Concerning patients with end-stage respiratory disease, it seems logical to include them in such a program to improve or stabilize the degradation of their respiratory function. To allow an efficient physiotherapy, management of pain is crucial and indication of epidural analgesia should be large in case of abdominal or lung surgery. The aim of this analgesia is a reduction in opioid requirement with occurrence of respiratory insufficiency or adverse events (hallucinations, urinary retention, etc.). At the opposite, a good analgesia may prevent respiratory complications, and some studies promote the anti-inflammatory effect of regional analgesia.

### 9.4.3 Analgesia

Analgesic strategy is a key component of reduction of the postoperative risk of pulmonary complications. A correct analgesia makes the physiotherapy possible without pain, and volumes in incentive spirometry are improved. The gold standard for thoracotomy was epidural analgesia, but the development of minimally invasive surgery (video-assisted thoracoscopy) changes this strategy to propose either paravertebral block or local wound infiltration. A current study demonstrated that paravertebral block provided better dynamic pain relief and reduced morphine consumption compared to local infiltration [26]. A common oral analgesic support is associated to allow the patient to cough, to move, and to quickly walk outside.

### 9.4.4 Prevention of Postoperative Complication

Prevention is an important field in this kind of patients to adapt means to the clinical pathway. Among actions, it is really important to attain tobacco and alcohol withdrawal a few weeks before the surgery and to avoid vitamin or iron deficiency [27]. Many scores have been established to predict risk of postoperative complications and especially respiratory complications. The most interesting was the scale developed by Canet et al. in which type of surgery (abdominal, thoracic or peripheric, and scheduled

or emergent), length of operation, and preoperative status (anemia, $SpO_2$, respiratory infection) are pondered in the final score [28]. This validation was reported on a large population of 2464 subjects. Recently, Canet et al. developed an accurate scale for respiratory complications to easily facilitate risk assessment. The main risk factors are low preoperative $SpO_2$, one preoperative respiratory symptom, chronic liver disease, history of congestive heart failure, surgical procedure lasting >2 h, and emergency [29]. No validation was performed on a cohort of severely ill patients like end-stage respiratory disease; nevertheless preexistent comorbidity probably impairs the postoperative course. A recent study about lung resection was performed on patients included in a rehabilitation program ($n = 99$). Some factors were predictive of lower postoperative activity as elderly (>75 years old), predictive FEV <70%, and poor activity (METS <3) in preoperative period or pain and dizziness on day 1 [30].

## Conclusion

Anesthesia in patient with end-stage respiratory disease corresponds to a global strategy with a complete preoperative assessment to anticipate any postoperative respiratory failure and indication of NIV or any other support during surgery and a large association with regional anesthesia (Fig. 9.1). Monitoring of driving and airway pressure is important in case of general anesthesia as the choice of anesthetics. The main risk is dynamic hyperinflation or pneumothorax. Prehabilitation and inspiratory exercises are the next challenges to limit respiratory complications in the postoperative course.

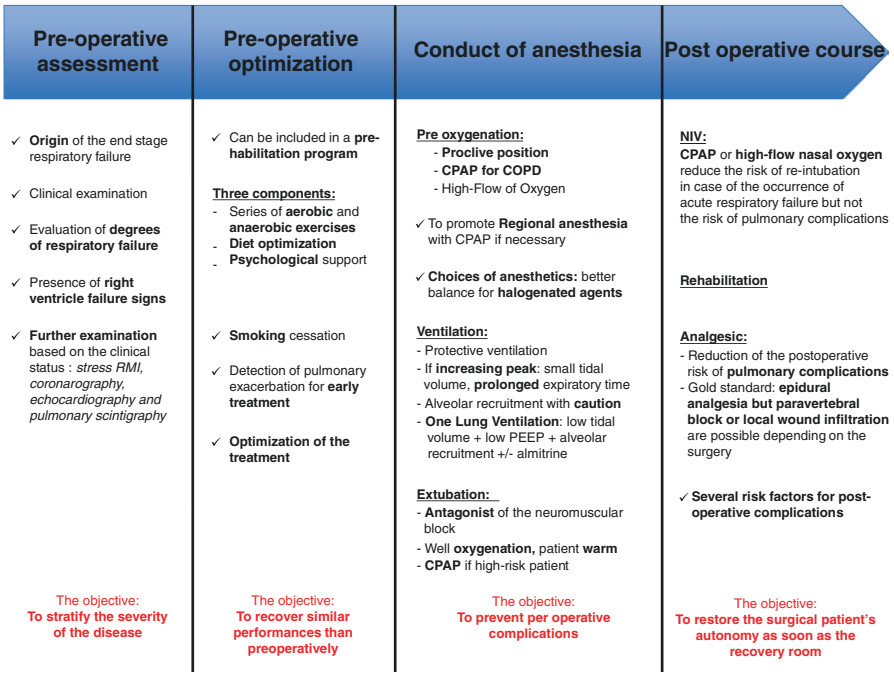


**Fig. 9.1** Respiratory strategy in patients with end-terminal respiratory disease in the perioperative period. Chronological approach

**Key Points**

- Preoperative optimization includes behavioral (smoking cessation, education) and physical exercises.
- The anesthetic goals include optimization of fluid preload, control of the heart rate, protective ventilation, and optimal analgesia.
- Regional anesthesia alone or in association with general anesthesia in the operative period and in the postoperative course may reduce the risk of postoperative pulmonary complications.
- Protective ventilation (low tidal volume with controlled airway pressure) especially during lung surgery and limiting dynamic hyperinflation are recommended.
- Noninvasive ventilation should be administrated in the recovery room to allow alveolar recruitment.
- Patients have to be informed about the risk of postoperative pulmonary complications with an eventual need of respiratory assistance (NIV, tracheotomy, etc.).

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# Part III

# Renal and Metabolic Risks

# The Patient with End-Stage Renal Disease

10

Antoine Dewitte and Olivier Joannès-Boyau

## 10.1 Introduction

Kidney disease is defined as an abnormality of the kidney structure or function which can occur abruptly and either resolve or become chronic. Chronic kidney disease (CKD) is a general term for heterogeneous disorders with variable clinical presentation, in part related to cause, severity and the rate of progression. Previous international guidelines classified the severity of CKD in five stages with stage 5, also called end-stage renal disease (ESRD), being the most serious illness. Recently, these guidelines reclassified CKD based on its cause, glomerular filtration rate, and albuminuria category (Fig. 10.1) [1]. Symptoms are usually due to complications of decreased kidney function that can affect all organ systems, and, when severe, CKD can be treated only by dialysis or transplantation. Although the need for those treatments arises in only 1% of patients with CKD, it remains a growing concern worldwide with the increasing prevalence of hypertension, diabetes mellitus, and metabolic syndrome and the most expensive of chronic diseases [2]. These patients are also exposed to increased risk of acute kidney injury (AKI) that may accelerate progression of CKD or adverse effects of drugs. ESRD patients may require anaesthesia and surgery for numerous reasons, including vascular access procedures, parathyroidectomy, renal transplantation, invasive procedures or elective and emergency surgery for reasons that are unrelated to their renal disease. ESRD patients have then a higher perioperative morbimortality and an increased intensive care and hospital length of stay [3–6]. This may be attributed to numerous factors: a hemodynamic instability with an increased need for vasopressors or antihypertensive agents, a higher incidence of myocardial

A. Dewitte • O. Joannès-Boyau (✉)
Hôpital Magellan, Centre Hospitalier Universitaire (CHU) de Bordeaux, Service d'Anesthésie-Réanimation 2, F-33000 Bordeaux, France
e-mail: olivier.joannes-boyau@chu-bordeaux.fr



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| Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012 | | | | Persistent albuminuria categories Description and range | | |
|---|---|---|---|---|---|---|
| | | | | A1 | A2 | A3 |
| | | | | Normal to mildly increased | Moderately increased | Severely increased |
| | | | | <30 mg/g <3 mg/mmol | <30–300 mg/g 3–30 mg/mmol | >300 mg/g >30 mg/mmol |
| GFR categories (ml/min/ 1.73 m²) Description and range | G1 | Normal or high | ≥90 | | | |
| | G2 | Mildly decreased | 60–89 | | | |
| | G3a | Mildly to moderately decreased | 45–59 | | | |
| | G3b | Moderately to severely decreased | 30–44 | | | |
| | G4 | Severely decreased | 15–29 | | | |
| | G5 | Kidney failure | <15 | | | |

**Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.**

**Fig. 10.1** Prognosis of CKD by GFR and albuminuria category [1]

dysfunction, an increased time on mechanical ventilation, perioperative fluid and electrolyte disturbances such as hyperkalaemia [7] and increased bleeding complications [8].

## 10.2 Preoperative Management

### 10.2.1 Evaluation of Comorbidities

ESRD is caused by a variety of diseases with diabetes mellitus and hypertension in the foreground, followed by chronic glomerulonephritis, cystic kidney disease, interstitial nephritis and other diseases such as obstructive uropathy or lupus nephritis. Kidney failure leads to the commonly recognized symptoms of uraemia, but patients with end-stage renal disease suffer from various concomitant medical diseases affecting all organ systems, which have an impact on postoperative outcome. Their medical history is then complex, and it is important to take a full preoperative history and also to evaluate the medications taken by the patients, not just for risk stratification but also for the development of a tailored perioperative treatment regime including advanced haemodynamic monitoring.

#### 10.2.1.1 Cardiovascular System

Cardiovascular disease remains the most important limiting factor affecting postoperative morbidity and mortality [9]. Cardiovascular disease is the major cause of increased morbidity and mortality in dialysis patients and accounts for over 50% of deaths, while the risk of cardiovascular disease is 10–30 times higher in dialysis patients than in the normal population. Coronary artery disease impacts 25% of patients with chronic kidney disease [10]. Several factors may contribute to the development and progression of cardiovascular disease in patients on renal replacement therapy. These include both the traditional cardiovascular risk factors recognized in the general population and additional risk factors particular to chronic kidney disease. Damage starts in early stages and frequently in the form of dilated cardiomyopathy, congestive cardiac failure, left ventricular hypertrophy and pulmonary hypertension. Accelerated arteriosclerosis is promoted by diabetes and dyslipidaemias, while hypertension and cardiomyopathy is usually due to both volume and pressure overload and high levels of renin-angiotensin. Atrial fibrillation is also more prevalent in patients with ESRD than in the general population, and it is associated with increased perioperative risk for stroke and mortality. If possible, preoperative electrolyte disturbances are corrected with dialysis in order to minimize the risk of new-onset or recurrent atrial fibrillation or other cardiac dysrhythmias. An electrocardiogram (ECG) should therefore be considered as part of standard preoperative assessment.

Hypertension plays an important role in causing cardiac damage by producing left ventricular hypertrophy, which predisposes the patient to ischaemia. The prevalence of hypertension is up to 90% in patients with a glomerular filtration rate below 30 mL/min and is both a cause and a consequence of chronic kidney disease. The impairment of coronary perfusion in a hypertrophic heart results in regional impairment of left ventricular contraction and left ventricular dilatation, leading to systolic dysfunction. The risk of cardiovascular death in patients on dialysis has been reported to be 2.2 times greater in those with a pre-dialysis blood pressure of 130/80 mmHg or greater than in those with a blood pressure of less than 130/80 mmHg [11]. Foley et al. have reported that, after adjusting for age, diabetes, ischaemic heart disease, haemoglobin and serum albumin, each 10-mmHg rise in mean arterial blood pressure is associated with concentric left ventricular hypertrophy and the development of ischaemic heart disease and cardiac failure [12].

The optimal preoperative cardiac evaluation for dialysis patients is not well defined but generally depends upon the level of risk. According to the ESC/ESA guidelines on noncardiac surgery [13], effective perioperative cardiac management includes preoperative risk stratification based on preoperative assessment of functional capacity, type of surgery, cardiac risk factors and cardiovascular function. The ESC/ESA guidelines discourage indiscriminate routine preoperative cardiac testing, because it is time- and cost-consuming and resource limiting and does not improve perioperative outcome. They rather emphasize the importance of individualized preoperative cardiac evaluation and the cooperation between anaesthesiologists and cardiologists.

Patients already taking beta-blockers should continue taking their regular dose, including the morning of surgery, in order to minimize the chance of development

of tachycardia or ischaemia. However, prophylactic initiation of beta-blockers prior to surgery is not recommended as this intervention may increase the risk of hypotension, stroke and death.

#### 10.2.1.2 Endocrine System and Nutritional Status

Diabetic nephropathy is the most common cause of ESRD in Europe. Diabetes mellitus is seen in up to 30% of patients who need renal replacement therapy and can aggravate hypertension and cardiovascular disease, resulting in a greater risk of stroke or myocardial infarction [14]. Hence, screening and treatment of coronary artery disease are essential in diabetic patients undergoing surgery. Many issues regarding the perioperative care of dialysis patients with diabetes are the same as for diabetic patients without ESRD. However, dialysis patients with type 1 diabetes may be more brittle than patients who do not have ESRD. Given the wide variations in glucose metabolism with surgery, the management of these patients may therefore be extremely difficult.

As GFR falls, phosphate excretion falls leading to reduced absorption of calcium from gastrointestinal tract and vitamin D deficiency. Hyperactivity of parathyroid glands attempts to maintain calcium. This may play a role in the pathogenesis of cardiovascular disease in CKD. A high degree of fibrosis and myocardial calcium content can lead to the development of myocardial hypertrophy and diastolic dysfunction of the left ventricle [15]. Secondary hyperparathyroidism and increased calcium phosphate product have been found to be associated with calcification of the cardiac valves and coronary arteries. It has also been suggested that hypophosphatemia is mainly responsible for cardiac valve calcification. Calcium-based chelators are widely used for phosphate control; however, high doses are required, which can lead to frequent episodes of hypercalcaemia, thus contributing further to metastatic calcification. This secondary hyperparathyroidism also leads to osteomalacia culminating into a clinical entity known widely as renal osteodystrophy. The result is bone demineralization making these patients susceptible to spontaneous pathological fractures.

Malnutrition is common in ESRD patients and its pathogenesis is complex. Under-dialysis leads to anorexia and abnormalities in taste which impact dietary nutrition intake. Increasing dialysis adequacy can improve nutritional intake. Some of the other factors involved in ESRD-related malnutrition include restrictions in diet and fluid which reduce the calories available and make food less attractive, medications which impair absorption of nutrients, bowel function and/or appetite, loss of nutrients during haemodialysis, dialysis-induced catabolism and chronic inflammation. Protein-energy wasting, inflammation and cardiovascular disease may increase mortality in the dialysis population [16]. Poor nutrition reduces tissue repair and should be corrected to minimize the risk of wound infection or dehiscence. In the case of elective surgery, there should be adequate time to involve a dietician, increase dialysis adequacy and improve nutritional intake prior to surgery.

#### 10.2.1.3 Haematological System

Normochromic, normocytic anaemia is a known complication of ESRD secondary to decreased erythropoietin synthesis and release, decreased red cell life span, increased haemolysis and bleeding or repeated loss during haemodialysis. Compensatory mechanisms to overcome the decrease in oxygen carrying capacity include an increase in cardiac output and 2,3-DPG causing a right shift of oxygen dissociation curve and thus improving tissue oxygenation. Anaemia is also linked to cardiovascular morbidity and mortality. In a study by Harnett et al., the independent relative risk of mortality in dialysis patients was calculated to be 1.18 per 1.0-g/dL decrease in haemoglobin level [17]. Ideally, the preoperative haemoglobin concentration should be at the recommended target range of 11–12 g per dL (haematocrit 33–36%) in patients with CKD who receive erythropoiesis-stimulating agents [18]. The guidelines do not recommend a specific haemoglobin level at which to initiate these agents, but they are usually given when a patient's haemoglobin level is less than 10 g per dL (100 g per L), when the rate of haemoglobin decline suggests a need for a blood transfusion and when the reduction of transfusion-related risks, such as alloimmunization, is a goal. For patients undergoing elective surgery, if the patient has haemoglobin less than target, erythropoietin-stimulating agents may be administered preoperatively. Iron studies should also be performed since iron deficiency can contribute to anaemia and erythropoietin resistance.

#### 10.2.1.4 Electrolytes and Acid Base Status

Inability to excrete water, electrolytes and free acids results in metabolic acidosis, hyponatraemia, hyperchloraemia and hyperkalaemia. For every 0.1 unit change in pH, potassium increases by 0.6 mEq/L. Hypermagnesaemia usually follows hyperkalaemia and can cause neuromuscular weakness, respiratory failure, bradycardia, hypotension and heart block. The potassium concentration that is acceptable for surgery depends on the urgency of the surgery. There are no guidelines that definitively state a maximum safe level of potassium prior to induction of anaesthesia but all patients with an elevated serum potassium concentration should have a 12-lead electrocardiogram. The potassium concentration that is deemed acceptable for induction of individual patients may vary depending on chronicity of hyperkalaemia and type of surgery. Surgery with anaesthesia that faces chronic hyperkalaemia ($K < 6$) and no ECG changes is usually well tolerated by the majority of patients. Chronic dialysis patients often have an increased tolerance for hyperkalaemia, as ECG changes are frequently not seen until the serum potassium concentration exceeds 6.0–6.5 mEq/L.

The patient's volume status or estimated dry weight should also be appreciated preoperatively, notably by the frequency of dialysis and when it was last performed. The optimal volume status prior to surgery is based in part upon estimates of anticipated fluid to be administered and/or lost during surgery. If euvolaemia or estimated dry weight is not achieved and/or the patient receives a large volume of fluid during

surgery, hypervolaemia and possibly pulmonary oedema can occur in the immediate postoperative period, thereby necessitating dialysis. On the other hand, in case of hypovolaemia, there is a risk of hypotension during anaesthesia-induced systemic vasodilatation, which can cause many significant complications, including but not limited to thrombosis of the arteriovenous access.

#### 10.2.1.5 Coagulation

An increased tendency of bleeding at sites of surgery may be present in dialysis patients. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) remain normal but bleeding time (BT) is prolonged. However, not all uraemic patients have a bleeding diathesis, and some are actually hypercoagulable. It is likely that multiple factors are responsible for the platelet dysfunction in uraemia. These include retention of uraemic toxins due in part to inadequate dialysis, anaemia, excess parathyroid hormone and the use of antiplatelet agents. Standard coagulation tests including prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR) and platelet count are usually obtained in all patients, whereas a bleeding time is not recommended as a preoperative screening test. For most patients taking aspirin for primary or secondary prevention of cardiovascular disease, the dose is held for 5–7 days before noncardiac surgery unless there are specific indications for its continuation. Aspirin is restarted after surgery, when the perioperative risk of major bleeding has passed. However, the approach to perioperative aspirin administration may differ for certain types of surgery. Clopidogrel should be stopped at least 7 days prior to surgery. The approach to patients receiving dual antiplatelet therapy after percutaneous coronary intervention should be discussed individually.

#### 10.2.1.6 Gastrointestinal System

Anorexia, nausea and vomiting are frequent in CKD patients. Delayed gastric emptying time, increased acidity and gastric volume usually indicate $H_2$ blockers and proton pump inhibitors.

### 10.2.2 Renal Replacement Therapy Management

Preoperative anaesthetic assessment includes determination of the type of dialysis (haemodialysis, peritoneal dialysis), the type and location of dialysis access, the frequency dialysis prescription, the usual fluid intake (that may be restricted), the usual daily urine output, the “dry weight” and the medications given at dialysis that may not be on usual medication list. Haemodialysis patients should be dialyzed the day before surgery, if possible. However, haemodialysis treatments should not be added prior to surgery, since intensive haemodialysis has not been shown to improve outcomes. It is important to institute measures that avoid prolonged anticoagulation and the amount of ultrafiltration should be carefully adjusted to ensure that the patient is at or close to dry weight prior to surgery. Peritoneal dialysis patients

should also be at their dry weight prior to surgery. The major indications for urgent preoperative dialysis are hyperkalaemia and volume overload.

### 10.2.3 Premedication

If midazolam is administered in the immediate preoperative period to treat anxiety, the dose should be reduced and titrated according to the effect. The elimination of midazolam and its main metabolite, a1-hydroxymidazolam, is reduced in patients with ESRD. Furthermore, protein binding of midazolam is decreased in ESRD, resulting in an increased plasma level of free fraction of midazolam.

## 10.3 Intraoperative Anaesthetic Management

### 10.3.1 Vascular Access

The haemodialysis vascular access is often described as the patient's "lifeline". They should not be used for purposes other than dialysis except in emergency. An arteriovenous (AV) access may be at risk for thrombosis from procedure-associated hypotension. Access function should be checked as part of the postoperative evaluation, and displaying a sign at the patient's bedside to save the designated arm is important. If necessary, placement of central venous catheters in the subclavian vein should be avoided, if at all possible, because of the risk of central stenosis, which could imperil the fistula or graft. Central lines should also not be placed on the same side as the arteriovenous access. Knowledge of the patients' vascular anatomy, such as an occluded internal jugular, subclavian or femoral vein, may help the anaesthesiologist establish central venous access. Peripherally inserted central catheter (PICC) lines should also be avoided in dialysis patients to preserve the superficial veins for future arteriovenous fistulas.

### 10.3.2 Local or Regional Anaesthesia

When appropriate**,** local or regional anaesthesia should be proposed in the absence of a bleeding diathesis or residual anticoagulation after heparin administration that may be present in patients up to 4 h after haemodialysis. They may avoid a potentially hazardous general anaesthesia in a patient with multiple comorbidities and the need of multiple IV anaesthetic agents that may have delayed metabolism and excretion. However, doses of sedatives and/or opioids should be reduced and titrated to effect in patients with ESRD since these agents may have delayed metabolism and excretion. Furthermore, the volume of distribution and degree of plasma protein binding of anaesthetic drugs may be altered, resulting in higher-than-expected plasma concentrations.

### 10.3.3 General Anaesthesia

The metabolism of different anaesthetic agents used in general anaesthesia varies in patients with ESRD. The optimal choice of the anaesthetic agent varies based upon underlying metabolism, concurrent comorbid conditions and the surgical procedure.

#### 10.3.3.1 Propofol

The pharmacokinetic and pharmacodynamic responses to propofol are not markedly altered by ESRD [19]. The induction dose should be reduced (e.g. 1–2 mg/kg) and titrated carefully in dialysis patients who are hypovolaemic and elderly or have known coexisting heart failure [20].

#### 10.3.3.2 Neuromuscular Blocking Agents Used for Induction

In patients requiring rapid sequence induction and intubation due to risk of vomiting and inhalation, succinylcholine can be used safely as neuromuscular blocking agent (NMBA) to facilitate laryngoscopy if the potassium concentration is <5.5 mEq/L and there are no electrocardiographic changes [21]. The hyperkalaemia response after succinylcholine administration is not exaggerated in ESRD patients. As in healthy patients, a transient potassium increase of approximately 0.5–1 mEq/L is observed. However, patients with ESRD have reduced levels of plasma cholinesterase, causing a prolonged neuromuscular block. If potassium level at the time of induction is ≥5.5 mEq/L, rocuronium may be used at a relatively large dose (1 mg/kg) as an alternative. Although rocuronium is primarily eliminated by direct liver uptake and excretion in bile, some is excreted renally, with reduction in clearance by 33–39% in patients with ESRD. Hence, neuromuscular blockade is somewhat prolonged unless sugammadex is used to reverse its effects [22].

Concerning the nondepolarizing NMBAs, atracurium (0.5 mg/kg) or cisatracurium (0.15 mg/kg) are preferred to facilitate laryngoscopy since their elimination is independent of renal function [23]. These agents undergo Hofmann elimination, an organ-independent elimination pathway occurring in plasma and tissue, which is not altered in ESRD [24]. Due to the interindividual variability to muscle relaxants, it is necessary to monitor the degree of neuromuscular blockade in patients with ESRD.

### 10.3.4 Inhalational Anaesthetics

Isoflurane, sevoflurane or desflurane is usually used to maintain general anaesthesia since elimination occurs predominantly via exhalation, independent of renal function. Concerns have been expressed regarding the theoretical renal toxicity of sevoflurane due to its inorganic fluoride ion metabolite [25] and formation of a substance known as “Compound A”. However, sevoflurane has not been associated with clinically significant renal injury, and it has been used widely and safely in patients with chronic stable renal insufficiency and in dialysis patients [26, 27].

## 10.4 Postoperative Anaesthetic Care

### 10.4.1 Pain Management

Usual drugs for pain management can be used in ESRD patients, but narcotic agents including morphine and meperidine should be used judiciously if at all as they have active metabolites (as morphine 6 glucuronide that is badly removed and highly active in ESRD patients) and may have prolonged activity in the setting of renal dysfunction. Fentanyl and hydromorphone are better choices [28]. For patients with creatinine clearance below 30 mL/min, the World Health Organization (WHO) recommends three specific steps for drugs: step one is for paracetamol, step two for tramadol and buprenorphine and step three for fentanyl. Indeed, the clearance and removal of these drugs and their active metabolites are not so impacted by ESRD.

### 10.4.2 Global Management

Patients may have faced renal aggression during surgery and their current renal function should be addressed postoperatively. The volume status and the remained diuresis of the patient must be evaluated to adapt rehydration and dialysis schedule. Most of the time, in the absence of severe bleeding, ESRD patients have fluid overload postoperatively and infused volume should be decreased. A dialysis run may be scheduled the day after surgery in function of metabolic disturbances and volume status, but if necessary, the dialysis may be provided the same day and directly in the intensive care unit (metabolic emergency, severe volume overload, hemodynamic instability with non-transferable patient, etc.). Usual drug dosing is adapted to the real clearance of the patient that may have changed after surgery, but dialysis should be taken into account as most of drugs are highly removed during the dialysis session. As soon as possible, the patient will be seen by the nephrologist to evaluate the impact of surgery on renal function and start again the dialysis every two days if he used to be dialysed before surgery.

**Conclusion**

The management of ESRD patients in perioperative is based on three important steps. Firstly, evaluate the level of renal disease and its impact on patient conditions and comorbidities. Secondly, use adapted drugs and avoid new insults that may impair the remaining kidney function or create metabolic disorders. Lastly, take care of fluid's volume variations and electrolyte disturbances in the patient. Nephrologist should be involved before and after the perioperative period to adjust treatment and follow-up of the patient in taking into account the impact of anaesthesia and surgery.

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# The Patient with End-Stage Liver Disease

# 11

Emmanuel Weiss and Catherine Paugam-Burtz

Cirrhosis, the end-stage of liver diseases, is an increasing cause of morbidity and mortality [1]. The decompensation of the liver function is a key event during the natural history of this disease as it substantially worsen patient prognosis. Surgery and anesthesia are well-known cause of cirrhosis decompensation that may lead, at worst, to "acute on chronic liver failure" if it is associated with organ failures. In this context, it is not surprising that the reported in-hospital mortality after various non-transplant surgical procedures ranges from as much as 8.3–25% in selected cirrhotic patients compared to 1.1% in non-cirrhotic patients [2, 3]. In a recent 7-day cohort study including 46,539 patients that underwent surgery in 498 hospitals in 28 European countries, liver cirrhosis was associated with an increase of postoperative mortality by more than threefold [4]. Despite this poor outcome, improvements in the medical management and life expectancy have increased the eligibility of these patients to surgery. For these reasons, this chapter will (1) review pathophysiological modifications induced by cirrhosis in order to improve their perioperative management, (2) summarize recent data on surgical risk assessment in these patients, and (3) provide therapeutic approaches for perioperative optimization in this unique group of surgical candidates.

E. Weiss • C. Paugam-Burtz (✉)
Department of Anesthesiology and Critical Care Medicine, APHP, Hôpital Beaujon, Hôpitaux Universitaires Paris Nord Val de Seine, F-75018 Paris, France

Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France

Inserm UMR_S1149, Center for Research on Inflammation, Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France
e-mail: catherine.paugam@aphp.fr



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## 11.1 Preoperative Evaluation of Patients with End-Stage Liver Disease

### 11.1.1 Pathogenesis of Cirrhosis

In the normal liver, portal blood runs through hepatic sinusoids where fenestrated endothelia allow extensive metabolic exchange with hepatocytes that execute most of known liver functions. Sinusoidal blood is then collected by terminal hepatic venules that flow into one of the three hepatic veins and finally the caval vein.

In cirrhosis, extensive fibrosis is accompanied by distortion of the hepatic vasculature and that leads to shunting of the portal and arterial blood supply directly into the portal outflow, compromising exchange between hepatic sinusoids and the adjacent liver parenchyma, i.e., hepatocytes. The major clinical consequences of cirrhosis are impaired liver function and increased resistance to portal inflow, i.e., portal hypertension.

### 11.1.2 Assessment and Prognosis of Liver Dysfunction

Cirrhosis should no longer be regarded as a terminal disease, and the concept of dynamic process is now accepted. The natural history of cirrhosis depends on both the cause and treatment of underlying liver disease. Yearly rate of decompensation varied between 2 and 10% and can even be higher in case of alcoholic cirrhosis with continued alcohol use [5]. In all types of end-stage liver disease, once decompensation has occurred, mortality without liver transplantation is as high as 85% over 5 years. The Child-Pugh-Turcotte (CPT) score (Table 11.1) [6], simple and reproducible, allows the prediction of 1-year survival with values of 100, 80, and 45% in case of classes A, B, and C, respectively [7]. More recently, the Model for End-Stage Liver Disease (MELD) score has been developed to provide a more accurate prediction of short-term (3 months) mortality. Initially designed to predict mortality in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS), it is based

**Table 11.1** Child-Turcotte-Pugh's classification [6]

| Parameter | 1 point | 2 points | 3 points |
|---|---|---|---|
| Hepatic encephalopathy (grade) | None | 1–2 | 3–4 |
| Ascites | Absent | Mild | Moderate |
| Prothrombin time (s prolonged) | <4 | 4–5 | >6 |
| or | | | |
| International normalized ratio | <1.7 | 1.7–2.3 | >2.3 |
| Serum albumin (g/dL) | >3.5 | 2.8–3.5 | <2.8 |
| Total bilirubin (g/dL) | <2 | 2–3 | >3 |
| CTP class | A | B | C |
| Points | 5–6 | 7–8 | 10–15 |

on serum creatinine, international normalized ratio (INR), and serum bilirubin and ranges from 6 to 40 [8]. Three-month-mortality rates are 1.9%, 20%, and 71% for MELD score values lower than 9, between 20 and 29, and 40, respectively [8].

### 11.1.3 Extrahepatic Pathophysiological Modifications Induced by Cirrhosis

#### 11.1.3.1 Cardiovascular Modifications

Patients with cirrhosis and portal hypertension exhibit a cardiovascular hyperdynamic syndrome characterized by increased heart rate and cardiac output and reduced systemic vascular resistance and arterial blood pressure [9]. These alterations intensify with the progression of the liver disease. Briefly, portal hypertension increased the shear stress on the splanchnic vessel walls leading to increased production of various vasodilators (such as nitric oxide), causing splanchnic vasodilation. Other factors including bacterial translocation or hyporesponsiveness of the splanchnic vessels to vasoconstrictors also contribute to the splanchnic vasodilation. The shunting of blood and the excess of vasodilators from the splanchnic to the systemic circulation following the opening of portal-systemic shunts related to increased portal pressure also leads to systemic arterial vasodilation. Altogether, these modifications lead to a reduction in the effective blood arterial volume, thereby stimulating endogenous vasoconstrictor systems (i.e., sympathetic nervous system, renin-angiotensin-aldosterone system), favoring water and salt retention, and triggering a hyperdynamic circulation in these patients [10].

In parallel, these patients can develop an authentic cirrhotic cardiomyopathy that associates impaired contractile responsiveness to stress, diastolic dysfunction, and electrophysiological abnormalities (e.g., prolonged QT interval and abnormal chronotropic response) without any other cause of cardiac disease. Thus, during the course of cirrhosis, there is a progressive deterioration of cardiac function that plays an important role in the pathogenesis of the impairment of effective arterial blood and correlates with the degree of liver failure.

Altogether, as vasodilation intensifies with disease progression, cardiac output cannot increase further, leading to arterial hypotension, activation of vasoconstrictors, and continuous renal sodium and water retention, accumulating as ascites. Refractory ascites, hyponatremia, and hepatorenal syndrome (HRS) are extreme manifestations of this process.

#### 11.1.3.2 Kidney Function Alterations in Cirrhosis

Often multifactorial, acute kidney injury (AKI) occurs in approximately 20% of hospitalized patients with cirrhosis and has a poor prognostic impact [11]. This prevalence may be underestimated if the diagnosis is made on serum creatinine. Indeed, muscle mass is frequently low in cirrhotic patients and the release of creatinine reduced [12]. Therefore, patients may have a normal serum creatinine in the setting of a very low glomerular filtration rate. In most of cases (70%), AKI mechanism is prerenal and results from renal hypoperfusion without glomerular or tubular

lesion. Indeed, abovementioned circulatory modifications make cirrhotic patients especially susceptible to absolute or relative hypovolemia resulting from gastrointestinal bleeding, diuretic use, sepsis, or large volume paracentesis. HRS is the result of a persistent renal hypoperfusion related to systemic vasodilation in the absence of precipitating event (e.g., hypovolemia or nephrotoxic drug). It is a diagnosis of exclusion that is specific for decompensated cirrhosis and differs from other prerenal AKI because it is not volume responsive. To conclude to HRS, strict criteria should be met [13]: (1) cirrhosis with ascites, (2) serum creatinine >133 μmol/L (or 1.5 mg/dL) after at least 2 days or diuretic withdrawal and volume expansion with albumin (1 g/kg body weight), (3) absence of shock, (4) no current or recent treatment with nephrotoxic drugs, and (5) absence of parenchymal disease as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells/high power field), and/or abnormal renal ultrasonography. Although albumin and vasoconstrictors administration can improve kidney function, the only curative treatment of HRS remains liver transplantation. Indeed, HRS occurrence represents a significant turn in the history of cirrhosis as it associated with a devastating prognosis (mortality rate up to 90%) without liver transplantation.

#### 11.1.3.3 Pulmonary Complications of Cirrhosis

Regardless of the etiology, chronic liver disease has well-established effects on respiratory function. Firstly, ascites and pleural effusion can lead to a marked lung restriction and atelectasis. Hepatic hydrothorax, a pleural effusion that develops in patients with cirrhosis in the absence of substantial cardiac or pulmonary disease, may occur in as many as 10% of patients with chronic liver disease [14]. Acute pulmonary edema is favored by the high rate of cardiac diastolic dysfunction shown in these patients (48% and up to 88% in CPT classes A and C, respectively) [15]. More specifically, two distinct pulmonary vascular disorders, hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH), may occur as a consequence of hepatic parenchymal or vascular abnormalities. HPS, which is found in approximately 20% of patients, refers to the triad of portal hypertension, hypoxemia, and intrapulmonary vascular dilations resulting in a right to left shunt. Although application of oxygen improves hypoxemia, mechanical ventilation during general anesthesia might aggravate intrapulmonary shunting [16]. POPH results from an obstruction to arterial flow in the pulmonary arterial bed. It must be screened using echocardiography in patients with liver disease and symptoms of dyspnea [17]. Portopulmonary hypertension is indistinguishable from other forms of pulmonary hypertension, and its cause is far from understood [18]. Treatment with agents approved for POPH (i.e., prostacyclin analogues, phosphodiesterase inhibitors, or endothelin receptor antagonists) for 3–6 months may be useful in improving hemodynamics and exercise capacity in patients with POPH [19].

#### 11.1.3.4 Coagulopathy in Cirrhosis

Cirrhosis is associated with alterations of the coagulation system involving all phases of hemostasis: primary hemostasis (platelet-vessel wall interactions), coagulation

**Table 11.2** Alterations of hemostasis found in patients with cirrhosis (adapted from [20])

| | Anti-hemostatic drivers | Prohemostatic driver |
|---|---|---|
| Primary hemostasis | Thrombocytopenia | Elevated level of von Willebrand factor |
| | Abnormal platelet function | Low level of ADAMTS13 |
| | Decreased production of thrombopoietin | |
| | Increased production of nitric oxide and prostacyclin | |
| Secondary hemostasis | Low levels of factors II, V, VII, IX, X, and XI | Elevated level of factor VIII |
| | Vitamin K deficiency | Low levels of protein C, protein S, antithrombin, and heparin cofactor II |
| | Dysfibrinogenemia | Inherited thrombophilia |
| Fibrinolysis | Low levels of α2-antiplasmin, factor XIII and TAFI | Low level of plasminogen |
| | Elevated level of t-PA | |

(thrombin generation and inhibition), and fibrinolysis (clot dissolution) [20]. However, contrary to common belief, cirrhosis is associated with alterations of both pro- and anti-hemostatic drivers (Table 11.2) [20], and the coagulation system is in fact rebalanced. While it is important to recognize that procoagulant factors (factors II, V, VII, IX, X, and XI) are decreased in cirrhosis, one may not forget that anticoagulant factors (antithrombin and protein C) and fibrinolytic proteins produced in the liver are also reduced. Similarly, low platelet count may be counterbalanced by increased platelet aggregability caused by highly active von Willebrand multimers [21] or procoagulant changes in fibrin clot structure. Altogether, these data suggest the establishment, in cirrhotic patients, of a restored, albeit fragile, hemostasis equilibrium that can quickly move toward an acute bleeding risk. Nevertheless, to date, routine coagulation tests (such as prothrombin time) are assessing the defect in procoagulant drivers in isolation, and not the thrombotic risk of these patients [22]. Thus, there is increasing evidence that changes in both coagulation factors and platelet count regularly observed in cirrhotic patients cannot be interpreted as a reliable indicator of diffuse bleeding risk. Moreover, the increased thrombotic risk of these patients is now well documented. Cirrhosis is a risk factor for thromboembolic disease [23]. In practice, despite the lack of clear evidence, PT <30%, hypofibrinogenemia <1 g/L, and thrombopenia <50 G/L are regularly considered as threshold values that may motivate prophylactic correction of hemostasis disorders.

#### 11.1.3.5 Sepsis in Cirrhosis: Immune Dysfunction and Nutritional Status

Patients with cirrhosis have increased risk of developing bacterial infection, sepsis, sepsis-induced organ failure, and sepsis-related death [24]. Bacterial infections increase mortality of cirrhotic patients fourfold with 30% of these deaths occurring within the year after sepsis. Furthermore, in-hospital mortality of patients with cirrhosis who have septic shock is higher than in other patients and exceeds 70% [24–26]. Such susceptibility is related to immune system alterations referred to as

cirrhosis-associated immune dysfunction (CAID) that associates an immune paralysis (also called immunodeficiency) and systemic inflammation features [27]. While immune paralysis (also called immunodeficiency) is due to an impaired response to pathogen (e.g., involving reduced HLA-DR/co-stimulatory molecule expression on monocytes/macrophages or decreased phagocytosis-mediated bacterial clearance), systemic inflammation is a consequence of persistent and inadequate stimulation of cells of the immune system that may cause tissue damages and favor the development of organ failures [24].

Predisposition of cirrhotic patients to develop infections is also linked with nutritional status. Indeed, malnutrition is particularly frequent in patients with cirrhosis (up to 70% of the patients in the waiting list for liver transplantation) and especially severe in those with alcoholic liver disease. Malnutrition can be measured by anthropometric measurements (e.g., involuntary weight loss and BMI), but albuminemia and prealbuminemia are not suitable in cirrhosis as they are influenced by liver disease. In this context, measurement of muscle depletion (i.e., sarcopenia) using CT scan is particularly interesting as it is independently associated with poor outcome (see below).

#### 11.1.3.6 Cirrhosis and Anesthesia

Concerns related to hepatotoxicity of intravenous and even of inhaled anesthetic agents can be considered as historic. Anesthetics for which elimination primarily depends on renal clearance or redistribution (such as propofol, etomidate, fentanyl, sufentanil) are usually the first-choice drugs, However, pharmacokinetics of drugs is highly variable in severe cirrhotic patients because of major changes in distribution volumes and sodium retention, albumin plasma levels, metabolism, and elimination processes. Furthermore, hepatic perfusion is reduced and cirrhotic liver is more susceptible to hypotension and hypoxia [28]. Therefore, the effect of a bolus is unpredictable, and anesthetic agent administration should be titrated [28]. Noteworthy, intraoperative hypotension has been shown to negatively impact cirrhotic patient postoperative outcome.

## 11.2 Surgery and Cirrhosis: What Complications Can Be Expected?

Patients with cirrhosis can undergo two different kinds of surgery: surgery related to their liver disease such as hepatocellular carcinoma resection, repair of ascites-related abdominal hernia, and “non-hepatic” surgery.

In the first situation, if liver resection is usually performed in well-selected cirrhotic patients, surgery of complication is per se frequently performed on advanced cirrhosis with a high risk of acute liver decompensation. In case of hepatic resection, direct traumatic effect on the liver and ischemia/reperfusion injury increase the risk of postoperative liver failure that ranges between 5 and 8% in patients with cirrhosis despite appropriate preoperative evaluation [29]. Perioperative management of cirrhotic patients requires therefore having a good knowledge of specific

complications of this disease, such as refractory ascites or renal insufficiency. For this reason, patients should reasonably be managed in specialized liver units.

"Non-hepatic surgeries" can include, for example, colorectal, cardiovascular, orthopedic, or thoracic surgery. In the first study investigating 793 cirrhotic patients, major surgery-related morbidity was 30% and mortality 11.6%. Most frequent complications were infections (postoperative pneumonia (8%), bloodstream (6.3%), surgical site (2.6%)), ventilator dependence (7.8%), bleeding, and new-onset or worsening of ascites (6.7%) reflecting liver disease decompensation [2]. More recently, a study by Lin et al. enrolled 24,282 cirrhotic patients undergoing non-hepatic surgery that were matched with 97,127 controls by age, sex, type of surgery, and anesthesia. Patients with cirrhosis were also prone to develop postoperative sepsis (6% septicemia, 3% pneumonia, 1% deep wound), postoperative bleeding, and acute renal failure [30]. This susceptibility of cirrhotic patients to sepsis has been developed above in this chapter. In practice, postoperative morbidity of cirrhotic patients is also related to late complications that may be more frequent than early ones [2]. Surgical stress combined with infections is the basis for cirrhosis decompensation that can take the form of renal failure, digestive hemorrhage or worsening of synthesis and excretion functions of the liver. Postoperative liver failure has a devastating prognosis with a transplant-free mortality higher than 70% [31]. In these cases, a multidisciplinary approach is required to discuss specific treatments such as TIPS or liver transplantation [32].

## 11.3 Surgery and Cirrhosis: What Are the Risks?

Postoperative morbidity and mortality rates in cirrhotic patients undergoing various types of surgery reported in the literature are displayed in Table 11.3. Taking studies assessing general surgical risk (including various surgeries) in cirrhotic patient as example, morbidity ranges from 14 to 50% and mortality from 1.2 to 19%. In the majority of the studies, an increased postoperative risk was found, from the first stage of liver disease [30, 33]. Study of survival curves shows that this excess in mortality is related to early postoperative period before a merging of survival curves probably due to the natural prognosis of cirrhosis.

Postoperative morbidity and mortality show a quasi-linear rise in proportion to the severity of cirrhosis, whatever the type of surgery the scoring system used (i.e., CTO and MELD scores, see above) [2, 30, 34, 35]. In elective cardiac surgery, for example, postoperative morbidity varied between 10 and 53% in CTP A, 56 and 100% in CTP B, and 100% in CTP C [36–39]. Similarly, postoperative mortality varied between 3 and 11% in CTP A, 18 and 41% in CTP B, and 67 and 100% in CTP C [36–39]. The same prognosis predictive ability was found for MELD score in a cohort of 168 cirrhotic patients that underwent tricuspid valve surgery: mortality rates were 4 and 29% in case of MELD score lower and higher than 15, respectively [18]. As shown in Table 11.3, CTP and MELD scores were also found to predict morbidity and mortality among patients undergoing abdominal, orthopedic, and ENT surgery [19, 33, 40, 41] although their impact may differ according to the type of surgery studied (Table 11.3).

