Cardiac Surgery Risks in Liver Dysfunction

73

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Key Concepts

- The incidence of chronic liver diseases and cirrhosis is steadily increasing and is therefore common that patients with advanced liver dysfunction are addressed for cardiac surgery interventions;
- Patients in Child Pugh class A can be assimilated to the general population and are candidates to elective cardiac surgery; Patients in Child Pugh class B can undergo elective cardiac surgery with adequate preoperative preparation and adapted intraoperative strategy;
- Elective cardiac surgery is contraindicated in Child Pugh class C patients, acute hepatitis, alcoholic hepatitis, acute liver failure and in case of severe extrahepatic complications;
- Endovascular procedures (Transcatheter Aortic Valve Implantation) are associated with acceptable mortality and morbidity rates in patients with advanced liver dysfunction and are preferred to open surgery when available and technically possible.

73.1 Introduction

The incidence of chronic liver diseases and cirrhosis is steadily increasing. The age-adjusted prevalence for 2016 in 35 countries for males and females ranged from 447 (Iceland) to 1100 (Romania) cases per 100,000 inhabitants, with a median of 833 [1]. It is therefore common that patients with advanced liver dysfunction are addressed for cardiac surgery interventions. Liver disease has been long time considered an important risk factor for both major morbidity and mortality following cardiac surgery as a result of cardiovascular disorders, haemostatic and coagulation disorders, renal impairment and bacterial infection. Several risk score models have been specifically developed for cardiac surgery to assess a patient's surgical candidacy based on the potential unfavourable outcome (major complications and mortality), the most used being the Society of Thoracic Surgeons (STS) system and the European System for Cardiac Operative Risk Evaluation (EuroSCORE) model. Both scores are of limited use as they fail to include all major factors that may render patients at higher risk for surgery. It is problematic to distinguish patients who may benefit from cardiac surgery from those whose perioperative risk exceeds benefit. Consequently, for patients with advanced liver dysfunction, the operative benefit needs to be carefully weighted after a specific assessment and the therapeutic management adapted to the particular clinical picture of the individual patient.

The aims of this chapter are to reveal the impact of the pathophysiological changes induced by advanced liver dysfunction on the surgical and anaesthetic outcomes in cardiac surgery and to outline the particular aspects of the pre, intra and postoperative management used to optimize the outcome in this group of patients.

73.2 Advanced Liver Dysfunction Physiopathological Changes Relevant for Cardiac Surgery

73.2.1 Haemostasis and Coagulation Disorders

Advanced liver dysfunction is associated with various anomalies, particularly protein synthesis impairment, that affect

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Table 73.1 Haemostasis abnormalities in cirrhotic patients

Coagulation factor defects	Thrombocytopenia and platelet dysfunction	Increased fibrinolysis	Prothrombotic changes
– Decreased liver synthesis of fibrinogen (factor I), thrombin (factor II), factors V, VII, IX, X, XI – Vitamin K deficiency in alcohol induced liver disease	– Decreased liver synthesis of thrombopoietin – Bone marrow suppression (hepatitis virus C, infection, alcohol, antiviral therapy) – Increased platelet sequestration in the spleen – Platelets dysfunction secondary to uremia, infection, endothelial cells abnormalities (platelets inhibition by NO and prostacyclin)	– Increased levels of tissue plasminogen activator (tPA) – Decreased liver synthesis of alpha 2 antiplasmin, coagulation factor XIII, thrombin-activatable fibrinolysis inhibitor (TAFI) – Fibrinolytic activity of ascitic fluid	– Decreased liver synthesis of protein S, protein C, fibrinolytic factors – Inflammatory changes in endothelial cells – Decreased liver clearance of von Willebrand factor (vWF)

almost all aspects of haemostasis and coagulation. According to Shah et al., impaired haemostasis in cirrhotic patients is due to four types of abnormalities that may coexist in the same patient: coagulation factor defects, thrombocytopenia and platelet dysfunction, increased fibrinolysis, prothrombotic changes [2] (Table 73.1).

The above-mentioned abnormalities lead to pro-haemorrhagic and procoagulant impairment of both primary and secondary haemostasis and fibrinolysis. If haemostasis abnormalities in advanced liver dysfunction are a certitude, debates still exist concerning the threshold values of laboratory tests that indicate an increased haemorrhagic risk and impose corrective measures prior to surgery. Conventionally proposed correction thresholds are PT < 50%, fibrinogen level <1 g/L or platelet count less than 50,000/mm^3, but international normalized ratio (INR) values should not be used to guide therapy.

Corrective measures may include comorbidities control (infection treatment, optimization of renal status, avoid accentuating portal hypertension), vitamin K and cryoprecipitate administration, platelets and red blood cells transfusion, administration of antifibrinolytic agents (tranexamic acid, epsilon aminocaproic acid). Recent advancements in surgical and anaesthetic approaches have led to significant reduction in blood transfusion requirements.

73.2.2 Renal Function Impairment

Renal function impairment in cirrhotic patients has a multifactorial aetiology related to hemodynamic changes (splanchnic vasodilatation, decline in renal perfusion despite activation of the renin-angiotensin system and intense renal vasoconstriction, balance alteration between vasoconstrictor and vasodilator mediators) that alter renal vascular reactivity. Other causes of renal dysfunction (prerenal, renal or postrenal) must be systematically excluded. Prerenal causes related to true or relative hypovolemia frequently occur in cirrhotic patients due to diuretic treatment, diarrhoea, ascites drainage. Nephrotoxic drugs and those inducing a decrease in renal blood flow (eq. anti-inflammatory drugs) should be avoided in cirrhotic patients. Patients with alcoholic cirrhosis may develop mesangial nephropathy with IgA deposits, while a patient with post-hepatitis C cirrhosis may develop cryoglobulinemia related nephropathy. An important aspect to be signalled is the overestimation of the renal function in cirrhotic patients, urea and creatinine synthesis are usually diminished (decrease in lean body mass and hypoproteinemia) and do not reflect glomerular filtration ratio (GFR).

