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Review article

Early circulatory complications in liver transplant patients

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1. Introduction

Orthotopic liver transplantation (LT) is considered a beneficial definitive treatment option for acute and chronic end-stage liver disease (ESLD). The short- and long-term outcomes, and survival of liver transplant recipients have improved over the years as a result of advances in anesthesiological management and surgical techniques, better individualized postoperative care, and new, more effective anti-rejection drugs. Complications such as hemorrhage, cardiovascular and cerebrovascular disease, vascular or biliary issues, metabolic disorders, infections, and 'distant' organ dysfunction can still occur soon after the transplant, however, even though the number and severity of such postoperative adverse events have diminished. Intra- and postoperative hemodynamic disturbances often result in inadequate or fluctuating blood pressure, or a 'low flow state'. These events are associated with adverse outcomes, such as graft dysfunction, prolonged dependence on mechanical ventilation, acute renal injury, sepsis, and an increase in post-transplant morbidity and mortality [1–3].

This review describes the most relevant circumstances leading to hemodynamic instability and cardiovascular complications in the early post-transplant period. Common consequences on systemic organs, and strategies currently used to prevent or manage postoperative circulatory complications are also briefly summarized.

2. Hemodynamic changes after liver transplantation

The LT procedure may significantly affect the recipient's cardiac function: postoperative fluid redistribution, changes in oncotic pressure, possible anemia, and the restoration of systemic and pulmonary vascular tone can cause unpredictable mechanical stress on left ventricular (LV) systolic and diastolic function.

Several studies have demonstrated that preoperative cardiocirculatory abnormalities tend to fade with time after LT [4–6]. Whatever the etiology of cirrhosis, the associated basic hyperdynamic and cardiomyopathic features gradually improve already during the post-transplant course, and usually disappear entirely in 6–12 months after LT. A small proportion of recipients continue to have chronic and stable vascular alterations, however, and they retain a systemic hyperdynamic state even long after their LT. Cardiac output reportedly decreases in parallel with an increase in systemic vascular resistance and normalization of portal hypertension. Echocardiographic findings demonstrate a regression of LV hypertrophy and thickness, a reduction in LV mass, and an improvement in diastolic function. From weeks to months after LT, there is a gradual recovery from the basal hyperdynamic systolic dysfunction and abnormal systolic response to physical stress, which is responsible for a subjective clinical improvement and a greater cardiac workload and exercise capacity [7]. The vast majority of liver recipients' hyperdynamic syndrome normalizes, their structural and electrophysiological abnormalities decrease, and their myocardial performance improves [5].

The early circulatory changes induced by the rapid recovery of their new liver may result in significant cardiovascular stress for recipients. Portal pressure is restored very soon after LT (largely in the first week after the procedure), leading to a reduction in the portal vein to inferior vena cava pressure gradient. This condition coincides with a gradual recovery of systemic vascular tone and peripheral vascular resistance. The subsequent increase in preload and afterload gives rise to higher volumes of the cardiac chambers and a rise in blood pressure, causing further stress on the critical reserves of cirrhotic cardiomyopathy.

Because of late-onset improvements in the structural and functional characteristics of the myocardium, a normal, physiological stress response may not be produced and sustained, so there may be a greater risk of acute heart decompensation during periods of increased demand. The LT recipients at risk are those with latent pre-existing congestive heart failure (HF), a situation that can deteriorate rapidly as a consequence of the above-described hemodynamic changes [8,9].