**Table 11.3** Postoperative morbidity and mortality reported in patients with cirrhosis

| Author/type of surgery | Date | *N* | Global morbidity (%) | Global mortality (%) | Mortality according to MELD score (%) | Morbidity/mortality (%) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Child Pugh A | Child Pugh B | Child Pugh C |
| **General surgical risk assessment** | | | | | | | | |
| Ziser A | 1999 | 733 | 30 | 11.6 | – | 23/8.4 | 41.5/17 | |
| Farnsworth N | 2004 | 40 | – | 17.5 | – | –/15 | –/9 | –/60 |
| Del Olmo JA | 2003 | 135 | 50 | 16.3 | – | 40/7 | 68/32 | 64/54 |
| Northup PG | 2005 | 140 | – | 16.4 | MELD <10:6 | – | – | – |
| | | | | | MELD = 25:26 | | | |
| Teh SH | 2007 | 772 | – | 19 | MELD <8:5.7 | – | – | – |
| | | | | | MELD >20:50 | | | |
| Hoteit MA | 2008 | 195 | 32 | – | – | – | – | – |
| Costa BP | 2009 | 190 | 24 | 13 | iMELD <35:4 | 27.05 | 20/14 | 26/31 |
| | | | | | iMELD >45:50 | | | |
| Cho HC | 2010 | 490 | – | 3.5 | MELD <14:2.8 | –/1 | –/9.5 | –/36.4 |
| | | | | | MELD >20:20 | | | |
| Lin CS | 2013 | 24,282 | 13.8 | 1.2 | – | – | – | – |
| **Abdominal surgery** | | | | | | | | |
| *Mixed abdominal surgery* | | | | | | | | |
| Telem DA | 2010 | 100 | NA | 7 | MELD >16:29 | –/2 | –/12 | –/12 |
| Befeler AS | 2005 | 53 | 25 | 0.17 | – | – | – | – |
| Northup PG | 2005 | 67 | – | 24 | | – | – | – |
| *Umbilical hernia repair* | | | | | | | | |
| Carbonell AM | 2005 | 1197 | 16.5 | 2.5 | – | – | – | – |
| Telem DA | 2010 | 21 | 71 | 5 | – | – | – | – |
| Eker HH | 2011 | 30 | 7 | 0 | – | – | – | – |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Marsman HA | 2007 | 34 | | | | | | |
| Hernia repair | | | 18 | 0 | – | – | – | – |
| Conservative | | | 77 | 15 | – | – | – | – |
| *Cholecystectomy* | | | | | | | | |
| Puggioni A (meta-analysis) | 2003 | 351 | 21 | 6 | – | – | – | – |
| Perkins L | 2004 | 33 | | 7 | – | – | – | – |
| Bingener J (laparoscopic) | 2008 | 99 | 18 | 6.3 | – | 30/– | 22/– | – |
| El Awadi S | 2008 | 110 | | | | | | |
| Open | | | 35 | 0 | – | –/0 | –/0 | – |
| Laparoscopic | | | 13 | 0 | | | | |
| El Nakeeb A | 2010 | 120 | | | | | | |
| Open | | | 15 | 0 | – | –/0 | –/0 | – |
| Harmonic scalpel clipless laparoscopic | | | 8.3 | 0 | | | | |
| Bessa | 2011 | 40 | | | | | | |
| Open | | | 35 | 0 | – | –/0 | –/0 | – |
| Harmonic scalpel clipless laparoscopic | | | 25 | 0 | | | | |
| Delis SG (laparoscopic) | 2010 | 220 | 19 | 0 | – | 18.5/0 | 23/0 | NA |

(continued)

**Table 11.3** (continued)

| Author/type of surgery | Date | *N* | Global morbidity (%) | Global mortality (%) | Mortality according to MELD score (%) | Morbidity/mortality (%) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Child Pugh A | Child Pugh B | Child Pugh C |
| Csikesz NG | 2009 | 14,007 | – | – | – | –/2 | – | |
| *Colorectal* | | | | | | | | |
| Meunier K | 2008 | 41 | 77 | 26 | – | 65/23 | 81/29 | 100/21 |
| Csikesz NG | 2009 | 6120 | – | – | | –/6 | –/17 | |
| Nguyen GC | 2009 | 4042 | 43 | 14 | – | – | – | – |
| *Hepatic* | | | | | | | | |
| Delis SG | 2009 | 69 | 36 | 7.2 | MELD <10:0 | – | – | – |
| | | | | | MELD >9:19 | | | |
| Hsu KY | 2009 | 1017 | 31 | 2 | MELD >8:4.0 | – | – | – |
| Kamiyama T | 2010 | 983 | 16 | 0.5 | – | – | – | – |
| Citterio | 2016 | 543 | 48.8 | 0.9 | – | – | – | – |
| **Cardiothoracic and vascular surgery** | | | | | | | | |
| *Elective cardiac surgery* | | | | | | | | |
| Suman A | 2004 | 44 | 27 | 16 | | 9.7/3 | 66/41 | 100/100 |
| An Y | 2007 | 24 | 60 | 25 | | 53/6 | 100/67 | 100/100 |
| Filsoufi F | 2007 | 27 | | 26 | | 22.11 | 56/18 | 100/67 |
| Csikesz NG | 2009 | 1539 | – | 13 | | –/11 | –/24 | – |
| Shaheen AAM | 2009 | 711 | 43.3 | 17 | | – | – | – |
| Ailawadi G | 2009 | 168 | – | 6.5 | MELD <15 = 4.1 | – | – | – |
| | | | | | MELD >15 = 29.2 | | | |
| Morisaki A | 2010 | 42 | 31 | 9.8 | | – | – | – |
| Marui A | 2011 | 332 | 40.8 | 1.8 | | – | – | – |
| Lopez-Delgado JC | 2013 | 58 | | 12 | – | –/0 | –/23.8 | –/66.6 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *Elective aortic aneurysm repair* | | | | | | | | |
| Csikesz NG | 2009 | 902 | – | 7.4 | – | –/7 | –/9 | |
| *Lung cancer surgery* | | | | | | | | |
| Iwata | 2007 | 33 | 18.2 | 6.5 | – | – | – | – |
| **Orthopedic (hip and knee) surgery** | | | | | | | | |
| Cohen SM | 2005 | 29 | 18 | 14 | – | 14/4 | 29/14 | 100/100 |
| Neuwman JM | 2016 | 68,865 | 22 | 29 | – | – | – | – |
| **Other surgery** | | | | | | | | |
| *Transurethral resection of the prostate(TURP)* | | | | | | | | |
| Nielsen SS | 2001 | 30 | – | 6.7 | – | – | – | – |
| *ENT surgery* | | | | | | | | |
| Kao HK | 2010 | 62 | 43 | 45 | – | 38/5 | 47/23 | 100/67 |

These results deserve some comments. First, whatever the size of the population included, all these studies are retrospective, and no prospective validation of the prognostic ability of MELD or CPS is currently available. Secondly, their retrospective design limits their external validity. Indeed, patients that were retrospectively included underwent surgery after a selection process that probably differs across centers and remains poorly explained. In keeping, the number of patients disqualified for surgery is missing, and nearly all included patients have CPS grade A and B cirrhosis. Finally, while the impact of cirrhosis severity on outcome varies according to the type of surgery, different types of surgery with various proportions are pooled in most of the studies. Thus, although outcome of cirrhotic patients undergoing surgery seems to improve overtime, such results should be treated with caution owing to the lack of homogeneity between studies.

Beside the severity of underlying liver disease, several other risk factors for postoperative morbidity and mortality have been showed. In the work from Ziser et al., "non-hepatic" mortality risk factors involved preoperative status (ASA score, preoperative sepsis, and renal insufficiency), comorbidities (chronic obstructive pulmonary disease history), a high surgical severity score, and occurrence of intraoperative hypotension [2]. Some studies also identified some other preoperative factors reflecting liver function such as ascites and serum albumin and some intraoperative ones such as transfusion requirement or surgery duration [3, 42, 43]. Altogether, some factors, i.e., ASA score, age, and emergency surgery, were constantly identified whatever the type of surgery [34, 43–45]. Some teams attempted to refine individual risk prediction. Among them, Cleveland "Mayo Clinic" provides on his website a four-variable model allowing calculation of the postoperative death probability following major surgery in a cirrhotic patient. This model, easy to calculate on the website (http://www.mayoclinic.org/meld/mayomodel9.html), includes age, MELD, ASA class, and cirrhosis etiology. For example, according to this calculator, the 30-day probability of death for a 60-year-old ASA3 patient with hepatitis C-related cirrhosis and MELD score equal to 15 has a 30-day death probability of 14.2%. Although the external validity of this model remains questionable as it comes from the retrospective analysis of a large, albeit monocentric, cohort of cirrhotic patients [34], this kind of approach allows an individual evaluation of the risk tailored to each patient. In patients who are candidates for liver transplantation, such risk assessment may be used to plan management. In low-risk patients, postoperative mortality is low enough that most patients may find the risk of surgery acceptable. Nevertheless, the surgery should ideally be performed at institutions with a center for liver transplantation. In patients with high-risk score, the risk of mortality is so high that elective procedures may be postponed until after liver transplantation. Finally, patients with medium risk should have most of their evaluation for liver transplantation completed before the surgery so that emergency liver transplantation could be performed, if required. Preoperative TIPS aiming at decrease portal hypertension before surgery has also been described in very small series of patients or in case reports, but their effect on postoperative morbidity and mortality remains to be studied.

Finally one should keep in mind that, in the specific context of liver surgery, the impact of MELD score, albeit significant, is lowered by several other important

factors including portal hypertension and planned extension of hepatectomy that interact to predict outcome [46].

## 11.4 Surgery and Cirrhosis: How to Optimize Patient Management?

First of all, a team-based approach involving hepatologists, surgeons, anesthesiologists, and intensivists with experience in treating cirrhotic patients, ideally at a specialist center, appears required [34, 43].

In this view, different ways of optimization involving different actors can be considered.

### 11.4.1 Surgical Considerations

Surgery should ideally be elective, due to the higher than average risk associated with emergency surgery in these patients [3, 33, 34, 43]. The choice of surgical technique is of importance in these patients, particularly in case of emergency surgery. Gallstones and hernia are particularly frequent in the cirrhotic population due to increased abdominal pressure and the outcome following cholecystectomy, and hernia repair surgery was frequently investigated. In this context, laparoscopic-modified techniques appear to reduce postoperative morbidity. Laparoscopic cholecystectomy is associated with lower bleeding complications and shorter operating time and hospital stay despite a higher conversion rate to open surgery during the procedure, especially in the case of emergency surgery [47–49]. Concerning umbilical hernia, it is now clear that elective surgical repair (after ascites treatment) should be preferred to conservative management [50]. Laparoscopic repair offers the advantage to avoid any skin incision (precluding ascites fluid leak) and to avoid exposing prosthetic mesh to necrotic infected tissue [51, 52]. Such benefit of minimally invasive technique is also well described in for liver resection surgery. In carefully selected candidates, laparoscopic liver resection allows shorter hospital length of stay, earlier return of bowel activity, and lesser requirement of analgesics, as compared to open techniques [53].

### 11.4.2 Anesthetic Considerations

#### 11.4.2.1 Preoperative Detection and Correction of Malnutrition

There are not so many ways to prevent postoperative complications, especially infectious ones. Preoperative detection and correction of malnutrition/sarcopenia is one of them. Thus, nutritional status should be evaluated preoperatively (see above). In case of denutrition, a nutrition rehabilitation strategy should be adopted in order to optimize caloric and protein intake [54].

The challenges of anesthetic management in these patients are directly related to the extrahepatic pathophysiological modifications induced by cirrhosis developed before.

#### 11.4.2.2 Hemodynamics

Cirrhosis-related cardiovascular modifications favor the occurrence of hypotension and acute kidney injuries in these patients. In this context, perioperative hemodynamic optimization in order to maintain effective intravascular volume to ensure tissue perfusion and cellular oxygenation is even more important in these patients. There is evidence of this in the reported independent impact of intraoperative hypotension on morbidity and mortality suggesting that cirrhotic liver is more sensitive to ischemia [2]. On the other hand, excessive fluid administration may worsen ascites and peripheral edema and have little effect on intravascular volumes. Perioperative hemodynamic optimization through cardiac output (or stroke volume) monitoring is mandatory, as recommended in non-cirrhotic major digestive surgery [55, 56]. Any device allowing direct or indirect evaluation of left ventricular stroke volume and responsiveness to fluid loading could be used. Due to low basal systemic vascular resistances that characterize these patients and to the concomitant effect of anesthetic drugs, the prompt use of vasonconstrictor agents is often necessary. Beside hemodynamics management, kidney function preservation also requires to avoid any nephrotoxic medication.

#### 11.4.2.3 Blood Product Administration

Administration of coagulation factors in an attempt to correct anomalous laboratory tests is not justified and is potentially harmful as there is no correlation between routine coagulation tests and the incidence of bleeding complications after invasive procedures in patients with cirrhosis [22]. The lack of reliable assessment tool of coagulopathy in liver disease remains problematic. As mentioned above, in practice, despite the lack of clear evidence, PT <30–50%, hypofibrinogenemia <1 g/L, and thrombopenia <50 G/L are regularly considered as threshold values that may motivate a correction of hemostasis disorders. Nevertheless, the use thromboelastography and thromboelastometry, two bedside devices measuring the viscoelastic properties of a clot in an in vivo time-dependent manner, may improve the monitoring of the coagulopathy and guide the administration of blood products. At that time, the lack of standardization of viscoelastic test parameters in cirrhosis may explain their insufficient ability to predict the hemorrhagic risk. Indeed, if ROTEM use does not decrease blood loss during surgery, it may reduce fresh frozen plasma transfusions (while increasing fibrinogen ones) during major hemorrhage in cirrhotic patients [57, 58].

#### 11.4.2.4 Ventilation

Due to their high potential to develop lung restriction and atelectasis secondary to ascites and pleural effusion, protective ventilation associating tidal volume of 6 mL/kg of ideal body weight, 6–8 $cmH_2O$ PEEP, and recruitment maneuvers (as described in the IMPROVE study) appears particularly recommended in these patients [59].

#### 11.4.2.5 Appropriate Treatment of Sepsis

As mentioned above, postoperative infectious complications are extremely frequent in the cirrhotic population. In this view, these episodes should be diagnosed early and an effective treatment promptly introduced in order to reduce postoperative morbimortality. However, the choice of antibiotic could be difficult. Indeed, cirrhotic patients are highly susceptible to develop infections caused by resistant bacteria as risk factors of multiresistance concentrate in this population (mainly repeated hospitalizations and antibiotic exposure for example through fluoroquinolone-based prophylaxis against spontaneous bacterial peritonitis) [60]. Albumin should be administered in patients with spontaneous bacterial peritonitis in association with antibiotics (and in association with terlipressin in patients with type 1 hepatorenal syndrome) [61]. However, so far, the beneficial effect of albumin has not been demonstrated for infections other than spontaneous bacterial peritonitis [62]. An ongoing randomized controlled trial is currently addressing this question.

**Conclusion**

Optimal anesthetic management of patients with liver disease remains a challenge. It based on preoperative evaluation of the severity of underlying liver disease and of the benefit expected from the surgery in order to weight the benefit/risk balance. Ways to improve patient management include optimization of preoperative nutritional status, intraoperative hemodynamics, and postoperative infection treatment. Finally, a multidisciplinary approach is required, and management of most severe cases must be discussed between hepatologists surgeons, anesthesiologists, and intensivists. The possibility of an overall project of liver transplantation should especially be evaluated.

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# The Severely Obese Patient

# 12

Lorrie Tremblay, Jean S. Bussières, and Paul Poirier

## 12.1 Introduction

According to the World Health Organization (WHO), the prevalence of obesity worldwide has more than doubled since 1980, and it has become a major health issue. Overweight and obesity are now linked to more deaths worldwide than underweight, and developing countries are increasingly affected by weight issues. Moreover, there is an increased proportion of patients with severe obesity [1]. Currently, more than two billion persons worldwide are now overweight or obese [2].

Obesity is a multisystemic disease and obese patients may present a higher risk of complication in the perioperative setting. They pose significant challenges to the anesthesiologists caring for them in the operating room as well as in the intensive care unit (ICU).

## 12.2 Definition

Obesity has been defined multiple ways, but the most commonly used definition is the body mass index (BMI): weight /height ($kg/m^2$). The WHO defines obesity with a BMI > 30 $kg/m^2$. Obesity is further classified in three different categories, depending on the BMI value (Table 12.1). According to the American Society of Anesthesiologists, patients with BMI > 40 $kg/m^2$ are defined as morbidly obese, and those with BMI > 50 $kg/m^2$ have super morbid obesity [3, 4]. The American Heart

L. Tremblay • J.S. Bussières (✉)
Department of Anesthesiology, Institut Universitaire de Cardiologie et de Pneumologie de Québec, Quebec City, QC, Canada
e-mail: jbuss@criucpq.ulaval.ca

P. Poirier
Department of Cardiology, Institut Universitaire de Cardiologie et de Pneumologie de Québec, Quebec City, QC, Canada



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**Table 12.1** Obesity classification according to body mass index (BMI)

| Class | BMI (kg/m$^2$) |
|---|---|
| Underweight | <20.0 |
| Normal range | 20.0–24.9 |
| Obese class 1 | 25.0–29.9 |
| Obese class 2 | 30.0–34.9 |
| Obese class 3 | 35.0–39.9 |
| Obese class 4 | 40.0–49.9 |
| Obese class 5 | 50.0–59.9 |
| Obese class 6 | ≥60.0 |

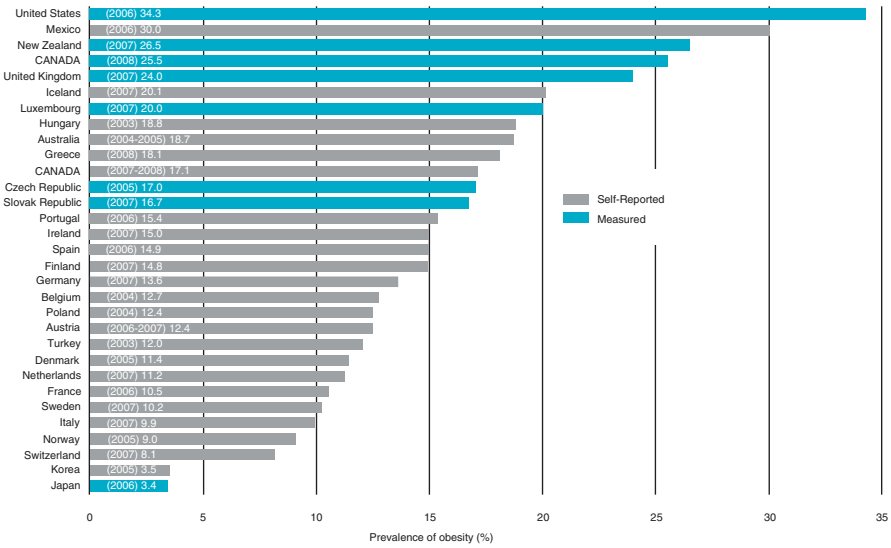



**Fig. 12.1** Prevalence of obesity in OECD countries, 2004–2008. Recent obesity estimates indicate that measured obesity ranges from 10.5% in France, 25.5% in Canada, and up to 34.3% in the United States. From: Obesity in Canada. A joint report from the Public Health Agency of Canada and the Canadian Institute for Health Information. 2011

Association has published another classification including adult patients with BMI over 60 kg/m$^2$ as well as characterizing obesity in children [3] (Fig. 12.1).

## 12.3 Comorbidities Associated with Obesity

### 12.3.1 Metabolic Syndrome

Obesity is further classified according to fat distribution, namely, the android and gynecoid obesity (Fig. 12.2). This distinction has important clinical implications [5].

Android (or central) obesity mainly involves the upper part of the body and often implies intra-abdominal visceral fat accumulation. This type of obesity predominates

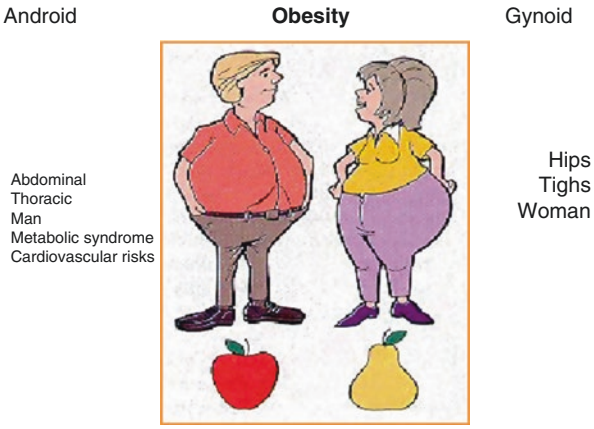



**Fig. 12.2** Types of obesity related to gender. The fat distribution is more abdominal and thoracic in man (android obesity), while it is found on hips and thigh in woman (gynoid obesity). From: Prise en charge de l'obèse dans Anesthésie et réanimation, Ed Fellahi, 2014

in men and can lead to the metabolic syndrome, a group of risk factors known to predispose to type 2 diabetes and cardiovascular disease. Indeed, from a physiological standpoint, adipose cells should not be regarded only for its role in energy balance and storage. Abdominal fat does participate in a prothrombotic and pro-inflammatory cascade that affects fatty acid metabolism and contributes to the development of insulin resistance [6]. There are several definitions of the metabolic syndrome, but recognition is mostly based on the finding of at least three of the following five criteria: (1) glucose intolerance, (2) abdominal obesity, (3) increased blood pressure, (4) low high-density lipoprotein (HDL) levels, and (5) increased triglyceride (TG) level [7]. The metabolic syndrome may have a negative impact on outcomes after noncardiac and cardiac procedures. It increases the risk of perioperative and postoperative complications [8]. In contrast, women more often present with a gynecoid (or peripheral) obesity that involves predominantly the accumulation of fat at the thighs and hips levels. The intra-abdominal cavity being relatively spared from significant fat accumulation, they may avoid the complications associated with the metabolic syndrome. Consequently, indirect measures of central fat distribution such as the waist circumference may be better markers of obesity-related comorbidities such as coronary artery disease [9]. Also, abdominal obesity may be of importance in the postoperative period. Not surprisingly, in a large cohort of patients who underwent isolated CABG, a strong association between BMI-defined obesity and adverse postoperative events was found. More interestingly, adiposity, assessed according to WC, was associated with an increased risk of postoperative adverse events, independently of BMI. This data suggest that WC and BMI, both markers of different features of adiposity, are both associated with postoperative complications [10].

### 12.3.2 Cardiomyopathy

Cardiomyopathy is a common finding among the severely obese patients, and it can lead to diastolic and/or systolic heart failure [11]. A significant accumulation of body fat causes an increase in overall metabolism, blood volume, and cardiac

output. The heart chambers dilate in response to a chronic volume overload, thus increasing stress on ventricular walls. The myocardium adapts to this phenomenon through hypertrophy. This eventually leads to left ventricular dysfunction and diastolic heart failure. With long-standing severe obesity, myocardial hypertrophy fails to compensate for this additional stress imposed on the ventricles. Systolic heart failure may eventually develop. This often occurs after several years of severe obesity (BMI > 50 kg/m$^2$) [12]. It should be noted that the ventricular remodeling associated with obesity may be reversible after significant weight loss [13–15]. Because pulmonary comorbidities are frequently found in this population, right ventricular dysfunction is a common finding. Repeated hypoxic episodes lead to pulmonary hypertension and ensuing right ventricular dilatation and eventually failure [14].

### 12.3.3 Respiratory Comorbidities

Obesity impacts respiratory function in various ways. The burden on respiratory mechanics and diaphragmatic excursion will be greater if the bulk of tissue is in the upper chest and abdominal area, as seen with central obesity. Chest compliance is diminished, and reduced lung volumes confirm the presence of a restrictive syndrome. Also, the increased circulating blood volume adds to this restrictive physiology by decreasing lung compliance. The functional residual capacity (FRC) is primarily affecting lung volume. This lower FRC, especially in the supine position, often leads to lung volumes being lower than the closing capacity, causing ventilation-perfusion mismatch and hypoxemia even during normal breathing [16]. This phenomenon is increased during general anesthesia. Overall, obese subjects present an increased work of breathing, and to compensate, they tend to adopt a breathing pattern with reduced tidal volumes and higher respiratory rates. Obesity-induced bronchial hyperactivity is frequent in this population, and it can be resistant to standard asthma treatment [17]. An abundance of soft tissue in the cervical region predisposes to upper airway obstruction. Therefore, obstructive sleep apnea (OSA) affects up to 40% of obese patients [18]. Patients with severe undiagnosed OSA are particularly at risk of respiratory depression during the postoperative period, especially with the administration of opiates. The patient suffering from OSA who is not adequately managed with a continuous positive airway pressure (CPAP) could then present episodes of significant desaturation, even a few days after the procedure [19]. Moreover, the treatment of moderate to severe OSA with a CPAP reduces the risk of cardiovascular complications in the long term and should be instituted when feasible [20].

The obesity hypoventilation syndrome (Pickwickian syndrome) is characterized by daytime hypercapnia related to central hypoventilation. The physiopathology of this condition remains imprecise. It is estimated that this syndrome affects about 11% of severely obese patients suffering from OSA [21]. These patients are particularly vulnerable to postoperative respiratory complications and often present with significant right ventricular dysfunction. Of importance, waist circumference (WC) has been shown to be associated with an increased risk of postoperative atrial fibrillation, prolonged mechanical ventilation and reintubation, renal failure, and new

postoperative renal replacement therapy, blood stream infection, sternal wound infections, and intensive care unit and hospital length of stay independently of BMI. These associations were independent of BMI, a marker of total adiposity in contrast to WC, which represents a marker of central obesity. These findings suggest that, besides total adiposity per se, fat mass distribution also influences clinical outcomes after isolated CABG [10].

### 12.3.4 Other Comorbidities

Obese patients have a higher incidence of type 2 diabetes, chronic kidney disease, osteoarthritis, hiatal hernias and certain types of cancer. They may also develop non-alcoholic fatty liver disease, which can progress to cirrhosis. The obesity-related state of chronic inflammation and impaired fibrinolysis place patients with high BMI at risk for thromboembolic complications, especially in the perioperative period.

## 12.4 Preoperative Evaluation

Preoperative assessment of obese patients should focus on their airway as well as their cardiopulmonary status.

### 12.4.1 Cardiac Assessment

Some obese patients presenting for surgery are relatively healthy, and thus, the need for further cardiac evaluation should be based on the patient's specific risk factors for cardiovascular disease and the risks associated with the surgery itself [14]. A patient's ability to perform at least four metabolic equivalents (METs) should be reassuring that its cardiopulmonary status is adequate to undergo most low- and intermediate-risk surgeries without further testing [22]. Unfortunately, obese patients may have limited functional capacity because of weight-related issues. Also, dyspnea on exertion, non-anginal chest pain and lower limb edema are frequent complaints in this population.

Features of the metabolic syndrome should be actively sought, as it is frequently associated with coronary artery disease [7]. A preoperative electrocardiogram should be obtained if coronary artery disease is suspected based on history or risk factors. A new left bundle branch block can be a sign of occult CAD. An ECG showing right axis deviation or a right bundle branch block should raise suspicion of possible right ventricular dysfunction and pulmonary hypertension, and further investigation is appropriate [14].

An algorithm for the assessment of severely obese individuals undergoing non-cardiac surgery has been published and may help in planning appropriate investigations in this population [14]. Known coexisting cardiac conditions should be stable prior to surgery and optimized if necessary.

### 12.4.2 Respiratory Assessment

OSA is usually diagnosed based on the apnea-hypopnea index (AHI) following a sleep study using an overnight polysomnography. Treatment with a CPAP is recommended for moderate (15–30 events/h) and severe OSA (>30 events/h) [23]. A polysomnography is a costly exam, time-consuming, and not always readily available in the perioperative setting. The "STOPBANG" questionnaire (Table 12.2) is validated in the surgical population for preoperative screening for OSA [24]. It has a high sensitivity in detecting severe OSA using a cutoff score ≥3 (100% sensitivity) but with only moderate specificity. In the obese population, using a cutoff score of four provides a better balance between sensitivity and specificity, yielding lower false-positive rates. If a patient scores 0–2 on the questionnaire, moderate or severe OSA can be confidently ruled out [25].

OSA increases the risk of perioperative complications [23]. Identifying patients at high risk for OSA before surgery will target perioperative precautions and interventions that may help reduce perioperative complications. OSA should ideally be diagnosed during the preoperative period in order to adjust a continuous positive airway pressure (CPAP) device, and this may decrease perioperative complication rates. According to the Society of Anesthesia and Sleep Medicine guidelines, when management of comorbid conditions has been optimized, patients with diagnosed, partially treated, untreated, or suspected OSA may proceed to surgery, provided that strategies for mitigation of postoperative complications are implemented [23]. The obesity hypoventilation syndrome can be suspected in patients with severe OSA and severe obesity. Elevated serum bicarbonate levels (>27 mmol/L) should raise suspicion that this condition is present. The diagnosis can be confirmed during the preoperative assessment by arterial blood gases showing a $PCO_2 > 45$ mmHg and a $PO_2 < 70$ mmHg (at room air) if there are no other pathologies to explain these findings [25].

**Table 12.2** "STOPBANG" questionnaire to detect obstructive sleep apnea (OSA)

| | |
|---|---|
| **S**noring | Snoring loudly |
| **T**iredness | Daytime fatigue |
| **O**bserved | Stop breathing observed during sleep |
| **P**ressure | High blood pressure |
| **B**MI | BMI ≥ 35 kg/m$^2$ |
| **A**ge | ≥50 years |
| **N**eck circumference | ≥40 cm |
| **G**ender | Male |

1 point each time answering yes
0–3 points: low risk of OSA
4–5 points: moderate risk of OSA
6–8 points: high risk of OSA

### 12.4.3 Airway Assessment

#### 12.4.3.1 Predictive Factors of Difficult Mask Ventilation and Intubation

Until recently, the literature reported risk factors for difficult mask ventilation (DMV) and difficult intubation (DI) separately. Kheterpall et al. have published a retrospective series of over 175,000 anesthesias [26]. In this cohort, he reported an incidence of 0.04% (1:250) of the combination of DMV as DI. He also established a list of predictors (Table 12.3) regrouped in risk index classification (Table 12.4). According to this new classification, it is rather the addition of factors that increases the risk of difficult ventilation/intubation and BMI is only one factor among many. But in an obese patient, it is frequent to find several concomitant factors that increase the risk of managing the airway: increased neck circumference, obstructive sleep apnea, limited cervical extension, male gender, and a BMI > 30 kg/m$^2$. Thus, an obese patient increases quickly his/her risks classification of DMV and DI increased. The environment may also influence the level of the DI process in obese patient. A recent publication showed an increase from 8 to 16% of DI in obese patient in the ICU compared with a similar population in the OR [27]. During the preoperative evaluation, the possibility of an awake intubation should be discussed with the patient. Final decision regarding airway management should be taken by the anesthesiologist in charge on the day of the surgery following optimal positioning on the operating table.

**Table 12.3** Difficult mask ventilation combined with difficult laryngoscopy prediction score[a]

| Predictor | Weighted points | Unweighted points |
|---|---|---|
| Mallampati III or IV | 6 | 1 |
| Neck radiation changes or neck mass | 5 | 1 |
| Male sex | 5 | 1 |
| Limited thyromental distance | 5 | 1 |
| Presence of teeth | 5 | 1 |
| Body mass index ≥30 kg/m$^2$ | 4 | 1 |
| Age ≥ 46 | 3 | 1 |
| Presence of beard | 3 | 1 |
| Thick neck | 2 | 1 |
| Sleep apnea | 2 | 1 |
| Unstable cervical spine or limited neck extension | 2 | 1 |
| Limited or severely limited jaw protrusion | 2 | 1 |
| Total possible | 44 | 12 |
| Validation cohort c-statistic | 0.81 (0.78–0.84) | 0.81 (0.78–0.84) |

[a]Ketherpal et al. Anesthesiology. 2013

**Table 12.4** Risk index classification system—validation cohort[a]

| Preoperative risk class | Total patients, (*n*) | Patients with DMV combined with DL, % (*n*) | Odds ratio (IC 95%) |
|---|---|---|---|
| Class I (0–3 risk factors) | 57,439 | 0.18 (107) | Reference |
| Class II (4 risk factors) | 10,534 | 0.47 (50) | 2.56 (1.83–3.56) |
| Class III (5 risk factors) | 5815 | 0.77 (45) | 4.18 (2.95–5.93) |
| Class IV (6 risk factors) | 2775 | 1.69 (47) | 9.23 (6.54–13.04) |
| Class V (7–12 risk factors) | 1509 | 3.31 (50) | 18.4 (13.1–25.8) |

*DMV* difficult mask ventilation, *DL* difficult laryngoscopy
[a]Ketherpal et al. Anesthesiology. 2013

#### 12.4.3.2 Evaluation of the Risk of Aspiration

It was demonstrated recently that the obese patient's stomach contains no more gastric liquid and that this liquid is not more acidic than in nonobese patients [28]. In addition, normal gastroesophageal physiology is preserved in this population [29]. Clinical data allow us to omit systematic rapid sequence induction and the cricoid pressure in obese patients. But the use of antacid gastric preparation such as histamine H2 receptor antagonist or protons pump inhibitors is simple to use and should be prescribed to all obese patients in order to get safe stomach content, i.e., gastric volume < 25 mL and pH < 2.5 to prevent pulmonary damage when aspiration may occur [30]. The most frequently described aspirations setting in obese patients were observed in the presence of difficulties during maneuvers of ventilation or intubation.

However, obese subjects who underwent bariatric surgery have altered function of the esophagogastric junction and are at risk of regurgitation as this is the case in nonobese patients presenting gastroesophageal reflux symptoms [31]. In addition to gastric preparation, these patients should be induced with a rapid sequence and cricoid pressure. The premedication should be mild. Sublingual or oral benzodiazepines give very good results.

## 12.5 Anesthesia Management

### 12.5.1 Airway Management

Whether for inducing general anesthesia or for an awake intubation, the adequate positioning of the obese patient and the optimal preoxygenation are essential for a safe airway management.

### 12.5.2 Position for Preoxygenation and Intubation

The supine position is undoubtedly the worst enemy regarding the oxygen reserve in the obese patient. The weight of the abdomen compresses the functional residual capacity (FRC) and even more when the patient has a paralyzed diaphragm. The

impact on FRC of different positions of the obese patient on the operating table has been evaluated [32]. Preliminary results suggest that reverse Trendelenburg and beach chair positions are superior to the decubitus position to ensure a safe apnea period [32]. Furthermore, when a preoxygenation is performed in spontaneous ventilation, the patient is often unable to overcome the restriction of lung compression due to the abdominal content. Therefore, oxygen reserve is built up via deeper lung volumes. Using a CPAP or a BiPAP can defeat this restrictive syndrome and provide efficient preoxygenation [33].

We recently showed that reverse Trendelenburg position used in association with noninvasive positive pressure preoxygenation compared with the association of beach chair position with spontaneous ventilation allowed 16% longer (42 s) safe non-hypoxic apnea time (Sat $O_2 > 90\%$) (258 ± 42 vs. 217 s ± 17, $p = 0.0053$) and faster recovery to Sat $O_2 = 97\%$ (68 ± 11 vs. 88 s ± 17, $p = 0.029$) following ventilation when reaching Sat $O_2 = 90\%$ after tracheal intubation [34]. These results confirmed our laboratory data which demonstrated in awake obese patient the advantage of the association of reverse Trendelenburg position and noninvasive positive pressure preoxygenation to get better FRC compared to the association of beach chair or supine position with spontaneous ventilation [35] (Fig. 12.3).

It was reported that the ramp position allows a better visualization of the larynx in the obese patient (Fig. 12.4) [36]. Initially, this positioning required the superposition of blankets or cushions that were to be withdrawn after intubation. Nowadays, modern operation tables can be adjusted adequately to the desired position for anesthetic induction and easy return to a neutral position [37]. The operation table must

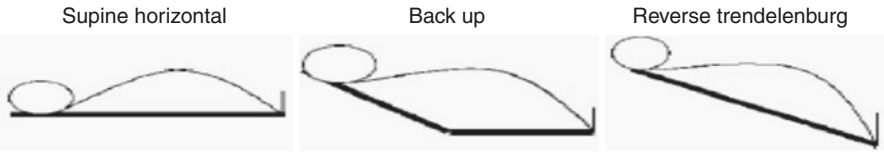



**Fig. 12.3** Different anesthesia positioning for the morbidly obese patient. Adapted from Boyce JR. Obes Surg. 2003

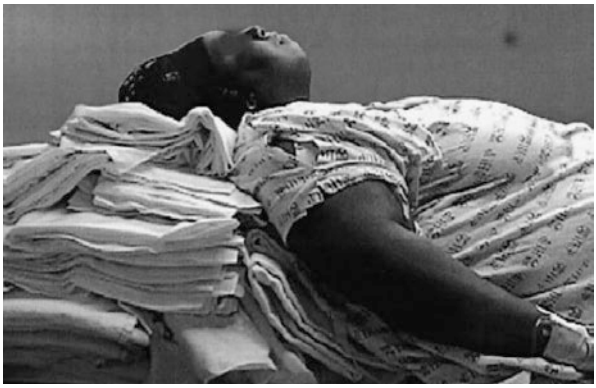


**Fig. 12.4** Positioning for direct laryngoscopy from Brodsky. Head, shoulders, and upper body significantly elevated above the chest, with sternal notch aligned to the external auditory meatus to create a horizontal line. (Adapted from: Boyce JR. Obes Surg. 2003)

be sufficiently resistant to allow easy and safe position changes. The use of a ramp position can be associated with the reverse Trendelenburg position to improve the laryngeal view obtained at laryngoscopy and to increase the FRC of obese patient. This type of positioning is critical in obese patient for anesthesia induction and can be also used to improve the conditions of an awake intubation. Associated with an adequate preoxygenation, it provides to the anesthesiologists optimal conditions for a safe control of the obese patient's airway.

### 12.5.3 Intubation

The intubation of an obese patient should be very well planned. If the assessment of the risk of DMV and DI suggests a high risk of difficulty, it is better to opt for an awake intubating technique under local anesthesia and sedation. The use of a flexible optical bronchoscope (FOB) is then the most frequently used technique. Particular attention should be emphasized to the quality of sedation and local anesthesia of the upper airways. If the assessment of the risk of intubation is acceptable, a technique under general anesthesia can be indicated with the following precautions: (1) gastric preparation if necessary, (2) adequate positioning of the patient on the operating table, and (3) preoxygenation with positive pressure in the absence of risk of gastric regurgitation. The availability of the difficult intubation material is always essential when a doubt is present for securing the airway.

The choice of induction agents is important. An adequate hypnotic agent dosage; muscle relaxation using succinylcholine, for its rapid action but especially for its relatively quick and predictive recovery (Table 12.5) [38]; and a mild dose of narcotic to allow a return to spontaneous ventilation as soon as the patient's muscle strength is recovered contribute all to its success. With the recent availability of sugammadex, a rocuronium and vecuronium antagonist, anesthesiologist may consider these muscle relaxants since sugammadex is quickly effective at high dosage to reverse profound blockade needed for intubation [39, 40].

After induction and obtaining adequate muscle relaxation, it is relevant in the absence of risk of gastric reflux to attempt mask ventilation to ensure its efficacy. This information is useful especially if a real difficult intubation is present. Moreover, it is pertinent clinical information for future anesthesia. All initial intubation techniques are possible to the extent that the anesthesiologist is familiar with the chosen intubation technique. Complementary or alternative intubating techniques must be

**Table 12.5** Pharmacokinetics of succinylcholine at 1 mg/kg according to ideal weight, lean weight, and real weight for a patient of 122 kg

| | | Beginning | Recuperation | Conditions | | |
|---|---|---|---|---|---|---|
| BMI (kg/m$^2$) | Dose (mg) | Time for max (sec) | Time for T1 = 90% (sec) | Excellent | Good | Poor |
| Ideal (22) | 61 | 91 | 429 | 4 | 7 | 13 |
| Lean (28) | 80 | 84 | 495 | 6 | 4 | 2 |
| Real (rw) | 122 | 87 | 589 | 5 | 4 | 0 |

immediately available such as Eschmann guide, videolaryngoscope, and laryngeal mask (LMA). Laryngeal mask may be used to establish a temporary permeable airway and gain extra valuable time to use another intubation strategy [41]. It is rare that anesthesiologist cannot efficiently secure the airways in a timely safe manner obtained by adequate positioning and preoxygenation prior to induction.

### 12.5.4 Perioperative Ventilation

In the obese patient, the mass of the abdomen tends to push the diaphragm in a cephalad position. Therefore, the tracheal carina is in a more cephalad position favoring endobronchial intubation. Auscultation is often difficult in obese patients. If desaturation associated to high-pressure ventilation is observed, performing a proximal repositioning of the endotracheal tube (ETT) must be considered, with the assistance of the fiber-optic bronchoscopy (FOB) if available.

Over the past few years, the use of protective ventilation has demonstrated its efficacy in the lung and esophageal surgery initially and then in abdominal surgery [42]. In cardiac surgery, initial studies have demonstrated a decrease in pulmonary inflammatory markers with this ventilatory approach. In a retrospective cohort of over 3000 patients [43], we have demonstrated a significant decrease in organ dysfunction in postoperative cardiac surgery and a decrease in the length of stay in intensive care when small tidal volumes (<10 mL/kg) were compared using a current large volumes (>12 mL/kg) during the perioperative period. This study allowed identifying two risk factors favoring the use of large tidal volumes (>12 mL/kg): (1) female gender and (2) BMI > 30 kg/m$^2$. In other words, the tidal volume must be calculated from the theoretical ideal weight corresponding to weight for a BMI of 22 kg/m$^2$. With these small tidal volumes, it is imperious to systematically use a positive end-expiratory pressure (PEEP) [44–48] rather than raising the inspired fraction of oxygen ($FiO_2$) that might increase atelectasis [49]. The tolerance of high oxygen arterial pressure ($PaO_2$) provides no benefit and can be deleterious by decreasing the cardiac output by 20% [44, 45] and coronary flow from 8 to 29% [46]. Recruitment maneuvers and PEEP level readjustment should be performed as needed during the procedure. Finally, the use of lower tidal volumes may require a higher respiratory rate to maintain normal $CO_2$ blood level concentration and avoid the deleterious effects of hypercarbia.

### 12.5.5 Medication and Pharmacokinetics

Pharmacokinetic changes in the obese population are complex. They depend on the relative impact of their increased cardiac output, extracellular fluid volume, fat mass, and lean mass. There is a risk of accumulating lipid-soluble drugs and peak plasma concentration of certain drugs may be reduced. Thus, accurate dosing of anesthetic drugs presents a challenge. In general, most anesthetic drug dosing should be based on the obese patient's ideal or lean mass. There are notable exceptions: succinylcholine,

neuromuscular block reversal agents, and propofol maintenance infusion should all be adjusted according to total body weight [16]. A recent meta-analysis indicated that recovery after anesthesia was significantly faster with desflurane than with sevoflurane, isoflurane, or propofol in severely obese adult patients undergoing major abdominal surgery. It should be noted that the difference in discharge time from the recovery room was not clinically significant according to this study, but patients exhibited higher oxygen saturation in the recovery room in the desflurane group [50].

### 12.5.6 Glycemic Control during Anesthesia

Few studies look specifically at blood sugar management in the perioperative period and its impact on outcomes [51]. Evidence comes mainly from the cardiac surgical setting. The risks associated with intensive insulin therapy and hypoglycemia in critically ill patients were highlighted in two landmark studies [52, 53]. The optimal blood sugar target in the perioperative period remains unknown for both obese and nonobese patients with type 2 diabetes. The Society for Ambulatory Anesthesia (SAMBA) and other authors suggest initiating treatment with an insulin infusion in critically ill patients at a blood sugar no greater than 180 mg/dL. After treatment is initiated, aiming at a blood sugar between 140 and 180 mg/dL is recommended. However, lower targets may be beneficial in certain populations. The use of subcutaneous insulin is more appropriate for noncritical patients.

### 12.5.7 Emergence

The postoperative ventilation time is frequently longer in obese patient to ensure the warming, reversal of curarization, and the awakening until patient's full cooperation. It is best to delay extubation until these criteria are reached. Urgent reintubation might be tempestuous or even catastrophic without optimal preparation of the extubation.

## 12.6 Analgesia and Prevention of Postoperative Complications

### 12.6.1 Analgesia

Severely obese patients have a high incidence of OSA, and it predisposes them to opioid-induced airway obstruction. Providing adequate and safe analgesia in this population can be challenging. In order to achieve pain relief, multimodal analgesia should be privileged with opioid-sparing drugs in addition to regional anesthesia when possible. Acetaminophen has an opioid-sparing effect; it works in synergy with nonsteroidal anti-inflammatory drugs (NSAID) when these two drugs are combined. The continuous use of ketorolac during the first 24 h after surgery leads to a lower

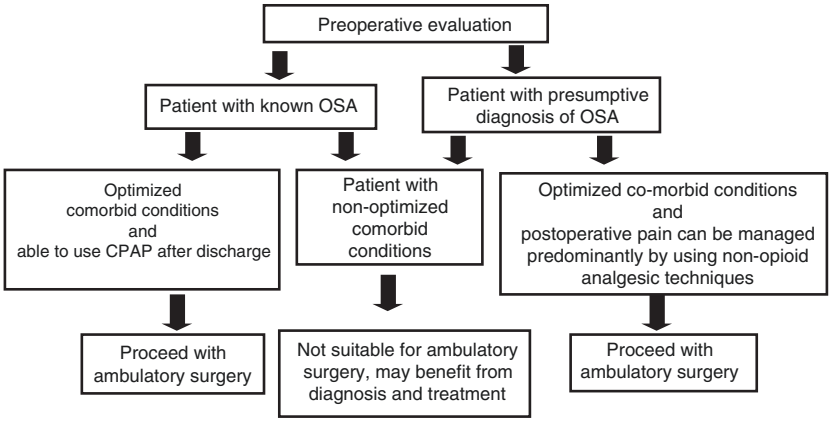
requirement for narcotics [54]. When facing severe pain, systemic adjuvants can reduce the need for narcotics. Alpha-2 agonists have analgesic effects, with dexmedetomidine being more effective than clonidine [55, 56]. Low-dose ketamine is also an adjuvant to consider [57]. These agents both have an advantage in maintaining airway tone and respiratory drive. Regional anesthesia techniques have become an integral part of multimodal analgesia. Even if these techniques can be challenging when used on severely obese patients, because of obscured landmarks, it remains an excellent option when feasible. Notably, epidural blocks have the highest efficacy, and they have the potential to be used as the sole analgesic modality [54].

### 12.6.2 Day Surgery

Nowadays, 70% of all surgical procedures are done on an ambulatory basis [58]. There has been controversy in the past, as to whether outpatient surgery can be safely performed in obese patients. Evidence suggests that BMI should not be the only criteria used to decide if ambulatory surgery is reasonable for a given patient, since studies have shown similar incidence of adverse outcomes for both obese and nonobese having day surgery (reference). Optimization and stabilization of comorbid conditions are probably more important risk factors to consider. Although an elevated BMI is not necessarily associated with increased complications, it should be kept in mind that there is still limited evidence that outpatient surgery is safe for patients with severe obesity. Also, ambulatory surgery should be elected very carefully for patients with a BMI > 50 kg/m$^2$ [59]. OSA or suspected OSA is not a contraindication for outpatient surgery, assuming proper patient selection and appropriate steps are taken to minimize the risks of postoperative complications (avoidance of general anesthesia, minimizing doses of potent narcotics, optimizing co-analgesia, judicious use of regional anesthesia, etc. The Society for Ambulatory Anesthesia suggests an algorithm to assist in the decision-making (Fig. 12.5) [60].

### 12.6.3 Rhabdomyolysis

Rhabdomyolysis is a skeletal muscle disorder that involves releasing of toxic cell constituents in the systemic circulation, with the potential risk of renal damage. This complication occurs more commonly in severely obese patients during surgery [61]. The excessive weight that these patients carry increases the compressive pressure on muscle, leading to muscular ischemic necrosis and release of muscle toxins into systemic circulation. Male patients undergoing prolonged surgery (>250 min) are at increased risk. Muscles in the gluteal region are more commonly affected, although the shoulder girdle and upper arms can also be affected in certain circumstances [62]. Muscular pain is a predominant symptom but this condition can be asymptomatic. Diagnosis involves measurement of serum creatine kinase (CK). Patients with measured CK > 20,000 are at risk of developing acute renal failure [62]. Early diagnosis and aggressive management with fluids and diuretics are essential to prevent kidney injury.




**Preoperative Considerations:**

- Comorbid conditions include hypertension, arrhythmias, heart failure, cerebrovascular disease, and metabolic syndrome.
- If OSA is suspected during the preoperative evaluation, one could proceed with a presumptive diagnosis of OSA albeit with caution.
- Educate surgeon, patient and family (see the text for details)

**Intraoperative Considerations:**

- Non-opioid analgesic techniques, when possible.