The most severe form of renal dysfunction is represented by the hepatorenal syndrome (HRS).

Definition
Hepatorenal syndrome combines functional renal failure (anuria secondary to diminished blood pressure), a decrease in sodium levels and irreducible ascites.

The hepatorenal syndrome occurs in advanced stage of cirrhosis, spontaneously or caused by complications (haemorrhages, infections, ascites puncture). Hepatorenal syndrome may be acute and short-term lethal or with a slower progression, the latter responding to vasoactive drugs or transjugular intrahepatic portosystemic shunt (TIPS) placement.

Therapeutic management generally relies on prevention (avoidance of nephrotoxic agents, drugs that induce arterial hypotension, diuretics, infection screening) and early recognition. If severe acute kidney injury/hepatorenal syndrome installs, patients should be treated with vasoconstrictors in combination with intravenous albumin according to the revised consensus recommendations of the International Club of Ascites [3].

73.2.3 Cardiovascular Alterations

Advanced liver dysfunction is associated with cardiovascular changes secondary to neurohumoral and vascular dysregulations, portal hypertension and portosystemic shunts. These changes include hyperdynamic circulation (increased cardiac output), decreased blood pressure, decreased vascular resistance and cirrhotic cardiomyopathy. The importance of cardiovascular abnormalities is associated with the degree of liver failure.

Arteriolar vasodilation is the hallmark of cardiovascular alterations and finally leads to decreased circulating blood

volume. A vicious cycle (compensatory vasoconstrictor mechanisms that promote water and salt retention) is initiated as baroreceptors are stimulated.

An authentic cirrhotic cardiomyopathy has also been identified, different from other cardiomyopathies that may occur in patients with advanced liver dysfunction such as alcoholic cardiomyopathy.

Definition
Cirrhotic cardiomyopathy is defined as the presence of structural and functional cardiac abnormalities in patients with cirrhosis, without other associated heart disease.

Cirrhotic cardiomyopathy is characterized by systolic and diastolic dysfunction, as well as by conduction disorders that may become clinically evident following physiological or surgical stress, and cause heart failure. Pathogenic mechanisms include alteration of the β-adrenergic signalling pathway and exposure to cardiodepressant factors.

Decreased cardiac contractility as a response to stressors and the degree of impairment is similar regardless of the etiology of liver disease.

The exact prevalence of cirrhotic cardiomyopathy remains unknown, however one of the typical anomalies, QT interval prolongation, appears to be present in the majority of patients with Child B or C cirrhosis. No specific treatment was suggested for these changes and the recommendations for the treatment of liver disease and heart failure should be followed [4].

73.2.4 Disorders of the Immune System

The incidence of bacterial infections during hospitalization of cirrhotic patients is 4 times higher than the one registered in the general population (40% versus 10%) [5]. This phenomenon is due to reticuloendothelial system abnormalities, humoral and cellular immunity as well as neutrophil dysfunction. In cirrhotic patients, the reduced phagocytosis capacity of the Kupffer cells together with intrahepatic vascular shunts that bypass the Kupfferian system contribute to bacteraemia secondary to bacterial translocation. The toxic action of alcohol further contributes to accentuating immune disorders. An appropriate empirical antimicrobial treatment should be promptly initiated when bacteraemia is proved.

73.2.5 Pulmonary Disorders

Pulmonary and pleural disorders occurring in patients with advanced liver dysfunction are generally represented by hydrothorax, hepatopulmonary syndrome and portopulmonary hypertension.

Definition
Hepatic hydrothorax defines the pleural effusion occurring in cirrhotic patients in the absence of any lung, pleural or cardiac disease.

The hepatic hydrothorax occurs in 5–10% of patients with ascites and results from the passage of ascitic fluid from the peritoneal cavity into the pleural cavity through diaphragmatic gaps due to the pressure gradient between the two cavities [6]. Pleural effusion is mostly right-sided and its volume can cause dyspnoea. A low-salt diet is mandatory for controlling this condition associated or not with a combination of furosemide and spironolactone.

Definition
The hepatopulmonary syndrome is a rare complication associating severe hypoxemia (PaO_2 < 70 mHg), pulmonary vasodilatation and an increased in the alveo-capillary oxygen gradient (>20 mmHg) [7].

Pulmonary vasodilation (precapillary and capillary vasodilatation, arteriovenous shunt bypassing the alveoli) is the man cause of this hypoxemia. Vascular abnormalities predominate in the middle and lower lung fields, leading to a worsening of hypoxemia in orthostatism. This condition is generally managed with drugs inhibiting NO synthesis and endothelin-1 inactivation.

Definition
Portopulmonary hypertension (PPHTN) is reported in 2–16% of cirrhotic patients with portal hypertension depending on the study and is a complication of portal hypertension involving pulmonary arterial vasoconstriction [8].

The mean pulmonary arterial pressure (mPAP) increases (>25 mmHg), pulmonary capillary wedge pressure decreases (<15 mmHg) and these changes result in an increase in transpulmonary gradient (the difference between the pulmonary artery pressure and the pulmonary capillary wedge pressure) and pulmonary vascular resistance (>120 dynes per s/cm^{-5}). The cause of PPHTN is unknown, most authors pleading for a vasoactive humoral substance reaching the pulmonary circulation through portosystemic collaterals. Portopulmonary hypertension causes dyspnea only when the mPAP exceeds 40–50 mmHg.

Blood gases are normal or show moderate hypoxemia. The prognosis for this condition is particularly severe and usually represents a contraindication to liver transplantation. Patients are generally treated with anticoagulants and diuretics part of the general measures to prevent pulmonary thromboembolism and volume overload. Patients that do not respond to general measures are treated with agents used for severe pulmonary hypertension (epoprostenol, iloprost, bosentan, sildenafil).