3. Incidence of cardiocirculatory complications after liver transplantation

Episodes of HF or hemodynamic decompensation are not unusual after LT because of the above-mentioned acute changes in vascular tone and splanchnic circulation, but there are only a few, not very recent publications on the real incidence of post-LT cardiac complications. Dec et al. [10] reported one or more cardiovascular complications in 70% of their LT recipients, including pulmonary edema, myocardial ischemia or infarction, ventricular tachycardia, and new dilated cardiomyopathy. In a series reported by the Mayo Clinic group, seven out of 754 adult LT recipients developed a reversible dilated cardiomyopathy within five days after the transplant. Clinical signs of congestive HF and pulmonary edema (such as four-chamber dilation on echocardiogram, or a marked decrease in the LV ejection fraction) were apparent in all patients [11]. In 2002, Therapondos et al. [8] reported finding that one in four of their LT recipients experienced cardiac events, both peri- and postoperatively, with a high incidence of postoperative pulmonary edema. An Asian paper reported a 10% incidence of acute HF, and a 7% incidence of myocardial infarction after LT procedures performed in the years 1993–2001 [12]. Similar data were reported by Eimer et al. [13] Patients who developed HF were slightly older, and had significantly higher mean pulmonary arterial systolic pressure, and right ventricular systolic pressure preoperatively. When Eleid et al. [14] retrospectively reviewed the incidence of cardiac complications in 393 LT patients, they found that 26 patients (6.6%), suffered from acute cardiac events, including 13 arrhythmias, 7 new-onset HF, and 6 myocardial infarctions. In 400 LT recipients managed at the University of Indiana, Safadi et al. [15] detected a 12% rate of adverse cardiac events within 30 days after LT, with a 7% incidence of non-fatal myocardial infarction, and an associated mortality of 9%. Finally Qureshi et al. [16] reported early-onset (<7 days) systolic HF and diastolic dysfunction in 6.9% and 2.5% of their LT patients, respectively.

4. Predictors of post-transplant cardiovascular complications

Several preoperative variables have been associated with a higher risk of acute adverse cardiac events and circulatory failure after LT, the best-known being: a) preoperative evidence on echocardiography of a significantly depressed LV systolic function; b) four-chamber enlargement with regional wall motion abnormalities; c) evidence of diastolic dysfunction; d) history of coronary artery disease (CAD), pulmonary hypertension, or significant valvular abnormalities. Other conditions predictive of new-onset, post-transplant HF include: diabetes, hypertension, dyslipidemia, elevated blood urea nitrogen levels, hemodialysis, high BNP (brain natriuretic peptide) levels, and prolonged QT intervals [15,17].

Safadi et al. [15] demonstrated that a history of CAD or stroke alone significantly raise the likelihood of adverse cardiac outcomes in the first 30-days after LT. Pathological cardiovascular stress test results and a greater interventricular septal thickness have also been recognized as important predictors of perioperative cardiac events.

Coronary calcium scores on coronary CT have been associated with a higher risk of post-transplant cardiovascular complications too [18–21]. In particular, preoperative coronary calcium scores >400 emerged as a good predictor of cardiovascular complications developing a month after LT. Preoperative medical conditions (e.g. diabetes, dyslipidemia, a family history of CAD, hypertension, smoking, and alcohol/cocaine abuse) were not identified as significant risk factors for post-transplant HF in the study conducted by Qureshi [16]. On the other hand, a history of cardiac disease, end-stage renal disease, high BNP levels, an increased left atrial diameter, high MELD, MELD-Na and i-MELD (integrated MELD) scores, large intraoperative transfusions of fresh frozen plasma (FFP) and red blood cells (RBC), and intraoperative cardiac arrest all correlated significantly with the occurrence of perioperative cardiac events [16,22].

Diastolic dysfunction has also been recognized as an important cause of cardiovascular impairment and unexpected death after LT [23]. This condition is generally clinically silent, but not infrequent, and it is revealed by physiological stress. Dowsley et al. [24] demonstrated that severe left atrial enlargement, and an increased E/E′ on preoperative echographic evaluation were associated with a greater risk of early-onset postoperative HF in LT recipients. The same authors considered left atrium size, measured on echocardiography with the left atrial volume index (values >40 mL/m^2), and LV wall stiffness as surrogate markers of cirrhotic cardiomyopathy, and sensitive predictors of a higher mortality within the first year after LT. Hemochromatosis and hypertrophic cardiomyopathy are other severe conditions related to a higher risk of postoperative HF [25]. Preoperative serum cardiac troponin levels have also proved a valid predictor of post-transplant adverse cardiovascular events. In studies by Coss et al. [26], and Watt et al. [27], high serum troponin levels prior to LT were frequently associated with post-transplant cardiovascular complications in asymptomatic recipients with or without diabetes or a history of cardiovascular disease. High troponin levels were also found a strong predictor of overall mortality and graft loss after LT.