**Postoperative Considerations:**

- Exercise caution in OSA patients who develop prolonged and frequent severe respiratory events (e.g., sedation analgesic mismatch, desaturation, and apneic episodes) in the postoperative period.

**Fig. 12.5** Decision-making in preoperative selection of a patient with obstructive sleep apnea scheduled for ambulatory surgery. *OSA* Obstructive sleep apnea, *CPAP* Continuous positive airway pressure. From: Anesth Analg, 2012;115(5):1060–68

## Conclusion

Preoperative evaluation of obese patient should include the potential multiple organic dysfunctions, mainly the respiratory and the cardiac ones. The meticulous evaluation of the superior airway is essential to plan the management of a potentially risky airway during anesthesia induction. Perioperative ventilation parameters should respect the principle of protective ventilation using the ideal body weight to determine the tidal volume and the liberal use of PEEP. During the postoperative period, narcotics should be used carefully.

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# Anaesthesia and Rare Metabolic Disorders

13

Markus M. Luedi and Frank Stueber

## 13.1 Introduction

Metabolic disorders occur due to abnormal metabolic processes caused by an acquired failure of a metabolic organ or an inherited abnormality of enzymes [1]. The US National Institutes of Health (NIH) Genetic and Rare Diseases Information Center (GARD) currently lists 515 entities as metabolic disorders grouped into 18 subclasses (Table 13.1). Here, we discuss current approaches to evidence-based perioperative management of patients with rare metabolic disorders, i.e. those metabolic diseases with a prevalence/incidence as little as 1:200,000 or fewer [2]. Very rare diseases, or diseases for which prevalence/incidence is unknown, or which are only known to occur in members of a particular family, are regarded as very rare and

**Table 13.1** Subclasses of metabolic disorders defined by NLM Medical Subject Headings (MeSH)[a]

| Acid-base imbalance | Iron metabolism disorders | Phosphorus metabolism disorders |
|---|---|---|
| Brain diseases, metabolic | Lipid metabolism disorders | Porphyrias |
| Calcium metabolism disorders | Malabsorption syndromes | Proteostasis deficiencies |
| DNA repair deficiency disorders | Metabolic syndrome X | Skin diseases, metabolic |
| Glucose metabolism disorders | Metabolism, inborn errors | Wasting syndrome |
| Hyperlactatemia | Mitochondrial diseases | Water-electrolyte imbalance |

[a]Some subclasses of metabolic disorders defined by MeSH overlap or include non-rare diseases, e.g. acid-base imbalances

M.M. Luedi • F. Stueber (✉)
Department of Anaesthesiology, Bern University Hospital Inselspital, University of Bern, Bern, Switzerland
e-mail: markus.luedi2@insel.ch; frank.stueber@insel.ch



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are not covered. As well, we do not discuss diseases that have not been reported in the English language literature. Our goal is not to be comprehensive, but, rather, to provide a general overview of anaesthesia and rare metabolic disorders.

## 13.2 Inborn Metabolic Brain Diseases

### 13.2.1 Pelizaeus-Merzbacher Disease

Pelizaeus-Merzbacher disease (PMD) is a recessive X chromosome-linked disorder that occurs in 1:200,000 to 1:500,000 males. The disease is characterized by hypomyelination of the central nervous system, leading to neurologic symptoms such as abnormal muscle tone (hypotonia in newborns and muscle spasticity in children), ataxia, nystagmus, psychomotor retardation seizures, and stridor [3]. PMD children die early due to respiratory complications such as aspiration pneumonia [3, 4]. Patients often suffer from joint contractures, which may require surgery. Anaesthetic evidence is restricted to case reports. Aspiration pneumonia, epilepsy, and gastroesophageal reflux disease must be considered preoperatively, and airway complications, exacerbation of spasticity, and seizures must be considered postoperatively [5].

### 13.2.2 Homocystinuria Type III/Hyperhomocysteinaemia

Homocystinuria type III is inherited as an autosomal recessive that affects the metabolism of methionine. It is caused by a tetrahydrofolate reductase deficiency and has a prevalence of 1:200,000 to 1:335,000. In contrast, type I results from deficient pyridoxine and cystathionine synthase, and type II results from a defective tetrahydrofolate methyltransferase.

Type III patients suffer from delayed motor development, psychiatric diseases, and seizures. The lack of methionine and concomitant high serum homocysteine levels can cause thromboembolic complications perioperatively. Also, perioperative neurological impairment has been described in association with the use of nitrous oxide [6]. Case reports such as by Yamada et al. recommend the use of prophylactic aspirin, heparin, and pneumatic foot compression systems to prevent thromboembolic complications perioperatively [6]. Nitrous oxide must not be applied [7–9]. Eschweiler et al. described the possibility of postoperative psychosis in such patients since oxidation products of homocysteine are robust glutamate agonists and affect central glutamatergic transmission [10].

Hyperhomocysteinaemia is a related disorder often presents with coronary artery disease and concomitant limited myocardial function as well as increased thrombotic events [11]. Aggarwal et al. stress the importance of reducing homocysteine levels and applying traditional prophylactic measures perioperatively to minimize the risk of thrombotic complications [11]. The risk for thromboembolic complications, and the accompanying probable need for anticoagulation, may contraindicate neuraxial anaesthesia [12].

### 13.2.3 Lesch-Nyhan Syndrome

The Lesch-Nyhan syndrome is a recessive, X chromosome-linked hypoxanthine-guanine phosphoribosyltransferase deficiency, which results in high purine levels and concomitant uric acidosis. It affects 1:380,000 males. Patients suffer from intellectual disability and present classical self-mutilation and musculoskeletal abnormalities including dysphagia, spasticity, and impaired drug metabolism [13]. Additionally, hyperuricemia causes renal dysfunction, which progresses to lethal renal failure. Three dimensions were described for consideration by anaesthesiologists: First, perioral scars derived from self-mutilation can cause a difficult intubation anatomy, and gastric reflux must be anticipated; second, seizures are common and must be recognized under general anaesthesia; and third, patients may show renal insufficiency caused by uric acidosis [14]. Overall, drug metabolism is impaired, but etomidate, ketamine, and thiopental are safe, whereas benzodiazepines and opioids must be used with caution [14].

### 13.2.4 Mucolipidosis II/I-Cell Disease

Mucolipidosis II is a lysosomal storage disease of the nervous system caused by a deficient N-acetylglucosamine-1-phosphotransferase. It is an autosomal recessive disease with an incidence of 1:100,000 to 1:400,000. The deficiency results in exocytosis of lysosomal enzymes rather than physiological sequestration in intracellular lysosomes. One consequence is that mucolipids and other macromolecules concentrate to toxic levels in lysosomes [15]. Usual clinical findings include both mental and physical disabilities and orofacial abnormalities. For anaesthesiologists, the main concerns are difficult airway anatomy due to facial dysmorphia, large tongue, restricted cervical movement, and hypertrophic adenoids and tonsils. Additionally, coronary artery atresia and consecutive acute heart failure have been described [16], whereas no pharmacological risks have been reported [17].

### 13.2.5 Oculocerebrorenal Syndrome/Lowe Syndrome

The oculocerebrorenal syndrome (Lowe syndrome) is an X chromosome-linked multisystem disorder of amino acid transport with an incidence of 1:500,000. It causes hepatic and polyuric renal insufficiency with organic aciduria, hydrophthalmos, intellectual disability, growth failure, easy fatigability, ocular abnormalities, and orthopaedic abnormalities; for the later, patients often need surgery [18, 19]. Intellectual disabilities are thought to be caused by white matter destruction, which is also thought to account for significant seizures [20]. Renal acidosis and hypokalaemia with associated cardiac side effects were described as the main issues for concern by anaesthesiologists [21]. As Saricaoğlu et al. point out, the acidosis facilitates passage of opioids across the blood-brain barrier, leading to deeper sedation and depressed reflexes, which increases the risk for pulmonary aspiration perioperatively [21]. Perioperative correction of electrolyte imbalances and differentiated

fluid management is of essence. Retrognathia is frequently observed; thus, careful airway management is mandatory as is the use of muscle relaxants due to both muscular weakness and electrolyte imbalances [22].

### 13.2.6 Carbamoyl-Phosphate Synthetase I Deficiency Disease

Carbamoyl-phosphate synthetase I deficiency causes hyperammonaemia. It is an autosomal recessive disease with an incidence of 1:800,000. During surgical stress under general anaesthesia or in metabolic distress, ammonia levels can increase dramatically in these patients, causing cerebral oedema and concomitant brain herniation. Regional anaesthesia and sedation are recommended to ensure sufficient control of cerebral function [23].

### 13.2.7 Hyperargininaemia/Arginase Deficiency

Hyperargininaemia/arginase deficiency is an autosomal recessive disorder of the urea cycle with an incidence of 1:300,000. Patients are affected by psychomotor retardation, seizures, and progressive spastic quadriparesis [24]. Kaul et al. described four major anaesthesia-associated risks threatening patients: Patients are at risk of hyperammonaemic cerebral oedema and severe hypotension upon induction of general anaesthesia because arginine stimulates vasodilatation. Aggressive perioperative fluid administration can counter the latter but increases the risk of the former. Additionally, patients are at risk for seizures, and volatile anaesthetics may trigger an epileptic crisis; potentially significant paresis increases the risk of unpredictable action of depolarizing and non-depolarizing muscle relaxants. To avoid the need for the muscle relaxants, the use of laryngeal masks in such patients is suggested [25].

Overall, patients with rare inborn metabolic brain diseases can present with psychomotor retardation, epilepsy, and abnormal muscle tone. Accordingly, impaired cognition, seizures, and associated respiratory complications, such as aspiration, should be anticipated. Orofacial abnormalities can cause difficult intubation. Drug metabolism can be impaired; therefore, specific caution is required when applying benzodiazepines, muscle relaxants, and opioids.

## 13.3 DNA Repair-Deficiency Disorders Leading to Metabolic Derangements

### 13.3.1 Cockayne Syndrome

Cockayne syndrome (also known as Weber-Cockayne syndrome or Neill-Dingwall syndrome) is an autosomal recessive progeria resulting from a nucleotide excision repair deficiency. It has an incidence of 1:500,000. Clinically, patients present facial dysmorphias, microcephaly and cerebral atrophy, concomitant intellectual deficiency, and delayed growth. A few cases have been studied specifically for

perioperative considerations, such as potentially difficult establishment of a safe airway upon induction of general anaesthesia. Because of the risk of haemodynamic instability resulting from administration of hypnotics, Tsukamoto et al. recommend not relying on haemodynamics to measure the depth of anaesthesia in patients with premature ageing, but recommend use of EEG devices such as BIS monitors as employed with geriatric patients [26].

### 13.3.2 Xeroderma Pigmentosum

Xeroderma pigmentosum is an autosomal recessive defect in a DNA repair mechanism. It has an incidence of 1:250:000. Although several subtypes have been described, all patients lack mechanisms for skin repair after actinic stress. Some subtypes additionally include neurological deficiencies, and patients usually die within their first decade of life. Guidelines to treat such patients perioperatively are lacking; however, some reports suggest that volatile anaesthetics worsen neurological symptoms and should not be used [27–29]. A Nepalese case series warned against potentially difficult airway scenarios upon induction of general anaesthesia and recommended avoiding muscle relaxants due to their potentially unpredictable effect. Additionally, both benzodiazepines and opioids can show a pronounced synergistic effect in patients with neurologic disabilities [30].

Overall, patients with rare DNA repair-deficiency disorders can present with intellectual disabilities, retarded growth, and orofacial abnormalities. Establishment of a safe airway may be complicated, and drug metabolism can be affected; thus, specific caution is required when using benzodiazepines, muscle relaxants, or opioids.

## 13.4 Lipid Metabolism Disorders

### 13.4.1 Barth Syndrome/3-Methylglutaconic Aciduria Type II

Barth syndrome is an X chromosome-linked disease, which leads to elevated excretion of 3-methylglutaconic acid. It has an incidence of 1:300,000. The clinical presentation of Barth syndrome is highly variable, manifesting as a multisystem disease including cardiomyopathies and concomitant heart failure, growth retardation, muscle weakness, and cyclic neutropenia [31]. Perioperatively, careful cardiocirculatory monitoring is essential, and neuromuscular blockers may cause problems due to their unpredictable kinetics and dynamics.

### 13.4.2 Congenital Generalized Lipodystrophy/ Berardinelli-Seip Syndrome

Congenital generalized lipodystrophy is an autosomal recessive disorder characterized by absence of adipose tissue and insulin resistance; every second patient suffers

from intellectual disability. It has an incidence of 1:500,000. Clinically, patients exhibit an athletic appearance, but present with an anabolic syndrome including hypertrophic cardiomyopathy, advanced bone age, sexual precocity, macroglossia, and tonsillar hyperplasia [32]. Perioperative essentials include the management of hypertrophic cardiomyopathy and recognition of probable difficulties in establishing a safe airway access [32]. Bennett et al. encourage short-acting agents and consideration of possible delayed emergence from sevoflurane anaesthesia due to lack of adipose tissue in the central nervous system and concomitant disproportional effects of fat-soluble agents [32].

Overall, patients with rare lipid metabolism disorders can present with cardiomyopathies, concomitant heart failure, intellectual disabilities, and retarded growth. Specific caution must be given when using volatile anaesthetics, benzodiazepines, muscle relaxants, and opioids. Short-acting agents should be considered.

## 13.5 Other Inborn Errors in Metabolism

### 13.5.1 Isovaleric Acidaemia

Isovaleric acidaemia is an autosomal recessive error in amino acid metabolism in which a deficient isovaleryl-CoA dehydrogenase leads to disorders in leucine metabolism. It affects 1:250,000. Under perioperative stress, an increase in plasma levels of isovaleryl-CoA metabolites can cause severe glucose disturbances, hyperammonaemia, hypocalcaemia, and non-anion gap metabolic acidosis [33]. Anaesthesiologists must aim to prevent metabolic crises by supporting anabolism (e.g. with sugar) and simultaneously reducing leucine intake. Additionally, both production and accumulation of isovaleryl-CoA from leucine metabolism must be reduced with a carnitine and glycine diet [33, 34].

### 13.5.2 Alkaptonuria

Alkaptonuria is an autosomal recessive disease cause by a deficiency in homogentisate 1,2-dioxygenase, an enzyme that converts homogentisic acid to maleylacetoacetic acid via tyrosine degradation in the liver. It occurs in 1:250,000 births. During a patient's lifetime, complications occur as homogentisic acid deposits form pigment-like polymers in different collagenous tissues including joints, kidneys, endocardium, and heart valves [35, 36]. Kastsiuchenka et al. point out that the medical triad of urine discoloration, degenerative joint disease, and grey sclera should raise suspicion of alkaptonuria and thus trigger extensive preoperative evaluation of potentially affected organs [36]. Neither pulse nor near-infrared spectroscopy cerebral oximetry is practical due to the high amounts of pigmenting homogentisic acid products deposited in the skin and the dura mater, respectively [36].

### 13.5.3 Glycogen Storage Disease Type IV/Andersen disease

Glycogen storage disease type IV is an autosomal recessive liver disease affecting glycogen storage. It occurs in 1:600,000 live births. Hypotonia, hepatosplenomegaly, liver failure, and hepatic cirrhosis lead to death by 5 years of age. Perioperatively, thigh monitoring and management of glucose and lactate levels are essential; continuous dextrose infusion has been described as a standard [37].

### 13.5.4 Alpha-Mannosidosis

Alpha-mannosidosis is an autosomal disorder of glycosylation resulting in a functional lack of alpha-mannosidase. It occurs in 1:500,000 births. The absence of the lysosomal enzyme leads to inhibition of glycoprotein catabolism accompanied by high levels of oligosaccharides in affected tissues. Clinically, patients suffer from intellectual disabilities and psychiatric disorders, musculoskeletal abnormalities, and abnormal pulmonary function [38]. Perioperative considerations include an anticipation of a potentially difficult airway and risk of airway obstruction, because affected patients require relatively high muscle tone to keep airways open [38].

### 13.5.5 Hyperkalaemic Periodic Paralysis

Hyperkalaemic periodic paralysis is an inborn autosomal dominant error in membrane electrolyte conductance that causes periodic myotonia or paramyotonia followed by episodes of muscular weakness or severe myotonic attacks including masseter spasm resulting from increased serum potassium levels [39–41]. It occurs in 1:200,000 births. Although neuromuscular blockers are not contraindicated [42], general anaesthesia with gases and succinylcholine may trigger prolonged symptoms, whereas a propofol-remifentanil target-controlled approach may enable intubation without muscle relaxants and may provide for reliable postoperative recovery of muscular tone [43]. Neuraxial and regional anaesthesia appear to be safe for use in these patients [40, 44].

### 13.5.6 Progeria/Hutchinson-Gilford syndrome

Progeria is an autosomal recessive disorder causing premature ageing characterized by conditions associated with geriatric patients, including fibrotic and atherosclerotic heart disease and failure, cerebrovascular disease, and severe osteoarthritis [45]. It occurs in 1:4,000,000 births. The advanced physiological age, which may be apparent even in newborns, in paediatric patients whose emotional and intellectual development is chronologically appropriate [45, 46], creates a unique circumstance. While the advanced physiological age requires specific measures known from geriatric anaesthesia, the chronological age requires adequate humane capabilities.

Cardiovascular comorbidities and complications due to severe osteoporosis, e.g. fracturing of the jaw during intubation, are the major perioperative challenges [47].

## 13.6 Summary

Overall, patients with rare inborn errors in metabolism can present with severe metabolic crises such as metabolic acidosis and glucose disturbances. Tight perioperative monitoring and management of disturbances is essential. Neuromuscular blockers and volatile anaesthetics must be considered carefully.

Rare metabolic disorders may be visible in paediatric cohorts and may include a wide spectrum of physiological derangements caused by a variety of disorders, such as DNA repair-deficiencies, alterations of lipid or iron metabolism, and numerous other entities. Since the prevalence of such disorders is, by definition, rare, experience is limited and perioperative specialists may be challenged. Patients with rare metabolic disorders needing anaesthesia often present with psychomotor retardation, epilepsy, abnormal muscle tone, cardiomyopathies, deranged electrolytes, and orofacial abnormalities. Such patients should be treated in centres with experienced staff and need thorough preoperative evaluation and correction of deranged physiology. They distinct intraoperative monitoring and care, as well as careful postoperative observation including escape strategies such as paediatric intensive care.

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# Part IV

# Neurological Risks

# Patients with Cerebral Diseases

# 14

C. Binet and A.C. Lukaszewicz

## 14.1 Introduction

Most of the time, postoperative neurologic deficits are related to the perioperative management, especially haemodynamic, in association with comorbidities. The main cause of perioperative neurological complications is stroke, related to hypoperfusion, embolic event or haemorrhage. Recently, the Society for Neuroscience in Anesthesiology and Critical Care (SNACC) defined perioperative stroke as an ischaemic or haemorrhagic event that occurs during surgery or within 30 days after surgery [1]. Perioperative stroke in high-risk cardiovascular surgery has been well documented, with an incidence in the range of approximately 1.9–9.7% [2, 3]. Conversely, the incidence of ischaemic stroke in noncardiac and nonmajor vascular surgery is in the range of 0.1–1.9% depending on comorbidities [4, 5]. This incidence might reach 10% in high-risk patients [4, 5]. Most of the data for noncardiovascular and non-neurosurgical population result from large retrospective series and databases, because prospective studies were limited by the low incidence of the event in this population. Additionally, clinically silent cerebral ischemia has been associated to postoperative cognitive impairment in cardiac surgery patients [6]. In this context, the high rate of death after perioperative stroke has to be underlined in the range of 20–60% [4, 5, 7].

In other instances, patients with chronic parenchymal disease or neurologic dysfunction might require specific management during the perioperative period. The prevention of perioperative seizure in epileptic patient requires special attention, but seizures are not associated with outcome in this context. The impact of perioperative procedures and drugs on brain ageing or cerebral inflammatory diseases (like in multiple sclerosis or Alzheimer's disease) remains unclear. In this chapter, we will

C. Binet • A.C. Lukaszewicz (✉)
Anesthesia and Critical Care Department, Neurological Hospital Pierre Wertheimer,
59 bvd Pinel, 69383 Lyon Cedex 03, France
e-mail: anne-claire.lukaszewicz@chu-lyon.fr



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summarize the recommendations, if any, for these patients with chronic brain pathologies. Nevertheless, we will not discuss neurosurgical patients or patients with high intracranial pressure.

## 14.2 Brain Victim from Surgery

### 14.2.1 Perioperative Thromboembolic Events

Surgical context promotes the appearance of the main contributing factors for thrombosis and thromboembolic events, secondary to systemic inflammation and hypercoagulability. The incidence of these perioperative adverse events reported in by studies may vary according to the definition of ischaemic events. Major cardiac or vascular surgeries have higher incidence of perioperative stroke, mainly because manipulations of the aortic arch or heart are recognized as a source of embolic stroke. In noncardiac and non-vascular surgeries, ischaemic events are related to premorbid conditions and insufficient vascular reserve like in elderly with history of cerebral attack or coronary or renal disease. Bateman et al. identified comorbidities associated with perioperative stroke from the national database of hospital discharge available in the United States [4]. It includes age, gender, diabetes mellitus, atrial fibrillation, congestive heart failure, history of prior stroke, renal disease or cardiac valvular disease. When adjusted on most of these factors, perioperative ischaemic stroke was consistently associated with worse outcome [4]. The risk of perioperative thromboembolic event is increased in patients under anticoagulation or antiplatelet therapies, with a rebound of hypercoagulability, when therapies are stopped. However, the management of discontinuation for anticoagulation and antiplatelet therapy has not been clarified. Cardiac arrhythmia, especially atrial fibrillation, combined with the hypercoagulable state is a consistent risk of cardioembolism [8]. However, the benefit of β-blockade on cardiac events was counterbalanced by the higher incidence of stroke and worse outcome in patients who underwent a noncardiac surgery, and the relation to perioperative hypotension has been suggested [9].

Limiting inflammatory consequences of surgery should benefit to high-risk patients for thrombosis. In this context, a beneficial impact of statins was suggested but remains uncertain in patients without preoperative administration [10, 11].

In-hospital perioperative strokes, even if in-hospital, present a worse outcome than community-onset strokes, probably because of the delayed recognition of symptoms and then the delay of neuroimaging and low rate of thrombolysis [12]. The main difficulty is the evaluation of the neurologic deficit duration and establishment of “last time known well”. Following anaesthesia, the last normal neurologic exam is at anaesthesia induction. In all cases, the suspicion of stroke must activate emergent multidisciplinary discussion for the rapid answer to two key questions: (1) Is there any contraindication for thrombolysis? (2) Is the timing adequate for endovascular clot retrieval? Magnetic resonance imaging will help for locating the occlusion of the vessel and dating the event. A careful risk-benefit analysis should be conducted in order to balance the risk of haemorrhage after recent surgery. Recent

intracranial and spinal surgeries remain well-recognized contraindications for thrombolysis. Other therapeutic options for surgical patients who may be at high risk of haemorrhage, such as intra-arterial selected thrombolysis, were suggested but are not fully evaluated. A clear procedure should be anticipated in each institution in order to ensure the best management when such postoperative deleterious event occurs.

### 14.2.2 Deficiency in Cerebral Autoregulation or Vascular Reserve

Haemodynamic events are the other mechanism for occurrence of postoperative stroke. The circumstances are less characterized, but anaesthetists should consider factors such as surgical positioning, limited cerebral autoregulation or "vascular reserve" in some patients.

It is well admitted that the sitting surgical position may expose the patient to cerebral hypoperfusion because of the important hydrostatic gradient between the head and heart levels. In such position, an intensive monitoring and haemodynamic resuscitation should prevent deleterious events. The more frequent and less intensively monitored is the common "beach chair" position for shoulder, breast or skull base surgeries. Even if the orthostatic gradient is lower in beach chair than sitting position, it could challenge cerebral perfusion, especially in patients with stenosis on main cephalic arteries, or intracranial arteriolar diseases. Perioperative cerebral oxygen saturation can be monitored by near-infrared spectroscopy, and some desaturations have been detected during surgery, but no clear association with neurological outcome was established [13]. A strategy of prevention of ischaemic events should be preferred than detection, since no reliable method of detection can be firmly recommended. In such patients, baseline level of arterial blood pressure should be maintained along surgery. In some case, this objective of management with elevated blood pressure should be balanced with the risk of significant bleeding in the surgical focus. The difficulty to target the best arterial pressure arises from the difficulty to assess an effective autoregulation for each individual. Moreover, the classical concept of autoregulation may not be applicable in many patients [14, 15]. In this concept, the recommendations would be the tight control of blood pressure with the lower limit at 30% of baseline measured before anaesthesia. The perioperative management of blood pressure may also have an impact on postoperative occurrence of delirium [16].

Since the interactions between cerebral and systemic haemodynamics [17] are difficult to anticipate and could do more harm than good, anaesthetists must particularly pay attention to other cerebral blood flow-regulating processes, like the vasoconstriction in response to hypocarbia. A recent review depicted the integrated effects of carbon dioxide and perfusion pressure on autoregulation phenomenon [18]. Carbon dioxide partial pressure in the blood is easy to monitor with a non-invasive method by capnography and becomes a standard in anaesthesiology. Then the adjustment of carbon dioxide level must be cautiously achieved for patients with limited cerebral "vascular reserve".

Positioning of the head is also of importance for adequate brain perfusion. Besides atherosclerosis, other imputable factors were identified like deviation from classical vessel configuration or compression. From study performed on cadavers, in order to avoid lowering of cerebral blood flow, the variations of the head from resting position should remain below 45° for flexion/extension, 45° for rotation and 30° for tilt [19].

Among patients with cerebral haemodynamic impairment, the patients with Moyamoya syndrome require particular strict perioperative anaesthetic management. Moyamoya disease (MMD) is characterized by chronic progressive stenosis at the termination of internal intracranial carotid [20]. Even if this syndrome remains rare in Europe in comparison with Asia (tenfold less), it affects young patients (third and fourth decades of life); the number of patients with MMD is increasing with significant progress in their medical management. With progression of carotid abnormalities, compensatory mechanisms will develop the enlargement of small arteriolar collaterals to bypass the occlusion but with impaired vasodilatory response. Such haemodynamic impairment may be compensated by the increase in oxygen extraction. We will address in this paragraph the management of Moyamoya patients for general surgery and not discuss the anaesthetic management for surgical cerebral revascularization (for review [21]). Before surgery, a detailed history of the disease is necessary for the preoperative evaluation. The anaesthetist will evaluate the severity of the arterial disease on cerebral magnetic resonance imaging (parenchymal lesions and vascularization) or conventional angiography. Cerebral blood flow studies such as transcranial Doppler ultrasonography, positron emission tomography and single-photon emission computed tomography with acetazolamide challenge could be helpful for the evaluation of the "cerebral blood flow reserve". Considering haemodynamic in Moyamoya disease, maintenance of cerebral blood flow is extremely dependent on systemic conditions and deteriorates with hypotension, hypocarbia or hypercarbia [22]. Arterial blood pressure should be carefully monitored and kept close to patient's baseline blood pressure. A haematocrit greater than 30% should avoid the risk of perioperative ischaemic events even if there is no specific recommendation. Because of the high risk of vascular events, postoperative care will preferably take place in the intensive care for the close monitoring of blood pressure and volemia. Antiplatelet agents should be started on the first postoperative day because some deterioration seems to occur as a consequence of emboli from microthrombus formation at sites of arterial stenosis.

In summary, although embolic and haemodynamic events with cerebral complications are expected in the context of cardiac and major vascular surgeries, their occurrence is rare but more insidious in general surgeries. Such observations force the clinician to identify the patients at high risk of perioperative stroke and the potential modifiable factors [1]. In such high-risk patients, anaesthesia procedure should be conducted according to haemodynamic objectives of blood pressure levels, stabilized haemodynamic and careful systemic carbon dioxide monitoring.

## 14.3 Brain Diseases and Predisposition to Postoperative Cerebral Disorders

In some patients, history of brain disorders or neurodegenerative diseases may predispose them to perioperative events or dysfunctions. On one hand, patient's medication may have an impact upon the course of anaesthesia; on the other hand, although still controversial, anaesthetics could impact the course of the disease.

### 14.3.1 Ageing, Postoperative Delirium and Cognitive Decline

Despite high incidence and serious implications, postoperative delirium is frequently under-evaluated because of its variable clinical presentation (hypoactive or hyperactive) and despite the availability of reliable diagnostic tools like Confusion Assessment Method [23]. Elderly patients are at higher risk of postoperative delirium [24], and, 3 months after surgery, cognitive impairment is still detectable in older patients with consequences on their quality of life and increased mortality risk [25, 26]. In a prospective case-control study in patients without severe preoperative cognitive disease, postoperative delirium was higher after emergent (17.9%) than elective surgery (6.7%), and physiologic or psychological preoperative conditions including anxiety and depression were associated factors [25]. In this context, the perioperative management of the patients with limited vital function supports the concept of perioperative care for improving outcome. Notably, for patients with previous disabilities, it seems reasonable to delay nonurgent surgery beyond 9–12 months after ischaemic stroke, according to data from Danish registry [27].

Besides pre-existing medical conditions, anaesthetics and inflammatory response to surgery were suggested as potential precipitating factors for delirium. Similar to other cognitive impairments, the leading hypothesis for the pathomechanism incriminated in delirium was a central cholinergic deficiency related to drugs that impair cholinergic function [28–30]. Drugs such as atropine, antihistamines, corticosteroids or benzodiazepines should be minimized in vulnerable patients [28]. Alternative drugs might be proposed in order to limit or prevent delirium, like haloperidol, dexmedetomidine or subanaesthetic dose of ketamine, but should be further investigated before being firmly recommended [31].

Recent investigations have illustrated the debate about the impact of type of anaesthesia (general or local) or genetic factors [32, 33] on incidence of postoperative cognitive dysfunction. In 225 patients over 60 years of age who underwent a cardiac surgery, postoperative delirium was associated with cognitive decline after 1 year [26]. These patients with significant postoperative cognitive decline were significantly older, less educated and less likely to be men or white but had a history of stroke and higher comorbidity score. Accordingly, some studies reported that chronic diseases developed with age like cardiac diseases [34] or cancer [35] seemed predisposed the patients to cognitive decline, regardless of the surgical treatment. On the other hand, in some patients, preoperative cognitive disorders may be improved by

surgery, especially when surgery decreases chronic pain and inflammation, improves cerebral blood flow or favours the functions in daily life. A common pathomechanism between postoperative delirium and dementia was suggested, but a recent study and meta-analysis rule out this association [36].

### 14.3.2 Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia in adults, affecting 35 million people worldwide. AD is characterized by progressive worsening of symptoms, including global cognitive decline in memory, orientation, judgement and reasoning. Because the incidence of AD is expected to increase continuously in the next future in the absence of significant therapeutic breakthrough, the anaesthetic management will have profound implication for anaesthesiology in elderly patients and patients already diagnosed with AD [37]. The experimental models for AD depicted a dysregulation of the homeostasis of tau protein and of processing of amyloid proteins. The imbalance in activities of enzymes that catalyses the phosphorylation/dephosphorylation of the tau protein results in its hyperphosphorylation and leads to neuronal cell death and degeneration. Besides, the alteration of amyloid protein metabolism results in its accumulation, then synaptic dysfunction and neuronal damage.

Despite in vitro studies and animal data, the possible relation between anaesthetic neurotoxicity, postoperative cognitive dysfunction and AD remains elusive. There is no rigorous clinical trial for either recommending or contraindicating anaesthetic procedures on the basis of neurotoxicity in the elderly. The impact of anaesthetics, especially inhaled anaesthetics, was investigated in experimental models and in patients with AD, because they might accelerate the progression of the disease [38]. The main hypotheses would be that inhaled anaesthetics (1) impact the processing and metabolism of β-amyloid protein, resulting in its accumulation instead of clearance from extracellular space into blood and cerebrospinal fluid, and (2) trigger hyperphosphorylation of tau protein and its aggregation. Among inhaled anaesthetics, isoflurane and sevoflurane were similarly described inducing apoptosis in experimental animal model and accumulation of β-amyloid metabolites in CSF in AD patients. Potential upstream mechanisms of inhaled anaesthetics are discussed also like the elevation of cytosolic calcium followed by the activation of apoptotic pathways, expression of inflammatory mediators or release of radial oxygen species and mitochondrial damage. By contrast, desflurane was not associated to aberrant processing of tau protein metabolites or postoperative cognitive decline. Most of these data were experimental but, if confirmed, might implicate changes in anaesthesiology of susceptible patients [39].

There is no absolute contraindication in AD for regional anaesthesia techniques. Pragmatically, the anaesthetist should consider the inability of some AD patients to understand their environment or to cooperate. Therefore, the lack of cooperation and unanticipated outbursts during the surgical procedure are arguments for general anaesthesia.

### 14.3.3 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease characterized by demyelination of the white matter in the central nervous system. Young adults and women are predominantly affected. The severity of symptoms may be highly variable, resulting in bedridden at worst.

The most common anaesthetist's concern is exacerbation of the pre-existing deficit [40, 41]. Nevertheless, anaesthetists should not automatically take the blame for postoperative worsened or new symptoms. Stressful condition, fever, infection, surgery and delivery may cause such exacerbations, making it very difficult to separate the effects of these factors and anaesthesia. The different anaesthetic options have to be discussed for every patient, regarding the progression of the disease, the respiratory function and the cardiac function.

A detailed history of the disease is necessary for the preoperative evaluation. Discontinuation of treatment for multiple sclerosis might be associated with disease recurrence, especially in patients with a highly active disease. Decision on discontinuation should be discussed with a neurologist, based on the presence of side effects and drug interactions.

Clinical assessment of respiratory dysfunction is a major issue for the preoperative evaluation. Respiratory dysfunction may appear in early stages of the disease, due to lack of respiratory muscle coordination caused by cerebellar impairment [42]. The preoperative assessment should at least include the ability to cough and clear respiratory secretions and the ability to exhale deeply. Obstructive sleep apnoea is another common sleep disorder in MS patients that should be identified in advance.

Cardiac evaluation is also important for anaesthetic management. MS treatment may cause cardiomyopathy and autonomic dysfunction is possible, resulting in an increased risk for haemodynamic instability during induction. Hypotension with reduced response to intravenous fluid or vasopressor therapy should be expected.

The choice for general or regional anaesthesia depends on the preoperative assessment and the surgical procedure. There are no specific precautions for inhaled and intravenous anaesthetic agents or opioids. For patients with significant motor impairment, succinylcholine might be avoided because of a potential hyperkalemic response. The response to nondepolarizing muscle relaxants is unpredictable. On one hand, a relative resistance to these agents has been described, due to an increased number of postjunctional receptors. On the other hand, lower doses of short-duration nondepolarizing relaxants should be used in MS patients with motor weakness. Baclofen, used to regulate spasticity, may cause muscle weakness, rendering the patient extremely sensitive to the action of nondepolarizing muscle relaxants. Despite this side effect, baclofen should not be stopped abruptly, because of the risk of delirium and convulsions. Because of the unpredictable response, neuromuscular monitoring is imperative.

Despite the lack of evidences, many anaesthetists, fearing forensic procedures, will consider the presence of pre-existing neurological disease, a contraindication for regional anaesthesia [43]. Above threshold concentrations, local anaesthetics are

neurotoxic. The loss of the protective effect of the myelin in patients with MS results in the spinal cord and nerves being exposed to higher concentrations. As a consequence, the safety of regional anaesthesia cannot be guaranteed. Nevertheless, it may be advantageous because of a decrease stress response to surgery. Epidural anaesthesia has been studied extensively in the obstetric population and is considered safe. For subarachnoid anaesthesia, controversy still exists. When performing epidural or spinal anaesthesia, recommendations are to use shorter-acting agents and the minimum dose necessary, with or without epidural opioids.

Whatever the anaesthetic management, body temperature should be monitored, since hyperthermia is responsible for disease exacerbation.

### 14.3.4 Parkinson's Disease

Parkinson's disease is a neurodegenerative disorder resulting in death of dopaminergic neurons of the pars compacta of the substantia nigra. Parkinson's disease patients suffer from neurological symptoms, such as the classical triad of resting tremor, muscle rigidity and bradykinesia, but also from systemic disorders and cognitive dysfunctions [44].

One of the anaesthetic considerations for patients with Parkinson's disease is the perioperative management of the treatment. The main deficit in Parkinson's disease is lack of availability of dopamine in the basal ganglia. The basic principle of the treatment is to compensate the lack of dopamine. L-DOPA, a prodrug converted to dopamine in the brain, is exogenous dopamine.

Abrupt withdrawal of levodopa may lead to skeletal rigidity, which interferes with adequate ventilation. The alternative approach is to use dopamine agonists, such as bromocriptine, lisuride, pergolide, piribedil, ropinirole, pramipexole and apomorphine. The other drugs used for Parkinson's disease are type B monoamine oxidase inhibitor (selegiline and rasagiline), catechol-O-methyltransferase inhibitors (COMT) and amantadine.

Treatment of Parkinson's disease should not be stopped. It is important to try to reproduce the exact time when a patient's drugs are due. Drugs should be administered through stomach tube if necessary. If needed, apomorphine can be injected, in replacement of the usual treatment.

Surgical treatment, especially deep brain stimulation, is another option. This procedure results in marked improvement in rigidity, tremor and bradykinesia. During surgical procedures, precautionary measures must be taken with patients treated by deep brain stimulation. The potential complications that could be observed are electric arc after defibrillation, electrical burns caused by electric bistoury and the neurological electrode. Bipolar electric bistoury should be used, and the control box of stimulation should be evaluated after procedure.

Other anaesthetic problems are non-neurological manifestations of Parkinson's disease. Dysautonomia is often a feature of Parkinson's disease [45]. Disturbances of gastrointestinal functions, such as gastroparesis, are probably the most common features, but orthostatic hypotension is the most disabling symptom regarding the

anaesthesia. Autonomic dysfunction and drugs may precipitate extremes of blood pressure during anaesthesia.

Because of norepinephrine secretion abnormality, administration of fluids and direct sympathomimetic drugs should be used preferently.

Because of poorly coordinated activity of the respiratory muscles, pulmonary dysfunctions of obstructive, restrictive and mixed type have been described in patients with Parkinson's disease [46]. The muscles of the upper airway are involved in the involuntary movements of Parkinson's disease. Atelectasis, post-extubation laryngospasm and postoperative respiratory failure should be feared.

Sialorrhoea and dysphagia are other manifestations of the disease. It can be responsible for increased risk of inhalation [47].

Regarding the anaesthesia protocol, the anaesthesiologist should consider every aspect of the disease mentioned above. There are no specific drugs to conduct general anaesthesia; regional anaesthesia is possible [48]. In case of postoperative nausea, drugs that precipitate Parkinson's disease, such as metoclopramide and droperidol, are strictly forbidden; dexamethasone and ondansetron should be used.

### 14.3.5 Epilepsy

Epilepsy is one of the most frequent chronic neurological diseases, beginning in childhood, and anaesthesia for patients with epilepsy is commonly encountered. The management of antiepileptic drugs (AEDs) and minimizing the risk of seizure are the most important anaesthetic considerations for epileptic patients. The anaesthesiologist must know the principal triggers of seizures during the perioperative period [49]: break of AEDs, dilution (haemorrhage or fluid administration), alcohol intoxication or withdrawal, drug metabolism interaction, toxics (antibiotics), fever and infections, hypoglycaemia, hyponatremia, hypocalcaemia, hypomagnesaemia, hypoxia, low cerebral blood flow, lack of sleep and emotions. Since the stop of AED is one of the most common causes of perioperative seizures, anticonvulsants should be used until the day of surgery, including in children and pregnant women [50]. The usual antiepileptic drugs must not be stopped, except for stiripentol, usually prescribed for children and responsible for awakening latency. The plasma dosing of antiepileptic drugs should not be done in a systemic way.

Moreover, it is important to consider the adverse effects of anticonvulsants, as well as the possibility of drug interactions with anaesthetic agents. First-generation AEDs such as phenytoin, carbamazepin and phenobarbital were responsible for enzyme inductions, whereas the latest-generation AEDs (levetiracetam, lamotrigine, gabapentin) induce fewer drug interactions. The choice of drugs to conduct general anaesthesia is based on the proconvulsant characteristics and on the possible drug interactions. This way, etomidate, ketamine at usual doses, fentanil, alfentanil and remifentanil should be used with caution [51]. Enflurane and sevoflurane should not be used at concentrations above 1.5 MAC and in the presence of hypocapnia [52]. The literature shows no epileptic activity induced by antibiotics, despite proepileptic activity in pharmacological studies. All antibiotics can be used safely in

patients with epilepsy. Anticholinesterase agents and anticholinergics (atropine, scopolamine) can be used in epileptic patients.

Epileptic patients may be resistant to some drugs, especially when taking carbamazepine and phenobarbital, because of enzyme induction. Some antiepileptic drugs have a depressant action on acetylcholine release at the neuromuscular junction. Phenytoin and carbamazepin decrease the duration of action of some neuromuscular blockers such as rocuronium, pancuronium, vecuronium and cisatracurium [53], due to increased hepatic metabolism of these drugs. On the contrary, the time of action of atracurium or mivacurium is not modified by antiepileptic drugs. The small increase of duration of succinylcholine is irrelevant under the clinical point of view. Because of drug interactions between antiepileptic drugs and neuromuscular blockers, intraoperative monitoring of neuromuscular blockade is recommended.

Local anaesthetics have proconvulsant (high doses) and anticonvulsant (small dose) properties due to the stabilizing effect on the membrane. It is difficult to know if seizures occurring after local anaesthesia would be related to systemic toxicity or to epileptic disease. Local anaesthesia can be performed for epileptic patients, but it is important to be prepared to treat any seizure [54].

**Conclusion**

Perioperative period constitutes a high risk of neurological complications in patients with limited vascular reserve. Besides stroke by emboli in major cardiovascular surgery, general surgeries may expose the patients to haemodynamic instability or inflammatory processes with severe consequences on brain metabolism. Such circumstances may favour postoperative cognitive dysfunction or worsening of degenerative cerebral disease with consequences on outcome. Specific anaesthetic strategies might be of interest, but further clinical data are mandatory.

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# Patients with Chronic Neuromuscular Diseases

15

Valentine Léopold, Alice Blet, Kathleen McGee, and Benoît Plaud

## 15.1 Introduction

Neuromuscular diseases are a group of acquired or congenital conditions, characterized by the impairment of either neuromuscular transmission or the muscle itself (myopathies). Myasthenia gravis is characterized by a defect in the transmission of the nervous signal due to a quantitative reduction of the acetylcholine postsynaptic receptor. These diseases are rare and in nonspecialized centres, clinicians and anaesthetists, in particular, are not often confronted with such patients. Respiratory and cardiac involvement are the main factors determining the prognosis. These diseases require careful preoperative screening. The use of some specific anaesthetic agents may be contraindicated or modified as they increase the risk of perioperative complications, mainly respiratory and cardiac. These patients undergo surgical procedures, which may be (1) related to the treatment of the aetiology of the disease (thymectomy in myasthenia), (2) functional surgery (correction of a spinal deformation in the case of myopathy) and (3) treatment of complications of the disease (cataract or cholecystectomy in Steinert myotonic dystrophy).

V. Léopold • K. McGee • B. Plaud (✉)
Anesthesia and Critical Care Department, Paris-Diderot University and Assistance Publique—Hôpitaux de Paris, Saint-Louis Hospital, Sorbonne Paris Cité University, 1, Avenue Claude Vellefaux, 75475 Paris Cedex 10, France
e-mail: benoit.plaud@aphp.fr

A. Blet
Anesthesia and Critical Care Department, Paris-Diderot University and Assistance Publique—Hôpitaux de Paris, Saint-Louis Hospital, Sorbonne Paris Cité University, 1, Avenue Claude Vellefaux, 75475 Paris Cedex 10, France

Inserm UMR S942, Lariboisière Hospital, Paris, France



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## 15.2 Anaesthesia and Myasthenia Gravis

In the United States, the prevalence of myasthenia gravis is 200 per 1,000,000 [1]. It may present at any age but affects mainly adults under 40 years of age (in 60% of cases) with a female majority. Myasthenia gravis is due to autoantibodies targeting the acetylcholine postsynaptic receptors (nAchR), resulting in a blockade of the transmission of the nervous message at the motor end plate (postsynaptic neuromuscular block) [2, 3]. The decrease in the number of functional postsynaptic receptors leads to a decrease in the amplitude of the endplate potential which is then insufficient to trigger the muscle cell depolarization and thus muscular contraction. When numerous neuromuscular junctions are affected, muscular weakness is observed [3], and strength returns to normal after resting. The most severe forms are characterized by the impairment of the respiratory muscles (both thoracic and diaphragmatic) and disorders of deglutition (20–30% of patients), which can cause life-threatening respiratory complications. The diagnosis is essentially clinical. The negativity of the anti-acetylcholine receptor autoantibodies does not eliminate the diagnosis. Associations with other autoimmune disorders (rheumatoid arthritis, Hashimoto thyroiditis, lupus erythematosus) are frequently found and should be systematically investigated. The prognosis is determined by the occurrence of complications, including disorders of deglutition and respiratory involvement [4, 5]. Therapeutic management of myasthenia gravis includes therapeutic education (knowledge of aggravating factors and signs of complications, contraindicated medication) and symptomatic drug therapy by anticholinesterase agents (neostigmine, pyridostigmine, ambenonium) [2, 3]. Severe forms may benefit from immunosuppressive therapy, intravenous immunoglobulins or plasmapheresis [6]. Thymectomy may lead to prolonged remission which may occur with some delay [4].