73.2.6 Liver Function Deterioration

Cirrhosis is associated with an increase in resistance to venous flow, especially at a post-sinusoidal level, which decreases the total hepatic flow at the expense of portal flow. The arterial self-regulation system is also significantly altered with little or no compensation of low-flow situations. Because of these changes, the oxygenation of centrilobular hepatocytes can be severely compromised in the circumstances of a cardiac surgery intervention with cardiac arrest and major hemodynamic stress.

The vulnerability of centrilobular hepatocytes to hypoperfusion and associated metabolic changes are explained by the particular architecture of the liver. The hepatic lobule is the *anatomical unit* of the hepatic parenchyma, centered by the centrilobular vein and limited at the periphery by portal spaces containing the portal triad (portal venule, hepatic arteriole, bile ductule). The functional organization of the liver parenchyma is not modeled on the anatomical structure represented by the hepatic lobule. The concept of hepatic acinus, the *functional unit* of the liver, is based on the vascular architecture, the central axis being represented by the line connecting two portal triads and the periphery by two adjacent centrilobular veins. The hepatic acinus can be divided in three metabolic zones from central axis to the center of the lobule. The periportal zone [1] is well oxygenated and less susceptible to ischemia, the centrilobular zone [3] is poorly oxygenated and very susceptible to ischemia, and the transition zone [2] has an intermediate susceptibility. The central zone of the acinus is specialized in oxidative metabolism and gluconeogenesis; the peripheral zone preferentially ensures glycolysis, biotransformation of xenobiotics (cytochrome P450) and alcohol metabolisation. This particular architecture explains the increase of centrilobular necrosis and deterioration of liver function in the early postoperative period.

All these cirrhosis associated disorders can alter the intraoperative and postoperative course in cardiac surgery worsening the outcome, but advanced liver dysfunction is not an absolute contraindication to cardiac surgery. With adequate patient selection, perioperative and anaesthetic management the outcome can be significantly improved.

73.3 Cardiac Surgery Risks and Outcome in Patients with Advanced Liver Dysfunction

It is estimated that approximately 10% of cirrhotic patients undergo surgery within the last 2 years of their life [9]. An increased surgical risk in this group of patients is indisputable due to difficult abdominal surgical conditions, anaesthesiologic issues, haemostatic and coagulation disorders, and increased risk of infection.

Cirrhotic patients can generally undergo two types of surgery: interventions related to their liver disease (resection of hepatocellular carcinoma, treatment of umbilical hernias) and extrahepatic interventions. In the first case, the perioperative management of these patients assumes a good knowledge of the specific complications such as refractory ascites, renal impairment or postoperative worsening of hepatic function with a major risk of decompensation.

The second type of surgery to which the cirrhotic patient is confronted is extrahepatic surgery for various cancers, orthopaedic issues, valvular or coronary heart diseases, or other thoracic diseases.

In practice, the postoperative morbidity in cirrhotic patients is not only related to the complications of the surgical site like infection or haemorrhage but also to long-term complications, more frequent than the first ones. Generally, there is an increase in the risk of infection in these patients. Surgical stress combined with a potential postoperative infection create the circumstances for hepatic decompensation, under the form of refractory ascites, renal impairment, digestive haemorrhage or hepatocellular function alteration.

The occurrence of postoperative hepatocellular insufficiency is associated with a mortality rate superior to 70% in the absence of transplantation.

Between 2.5% and 27% of patients with advanced liver disease present coronary heart disease [10]. A higher incidence of adverse events related to catheterization has been observed in cirrhotic, especially related to vascular access (severe bleeding, pseudoaneurysms, hematoma).

Cardiac surgery in cirrhotic patients is associated with an increased mortality, reaching 19.3% on the short term and 42% within 1 year [11].

Preoperative assessment of the individual surgical risk for each patient suffering from advanced liver disease allows separating patients who may benefit from cardiac surgery from those whose perioperative risk exceeds surgical benefits. Several risk evaluation systems have been developed and, in this section, we will analyse their ability to predict operative mortality in cirrhotic patients that need a cardiac surgery intervention.

In cardiac surgery, several specific scoring models have been developed to assess the risk of operative mortality, the most used being EuroSCORE II and STS.

EuroSCORE II has been developed in 2011 to update the original EuroSCORE model. The scoring system includes a limited number of patient related factors like age, gender, renal impairment, extracardiac arteriopathy, poor mobility, previous cardiac surgery, chronic lung disease, active endocarditis, critical preoperative state, diabetes on insulin, and omits all parameters relevant for liver function.

STS includes liver disease among the evaluated parameters as a binary selection (Yes or No) irrespective to the type and severity of the disease ("Indicate whether the patient has a history of hepatitis B, hepatitis C, cirrhosis, portal hypertension, oesophageal varices, chronic alcohol abuse or congestive hepatopathy").

Considering all severity stages, early postoperative morbidity and mortality after cardiac surgery in cirrhotic patients ranges from 31% to 66% and 10–25%, respectively. There appears to be an almost linear relationship between severity of liver damage, morbidity and mortality.

The surgical risk in cirrhotic patients is evaluated according to three main factors: liver function assessment, type and urgency of the procedure. Cirrhotic patients are at high surgical risk not only because of the cirrhosis itself but by the presence of coagulopathy, malnutrition, immune disorders, cardiomyopathy, pulmonary and renal impairment. Elective surgery is generally contraindicated in patients with acute hepatitis (especially if INR > 1.5), alcoholic hepatitis and acute liver failure (10–50% mortality rate).