Cirrhotic cardiomyopathy, which often coexists with the above diseases, should be seen as another important risk factor for early post-transplant HF, hemodynamic impairment and poor cardiovascular outcomes after LT.

5. Hemodynamic instability after liver transplantation

Common causes of hemodynamic instability after LT include severe hypovolemia (due hemorrhage, third-space losses, ascites, etc.), persistent hemodynamic effects of post-reperfusion syndrome (PRS), hypocalcemia-induced citrate intoxication (in cases requiring massive transfusions), and liver allograft failure. Myocardial infarction, congestive HF, arrhythmias, non-ischemic valvular and hypertensive heart disease, porto-pulmonary hypertension, and other acute cardiac or cardiopulmonary events can also have a major impact on postoperative hemodynamics. Serious cardiovascular events and HF in the early post-transplant period are major causes of LT-related morbidity and mortality [22]. They can occur in patients with no previous history of heart disease as well as in LT recipients with preoperative risk factors [28].

The following section lists the most common diseases responsible for severe circulatory disorders.

5.1. Unremitting hypotension due to prolonged vasoplegic syndrome or post-reperfusion syndrome

Profound and sustained vasodilation, with a significant decrease in arterial blood pressure and a poor response to norepinephrine and phenylephrine may persist in the immediate postoperative period due to a delayed recovery of vasoplegic syndrome or to PRS.

Vasoplegic syndrome (VS) was described by Ozal et al. [29] and Shanmugam et al. [30] as a refractory hypotensive state characterized by normal or increased cardiac output, decreased filling pressure, and decreased systemic vascular resistance. In the course of LT, the onset of VS has been defined [31–33] as a severe drop in systemic arterial pressure (<50 mm Hg), a decrease in systemic vascular resistance (SVR), a normal or increased cardiac output, tachycardia, no response to volume load or vasoconstrictive drugs, in the absence of recognized ongoing hypovolemia (hemorrhage, electrolyte abnormalities, severe anemia).

VS is a rare, but very serious event. It is the most severe form of hemodynamic instability occurring during LT, and has been associated with severe ischemia-reperfusion injury (IRI) to the liver and intestine, and a massive release of vasodilating factors. Other potential causes of VS include surgical trauma, neuroendocrine disorders, systemic inflammatory response, endotoxemia, and the transfusion of blood components [34]. Its incidence is unknown. In severe, refractory forms it can lead to vasoplegic shock, failure of microcirculatory activity, and inadequate organ perfusion [35]. An excessive production of nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) seems to play a fundamental part in the origin of VS[30]. Managing VS is extremely challenging, as vasoplegic shock is refractory to conventional vasopressive medication. The profound vasomotor dysfunction of VS seems to respond to methylene blue administration, however. The proposed etiologic mechanism behind VS [35,36] involves dysregulation of NO synthesis, and activation of vascular smooth muscle cell guanylate cyclase, with extreme vasodilation. Methylene blue (in bolus and/or continuous infusion) has proved capable of reversing a state of vasoplegia because it blocks NO and can inhibit prostacyclin synthesis, thereby improving hemodynamics and potentiating vasopressors. The suggested loading dose is 2 mg/kg over 30 min, followed by maintenance infusions of 0.5 mg/kg/h for 6 h [37]. The decrease in NO production indirectly increases vascular smooth muscle constriction, improves blood pressure, and increases myocardial contractility [32,38].