### 15.2.1 Preoperative Assessment

The severity of the disease is assessed on respiratory function. The scale of the Myasthenia Gravis Foundation of America has five stages of increasing severity [7]. When pharyngolaryngeal or thoracic muscles are involved, postoperative respiratory complications can occur [8]. Respiratory function should be evaluated prior to surgery by respiratory function tests (including maximum inspiratory pressure and vital capacity) to provide a baseline value and also for use in postoperative mechanical ventilation scores [9]. If the patient presents a mass in the anterior mediastinum (thymoma), a risk of tracheobronchial or vascular obstruction is possible at induction of anaesthesia, or even in a supine position. The realization of flow-volume curves in seated and lying position can help to evaluate the respiratory repercussion of the mediastinal mass [10]. Other autoimmune diseases associated with myasthenia gravis may have their own anaesthetic implications and should be looked for. Similarly, screening should also check for hydro electrolyte disorders in patients on long-term corticosteroid therapy. There is still controversy concerning management of medication before surgery. There is no consensus regarding the continuation of anticholinesterase therapy prior to surgery [8]. Some consider that anticholinesterases should

be stopped because of the risk of interaction with muscle relaxant and with neostigmine as reversal agent of neuromuscular blockade, while others propose to continue anticholinesterase therapy in order to maintain this clinical equilibrium. The latter pragmatic strategy is most often adopted as it takes into account the current needs of the patient and also the severity of myasthenia gravis. In severe patients, immunosuppressive treatment should be continued, in particular corticosteroid therapy. Moreover, in case of insufficient control of symptoms, preoperative administration of intravenous immunoglobulin or plasmapheresis may be beneficial [11]. Preoperative optimization of ventilatory function by physiotherapy is essential, especially for abdominal or thoracic surgery. A multidisciplinary approach (anaesthesiologist, neurologist, surgeon and physiotherapist) in the perioperative management of these patients is a key point. Premedication should avoid drugs with respiratory depressant effects. Benzodiazepines, which may aggravate myasthenia gravis, are contraindicated. Many drugs interfere with the neuromuscular junction and can worsen the disease and even lead to myasthenic crisis. These interactions should be taken into account in the preoperative period in order to minimize the risk of errors pre- and postoperatively [12, 13].

Table 15.1 shows the most common drugs that can worsen myasthenia gravis. There are two categories: absolute contraindication leading to clinical aggravation and relative contraindication of medications which should be used with caution after evaluating the benefit/risk ratio. Injection of iodine-based contrast media for radiological examination may induce acute decompensation. It is therefore not recommended in the case of the acute phase of myasthenia gravis. At the end of preoperative

**Table 15.1** Medication worsening myasthenia gravis

| | Absolute contraindication (clinical aggravation) | Relative contraindication (careful use) |
|---|---|---|
| Antibiotics | Aminoglycosides | Lincosamides |
| | Colistin | Cyclins |
| | Cyclines IV | Local aminoglycosides |
| | Telithromycin | Quinolone |
| | | Macrolides |
| Cardiovascular drugs | Quinidine | Lidocaine |
| | Procainamides | Calcium blocker |
| | Beta blocker | Furosemide |
| | | Bretylium |
| Psychoactive drugs | Diphenylhydantoin | Lithium |
| | | Benzodiazepines |
| | | Carbamazepine |
| | | Phenothiazine |
| | | IMAO |
| Others | Magnesium IV | Magnesium PO |
| | D penicillamine | Quinquina |
| | Quinine | Nicotinic derivate |

Adapted from [12, 13]

assessment, the patient should be informed of the benefits and risks of the anaesthetic strategy adopted and the risk of postoperative respiratory failure, which may require prolonged respiratory assistance (invasive or not). The possibility of a temporary tracheotomy in order to conduct respiratory weaning for the most severely affected patients and undergoing major surgery (abdominal or thoracic) will also be explained preoperatively. The decision of prolonged postoperative respiratory assistance is decided at the end of surgery taking into account basic criteria such as the initial severity of myasthenia gravis, current medication and repercussion of surgery on the respiratory function. In all cases, monitoring of these patients in a critical care unit must be anticipated. In most cases, early withdrawal of ventilation (e.g. at the end of the procedure) should be proposed.

### 15.2.2 Anaesthetic Management

#### 15.2.2.1 Anaesthetic Agents and Myasthenia Gravis

For general anaesthesia, two techniques are currently proposed: inhalational anaesthesia or intravenous anaesthesia with or without muscle relaxant [14]. Intravenous techniques should be preferred in myasthenia gravis, as the effect of halogenated agents on neuromuscular transmission is more pronounced in patients with myasthenia gravis than in healthy subjects [14].

#### 15.2.2.2 Muscle Relaxant

The use of muscle relaxants is limited to formal indications (e.g. facilitate tracheal intubation and the surgical procedure). The pathophysiology of myasthenia gravis explains the clinical characteristics of the disease and the modifications observed when muscle relaxants are used: the nicotinic acetylcholine receptor is the target of both muscle relaxants and the autoantibodies responsible of myasthenia gravis [8, 15]. The use of muscle relaxants is not contraindicated and should be adapted in order to allow withdrawal of ventilation at the end of surgery. There is a resistance to succinylcholine (depolarizing muscle relaxant), and the dose needed to achieve neuromuscular block is increased [16, 17]. Anticholinesterase therapy, if continued, reduces the metabolism of succinylcholine and leads to delayed recovery of neuromuscular blockade. Non-depolarizing muscle relaxants, regardless of their chemical classes and duration of action, require doses reduced by 50–75% because of a significant increase of sensitivity and therefore an increase in their duration of action. This reduction depends on the severity of myasthenia gravis. Neuromuscular function assessment by nerve stimulation (train of four, TOF) at the adductor pollicis prior to administration of a non-depolarizing muscle relaxant can predict sensitivity. In myasthenia gravis, a TOF ratio below 0.9 implies a higher sensitivity to muscle relaxant, whereas patients with a TOF ratio equal ou greater than 0.9 have the same sensitivity as healthy subjects [18]. Monitoring neuromuscular blockade is crucial to prevent overdosage and residual block and thus prolonged postoperative mechanical ventilation. Titration and monitoring enable a safe and optimized use of non-depolarizing muscle relaxants.

### 15.2.3 Postoperative Care

The possibility of postoperative admission to intensive care should be considered. In most cases, early withdrawal of mechanical ventilation is possible, using the same criteria as in non-myasthenic subjects. The use of non-depolarizing muscle relaxants increases the risk of respiratory complications [14]. Pharmacological reversal of neuromuscular blockade has a broad indication and is facilitated by neuromuscular monitoring. The assessment of full neuromuscular function recovery should take into account the basal value of TOF ratio. Neostigmine/atropine indication is standard, and the observation of four responses after TOF stimulation is necessary prior to pharmacological reversal. Neostigmine can be used at the standard dose except in case of anticholinesterase therapy, where the dose should be reduced. Neostigmine has a delayed onset of action and thus requires an interval of 10–15 min after administration before considering extubation. Aminosteroid muscle relaxant such as rocuronium can be antagonized using sugammadex. This agent exerts its effect by forming a specific complex with the aminosteroid muscle relaxant, without interacting with the neuromuscular junction, and thus can be used for patients taking anticholinesterase medication [19]. This strategy has been tested and successfully reported on several series of patients [20].

Several scores predicting postoperative mechanical ventilation have been proposed, but they are only indicative [8, 9–21, 22]. Postoperative muscle weakness may be linked to a residual effect of the anaesthetic agents (halogenated agent or muscle relaxant), myasthenic crisis or cholinergic crisis. There is controversy regarding immediate postoperative prescription of anticholinesterase medication. Indeed, delayed prescription could reduce the risk of cholinergic crisis and simplify the diagnosis of postoperative muscle weakness. In all cases, their reintroduction should be titrated, starting with half of the preoperative dose. In cases of respiratory failure, noninvasive ventilation is an interesting alternative to tracheal intubation [23].

### 15.2.4 Pregnancy and Myasthenia Gravis

Pregnancy has a variable influence on the course of the disease. It can lead to an aggravation (especially in the first three months of pregnancy and during the postpartum) or less frequently to the remission of the disease [1, 24]. On the other hand, myasthenia gravis has little influence on the course of pregnancy and childbirth. The delivery must be planned in a centre with intensive care facilities for the mother and the newborn. The treatment of myasthenia gravis should be optimized during pregnancy, childbirth and postpartum. Epidural analgesia is a medical indication in myasthenia gravis [25]. Morphine should be used in order to reduce the use of local anaesthetics. Clonidine should be avoided due to increased motor blockade. The combination of spinal anaesthesia and epidural anaesthesia is also possible in these patients [25]. If general anaesthesia is indicated, succinylcholine is not contraindicated and a higher dose is required (1.5–2 mg/kg). Neonatal myasthenia gravis could appear in 20–30% of newborn in the first 24 h. Hospitalization of the newborn in a continuing care unit is justified.

## 15.3 Anaesthesia and Muscular Disorders

These diseases are characterized by progressive damage of skeletal muscle, including respiratory muscles, cardiac striated muscle and smooth muscles (visceral included). Anaesthesia is required for multiple interventions: muscle biopsy for diagnosis assessment, functional surgery to improve quality of life (kyphoscoliosis surgery, tenotomy in dystrophinopathies), treatment of specific complications (cataract, cholecystectomy in Steinert's disease) and surgical emergencies (traumatic and visceral in particular).

### 15.3.1 Progressive Muscular Dystrophy or Dystrophinopathy

In these diseases, cardiac muscle involvement leads to overall cardiac failure (contractility disorder) associated with rhythm and conduction disorders with a high risk of sudden death. It is responsible for early death around the age of 25. Due to walking disorders, cardiac symptoms often do not arise despite the early involvement of cardiac pump function. The tolerance to a surgical procedure depends on the severity of the cardiac damage, especially for surgery with high risk of excessive blood loss.

Preoperative assessment has to determine the severity and extent of muscle damage, presence of deformities and retraction, deglutition disorder and respiratory or cardiac insufficiencies. Due to reduced physical activity, exercise tolerance is difficult to determine and the clinical severity of respiratory and cardiac function is often underestimated. Respiratory investigations (chest X-ray, pulmonary function tests and arterial blood gas analysis) and cardiac investigations (ECG, echocardiogram, stress testing, 24-h Holter ECG) are most often performed as part of the multidisciplinary follow-up of these children and should be available at anaesthetic preoperative assessment.

The degradation of cardiac and respiratory functions should be monitored by sequential evaluation of the left ventricle ejection fraction and pulmonary function tests. For a major surgical intervention (e.g. spinal surgery), the following pragmatic attitude is proposed based on the result of stress echocardiogram: a good prognosis is associated with an increased heart rate after dobutamine administration whether the ejection fraction is normal or impaired. However, the prognosis seems to be poor when the ejection fraction at rest is under 40% and decreases with dobutamine-induced tachycardia.

In the case of Duchenne muscular dystrophy, ventricular arrhythmias are associated with the progression of cardiac impairment and the risk of sudden death [26]. The echocardiography and the 24-h Holter ECG are useful in the evaluation of the surgical risk [27]. Several severe intraoperative complications are reported in the literature: respiratory failure (aspiration pneumonia due to impaired gastric emptying), cardiac complications (arrhythmias, heart failure, cardiac arrest), myoglobinuria and rhabdomyolysis [28, 29]. Dystrophinopathies are not associated with an increased risk of per-anaesthetic malignant hyperthermia (MH) (Table 15.2). However, syndromes mimicking an MH are reported and can probably be linked to the use of succinylcholine or halogenated agents or both. When used on fragile and pathological muscles,

**Table 15.2** Congenital muscular disorders and malignant hyperthermia risk

| Disease | Malignant hyperthermia risk |
|---|---|
| Duchenne muscular dystrophy | Same risk as in general population |
| Becker muscular dystrophy | Same risk as in general population |
| Myotonia and paramyotonia congenita | Same risk as in general population |
| Myotonic dystrophy type 1 and type 2 | Same risk as in general population |
| Central core disease | Increased risk |
| Multi-minicore disease, MmD (mutation of ryanodine receptor RYR1) | Increased risk |

Adapted from [30–34]

succinylcholine can cause massive rhabdomyolysis and death [35]. Therefore, in Duchenne muscular dystrophy and, by extension, in any primary muscular disorders, succinylcholine is absolutely and definitely contraindicated because of the risk of massive rhabdomyolysis. For general anaesthesia, anaesthetics drugs should be titrated because of variable interindividual sensitivity. Non-depolarizing muscle relaxants should be used only in case of imperative indication. If used, their sensitivity is increased. Therefore, reduced doses are required to avoid prolonged recovery [36, 37]. Nerve stimulator monitoring is mandatory and should be interpreted with caution because of both muscle atrophy and retractions. Residual neuromuscular blockade is frequent and pharmacological reversal is problematic. Neostigmine and atropine are difficult to use in dystrophinopathies due to their effect on secretions dryness (atropine), potential rhythm and conduction disorders (both), central effects (atropine), delayed onset and direct effects on muscle action potential (neostigmine). If an aminosteroid muscle relaxant like rocuronium is used, residual effect can be reversed using sugammadex. This strategy has been successfully evaluated [38].

Inhalational and intravenous anaesthetic agents can be used. Complications are reported with both [28, 29]. Intubation difficulties are more frequent [28, 29]. In case of major surgery, suitable hemodynamic monitoring is needed (invasive blood pressure in particular). Central temperature should be monitored as postoperative shivering can lead to rhabdomyolysis. Hyperthermia can also be observed independently of any MH symptoms as a consequence of massive rhabdomyolysis. The patient's position on the operating table should be very careful to prevent any excessive pressure on muscles.

Spinal surgery is beneficial to respiratory function and quality of life. It should be performed as early as possible, as respiratory and cardiac function will constantly deteriorate, making anaesthesia more and more challenging. As these patients are exposed to tracheobronchial congestion, atelectasis and aspiration pneumonia, chest physiotherapy and noninvasive ventilation may be required. Patients should thus be admitted to intensive care unit postoperatively. The possibility of a temporary or permanent tracheostomy, in the context of a delayed withdrawal of ventilation, must be exposed preoperatively.

### 15.3.2 Myotonic Dystrophy

There are two different diseases: myotonic dystrophy type 1 (DM1 or Steinert's disease) and myotonic dystrophy type 2 (DM2 or proximal muscular myopathy) [39]. Due to the low prevalence of DM2, only DM1 will be discussed.

DM1 is the most frequent inherited myopathy in adults. It is a common disorder observed in both women and men. DM1 is characterized by multisystemic impairment. The main prognostic factor is the severity of cardiac involvement. The need for a pacemaker depends on His bundle function as recorded on EKG. Respiratory manifestations are common and arise from peripheral muscle damage and neuronal loss in the brainstem. Surgical procedures under general anaesthesia can cause cardiac and/or respiratory decompensation. Ocular signs, especially cataract, have important diagnostic value, as they are constantly present after the age of 40. Digestive impairment can be wide: pharynx (deglutition abnormalities, dysphagia, pulmonary aspiration), oesophagus (dysphagia, hiatal hernia, regurgitation), stomach, intestine (reduction of peristalsis with alternating constipation/diarrhoea, subocclusion, megacolon, anal incontinence) and gall bladder (lithiasis, one-third of patients needing a cholecystectomy). DM1 can also affect the smooth musculature in the uterus (atony with prolonged labour and delivery and thus an increased risk of postpartum haemorrhage), the ureter (dilation) and blood vessels (arterial hypotension). Endocrine impairment arises through cortico-adrenal and thyroid insufficiency.

These patients have a shortened life expectancy. Causes of death are mainly respiratory (42%) and cardiac (29%) often by sudden death. Care and supervision are multidisciplinary and intensive.

The intraoperative period is marked by the risk of myotonic contractures that can be triggered by surgical manipulations [40, 41]. These myotonic contractures cannot be controlled by non-depolarizing muscle relaxants. All factors possibly triggering myotonic contractures should be avoided. Thus, intraoperative control of temperature is essential as postoperative shivering and hypothermia can trigger generalized contractures. Moreover, the risk of aspiration is increased because of frequent involvement of the smooth musculature of the digestive tract. If rapid sequence induction is needed (cholecystitis, bowel obstruction), rocuronium should be used (the shortest onset of all non-depolarizing muscle relaxants). Succinylcholine is formally contraindicated as several cases of generalized contractures with life-threatening rhabdomyolysis and hyperkalaemia have been reported [35].

As in other neuromuscular disorders, reversal of residual blockade with sugammadex, after rapid induction with rocuronium, has been reported as successful [42]. Local anaesthesia should be considered for certain types of surgery (including cataract extraction). When not feasible, general anaesthesia with tracheal intubation is preferred. Isoflurane has been used in some cases, although the greater risk of postoperative shivering compared to intravenous agents should be taken into account. DM1 is not associated with an increased risk of MH, and the reported complications of MH-like symptoms (hyperthermia, rhabdomyolysis, arrhythmia, hyperkalaemia) have

been associated with a particular context (young child, association of halogeneted-succinylcholine agents) revealing myopathy, therefore muscle fragility [32]. Only the central core myopathy is associated with an elevated risk of MH. These two diseases share the same genetic abnormality of the ryanodine receptor (Table 15.2) [33, 34]. If non-depolarizing muscle relaxant is indicated (apart from tracheal intubation), required doses are reduced because of increased sensitivity. Neuromuscular monitoring allows muscle relaxant titration. Anticholinesterases are contraindicated. Cases of generalized contractures have been reported after pharmacological reversal using neostigmine [39]. Postoperative care should be performed in an intensive care unit and should include early respiratory physiotherapy. This is essential as respiratory failure is one of the main postoperative complications [40].

## Conclusion

Patients with neuromuscular disorders include several anatomo-clinical entities. The involvement of the nicotinic acetylcholine receptor (myasthenia) *versus* the direct muscle involvement (myopathies) needs to be distinguished. This distinction helps to understand the pathophysiological and clinical characteristics and anaesthetic consequences of these conditions. These diseases are rare, but the complications to which these patients are exposed during the perioperative period are potentially serious and life-threatening. The preoperative assessment focuses on respiratory functions (myasthenia gravis and myopathies) and cardiac function (myopathies) as they can be altered. The surgery can be an inherent part of the treatment of the disease (thymectomy in myasthenia gravis) or is intended to improve the quality of life (corrective surgery for myopathies). Certain anaesthetic agents can cause specific complications that should be anticipated.

**Conflict of Interest** Benoît Plaud is consultant and lecturer for MSD™ France.
Alice Blet, Valentine Léopold and Kathleen McGee have no current conflict of interest.

## Key Points

- Neuromuscular diseases are divided into disorders of (1) the nicotinic acetylcholine receptor (nAchR), (2) the motor endplate (myasthenia gravis) and (3) the muscle fibre (myopathy).
- These are rare diseases. However, complications occurring in the perioperative period are potentially life-threatening.
- These patients undergo surgical procedures, which may be (1) related to the treatment of the aetiology of the disease (thymectomy in myasthenia), (2) functional surgery (correction of a spinal deformation in the case of myopathy) and (3) treatment complications of the disease (cataract or cholecystectomy during Steinert myotonic dystrophy). The preoperative screening of these patients is mainly oriented towards respiratory and cardiac function.
- Myopathies are a subgroup of inherited diseases characterized by primary muscle damage. The two most frequent types are Duchenne muscular dystrophy and myotonic dystrophy known as Steinert's disease.

- Anaesthetic management of patients with myopathies has to take into consideration impaired respiratory and cardiac and smooth muscle function, which worsen progressively over time.
- Intravenous anaesthetics should be preferred to inhalational anaesthetics as halogenated agents impair neuromuscular transmission.
- The risk of MH is strongly associated with the central core myopathy, these two diseases sharing the same genetic anomaly of the ryanodine receptor.
- Local anaesthesia is a good alternative when possible and is useful for postoperative pain control.
- Non-depolarizing muscle relaxants can be used, but the doses needed should be drastically reduced in myasthenia gravis and in myopathies. Monitoring of neuromuscular function is thus imperative in this context. Succinylcholine is strictly contraindicated in muscle diseases (generalized contracture, rhabdomyolysis).

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# Part V

# Other Risks

# The Patient with Septic Shock

16

Bruno Pastene, Gary Duclos, and Marc Leone

## 16.1 Definition of Sepsis

Sepsis is defined as "life-threatening organ dysfunction caused by a deregulated host response to infection." Septic shock is a "subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality." The patients with septic shock require vasopressors to maintain mean arterial pressure above 65 mmHg and have a lactate level above 2 mmol/L, despite adequate volume resuscitation [1]. The term "severe sepsis" disappeared from definitions.

## 16.2 Pathophysiology of Septic Shock

Sepsis is an inflammatory process due to the interaction of microbial components and the constituents of the host, resulting in a pro-inflammatory response attributable to the production of interleukin-1 and tumor necrosis factor. In parallel, there is a development of an anti-inflammatory response mediated by several mediators like interleukin-10, associated with an apoptotic process [2]. A close monitoring of the immune status of patients, based on the expression of HLA-DR on the monocytes, should facilitate the determination of the immune status of each patient.

All in one, the cytokine "storm" results in a reduced vascular reactivity to vasoconstrictors and loss of fluid by decreased permeability of the vascular wall. The vasodilation is mediated by the production of nitric oxide, a potent vasodilator. The production of inflammatory mediators reduces cardiac performance. Right and left ventricles are

B. Pastene • G. Duclos • M. Leone (✉)
Aix Marseille Université, Service d'Anesthésie et de Réanimation, Hôpital Nord, Assistance Publique-Hôpitaux de Marseille, APHM, Chemin des Bourrely, 13015 Marseille, France
e-mail: marc.leone@ap-hm.fr



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dilated and ejection fraction diminishes. Due to the intense vasodilation, resulting in a reduced afterload, the impairment of heart function is a clinically silent injury in most cases. This cardiac impairment is reversible within 7–10 days.

Microcirculation is deeply affected during septic shock, due to local clots, shunts, and tissue edema. As there is a misuse of oxygen, central venous saturation does not adequately reflect the oxygen use, as in hemorrhagic shock or cardiogenic shock. The relation between the level of mean arterial pressure and the microcirculation remains unclear, at least for levels between 65 and 85 mmHg.

## 16.3 Anesthetic Drugs and Septic Shock

### 16.3.1 Hypnotics for Induction

General anesthesia of a septic patient is almost exclusively practiced for urgent procedures. Rapid-sequence induction is the gold standard in this setting. Its hemodynamic impact is greater in septic patients. Few hypnotics are commonly used in this indication: hypnomidate, thiopental, propofol, and ketamine.

#### 16.3.1.1 Hypnomidate

Hypnomidate was widely used due to its hemodynamic properties. However, its metabolic effects (blockade of the 11beta-hydroxylase and adrenal insufficiency) with potential harm in the critically ill patient made its use controversial [3]. A meta-analysis including about 1000 patients concluded that its administration for rapid sequence intubation was associated with higher rates of adrenal insufficiency and mortality in patients with sepsis (RR 1.33; 95% CI 1.22–1.46 and RR 1.20; 95% CI 1.02–1.42, respectively) [4]. However, the conclusion of this meta-analysis has been discussed because of the data heterogeneity.

The metabolic effect of this drug was confirmed. Retrospective study of a large electronic intensive care unit (ICU) database [5] in 2013 shows no difference in ICU and hospital mortality, ICU and hospital length of stay, and vasopressor use and duration of mechanical ventilation. However, more patients in the hypnomidate group received steroids before and after intubation (52.9% vs. 44.5%, $p < 0.001$). A multicenter, retrospective, propensity-matched cohort study [6] found that the use of hypnomidate for intubation of septic patients did not increase vasopressor requirements within 72 h after intubation (primary outcome), ICU length of stay, and in-hospital mortality (secondary outcomes). A prospective controlled double blind study [7] found no benefit on ICU length of stay and mortality of a moderate-dose hydrocortisone therapy throughout the period of hypnomidate-related adrenal insufficiency in critically ill patients without septic shock. These findings are consistent with a meta-analysis compelling 5000 patients. This study concluded that hypnomidate administration was associated with an adrenal insufficiency (RR 1.42; 95% CI, 1.22–1.64; $p$ 0.00001) but not with a higher rate of mortality (RR 1.20; 95% CI 0.84–1.72) [8]. However, these findings largely rely on data from observational studies with a potential selection bias.

Current data do not allow to decide for or against hypnomidate for septic shock patients. However, its pharmacodynamic profile is potentially harmful, and other anesthetic drugs with identical or better hemodynamic properties are available.

#### 16.3.1.2 Propofol

Due to its excellent safety features, propofol is the most widely used drug in elective anesthesia. Propofol contains a phenolic hydroxyl group that donates electrons to the free radicals, thus acts as an antioxidant. Many studies highlighted the effects of propofol on the inflammatory pathways. Pretreatment with propofol reduced the mortality rate of rats and attenuated the pro-inflammatory cytokine responses (interleukin-6 and tumor necrosis factor-α) in an endotoxin shock model [9] through an inhibiting induction of high mobility group box 1 protein. In a porcine endotoxemia model [10], propofol reduced enzymatic and nonenzymatic endotoxin-induced lipid peroxidation, improving arterial oxygen tension.

At concentrations used during clinical anesthesia, propofol protects human umbilical vein endothelial cells against arachidonylethanolamine-induced injury, in part by suppressing apoptosis [11]. Propofol also downregulates macrophage nitrous oxide biosynthesis via inhibiting iNOS gene expression [12].

Nevertheless, propofol has significant hemodynamic effects. It suppresses the sympathetic response, decreasing systemic vascular resistance, cardiac contractility, and preload. Hence, it may lead to adverse effects if used in septic patients, in which the sympathetic response is already impaired.

An analysis of anesthesia records of 4096 patients reported predictors of hypotension after anesthetic induction [13]: ASA III–V, baseline mean arterial pressure <70 mmHg, age >50 years, use of propofol for induction, and increasing induction dosage of fentanyl. The authors recommended avoiding propofol induction in patients with baseline mean arterial pressure <70 mmHg. An animal study showed that propofol is the anesthetic drug with the most pronounced direct cardiac effect during sepsis, with a significant decrease in contractility of −38%, a reduction in lusitropy of −44%, and a direct vasodilator effect by increasing coronary flow by +29 [14].

Compared with midazolam, propofol increases preload dependency in septic shock patients [15]. Compared with dexmedetomidine, propofol increases preload dependency in endotoxemic rabbit model with fluid nonresponsiveness and norepinephrine infusion [16]. Despite its anti-inflammatory properties, who are yet to be confirmed by human studies, the hemodynamic effects of propofol make it unsuitable for the anesthesia of patients with septic shock.

#### 16.3.1.3 Thiopental

Thiopental remains the gold standard for rapid-sequence induction thanks to its rapid onset. Nevertheless, its negative hemodynamic [17] and inflammatory properties [18] (elevation of IL-10 from peripheral blood mononuclear cells in the presence of lipopolysaccharide) make it unsuitable for anesthesia of the patient with septic shock.

#### 16.3.1.4 Ketamine

Ketamine seems to be the most valuable choice for the anesthesia of patients with septic shock. Unfortunately, there is a lack of reliable data on its efficiency and safety. Nevertheless, several studies provided data showing that ketamine is the drug of choice in septic shock. The abolition of sympathetic vascular tone is an effect shared by most hypnotics. Hoka et al. [19] showed the preservation of baroreflex control of vascular resistance when using ketamine in rats. The authors wrote that "ketamine may contribute significantly to the maintenance of blood pressure in the subjects with hemorrhagic hypovolemia, since arterial baroreflex is considered to play an important compensatory role in such condition." In vivo, ketamine acts as a sympathomimetic, increasing heart rate, arterial pressure, and cardiac output [17].

The KETASED Collaborative Study Group produced a randomized, controlled, single-blind trial [20], involving 655 patients who needed sedation for emergency intubation. They compared the administration of 0.3 mg/kg of hypnomidate or 2 mg/kg of ketamine for tracheal intubation. The investigators found no difference in the maximum severity score during the first 3 days in the ICU, concluding that ketamine is a safe and valuable alternative to hypnomidate for endotracheal intubation in critically ill patients. Ketamine induces cardiovascular stability over a wide range of concentration in an isolated septic rat heart model, as compared with propofol, hypnomidate, and midazolam [14]. No data is available about the clinical use of ketamine for septic patients, but several studies strongly advocate its use for hemodynamically unstable patients and in emergency settings [21].

Another point of interest is the immunologic effects of ketamine. These effects have been summarized in a review article [22]. In brief, the mechanism is based on a ketamine-involved regulation of pro-inflammatory gene expression. Thus, ketamine suppressed the production of TNF-α, IL-1, and IL-6. Due to its hemodynamic and immunologic properties, and despite the lack of large-scale prospective randomized trials, ketamine seems to be the drug of choice for induction of general anesthesia for patients in septic shock.

### 16.3.2 Hypnotics for Maintenance

#### 16.3.2.1 Intravenous Anesthetics

Due to its pharmacokinetic properties (short duration of action, hemodynamic stability), midazolam is widely used for the sedation of ICU patients. Propofol may also be used but because of its cumulative toxicity (PRIS syndrome), its use is reserved for limited duration sedation.

Dexmedetomidine, an α-2 agonist, is more and more commonly used in ICU for cooperative sedation. Dexmedetomidine seems to have intrinsic anti-inflammatory properties, suppressing pro-inflammatory mediators. In a murine endotoxemia model, it reduced mortality rate with an inhibitory effect on inflammatory response [23]. In another model, the shift of sedation regimen from propofol to midazolam was associated with an improvement in sublingual microcirculatory perfusion [24].

#### 16.3.2.2 Volatile Anesthetics

In the operating room, volatile anesthetics are a valid choice for maintenance of general anesthesia in the critically ill patients, due to their pharmacologic properties. They are easily titrated to obtain a satisfactory level of sedation with little hemodynamic repercussion. Their short half-life allows a rapid reversal. However, no data from large-scale studies are available to confirm those assertions.

Volatile anesthetics as sevoflurane are used in cardiac surgery in a preconditioning strategy, since this drug decreases ischemia-reperfusion injuries in those patients thanks to its inhibitory action on the inflammatory pathway [25]. Studies have been performed in septic conditions to assess the protective effect of volatile anesthetics. Due to an attenuated inflammatory response, lipid peroxidation, and oxidative stress, sevoflurane, desflurane, and isoflurane significantly improved survival rate in murine models of cecal ligation-puncture-induced sepsis [26]. Those findings are consistent with those in the cardiac surgery preconditioning setting. Even if there is a lack of data regarding hemodynamic safety of volatile anesthetics, the profile of volatile anesthetics seems beneficial.

## 16.4 Hemodynamics of Patients with Septic Shock

### 16.4.1 Monitoring

#### 16.4.1.1 Depth of Anesthesia Monitoring of a Patient in Septic Shock

Identifying the best dosage of drugs remains challenging due to the cardiovascular effects of anesthetics, the change in pharmacokinetics due to fluid therapy, and the alterations of pharmacodynamics due to hypermetabolism. In routine, the dosages are lowered to prevent adverse effects although they must be sufficient to maintain an adequate level of sedation and analgesia.

Bispectral index monitoring with a goal between 40 and 60 is efficient to prevent awareness during surgery and to improve sedative drug delivery and postoperative delivery [27]. There is no study evaluating the effect of bispectral index monitoring specifically for septic patient. However, bispectral index monitoring was associated with a decrease of sedative drug doses, recall, and time to wake-up [28]. Furthermore, it could detect inadequate sedation during therapeutic or preoperative paralysis [29].

Guidelines on neuromuscular blockade stress on the train-of-four monitoring to prevent excessive dose infusion leading to prolonged skeletal muscle weakness or remaining blockade leading to respiratory failure after extubation [29]. In septic patients, cisatracurium pharmacokinetics is deeply altered due to both body fluid distribution and organ dysfunction leading to change in volume of distribution, elimination, and effect of neural transmission. These alterations result in a slower response with reduced effect, strengthening the need of paralysis monitoring [30].

#### 16.4.1.2 Hemodynamic Monitoring

Shock is defined as an acute circulatory failure associated with inadequate oxygen utilization by the cells. Circulation remains unable to deliver sufficient oxygen to meet demands of the tissues. Clinical examination and standard monitoring fail to assess fluid responsiveness during circulatory shock. Invasive monitoring of cardiac output is the cornerstone of an efficient hemodynamic optimization. Biomarkers such as blood lactates or central venous oxygen saturation ($ScvO_2$) should be used to detect inadequate tissue perfusion even without hypotension. A close monitoring is mandatory in the septic shock patient in the operating room, since fluid loss due to bleeding, inflammation related to surgical insult, and hemodynamic impairment due to deep anesthesia make her or his management challenging.

Fluid resuscitation is the first intervention for the management of a patient with shock. Preload is an important determinant of cardiac output (such as afterload and contractility). Preload can be optimized with fluid resuscitation to improve cardiac output, but excess of fluid results in adverse effects [31]. Fluid responsiveness can be defined by improvement of 15% of cardiac output after a 500 mL fluid infusion [32]. During shock, clinician should be able to predict fluid responsiveness before fluid administration. Static index such as central venous pressure (CVP) or pulmonary artery occlusion pressure (PAPO) is not reliable enough to guide a fluid resuscitation [33]. Dynamic index is a more reliable criterion than static index. These are based on changes in the relation between heart function and intrathoracic pressure during mechanical ventilation cycles. Pulse pressure variation (PPV) and stroke volume variation (SVV) are classically assessed via an arterial line. In a seminal study, the area under receiver operating characteristic curve was 0.89 (95% CI: 0.86–0.92) for PPV, compared with 0.57 (95% CI: 0.54–0.59) for central venous pressure. The authors defined a gray zone of PPV ranging from 9 to 13% for which fluid responsiveness could not be predicted reliably [34].

The assessment of aortic blood flow variation using a transesophageal Doppler is probably the method with the highest level of evidence. The use of noninvasive inflatable finger cuffs and variation of vena cava (inferior or superior) with echocardiography are other options. This strategy may prevent fluid overload [35]. Dynamic measures have several limitations because they require a sedated, mechanically ventilated patient in sinus rhythm.

Cardiac output monitoring is critical. However, a single value of cardiac output cannot be used to assess the global hemodynamic state. The cardiac output must be integrated with data about tissue perfusion (lactate clearance, $ScvO_2$, and clinical signs of shock). The best level of cardiac output is not a quantitative value but a confrontation between the patient needs and her or his cardiovascular performance. One should always keep in mind that supramaximal cardiac output using inotropic medication leads to complications and increased mortality [36].

Industry proposes several devices to measure cardiac output. All devices based on pulse contour analysis are considered as inaccurate in patients with septic shock. Their use can be discussed in emergent situations to follow the variations rather than absolute values. Similarly, volume clamp system using inflatable cuff wrapped around the finger to generate a real-time pulse contour analysis is not reliable in those patients due to the spontaneous vasoconstriction of finger arteries [37].

In our opinion, thermodilution is the gold standard for hemodynamic assessment. Continuous monitoring of cardiac output is available with new types of pulmonary artery catheter. This device provides information on other hemodynamic variables (CVP, PAPO) and tissue perfusion ($SVO_2$, oxygen utilization, oxygen delivery). However, this system did not demonstrate a positive effect on the outcome of patients [38].

Thermodilution provides intermittent measurements of cardiac output after infusion of cold bolus through the superior vena cava central line and its detection in the femoral artery by a dedicated catheter. This device measures global end-diastolic volume (volumetric marker of cardiac preload), cardiac function index, and extravascular lung water (quantitative index of pulmonary edema). Those variables are useful to conduct an adequate resuscitation with fluid, vasopressors, and inotropes. Thermodilution is coupled to a pulse contour analysis system. Hence, a real-time calculation of cardiac output is feasible. Potential drift over time makes regular calibration mandatory.

Echocardiography cannot provide continuous hemodynamic data. Performing transthoracic echocardiography in the operating room is challenging due to surgical field. However, it can help physician to characterize the hemodynamic state, to choose the best treatment options, and finally to assess the therapy response. Nevertheless, transesophageal echocardiography (TEE) provides reliable data, as cardiac output, left ventricular ejection fraction (mainly depending of contractility and afterload), left ventricular filing pressure (by analysis of transmitral flow), and preload responsiveness (respiratory variation of VTI or after fluid challenge, superior vena cava variation). All measurements are described in guidelines and require an adequate training [39]. Lung ultrasound also provides interesting variables. For instance, the observation of B-lines may suggest pulmonary edema.

Biological monitoring is critical to assess microcirculation during shock. It helps for shock diagnosis, therapeutic adjustment, and outcome determination. Plasma lactate levels increase in the cases of inadequate oxygen delivery, with 2 mmol/L as a cut-off. This is now part of the definition of septic shock [36]. A decrease in plasma lactate levels (10%/h) is associated with decreased mortality rate. Serial measurements of plasma lactate level are recommended to guide therapy in the critically ill patient [40].

In the septic shock patient, $ScvO_2$ (measured from superior venous cava catheter) provides information on the adequacy of oxygen transport. It reflects hemoglobin, oxygen consumption, arterial oxygen saturation, and cardiac output. A low level of $ScvO_2$ values (<70%) in the context of circulatory failure is a relevant marker for the need of fluid (if fluid responsiveness is found) or positive inotrope (if fluid responsiveness is not found). A supranormal $ScvO_2$ value is associated with impaired outcome in the patient with septic shock [41]. It probably reflects a deep microcirculatory failure. Venoarterial carbon dioxide difference ($pCO_2$ gap) (measurement of the difference in carbon dioxide between central venous blood and arterial blood) can be used. Values >6 mmHg suggest insufficient blood flow even for $ScvO_2$ values >70% [42].

#### 16.4.1.3 Clinical Management

The management of patients with septic shock should follow the Surviving Sepsis Guidelines [36]. In the operating room, the monitoring of preload should rely on dynamic index rather than on CVP, although the level of evidence is weak. One should keep in mind that it is critical to exclude the source of infection within the 6 h after diagnosis. Then, surgery should be performed even if the patient remains hemodynamically unstable, after a short period of resuscitation.

The management during surgery does not differ from that of a standard patient. The goal of mean arterial pressure ranges from 65 to 85 mmHg. In the normotensive patient, there is no interest to increase mean arterial pressure above the range 65–75 mmHg. In the hypertensive patient, data suggest targeting mean arterial pressure around 85 mmHg may prevent acute renal failure. However, the degree of organ perfusion seems more critical than the level of mean arterial pressure [43].

Fluid is the first intervention required in most situations. Balanced crystalloids are the best choice for these patients [36]. The use of normal saline should be probably avoided to prevent renal dysfunction due to metabolic acidosis, even if a randomized clinical trial did not confirm the beneficial effect of balanced crystalloids [44]. Hydroxyethyl starch should not be used in septic patients, due to their renal effects [45]. The use of albumin can be discussed in the patients requiring vasopressors with low albumin concentration.

Vasopressors are used if the response to fluid is negative and in unstable patients. They can be used early in the patients with severe hypotension or those with diastolic arterial pressure below 45 mmHg. Norepinephrine is the first choice. This agent should be used via a central venous line, but, if required, this drug may be used on a peripheral line (without any concomitant drug) for few minutes. There is no indication for dopamine. Epinephrine should be avoided for preventing arrhythmia. Phenylephrine is widely used for treating hypotension in the surgical theater. This practice can be highly deleterious due to the properties of this drug, and it should be definitively banned in the septic patient [36]. The role of vasopressin and its agonist terlipressin is unclear [46]. To date, there is no data showing a benefit to use these agents instead of norepinephrine. As they have only vasopressive effects, one should avoid using them in the patients without cardiac output monitoring.

Positive inotropes are used in less than 20% of patients, after fluid administration and onset of vasopressor. Their use is based on a level of $ScvO_2$ below 70%, after preload optimization, transfusion if required (Hb >8–9 g/dL), and sedation. The use of cardiac ultrasound may facilitate the diagnosis of myocardial dysfunction. However, one should keep in mind that increasing oxygen delivery to supranormal level was associated with increased mortality in critically ill patients. Thus, in our opinion, the administration of positive inotrope like dobutamine based only on ultrasound imaging can be unsafe. Monitoring of oxygen delivery should be strongly encouraged [36].

### 16.4.2 Antibiotic

Antibiotics and source control are the cornerstones of the management of the patient with septic shock. The initiation of an antibiotic treatment is considered as emergent, urgent, and delayed. Emergent is defined by the need for starting antibiotics

within 1 h after diagnosis has been made. Many studies report that delays in the initiation of appropriate antibiotic therapy in patients with severe infection are associated with increased mortality [47]. Each hour of delay in antibiotic administration is associated with a decrease in survival. Thus, guidelines recommend prompt introduction of antimicrobial therapy in patients with hemodynamic impairment and suspected infection [36]. In routine, it is suggested to start an empirical antibiotic treatment within the first hour after the diagnosis of septic shock.

Guidelines underline the need to provide antibiotics active against the potential bacteria responsible for the infective episode. Inappropriate initial antimicrobial therapy for septic shock occurs in approximately 20% of patients, resulting in a fivefold reduction of survival [48]. Blood samples for cultures and rapid diagnosis test are systematically required before the onset of treatment. However, the collection of samples during surgery should not delay the administration of antibiotics. In the patients with septic shock, antibiotics are required before the onset of the surgical procedure.

#### 16.4.2.1 Empirical Antimicrobial Treatment

Many patients with septic shock are potential candidates for emergent surgery. Various sources of infections include the abdomen, soft tissue, bone, and others. The use of broad-spectrum antibiotics leads to the emergence of multidrug-resistant pathogens, whose growing prevalence over the last years has become a significant public health threat. The presence of multidrug-resistant bacteria can lead to inadequate antimicrobial therapy, associated with poorer outcomes [49].

Since initial antimicrobial therapy for septic shock patients is empirical, the choice of the drug should be based on the host characteristics, site of infection, severity of infection, and local ecology. The risk factors for multidrug-resistant pathogens are commonly the use of antibiotic within 3 months, a length of stay longer than 5 days, a previous hospitalization (for at least 2 days) within 3 months, and immunosuppression.

With respect to intra-abdominal infection, 60% of spontaneous bacterial peritonitis episodes are produced by Gram-negative enteric bacilli—*Escherichia coli* and *Klebsiella* sp. being the most frequently isolated microorganisms. In approximately 25% of the cases, streptococci (frequently pneumococcus) and enterococci are involved. Secondary peritonitis is polymicrobial including Gram-negative bacteria (*E. coli*, *Enterobacter* sp., and *Klebsiella* spp.), Gram-positive bacteria (enterococci in ~20% of the cases), and anaerobes (*Bacteroides* sp. in ~80% of the cases). For patients with identified risk factors, multidrug-resistant pathogens (including *P. aeruginosa*, *Acinetobacter*, and methicillin-resistant *S. aureus* (MRSA)) and yeasts should be considered [50]. An international multidisciplinary task force called AGORA (Antimicrobials: A Global Alliance for Optimizing their Rational Use in Intra-Abdominal Infections) released a complete and comprehensive review of the management of complicated intra-abdominal infections (cIAI) to actively raise the awareness of the rational and judicious use of antimicrobial medications in the treatment of these infections, in modern health care [51]. Their conclusions are as follows: the choice of empiric antibiotics in patients with community-acquired intra-abdominal infection should be based on the severity of the infection, the individual risk for infection by resistant pathogens, and the local resistance epidemiology. Amoxicillin/clavulanate or

cephalosporins in combination with metronidazole are still good options for the treatment of non-severe IAIs, with piperacillin/tazobactam being a better choice if *P. aeruginosa* coverage is needed. The use of carbapenems should be limited to preserve the activity of this class of antibiotics because of the concern of emerging carbapenem resistance. Ciprofloxacin and levofloxacin are no longer appropriate first-line choices for empiric treatment in many regions because of the prevalence of fluoroquinolone resistance. Other options include aminoglycosides, particularly for suspected infections by Gram-negative bacteria, and tigecycline especially when multidrug-resistant pathogens are suspected. In most case, the addition of aminoglycosides to the pivotal beta-lactam makes it possible to have an efficient coverage of enterobacteriaceae producing extended spectrum beta-lactamases, which is a real challenge in those patients. For the management of multidrug-resistant Gram-negative infections, especially in critically ill patients, the use of "old" antibiotics, such as polymyxins and fosfomycin, should be first considered. Ceftolozane/tazobactam and ceftazidime/avibactam are new antibiotics that have been approved for treatment of intra-abdominal infections (in combination with metronidazole) including infection by enterobacteriaceae producing extended spectrum beta-lactamases and *P. aeruginosa*. As isolation of *Candida* species is an independent risk factor of mortality, the addition of an antifungal, echinocandins in those patients, is suggested for patients with documented or suspected fungal infection [52]. Controversies are still unresolved concerning the right selection of patient who may benefit from antifungal therapy. Two clinical scores are currently used: the *Candida* score (score ≥2.5: Se 81%, Sp 74%) and the peritonitis score (score ≥3: Se 84%, Sp 50). Recent guidelines recommend the discontinuation of those drugs if clinical samples are negatives for fungal infection [53].

Skin infections are frequently polymicrobial. Suspected bacteria should be *Streptococcus* sp. (40%), *S. aureus* (30%), anaerobes (30%), and Gram-negative bacteria (10–20%). The Infectious Diseases Society of America published guidelines about those infections [54]. In septic shock, an emergent surgical inspection and debridement are mandatory, in addition to an empirical antimicrobial therapy. It should include agents effective against both aerobes (including meticillin-resistant *S. aureus* according to local ecology and individual risk factors) and anaerobes. Piperacillin/tazobactam seems the best first option in many cases.

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# The Patient with Haemorrhagic Risk

# 17

Claire Pailleret Ringuier and Charles-Marc Samama

More than 1% of the general population suffers from a congenital bleeding disorder, primarily haemophilia, von Willebrand disease or inherited platelet disorders. The cornerstone of perioperative management of these patients is based on a close collaboration between anaesthesiologists, haematologists, surgeons and the patient's specialised care centre. Replacement therapy should be defined according to the level of the deficient clotting factor, the platelet function and the inherent surgical bleeding risk. The main acquired haemostatic disorders stem from the use of anti-thrombotic therapy, and several expert groups have established guidelines for their perioperative management.

## 17.1 Preoperative Screening for Bleeding Risk

Personal and family bleeding history and also the use of anti-thrombotic drugs should be assessed prior to surgery.

The Swiss group of Bonhomme et al. recently designed a simplified questionnaire to preoperatively screen patients with haemorrhagic diathesis (Table 17.1) [1]. A score ≥2 suggests a high likelihood of an inherited haemostatic disorder [1]. If the bleeding history is negative, no routine coagulation tests are required, regardless of ASA score, age, type of surgery or anaesthesia, since they are poor predictors of bleeding [2].