In order to estimate the surgical risk in cirrhotic patients different scoring systems have been proposed. Developed in 1964 by Child and Turcotte and modified by Pugh in 1973 (prothrombin time assessment), the Child Turcotte Pugh (CTP) score is mostly used to assess the liver functional reserve prior to derivative surgery (porto-systemic and spleno-renal shunts). Formulated more than 50 years ago, without evidence base, CTP score lacks discriminatory capacity and is not adequate for non-derivative surgery where morbidity and mortality have a more significant relationship with other factors than those included in the CTP score (total bilirubin, albumin, prothrombin time/INR, ascites, encephalopathy).

Due to the subjectivity of the CTP score, a new prognostic index in advanced liver disease called MELD (Model for End-Stage Liver Disease) has been developed by the Mayo clinic by using mathematical modelling. MELD is generalized, verifiable and can be computed with easily obtained variables (dialysis, creatinine, bilirubin, INR, sodium). MELD-XI is an adapted version of the original MELD score excluding INR and is of particular use in patients with cardiovascular diseases.

To date, the prognostic value of MELD score has been validated in different groups of patients with advanced liver disease, initially in candidates for liver transplantation and afterwards for another types of surgery.

Cardiac surgery is not contraindicated in cirrhotic patients but the risk-benefit ratio should be carefully evaluated. The performance of cardiac surgical interventions in patients with advanced liver diseases increased with 22% from 1998 to 2006 according to the New York State Department of Health Cardiac Surgery Registry review [12]. A better understanding of both diseases and prophylaxis (beta-blockers for portal hypertension, endoscopic treatment of oesophageal varices, transjugular intrahepatic portosystemic shunts, spontaneous bacterial peritonitis prophylaxis, suppression of viral replication) led to this decrease.

Compared to other types of extra-hepatic surgery, cardiac surgery is associated with major hemodynamic and circulatory changes due to significant bleeding requiring blood transfusion, hypoperfusion and hypotension, changes that impair hepatic function. Moreover, CPB circuit activates factor XII, stimulates inflammation and platelet aggregation (further detailed in subchapter Cardiopulmonary bypass and liver dysfunction).

The first study to analyse the predictive value of CTP class, CTP score and MELD score after cardiac surgery with cardiopulmonary bypass (CPB) as performed by Suman et al. in 2004. The reference outcomes were considered death within 3 months from surgery and hepatic decompensation. A CTP score >7 emerged as the strongest predictor of postoperative mortality but the authors did not manage to establish a threshold value for the MELD score. The results were confirmed in 2007 by Filsoufi et al. who added preoperative thrombocytopenia as a poor prognostic factor for hospital mortality. MELD score regained interest in 2009 when Ailawadi et al. determined that a MELD score >15 is a predictor of mortality in cirrhotic patients undergoing tricuspid valve surgery. In 2010, Thielmann et al. retrospectively evaluated 57 cirrhotic patients who underwent cardiac surgery with CPB and compared the predictive value of CTP class, MELD score and EuroSCORE and showed that MELD was superior to both CTP and EuroSCORE [13]. Several research groups proposed threshold values for MELD score ranging between 13 and 15 and corresponding to the transition from CTP B to C class.

Until 2012, most studies were unicentric and on limited number of patients.

In 2015, there was published a meta-analysis performed on 22 reports including 939 patients from eight countries in order to assess the value of advanced liver dysfunction graded according to CTP score as a risk factor for mortality and morbidity in cardiac surgery. We only considered studies that analysed cirrhotic patients that underwent valve surgery (repair or replacement of a single or multiple valves), CABG (coronary artery bypass grafting), pericardiectomy, ascending aorta surgery, patch repair of a septal defect or of the free ventricular wall. The mean in hospital mortality rates were 8.92%, 31.38%, and 47.62% for patients in CTP

class A, B and C compared to mean late mortality rates of 20.58%, 43.58%, and 56.48% respectively. Patients in class A had significantly lower in hospital (OR 0.30) and late (OR 0.34) mortality rate compared to patients in class B. When compared to class C, mortality rate was even lower (OR 0.16 for early mortality and 0.07 for late mortality). When comparing class B versus class C, the difference was not statistically significant. Morbidity rates were also analysed with quantification of a 4.37% mean reexploration rate, 3.83% mean neurological complication rate, 2.67% mean cardiovascular complication rate, 16.51% mean pulmonary complication rate, 22.15% mean renal complication rate, 5.75% mean hepatic complication rate, 8.09% mean gastrointestinal complication rate, 5.64% mean sepsis and multiple organ failure syndrome rate, 5.54% mean haemorrhage and cardiac tamponade rate, 9.16% mean infection rate [13]. Morbidity risk related to CTP class could not be assessed as not all studies reported results accordingly. These findings indicate that both in hospital and late mortality rates increase in accordance with CTP classification the lower rates being registered in class A patients. With adequate preparation, perioperative and anaesthetic management, cardiac surgery can be safely performed in CTP class A patients. Other studies confirmed our findings that patients in CTP class C register significantly higher mortality rates. The need for a surgical treatment should be carefully analysed in these patients and if it considered mandatory with no medical or interventional alternatives, liver function should be optimized prior to surgery as much as possible. For patients in CTP class B, further studies are necessary to determine if it is safe to conduct cardiac surgery in this group. The most frequent complications reported in cirrhotic patients are renal (21.15%), pulmonary (16.51%) and cardiovascular (12.67%). Hepatic failure accounts for less than 6% of complications but is associated with a more than 70% mortality rate. Compared to cirrhotic patients, a large recent study performed in 2017 on 40,652 patients with isolated CABG irrespective to comorbidities (general population) reported a 1.6–2.8% mortality rate depending on study year and a major complication rate between 3.8% and 7.8% [14].

Jacob et al. performed a similar meta-analysis on 19 studies published up to February 2014 and reached similar results—9% early mortality rate in CTP class A patients, 37.7% in class B and 52% in class C. They also quantified a within 1-year mortality rate of 27.2% in class A patients, 66.2% in class B and 78.9% in class C but did not evaluate postoperative morbidity [11].