PRS, on the other hand, is a relatively frequent event during graft reperfusion. It is characterized by a dramatic cardiovascular and metabolic derangement that occurs after unclamping the inferior vena cava and portal vein. PRS was first described by Aggarwal et al. [39] as a >30% decrease in mean arterial pressure (MAP) below the baseline value lasting for at least 1 min, and occurring during the first five minutes after reperfusing the liver graft. Severe PRS is characterized by substantial hemodynamic instability, with a marked decrease in heart rate, significant arrhythmias and sometimes asystole. Common hemodynamic features of PRS include a drop in the cardiac index, an increase in pulmonary capillary wedge pressure (PCWP), a decrease in the stroke volume index, and a rise in pulmonary arterial pressure (PAP) and the pulmonary vascular resistance index. Changes in right ventricular function and in the right ventricular-pulmonary artery coupling may also contribute to the hemodynamic signs of this syndrome.

Unremitting PRS may require the infusion of high doses of vasopressors and cardioactive drugs, as well as calcium, bicarbonate and fluids. The cardiovascular manifestations and circulatory disruptions of PRS may sometimes persist throughout the first postoperative period [40], negatively influencing the LT recipient's postoperative morbidity and mortality.

Hemodynamic instability due to VS and PRS should be distinguished from other causes of perioperative circulatory failure (such as acute cardiac dysfunction, pulmonary emboli, or anaphylactic shock). Severe hypotension following graft revascularization may be difficult to interpret as part of a PRS, VS, or simply a significant reperfusion hypotension.

The persistent activity of 'not clearly identified' factors of myocardial depression and other 'toxic mediators' released after a serious reperfusion syndrome that is slow to regress has also been included among the many conditions responsible for postoperative hemodynamic impairment [41]. Mediators such as proinflammatory cytokines (interleukin-6, interleukin 1β), prostacyclin, endotoxins, and tumor necrosis factor alpha, released into the systemic circulation in response to severe ischemia-induced injury of the liver and splanchnic organs, may reduce postoperative ventricular function and affect hemodynamic stability [42,43].

5.2. Early allograft dysfunction and primary non-function (PNF)

Post-transplant hemodynamic disturbances may also occur as complications of early allograft dysfunction or primary non-function (PNF). Early graft dysfunction is mainly characterized by a poor liver metabolism and function, transient clinical and laboratory changes, and mild or no encephalopathy, and it tends to improve within a week. In contrast, PNF is the result of irreversible graft failure with no detectable technical or immunological problems, and may have a major impact on a patient's prognosis and clinical outcome after LT. PNF is responsible for catastrophic clinical and laboratory deterioration, with

hyperkaliemia, an increase in serum lactate, neurological disorders, severe coagulopathy, and ultimately hemodynamic instability and oliguric renal failure up to the second week post-transplant. Other clinical signs include persistent encephalopathy, marked hypoglycemia, and little or no bile production, associated with gradually rising serum AST levels [44]. A prompt return of PNF patients to the organ transplant waiting list and a subsequent successful repeat LT is the only way to prevent their rapid death.

5.3. Decompensation of cirrhotic cardiomyopathy and heart failure

LT poses a severe challenge to the cardiovascular system, and liver recipients with prior cardiomyopathies are more prone to severe circulatory complications in the postoperative period. Cirrhotic cardiomyopathy is a well-known cardiac complication of ESLD, and associated with a high risk of acute HF and a poor prognosis after LT. It is essentially characterized by [45]: a) systolic dysfunction, which reduces cardiac performance and impedes the physiological increase in cardiac output and ejection fraction in response to physical exercise or pharmacological stress; b) diastolic dysfunction, resulting from myocardial subendothelial edema and hypertrophy, and inducing abnormal LV relaxation with elevated filling pressures; c) increased LV end-diastolic pressure, and stretching of the myocardial fibers; and d) electrophysiological abnormalities, a prolonged QT interval, defective electromechanical coupling and dissociation, and chronotropic incompetence (an impaired cardiac response to physiological and pharmacological stimuli aiming to increase heart rate).