C.P. Ringuier • C.-M. Samama (✉)
Umr_s1140 Université Paris Descartes, Faculté de Pharmacie, AP-HP, Hôpital Cochin, Paris, France
e-mail: marc.samama@aphp.fr



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**Table 17.1** Standardised questionnaire for pre-anaesthesia screening for inherited haemostatic disorders

| The following items may suggest a possible haemostatic disorder | No | Yes | Situation never encountered |
|---|---|---|---|
| 1. Have you previously consulted a doctor or received a treatment for prolonged or unusual bleeding, for example, nosebleeds or small cuts? | | | |
| 2. Do you have a tendency to develop bruises larger than 2 cm or large haematomas in the absence of a bump or wound or else after a minor bump or wound? | | | |
| 3. Have you had to go back to your dentist because of bleeding after a tooth extraction? | | | |
| 4. Have you experienced major bleeding after surgery, for example, adenoidectomy or tonsillectomy, or after circumcision? | | | |
| 5. Do any of your close family members have a coagulation disorder that causes major bleeding, such as von Willebrand disease or haemophilia? | | | |
| 6. For women: | | | |
| (a) Have you consulted a doctor or received a treatment for heavy menstrual bleeding (e.g. oral contraceptives ("pill"), iron treatment, medication to thicken the blood such as Exacyl)? | | | |
| (b) Did you experience abnormal bleeding after childbirth? | | | |
| Score calculated by number of Yes answers to these six questions | | | |

From Molliex et al. [1]

## 17.2 Perioperative Management of Inherited Bleeding Disorders

Some of the rules for perioperative management are common to all inherited bleeding disorders:

Preoperative management of congenital bleeding disorders requires a close multidisciplinary approach involving anaesthesiologists, haematologists, surgeons and the patient's specialised care centre.

Surgery should take place in a specialised centre or in collaboration with such centre and should be scheduled early in the day on weekdays [3].

Preoperative use of antifibrinolytic agents such as tranexamic acid is an adjuvant therapy of choice [3] and can be given as a 1 g intravenous bolus shortly before anaesthesia induction or started orally (1 g 3–4 times a day) 24–48 h before surgery.

Aspirin and NSAIDs should be avoided for postoperative analgesia, particularly in patients with primary haemostatic disorders.

When levels of the deficient factor are maintained at normal levels, antithrombotic prophylaxis can be considered in patients at risk of thromboembolism.

Inherited bleeding disorders are commonly classified into two main categories: disorders of primary haemostasis and inherited coagulation defects.

## 17.2.1 Perioperative Management of Congenital Primary Haemostatic Disorders

### 17.2.1.1 Perioperative Management of von Willebrand Disease

von Willebrand disease (vWD), an autosomal dominant disorder, is the most common inherited bleeding disorder with a prevalence of 1%. It is caused by a quantitative or qualitative deficiency of von Willebrand factor (vWF), which mediates platelet adhesion to the damaged vascular wall and serves as carrier protein for factor VIII (FVIII) protecting it from rapid plasma proteolysis.

Diagnosis is based on plasma assays of vWF (vWF:Ag), its functional activity (ristocetin cofactor activity (vWF:RCo)) and FVIII (FVIII:C).

Depending on whether the deficiency is proportional or not, vWD can be classified into three main groups [4]:

Type 1: partial quantitative deficiency of vWF. This is the most common form.
Type 2: qualitative defects in vWF are divided into four subtypes: 2A (decreased affinity for platelet GPIb associated with the absence of high molecular weight vWF multimers), 2B (increased affinity), 2M (decreased vWF affinity for platelet GPIb with the presence of all multimers) and 2N (decreased affinity for FVIII).
Type 3: complete absence of vWF. This is the most severe form.

vWF:RCo and FVIII levels should be assayed in the week before surgery and the absence of vWF inhibitor should be ascertained (type 3).

#### Principles of Perioperative Replacement Therapy

There are two treatments of choice for vWD and the indication depends on the type: desmopressin (1-deamino-8-D-arginine vasopressin, also called DDAVP) and infusion of vWF/FVIII concentrates.

In responders, DDAVP (Minirin®) induces a two- to fourfold increase in FVIII and vWF levels 30–60 min after infusion via release of endogenous vWF stored in endothelial cells, with a return to baseline occurring after 6–9 h [5]. This is the treatment of choice for type 1 patients with baseline vWF level >10 IU/dL. It can also be used in some patients with the 2A, 2M or 2N subtype [4]. The response to DDAVP should be assessed prior to surgery because there is large interindividual variability. In particular, some von Willebrand subtypes exhibit increased clearance of vWF and would require more closely spaced infusions [4]. In type 2B, DDAVP is contraindicated because of the risk of appearance or aggravation of thrombocytopenia.

In responders, DDAVP should be administered subcutaneously or intravenously 30–60 min before surgery (Fig. 17.1). Repeat doses can then be given every 12–24 h. Tachyphylaxis and hyponatraemia may occur, which is why fluid intake should be limited and serum sodium monitored in case of repeated doses [5].

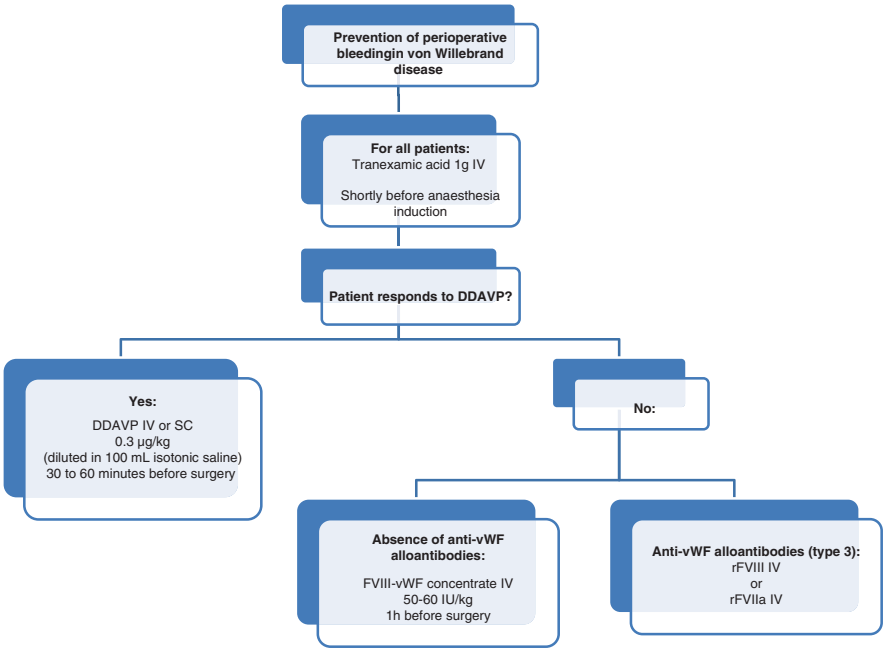


**Fig. 17.1** Algorithm for surgical management of patients with von Willebrand disease. *DDAVP* desmopressin, *IV* intravenous, *SC* subcutaneous

**Table 17.2** Recommended haemostatic target levels for Willebrand ristocetin cofactor (vWF RCo)/factor VIII (FVIII) according to type of surgery

| | | Haemostatic target levels |
|---|---|---|
| Invasive intervention | Days | vWF RCo/FVIII (%) |
| Major surgery | D0 | 100 |
| | D1–D5/10 | ≥50 |
| Minor surgery | D0 | ≥50 |
| | D1–D2/D4 | ≥30 |

From Laffan et al. [7]

When desmopressin is contraindicated or ineffective, replacement therapy with either vWF alone or in combination with FVIII is used. Several vWF/FVIII products are available on the market, each having a different vWF:RCo/FVIII:C ratio. These combined products simultaneously increase vWF and FVIII levels, in contrast to vWF concentrates where there is a delay of 6–12 h before endogenous FVIII begins to increase. A loading dose of FVIII-vWF concentrate is recommended 1 h before surgery (Fig. 17.1).

Furthermore, in December 2015 the US Food and Drug Administration (FDA) approved the first recombinant vWF (Vonvendi®, Baxalta, USA) for the treatment of bleeding events in von Willebrand patients [6].

There are not yet enough validated data to clearly define the haemostatic target levels of vWF and FVIII and the duration of postoperative replacement therapy (Table 17.2).

vWF:RCo and FVIII levels should be measured daily during the postoperative period. When FVIII level rises above 50%, replacement therapy should be continued with a vWF concentrate alone, so as to decrease the risk of venous thrombosis [4].

**Special Cases**

von Willebrand Disease with Inhibitors

In type 3 patients who develop anti-vWF alloantibodies after multiple infusions of vWF concentrates, administration of recombinant FVIII at high doses or recombinant factor VIIa (rFVIIa) (NovoSeven®, Novo Nordisk, Plainsboro, NJ, USA) should be considered (Fig. 17.1) [4].

Pregnancy and von Willebrand Disease

The physiological two- to threefold increase in vWF and FVIII levels that occurs during pregnancy generally suffices to correct the vWF deficiency in patients with type 1 but not type 2 or 3. Several learned societies have issued recommendations for the peripartum management of these patients, and they all agree that Caesarean section, vaginal delivery and neuraxial anaesthesia can be performed safely when vWF:RCo and FVIII levels are ≥50% during the third trimester [7]. On the other hand, in patients with vWF/FVIII ≤50%, who generally have type 2 or 3, there are no clear guidelines on the target levels to be achieved by replacement therapy at the time of delivery nor on the optimal duration of postpartum replacement therapy. Some authors recommend that vWF:RCo/FVIII haemostatic target levels should be between 150 and 200% shortly before delivery and be maintained at these levels for the first 4–7 days postpartum [8]. Furthermore, neuraxial anaesthesia is contraindicated in types 2 and 3 [7].

#### 17.2.1.2 Perioperative Management of Inherited Platelet Disorders

The inherited platelet disorders are characterised by abnormal expression of platelet receptors or granule secretion, affecting one or more steps of platelet activation [9].

Among the most severe inherited platelet function disorders, two are of particular interest: Glanzmann thrombasthenia, caused by quantitative or qualitative abnormalities in the platelet fibrinogen receptor, glycoprotein GPIIb-IIIa, and Bernard-Soulier syndrome, characterised by defective platelet adhesion to vascular subendothelium linked to an abnormality in the GPIb-IX-V receptor complex.

Multiple platelet transfusions may induce the formation of antibodies directed against the HLA system and/or against glycoproteins GPIIb-IIIa in patients with Glanzmann thrombasthenia; patients should be screened for the presence of such antibodies in the week before surgery.

For minor surgery and mild forms of platelet disorders, local haemostatics, together with systemic tranexamic acid and, in some cases, with DDAVP, are usually sufficient in most cases. DDAVP is not effective in platelet disorders characterised by platelet effector receptor defects (Fig. 17.2) [9].

For major surgery in patients with moderate to severe platelet disorders, prophylaxis is based on transfusion of HLA-matched apheresis platelets together with the adjuvant treatments noted above (Fig. 17.2) [3, 9].

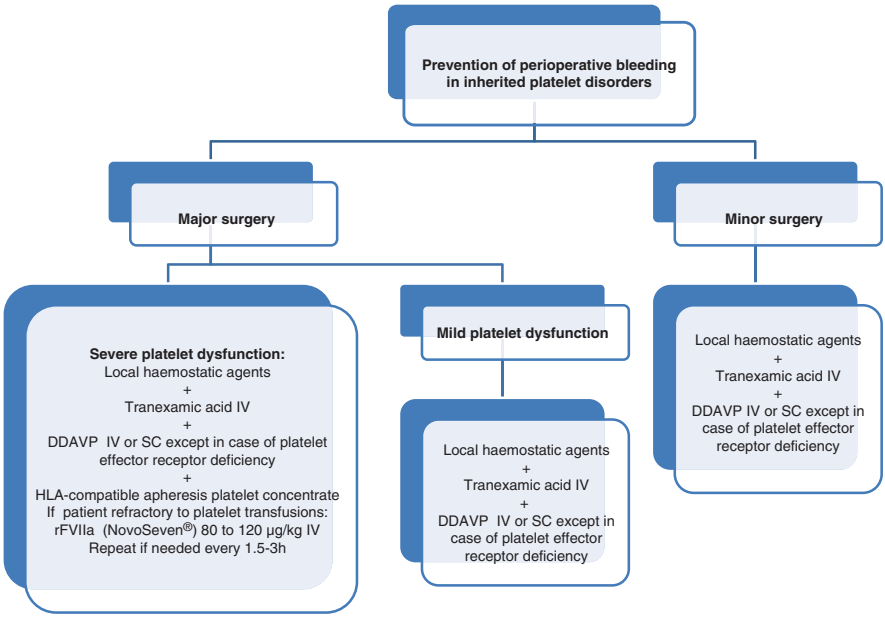


**Fig. 17.2** Algorithm for surgical management of inherited platelet disorders. *DDAVP* desmopressine, *IV* intravenous, *SC* subcutaneous

The presence of antibodies is not always a predictor of refractoriness to platelet transfusion and should not by itself be a contraindication to platelet transfusion. Recombinant FVIIa (NovoSeven®) is another alternative in immunised or nonimmunised patients refractory to platelet transfusions (Fig. 17.2) [3].

Postoperatively, platelet transfusions or rFVIIa can be administered for variable lengths of time, sometimes until wound healing.

It should also be noted that spinal anaesthesia is contraindicated.

## 17.2.2 Perioperative Management of Inherited Coagulation Disorders

### 17.2.2.1 Perioperative Management of Haemophilia

Haemophilia is a recessive X-linked disorder caused by a deficiency of factor VIII (FVIII) (haemophilia A, accounting for 80% of haemophilia) or factor IX (FIX) (haemophilia B).

The severity of haemophilia is arbitrarily divided into three groups: severe when FVIII or FIX <1%, moderate 1–5%, and mild >5%.

Diagnosis is suspected in the case of a prolonged aPTT (activated partial thromboplastin time) and confirmed by assay of FVIII and FIX.

In the week before surgery, it is essential to measure FVIII and IX levels and to screen for FVIII and FIX inhibitors [3].

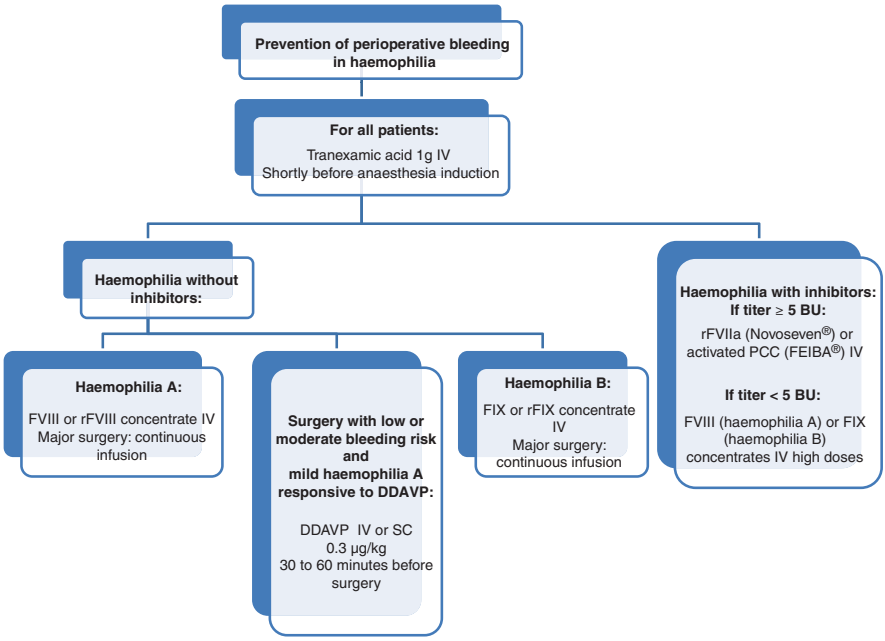


**Fig. 17.3** Algorithm for surgical management of patients with haemophilia. *DDAVP* desmopressine, *IV* intravenous, *SC* subcutaneous

### Principles of Perioperative Replacement Therapy

The deficient factor should be administered shortly before induction of anaesthesia in order to avoid a too early decline in plasma levels of the factor during surgery.

FVIII concentrates are the treatment of choice in haemophilia A (Fig. 17.3). In the absence of inhibitors, each unit of FVIII administered per kg of body weight increases the plasma level by 2 IU/dL [10]. FVIII should be administered by slow intravenous injection not exceeding 3 mL/min. The half-life is 8–12 h.

For FIX deficiency, it is preferable to use a product that contains only FIX instead of prothrombin complex concentrates (PCC) which contain other coagulation factors that could increase the risk of thrombosis (Fig. 17.3). In the absence of inhibitors, each unit of plasma-derived or recombinant FIX administered per kg of body weight increases the level of FIX by 1 IU/dL and 0.8 IU/dL, respectively [10]. The half-life of FIX is 18–24 h.

European guidelines for the haemostatic target levels of the deficient factor and the duration of postoperative replacement according to type of surgery are shown in Table 17.3.

In the case of major surgery, continuous infusion should be preferred because it produces more stable factor levels and reduces factor consumption as compared to discontinuous administration [12].

**Table 17.3** Recommended haemostatic target levels for factor VIII (FVIII) and factor IX (FIX) according to type of surgery

| Invasive intervention | Days | Haemostatic target level FVIII/FIX (%) |
|---|---|---|
| Major surgery | D0 | ≥80 |
| | D1–D7 | ≥50 |
| | D8–D21 | ≥30 |
| Minor surgery | D0–D4 | ≥50 |
| | D5–D6/D8 | ≥20 |

From Hermans et al. [11] and Mensah et al. [3]

It is generally not necessary to measure the factor levels during surgery, but postoperatively, FVIII and FIX should be assayed daily. Unlike FVIII, FIX levels do not rise in response to inflammation, such that longer postoperative replacement therapy is usually necessary.

### Special Cases

#### Mild Haemophilia A

For minor or intermediate surgery, perioperative management is based on DDAVP as described for vWD, provided that patient is a responder (Fig. 17.3) [5].

#### Haemophilia with Inhibitors

In patients who develop inhibitors**,** perioperative management is usually based on administration of rFVIIa or activated PCC (FEIBA factor eight inhibitor bypassing agent®, Baxter Healthcare Corp, Thetford, Norfolk, UK) (Fig. 17.3) [3]. The purpose of these agents is to increase the formation of thrombin, a key enzyme that cleaves fibrinogen to fibrin, by bypassing the intrinsic tenase complex formed by activated FIXa and FVIIIa.

## 17.2.2.2 Perioperative Management of Rare Coagulation Factor Deficiencies

The rare coagulation factor deficiencies (RCFD) account for 3–5% of inherited coagulation disorders [13]. They include deficiencies of factors II, V, VII, X, XI and XIII, quantitative or qualitative deficiencies of fibrinogen and combined deficiencies of factors V and VIII and of vitamin K-dependent factors. FVII and FXI deficiencies account for two-thirds of RCFD.

These RCFD are mostly characterised by the lack of a clear correlation between the residual level of the deficient factor and the bleeding phenotype. Only deficiencies of FX, XIII and fibrinogen are well correlated with bleeding phenotype [13].

Except for FXIII deficiency, the RCFD exhibit a prolonged PT and/or aPTT.

The choice of preoperative replacement depends on the factor level, bleeding phenotype and type of surgery.

In asymptomatic patients, the current trend is to forego prophylactic treatment.

For minor surgery, prevention of bleeding is based on the use of antifibrinolytic agents [14].

**Table 17.4** Recommended haemostatic target levels, half-life of transfused factor and replacement protocol in major surgery

| Factor deficiency | Haemostatic target level (IU/dL) | Half-life of factor | Replacement | |
|---|---|---|---|---|
| | | | Product | Posology |
| Fibrinogen | 1 g/L | 2–4 d | Fibrinogen concentrate | 50–100 mg/kg, repeat at lower dose if needed/2–4 days |
| Factor II | 20% | 3–4 d | PCC | 20–30 IU (FIX)/kg then 10–20 IU (FIX)/kg/48 h if needed |
| Factor V | 15–20% | 36 h | FFP | 15–25 mL/kg then 10 mL/kg/12 h if needed |
| Factor VII | 15–20% | 4–6 h | Activated recombinant FVII | 15–30 µg/kg, repeat if needed every 4–6 h |
| | | | FVII concentrate | 10–40 IU/kg/4–6 h |
| Factor X | 15–20% | 40–60 h | PCC | 20–30 IU/kg then 10–20 IU/kg/24 h if needed |
| Factor XI | 15–20% | 40–70 h | FXI concentrate | 10–15 IU/kg |
| | | | | Max 30 IU/kg |
| Factor XIII | 2–5% | 10–14 d | Recombinant FXIII (deficient in FXIII-A) | 35 IU/kg |
| | | | FXIII concentrate | 10–40 IU/kg |

From Bolton Maggs et al. [15], Mannucci et al. [16], Mumford et al. [14]
*PCC* prothrombin complex concentrate, *FFP* fresh frozen plasma, *h* hours, *d* days

For major surgery, Caesarean section or during labour in patients with a severe deficiency, haemostasis management is based on replacement therapy with recombinant or plasma-derived products. When factor concentrates are unavailable (FII, FV and FX), PCC or fresh frozen plasma (FFP) may be used (Table 17.4) [14], although they carry a risk of thrombosis [15]. The haemostatic target level for each factor is not known with certainty. In major surgery, replacement therapy is generally used when the factor residual level is less than 20% (Table 17.4) [14, 15]. Globally, haemostatic target levels are similar for pregnant women in labour [14].

## 17.3 Perioperative Management of Acquired Haemostatic Disorders

### 17.3.1 Perioperative Management of Acquired Primary Haemostatic Disorders

#### 17.3.1.1 Perioperative Management of Acquired Thrombocytopenia

Moderate or severe thrombocytopenia can increase the risk of bleeding during invasive procedures. This risk can be prevented by prophylactic platelet transfusion. The

**Table 17.5** Recommended threshold platelet counts according to the type of invasive procedure

| Type of invasive procedure | | Threshold platelet counts (G/L) |
|---|---|---|
| Surgery | General | 50 |
| | Caesarean | 50 |
| | Neurosurgery | 100 |
| | Posterior segment of eye | 100 |
| Vaginal delivery | | 30 |
| Neuraxial anaesthesia | Spinal anaesthesia | 50 (50 could be discussed on a case by case basis) |
| | Epidural anaesthesia | 80 (30 could be discussed on a case by case basis) |

From Haute Autorité de Santé [19]

threshold platelet count for transfusions depends mainly on the aetiology of the thrombocytopenia, the type of invasive procedure and anaesthesia.

Guidelines for the threshold platelet counts for transfusions in the perioperative setting are based on a review by an expert panel [17–19]. They are shown in Table 17.5, according to the type of invasive procedure.

The recommended dose of platelets to be transfused is $0.5–0.7 \times 10^{11}$ ABO- and Rh-compatible platelets per 10 kg of body weight [19].

#### Special Case of Immune Thrombocytopenic Purpura (ITP)

ITP is characterised by peripheral immunologic destruction of normal platelets. Platelet transfusion is therefore not recommended as first-line treatment [20].

In patients scheduled for elective surgery, preoperative polyvalent immunoglobulins (Ig) at a dose of 400 mg/kg daily for 5 days or 1 g/kg by single infusion, in combination with high-dose corticosteroids, have been proposed to rapidly increase the platelet count [20].

For urgent surgery, platelet transfusion, possibly repeated every 30 min to 8 h, may be warranted in combination with polyvalent Ig and corticosteroids which improve the yield of the transfusion [20].

### 17.3.1.2 Perioperative Management of Patients Treated with Antiplatelet Agents

Perioperative management of these patients must weigh the risk of thrombosis if the antiplatelet treatment is interrupted against the risk of bleeding if treatment is maintained perioperatively.

Perioperative maintenance of aspirin usually has no impact on bleeding events [21, 22]. Aspirin should therefore be maintained in the large majority of cases, except for major surgery in patients at low cardiovascular risk or in case of surgery in enclosed spaces such as neurosurgery or spinal canal surgery [23], in which case withdrawal of aspirin 3 days before surgery is sufficient. Moreover, maintenance of

aspirin does not contraindicate neuraxial anaesthesia. Spinal rather than epidural anaesthesia should then be preferred [24].

In contrast, clopidogrel, ticagrelor and prasugrel increase perioperative bleeding. Clopidrogel and ticagrelol should be discontinued 5 days before and prasugrel 7 days before surgery [23, 25, 26].

Substituting these agents preoperatively with aspirin alone is common practice [25]. When neuraxial anaesthesia is planned, the guidelines recommend stopping ticagrelor, clopidogrel or prasugrel 5, 7 or 7–10 days before surgery, respectively [24].

Patients with a coronary stent or who had a recent acute coronary event are at high risk of thrombosis if antiplatelet treatment is withdrawn in an untimely manner [23].

Thrombotic risk remains high for 4–6 weeks following bare-metal stent implantation and 6–12 months after drug-eluting stent implantation, requiring maintenance antiplatelet bitherapy during these periods. Bitherapy is also recommended for 1 year after myocardial infarction.

Any non-urgent surgery should therefore be postponed beyond the period of thrombotic risk specific to each type of stent [23]. Nowadays, most drug-eluting stents are second-generation stents which carry a lower thrombogenic risk; in such cases surgery can be delayed for 3–6 months.

If surgery cannot be deferred, the rule is to maintain aspirin and to stop antiplatelet bitherapy only if the surgery carries an intermediate to moderate risk of bleeding. Substitution of the thienopyridines by cangrelor, a reversible P2Y12 platelet inhibitor with a very short half-life, might be a promising approach [27].

In the case of bleeding, as antiplatelet agent, antidote is not yet available. Platelet transfusion can be used, although its efficacy in patients treated with ticagrelor is uncertain because circulating ticagrelor and its active metabolite are likely to inhibit the fresh platelets [28].

### 17.3.2 Perioperative Management of Acquired Coagulation Disorders

This chapter will not discuss acquired coagulation disorders of hepatic origin because these are addressed in Chap. 11.

#### 17.3.2.1 Perioperative Management of Patients on Vitamin K Antagonists

Perioperative management of a patient treated with vitamin K antagonists (VKA) requires an assessment of the degree of urgency of the procedure and of the balance between the thrombotic risk and the bleeding risk. Urgency refers to the need to perform the procedure before the time needed to reach the safe haemostatic target level defined as an INR < 1.5 or <1.2 in neurosurgery, by administration of vitamin

K alone. This time period corresponding to hepatic synthesis of new, functional coagulation factors is estimated to be a minimum of 12–24 h [29].

**Elective Surgery**

For procedures where bleeding risk is low, such as cataract surgery or gastrointestinal fibroscopy, VKA can be continued as long as the INR stays in target range [26].

For procedures with a moderate to high bleeding risk, VKA should be stopped 4–5 days before the procedure in order to reach a subnormal INR [30]. Most studies show that preoperative bridging with heparin is associated with a more than threefold increase in the risk for major bleeds without reducing the risk of thromboembolism [31, 32].

Therefore, perioperative bridging anticoagulation should be reserved exclusively for patients at high risk for thromboembolism such as patients with a mechanical heart valve, atrial fibrillation with a very high $CHA_2DS_2$-VASC or $CHADS_2$ score, venous thromboembolic disease (VTE) at high risk for thromboembolism defined as an episode within the previous 3 months or recurrent VTE defined as more than two episodes at least one of which had no precipitating factor [32].

In these cases, bridge therapy with therapeutic doses of heparin should be started 24–48 h after the last dose of VKA (according to half-life of the VKA). The INR should be measured the day before surgery. If INR > 1.5, vitamin K 5 mg per os should be administered [30].

VKA can be reintroduced 48–72 h after surgery, or if this is impossible, therapeutic doses of heparin can be given if the bleeding risk is controlled. In the meantime, thromboprophylaxis should be initiated when indicated.

**Urgent Surgery**

For patients who need urgent surgery, administration of three-factor (II, IX, X) or four-factor (II, VII, IX, X) PCC will quickly reverse the anticoagulant effect [30]. The PCC dose is adjusted for body weight and the INR at the time of the emergency. If the INR is unavailable, the PCC dose is 25 IU/kg of FIX equivalents [30]. Because of the short half-life of FVIIa of 6–8 h compared to that of VKA, vitamin K 5–10 mg should be given intravenously to sustain the reversal effect.

If surgery can be deferred for 12–24 h, anticoagulant reversal can be achieved by administration of 5–10 mg vitamin K alone.

#### 17.3.2.2 Perioperative Management of Patients Treated with Direct Oral Anticoagulants (DOAC)

DOAC have targeted anti-IIa action (dabigatran, Pradaxa®, Boehringer Ingelheim) or anti-Xa action (rivaroxaban, Xarelto®, Bayer; apixaban, Eliquis®, Bristol Myers Squibb; edoxaban, Lixiana; Daiichi-Sankyo, Parsippany, New Jersey, USA). Every year, 10–13% of patients on DOAC therapy require surgery or an invasive procedure.

Several expert groups have issued recommendations for perioperative management of these patients [33–35].

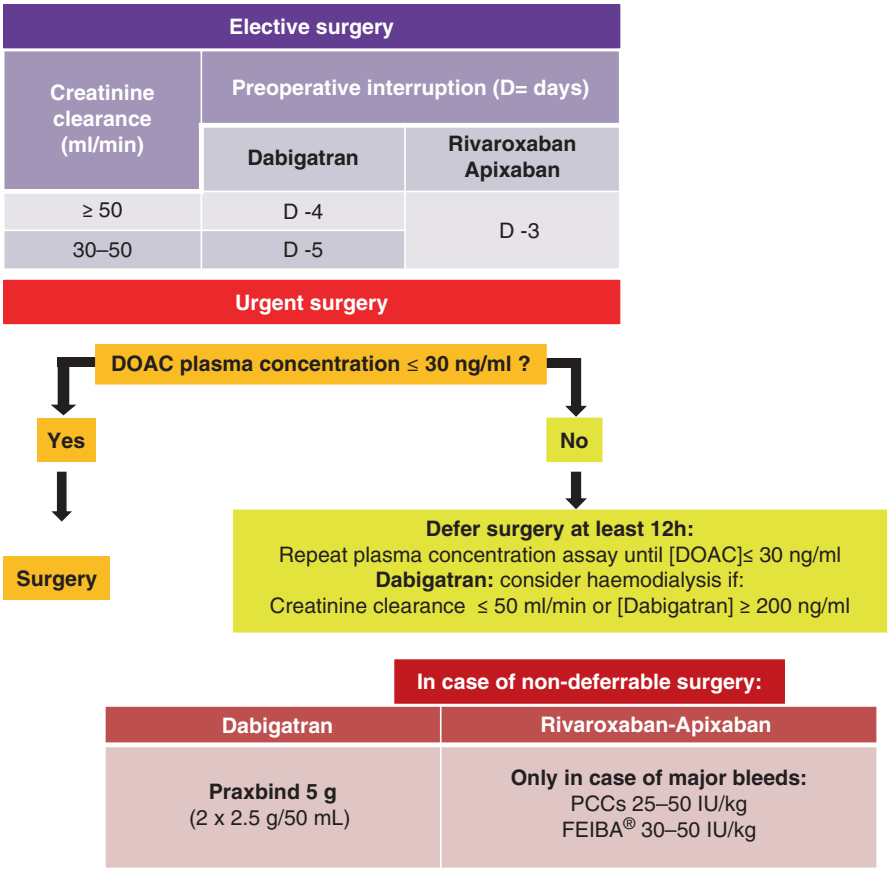


**Fig. 17.4** Management of DOAC in case of elective or urgent surgery with moderate to high bleeding risk

## Elective Surgery

Anti-Xa DOAC are generally stopped 3 days before surgery. Dabigatran, which is eliminated mainly via renal excretion, should be stopped 4 or 5 days before surgery depending on creatinine clearance calculated by the Cockcroft and Gault (Fig. 17.4) [35]. No preoperative haemostasis testing or bridge therapy is necessary.

Anticoagulation is restarted postoperatively, first with prophylactic LMWH when indicated and then by resumption of the DOAC on the third or fourth postoperative day, when bleeding risk has subsided.

For interventions with low bleeding risk, the DOAC should not be taken the evening before and the morning of the intervention. It can be resumed on the day of surgery, at the theoretical dosing time and 6 h after the procedure [35].

For spinal or epidural anaesthesia or neurosurgery, the last DOAC intake should be 5 days before surgery in the absence of renal impairment to ensure elimination [35].

### Urgent Surgery

A safe DOAC concentration has been extrapolated from clinical trials and arbitrarily set at 30 ng/mL [36].

If DOAC plasma concentrations cannot be measured, normal standard coagulation tests (PT, aPTT) allow the presumption that residual DOAC activity is low, with the exception of apixaban.

If DOAC intake is recent (within previous 2 h for dabigatran and rivaroxaban or previous 6 h for apixaban), activated charcoal can be given to decrease the DOAC plasma concentration by limiting its absorption [37].

In patients treated with dabigatran who have renal impairment or dabigatran levels ≥200 ng/mL in whom surgery can be postponed, haemodialysis should be considered [37].

If surgery cannot be delayed more than 8 h and the DOAC plasma concentration is >30 ng/mL, idarucizumab (Praxbind® 2.5 g/50 mL) at a dose of 5 g can be administered in case of dabigatran treatment (Fig. 17.4) [38]. This specific antidote is a humanised monoclonal antibody fragment (Fab) exhibiting high affinity binding to dabigatran.

However, its actual benefit and its safety are uncertain [39].

Administration of a second 5 g dose may be considered in case of recurrence of clinically relevant bleeding or in patients requiring a second surgery who have prolonged clotting times.

In case of factor Xa inhibitors treatment and nondeferrable surgery, the recommendation is to perform surgery and use nonactivated or activated PCC (FEIBA®) as second-line treatment "only in case of abnormal bleeding" (Fig. 17.4).

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# The Transplanted Patients: Can We Improve Outcomes of Non-transplant Surgery?

18

Christopher P.R. Walker, Paul Harris, Janos Fazakas, Janos Gal, and Nandor Marczin

## 18.1 Introduction

Recipients of solid organ transplantation represent some of the most unique cohort of patients who have experienced, survived and adopted to the most extensive physical, medical and psychological traumas on the transplant waiting lists, and during and after transplantation. They accept the reality that the transplant implantation may be followed by subsequent transplant-related surgical procedures such as a series of biopsies. Perhaps it is less recognised that the transplant status and immunosuppression predispose for additional surgical need especially trauma and malignancies more often than for the general population [1–4].

For the medical and surgical teams, these represent additional demands with variable expertise and comfort level in different settings ranging from the transplant centre or a teaching hospital with close partnership with the transplant centre or in

C.P.R. Walker • P. Harris
Department of Anaesthetics, The Royal Brompton and Harefield NHS Foundation Trust, Harefield, UK

J. Fazakas
Department of Transplantation and Anaesthesia and Intensive Therapy, Semmelweis University, Budapest, Hungary

J. Gal
Department of Anaesthesia and Intensive Therapy, Semmelweis University, Budapest, Hungary

N. Marczin (✉)
Department of Anaesthetics, The Royal Brompton and Harefield NHS Foundation Trust, Harefield, UK

Department of Transplantation and Anaesthesia and Intensive Therapy, Semmelweis University, Budapest, Hungary

Imperial College London, London, UK
e-mail: n.marczin@imperial.ac.uk



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a district general hospital. Elective procedures even in a general hospital setting should be quite straightforward as there is sufficient time for full planning and consultations with the transplant centres. With major emergency admission, however, senior expertise may not be readily available, and there may not be sufficient time for in-depth consultations [5].

In this review, we focus on new emerging information on the prevalence and outcomes of these operations and conclude that outcomes of high-risk patients and emergency operations are poor. To overcome these negative trends, we aim to arrive at recommendations on how modern anaesthetic management could be refocused and improved. We will provide a detailed analysis for heart transplant recipients and highlight special aspects of lung, renal and liver transplantation.

## 18.2 Quality of Life, Physical and Exercise Capacity After Transplantation

A successful transplant enables patients with end-stage organ failure to live a high quality of productive life and physical conditions exceeding many in the normal population. Some patients regularly compete in the national and worldwide transplant games and Olympics demonstrating what can be achieved on an individual and team level. Our heart and lung transplant patients have participated in an expedition to take on the volcano climb challenge in South America and completed an epic two-week adventure, which is thought to have been the highest ever climb made by a group of transplant patients.

While such extraordinary achievements do not apply to all heart transplant recipients, the majority will transform into an active person with a potentially excellent quality of life [6]. However, unique physiological changes after heart transplantation limit exercise performance in general. Cystic fibrosis patients, single-lung transplant recipient, older patients and those developing bronchiolitis obliterans syndrome also show significantly decreased physical ability ratings following lung transplantation [7].

These findings have important implications to the physical conditioning of patients presenting for non-transplant surgery. Those without frequent episodes of infections and free of limitations from chronic rejection are comparable in their daily activities and exercise abilities to their normal counterparts in the non-transplant population. Those with moderate to severe chronic rejection will present with important limitations related to graft function and general health status. While these patients can walk independently and pursuing an autonomous life, they may be considered high risk for noncardiac and non-transplant-related surgical outcomes.

## 18.3 The Spectrum and Complications of Non-transplant Surgery

Marzoa and colleagues have provided a relatively recent account on late noncardiac surgeries (mainly malignancies) in their heart transplant population [8]. The major interventions were elective (85%) comprising of urologic (30%), abdominal (25%),

vascular (12%), ENT (11%), skin and soft tissue (9%) and orthopaedic (6%). Mortality was 1% in the overall elective procedures but more than 16% in the emergent setting. A preoperative risk stratification to the middle−/low-risk cohort exhibited low (0%) mortality, whereas 16% of patients died with preoperative high-risk scores. The most frequent complication was related to postsurgical infection (6.9%), while none of the patients displayed allograft dysfunction or an acute rejection episode perioperatively.

Zeyneloglu et al. have also demonstrated the relative safe conduct of non-transplant surgery after liver transplantation [9]. In their series 22 patients underwent more than 30 surgical procedures. General and regional anaesthesia was associated with preserved liver and renal function with all patients surviving the predominantly low-risk surgical interventions.

A recent systematic review of more than 70,000 transplant recipients identified emergency abdominal surgery for graft-unrelated acute diseases in 2.5% of patients [10]. The solid organs transplanted in these patients were the heart in 66% of patients, the lung in 22%, the kidney in 9% and the liver in 3%. Gallbladder diseases, gastrointestinal perforations, complicated diverticulitis, small bowel obstructions and appendicitis were the main indications. Such surgery was associated with high morbidity in one third of patients with mortality rates close to 20%. These further emphasise the particularly challenging perioperative management of transplanted patients in the emergency setting.

Transplant recipients on long-term immunosuppression have various bone complications and require orthopaedic procedures for accelerated osteoarthritis and fractures [11, 12]. Klatt et al. observed 17% infection rates following total knee arthroplasty with another 20% additional overall complication rate potentially related to immunosuppression [13]. Reid et al. found very high rates of medical complications within 90 days after lower limb fractures, with 40% of patients having acute renal failure, a quarter developing urinary tract infection, 8% having a superficial surgical site infection and as much as 8% suffering from non-orthopaedic sepsis [12].

## 18.4 Anaesthetic Implications: A Framework for Quality Improvement

Our overall interpretation of the outcome data is that in most elective situations, there is sufficient anaesthetic and surgical attention and care dedicated to the transplanted organ and general haemodynamic stability to ensure optimal allograft and vital organ function. However, this is not achieved with the higher-risk subset of patients or during the emergency presentation of surgical disease. Moreover, we do not successfully negate the multiple negative side effects of chronic immunosuppression, and in general, we tend to err on too much immunosuppression and pay the price by postoperative infections.

There could be multiple contributing mechanisms to such failures including (1) gaps in our understanding and defining high-risk populations, (2) mismanaging critical events by not recognising negative trends due to inappropriate monitoring

and/or missing opportunities to intervene effectively and (3) staging imbalance between immunosuppression and microbial surveillance especially unrecognising "endogenous" postoperative immunosuppression [14–16].

We strongly believe that anaesthesia management of the transplanted patient should go beyond "routine" anaesthetic practice. A new ambitious mission and a significant paradigm change in our practice are required that demand a systematic quality improvement in every domain of our engagement from preoperative assessment through intraoperative management to postoperative recovery. The emphasis should be on integration of protecting the allograft and managing comorbidities and perioperative risks together by:

- Recognising the high-risk patient preoperatively.
- Understanding the reduced physiological and functional reserve of these patients and the importance of reduced critical time window for optimisation.
- Comprehensive intra- and postoperative monitoring to detect even subtle changes in homeostasis.
- Precise maintenance of homeostasis by aggressive therapeutic modalities.
- Taking ownership of assessing, monitoring and optimising perioperative immunosuppression in its globality.
- Meticulous attention to infection prevention and control.

## 18.5 Heart Transplant Recipients

### 18.5.1 Physiology of the Transplanted Heart

The transplanted heart rarely provides the recipient with completely normal cardiac function. The organ's intrinsic muscle function may be preserved, but its altered physiology results from denervation and the anatomical consequences of surgical implantation [1, 4, 17].

*Electrophysiology.* Both sympathetic and parasympathetic efferent nerve fibres are severed during surgical implantation as well as sensory afferents. Reinnervation may occur, in some cases detectable as early as 5 months post-implantation, though more usually is not physiologically significant [18–20]. Denervation will result in symptomless ischaemia (no angina pectoris), increase in body water and left atrial pressures and elevated resting heart rate (approx. 90–110 bpm). The denervated heart will not mount a tachycardia as part of any reflex sympathetic response. Thus, any increase in cardiac output will be dependent on increasing heart rate and increasing circulating volume. The cardiovascular responses to surgical stimulation are lost. Carotid sinus massage and the Valsalva manoeuvre do not affect heart rate.

A significant fraction of patients exhibit conduction defects, especially right bundle branch block and implantation of a permanent pacemaker. Dysrhythmias are common and likely contributing factors include absent vagal tone, rejection (previous or active episodes) and raised endogenous catecholamines.

*Cardiac performance.* Exercise function may be reduced to 60–70% of that of normal subjects due to the absence of reflex tachycardia to exercise, increasing preload-related filling pressures and coexistent diastolic dysfunction [3, 4, 17].

The neuroendocrine response to heart transplantation may include elevation of plasma renin, natriuretic peptides, vasopressin and noradrenaline. This may contribute to diastolic dysfunction and the exaggerated hypertensive disease seen in patients and limit the heart's response to the demands of exercise.

Skeletal muscle mass and function may be diminished by poor preoperative condition, as end-stage cardiac failure progresses, and the need for corticosteroids postoperatively as part of the immunosuppressive regime.

*Cardiac allograft vasculopathy.* CAV is a diffuse, nonfocal concentric thickening of the donor coronary arteries [21, 22]. The predominant pathological feature is concentric intimal hyperplasia as opposed to the discrete endothelial lipid core seen in atherosclerotic coronary arterial disease. The final common pathway is one of the immune activation leading to intimal hyperplasia most likely due to the cumulative injury from ischaemia-reperfusion injury, mechanical damage, cytomegalovirus infection and inherent endothelial damage (hypertension, diabetes, immunosuppression, hyperlipidaemia). The diffuse and extensive nature of the disease reduces the chances of successful revascularisation treatments significantly. Within 5 years of transplantation, only 70% of patients are CAV-free and this drops to 40% by 10 years.

*Pharmacology.* Due to denervation, vagolytic drugs such as atropine and glycopyrrolate have no effect unless a degree of reinnervation has occurred. There is lack of reflex tachycardia in response to glyceryl trinitrate, sodium nitroprusside and local anaesthetic neuraxial blocks. The effect of beta-blockers may be exaggerated due to up-regulation of beta-adrenoceptors and due to the risk of excessive bradycardia; their use is not recommended.

Conversely, direct chronotropes and pressors are required to increase heart rate and systemic vascular resistance. Isoprenaline, dobutamine, metaraminol, adrenaline and noradrenaline all exert a direct adrenoceptor action. Ephedrine may be less effective as at least some of its activity is presynaptic, and myocardial catecholamine storage is chronically depleted.

Most antiarrhythmic drugs remain effective, but their potent negative inotropy may be revealed, as the heart is unable to initiate any reflexes to counter this. Amiodarone is the most widespread antiarrhythmic used following heart transplant and is effective in treating acute arrythmias. Chronic amiodarone use is avoided as cyclosporine levels are affected. Digoxin is less effective at delaying AV conduction in the denervated heart. Adenosine is effective at blocking AV nodal conduction but exhibits a supersensitivity response. Thus, the initial dose should be reduced to 1 mg.

Denervation will affect the activity of some anaesthesia drugs [1, 3, 4]. Tachycardia associated with pancuronium is not seen, and bradycardia in response to succinylcholine, neostigmine and with some synthetic opioids (e.g. fentanyl) is absent. The advent of sugammadex has offered an alternative for reversing neuromuscular blockade with rocuronium, and it has been used without adverse effect in heart transplant patients [23].

### 18.5.2 Preoperative Assessment

This must be extensive and should provide a detailed picture on the individual patients existing limitations and assessment of the implications of these to intraoperative and postoperative functions [1, 3, 4]. In the elective setting, this is best done by directly accessing the last comprehensive transplant review (cardiac transplant "MOT"). Transplant physicians methodically review heart transplant patients at least annually or more frequently pending complications. Thus, the patients have regular assessment of cardiac function and any associated organ dysfunction that may exist (e.g. renal function with cyclosporine use). The transplant team is an invaluable source of information and should be in regular contact when a patient presents for a noncardiac procedure.

Transthoracic echocardiography imaging provides a good snapshot of biventricular systolic function, diastolic performance, existence of valvular comorbidities and frequent information on pulmonary pressures. Coronary artery imaging is paramount given the silent nature of any myocardial ischaemia. Electrophysiology evaluation should include a current ECG to uncover ischaemia and arrhythmias, and pacemaker advice should be thought if present ensuring an up-to-date pacemaker check is available.

Cardiac history is also informative regarding any lasting symptoms of the original heart failure condition with residual cardiorenal alterations and hepatic dysfunction due to end-stage RV failure [24]. Patient journey, especially significant complications of cardiac allograft implantation, primary graft failure, bridging or salvage mechanical support, frequent rejections and documented development of accelerated atherosclerosis, should ring alarm bells for concerns.

All patients should be carefully assessed for any significant change in performance status or the occurrence of any new symptoms covering the period from the last transplant review. Should these generate any suspicion for change of status, elective procedures should be postponed and patient referred back to the transplant unit.