The predictive value of the MELD score was evaluated by fewer studies compared to CTP class. In 2010, Thielman proposes 13.5 as a cut-off value for postoperative in-hospital morbidity and considers MELD score as having a superior predictive value compared to CTP classification and EuroSCORE [13]. In 2017, Sabry et al. proposed a MELD score of 12 as a threshold value for postoperative morbidity after analysing 90 adult patients with chronic hepatitis C virus undergoing cardiac surgery with CPB [15]. As one can notice, MELD threshold value varies largely among studies given the heterogeneity of the evaluated population (from general population to patients awaiting liver transplantation). MELD score predicts short term mortality in cirrhotic patients undergoing cardiac surgery but further studies on homogeneous populations are needed to reach a consensus regarding the threshold value for considering the patient at high risk.

Risk stratification, preoperative evaluation and preparation, adequate operative and postoperative care are mandatory in cirrhotic patients to maintain an optimal risk-benefit ratio.

73.4 Preoperative Preparation of Cirrhotic Patients Prior to Major Cardiac Surgery

In cirrhotic patients, surgery should ideally be elective as these patients are at risk especially in case of urgent surgery. However, if the latter case cannot be avoided, the choice of the surgical technique is important.

Cirrhosis generally recognizes three etiologies: metabolic, cholestatic and non-cholestatic. Patients with metabolic liver disease maintain normal hepatic reserve for a long period of time and generally do not develop portal hypertension compared to cholestatic liver disease associated with portal hypertension and liver failure due to cholangitis in advanced stages, and non-cholestatic liver disease that involves portal hypertension and diminished hepatic reserve.

Patients with metabolic and cholestatic liver disease (except advanced stages) can be assimilated to the general population as they present a slightly increased risk.

Non-cholestatic liver disease (alcoholic liver disease, viral hepatitis, non-alcoholic steatohepatitis) is the major cause of cirrhosis worldwide and cardiac surgery risk should be particularly evaluated in this group of patients.

The preoperative evaluation begins with a clinical history and full physical examination. A history of jaundice, poorly controlled ascites, physical exhaustion, gastrointestinal haemorrhage generally indicates advanced liver dysfunction and high operative risk. One should pay attention to changes suggestive of portal encephalopathy like sleep disorders, concentration difficulties, confabulation, altered handwriting. Portal hypertension is suggested by thrombocytopenia (<150,000), increased prothrombin time/INR, and normochromic normocytic anemia. Transaminases can register normal values and are not to be considered an indicator of liver dysfunction severity.

Additional to laboratory tests, preoperative abdominal ultrasound examination is mandatory to evaluate ascites and exclude a hepatocellular carcinoma. In patients with viral hepatitis B, viral replication should be excluded prior to surgery as it could lead to postoperative acute hepatitis. An

endoscopic examination should be performed prior to transesophageal echocardiography to exclude major varices at risk of bleeding.

The general status of these patients can be improved preoperatively. Nutritional assessment followed by renutrition strategy (high carbohydrate/lipid content and low sodium diet), vitamin K and protein administration are able to ameliorate prothrombin time/INR. Prophylactic administration of coagulation factors to correct hemostasis abnormalities is unjustified and potentially dangerous.

Portal hypertension can be managed with non-selective beta-blockers if the cardiac status allows it. The use of TIPS in candidates to cardiac surgery is a controverted measure. Although it decreases the portosystemic gradient, ascites and bleeding risk, TIPS could lead to heart failure, hepatic decompensation and exacerbate encephalopathy.

Hemodynamic optimization, adequate volemic management, and avoidance of nephrotic drugs are also fundamental points in the perioperative management of these patients. The impact of hypotension on morbidity and mortality (independently of other risk factors) suggests a particular susceptibility of the cirrhotic liver to ischemia, but excessive volume expansion is likely to aggravate ascites and lower limbs edema without an effective benefit on the circulating blood volume. Thus, hemodynamic optimization while monitoring the cardiac output or stroke volume is necessary.

Ascites, both peritoneal and pleural, leads to atelectasis and restrictive ventilatory defects in cirrhotic patients. Perioperative protective ventilation associating a tidal volume of 6 ml/kg of ideal weight and a PEEP (Positive end-expiratory pressure) of 6–8 cm H_2O appears particularly useful and reduces the incidence of postoperative pulmonary complications.

Finally, early recognition, timely and appropriate treatment of any perioperative infection can reduce postoperative morbidity and mortality.

Preoperative conversion of a CTP class C patient to CTP class B could improve postoperative survival.

73.5 Anaesthetic Management of Patients with Advanced Liver Dysfunction Undergoing Cardiac Surgery

The liver plays a major role in the metabolization, distribution and elimination of many drugs through two main mechanisms:

- Biotransformation through the cytochrome P450 pathway (oxygen-dependent—oxidation, reduction or hydrolysis) allowing the transformation of many hydrophobic compounds into hydrophilic compounds;
- Glucuronidation, glutathione or sulphate conjugation often succeeding first pathway (except for water-soluble molecules such as morphine), forming a more hydrophilic and acidic compound easily excreted in bile.

First pathway is altered in the early phases of liver dysfunction and the second phase, in the later phases. Generally, liver dysfunction interferes the metabolization of anaesthetic drugs secondary to alteration of the cytochrome P450 pathway, hypoproteinaemia (decreased binding) and decreased biliary excretion.

Many anaesthetic drugs are bound to plasma albumin and usually inactive in this phase. In case of hypo-albuminemia, the free fraction of these agents is therefore greater with a potentially increased pharmacological effect or toxicity. On the other hand, in case of portal hypertension, the first pass effect is reduced because of portosystemic shunts with, consequently, an increase in the bioavailability of drugs.