Cirrhotic cardiomyopathy is often misdiagnosed because it is largely asymptomatic at rest, or confused with other symptoms of advanced liver cirrhosis, such as exercise intolerance, fatigue and dyspnea. It becomes significant, however, when pathophysiological, pharmacological or surgical events challenge the patient's cardiovascular system. Occult cirrhotic cardiomyopathy may manifest with unexpected and often severe LV systolic and diastolic dysfunction, sometimes rapidly arising post-transplant when the redistribution of significant blood volumes leads to marked right and LV volume overload, and a contemporary increase in afterload. Rapid postoperative reversion of systemic vasodilation prompts a sudden increase in the cardiac workload, causing further stress to the weakened heart (systolic stress). Acute diastolic function impairment may also occur as a consequence of the modified postoperative hemodynamic profile, raising the risk of acute LV failure and pulmonary edema, even with only a slight increase in blood pressure.

The onset of congestive cardiac failure leaves the heart unable to cope with any surgery-related stress or substantial metabolic derangement, and may directly affect transplant patients' immediate and late survival chances. Acidosis, hypothermia, electrolyte disruption, critical anemia, and exposure to cardiac-depressant drugs can also impair the patient's weakened cardiac contractility, leading to hemodynamic instability and blood pressure fluctuations.

Right ventricular (RV) function is sometimes impaired in the anhepatic and early reperfusion stages, and may also contribute to hemodynamic instability in the early postoperative period. In the setting of a complicated post-LT course, especially in high-MELD patients, RV function is particularly affected by changes in preload and afterload. This suggests that the cirrhotic cardiomyopathy of advanced liver disease may also impair RV response to stress: an adequate RV contractility is essential to venous return from the graft and splanchnic organs [46].

It is not unusual for severe LV dysfunction to ensue after LT, even in patients with no known preoperative risk factors for HF. This is because reliable strategies for earmarking patients susceptible to cardiovascular complications are still lacking in the commonly-adopted preoperative work-up at many hospitals. A 'silent history' during physical examination, electrocardiography, and echocardiography at rest rarely predict the real risk. Due to the markedly-reduced afterload in cirrhotic patients, even measuring the LV ejection fraction and cardiac output under stress cannot precisely identify occult LV systolic functional impairment [47].

More invasive preoperative investigations may help in the risk stratification of cardiovascular disorders and improve post-LT outcomes. Such investigations often involve combinations of: Doppler echocardiography; dobutamine stress echocardiography; myocardial perfusion imaging; myocardial perfusion scintigraphy; real-time stress myocardial contrast perfusion echocardiography; cardiopulmonary exercise testing; coronary artery calcium scoring on cardiac computed tomography; cardiac magnetic resonance imaging; coronary angiography; or computed tomographic coronary angiography.

Acute ionic hypocalcemia is another unfavorable condition that sometimes goes undetected, and may promote postoperative hemodynamic impairment. Patients with ESLD receiving large amounts of citrated blood products as a consequence of massive hemorrhage may have a reduced cardiac index, stroke index, and LV work index [48]. Hypocalcemia is an ominous sign during massive hemorrhage, and seen as a predictor of mortality [49]. After LT, hypocalcemia may depend on the volume of blood products administered, the transfusion rate, the patient's volemia, or the liver's metabolic capacity and blood flow. As stored blood is anticoagulated with citrate (3 g/unit RBC), the transfusion of large amounts of RBC leads to citrate intoxication, calcium chelation and hypocalcemia. Correcting metabolic acidosis with rapid infusions of sodium bicarbonate ($HCO3$) may also lower the percentage of ionized calcium, as free calcium binds rapidly to $HCO3$.

Autonomic neuropathy is a frequent complication of ESLD and an often hidden but important cause of postoperative hemodynamic instability and inadequate response to fluid loading and vasopressors. Impaired reflex vasoconstrictor responses to surgical manipulations and changes in circulating volume may raise the risk of intraoperative hypotension under general anesthesia, and cause maladaptive cardiovascular responses under stressful postoperative conditions [50] Cirrhosis-associated autonomic dysfunction has also been implicated in the onset of severe arterial hypotension and the need for significant for vasopressor therapy during the LT procedure in recipients with familial amyloidotic polyneuropathy [51].