Review and plans for immunosuppression should constitute a central part of preoperative workup [25]. Review of rejection episodes should provide an indication for compliance with and efficiency of immunosuppressive regimes. Up to date report and advice should be directly sought from the principal transplant physician taking into consideration the extent of surgery, suitability of oral or intravenous administration and multiple factors that may influence plasma levels and depth of immunosuppression [1, 2]. The signs of chronic complications attributable to chronic immunosuppression such as worsening hypertension, diabetes, renal function, neurotoxicity with calcineurine inhibitors or bone marrow depression with azathioprine and MMF resulting in anaemia/leucopenia and reduced platelet counts should be carefully acknowledged [1, 3, 4]. Not only these side effects bare direct relevance to the conduct of anaesthesia, but also they may indicate the patient's heightened response to normal immunosuppression or overzealous immunosuppressed state. A detailed plan for continuing or temporarily suspending some immunosuppression medications, monitoring drug levels and provisions for the postoperative period with different scenarios have to be documented.

Robust attempts should be dedicated to ensuring infection-free status preoperatively bearing in mind that regular signs may be blunted and presentations may be atypical in these patients. If infections are suspected, full bacterial, viral and fungal screens should be obtained with consultation of the transplant microbiologist. Biomarkers such as leucocytosis, C-reactive protein levels and procalcitonin may help in the decision making [26, 27]. CMV status should be confirmed and blood bank notified for the need of CMV-free blood products. Surgical prophylaxis should be rigorously addressed taking into consideration the patient infectious history, current anti-infection medications, the treating hospital microdata and surgical procedure.

Conducting such detailed preoperative workup likely exceeds possibilities in most general hospitals and even academic centres. We, however, strongly feel that significant improvements are needed to guarantee the high-quality care and to reduce the currently unacceptable high perioperative risks of morbidity and mortality. Beyond awareness of the magnitude of this problem, progress may require organisational change. We propose that all major anaesthetic departments develop a leading role for a senior anaesthetist with interest in transplantation with special focus on non-transplant surgery. Such consultants would then serve as "transplant liaison" between the host institutions and the relevant transplant centres with more than average knowledge on the general transplant field especially immunosuppression and relevant infection control.

### 18.5.3 Intraoperative Management

Based on currently unacceptable outcomes, here we propose a total paradigm change in three principal domains.

Firstly, we need to ensure sufficient seniority in managing these complex patients. Anaesthetic management should be consultant led in planned high-risk procedures with little if any delegation to junior staff of the critical conducts. Similarly, the principle of seniority should also be applied to the emergency ensuring senior input into the planning phase and efforts made to senior presence at critical stages of the operation such as induction, surgical manipulations and emergence.

The second area is improved intensity of monitoring of the cardiovascular status in the perioperative period. We propose mandatory invasive monitoring for all high-risk patients and intraoperative echocardiography for all patients with at least moderate degree of cardiac systolic or diastolic dysfunction. Beat-to-beat arterial blood pressure monitoring ensures that acute changes in MAP are detected without delay, prompting immediate treatment measures to achieve haemodynamic stability. Transoesophageal echocardiography has revolutionised cardiac anaesthesia and is making its way into emergency rooms and intensive care with most trainees now achieving reasonable exposure to this diagnostic tool and many of them completing some formal training even accreditation. Given the relatively simple interpretation of volume loading and contractile dysfunction, TOE can facilitate more goal oriented and targeted treatment of common cardiovascular events. We also advocate

monitoring of cardiac output and/or measures of organ perfusion especially dynamic trends during the operation. Examples of these could be Vigileo utilising the arterial blood pressure monitoring, cerebral oximetry and urine output.

The third component of our recommendation is the familiarity with and immediate availability of the full spectrum of inotropic support including vasopressin, levosimendan and selective pulmonary vasodilators. These should be applied early on during haemodynamic instability based on detailed assessment of preload, contractility and afterload. Hypotensive episodes must be rectified promptly as coronary blood flow may be poor in the context of CAV. If cardiac function deteriorates during the procedure, direct-acting inotropes such as adrenaline, milrinone or levosimendan may be necessary. Their use mandates central venous access and admission to the critical care unit postoperatively. Levosimendan may be used 24 h preoperatively to improve cardiac function.

These three components would allow careful tailoring of the anaesthetic technique by close monitoring of patient responses and immediate restoration of normal haemodynamics. Similarly, the potential negative effects of various physiological alterations such as hypercapnia, acidosis, surgical manipulations and blood loss would be immediately recognisable and corrected.

### 18.5.4 Postoperative Period

Any significant intraoperative anaesthetic or surgical event, the requirement of ongoing vasoactive support should prompt admission of the patient to intensive care unit. This would guarantee continued close monitoring and multidisciplinary expert involvement in all aspect of postoperative management including prompt but controlled weaning whenever possible.

Beyond cardiac and end-organ dysfunction, the main task is to differentiate between SIRS response to surgery and early stages of infections and sepsis. The microbiologists should be readily available to monitor these patients, and close dialogue with the transplant unit should take place with any complication. Biomarkers such as leucocytosis, C-reactive protein levels and procalcitonin may help in the diagnosis and monitoring therapeutic responses.

## 18.6 Special Considerations in Lung Transplant Recipients

In our opinion the single most relevant problem in these patients is the susceptibility of the transplanted lung to develop infections in immunosuppressed patients in response to airborne pathogens [1, 2]. Predisposing factors include the necessary immunosuppression, the direct communication of the lung with the outside world, the lack of innervations below the carina and the absence of cough reflexes, attenuated mucociliary clearance and potential obstruction of airways at the site of bronchial anastomosis [28].

The second problem lies in the difficulties differentiating acute rejections from infective episodes. While the basic pathological features are greatly different, physiological impact and clinical presentation are similar. Lung transplant recipients measure their lung function at home, and a 20% sudden reduction prompts admission to the transplant centre where diagnosis is made by bronchoscopy, bronchoalveolar lavage and cultures.

Chronic rejection, otherwise known as obliterative bronchiolitis—a progressive obliteration of the small airways at the bronchiole level by dense fibrous tissue—can be an early phenomenon that also reduces lung function. Diffusion capacity is reduced most likely as a side effect of immunosuppression [1, 2]. These changes rarely cause manifest hypoxia, but these patients are vulnerable for hypercapnia during hypoventilation and prone to $CO_2$ retention especially during emergence.

Single-lung transplantation represents a complex situation especially during acute and chronic rejection of the transplanted lung as ventilation is largely delivered to the hyperinflated end-stage COPD lung with perfusion favouring the transplanted lung. The presence of pulmonary fibrosis or hypertension with single-lung transplant exemplifies different and complex mechanisms of ventilation/perfusion mismatch.

The preoperative evaluation should include lung imaging, including CT for high-risk patients and spirometry; otherwise all other aspects described for heart transplants should be completed.

The principal focus of intraoperative management should be directed at adequate gas exchange, at minimising cardiovascular effects of mechanical ventilation and at protecting the lung from infections.

Haemodynamic instability may occur at various stages. Hypovolaemia is common in lung transplant recipients. The single-lung COPD scenario represents a realistic tamponade situation due to dynamic hyperinflation of the native lung with potential mediastinal shift, reduction of venous return and cardiovascular collapse upon induction. The authors regularly use invasive blood pressure monitoring in this setting together with limiting inspiratory pressures, titrated tidal volumes and long expiratory times to avoid hyperinflation.

Avoiding endotracheal intubation is a useful principle in these patients, but this should be weighed against aspiration risks and the benefits of full control of ventilation and gas exchange. Secretions should be aggressively removed by frequent bronchial toilet, but this should be performed with full asepsis. Early extubation is warranted once the patient can cough and clear airway secretions.

The postoperative period should be devoted to avoidance of $CO_2$ retention, adequate pain control to allow active cough and breathing exercises with early physiotherapy.

## 18.7 Special Considerations for Kidney Transplant Recipients

A patient with previous kidney transplant suffers from multiple conditions [28]. The single functioning transplanted kidney is affected by the original systemic disease such as diabetes mellitus or hypertension. It is one of the major targets of the side

effects of immunosuppression especially of the calcineurin inhibitors, and it may be affected by the chronic rejection process [29]. The patient has extrarenal advanced manifestations of diabetes or hypertension and the additive side effects of systemic immunosuppression. Perioperative management therefore has three principal goals: to protect the functioning kidneys, optimise cardiovascular performance and avoid infections [1–3].

### 18.7.1 Preoperative Considerations

The preoperative assessment should include urea and electrolytes, estimated glomerular filtration rate, urinalysis and urine output. These should be compared to most recent routine results as any pathology that results in the need for surgery may have affected graft function. The timing of renal transplant is also important as graft function may be in a state of flux, either improving shortly after transplantation or deteriorating over time.

Regarding cardiovascular function, a degree of coronary artery disease should be assumed in all diabetic and hypertensive patients. History and examination should focus on dyspnoea, orthopnoea, chest pain, weight gain and oedema. ECG is mandatory before any surgery and there should be a low threshold for transthoracic echocardiography. Guidance should be sought from the transplant team as all patients will have had full cardiovascular workup pre-transplant. Coronary angiography should be avoided unless clear indication due to the risk of contrast-induced nephropathy. Peripheral vascular disease is common, particularly cerebrovascular, and patients may well be anticoagulated.

Diabetes will be encountered commonly, both as the underlying pathology requiring transplantation but also as new post-transplant diabetes, brought on by immunosuppressive drugs. Both have a negative impact on graft survival and increase the risk of infection and wound breakdown.

### 18.7.2 Perioperative Considerations

Premedication with benzodiazepines may be warranted, appreciating that these drugs have renally excreted metabolites. Prokinetics, such as metoclopramide and inhibition of gastric secretions with either H2 antagonists or proton pump inhibitors, are recommended in diabetic patients, to reduce the risk of pulmonary aspiration. Patients should not be starved any longer than necessary preoperatively, and the use of intravenous fluids in the 6 h starvation window is advised.

Dictated by the high incidence of adverse events, especially acute kidney injury after noncardiac surgery [12], a more aggressive intraoperative cardiovascular management is warranted in these patients. We suggest that the combination of moderate kidney impairment and significant cardiac dysfunction should be considered high risk for postoperative adverse outcomes. For these kidney recipients, we recommend using invasive monitoring and perioperative TOE to ensure that central and kidney perfusion pressures and flows are maintained during surgery.

Intravascular access, particularly central venous, may be challenging because of the use of these vessels for previous short- or long-term haemodialysis, and arterial access options may be limited by previous or current arteriovenous fistula in the upper limb.

Urinary catheterisation and hourly urine output are recommended for moderate to major surgery or if any preoperative deterioration in renal function has occurred. However, they are an infection risk in an already immunosuppressed population; thus judicial use is advised. Nasogastric drainage may be indicated, particularly in acute surgery and diabetic patients.

Anaesthetic agents should be chosen that rely less on renal excretion if possible. Intravenous inductions should be administered cautiously in case of coexistent cardiovascular disease. Caution should be applied regarding morphine, due to the production of the antanalgesic morphine-6-glucoronide and the neuroexcitatory normorphine and aminosteroid muscle relaxants, which can produce a prolonged neuromuscular blockade.

Fluid management is important and is guided by central venous pressure and venous oxygen saturations, as well as urine output. Most patients will tolerate modest anaemia, and blood transfusion is best avoided as it may cause alloimmunisation and the production of HLA antibodies targeted against the transplanted kidney.

The renal allograft is normally transplanted into the right iliac fossa, using the iliac vessels and donor ureter to recipient bladder. The native kidneys are not normally removed, unless they are very large, chronically infected or the source of uncontrolled arterial hypertension. The transplanted kidney lies superficially; thus it must be protected during surgical positioning. In addition, patients may have functional or non-functional arteriovenous fistula in the upper limb, which will require padding and protection. Musculoskeletal problems are common; thus neck protection and attention to nerve compression should be addressed.

All the preoperative considerations have important postoperative implications. The dominant focus should be renal function and fluid balance, cardiovascular complications, control of diabetes and prevention of infection [28]. Postoperative recovery may be hindered by diabetic neuropathy and susceptibility to wound healing problems and infections. Worsening renal function should prompt reinstitution of antirejection regime as soon as possible, using nasogastric or intravenous routes if normal oral intake is not possible or contraindicated. Close liaison with the transplant centre is vital as any deterioration in renal function may require the increase in dose of current immunosuppressants or the need for additional agents together with effective anti-infection strategies.

## 18.8 Special Considerations for Liver Transplant Recipients

Liver transplantation represents two additional principal dilemmas. First, the synthetic function of the transplanted liver plays a principal role in coagulation, albumin and plasma protein bioavailability and metabolic regulation, all determinant of surgical outcomes [30]. Secondly, while other transplanted organ dysfunction

can be temporarily supported by mechanical devices (ECMO/VAD for the heart, mechanical ventilation for the lung, RRT for the kidneys), the results of liver replacement therapy (MARS, Prometheus) remain controversial [31–33]. Hence, preservation of allograft function and provision of adequate perfusion and substrate delivery and minimising inflammatory and immune damage remain even more paramount. This would dictate that immunosuppressive state is guaranteed during non-transplant surgery which then increases the risk of perioperative infections [28].

The preoperative assessment should include all aspects described above for the heart with a special focus on graft function. Fortunately, the main components of liver function and viability can be evaluated exactly by various biomarker sets and noninvasive or minimally invasive investigations [28]. Synthetic function is evaluated by coagulation profile, haemostasis parameters, coagulation factors, levels of albumin and total plasma proteins. Cellular damage is monitored by cytosolic enzyme release including transaminases and lactate dehydrogenase (ALAT, ASAT, LDH). Measurement of serum bilirubins, the enzymes ALP, GGT, indocyanin green excretion and PDR should provide sufficient information regarding biliary function. Imaging modalities including X-ray, CT and NMR would be informative regarding anatomy and structure.

Echocardiography represents a crucial tool in the assessment of the liver transplant patient [34, 35]. Extended investigation provides important assessment of liver regional haemodynamics including portal, arterial and vein flow patterns. It also provides a detailed profile of cardiac structure and function, essential component as at least 50% of liver patients have cardiovascular and diabetic comorbidities. It may also inform about the degree of pulmonary hypertension and adaptation of the right ventricle [34].

Due to the risk of coagulopathy, general anaesthesia is mostly preferred to regional techniques although limited published evidence suggests that spinal and regional anaesthesia was successfully used in a few liver transplant patients during hip replacement [2, 9, 36].

The overall goal of the postoperative period is to protect the graft from rejection while preventing infectious complications and minimising ischaemic damage to the allograft. Ultrasound imaging of right ventricle and exact quantification of portal and liver vascular flow patterns and the use of indocyanine green plasma disappearance rate to monitor hepatic blood flow and metabolism should provide detailed information to guide therapy. Pulmonary hypertension and right ventricular dysfunction should be treated aggressively with selective pulmonary vasodilators, pressor agents and inotropes if necessary. Coagulation profile (ACT, PT/aPTT, INR, factor analysis) should be monitored frequently by laboratory means and using point of care devices (such as TEG ROTEM). While toxins and cell lysis metabolites could be removed by hemofiltration, there are no effective tools to promote liver cellular viability. Thus, prevention of injury is the only realistic option.

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# Aged Patients with a Frailty Syndrome

# 19

Claudia Spies, Rudolf Mörgeli, Alissa Wolf, Anika Müller, and Oliver Birkelbach

## 19.1 Introduction

Frailty, seemingly an abstract term that can be broadly defined, can be a serious and influential syndrome in elderly patients. The syndrome is multidimensional, involving limited compensatory mechanisms, lower reserves against stressors, as well as an increasing dysfunction in physiological systems. Frailty is being increasingly recognized as a crucial risk factor for surgical procedures in elderly patients and has been shown to have profound implications on short- and long-term outcomes, including length of hospitalization, cognitive function, institutionalization, and mortality rates [1, 2]. An appropriate risk stratification for these elderly patients is important, as there is growing evidence for the benefit of perioperative interventions [3, 4]. By using objective parameters for the diagnosis of frailty, it is possible to identify these high-risk patients accurately and consistently. The timely diagnosis allows healthcare providers to develop a personalized therapeutic strategy for the perioperative care, thus limiting the development of complication rates and improving outcome [5].

### 19.1.1 A Growing Challenge

With increasing life expectancy and the current development in age structure, the provision of the healthcare in the coming years will present a tremendous challenge. In nearly all regions of the world, the elderly represent the fastest-growing segment of the population [6]. There is a higher incidence of frailty in the elderly due to accumulation of risk factors and physiological aging processes. Individuals above

C. Spies (✉) • R. Mörgeli • A. Wolf • A. Müller • O. Birkelbach
Department of Anesthesiology and Operative Intensive Care Medicine (CCM, CVK), Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin and Berlin Institute of Health, Berlin, Germany
e-mail: Claudia.Spies@charite.de



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65 years of age already represent approximately 8% of the world population, and this age group already accounts for 14–20% of the population of North America, Europe, and Australia. Projections estimate that the proportion of this age segment will double worldwide by 2050 [6].

A manifestation of this trend can be seen in the proportion of elderly patients undergoing surgery each year. Currently, more than half of all surgical procedures are performed on patients with over 65 years of age [7]. A systematic review of frailty, incorporating 31 studies in persons 65 years or older, found an overall weighted frailty prevalence of 10.7% [8]. This prevalence increases with age, so that up to 50% of individuals above 85 years of age are frail [9]. Frailty also increases the chances of requiring surgery, and it has been shown that up to 25–56% of the elderly undergoing surgery are frail [10, 11]. These patients have been shown to have a significantly higher risk of developing postoperative complications, and the risk of mortality within 12 months is up to five times higher than in non-frail patients [2].

### 19.1.2 Implications

However, the fate of these patients cannot be solely described by death rates. In order to return to their current functional state, 88.8% of elderly patients would undertake a high-burden treatment and 98.7% a low-burden treatment, despite the risk of death. Nevertheless, the same population would *reject* therapy if it would result in severe functional (rejection rate of 74.4%) or cognitive (rejection rate of 88.8%) impairment [12]. Although patients in otherwise good health usually do return to their previous state of health, frail patients tend to lose their ability to function independently after hospitalization [13].

Frailty is often not diagnosed in these elderly patients, and interventions are rarely performed. Measures to support the functional capacity of patients are not well implemented, so that patients only receive appropriate (and expensive) geriatric attention once a severe loss of autonomy has already taken place. This neglect of the frailty syndrome has been estimated to cost over ten billion euros per year [14].

Cognitive impairment also poses a tremendous risk factor for postoperative loss of autonomy [15, 16]. While up to 22% of patients over 71 years of age suffer from cognitive impairment (without dementia) [17], routine clinical screening is still not implemented. Incidentally, many patients are scheduled for surgery with a non-detected preoperative cognitive impairment, which often deteriorates postoperatively into long-term cognitive decline.

It is important to note that, although older individuals are most susceptible to develop frailty, the syndrome is by no means confined to the elderly. The incidence of frailty in younger individuals may rise due to an increase in cancer rates, cardiovascular disorders, and sedentary lifestyles [18–20].

Due to the enormous individual and socioeconomic burden caused by frailty, there is a dire need to generate awareness and develop preventive strategies that will ease its ramifications.

## 19.2 The Frailty Syndrome

The term "syndrome" underscores the multifactorial etiology [21], as frailty is caused by dysregulations across different organ systems in combination with physiological aging processes [11, 22]. These factors render the individual vulnerable to stressors and are closely associated with other geriatric syndromes [23]. The systematic assessment of frailty's characterizing traits can betray its presence, alerting healthcare providers to the devastating impact of synergism among them.

### 19.2.1 Defining Frailty

There is currently no general unified clinical definition to describe frailty, or to describe the lack of physiological reserves. The numerous available frailty instruments have recently been linked to the International Classification of Functioning, Disability, and Health (ICF), which represents a standardized and hierarchically coded language developed by the World Health Organization regarding health conditions and their positive (functioning) and negative (disability) consequences. The ICF components Body Functions and Activities and Participation were frequently linked to the frailty instruments, whereas Body Structures, Environmental and Personal Factors were only sparingly represented among (mainly multidomain) frailty instruments [24]. Until future standardization is available, frailty can be best assessed by systematically analyzing its main characteristics, which are frequently distributed into physical, cognitive, and social domains [23].

Frail patients are much more likely to fall, become disabled, or institutionalized than non-frail patients [13, 25]. The **physical domain** tends to be prioritized in an attempt to maintain, or regain, patient autonomy. This domain encompasses a poor or declining nutritional status, low level of physical activity, reduced mobility, lack of energy, and reduced muscle strength. Activities of daily living can also be placed under this domain, as it ascertains the patient's current level of autonomy.

Cognitive impairment can be just as debilitating as functional disability. There is evidence linking frailty to psychological distress, cognitive impairment, and even structural brain abnormalities [15, 26, 27]. The **cognitive domain** encompasses mainly preoperative cognitive deficits and depression. Even mild cognitive deficits before surgery can spiral into permanent, progressive, or even life-threatening conditions following the procedure. Depression is also an important and critical indicator of frailty, affecting daily function and quality of life [28, 29]. Evaluation is not always simple, and dementia, chronic pain, anxiety, and delirium are some examples of conditions that can (all) coexist and hamper assessment.

Particular attention should be given to *postoperative delirium* (POD) and *postoperative cognitive dysfunction* (POCD), as the pro-inflammatory component of frailty renders the patient particularly prone to the development of these conditions. POD reflects a cerebral dysfunction, as a form of acute organ failure. The condition can be devastating, affecting short- and long-term outcome, length of hospitalization, and increasing mortality. The effects can proceed into a chronic stage, POCD, where

the patient experiences a progressive cognitive decline in the weeks or months following operation, possibly leading to dementia [30]. In order to limit its effects, delirium must be promptly recognized and treated [31].

The **social domain** involves social isolation and lack of social support, as these can contribute significantly to the development of the syndrome. The level of support available to elderly patients is greatly dependent on their environment. Whether a patient lives at home, with or without a partner, whether there is stable contact with friends or relatives, as well as eventual hobbies and activities, can be immensely relevant to their level of activity, cognitive abilities, and quality of life.

There are several smaller domains that can be used to supplement the aforementioned. These include health factors such as chronic pain, comorbidities, medical history, and current medication/medication compliance.

### 19.2.2 Physiological Aspects

The physiological changes that take place in elderly individuals contribute significantly to the development of frailty. Aside from changes in cognitive function, the risk of dementia and depression is high among the elderly [15]. Diminished taste and poor dentition contribute to malnutrition. Muscle composition is altered, with fewer type 2 fibers and a successive reduction in mass and strength, as well as reduced reflexes [32]. This contributes to the risk of falls, and since bone mass is also reduced in the elderly, the risk of fracture is also increased. In turn, falls or the fear of falls can lead to reduced physical activity and social isolation, thus increasing disability and depression rates. Deterioration of hearing or sight can further aggravate the situation. Heart function is also affected, with hypertension, atherosclerosis and higher rates of arrhythmia and fibrosis. Cardiac problems can lead to fatigue, compromising physical activity and aggravating the musculoskeletal degradation, and to polypharmacy, which can easily cause undesirable side effects. The immune system is less effective, so that the elderly are more susceptible to bacterial and viral infections. These changes trap the individual into a vicious cycle, leading to a steady decrease in functional capacity (Fig. 19.1) [33], culminating in loss of autonomy.

## 19.3 Diagnosing Frailty

Despite the numerous scoring systems employed in the perioperative and intensive care settings to assess a multitude of relevant parameters, the detection of age- and health-related limitations on functional capacity has been insufficiently established. For instance, the Acute Physiology and Chronic Health Evaluation (APACHE), the Simplified Acute Physiology Score (SAPS), and the Mortality Probability Model (MPM) are the most prominent models for the prediction of outcome. Their common limitation is that none of them takes into consideration the particular restrictions usually found in the elderly. Frail patients are especially vulnerable to the

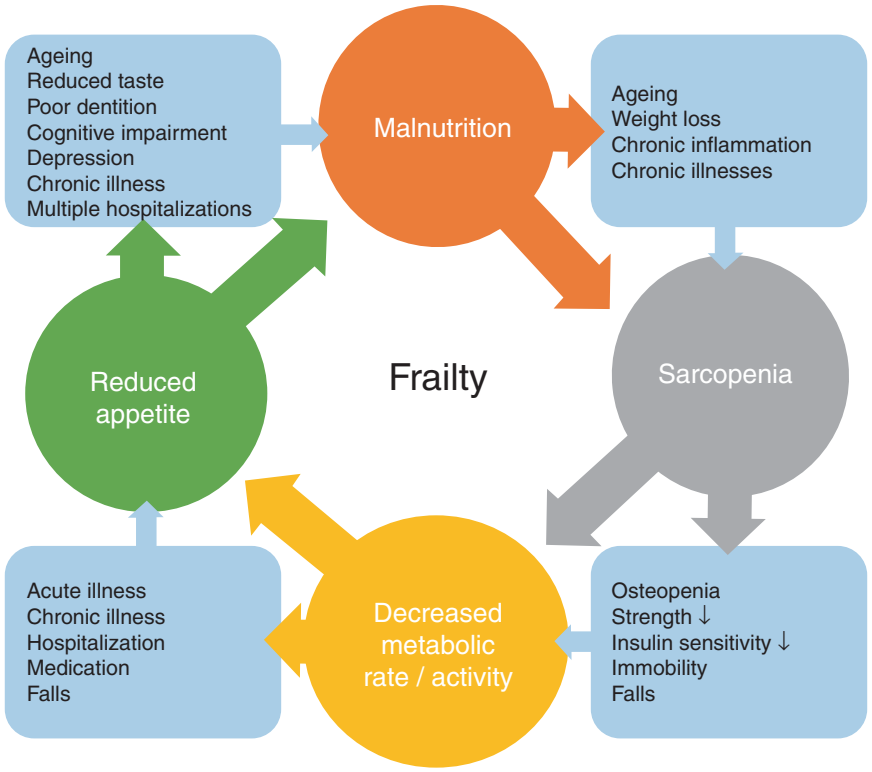


**Fig. 19.1** The frailty cycle (adapted from Ahmed et al. [33])

different stressors in the perioperative context. An individual and interdisciplinary risk assessment is essential for detecting any conditions that have a diagnostic or therapeutic consequence for the intra- or postoperative period.

### 19.3.1 Frailty Models

Although there are more than 50 instruments used to assess frailty [34], there are only two definitions that are widely used: the Deficit Accumulation Model from Rockwook and Mitnitski, which takes factors from multiple domains into consideration, and the Frailty Phenotype Model from Fried, which is primarily based on aspects of physical decline.

The **Deficit Accumulation Model** [35, 36] represents a multidimensional risk assessment, which analyzes patient history for deficits accumulated across several domains. The model incorporates 30–70 aspects, including physical condition, comorbidities (such as stroke, diabetes, and cardiorespiratory conditions), as well as activities of daily life (ADL), to calculate a numerical index on a 7-point Clinical Frailty Scale.

**Table 19.1** Main aspects of the Frailty Phenotype Model (adapted from Fried et al. [13])

| Characteristics of frailty | Description |
|---|---|
| Shrinking: weight loss (unintentional) and sarcopenia (loss of muscle mass) | Unintentional weight loss ≥10 lbs (4.5 kg) within the last year |
| Weakness | Grip strength: ≤20th percentile (by gender and body mass index) |
| Poor endurance; exhaustion | Exhaustion (self-reported) |
| Slow gait speed | Walking time/15 ft (4.57 m): ≤20th percentile (by gender and height) |
| Low activity | Kcals/week: ≤20th percentile<br>Metabolic equivalent <3 |
| Frailty phenotype<br>Number of positive criteria | Frail: ≥3 criteria<br>Intermediate/pre-frail: 1–2 criteria |

In comparison, the **Phenotype Model** [13] defines frailty as a clinical syndrome, whereas it is noted whether the following characteristics are present: unintentional weight loss, self-reported exhaustion, weakness, slow gait speed, and low physical activity (see Table 19.1). The patient is deemed to be frail if three or more of these traits are present, and pre-frail if only one or two traits are observed. If none of the criteria is present, the patient is deemed to be non-frail.

Although there is no consensus on which components should be included in the frailty assessment and none of the instruments can be considered a gold standard [37], the physical phenotype model from Fried has been the most frequently used definition [34]. In addition to the physical dimension of the Frailty Phenotype, additional instruments can be used to account for cognitive and social aspects.

### 19.3.2 Instruments of Assessment

Clinical management of frail elderly patients requires multidisciplinary cooperation between anesthesiologists, surgeons, intensivist, geriatrists, nurses, pharmacologists, physiotherapists, and nutritional assistants. The assessment of domains can be conducted using clinical tests (see Table 19.2) or questionnaires. In the absence of consensus, the instruments used must be critically selected based on the type of treatment and interventional capabilities. In case of emergency, per instance, when there is no time for a comprehensive geriatric assessment, surrogate markers should be employed.

The following describes some of the most commonly used instruments in the assessment of frailty:

*Unintentional weight loss/body mass index* (*BMI*): the unintentional weight loss of more than 4.5 kg in the previous year, or a low BMI, can be a marker for malnutrition, sarcopenia, or incipient cachexia [13].

*Exhaustion*: self-reported lack of energy or fatigue. This may indicate malnutrition, low cardiovascular and/or respiratory reserves, reduced endurance, or depression [13].

**Table 19.2** Dimensions of frailty and operationalization possibilities (adapted from De Vries et al. [38], Fuchs et al. [39])

| Domain | Component | Operationalization |
|---|---|---|
| Physical | Nutritional status | Body weight, appetite, BMI, weight loss |
| | Physical activity | Level of physical activity in daily life |
| | Mobility | Walking speed, mobilization support |
| | Energy | Fatigue, exhaustion |
| | Strength | Grip strength, Chair Rise Test, climbing stairs |
| Cognitive | Cognitive performance | Memory, diagnosed dementia, cognitive impairments |
| | Mood | Depression, sadness, anxiety, nervousness |
| Social | Social resources | Social binding, living and financial situation, support potential |

*Grip strength*: a simple test where the patient is required to grip a dynamometer, using their dominant hand, as strongly as possible. The test is used to assess muscle strength, and scoring is based on gender and BMI, where a result below the 20th percentile is deemed abnormal [13, 40].

*Gait speed*: this test is used to measure the normal walking speed of a patient, based on gender and height. The test is repeated three times, and the average time is used for the evaluation. There are several versions of this test, and they vary regarding the start (static or dynamic) and distance to be covered (2–15 m) [41]. The most widely used version is from Fried, which uses 4, 57 m (15 feet) and a dynamic start [13, 25, 34]. Whereas the type of start has been shown not to be relevant, there are several cutoff speeds (m/s) that can significantly predict outcome [42].

*Timed Up and Go* (*TUG*) *test*: this is another version of the gait speed test. Here the patient must stand up from a chair, walk a distance of three meters, turn around, return to the chair, and sit down again. The entire process is timed, whereas a time $\geq$20 s can be predictive of reduced physical capacity. Ultimately, this test assesses not only mobility, muscle strength, and nutritional status but also cognition and cardiovascular/respiratory reserves [43].

*Low levels of activity*: self-reported level of activity in terms of kilocalories per week, based on gender, with a cutoff at the lowest 20th percentile [13]. This estimation is rather complex, so that the metabolic equivalent (MET) can be used as an alternative, whereas a MET under 3 is considered abnormal [44].

*Modified frailty index* (*MFI*): this compact 11-point questionnaire assesses several domains of frailty, and it is tailored for the acute setting, avoiding elements such as gait speed or grip strength [1].

Activities of daily living (ADL)/instrumental activities of daily living (IADL) [45]: the ADL questionnaire is used to assess the ability of the patient to manage certain activities, such as eating, dressing, and bathing. The IADL encompasses additional activities, such as grocery shopping, cooking, and laundry. These tests, although subject to a ceiling effect, are used to evaluate the physical and cognitive autonomy of the patient [46].

*Mini-Mental State Examination* (*MMSE*): this 30-question survey evaluates attention, memory, and visuospatial skills. A score of ≤23 indicates reduced cognitive abilities. Repetitive testing might have an impact on the results, so a second version (MMSE®-2™) is required to reduce memory effects [47].

*Mini-Cog*: this is a short test, requiring less than 5 min to complete, involving a 3-word memory test and clock drawing. It has a similar sensitivity and specificity to cognitive impairment as conventional neuropsychological tests [48].

*Geriatric Depression Scale*: this is a 15-point questionnaire requiring only yes or no answers. A score of six or above can indicate depression, although a score below six cannot rule out the condition [49].

*Social history*: should include aspects of social binding (type and frequency of social contacts), living arrangements (house/apartment, stairs/elevator), living alone or with a partner, need and availability of caregivers, access to groceries or healthcare facilities, financial situation, access to immediate help by neighbors and friends, and other factors [38, 50].

*Biomarkers*: can also be used to assess frailty, as malnutrition and the dysregulation of the immune-endocrine system can lead to reduction in muscle mass, weakness, and chronic inflammation [11]. Such biomarkers include concentrations of albumin, vitamin D and B12, testosterone levels in men, hemoglobin, white blood cell, C-reactive protein, and interleukin-6 levels [51–53].

There are several other aspects that can be easily added to supplement these assessments. Many can be evaluated by simple clinical tests, blood examinations, or from studying the patient's medical history. In emergency situations, or by centers with limited resources, shorter tests or surrogates are available. Of the previous tests, slow gait speed [54] and grip strength [55] have been shown to be the most relevant in terms of outcome, so that they may be particularly suitable surrogate markers. Low albumin levels, as a marker for sarcopenia and inflammation, was also shown to be a predictor of poorer outcome [56–58].

### 19.3.3 Individual Risk Evaluation

The implementation of a comprehensive geriatric assessment has shown excellent results in terms of identifying frail patients and improving their outcome. In fact, even non-frail patients can benefit from the systematic and consistent use of this test battery. The study of Hall et al. revealed a decrease in the number of patients who died in the first few days, weeks, and months after major, elective, non-cardiac surgery, showing that preoperative frailty screening could significantly reduce postoperative mortality [5]. After the introduction of screening, the 30-day total mortality fell from 1.6 to 0.7%. When looking exclusively at frail patients, the 30-day mortality rate dropped from 12.2 to 3.8%, but even the mortality rates of non-frail patients fell from 1.2 to 0.3%. A significant decrease in mortality was also seen in frail patients after 180 and 365 days. However, the study did not clarify which medical measures led to such a drastic decrease in postoperative mortality. The authors

hypothesized that outcome was improved by multifactorial aspects, such as improved preoperative decision making, intraoperative management, and postoperative measures. Thus, awareness of frailty possibly affects outcome due to a heightened attention to the provision of care.

The primary goal is to identify and evaluate factors that pose a risk to the geriatric patient. Such factors involve emerging or current disabilities and dysfunctions, as well as a reassessment of already diagnosed conditions. Thus, it is often possible to detect disorders at an early stage, where it is feasible (and economic) to contain or reverse their effects through appropriate therapeutic measures.

## 19.4 Anesthesiological Approach to Frailty

### 19.4.1 Interdisciplinary Process Planning

An individual and interdisciplinary risk assessment is indispensable, and the provision of care to high-risk patients under the aspect of frailty should be carried out as a shared decision process between anesthesiology and the operative disciplines [25]. This leads to reduced rates of institutionalization, 30-day readmission, and costs [59, 60].

Frailty evaluation must be practicable, and the extent and focus of the assessment must be appropriate to the capabilities and goals of the healthcare center. Depending on the goals set, it may be important to establish a selection process for patients suspected of frailty, so as to optimize time and resource investment.

Once frail patients have been identified, priority is to avoid functional decline and ensure short hospitalization periods [61]. There are a number of factors that must be considered to reduce risk to the frail patient, such as prehabilitation measures, type and extent of surgery, choice of anesthesia, as well as postoperative physiotherapy and analgesia. By choosing the treatment goals in a multidisciplinary setting, medical and procedural aspects can be quickly and efficiently addressed.

### 19.4.2 Preoperative Objectives

Establishing the actual state of the patient before the operation can provide healthcare providers with valuable opportunities regarding the optimization of modifiable factors.

Although prehabilitation studies have been relatively small, the use of presurgical exercise and strengthening regimens, some as short as 3 weeks, may already provide significant changes in physical status and outcome [62–64]. Balance, endurance, and resistance exercises should be implemented early in the treatment [65] and continued postoperatively. Outcome parameters, including length of hospitalization, can be affected by the preoperative function [66].

There is a strong synergism between depression and frailty [67, 68], so that depression should be treated as soon as the condition is detected.

Nutritional support should be offered, as the preoperative nutritional status of the patient has been shown to have significant effects in outcome [66, 69]. This may include assessment and counseling by a nutritionist, as well as supplements, such as vitamins D and B12 [70].

Polypharmacy (more than 5 drugs) has been established as a risk factor and even suggested as a surrogate parameter for frailty in acute cases [28, 61]. The critical evaluation of choice and dose of medication can reduce the total medication requirement, either by combined delivery, by dose adaptation, or even by discontinuing unneeded medication.

Social interaction and connections are influential aspects for the elderly frail, and social support should be provided early during treatment [71]. Activate the patient's social network by encouraging the involvement of family members in the decision making.

Cognitive screening should take place before start of treatment, as reduced cognitive abilities are in itself a risk factor for adverse postoperative outcome and mortality [16]. A preoperative cognitive dysfunction can significantly increase the rate of postoperative delirium, especially among frail patients [16, 72]. Additionally, testing serves as a baseline to detect subsequent cognitive decline.

### 19.4.3 Perioperative Management

After addressing all modifiable risk factors, and the patient's condition has been improved as much as can be reasonably expected, certain aspects of the perioperative management can further protect the frail patient. Although many of these factors should be broadly implemented, frail patients can profit significantly from a strict adherence to these measures.

Clear and realistic goals should be discussed with the patient, keeping in mind their individual risk profile. Fast-track concepts should be preferred, as these patients are particularly vulnerable to the stress of trauma and hospitalization [61].

The invasiveness of the procedure and the time under anesthesia can both influence outcome, so that the type and extent of surgery must be carefully considered. Minimal invasive surgery and short procedures should be favored when possible. Although there is limited evidence that regional or axial anesthesia is preferable to general anesthesia in terms of outcome (possibly due to the regular use of sedatives in awake patients), these methods may provide better analgesia in the postoperative period, reducing stress and supporting physiotherapeutic measures.

Preoperative fasting should be strictly imposed, but beware of dehydration. An increase in the fluid-fasting period is related to an increased rate of postoperative delirium [73]. According to the guidelines [74], encourage the intake of clear fluids up to 2 h before the operation, and should the operation be delayed, consider the provision of intravenous fluids.

*Premedication* should only be given in exceptional cases, not routinely. The risk of postoperative delirium is severely increased by premedication with benzodiazepines. Though anxiety remains an indication for premedication, a dose reduction is

**Table 19.3** Effect of anesthetic drugs in the elderly (adapted from Kanonidou et al. [61])

| Drug | Pharmacokinetics | Dose |
|---|---|---|
| Thiopental | ↓ Volume | ↓ |
| Etomidate | ↓ Volume | ↓ |
| Propofol | ↓ Clearence | ↓ |
| Midazolam | ↓ Clearence | ↓ |
| Morphine | ↓ Clearence | ↓ |
| Remifentanil | ↓ Clearence | ↓ |
| Cis-Atracurium | – | ↔ |

highly advisable. Patients should be monitored after premedication due to the risk of paradox effects or respiratory suppression [75].

In fact, usual *pharmacodynamics* and *pharmacokinetics* can be severely altered in elderly patients, particularly in the frail. Several factors, physiological and pathological, serve to enhance the effect of many drugs [76]. Reduced liver and kidney function, reduced albumin (protein binding), dehydration (leading to higher serum concentration), and an overall reduced neural mass, along with changes in neurotransmitter and receptor densities, can prolong and increase the drug effect of many anesthetic drugs (Table 19.3) [61, 77]. Preference should be given to short-acting substances, and dosage should be reduced or titrated to the needs of the patient. Use intraoperative neuromonitoring, and when possible, use drugs that are independent of hepatic or renal elimination, such as remifentanil and cisatracurium [75].

*Fluid management* is crucial for these patients, and a broad indication should be given to advanced monitoring, such as arterial blood pressure measurements. Beware that many elderly patients, due to restricted compensatory mechanisms, are prone to exaggerated blood pressure responses to anesthetics, blood loss, or inadequate fluid administration. Electrolyte shifts have been associated with POD and should be closely monitored [78, 79], especially in case of impaired kidney function, long procedures, or large fluid shifts. Hypotension is to be avoided, in particular since a reduced cerebral perfusion can contribute to the development of postoperative delirium [80].

Due to reduced muscle mass and reduced metabolism, *thermoregulation* is also impaired in frail patients. Even mild hypothermia can disrupt circulation and blood clotting, as well as increase the rate of postoperative infections [81]. Warm the patient early during the anesthesia, and monitor temperature throughout the procedure.

*Positioning* of the frail patient during the surgical procedure must be carefully controlled. Due to impaired peripheral circulation, these patients are more prone to incurring neural damage, venous thrombosis, and skin damage.

According to current guidelines [82], intraoperative monitoring via electroencephalogram (EEG) should be routinely employed in this patient collective. Particular attention should be given to avoid burst suppression periods in the EEG analysis. Burst suppressions imply an excessive level of anesthesia and can have devastating cognitive consequences following surgery [83]. Alpha band coherence in EEG (see Fig. 19.2) can indicate appropriate anesthetic depth, but beware this coherence is reduced in the elderly [84].

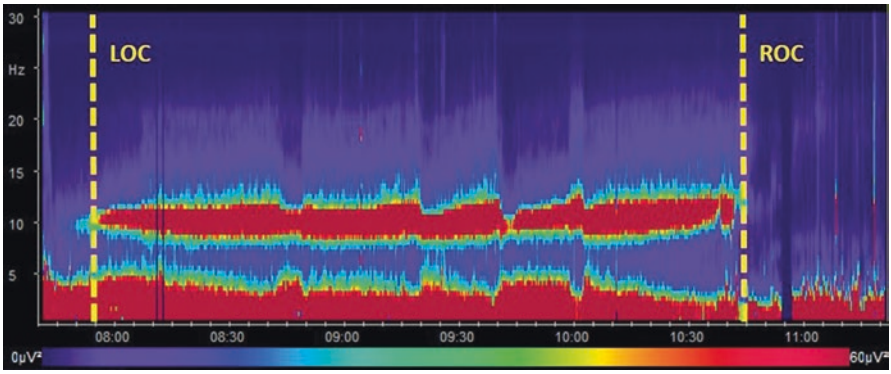


**Fig. 19.2** EEG spectrogram of propofol anesthesia showing typical alpha band (8–12 Hz) dynamics during loss of consciousness (LOC) and regain of consciousness (ROC)

Due to dysregulation of pharmacokinetics (impaired elimination, drug distribution, etc.), ensure that no residual neuromuscular block persists before allowing the patient to emerge from anesthesia.

There are several factors that can help reduce perioperative stress. The use of validated instruments to achieve an adequate analgesia can help avoid over- or underdosage of analgesics. Delirium monitoring should be implemented in the recovery room, and the occurrence of POD should be promptly countered with an adequate therapy [79].

### 19.4.4 Postoperative Considerations

In the postoperative phase, it is important to continue the interventions initiated, such as nutritional counseling and physical exercises. Rehabilitation should commence as soon as possible, keeping in mind that hospitalization period should be kept to a minimum.

A proper analgesia protocol using validated scales should be continued, as this not only reduces perioperative stress but also supports physiotherapeutic interventions. Also keep in mind that delirium can still occur several days after surgery, so that proper assessment is also required in peripheral units [85].

Beware of complications, such as pulmonary infections and renal failure. Frail patients are particularly vulnerable to complications during the postoperative phase, as they have a limited ability to compensate the stress of hospitalization and surgical trauma [86, 87].

Social binding should also be utilized. Activated social contacts and visitors can help limit depression and motivate the patient to a speedy recovery by encouraging movement, eating, and drinking, ultimately improving therapeutic compliance [88].

Healthcare systems and hospitals should implement multifaceted strategies delivered by an interdisciplinary team for the entire period of hospitalization, so

as to prevent functional and cognitive decline in hospitalized older individuals and maximize their independence at the time of discharge. An example of such a program is the Hospital Elder Life Program (HELP), which was designed to assist older patients retain autonomy, avoid postoperative complications, falls, as well as unplanned readmissions. The HELP staff members, consisting of Elder Life Specialist, Elder Life Nurse Specialist, geriatrician, and trained volunteers, conduct patient-centered interventions, such as the daily visitor program for orientation, social support, exercise program (early mobilization), assistance during meals, education program for family and staff members, and facilitation of the transition from hospital to home [89]. The HELP program has been shown to be effective in the prevention of delirium, cognitive and functional decline, as well as in the reduction of hospitalization length and institutionalization rates [90].

**Conclusions**

Awareness and assessment of frailty prior to surgical procedures can help identify vulnerable patients. There is a variety of evaluation methods, ranging from comprehensive geriatric assessments to the quick analysis of surrogate parameters. When possible, preoperative interventions must be initiated to boost the status of the patient. Adequate intraoperative and postoperative measures can help avoid complications, as well as significantly improve outcome, survival, and quality of life of elderly frail patients.

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# The Allergic Patient

# 20

Paul Michel Mertes and Charles Tacquard

## 20.1 Introduction

Anaphylaxis is a rare but potentially life-threatening complication of anesthesia. Its incidence is estimated at 100.6 (76.2–125.3) per million procedures with a marked female predominance [1]. This complication is associated with a significant morbidity and mortality. The mortality rate for anaphylaxis during anesthesia ranges from 0 to 1.4% in Western Australia to 4.76% in Japan [2]. Anaphylaxis to neuromuscular blocking agents is associated with a mortality of 4% in France and 9% in the UK, despite adequate resuscitation [3, 4].

In some cases, this complication can be completely unpredictable and occur in patients with no previous allergic background [5]. Anesthetists must then recognize this complication and provide the appropriate treatment in accordance with current guidelines [6]. They must also ensure that the patient complies with the allergic assessment [7].

The situation is more difficult when patients report previous food or drug allergies. In these cases, anesthetists must distinguish between different possibilities. The patient may be allergic to drugs used during anesthesia. Some allergies may cross-react with anesthetic or surgical materials (gloves, skin disinfectant, dyes). Sometimes, patients report an allergic reaction to a previous anesthesia without any allergic assessment. When these patients are seen before a surgical procedure, the anesthetist must investigate the situation even if this means postponing surgery. Sometimes, however, surgery cannot be delayed or the patient is seen in an emergency. In this case, anesthetists must choose the appropriate anesthesia to minimize the risk.