In well-compensated patients with close to normal liver function (CTP class A), the pharmacokinetics of anaesthetic drugs is almost unchanged. The more serious the cirrhosis is (portal hypertension, hepatocellular insufficiency), the more important and difficult to predict are the pharmacological changes.

Benzodiazepines, such as midazolam, should be avoided in cirrhotic patients as they could trigger hepatic encephalopathy. If such drugs are administered and the neurological state of the patient alters, flumazenil remains an effective antidote.

Propofol is not metabolised by the liver and does not suffer any major pharmacodynamic variation in cirrhotic patients. Similarly, inhaled anaesthetic agents, especially isoflurane, are poorly metabolized by the liver (0.2%) and are safe to be used in such cases [16]. Morphine on the other hand is metabolized by hepatic glucuronidation to an intermediate metabolite with renal elimination. Its half-life is prolonged in patients with CTP class B and C cirrhosis. If opioid administration is necessary, remifentanil could be safely used as it is not metabolized by the liver.

For curarisation, atracurium and doxacurium (for long interventions) are preferred as they do not undergo hepatic metabolization. Succinylcholine may have a prolonged effect due to a decrease in plasma cholinesterase activity.

73.6 Operative Management of Cirrhotic Patients Undergoing Major Cardiac Surgery. Cardiopulmonary Bypass and Liver Dysfunction

The key elements of operative management in cirrhotic patients are adequate visceral perfusion, correct hydroelectrolytic balance, thermoregulation, preventing hepatic decompensation, avoiding bleeding diathesis. Although not all centres are able to perform it, thromboelastography is a rapid method that evaluates the degree of coagulopathy and indicates potential optimization measures.

Cirrhotic patients poorly tolerate large volume oscillations and haemodilution is generally not recommended in this group of patients as its effects are unknown even if it was demonstrated to improve hepatic flow, both arterial and portal venous, in general population.

Compared to other major surgeries, most cardiac surgery interventions are performed on pump. The impact of cardiopulmonary bypass (CPB) upon liver function is incompletely elucidated. The materials used are not perfectly biocompatible and the established circulation is not physiological. CPB triggers a consumption of coagulation factors, an increase in the oxidative stress and a generalized inflammatory reaction resulting in the release of stress hormones and hepatotoxic cytokines. Finally, at the end of the intervention, when the aortic-cross clamp is removed, there is a sudden reperfusion with fully anticoagulated blood, immunologically primed and highly oxygenated.

The consequences of CPB could be summarized as follows:

- Immunological consequences
  - Activation of complement system (classical and alternative pathways) and liberation of active fractions C3a and C5a in the early phases (starting with aortic cannulation) as blood comes in contact with a foreign surface (cannulae, membrane oxygenator, circuits);
  - Neutrophils activation especially in lungs secondary to complement activation;
  - Prostaglandins augmentation—prostacyclin, thromboxane A2 secondary to free radicals liberation, complement activation, formation of heparin—protamine complexes;
  - Increase of pro-inflammatory cytokines (TNF-α, IL-6 and IL-8) 2–6 h after removal of aortic clamp;
  - Alteration of both humoral and cell-mediated immunity, quantitatively (decreased T, B and NK lymphocytes), qualitatively (decrease of CD4/CD8 ratio) and functionally. In cirrhotic patients, given the preoperative anergy, the risk of postoperative complications is particularly increased;
- Hematologic consequences:
  - Initial neutropenia secondary to hemodilution and lung accumulation of neutrophils followed by hyperleukocytosis (neutrophilia) correlated with an inflammatory response;
  - Activated neutrophils release proteases, free radicals, cytokines and lipid mediators. In the postoperative phase, neutrophils are desensitized and lose their abilities—chemotactic, phagocytosis and elastase production or free radicals—which would lead to septic risk;
  - Early thrombocytopenia secondary to hemodilution, CPB circuit and sequestration in the liver, spleen and lungs. Thrombocytopenia is aggravated by protamine administration;
  - Hemolysis particularly in case of abundant blood aspiration.
- Metabolic consequences:
  - Liberation of stress hormones (catecholamines, antidiuretic hormone, cortisol, glucagon) especially with normothermic CPB. Insulinemia is reduced with hypothermic CPB but not with normothermic CPB;
  - Increase in peripheral vascular resistance;
  - Desensitization of myocardial adrenergic receptors;
  - Hypocalcaemia;
- Visceral consequences:
  - Myocardial sideration of ischemic cause secondary to aortic clamping. Myocardial protection and cardioplegia are of particular importance in reducing ischemia-reperfusion myocardial injuries;
  - Extravascular lung water (EVLW) accumulation which may cause respiratory distress syndrome;
  - Pulmonary restrictive syndrome secondary to inflammatory reactions, sternotomy, prolonged decubitus and potential phrenic nerve lesions. Additional pulmonary injuries may be determined by complement activation, neutrophils sequestration and free radicals that damage the endothelium. Nowadays, membrane oxygenators reduce the incidence of pulmonary complications compared to ancient bubble oxygenators. The partial pressures of arterial oxygen (PaO2) and postoperative pulmonary vascular resistance are improved with normothermic CPB;
  - Neurological consequences are difficult to assess but cognitive disorders have been signalled in 22.5% of patients after CABG due to microembolism, hemodynamic or rheologic changes;
  - Renal impairment in CPB occurs secondary to hypotension with hypoperfusion, hemolysis and microembolism;
  - Hepatic dysfunction.

According to Di Tomasso et al., hepatic dysfunction secondary to CPB is due to microembolism, free radicals generation, inadequate tissue perfusion, dilutional anaemia and haemodynamic changes and we would add activation of multiple humoral (coagulation, complement, kinin-kallikrein, cytokines, fibrinolysis) and cellular (platelets, neutrophils, endothelial cells) systems [17]. Many factors contribute to these changes: blood contact with foreign surfaces, air-blood interface, hypothermia and reheating, blood cells trauma, intraoperative hypotension. Of particular interest in cirrhotic patients is the potential liberation of endotoxins secondary to intestinal ischemia.