A quite rare, but well-known cause of severe post-LT circulatory dysfunction is the so-called stress-induced cardiomyopathy, also known as *Takotsubo cardiomyopathy* or *acute broken heart syndrome* (ABS). Its clinical signs are very similar to those of an acute coronary event, with dyspnea, chest pain, syncope, altered mental status, cold extremities, increased serum lactate levels, and often cardiogenic shock [52,53]. This syndrome is probably caused by serious perioperative hemodynamic changes, intense surgery-related stress to the myocardium, or other unanticipated factors that stimulate a substantial catecholamine surge. A massive release of catecholamines leads to diffuse microvascular spasm, together with myocardial stunning and symptoms of heart failure [54] . The preoperative cardiological work-up does not usually arouse any suspicions of ABS (preoperative stress tests are usually negative), and echocardiographic images show no sign of impaired myocardial contraction. Once ABS becomes manifest, transthoracic or transesophageal echography may reveal severe hypokinesis in various regions of the LV, high left atrial pressure, severe LV diastolic dysfunction, frequent premature ventricular contractions, and mitral insufficiency [55,56]. The treatment for Takotsubo cardiomyopathy is much the same as for acute coronary syndrome or cardiogenic shock with other causes. In cases of refractory cardiogenic shock, an extracorporeal membrane oxygenator (ECMO) or counterpulsation with an intra-aortic balloon pump have sometimes been used successfully [57,58].

Another very rarely reported cause of early postoperative hemodynamic instability is *new-onset post-transplant dilated cardiomyopathy*. Described in small case series [11] is associated with major cardiovascular complications such as pulmonary edema, decompensation of pre-existing but compensated heart disease, respiratory failure, and fluid retention. In the above studies, myocardial depression in the early post-liver transplant period, was associated with four-chamber

dilatation on echocardiogram, and with marked decreases in cardiac index and LV ejection fraction (from a pre-operative median baseline of 60% to 20%). No history or diagnostic findings of coronary artery disease were detected. HF from cardiomegaly and significantly reduced cardiac function turned out to be reversible within days or weeks, but all patients required reintubation, mechanical ventilation, afterload reduction, inotropes, and intensive supportive care.

5.4. Postoperative cardiac arrhythmias

Severe and persistent arrhythmias are almost constantly associated with substantial perioperative hemodynamic derangement. The most important risk factors for post-transplant arrhythmias are listed in Table 1 [59,60].

Structural and histologic alterations in cardiac fibers occurring with ESLD are mainly responsible for electrical instability and electrocardiographic abnormalities; the cardiocirculatory changes and the stressful hemodynamic events of the early postoperative period may aggravate the intrinsic electrophysiological disturbances and then the risk of arrhythmia. Cardiac arrhythmias may be evoked by many factors, independently from myocardial ischemia or previous cardiac disease. Atrial fibrillation and flutter, premature atrial and ventricular contractions, ventricular arrhythmias, atrioventricular re-entry tachycardia, prolonged QT intervals, increased QT dispersion, chronotropic incompetence, and electromechanical uncoupling are all common early-period arrhythmias. Hemodynamic disorders and blood pressure instability depend on the severity and duration of arrhythmias [60,61] In particular, a prolonged QT interval, requent in liver cirrhosis) predisposes patients to severe ventricular tachycardia, which can lead to repetitive ventricular arrhythmias and significant hemodynamic deterioration, *torsade de pointes*, and/or potentially fatal ventricular fibrillation [62]. Fatal arrhythmias in LT may be triggered by reperfusion injury, electrolyte abnormalities, and various types of medication, including anesthetics and sedatives, which influence the QT interval [63]. In addition to the risk factors listed in Table 1, changes in the levels of plasma calcium, serum bile salts, serum uric acid, plasma renin, aldosterone, atrial natriuretic factor, and gonadal hormones are other important risk factors for the onset of prolonged perioperative QT intervals [64]. Some drugs, such as fluoroquinolones, vasopressin, terlipressin, neuroleptics, and medication to prevent postoperative nausea and vomiting, may also affect the QT interval and should be used with caution after LT.