P.M. Mertes (✉) • C. Tacquard
Department of Anesthesia and Intensive Care, Hôpitaux Universitaires de Strasbourg, Nouvel Hôpital Civil, EA 3072, FMTS de Strasbourg, Strasbourg, France
e-mail: paul-michel.mertes@chru-strasbourg.fr; charles.tacquard@gmail.com



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This chapter will review the most frequent allergies faced by anesthetists and their implications for future anesthesia. After a brief description of the epidemiology of these reactions during anesthesia, we review the main current guidelines for allergies reported during the anesthetic assessment or in an emergency anesthesia setting.

## 20.2 Epidemiology of Perioperative Allergy

The epidemiology of immediate hypersensitivity reactions differs according to geographic location and clinical practices. Their incidence ranges from 1:353 in the UK to 1:11,000 anesthesia in Australia [8, 9]. Allergy is the first mechanism of these reactions.

In anesthesia, several substances are often responsible for allergic reactions.

*Neuromuscular blocking agents (NMBAs)* are the first class involved in allergic reactions in several countries [1, 4, 10]. In France, the incidence of these reactions is estimated to be 184.0 (139.3–229.7) reactions per million procedures [1] representing about 60% of all allergic reactions during anesthesia. The incidence of allergic reaction to NMBAs seems to be lower in Spain or in the USA [2]. Suxamethonium and rocuronium have the highest risk with an incidence of 1/2080 and 1/2449 new patient exposures, respectively. Atracurium seems to be safer with an estimated incidence of 1/22,450 new patient exposures [10]. Cisatracurium also seems to be safe with an involvement in only 5.9% of allergic reactions during anesthesia in France despite a market share of 29.6% [11].

*Antibiotics* are an increasing cause of allergic reactions during anesthesia. In France, they were responsible for 18.1% of perioperative allergic reactions in the last GERAP study in 2007 versus only 2% in the early 1980s [11]. In other countries such as Spain and the USA, they account for 40–50% of allergic perioperative reactions [12–14]. Penicillins and cephalosporins are the main antibiotics causing allergic reactions during anesthesia. The extended use of cephalosporins for surgical prophylaxis has led to an increasing number of hypersensitivity reactions to antibiotics, especially cefazolin [15].

Suspected allergy to beta-lactams is difficult to address because it is the first self-reported drug allergy with approximately 10–15% of hospitalized patients [16, 17]. These reactions are often overreported and under-investigated. The diagnosis is ruled out in 90% of these patients after an appropriate allergic assessment [17]. Moreover, subsequent exposure was well tolerated in 80–90% of these patients [16]. In the general population, adverse reactions to penicillin range from 0.2 to 5% depending on the study methodology [18, 19]. Anaphylaxis to parenteral penicillin is estimated to occur in 32 of 100,000 exposed cases in Europe [20]. The risk of fatal anaphylaxis ranges from 0.0015 to 0.002% of penicillin-treated patients [21].

Other antibiotics may also be incriminated. Vancomycin and quinolones may induce immediate hypersensitivity reactions even if the mechanism is not necessarily IgE-mediated as these drugs have direct histamine-releasing properties.

Until recently, *latex allergy* was a major cause of anaphylaxis during anesthesia. After the HIV epidemic, the high demand for natural rubber latex (NRL) products led to the marketing of more protein-containing latex products. This resulted in an increase in the number of allergic reactions to latex. Some groups were particularly at risk: patients with spina bifida or with multiple surgery, healthcare workers, and patients with a latex-fruit syndrome [6].

Indeed, some latex allergens cross-react with food allergens. The most frequently involved are kiwi, chestnut, avocado, and banana, but other foods containing class I chitinases are involved. The prevalence of patients with NRL allergy and associated food allergy ranges from 21 to 58% [22]. Several preventive measures were taken to reduce the risk of NRL allergy: avoidance of latex for spina bifida surgery and for multiple surgeries in children, the use of better quality latex, and awareness raising of healthcare workers to the allergic risk of latex. These measures have been successful with a decrease in the prevalence of NRL sensitization from 6.1% in 2002–2005 to 1.2% in 2010–2013 [23] in the general population. In the operating room, allergy to latex was the second cause with an IgE-mediated reaction in 2005–2007 [11] in France but is now only the fourth in 2011–2012 [24].

Reactions to *hypnotics* are now relatively uncommon. Barbiturates were mainly responsible because of their ability to induce direct histamine release even if they were also associated with true IgE-mediated reactions [25]. Cremophor EL used as solubilizer for some hypnotics was frequently responsible for these reactions. The switch to 10% soybean emulsion in propofol significantly reduced the rate of hypersensitivity reactions [26]. Allergy to other hypnotics (midazolam, etomidate and ketamine) seems to be rare [11].

In the last French survey, allergy to *opioids* accounted for only 1.6% of all perioperative allergies. The mechanism of reactions to opioids mainly involves nonspecific skin mast cell activation.

Other analgesics such as *nonsteroidal anti-inflammatory agents (NSAIDs)* are involved in hypersensitivity reactions. Most of them result from Cox1 inhibition. Allergy to NSAIDs is possible although rare. There is no cross-reaction between NSAIDs.

Allergy to *local anesthetics* is rare considering their widespread use [11, 27]. Benzoic acid esters can induce reactions through their metabolites (para-aminobenzoic acid). An intra-class cross sensitivity is possible. The risk is lower with the local amide anesthetics currently used during anesthesia. Most of the hypersensitivity reactions reported with local anesthetics are due to a non-IgE-mediated mechanism (vasovagal syncope, overdosage, intravascular administration, vasopressor symptoms). Allergic reactions to local anesthetics are mainly delayed reactions leading to eczema. In the case of positive skin tests to local anesthetics, allergy to methylparaben, paraben, or metabisulfite used as preservatives must also be considered.

*Chlorhexidine*, used as a skin disinfectant but also found in coated central venous catheters, urethral gels, and ophthalmic washes, is a possible cause of perioperative allergic reactions. The incidence of these reactions differs according to the country. In the UK chlorhexidine was responsible for 5% of all perioperative IgE-mediated reactions [4]. In Denmark, the risk appears to be greater and 9.6% of perioperative allergies are due to chlorhexidine [28]. In France, this risk is a lot lower, probably because of the restricted use of chlorhexidine for skin disinfection in the operating room.

The incidence of allergy related to *colloids* ranges from 0.033 to 0.22% with a higher risk for gelatins [5, 29].

*Dyes*, used by surgeons for lymph node mapping in cancer surgery, are now important allergens in the operating room. The incidence of allergic reactions to dyes is increasing with their wider use [30].

### 20.2.1 How to Investigate a Perioperative Allergic Reaction?

After an immediate hypersensitivity reaction, anesthetists must rapidly institute the appropriate treatment in accordance with current guidelines. Then, after initiating the appropriate treatment, anesthetists must take blood samples to confirm the diagnosis of a hypersensitivity reaction. Tryptase measurement is widely recommended. It should be performed during the first 1–2 h after the reaction. A baseline measurement of tryptase levels at least 24 h later is useful to rule out systemic mastocytosis. In some guidelines histamine measurement is also recommended to confirm the reality of a non-IgE-mediated hypersensitivity reaction. To avoid false positive measurement of histamine, cooling the tube to 4 °C and early centrifugation are mandatory.

Anesthetists must inform the patient about the reaction and emphasize the importance of a detailed allergic workup to confirm the diagnosis and identify safe drugs that can be used for future anesthesia. The timing of the reaction and blood sampling, possible causal agents, and the treatments administered must be recorded and shared with the laboratory and the allergist.

The patient should be referred for a detailed allergy workup 4–6 weeks after the reaction. Skin tests (prick test and intradermal reaction) are the gold standard for perioperative hypersensitivity reactions. They should be performed in experienced centers under strict supervision and in accordance with current guidelines. When the clinical history and skin tests are discordant, specific IgE antibodies and in vitro cellular assays (basophil activation test) are useful. Provocation tests are not possible for all anesthetic drugs (muscle relaxants and hypnotics) but can be helpful when skin tests to antibiotics, local anesthetics, or NSAIDs are negative.

At the end of the allergy assessment, the safest protocol for subsequent anesthesia is determined in collaboration between the allergist and anesthesiologist. The patient must be informed and carry an allergy alert card [31].

## 20.3 Management of Patients Claiming to be Allergic (Table 20.1)

### 20.3.1 To Anesthetic Drugs (General or Local Anesthetics)

#### 20.3.1.1 Scheduled Procedure

When patients describe a previous history of allergy during anesthesia, anesthetists must obtain the previous anesthesia protocols. If the history fits a possible allergic reaction, the patient must be referred for an allergo-anesthesia consultation in order to assess the reactions. All agents used during the suspected anesthesia and latex should be tested. In case of allergy to NMBAs, cross sensitivity should be assessed. In case of allergy to local anesthetics, a subcutaneous challenge test can be performed to confirm the absence of any sensitization in case of high clinical suspicion and negative skin tests.

When the previous anesthesia protocol is not available, all muscle relaxants and latex should be investigated during an allergo-anesthesia consultation [6].

**Table 20.1** Summary of procedures to follow in case of claimed allergy with no previous allergic investigation

| The patient claimed to be allergic to | Scheduled procedures | Emergency procedures |
|---|---|---|
| General anesthetics | • Examine previous anesthesia protocols | • Consider local-regional anesthesia |
| | • Allergo-anesthetic assessment: test all drugs used during the suspected reaction + latex | • If not possible: avoid muscle relaxants and histamine-releasing drugs + latex free environment |
| | • If previous protocol unavailable: test all muscle relaxants and latex | |
| Local anesthetics | • Examine previous anesthesia protocols | • Consider general anesthesia |
| | • Allergo-anesthetic assessment: skin test + challenge test if negative | |
| Beta-lactams | • Replacement for surgical prophylaxis in accordance with local protocols for low-risk patients/surgery | • Replacement for surgical prophylaxis in accordance with local protocols for low-risk patients/surgery |
| | • Allergic assessment for high-risk patients/surgery[a]: skin tests + challenge test if negative | • Consider cefepime and carbapenems as a possible treatment if claimed allergy to penicillin |
| | | • When no other treatment option: consider rapid desensitization (specialized advice) |

(continued)

**Table 20.1** (continued)

| The patient claimed to be allergic to | Scheduled procedures | Emergency procedures |
|---|---|---|
| Other antibiotics | • Avoidance for surgical prophylaxis | • Avoidance of suspected antibiotic |
| | • Allergic assessment in case of multiple antibiotic allergies | |
| Latex | • Allergic assessment: skin tests + challenge test if negative | • Latex-free environment, first place in operating list |
| | • Latex-free environment, first place in operating list | • Inform all relevant parties |
| | • Inform all relevant parties | |
| Kiwi, chestnut, avocado, and banana | • Allergic assessment for latex (see above) | • Consider latex-free environment |
| Morphine or codeine | • Allergic assessment: skin tests + challenge test if negative | • Avoidance of morphine and codeine |
| | | • Other opioids are available |
| Iodinated contrast media | • Allergic assessment: skin tests + challenge test if negative | • Avoidance of the pharmaceutical class |
| Povidone-iodine | • Allergic assessment: skin tests | • Substitution for chlorhexidine |
| Seafood | • No contraindication for any iodinated drugs or protamine | |
| Egg or Soy | • No contraindication for propofol | |
| Peanut | • No contraindication for any anesthetic drug | |
| Red meat or alpha-gal | • Avoidance of gelatin colloids | |

[a]Allergy to multiple antibiotics, history of immediate or non-immediate hypersensitivity reaction to penicillin/cephalosporins with a requirement for frequent antibiotics (bronchiectasis, cystic fibrosis, diabetes, primary and secondary immunodeficiencies, or asplenia/hyposplenism), or requiring a specific treatment with beta-lactam. Major surgery with a high risk of infectious complications (cardiothoracic surgery, major abdominal surgery)

### 20.3.2 Emergency Procedure

When the patient is seen for an emergency procedure, the time before surgery is too short to properly investigate the patient for allergies. Anesthesia must then take place in a latex-free environment. If the previous reaction occurred during a general anesthesia, local-regional anesthesia should be considered. When local-regional anesthesia is not an option, NMBAs and histamine-releasing products should be avoided whenever possible.

### 20.3.3 To Antibiotics

#### 20.3.3.1 Scheduled Procedure

Around 30% of patients seen during the preoperative anesthetic assessment claimed to have a drug allergy, and 25% of these patents claimed to be allergic to

ß-lactams [32]. Investigating each patient for this allergy is time-consuming and expensive. It represents a challenge for our healthcare systems and cannot be recommended.

When the risk of a postoperative need for a beta-lactam is low, replacement by another class of antibiotic for surgical prophylaxis appears to be effective. Systematic replacement with a cephalosporin in the case of allergy to penicillins may no longer be proposed because of the cross sensitization between penicillins and first and early second-generation cephalosporins due to the side-chain R1 homology. Cross-reactivity between penicillins and first or early second-generation cephalosporins occurs in up to 10% of cases versus 2–3% for third-generation cephalosporins [33]. Other classes of antibiotics should be used in accordance with local antibioprophylaxis protocols. Although cross sensitization is not described, clindamycin-induced hypersensitivity reactions are also possible [34]. Vancomycin should be used cautiously with slow IV administration in order to avoid a histamine-release syndrome known as "red man syndrome."

Patients with suspected multiple antibiotic allergies, a history of immediate or non-immediate hypersensitivity reaction to penicillins/cephalosporins requiring frequent antibiotic treatment (bronchiectasis, cystic fibrosis, diabetes, primary and secondary immunodeficiencies or with asplenia/hyposplenism) or requiring a specific treatment with beta-lactams, should be more closely investigated for beta-lactam allergy [21]. Patients requiring major surgery with a high risk of infectious complications (cardiothoracic surgery, major abdominal surgery) may also be investigated. For these patients, avoidance of beta-lactams leads to a higher risk of clinical failure in case of infection [35].

Allergic assessment for beta-lactam allergy is difficult. It should be performed in experienced centers with skilled staff and in accordance with current guidelines. Allergic assessment includes skin prick testing for major penicillin and cephalosporin determinants. When negative, intradermal reactions are performed. If skin tests are not contributive, a full-dose challenge should be performed under strict supervision to rule out the beta-lactam allergy [21].

### 20.3.4 Emergency Procedure

For surgery and/or patients with a low risk of infectious complications, avoidance of the pharmaceutical class of antibiotics is effective.

The situation is more complicated in the case of beta-lactam allergy in patients with a specific beta-lactam requirement (see above). A proper allergic assessment is not possible because of the emergency setting. The switch to another pharmaceutical class is possible but associated with a higher risk of clinical failure [35]. In the case of self-reported penicillin allergy, hypersensitivity reactions to cefepime and carbapenems are rare, and these antibiotics should be considered as a potential treatment for infectious complications [36]. When the patient is suspected to be allergic to an antibiotic but requires a specific treatment by this antibiotic (e.g., in the case of multidrug-resistant bacteria), a rapid desensitization has been proposed with incremental doses of antibiotics. Immune tolerance only lasts for the time of the therapy [37].

### 20.3.5 To Latex

Patients claiming to be allergic to latex or at risk of latex allergy (atopy, latex-fruit syndrome, spina bifida, multiple surgeries) must be referred to an allergy specialist. If the latex allergy is confirmed or if the time between anesthetic assessment and surgery is not compatible with an allergic assessment, the patient must be operated first on the list and a latex-free environment is mandatory. All relevant parties should be warned of the patient's allergy [6]. An updated list of latex-containing equipment must be available in the anesthesiology department.

### 20.3.6 To Morphine or Codeine

Morphine and codeine phosphate are known to induce non-specific skin mast cell activation resulting in pruritus, urticaria, and mild hypotension. This histamine-releasing effect explains why allergic reactions to opioids are over-reported. IgE-mediated reactions to morphine and codeine are rare but remain possible. There is no evidence for cross-reactivity between different subclasses of opioids (phenanthrenes, phenylpiperidines, and diphenylheptanes), but cross-reactivity between morphine and codeine is frequent [38]. Patients claiming an allergy to morphine or codeine should be referred to an allergy specialist for assessment and skin tests. Because of the histamine-releasing effect of morphine and codeine, skin tests are difficult to interpret, and the maximal recommended concentration should not be exceeded. A challenge test should be considered when skin tests are not conclusive [5]. If the patient is allergic to morphine or codeine, they are both contraindicated, but other opioids remain available [6].

### 20.3.7 To Iodine

Iodine is not an antigenic determinant per se. The patient may be allergic to iodinated contrast media or to povidone-iodine, used as skin disinfectant. The patient should be questioned in order to determine whether the reaction occurred during an imaging session or skin disinfection.

If iodinated contrast media are suspected, the patient should be investigated using skin tests and in vitro tests for diagnosis of both immediate and non-immediate reactions. Drug provocation tests are possible. Cross-reactivity between iodinated contrast media is frequent and this should be considered for testing [39].

Hypersensitivity to povidone-iodine is rare. The allergenic determinant is mainly povidone for immediate hypersensitivity reactions, but nonoxynol may also be involved in non-immediate hypersensitivity reactions. Skin tests are useful for diagnosis. In the case of allergy to povidone-iodine, an avoidance strategy is appropriate. Other skin disinfectants such as chlorhexidine can be used. There is currently no evidence for cross-reactivity between iodinated drugs.

### 20.3.8 To Seafood (Fish, Shellfish)

There is no relation between seafood allergy and iodinated drug allergy. These drugs can be used safely in patients declaring seafood allergies [40].

Protamine sulfate is frequently responsible for non-IgE-mediated hypersensitivity reactions. Protamine allergy is also possible and protamine sulfate is contraindicated if the allergy is documented. Conversely there is no evidence suggesting that protamine sulfate should be avoided in case of fish allergy [6, 41].

### 20.3.9 To Egg or Soy

Egg lecithin and soy oil are currently used for the fatty emulsified formulation of propofol. Although rare, several cases of propofol hypersensitivity reactions have been described, and some of them were attributed to cross sensitization with food allergies. Food allergies are increasing in the general population and egg and soy are often found to be responsible for these allergies. Anesthetists exclude propofol from the anesthetic protocol because of the fear of cross-reactions between food allergies to soy or egg and propofol.

There is currently no evidence to support this assumption. Two recent studies showed that the use of propofol in patients with egg or soy allergy was not associated with an increased risk of hypersensitivity reaction, so propofol appears to be safe for these patients [42, 43].

### 20.3.10 To Red Meat or Alpha-gal Protein

Red meat allergy is rare (only 3% of food allergies) and beef is the most common meat allergy. This allergy is associated with hypersensitivity reactions to bovine-derived gelatin drugs such as gelatin colloids or the stabilizing agents in some vaccines. The carbohydrate determinant galactose-alpha-1,3-galactose (alpha-gal) was found to be a potential mediator of the onset of red meat allergy. Consequently, gelatin colloids should be avoided in patients reporting a red meat allergy [44, 45].

### 20.3.11 To Peanut

Cross sensitization between peanut and anesthetic drugs has never been described. No adjustment is required in these patients.

## 20.4 Management of Hypersensitivity Reactions During Anesthesia

Immediate hypersensitivity reactions are recognizable by the association of suggestive symptoms (Table 20.2) and a chronological relation between exposure to an antigen and the reaction.

**Table 20.2** Symptoms of immediate hypersensitivity reactions according to their severity grade

| Severity grade | Symptoms |
|---|---|
| I | Cutaneous signs: erythema, urticaria with or without angioedema |
| II | Presence of measurable but not life-threatening symptoms: cutaneous effects, arterial hypotension, cough, or difficulty in mechanical ventilation |
| III | Presence of life-threatening symptoms: cardiovascular collapse, tachycardia or bradycardia, arrhythmia, severe bronchospasm |
| IV | Circulatory failure, cardiac and/or respiratory arrest |

**Table 20.3** Doses of epinephrine according to the severity of the reaction

| | |
|---|---|
| Grade I | No epinephrine |
| Grade II | Epinephrine 10–20 µg every 1–2 min |
| Grade III | Epinephrine 100–200 µg every 1–2 min |
| Grade IV | Epinephrine 1–2 mg every 1–2 min |

Consider relay with intravenous infusion of epinephrine at a dose of 0.05–0.1 µg/kg/min.

When an immediate hypersensitivity reaction is suspected, anesthetists must rapidly initiate the appropriate treatment. The treatment of these reactions has been well codified in guidelines from ENDA/EAACI in 2011 [6].

General resuscitative measures should be applied in all cases, and the treatment should be adapted to the clinical severity and patient history. All suspected drugs should be withdrawn. The surgical team should be informed and the decision to continue surgery or not should be taken together, considering the severity of the reaction. Assistance should be requested in case of severe reactions.

Treatment of immediate hypersensitivity reactions includes:

- 100% oxygen administration and rapid airway control if necessary.
- Passive leg raising and then vascular filling with rapid infusion of crystalloids. Colloids are used when vascular filling with crystalloids exceeds 30 mL/kg. Colloid products suspected to induce allergic reactions should be avoided.
- Direct administration of intravenous bolus epinephrine every 1–2 min until the restoration of good hemodynamics. The initial dose depends on the severity of the reaction (Table 20.3). An intravenous infusion of epinephrine is possible in relay at a dose of 0.05–0.1 µg/kg/min. For patients on beta-blockers, the dose of epinephrine must be increased.
- In case of refractory hypotension despite epinephrine, combination with methylene blue (1–3 mg/kg) may be helpful [46, 47].
- Sugammadex has been suggested as an effective treatment for suspected reaction to steroidal NMBAs (rocuronium and vecuronium), but this remains very controversial. Skin tests and basophil activation tests have failed to confirm any efficacy, and clinical cases of a lack of effect have been reported [48, 49]. However, allergic reactions to sugammadex and several cases of a worsening of the reaction after sugammadex administration have been described. It should be used carefully and only in case of reactions resistant to epinephrine [50].

- Cardiac arrests should be treated according to current guidelines.
- Corticosteroids (200 mg hydrocortisone every 6 h) are a second-line treatment and may prevent late manifestation of shock.
- For grade I reactions, $H_1$ antihistamines might be helpful.

Because of the risk of labile blood pressure, intensive monitoring should be maintained at least 24 h after the reaction.

Increase doses of epinephrine if the patient is receiving beta-blockers

**Conclusion**

Despite its low incidence, the risk of perioperative anaphylaxis should not be ignored because of the significant associated morbidity/mortality. Claimed allergies, often overreported and under-investigated, are confusing and anesthetists must bear in mind the recommended management for each allergen. When they occur, perioperative immediate hypersensitivity reactions must be treated in accordance with current guidelines, and an allergo-anesthetic assessment is mandatory after the reaction.

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# The Addicted Patient

# 21

Pierre Beaulieu

## 21.1 Introduction

Most drugs of abuse can alter a person's thinking and judgment, leading to health risks, including addiction, drugged driving, and infectious disease. Addiction can be defined as a form of maladaptive memory [1]. It begins with the administration of substances (e.g., cocaine) that directly and intensely activate brain reward circuits. Most of those who initiate drug use do not progress to become addicts, but many variables operate simultaneously to influence the likelihood of developing an addiction (Table 21.1, [1]).

Furthermore, abuse of tobacco, alcohol, and illicit drugs is costly. In the USA it is more than $700 billion annually spent in costs related to crime, lost work productivity, and healthcare [2].

Addiction was historically viewed as a disease of "weak personality" and was not systematically addressed by the scientific and medical communities until the latter half of the twentieth century. Addictions are now commonly accepted as diseases of the brain caused by the impact of the drug itself on the brain and modified by various environmental factors (see Table 21.1). Further, the presence of specific variants of multiple genes may enhance or decrease the vulnerability to developing specific addictions [3].

Epidemiology provides the foundation for understanding drug use, abuse, and dependence by demonstrating the distribution and determinants of these disorders. Recent findings from several studies of nationally representative samples in the USA reveal that the lifetime prevalence of alcohol use disorders is approximately 8%, and illicit drug use disorders is 2–3% [4].

P. Beaulieu, M.D., Ph.D., F.R.C.A.
Department of Anesthesiology, Faculty of Medicine and CHUM, Montreal, QC, Canada
e-mail: pierre.beaulieu@umontreal.ca



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**Table 21.1** Variables affecting onset and continuation of drug abuse and addiction (reproduced from [1], with permission)

| |
|---|
| *Agent (drug)* |
| Availability |
| Cost |
| Purity/potency |
| Mode of administration |
| Chewing (absorption via oral mucous membranes) |
| Gastrointestinal |
| Intranasal |
| Subcutaneous and intramuscular |
| Intravenous |
| Inhalation |
| Speed of onset and termination of effects (pharmacokinetics: combination of agent and host) |
| *Host (user)* |
| Heredity |
| Innate tolerance |
| Speed of developing acquired tolerance |
| Likelihood of experiencing intoxication as pleasure |
| Metabolism of the drug (nicotine and alcohol data already available) |
| Psychiatric symptoms |
| Prior experiences/expectations |
| Propensity for risk-taking behavior |
| *Environment* |
| Social setting |
| Community attitudes |
| Peer influence, role models |
| Availability of other reinforcers (sources of pleasure or recreation) |
| Employment or educational opportunities |
| Conditioned stimuli: environmental cues become associated with drugs after repeated use in the same environment |

Furthermore, in 2014, an estimated 27.0 million Americans aged 12 or older were current (past month) illicit drug users. The most commonly used illicit drug in the past month was marijuana, which was used by 22.2 million people aged 12 or older. An estimated 6.5 million people reported nonmedical use of psychotherapeutic drugs in the past month, including 4.3 million nonmedical users of prescription pain relievers (Fig. 21.1).

These addicted patients may present for anesthetic care in a variety of circumstances: in obstetrics for labor or cesarian sections, in trauma for emergency surgeries, in lifesaving situations (resuscitation), and in everyday elective surgeries. Therefore, it is important for anesthesiologists to know about the most common illicit drugs being used, their clinical presentation and side effects, and to know what anesthetic options would be beneficial or detrimental [5].

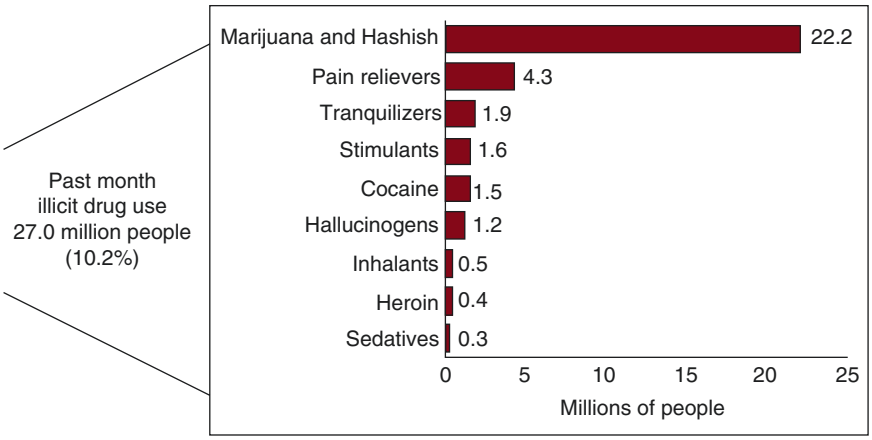


**Fig. 21.1** Numbers of past month illicit drug users among people aged 12 or older in 2014 in the USA. From Center for Behavioral Health Statistics and Quality [47], with permission

In this chapter, we present some of the most frequently used illicit substances and their effects and importance for anesthesiologists. We also discuss the management of addicted patients prior to administering anesthesia or analgesia, allowing us to predict adverse drug interactions, predict tolerance to some anesthetic agents, and recognize drug withdrawal signs and symptoms.

### 21.1.1 Neurobiology of the Addicted Patient

All drugs of abuse affect the brain's "reward circuit," with the mesolimbic dopamine pathway being of particular importance. This pathway includes dopaminergic neurons extending from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) [6]. Dopamine levels that are either too high or too low are suboptimal and may lead to impulsive and risk-taking acts including excessive substance use. Natural rewards and abused substances appear to induce similar activity in reward circuitry and connected regions, including the amygdala, hippocampus, and frontal cortex [6]. Furthermore, the crucial role of other neurotransmitters (e.g., glutamate, GABA, cannabinoids, opioids, serotonin) in reward processing and in the neuroadaptations associated with addiction has recently been appreciated [7]. It is now recognized that drugs of abuse disrupt (either increasing or decreasing) the strength of excitatory synapses by tapping into traditional mechanisms of plasticity, including long-term potentiation (LTP) and long-term depression (LTD) [7].

Synaptic plasticity is controlled presynaptically through the regulation of glutamate release and postsynaptically through the insertion or removal of AMPA or NMDA glutamate receptors, and drugs of abuse interfere with these processes [8]. The shift from normal healthy desire to drug craving with increased levels of drug use is also associated with changes in limbic, striatal, and cortical brain systems [9].

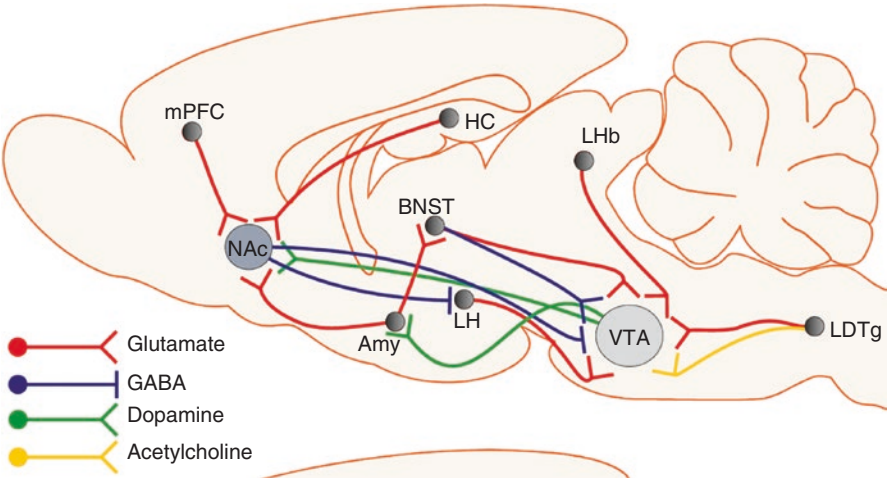


**Fig. 21.2** Brain regions of major importance for the acute and chronic addictive effects of drugs of abuse. Reproduced from Parsons and Hurd [10], with permission. The drawing shows many pathways that participate in rewarding/drug-seeking behavior. *Amy* amygdala, *BNST* bed nucleus of stria terminalis, *HC* hippocampus, *LDTg* laterodorsal tegmental nucleus, *LH* lateral hypothalamus, *LHb* lateral habenula, *mPFC* medial prefrontal cortex, *NAc* nucleus accumbens, *VTA* ventral tegmental area

Mesocorticolimbic dopamine pathways, which arise from the midbrain VTA, have a critical role in the mediation of reward. In particular, the VTA dopamine projection to the NAc (part of the ventral striatum) has a prominent role in positive reinforcement (Fig. 21.2). In brief, amygdala circuits contribute to the formation of associative reward- and fear-related memories, hippocampal circuits are critical for declarative memory functions, and frontal cortical circuits mediate control of executive functions. In turn, innervation of the NAc by each of these circuits allows sensory and emotional information to be converted into motivational actions through the output to extrapyramidal motor systems. Dopamine signaling in the dorsal striatum has a key role in the development of compulsive forms of reward seeking and consumption [10].

Natural rewards, such as food, sex, and exercise, and drugs of abuse—including psychostimulants (such as cocaine and amphetamine), nicotine, alcohol, opioids, and cannabinoids—increase NAc dopamine levels, and this neurochemical response contributes to subjective reward and positive reinforcement [11]. Furthermore, certain mechanisms seem to be common for many drugs, for example, activation of the extracellular signal-regulated kinase (ERK) pathway in specific brain structures is necessary for effects of and tolerance to cocaine, nicotine, MDMA, phencyclidine, alcohol, and cannabinoids after both acute and chronic treatments in rodents [10].

Finally, genes account for about 50% of a person's risk of becoming addicted, and environmental factors influence the effect of these genes—an area of research called epigenetics. Progress in genetics/epigenetics research will lead to more refined prevention and treatment interventions targeted to individual risk or to modifiable environmental influences [2].

### 21.1.2 Psychological Aspects of the Addicted Patient

Like most other mental health problems, drug use disorders have no single cause. However, there are a number of biological, psychological, and social factors, known as risk factors, that can increase an individual's vulnerability to developing a chemical use disorder. Psychologically, intoxication with or withdrawal from a substance can cause everything from euphoria as with alcohol, ecstasy, or inhalant intoxication, to paranoia with marijuana or steroid intoxication, to severe depression or suicidal thoughts with cocaine or amphetamine withdrawal [12]. Epidemiological studies found the prevalence of substance use disorder, a common key feature of several serious psychiatric illnesses such as bipolar disorder, schizophrenia, major depressive disorder, and attention deficit hyperactivity disorder, to be high compared to the general population [13]. Furthermore, it seems that psychiatric diseases make the brain more susceptible to addiction. This observation is supported by studies in animal models suggesting that psychiatric disorders potentiate behavioral and reinforcing effects of drug of abuse [13].

There are many forms of evidence-based behavioral treatments for substance abuse. Some of the most strongly supported include *cognitive behavioral therapy* (CBT) that can help addicted patients overcome substance abuse by teaching them to recognize and avoid destructive thoughts and behaviors, *motivational interviewing* that involves structured conversations that help patients increase their motivation to overcome substance abuse, and *contingency management* that provides tangible incentives to encourage patients to stay off drugs [14]. These behavioral treatments can sometimes be particularly effective when combined with pharmaceutical treatments that either mimic the effects of the drug in a controlled way (such as methadone and buprenorphine for opioid addiction or nicotine chewing gum for cigarette addiction) or reduce or eliminate the "high" the user gets from the drug (such as naltrexone for opioid or alcohol addiction) [14].

## 21.2 Presentation of the Drugs

As already stated in Sect. 21.1, it is important for anesthesiologists to know about the most common illicit drugs being used, their clinical presentation, and side effects. This information is presented in this section.

### 21.2.1 Alcohol

Ethyl alcohol, or ethanol, is an intoxicating ingredient found in beer, wine, and liquor. Alcohol is produced by the fermentation of yeast, sugars, and starches. It is a central nervous system depressant that is rapidly absorbed from the stomach and small intestine into the bloodstream. Thirty years ago, little was known about the genetic basis of alcohol dependence or the nervous system changes that occur as a result of prolonged heavy drinking. Alcohol dependence was thought to be a disease of middle age. Disulfiram (Antabuse®) was the only medication approved for

treating alcohol dependence, producing acute sensitivity to alcohol. Other treatments included various behavioral approaches, mostly group counseling and referral to Alcoholics Anonymous (AA) [15].

The fifth edition, DSM-5, integrates the two DSM-IV disorders, alcohol abuse and alcohol dependence, into a single disorder called alcohol use disorder (AUD) with mild, moderate, and severe subclassifications.

Concerning the etiology of alcoholism, the disease itself is considered to be a consequence of an interactive influence of the environment and genetic factors.

Recent molecular pharmacology studies demonstrated that alcohol has only a few known primary targets: NMDA, $GABA_A$, glycine, serotonin, and nicotinic receptors as well as L-type $Ca^{2+}$ channels and G-protein-activated inwardly rectifying $K^+$ channels. Addictive behavior toward alcohol as measured by alcohol-seeking and relapse behavior involves the activity of the mesolimbic dopaminergic system which plays a crucial role during the initiation phase of alcohol consumption. Following long-term, chronic alcohol consumption virtually all brain neurotransmission seems to be affected, making it difficult to define which of the systems contributes the most to the transition from controlled to compulsive alcohol use. However, compulsive alcohol drinking is characterized by a decrease in the function of the reward neurocircuitry and a recruitment of antireward/stress mechanisms comes into place, with a hypertrophic corticotropin-releasing factor system and a hyperfunctional glutamatergic system being the most important ones [16].

Alcohol affects every organ in the drinker's body and can damage a developing fetus. Intoxication can impair brain function and motor skills; heavy use can increase risk of certain cancers, stroke, and liver disease. Alcoholic liver disease (ALD) is a major cause of chronic liver disease, leading to cirrhosis and liver cancer. The spectrum of ALD includes steatosis, alcoholic steatohepatitis (ASH), cirrhosis, and hepatocellular carcinoma (HCC) [17]. Alcohol metabolism involves several enzymes, including alcohol dehydrogenase, acetaldehyde dehydrogenase, and CYP2E1. Since the risk of developing ALD is mediated by genetic polymorphisms in these enzymes, an understanding of the genetic predisposition of the individual is required. Moreover, CYP2E1 is involved in the metabolism of various other drugs, potentiating drug-drug interactions. Another important aspect of ALD progression is its comorbidity with chronic viral hepatitis. The interaction between alcohol and medications used to treat HCV can exacerbate the degree of hepatotoxicity [17].

Efforts to develop medications for alcohol use disorders have expanded rapidly in recent years. In addition to *disulfiram, naltrexone* and *acamprosate* are now approved for use in treating alcohol dependence. When used in conjunction with behavioral therapies, medications improve the chance for recovery and the lives of those who suffer from alcohol dependence. Several behavioral approaches, such as motivational enhancement therapy, cognitive behavioral therapy, and twelve-step facilitation therapy, are effective in treating alcohol dependence [15].

### 21.2.2 Cannabis

The cannabis plant, which is also known as hemp or marijuana, is one of the oldest documented medicines in history. Cannabis contains 545 chemical compounds of which 104 are cannabinoids, the rest being flavonoids, terpenes, fatty acids, and more, all with potential medical uses. The best-characterized constituent is $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC), the principal psychoactive component of cannabis. Other important constituents include cannabidiol (CBD) and cannabinol (CBN). The former lacks psychoactive capabilities, whereas the latter is a mildly psychoactive chemical. Cannabinoids produce their effects through the activation of two distinct G-protein-coupled receptors termed cannabinoid $CB_1$ and $CB_2$ receptors. The $CB_1$ receptor is expressed, at high levels, in the central nervous system (CNS) and along pain pathways, whereas the $CB_2$ receptor is found predominantly, although not exclusively, outside the CNS, where it is most densely expressed in peripheral tissues with immune functions. The isolation of endogenous ligands (endocannabinoids), mainly anandamide and 2-arachidonoylglycerol, completed the discoveries in the cannabinoid field [18].

In animal models, both $\Delta^9$-THC and synthetic $CB_1$ receptor agonists enhance brain reward function, produce rewarding effects in the paradigm of conditioned place preference (CPP), and are voluntarily self-administered (intravenously and also directly into the NAc shell and posterior VTA) [19]. These effects are critically reliant on $CB_1$ receptor signaling and are highly dose sensitive, with a rapid shift to negative reinforcing effects with increasing dose. Although enhancement of endocannabinoid (eCB) levels does not produce rewarding effects per se, eCB signaling at cannabinoid receptors participates in the mediation and modulation of both natural and drug-induced reward. Long-term drug use leads to neuroadaptive downregulation of eCB signaling resulting from diminished $CB_1$ receptors and/or $CB_2$ receptor function as well as possible disruptions in eCB biosynthesis and/or clearance [10].

Cannabis is the most widely used illicit drug in the world. Furthermore, approximately 100 million Americans have used illicit marijuana, with 8–10% developing cannabis dependence [20]. Marijuana has medicinal effects [21], including antiemetic properties, muscle-relaxing and anticonvulsant properties, and pain-relieving properties [22]. These medical benefits come at the cost of many side effects, especially psychoactive ones.

Tolerance to most of the effects of cannabis can develop rapidly after only a few doses but also disappears rapidly. Withdrawal symptoms consist of restlessness, irritability, mild agitation, insomnia, nausea, and cramping [1]. It affects only heavy smokers (on a daily basis) who suddenly stop taking it. No specific treatment has been proposed.

### 21.2.3 Cocaine

Cocaine is a powerfully addictive stimulant drug made from the leaves of the coca plant native to South America. Although healthcare providers can use it for valid medical purposes, such as local anesthesia for some surgeries, cocaine is an illegal

drug. Street dealers may mix it with other drugs such as amphetamine. People snort cocaine powder through the nose or rub it into their gums. Others dissolve it in water and inject it or inject a combination of cocaine and heroin, called a speedball. Another popular method of use is to smoke crack cocaine [23].

Cocaine increases levels of dopamine in brain circuits controlling pleasure and movement. Short-term effects include vasoconstriction, hypertension, tachycardia, nausea and abdominal pain, extreme happiness, increased energy and body temperature, irritability, and paranoia. Long-term effects include epistaxis, higher risk of contracting HIV, hepatitis C, other blood-borne diseases, malnourishment, restlessness, and severe paranoia with auditory hallucinations. Withdrawal symptoms include depression, tiredness, increased appetite, insomnia, vivid unpleasant dreams, slowed thinking and movement, and restlessness.

While no government-approved medicines are currently available to treat cocaine addiction, researchers are testing some treatments, including *disulfiram, modafinil*, and *lorcaserin* (used to treat obesity). Furthermore, cognitive behavioral therapy (CBT), community reinforcement approach, contingency management, or motivational incentives, the matrix model and step facilitation therapy are psychological approaches also used.

### 21.2.4 Heroin and Prescription Opioids

In the decades before 1990, physicians were criticized for undertreating pain. In the late 1990s, however, there was a paradigm shift. Pain came to be referred to as the "fifth vital sign," and physicians were encouraged to address and aggressively treat pain [24]. Since that time, opioid prescribing, along with opioid sales, and associated complications have increased worldwide. The current state of opioid therapy and abuse continues to increase the tension between the twin challenges of opioid therapy for chronic pain and its abuse leading to dependency, addiction, hyperalgesia, and death among other various complications [25]. Therefore, opioid abuse has become a significant public health problem globally, specifically in the USA and Canada. Estimates suggest that more than 10% of chronic pain patients misuse opioid analgesics. Furthermore, in the USA from 1999 to 2011, consumption of hydrocodone more than doubled and consumption of oxycodone increased by nearly 500% [26]. During the same time frame, the opioid pain reliever-related overdose death rate nearly quadrupled. According to the US Centers for Disease Control and Prevention (CDC), the unprecedented increase in consumption has led to the "worst drug overdose epidemic in US history" [26]. Given the magnitude of the problem, in 2014 the CDC added opioid overdose prevention to its list of top five public health challenges.

Possible reasons for this "opioid epidemic" have been proposed (Table 21.2) [27].

Furthermore, the problem of co-occurring chronic pain and opioid addiction involves a cycle of behavioral escalation in which nociception triggers pain hypervigilance and catastrophizing, amplifying pain with emotional anguish (Fig. 21.3) [28]. Recurrent self-administration of opioids in response to pain and negative emotions results in associative learning processes that bias attention toward

**Table 21.2** Possible reasons for the US opioid epidemic (from [27], with permission)

| | |
|---|---|
| Physician related | Inadequate and inaccurate training on opioid pharmacology and risks |
| | Lack of access to multidisciplinary chronic pain care |
| | Ease of prescribing opioids compared to other chronic pain therapies |
| Patient related | Strong appeal of immediate pain relief provided by opioids |
| | Focus on pain rather than psychological distress as a treatment target |
| | More value placed on pain relief that functional improvement |
| Society and health system related | Acceptance of right to pain treatment and interpretation of this right in terms of access to opioid therapy |
| | Better insurance coverage for medication than for other chronic pain therapies |
| | Aggressive marketing of sustained-release opioids by pharmaceutical companies |

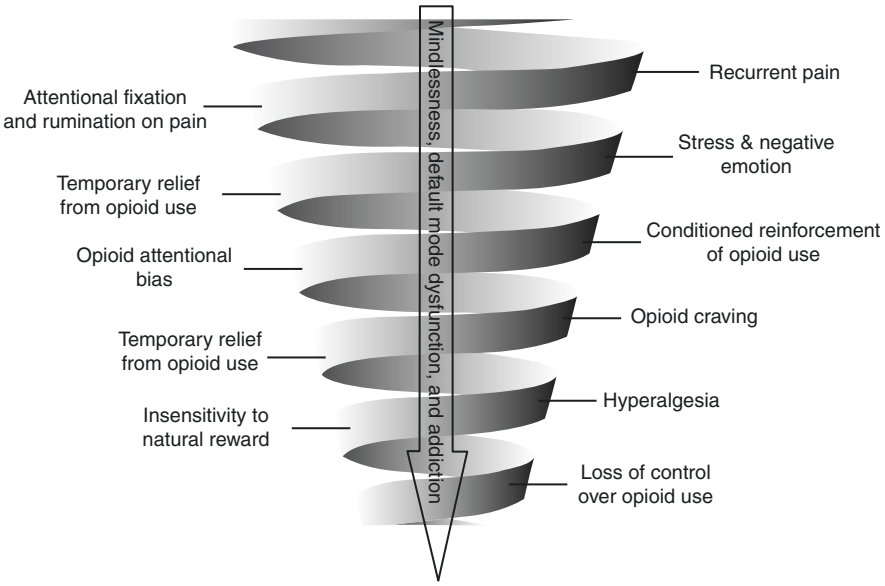


**Fig. 21.3** The downward spiral of chronic pain and opioid addiction. From Garland et al. [28] with permission

opioid-related cues, strengthening the habit of opioid use despite tolerance to opioid analgesia. This downward spiral may ultimately result in mindless, uncontrolled opioid use and addiction.

Opioids are a class of drugs that include the illegal drug heroin as well as powerful analgesics available legally by prescription, such as morphine, codeine,

hydrocodone, hydromorphone, oxycodone, buprenorphine, fentanyl, or methadone. Tramadol is also used, although it is not only an opioid agonist but also an adrenaline and serotonin reuptake inhibitor at the spinal level. These drugs are chemically related and interact with opioid receptors (mu, kappa, and delta) on nociceptors at peripheral, spinal, and brain levels. The mu receptor is primarily responsible for the analgesic and euphoric properties of opioids, and many of the opioid analgesics in use today are full mu agonists (morphine, hydromorphone, oxycodone). Buprenorphine is a partial mu agonist that was approved as an office-based treatment for opioid dependence. Because it is a partial agonist, there is less risk of overdose, and long-term use is associated with less severe withdrawal symptoms [24].

Opioid analgesics are generally safe when taken for a short time and as prescribed by a doctor, but they are frequently misused (taken in a different way or in a greater quantity than prescribed or taken without a doctor's prescription) because they produce euphoria in addition to pain relief [29].