In general population, transient elevation of bilirubin and hepatic enzymes is noticed in the early postoperative period, but in cirrhotic patients decompensation can occur. “Shocked liver” (hepatic ischemia), the extreme form of CPB related hepatic dysfunction determined by marked

hypotension and haemodynamic instability (perfusion quantitative and qualitative variations, rheologic changes), could become fatal in cirrhotic patients. The centrilobular zone is particularly sensitive to ischemia compared to bile ducts affected by lobular congestion (in case of right heart failure). CPB is considered one of the major determinants of postoperative hepatic morbidity in cardiac surgery. Di Tomasso et al. signalled a higher rate of refractory coagulopathy, infections, right ventricular failure, portal hypertension and hepatorenal syndrome in patients with preoperative liver dysfunction [17].

Patients in CTP class A tolerate CPB same as the general population but in class B, CPB should be avoided if possible. If on pump surgery is unavoidable, normothermic CPB should be used and its duration reduced to the minimum under a strict hemodynamic and coagulation monitoring. Mean arterial blood pressure should be maintained above 60 mmHg in the context of a dry approach with avoidance of fluid overload. Anaesthetic considerations previously mentioned are to be considered during the intervention.

Patients in CTP class C or with a history of complications related to portal hypertension are associated with a high mortality risk in case of open cardiac surgery. Endovascular procedures and optimal medical treatment should be considered in these cases.

73.7 Postoperative Care of Cirrhotic Patients After Major Cardiac Surgery

The cirrhotic patient carries a higher risk of prolonged hospitalization in the intensive care unit. The common cause of perioperative mortality is sepsis. Bacteraemia is frequent, mostly secondary to bacterial translocation correlated with deficient immune response. At the slightest suspicion, an empiric antibiotherapy should be quickly initiated. Postoperative leucocytosis and hyperbilirubinemia further increase the mortality risk.

Postoperative hepatic dysfunction in cirrhotic patients ranges from temporary hyperbilirubinemia related to intraoperative haemolysis, to decompensation and liver failure depending on the preoperative hepatic reserve and aetiology of liver dysfunction. Hyperbilirubinemia can be marked and prolonged if the evolution is complicated with cardiogenic shock and prolonged mechanical ventilation. Cholestasis may also occur due to hepatic ischemia and congestion. Its consequences are variable, from digestion impairment to cholangitis. Prolonged cholestasis and hyperbilirubinemia correlate with postoperative morbidity and mortality.

Major supportive measures in the postoperative period include hemodynamic support to avoid hepatic ischemia, early reinitiation of adequate enteral nutrition, haemorrhage and sepsis prevention.

Fresh frozen plasma (FFP) can be used to correct identified coagulopathies while monitoring the central venous pressure to avoid fluid overload. If FFP is not sufficient or not indicated (fluid overload), cryoprecipitate or desmopressin represent alternative methods.

Fluid administration (oral or intravenous) and sodium intake restriction are recommended to prevent postoperative ascites. If the patient received a diuretic treatment with furosemide prior to surgery, the treatment should be continued postoperatively while monitoring hydroelectrolytic balance and renal function.

Postoperative pain relief is another issue to be considered. Patients in CTP class A tolerate morphine and fentanyl administration but the dose should be reduced in class B patients. Nonsteroidal anti-inflammatory drugs are to be avoided as they are nephrotoxic and increase the risk of gastrointestinal haemorrhage. Acetaminophen administration is not contraindicated, but doses should be reduced (<2 g/day). Special care should be paid not to provoke somnolence as it could mask incipient signs of hepatic encephalopathy.

Prophylaxis of gastrointestinal haemorrhage with intravenous ranitidine, somatostatin and metoclopramide is recommended especially in patients with portal hypertension.

Correct partial arterial pressure of oxygen and a haemoglobin level superior to 9 mg/dL assure a good hepatic oxygenation in the absence of hypotension.

73.8 Endovascular Procedures in Cirrhotic Patients

The emergence of endovascular cardiac interventions and especially transcatheter aortic valve implantation (TAVI) completely changed the management of aortic stenosis and expanded the range of potential candidates to aortic valve replacement. Patients previously considered at high risk for surgical aortic valve replacement (SAVR) are now potential candidates to TAVI.

In 2017, Alqahtani et al. published an extensive study comparing the outcomes of TAVI and SAR in cirrhotic patients. They analysed 1766 cirrhotic patients treated over a 12 years period, and propensity matched 268 patients (134 with TAVI and 134 with SAVR). The reported postoperative mortality was significantly lower with TAVI (8.2%) compared to SAVR (20.2%) same as blood transfusion rate and hospital length of stay [18].

Yassin et al. on the other hand, compared the outcomes of TAVI in cirrhotic and non-cirrhotic patients and found that cirrhotic patients registered no increase in the risk of in-hospital mortality or postprocedural complications [19].

All studies analysing the outcomes of TAVI in cirrhotic patients up to date are performed on small matched groups with low incidence of specific complications. Authors report

decreased renal, pulmonary, infectious and neurological complication rates with TAVI compared to SAVR but with no statistical significance given the reduced number of cases. They are unanimous in stating that TAVI is a safe procedure in patients with advanced liver dysfunction being associated with lower mortality rates and length of stay.

The major advances of TAVI in cirrhotic patients are represented by the absence of CPB, shorter anaesthesia, lesser requirement of blood and blood products transfusions.

73.9 Early Ischemic Liver Injury After Cardiac Surgery

Ischemic hepatitis occurs in the presence of a combination of hepatic hypoxia and hepatic venous congestion and is a rare complication of cardiac surgery with CPB. Also called "shocked liver", it characterized by massive elevation of aspartate aminotransferases (AST) up to 20 times normal values [20]. At the cellular level, ischemic hepatitis occurs in two phases that correspond to an ischemia/reperfusion mechanism.