Table 1
Risk factors for postoperative arrhythmias after LT.

Perioperative
Potential coexisting cirrhotic cardiomyopathy
Renal dysfunction
Impaired autonomic function of end-stage liver disease
Enlarged left atrium
Coronary heart disease
Recipients who smoke, or have hypertension or diabetes
Advanced age
Atrial interstitial fibrosis
Surgery-related
Fluid imbalance
Surgery-induced inflammatory syndrome
Metabolic abnormalities
High sympathetic nervous system activity
Postoperative
Electrolyte abnormalities
Fluid imbalance
Renal dysfunction
Hypoxemia and hypercarbia
Cardiac ion channel remodeling
Metabolic abnormalities
High sympathetic nervous system activity
Diuretics
Other medications

5.5. Sepsis-induced circulatory dysfunction

Early postoperative infections are the most important cause of critical illness, morbidity and complications, and prolonged stays in the ICU after LT. Recognized risk factors for postoperative infections include recipient MELD scores >30, renal failure, preoperative infections or colonization, infections with viruses such as cytomegalovirus, serious IRI, large intraoperative blood transfusions, graft dysfunction, rejection, profound immunosuppression, dialysis, prolonged mechanical ventilation, repeat surgical procedures, re-transplantation, and prolonged stays in the ICU [65].

Severe bacterial and fungal infections in the first few weeks after LT can lead to complications such as bacteremia and sepsis, demanding lengthy ICU stays, which in turn raise the risk of nosocomial and ventilator-associated pneumonia, bloodstream infections, infections due to associated invasive devices (central venous catheter CVC, urinary catheter, tracheal tube, drainages, etc) and antibiotic-related infection by *C. difficile*.

Post-transplant complications such as bleeding, biliary or vascular obstruction, complex choledocho-jejunostomy and wound dehiscence are important causes of intra-abdominal infections. Urgent re-operations are needed to treat such complications and prevent systemic sepsis, but they can have serious hemodynamic consequences in unstable hypovolemic recipients, and they raise the risk of 'distant' organ dysfunction [66]. Unrelenting postoperative sepsis and septic shock are always associated with profound circulatory disturbances and require complex and aggressive treatment in the ICU. Sepsis-induced exacerbation of existing cirrhotic cardiomyopathy is among the various factors potentially responsible for the further impairment of LT patients' weak circulatory reserves. Sepsis-related myocardial depression has been clearly characterized as a decreased LV ejection fraction with preserved stroke volume, elevated filling pressure, and diastolic dysfunction [67]. Although the phenomenon of sepsis-induced cardiomyopathy has proved reversible, the process of restoring contractility and remodeling wall akinesis can take some time (1–2 weeks). In the meantime, the persistent myocardial stunning and intrinsic dysfunctional contractility expose transplanted patients to a high risk of hemodynamic decompensation. Cardiac failure is life-threatening in LT recipients with septic shock: it sometimes proves impossible to maintain a sufficient mean arterial pressure (>65 mmHg) despite the infusion of very high doses of inotropes, vasopressors, and substantial loads of fluids. In patients with profound unremitting shock after LT mechanical circulatory support may be a valuable adjunct to give the failing cardiocirculatory system extra time to recover, and to maintain organ perfusion until cardiac function recovers spontaneously. ECMO has been used as a rescue therapy for adult LT recipients with refractory bacterial septic shock, serious cardiac dysfunction, and evidence of organ hypoperfusion [68].