Opioids are available in a wide range of formulations: short-acting orally administered opioids (e.g., immediate-release morphine, hydromorphone, codeine, fentanyl, hydrocodone, and oxycodone) with a rapid onset of action (10–60 min) and a relatively short duration of action (2–4 h), used for acute or breakthrough pain, and extended-release or long-acting opioids with a slower onset of action (30–90 min) and a longer duration of action (4–72 h), typically used for chronic pain conditions [24]. In an attempt to reduce the risk of opioid abuse, PO formulations containing both a strong opioid and an opioid antagonist have been developed in the USA [30]:

Suboxone® (buprenorphine-naloxone) given SL for opioid dependency.
Embeda® (morphine-naltrexone).
Targinact® (oxycodone-naloxone).
OxyNal® (oxycodone-naltrexone).

Specific recommendations to enhance efforts to prevent opioid abuse include [25] (1) prescriber and patient education, (2) careful initiation of opioid therapy in acute pain with limited duration therapy, (3) appropriate initiation and maintenance of chronic opioid therapy, (4) prescription drug monitoring programs, (5) opioid overdose prevention strategies, and (6) expansion of access to medications for addiction treatment and use of abuse-deterrent technology. In addition, best-practice recommendations from a variety of professional societies recognize the need to balance the benefits of opioids in managing pain with the potential risks conferred, particularly by chronic use. Recommendations support the universal application of risk mitigation strategies.

Factors associated with increased risk of prescription opioid abuse in cross-sectional studies include younger age (18–25 years), male gender, psychiatric disorders (e.g., depression, bipolar disorder), exposure to violence or sexual assault, a history of substance use disorders (in particular illegal drug use), and a family history of substance use disorder [24].

At some point, patients suffering from chronic pain may have to undergo a surgical procedure related to their condition, such as prosthetic replacement because of arthritis, or a procedure unrelated to the initial chronic lesion, such as cardiac or trauma surgery [31]. Optimal perioperative management is directed toward preventing inadequate pain relief due to an inadequate dosage of opioids.

### 21.2.5 Hallucinogens (Ketamine)

Hallucinogens are a diverse group of drugs that alter perception (awareness of surrounding objects and conditions), thoughts, and feelings. They cause hallucinations or sensations and images that seem real though they are not. Hallucinogens can be found in some plants and mushrooms or synthetized. Common hallucinogens include dimethyltryptamine (DMT), D-lysergic acid diethylamide (LSD), peyote (mescaline), psilocybin, and ketamine [32].

Hallucinogens interfere with actions of brain chemicals responsible for functions that include mood, sensory perception, sleep, body temperature, muscle control, pain perception, and memory. The effects of hallucinogens can begin within 20–90 min and can last as long as 6–12 h. Along with hallucinations, other short-term effects of hallucinogens include increased heart rate, nausea, intensified feelings and sensory experiences, and changes in sense of time. Persistent psychosis and flashbacks are two long-term effects associated with some hallucinogens. Evidence indicates that certain hallucinogens can be addictive or that people can develop a tolerance to them [32].

Ketamine is a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptor and has been long used as an anesthetic agent in humans and veterinary medicine. In addition, ketamine, as a dissociative anesthetic, has a unique psychological effect which displays both mood controlling and reinforcing properties [33]. The use of subanesthetic ketamine infusions has been extended from treatment-resistant depression to bipolar disorder, anxiety, and chronic pain. Furthermore, a number of studies have demonstrated a significant and rapid antidepressant effect of ketamine. Ketamine has become a recreational drug in the context of "raves," and the nonmedical use of ketamine has grown steadily worldwide in the past a few decades. It is hypothesized that ketamine blocks NMDA receptors on γ-aminobutyric acid (GABA) neurons inside the thalamic reticular nucleus, which leads to disinhibition of dopaminergic neurons and increased release of dopamine.

The recreational use of ketamine has increased dramatically in many parts of the world. In the USA, it is estimated that approximately 2.3 million teens and adults have used ketamine in their lifetime. Furthermore, the number of ketamine-related death has increased tenfolds in the UK from 1999 to 2008 [33]. Although ketamine is a relatively safe substance in medical settings, its abuse has posted severe harms on individuals and society. One of the major concerns is driving under the influence of ketamine. Indeed, the popularity of ketamine as a club drug has led to increased reports of driving under the influence of ketamine, the drug being the third most used illicit drugs among drivers tested positive for psychoactive drugs in Shanghai,

China [33]. Currently, there is no specific treatment for treating patients who abuse ketamine, but antibiotics, nonsteroidal anti-inflammatory drugs, steroids, and anticholinergic drugs have been demonstrated to be effective.

### 21.2.6 Ecstasy

*3,4-Methylenedioxy-methamphetamine* (MDMA) is a synthetic drug that alters mood and perception (awareness of surrounding objects and conditions). It is chemically similar to both stimulants and hallucinogens, producing feelings of increased energy, pleasure, emotional warmth, and distorted sensory and time perception [34]. MDMA is a commonly used illicit drug and is the sole or one of the ingredients in ecstasy or "molly." MDMA is commonly consumed on weekends in warm crowded environments and combined with dancing. While MDMA is common agent of abuse, the risk of serious adverse events is lower than other illicit agents. Furthermore, the risk of adverse events for a single tablet or powder packet of MDMA is not a precise science due to the inability to assure purity, potency, unadulteration, and stability of products [35]. Indeed, from the late 1990s to today, 80–90% of the tablets sold as MDMA contain MDMA although the doses in tablets are highly variable. MDMA interacts with monoamine transporters to stimulate non-exocytotic release of serotonin, dopamine, and norepinephrine in the brain. This causes an elevation of mood and increased energy while also causing the secretion of numerous hormones including cortisol, oxytocin, and antidiuretic hormone [35]. Presumably, MDMA-induced cortisol elevations enhance the feeling of increased energy and lack of fatigue. While most people derive a raised mood, increased energy, and pleasant visual hallucinations from MDMA, anxiety and panic attacks have been reported. The panic attacks usually resolve within a few hours, but in rare case they have persisted for several months. Hyperpyrexia resulting in rhabdomyolysis or heat stroke has occurred due to serotonin syndrome or enhanced physical activity without recognizing clinical clues of overexertion, warm temperatures in the clubs, and dehydration. Hyponatremia can occur from free water uptake in the collecting tubules secondary to the ADH effects and from over consumption of water to prevent dehydration and overheating. Dilutional hyponatremia can induce mental status changes and, as a result of cerebral edema, can induce seizures and coma [35].

Other adverse effects of MDMA include metabolic acidosis, hypertension, arrhythmias, and disseminated intravascular coagulopathy.

### 21.2.7 Tobacco

Tobacco use is the leading preventable cause of disease, disability, and death in the USA. According to the Centers for Disease Control and Prevention (CDC), cigarette smoking results in more than 480,000 premature deaths in the USA each year—about one in every five US deaths—and an additional 16 million people

suffer with a serious illness caused by smoking. In fact, for every one person who dies from smoking, about 30 more suffer from at least one serious tobacco-related illness [36].

Tobacco smoke is a complex mixture of chemicals such as carbon monoxide, tar, formaldehyde, cyanide, and ammonia—many of which are known carcinogens.

Cigarette smoking accounts for about one-third of all cancers, including 90% of lung cancer cases. Smokeless tobacco (such as chewing tobacco and snuff) also increases the risk of cancer, especially oral cancers. In addition to cancer, smoking causes lung diseases, such as chronic bronchitis and emphysema, and increases the risk of heart disease, including stroke, heart attack, vascular disease, and aneurysm [37]. Smoking has also been linked to leukemia, cataracts, and pneumonia. On average, adults who smoke die 10 years earlier than nonsmokers.

Behavioral treatments employ a variety of methods to help smokers quit, ranging from self-help materials to counseling. Nicotine replacement therapies (NRTs) were the first pharmacological treatments approved by the Food and Drug Administration (FDA) for use in smoking cessation therapy. Current FDA-approved NRT products include nicotine chewing gum, the nicotine transdermal patch, nasal sprays, inhalers, and lozenges. They are most successful when used in combination with behavioral treatments. *Bupropion* and *varenicline* are two FDA-approved non-nicotine medications that have helped people quit smoking.

Scientists are currently developing new smoking cessation therapies. For example, they are working on a nicotine vaccine, which would block nicotine's reinforcing effects by causing the immune system to bind to nicotine in the bloodstream preventing it from reaching the brain.

### 21.2.8 Methamphetamine and Stimulant Medications (Amphetamines and Methylphenidate)

Methamphetamine (also called meth, crystal, chalk, and ice, among other terms) is an extremely addictive stimulant drug that is chemically similar to amphetamine. It takes the form of a white, odorless, bitter-tasting crystalline powder. Methamphetamine is taken orally, smoked, snorted, or dissolved in water or alcohol and injected. Smoking or injecting the drug delivers it very quickly to the brain, where it produces an immediate, intense euphoria [38]. Methamphetamine can be prescribed by a doctor to treat attention deficit hyperactivity disorder and other conditions, although it is rarely used medically and only at doses much lower than those typically abused. People who use methamphetamine for long period of time may experience anxiety, confusion, insomnia, and mood disturbances and display violent behavior. They may also show symptoms of psychosis, such as paranoia, visual and auditory hallucinations, and delusions. Long-term methamphetamine use has many negative consequences for physical health, including extreme weight loss, severe dental problems, and skin sores caused by scratching [38].

Stimulant medications including amphetamines (e.g., Adderall®) and methylphenidate (e.g., Ritalin® and Concerta®) are often prescribed to treat children,

adolescents, or adults diagnosed with attention deficit hyperactivity disorder (ADHD). Prescription stimulants have a calming and "focusing" effect on individuals with ADHD. They are prescribed to patients for daily use and come in the form of tablets or capsules of varying dosages. Treatment of ADHD with stimulants, often in conjunction with psychotherapy, helps to improve ADHD symptoms along with the patient's self-esteem, thinking ability, and social and family interactions. Stimulants can increase blood pressure, heart rate, and body temperature and decrease sleep and appetite. When they are abused, they can lead to malnutrition and its consequences. Repeated abuse of stimulants can lead to feelings of hostility and paranoia. At high doses, they can lead to serious cardiovascular complications, including stroke [39].

## 21.3 Perioperative Approach to Patients with Addiction

As the use and abuse of drugs/substances increases, the likelihood of an anesthesiologist encountering addicted patients during clinical practice, perioperatively, also will increase. All anesthetic and analgesic plans can be divided into preoperative considerations, intraoperative management, and postoperative recovery and analgesia. Optimal patient care always begins in the preoperative period with the patient assessment. It is critical to obtain information about patient drug use and other associated treatment in order to construct an appropriate plan. Thereafter, performing appropriate screening and assessment is essential [40]. Table 21.3 provides a summary of the main addicted drugs together with specific anesthetic considerations for each of them [5, 31, 40–47].

For example, it is important to know if the patient has recently been taking his medication (e.g., in the case of long-term opioid therapy), the time of the last dose and at what dosage, or a drug of abuse (cannabis, ecstasy, etc.). Appropriate screening tests, if applicable, are performed. It is crucial to explain to the patient the anesthetic plan, simply explaining how she/he will be managed throughout the perioperative period.

The intraoperative management of an addicted patient should rely on three areas [40]: managing intoxication (if the patient is still intoxicated, especially in emergency surgical situations), preventing or treating withdrawal, and achieving adequate recovery and effective analgesia. For the latter, multimodal analgesia and regional anesthesia are strongly advocated techniques.

In the postoperative period, the goals are patient's comfort and safety. Patient comfort consists of providing adequate analgesia and continued prevention or management of withdrawal (if applicable, as for long-term opioids) [40]. Safety is also a concern as drug (opioid) tolerance is certainly present, and patients will require higher doses with potentially the development of adverse events.

With regard to the frequent situation of chronic intake of opioids, it has a significant impact on postoperative pain management. Chronic pain is frequently associated with anxiety, depression, and polymedication (opioids, NSAIDs, anticonvulsants, antidepressants, muscle relaxants, α-adrenergic agonists,

**Table 21.3** Summary of main factors to consider in commonly abused drugs or substances (modified from NIDA [43] with permission)

| Drug/ substance | Street/other names | Common forms | Short-term effects (acute intoxication) | Long-term effects (chronic intoxication) | Other health effects | Withdrawal symptoms | Behavioral therapy | Medication therapy | Implications for the anesthesiologist |
|---|---|---|---|---|---|---|---|---|---|
| Alcohol | – | Beer, wine, and liquor | Impairment of brain function and motor skills | Increased risk of certain cancers, stroke, and liver disease (steatosis, alcoholic steatohepatitis, cirrhosis, hepatocellular carcinoma) | Presence of ascites, esophageal varices, malnutrition, cardiomyopathy, arrhythmias, pancreatitis, pneumonia, fetal alcohol exposure | Trouble sleeping, shakiness, irritability, anxiety, depression, restlessness, nausea, sweating | Motivational enhancement therapy, cognitive behavioral therapy, 12-step facilitation therapy | Disulfiram, naltrexone, acamprosate | Evaluate electrolytes, liver function, coagulation, ECG, CXR. Resistance to anesthetics in chronic states. CYP2E1 drug interactions. Hypotension from dehydration, cardiomyopathy, or a diminished adrenocortical response to stress. Increased risk of bleeding, aspiration if intoxicated. Withdrawal prophylaxis using lorazepam, haloperidol, clonidine, or dexmedetomidine |

(continued)

**Table 21.3** (continued)

| Drug/ substance | Street/other names | Common forms | Short-term effects (acute intoxication) | Long-term effects (chronic intoxication) | Other health effects | Withdrawal symptoms | Behavioral therapy | Medication therapy | Implications for the anesthesiologist |
|---|---|---|---|---|---|---|---|---|---|
| Cannabis or marihuana or marijuana | Blunt, bud, dope, ganja, grass, green, herb, joint, Mary Jane, pot, reefer, sinsemilla, skunk, smoke, trees, weed; hashish, boom, gangster, hash, hemp | Greenish-gray mixture of dried, shredded leaves, stems, seeds, and/or flowers; resin (hashish) or sticky, black liquid (hash oil) | Enhanced sensory perception and euphoria followed by drowsiness/ relaxation, slowed reaction time, problems with balance and coordination, increased heart rate and appetite, problems with learning and memory, hallucinations, anxiety, panic attacks, psychosis | Mental health problems, chronic cough, frequent respiratory infections | Youth: possible loss of IQ points when repeated use begins in adolescence<br>Pregnancy: babies born with problems with attention, memory, and problem-solving | Irritability, trouble sleeping, decreased appetite, anxiety | Cognitive behavioral therapy<br>Contingency management or motivational incentives<br>Motivational enhancement therapy<br>Behavioral treatments geared to adolescents | No approved medications to treat marijuana addiction | Tachycardia/hypertension (low doses) or bradycardia/ hypotension (high doses). Supraventricular or ventricular ectopic activity and reversible ST segment and T wave abnormalities. Enhanced depression of the CNS with other sedatives. Potential upper airway irritability, edema and obstruction, chronic cough, bronchitis, emphysema, and bronchospasm. Cannabis use increases the propofol dose required for induction when inserting a laryngeal mask. Dexamethasone administration is advocated during surgery. |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Cocaine | Blow, bump, C, candy, Charlie, coke, crack, flake, rock, snow, toot | White powder, whitish rock crystal | Vasoconstriction; mydriasis; increased body temperature, heart rate, and blood pressure; heart attack; stroke, arrhythmias, headache; abdominal pain and nausea; euphoria; increased energy, alertness; insomnia, restlessness; anxiety; erratic and violent behavior, panic attacks, paranoia, psychosis, seizure, coma | Loss of sense of smell, epistaxis, nasal damage, and trouble swallowing from snorting; infection and death of bowel tissue from decreased blood flow; poor nutrition and weight loss from decreased appetite | Pregnancy: premature delivery, low birth weight, neonatal abstinence syndrome.<br>Risk of HIV, hepatitis, and other infectious diseases from shared needles. Chronic nasal cocaine use can cause septal destruction and soft palate necrosis | Depression, tiredness, increased appetite, insomnia, vivid unpleasant dreams, slowed thinking and movement, restlessness | Cognitive behavioral therapy<br>Community reinforcement approach plus vouchers<br>Contingency management or motivational incentives<br>The matrix model<br>Twelve-step facilitation therapy | No approved medications to treat cocaine addiction | Agitation and altered sensorium make regional anesthesia difficult. Cocaine use can induce thrombocytopenia. Hypertension with arrhythmias or hypotension may occur with the latter requiring direct vasopressors such as phenylephrine for control. β-blockers are contraindicated because of the potential for unopposed α-adrenergic stimulation. Dexmedetomidine successfully used to manage hypertension and CNS excitability from withdrawal. There may be altered pain perception. Caution with nasogastric or orogastric tube. Potential pulmonary complications |
| Heroin | Brown sugar, China white, dope, H, horse, junk, skag, skunk, smack, white horse<br>*With OTC cold medicine and antihistamine:* cheese | White or brownish powder or black sticky substance known as "black tar heroin" | Euphoria, warm flushing of skin, dry mouth, heavy feeling in the hands and feet, clouded thinking, alternate wakeful and drowsy states, itching, nausea, vomiting, slowed breathing and heart rate | Collapsed veins, abscesses (swollen tissue with pus), infection of the lining and valves in the heart, constipation and stomach cramps, liver or kidney disease, pneumonia | Pregnancy: miscarriage, low birth weight, neonatal abstinence syndrome<br>Risk of HIV, hepatitis, and other infectious diseases from shared needles | Restlessness, muscle and bone pain, insomnia, diarrhea, vomiting, cold flashes with goose bumps ("cold turkey"), leg movements | Contingency management, or motivational incentives<br>Twelve-step facilitation therapy | Methadone<br>Buprenorphine<br>Naltrexone (short- and long-acting forms) | Difficult peripheral and central venous access. Delayed gastric empting. Sepsis, coagulopathy, and hemodynamic instability may increase the risk associated with general anesthesia. Regional anesthesia advocated. Concomitant liver disease, malnutrition, and reduced intravascular fluid volume. Tolerance to opioid analgesia and opioid-induced hyperalgesia: give opioids (high doses) and ketamine |

(continued)

**Table 21.3** (continued)

| Drug/ substance | Street/other names | Common forms | Short-term effects (acute intoxication) | Long-term effects (chronic intoxication) | Other health effects | Withdrawal symptoms | Behavioral therapy | Medication therapy | Implications for the anesthesiologist |
|---|---|---|---|---|---|---|---|---|---|
| Ketamine | Cat valium, K, special K, vitamin K | Liquid, white powder | Problems with attention, learning, and memory; dreamlike states, hallucinations; sedation; confusion and problems speaking; loss of memory; problems moving; raised blood pressure; unconsciousness; slowed breathing | Ulcers and pain in the bladder; kidney problems; stomach pain; depression; poor memory | Sometimes used as a date rape drug. Risk of HIV, hepatitis, and other infectious diseases from shared needles | Unknown | More research is needed to find out if behavioral therapies can be used to treat addiction to dissociative drugs | There are no approved medications to treat addiction to ketamine or other dissociative drugs | Benzodiazepines and haloperidol can be used. Contrary to classical teaching, ketamine does not increase intracranial pressure in brain injury |
| MDMA/ ecstasy | Adam, clarity, Eve, lover's speed, peace, uppers | Colorful tablets with imprinted logos, capsules, powder, liquid | Lowered inhibition; enhanced sensory perception; confusion; depression; sleep problems; anxiety; increased heart rate and blood pressure; muscle tension; teeth clenching; nausea; blurred vision; faintness; chills or sweating; rise in body temperature, liver, kidney, or heart failure and death | Long-lasting confusion, depression, problems with attention, memory, and sleep; increased anxiety, impulsiveness, aggression; loss of appetite; less interest in sex | Unknown | Fatigue, loss of appetite, depression, trouble concentrating | More research is needed to find out if behavioral therapies can be used to treat MDMA addiction | There is conflicting evidence about whether MDMA is addictive. There are no approved medications to treat MDMA addiction | Nondepolarizing muscle relaxants, benzodiazepines, and propofol are safe. Monitor temperature. Treatment with dantrolene is controversial but may be used. Correct hyponatremia slowly. Creatine kinase or myoglobin levels can be used for suspected rhabdomyolysis. Spontaneous pneumothorax and pneumomediastinum have been reported |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Metham-phetamine | Crank, chalk, crystal, fire, glass, go fast, ice, meth, speed | White powder or pill; crystal meth looks like pieces of glass or shiny blue-white "rocks" of different sizes | Increased wakefulness and physical activity; decreased appetite; increased breathing, heart rate, blood pressure, temperature; arrhythmias | Anxiety, confusion, insomnia, mood problems, violent behavior, paranoia, hallucinations, delusions, weight loss, severe dental problems, intense itching | Pregnancy: premature delivery; separation of the placenta from the uterus; low birth weight; lethargy; heart and brain problems. Risk of HIV, hepatitis, and other infectious diseases | Depression, anxiety, tiredness | Cognitive behavioral therapy (CBT)<br>Contingency management or motivational incentives<br>The matrix model<br>Twelve-step facilitation therapy | There are no approved medications to treat methamphetamine addiction | Pulmonary diseases and pulmonary hypertension reported. Caution with nasogastric tubes. Hemodynamic instability with evidence to continue prescription amphetamines during the perioperative period. Cardiomyopathy and myocardial ischemia reported |
| Opioids (prescription) | Many names | Tablet, liquid, capsule, suppository, lozenge, sublingual tablet, film, buccal tablet | Pain relief, drowsiness, nausea, constipation, euphoria, confusion, slowed breathing, death | Mostly unknown. Endocrine problems (hypogonadism); immunologic alterations? | Pregnancy: miscarriage, low birth weight, neonatal abstinence syndrome. Older adults: higher risk of accidental misuse or abuse. Risk of HIV, hepatitis, and other infectious diseases | Restlessness, muscle and bone pain, insomnia, diarrhea, vomiting, cold flashes with goose bumps ("cold turkey"), leg movements | Behavioral therapies that have helped treat addiction to heroin may be useful in treating prescription opioid addiction | Methadone<br>Buprenorphine<br>Naltrexone (short and long acting) | Similar to heroin |

(continued)

**Table 21.3** (continued)

| Drug/ substance | Street/other names | Common forms | Short-term effects (acute intoxication) | Long-term effects (chronic intoxication) | Other health effects | Withdrawal symptoms | Behavioral therapy | Medication therapy | Implications for the anesthesiologist |
|---|---|---|---|---|---|---|---|---|---|
| Tobacco | None | Cigarettes, cigars, bidis, hookahs, smokeless tobacco (snuff, spit tobacco, chew) | Increased blood pressure, breathing, and heart rate | Greatly increased risk of cancer, especially lung cancer when smoked and oral cancers when chewed, chronic bronchitis, emphysema, heart disease, leukemia, cataracts, pneumonia | Pregnancy: miscarriage, low birth weight, premature delivery, stillbirth, learning and behavior problems | Irritability, attention and sleep problems, increased appetite. Following smoking cessation, ciliary activity starts to recover within 4–6 days. The sputum volume takes 2–6 weeks to return to normal. There is some improvement in tracheobronchial clearance after 3 months. It takes 5–10 days for laryngeal and bronchial reactivity to settle. There is improvement in small-airway narrowing after 4 weeks, and marked improvement is seen after 6 months. One must be careful in stopping smoking in asthmatics as the asthma may worsen | Cognitive behavioral therapy (CBT) | – Bupropion | Best is to stop smoking for at least 8 weeks prior to surgery or at least 24 h. Anxiolytic premedication and smooth, deep anesthesia should prevent most problems. For outcomes such as cardiac complications, even very brief (e.g., overnight) abstinence may be beneficial, while for other such as pulmonary complications, weeks or months may be necessary. Risks of cardiac and respiratory complications, complications related to the healing of wounds and bones. Anesthesiologists should play a strong role in advising smokers to stop smoking. Smokers report a greater frequency of chronic pain, and requirements for postoperative analgesia are higher in smokers. Smokers have a decreased incidence of postoperative nausea and vomiting. CYP2E1 is induced by tobacco smoke: caution with muscle relaxants and sevoflurane. Dose requirements to maintain hypnosis with propofol are higher in smokers |
| | | | | | | | Self-help materials | Varenicline | |
| | | | | | | | Mail, phone, and Internet quit resources | Nicotine replacement (gum, patch, lozenge) | |

benzodiazepines). In addition, patients have a tendency to underestimate the doses they take, which increases the risk of withdrawal syndrome and increased intraoperative and postoperative pain. However, there may be incomplete cross-tolerance between opioids, and this is an argument in favor of opioid rotation, which, in some cases, could help in perioperative pain management. Patients already taking opioids required three to four times as much opioids in the postoperative period than patients not taking opioids before surgery [48]. Furthermore, in the patient taking opioids, chronically, there is a tolerance to all side effects except constipation, endocrine, gonadal, and immune suppression. Moreover, chronic opioid consumption is thought to induce some effects that are still poorly explained, e.g., delay in scar formation, increased complication rate, and increased risk of chronic pain [48].

As is the case with other patients under chronic opioid therapy, these individuals taking heroin or methadone show a hyperalgesic state. Such patients may need surgery for a procedure that is related to their condition (abscess drainage, valve replacement) or because of a common condition (appendectomy, fracture, osteosynthesis, etc.). Drug addicts should receive a baseline opioid dosage considering the last opioid used. The onset of withdrawal syndrome can be 6–18 h after the last administration of morphine and heroin and 24–48 h after methadone. It is worth mentioning that an ex-addict could experience a renewed dependence following the preoperative use of morphinic agents. In any case, care providers must reassure the patient and explain how his/her pain will be managed before the operation. A precise healthcare contract between the healthcare team and the drug-addicted patient should be considered for this purpose; this will help to gain the patient's trust. Furthermore, the message to the healthcare team is clear; i.e., opioid treatment should not be restricted in those patients; rather, any pain should be treated aggressively while keeping in mind the pharmacological and psychological differences present in such patients ("faking" patient). Care providers should also be careful not to emit any unsuitable judgment regarding the fact that the patient is an addict. Moreover, the perioperative period is not the best time to initiate weaning or to attempt rehabilitation in such patients. This can be considered by the addictology team after hospital discharge [48].

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# The Jehovah's Witness Patient

# 22

Chantal Lerminiaux and Philippe Van der Linden

## 22.1 History

The Jehovah's Witness religion is a proselytizing Christian movement which began as a bible study group formed by CT Russell in the late 1870s in Pennsylvania. The group underwent significant organizational and doctrinal changes under the leadership of JF Rutherford. The name Jehovah's Witnesses was adopted in 1931 to distinguish themselves from other bible study groups and symbolizes a break with the legacy of Russell's traditions. Claiming a worldwide membership of more than 8.2 million, the movement is directed by the Governing Body of Jehovah's Witnesses (also known as the Watch Tower Bible and Tract Society of Pennsylvania (WTS)), a group of elders located in Brooklyn, New York, which establishes all issues of doctrine, based on the literal interpretation of the bible except in cases in which it is obviously allegorical [1]. It was not until 1945 that a ban on blood transfusions was placed, based on several biblical passages (mainly Genesis 9:3; Leviticus 17:10–16; Acts 15:28–29). Jehovah's Witnesses believe that human blood is sacred and a potential vector for sin, whereas Christ's blood is holy and is the only one that can redeem them [2]. To keep up with advances in medicine, new guidelines have been developed to help the members deal with procedures such as cardiopulmonary bypass, blood harvesting including acute normovolemic hemodilution, autologous blood donation and cell saver, as well as organ transplant.

C. Lerminiaux, M.D.
Department of Quality and Security, Queen Fabiola Children University Hospital (QFCUH), Université Libre de Bruxelles, Bruxelles, Belgium

P. Van der Linden, M.D., Ph.D. (✉)
Department of Anesthesiology, Brugmann University Hospital—QFCUH, Université Libre de Bruxelles, 4 Place Van Gehuchten, B-1020 Brussels, Belgium
e-mail: philippe.vanderlinden@chu-brugmann.be



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It is a common misconception that a Jehovah's Witness patient receiving blood against his will or accepting blood will be subject to eternal damnation. Since the year 2000, the Jehovah's Witness is no more disfellowshipped for accepting blood: he is considered to have voluntarily dissociated himself from the church. This means that if he does repent, he can remain in the fold [1].

## 22.2 Ethical and Legal Issues

The ethical and legal issues raised by the refusal of a potentially lifesaving blood transfusion are intense, and they remain an ongoing matter of debate even among Jehovah's Witnesses [3]. The ethical dilemma encountered by the refusal of blood transfusion by Jehovah's Witnesses is illustrative of the conflict that can arise between diverging moral values of equal merit [3]. When evaluating the problem from the four basic principles of medical ethics defined by Beauchamp and Childress [4] (Table 22.1), respect for autonomy (patient's consent) and beneficence are opposing. While in the USA, patient autonomy is usually the most heavily weighted, in many European countries, the principle of beneficence gets more weight [1]. Notable differences, however, exist between European countries: a survey of 242 members of the European Society of Intensive Care Medicine evaluating attitudes to transfusion of exsanguinating Jehovah's Witness patients without consent showed significant variations, with French and Italian doctors more commonly transfusing than Dutch, British, and Scandinavian counterparts [5].To deal with this moral dilemma, DeMarco proposed an additional principle, called the "mutuality principle," which calls for the mutual enhancement of basic moral values, making the multi-principled theory developed by Beauchamp and Childress more coherent [6].

Key questions arising in cases involving Jehovah's Witnesses include:

- Does the patient have an appropriate decision-making capacity (principle of autonomy)?
- Is the patient truly a practicing Jehovah's Witness, free of coercion – what is the proper role of surrogates (principle of autonomy)?
- What are the relevant medical issues (the principles of beneficence and non-maleficence imply that strategies must be undertaken to prevent the need for transfusion)?

**Table 22.1** Principles of North American bioethics

| |
|---|
| 1. Respect for autonomy: based on the principle of respect for persons, it translates into the principle of informed consent in the healthcare setting |
| 2. Beneficence: requiring, other things being equal, to do good, or what will further the patient's interests |
| 3. Non-maleficence: requiring, other things being equal, to avoid harm to the patient, or what would be against the patient's interests |
| 4. Justice: requiring that medical goods and services are distributed fairly. It includes the legal position and human rights |

– Have all appropriated risks, benefits, and alternative to allogeneic blood transfusion been explained (principle of autonomy)?
– Is this an appropriate use of limited resource such as solid organ transplantation (principle of justice)?
– Does the perioperative team have the experience and the capabilities required to work in such a restrictive environment (principles of beneficence and non-maleficence)?

### 22.2.1 Consent, Competence, and Capacity

Medical consent, defined as patient's voluntary agreement to treatment, examination, or other aspects of healthcare, must be considered as a continuously evolving process in the management of a patient. Consent must be obtained from competent adults prior to examination or treatment. A valid consent requires from the patient that [7]:

– He or she is able to understand in broad terms the nature and purpose of the procedure.
– He or she is offered sufficient information to make an informed decision.
– He or she believes the information and is able to weigh it in the balance to reach a decision.
– He or she is acting voluntarily and free from coercion.
– He or she is aware that he or she can refuse.

For this to be the case, the patient must be competent or have the capacity to give consent, which implies the patient is able to understand and retain the information given to him or her regarding a specific procedure and to use that information to decide whether or not to undergo that procedure. The terms capacity and competence are often used interchangeably, but the former is the one most commonly used in law.

Regarding pediatric practice, in most Western countries, adolescents more than 16 years of age are assumed to be legally competent, which however does not invalidate the parental right to consent on their behalf [8]. A young patient under the age of 16 may have the capacity to make decision, depending on his ability to understand what is involved. In the UK, validity of consent is best explored by the Gillick competence (i.e., ability to consent on his or her own medical treatment, regardless of parental permission or knowledge) [9]. For Lord Fraser, a child under 16 years of age could give valid consent in accordance with following guidelines [7]:

– The young individual understands the advice that is being given.
– The young individual cannot be persuaded to inform or seek support from their parents and will not allow the healthcare provider to inform the parents of advice being given.

– The young individual's physical and/or mental health is likely to suffer unless they receive advice or treatment.
– It is the young individual's best interest to receive advice or treatment without parental consent.

In addition, as for competent adult, consent of a young individual requires to be valid that it is given voluntarily and free from coercion.

Therefore, four issues may compete for children less than 16 years of age [10]:

– Capacity for consent.
– Parental authority.
– Prevailing view in the event of dispute between parent and child.
– Power of the court.

In case consent is refused, an application to the court for a specific issue order can be made (parental authority and/or patient consent is removed and the procedure may go ahead). If there is not enough time for such an application, the doctors are empowered to act in the "best interest" of the patient [8].

It should be noted that, in most Western countries, the position of the courts in relation to parental objection to blood transfusion on religious grounds is now so well established that it is commonly possible for agreement to be reached without "going to law," with an arrangement that blood, or blood products, will only be given in certain clinical circumstances or when required by the doctors' duties to act in the child's best interests.

### 22.2.2 Advance Directives and Consent Forms

Advance directives are legally binding documents outlining treatments an adult individual would not consent in the future, should he or she lack capacity. To be valid, these directives must fulfill the following:

– The individual must have capacity at the time of signing.
– The directive must be signed with a witness present.
– The directive must indicate the decision applied to a specific treatment if the individual's life is at risk.

Blood refusal cards are a form of advance directive distributed by the WTS. However, as WTS provide information about the risk but not the benefit of transfusion, there is a clear concern about the validity of the information given to make an informed decision. In addition, there is also concern about whether an individual's decision to carry such a card is without external influence. Therefore in emergency situations, if any doubt exists on the validity of such blood refusal cards, some authors recommend treating in the patient's best interest and transfusing blood [11].

Several hospitals have consent forms designed for Jehovah's Witness patients that include a section for detailing specific exclusions from the consent. When

obtaining restricted consent, the patient should be interviewed in the presence of an independent witness, the benefits and risks of blood transfusion explained, and an attempt made to help the patient understand the rationale for the recommended treatment. If the patient did not change his opinion, the precise nature of the restrictions placed on the doctor by the patient should be documented in the patient's clinical chart. All parties involved should sign the consent form.

### 22.2.3 Obligation for a Physician to Take Care of a Jehovah's Witness Patient

Anesthesia providers may feel that refusal of standard care in the operating room or in the postoperative period, such as blood transfusion, places them in a very difficult position of not being able to fulfill their professional duties. According to the guidelines for anesthesia care of patients with do-not-resuscitate orders or other directives that limit treatment developed by the ASA, anesthesiologists have the right in non-emergent situations to excuse themselves from a patient's care nonjudgmentally as long as they refer the patient to another care provider in a timely fashion [12]. This referral could even be to another medical center that has developed expertise in caring for Jehovah's Witness patients. In life-threatening situations, the anesthesiologist is obligated to care for the patient, trying "as much as possible" to adhere to patient's wishes. If the anesthesiologist is concerned that he or she will not be able to comply, then he or she should inform the patient or his surrogate [1].

## 22.3 Perioperative Management

Elective surgery for Jehovah's Witness patients should be conducted in centers having the appropriate facilities by a senior team sensitive to patient's beliefs and with experience in techniques of "bloodless surgery." Providing medical care to patients without the use of allogeneic blood transfusion is one aspect of patient blood management. By providing bloodless care to patients, valuable lessons have been learned, facilitating blood conservation in general and therefore expertise in the field of patient blood management. Requiring a holistic approach across the whole perioperative period, it is an example of the paradigm shift described in transfusion medicine, away from the component-centric model, toward the patient-centric approach [13]. Before surgery, there must be full discussion between the patient, surgeon, and anesthetist. All risks have to be explained and "rules" for management established before commencement. Physicians should question the patient on specific blood product interventions and alternatives that the physician may or may not use (Table 22.2). Surgery must be planned and tailored to the needs of the individual patient. Non-operative techniques and staging of major surgical procedures should be considered. Other specialists likely to be involved in the patient's care should be advised and theater personnel informed so that any equipment, drug, and specialist will be available.

**Table 22.2** Acceptability of blood products and alternatives among Jehovah's Witnesses

| Type of blood product, alternative, or procedure | Acceptability | Specific concerns |
|---|---|---|
| Whole blood | Refuse | |
| Red blood cell | Refuse | |
| Autologous blood donation | Refuse | |
| Acute hypervolemic hemodilution | Accept | |
| Acute normovolemic hemodilution | May accept | If continuity is maintained with their vascular system |
| Intraoperative—postoperative cell salvage | May accept | If continuity is maintained with their vascular system |
| Hemoglobin solutions | May accept | |
| White cells | Refuse | |
| Interferons or interleukins | May accept | |
| Platelets | Refuse | |
| Platelet factor 4 | May accept | |
| Platelet gel | May accept | |
| Plasma | Refuse | |
| Cryoprecipitate | May accept | |
| Fibrinogen concentrate | May accept | |
| Vitamin K-dependent clotting factors | May accept | |
| Recombinant factors (VII and IX) | May accept | |
| Albumin | Most will accept | |
| Crystalloids and colloids | Accept | |
| Immunoglobulins | May accept | |
| Biological hemostats (collagen and cellulose pads, fibrin glues, sealants, etc.) | May accept | |
| Epidural blood patch | May accept | |
| Erythropoietin | Most will accept | |
| Cardiopulmonary bypass or extracorporeal membrane oxygenation | Most will accept | Continuity is maintained with their vascular system |
| Renal hemodialysis | Most will accept | Continuity is maintained with their vascular system |
| Plasmapheresis | Most will accept | Continuity is maintained with their vascular system |
| Organ and bone marrow transplant | May accept | |

### 22.3.1 Preoperative Optimization

The patient's preoperative status should be optimized to improve circulating erythrocyte mass and to reduce the risks of intraoperative hemorrhage.

Anemia is not only a strong predictor for allogeneic transfusion but also a risk factor for increased morbidity and mortality postoperatively. Guidelines for detection, evaluation, and management of anemia in elective surgical patients have been

published [14]. To allow for proper management, screening and detection of anemia should occur up to 30 days before the electively scheduled surgery [15]. Patients may benefit from iron supplementation before operation, not only those with iron deficiency anemia but also those with functional iron deficit. Either oral or intravenous iron can be used, but the latter one appears more effective, in particular in inflammatory states where hepcidin inhibits gut iron uptake and mobilization from storage sites. The effect of intravenous iron on erythropoiesis may only last up to 10 days, and patients may require repeated doses for preoperative optimization, especially when recombinant erythropoietin (rEPO) will be used. The presurgical use of rEPO has proved useful in Jehovah's Witness patients, its effects being partly governed by ferritin, transferrin, iron, vitamin B12, and folic acid concentrations. The hematopoietic response appears dose dependent with an increase in erythropoiesis observed after 3–4 weeks. Vitamin B12 and folic acid deficiencies should be detected and treated. After surgery, the inflammatory response reduces transferrin and serum iron concentration and induces a transient erythropoietin deficiency. Therefore, it has been recommended to administer intravenous iron and rEPO in the postoperative period, although the real efficacy of this approach remains to be demonstrated. It should be kept in mind that some rEPO preparations contain trace amounts of human albumin, which may conflict with the beliefs of some Jehovah's Witnesses.

Before surgery, drugs or herbal remedies (e.g., garlic or ginger) that may impair hemostasis should be discontinued in a timeline fashion, and antidote should be administered if deemed appropriate. If vitamin K had to be administered, the oral route is preferred over the intravenous one [16]. Subsequent management will depend on the detection of a preoperative defect either congenital or acquired. With other medical comorbidities, it should be important to anticipate and treat other potential factors associated with blood loss as, for example, proton pump inhibitors for gastrointestinal ulceration or progesterone for menstruation [8].

### 22.3.2 Minimization of Perioperative Blood Loss

Minimization of perioperative blood loss is essential as it increases postoperative mortality irrespective of the preoperative hemoglobin concentration [17]. This must include a rationalized approach to ordering blood tests to limit phlebotomy. The use of micro-sample tube and microanalyzers has been shown to be effective [18].

Regarding anesthetic care, venous congestion and venous ooze should be minimized by careful patient's positioning and avoidance of high intrathoracic pressures and hypercapnia. Using forced-air warmers and intravenous fluids warmers helps prevent coagulopathy associated with hypothermia. Serial measurement and correction of coagulation profile and ionized calcium should be considered in long cases [19]. Regional and central neuraxial anesthesia have been recommended as these techniques have been shown to be associated with less blood loss than general anesthesia [20]. This appears particularly true for major orthopedic surgery [21–23]. Controlled hypotensive anesthesia has also been proposed in a variety of surgical procedures and patient populations as a way of improving surgical field visibility and reducing intraoperative blood loss [8, 24].

Among the three main techniques for autologous transfusion, preoperative autologous blood donation is not accepted by Jehovah's Witnesses. Acute isovolemic hemodilution (ANH) could be accepted, providing a closed circuit is used. In case it is not, acute hypervolemic hemodilution, which does not involve withdrawal of blood, could be proposed. Although there is some evidence to suggest that ANH could reduce the risk of allogeneic transfusion [25, 26], this is less clear for its hypervolemic alternative. The third autologous transfusion technique entails the collection of the blood lost during surgery and/or the blood collected from drains, which is centrifuged, washed, and later reinfused. This effective technique [27], however, is not always accepted by Jehovah's Witnesses who may request the blood remains in continuity with their circulation [28]. This must therefore be assessed on a patient-by-patient basis either for the intraoperative period and the postoperative period.

Blood loss can also be minimized by the prophylactic use of "hemostatic" agents such as antifibrinolytics, aprotinin, and desmopressin. Tranexamic acid and epsilon-aminocaproic acid are synthetic lysine analogues that inhibit fibrinolysis by preventing plasminogen conversion to plasmin. Although dosages vary markedly among studies, their efficacy in reducing blood loss in different types of surgeries is well recognized [29, 30]. There is also increasing evidence that they are free of serious adverse effects like thrombotic complications [29, 31]. This is in contrast with aprotinin, a direct plasmin inhibitor, which has been shown to be slightly more effective in reducing blood loss than lysine analogues, but associated with an increased risk of mortality [29]. This point, however, remains highly debated in the literature, and aprotinin could now be used in most European countries on a named patient basis [8]. Desmopressin is a synthetic analogue of vasopressin, which stimulates endothelial release of tissue plasminogen factor and von Willebrand factor, enhancing platelet aggregation. Overall, the effect of desmopressin on perioperative blood loss appears modest, and its use should be reserved to patients with inherited platelet dysfunction [8] or those with recent antiplatelet drug administration and undergoing cardiac surgery [32].

In addition to these hemostatic agents, treatment of ongoing blood loss relies on the use of cryoprecipitate, fibrinogen concentrate, prothrombin complex concentrate, and recombinant clotting factors. Acceptance of these different agents must be assessed preoperatively on a patient-by-patient basis.

Regarding surgical care, key principle is scrupulous hemostasis. Other issues to be considered include the use of minimally invasive techniques (laparoscopic or endoscopic), of hemostatic devices such as diathermy and harmonic scalpels, infiltration of the wound with local vasoconstrictors, and application of topical hemostatics (biological pads, fibrin glues, sealants, etc.). Arterial tourniquets, tamponade balloons, and interventional radiology (embolization and/or intravascular occlusive devices) could be also of interest, depending on the anatomical location of bleeding. Finally, a staged procedure could be planned if surgery is expected to be complex [33].

### 22.3.3 Optimization of Anemia Tolerance

Humans are highly tolerant to acute anemia, providing that the circulating blood volume is maintained. In these acute conditions, fulfillment of tissue metabolic demand depends on an increase in cardiac output and an increase in peripheral oxygen extraction [34]. Enhancement of anemia tolerance requires on the one hand to maximize oxygen delivery and on the other hand to control tissue oxygen demand (Table 22.3). Optimization of cardiac output through adequate fluid loading and hyperoxic ventilation are the best therapeutic approaches to achieve this goal. Although anesthesia and hypothermia may help to control tissue oxygen demand, careful titration of sedation depth should be required to avoid the depressant effects of anesthetic agents on the cardiovascular system and thereby on cardiac output. Only mild to moderate hypothermia could be recommended because of the deleterious effects of more profound hypothermia on hemostasis.

Hemoglobin-based oxygen carrier (HBOC) solutions have been proposed as a potential alternative to blood transfusion in Jehovah's Witness patients with severe anemia. These solutions possess oxygen carrying capacities contributing to the delivery of oxygen to the tissues, but also potent oncotic properties that are interesting for the maintenance of the intravascular volume. Only the HBOC-201 (hemoglobin glutamer-250 bovine: Hemopure®, Biopure Corporation, Cambridge, MA) has been approved for the treatment of surgical anemia in adults in South Africa. In Western countries the development of HBOC has stagnated because of major safety issues [35]. However, some may be available on "compassionate grounds" [36]. Perfluorocarbons are liquid organofluorine compounds that dissolve large amount of oxygen. To be efficacious they require high arterial oxygen pressure. After initial promising results, their development has been stopped, also for safety concerns. Currently, they are only used in Russia and Mexico with very few data published in the international literature [37, 38].

**Table 22.3** Therapeutic approaches to increase tolerance of patients to anemia

| |
|---|
| • Tissue oxygen delivery optimization |
| – Optimization of the circulating blood volume |
| – Maintenance of myocardial function |
| – Hyperoxic ventilation |
| • Control of tissue oxygen demand |
| – Adequate sedation level |
| – Muscular relaxation in dedicated cases |
| – Normothermia or moderate hypothermia |
| • Stimulation of erythropoiesis |
| – Intravenous iron |
| – Subcutaneous erythropoietin |
| – Correction of vitamin B12 and folic acid deficiencies |

Mortality and morbidity of severe anemic patients who decline blood transfusion have been evaluated in a retrospective study of consecutive adult surgical patients managed in a patient blood management center between 2003 and 2012 [39]. The study confirms the previously reported risk of mortality and morbidity of severe anemia, particularly at nadir hemoglobin level below 6–7 g/dL. Patients with nadir hemoglobin level in the 7–8 g/dL ranges have better survival.

### 22.3.4 Postoperative Management

After surgery, Jehovah's Witness patients require a close degree of monitoring whenever major blood loss is anticipated. This may involve high dependency level of care [8]. Adequate oxygenation, maintenance of normovolemia with crystalloid and colloid solutions, and limited phlebotomy have to be considered. Postoperative cell salvage can be an option for some Jehovah's Witnesses. Pharmacological interventions include the administration of hemostatic agents to stop bleeding, iron and rEPO to promote erythropoiesis, and conservative use of anticoagulants and antiplatelet agents.

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