The reperfusion phase is crucial because it is the main cause of the majority of cellular damage. The ischemic phase is accompanied by an initially reversible edema of centrilobular hepatocytes and sinusoidal cells. If ischemia continues, cellular dysfunction occurs with activation of enzymes such as proteases and phospholipases and intracellular oxidative stress reactions.

The reperfusion phase occurs during the restoration of hemodynamics when hepatic blood flow increases and oxygen again reaches the hepatocytes.

In the case of prolonged ischemic phase, ischemia/reperfusion injury with cell necrosis will occur due to intracellular oxidative stress at the beginning of re-oxygenation, activation of Kupffer cells, and abnormalities of the sinusoidal microcirculation. Lactic dehydrogenase (LDH) is a marker of hepatic cytolysis. The xanthine/xanthine oxidase enzymatic system also plays a major role in cellular oxidative stress. Metabolites will contribute to free radicals formation (superoxide) that further activate the neutrophils which will secrete proteases. Free radicals and proteases are responsible for hepatic cytolysis mainly in the intermediate region.

Hepatic congestion secondary to increased central venous pressure also contributes to ischemic hepatitis.

"Shocked liver" syndrome generally installs in the first 48 h after the surgical intervention. The patient may present with nausea, vomiting, jaundice, turgescent jugular veins and hepatojugular reflux, hemorrhagic syndrome or even hepatic encephalopathy in patients with preexistent liver dysfunction. Laboratory testes reveal a marked increase of AST and alanine aminotransferase (ALT) up to 20 times normal values and also of LDH. Bilirubin level also increases but at a lesser extent. Coagulopathy is aggravated by hepatic ischemia with potential hemorrhagic diathesis. In non-cirrhotic patients, clinical symptoms and laboratory test results improve in a few days of normal hemodynamics is restored. In patients with prior liver dysfunction, it can evolve towards potentially fatal complications like hepatic encephalopathy, liver failure or multiple organ dysfunction syndrome (MODS).

The treatment of this condition relies mainly on prevention (maintenance of adequate blood perfusion and avoidance of major volume shifts during the intervention) and, if it occurs, the only option is represented by supportive measures (sepsis, hemorrhage and further ischemia risk minimization).

73.10 Conclusion

Pathophysiological changes associated with advanced liver dysfunction predispose to potentially fatal complications in cardiac surgery especially if the intervention is performed with CPB. Patients in CTP class A can undergo elective cardiac surgery same as the general population with almost similar outcome. In CTP class B patients, elective interventions are possible, preferably off pump after adequate preoperative preparation. In CTP class C patients, open cardiac surgery is contraindicated and endovascular treatment should be considered instead if technically possible. Anaesthetic and perioperative management have be adapted to specific metabolic, humoral, haematological and hemodynamic alterations to prevent postoperative morbidity and mortality.

Self Study

Questions

1. Which statement is true?
   (a) Cardiac surgery risk scores (STS, EuroSCORE II) correctly estimate mortality risk in cirrhotic patients.
   (b) Cardiopulmonary bypass has no impact on liver function.
   (c) In CTP class A patients the pharmacokinetics of anaesthetic drugs is almost unchanged.
   (d) Advanced liver dysfunction is an absolute contraindication to cardiac surgery.
2. Which statement is true?
   (a) Non cirrhotic patients register no changes of liver function tests in the postoperative period.

(b) Haemorrhagic complications are most common cause of postoperative mortality in cirrhotic patients undergoing cardiac surgery.
(c) TAVI is not indicated in CTP class C patients.
(d) Fresh frozen plasma (FFP) can be used to correct coagulopathies in the postoperative period.

Answers

1. Which statement is true?
   (a) EuroSCORE II system includes a limited number of patient related factors like age, gender, renal impairment, extracardiac arteriopathy, poor mobility, previous cardiac surgery, chronic lung disease, active endocarditis, critical preoperative state, diabetes on insulin, and omits all parameters relevant for liver function. STS on the other hand, includes liver disease among the evaluated parameters as a binary selection (Yes or No) irrespective to the type and severity of the disease
   (b) Hepatic dysfunction secondary to CPB is due to microembolism, free radicals generation, inadequate tissue perfusion, dilutional anaemia and haemodynamic changes and activation of multiple humoral (coagulation, complement, kinin-kallikrein, cytokines, fibrinolysis) and cellular (platelets, neutrophils, endothelial cells) systems.
   (c) CORRECT ANSWER. In well-compensated patients with close to normal liver function (CTP class A), the pharmacokinetics of anaesthetic drugs is almost unchanged. The more serious the cirrhosis is (portal hypertension, hepatocellular insufficiency), the more important and difficult to predict are the pharmacological changes.
   (d) CTP class A patients can safely undergo cardiac surgery. In class B, open cardiac surgery is possible, preferably off pump and after adequate preoperative preparation.
2. Which statement is true?
   (a) In general population, transient elevation of bilirubin and hepatic enzymes is noticed in the early postoperative period, but in cirrhotic patients decompensation can occur.
   (b) The cirrhotic patient carries a higher risk of prolonged hospitalization in the intensive care unit and the most common cause of perioperative mortality is sepsis. Bacteraemia is frequent, mostly secondary to bacterial translocation correlated with deficient immune response. At the slightest suspicion, an empiric antibiotherapy should be quickly initiated.
   (c) In CTP class C patients, open cardiac surgery is contraindicated and endovascular treatment (TAVI) should be considered instead if technically possible.
   (d) CORRECT ANSWER. Fresh frozen plasma (FFP) can be used to correct identified coagulopathies while monitoring the central venous pressure to avoid fluid overload. If FFP is not sufficient or not indicated (fluid overload), cryoprecipitate or desmopressin represent alternative methods.

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