5.6. Relative adrenal insufficiency

Though rare, unexplained hypotensive episodes soon after LT may also occur with overt clinical signs of relative adrenal insufficiency [69]. In critically-ill patients and those with advanced liver disease (with or without septic conditions), adrenal insufficiency is the result of inadequate activation of the hypothalamic-pituitary-adrenal axis, with the consequent insufficient release of cortisol in response to illness and stress. It manifests with catecholamine-resistant hemodynamic instability and is associated with high mortality rates [70,71].

If corticosteroids are not included in the post-transplant immunosuppressive regimen, the physiological adrenal response to stress may be blunted and cardiovascular instability may ensue, both during and after LT. This can happen especially when the recipient's neuroendocrine reserves are markedly strained by stressful situations such as sepsis, trauma, bleeding, and aggressive surgery. Severe adrenal insufficiency, sometimes appearing as multiple organ dysfunction, and later

responding successfully to corticosteroids, has been reported in LT recipients on steroid-free immunosuppression [72–74]. Unexplained post-transplant hypotension requiring substantial amounts of vasopressors may benefit from corticosteroid administration, at least up until liver function has been fully restored. The benefits of administering cortisol have yet to be fully elucidated, however, also as regards appropriate dosage and duration.

5.7. Post-LT cardiac tamponade

Cardiac tamponade is a serious condition that is relatively uncommon, but has been reported quite regularly in the setting of LT and hepato-biliary surgery. Its incidence is not clear. The common causes of cardiac tamponade are pericarditis, thoracic trauma, cancer, uremia, myocardial infarction, complications of CVC positioning, and surgery of the upper abdomen and thorax. In the setting of LT, cardiac tamponade may sometimes occur as a consequence of: a difficult dissection of the liver from the diaphragm (due to multiple and severe tissue adhesions); intrapericardial control of the suprahepatic inferior vena cava (occasionally necessary to remove the native liver); the need for enhanced exposure of surgical field; retransplant procedures; unintentional intraoperative pericardial entry; and exacerbation of previous pericardial effusion caused by inflammation [75,76]. Pericardial fluid collection may take more or less time: pericardial hemorrhage from surgical injury can progress to cardiac tamponade within minutes to hours, whereas the accumulation of pericardial fluid from non-hemorrhaging lesions may take days or weeks before a critical life-threatening event occurs. Severe hepatic and postoperative coagulopathy may be an important underlying factor that increases the amount of pericardial effusion [77].

Cases of pericardial effusion or bleeding on weak compression and/or slow distension are not always life-threatening. They may be well tolerated and cause no serious clinical signs. When the increase in intrapericardial pressure becomes critical, however, it will inevitably lead to a reduction in the compliance of the cardiac chambers and a restricted cardiac filling owing to the limited expansion of the pericardium. Acute tamponade with the accumulation of as little as 100–200 ml of blood may cause a precipitous decline in cardiac output with hypotension, tachycardia, and the rapid onset of hemodynamic collapse [78].

Apart from a clinical suspicion, and occasional findings on chest X-rays, more useful diagnostic information comes from directly viewing the quantity of fluid and its effect on the cardiac chambers with the aid of transthoracic or transesophageal echocardiography. Echographic signs of large effusions include right atrial wall invagination during end-diastole, and right ventricular wall invagination during early-diastole [77] Additional diagnostic findings include: distant heart sounds, low blood pressure, and elevated central venous pressure (CVP) (Beck's triad), low cardiac output refractory to volume resuscitation, and potential equalization of right-sided heart pressures with PCWP, together with the so-called *pulsus paradoxus.* This last finding consists of an inspiratory decrease in systolic blood pressure due to an increased venous return during inspiration, which causes the RV to expand while compressing the LV; the reverse occurs during expiration.

Liver recipients in whom a pericardial access is used during the transplant procedure must be carefully monitored, particularly when they begin to show the above signs. Early recognition and prompt pericardial evacuation and drainage are the only effective strategies to prevent progressive hemodynamic impairment and shock, with fatal outcomes [75].

5.8. Post-LT pulmonary embolism (PE)

The reported incidence of PE after LT is approximately in the range of 3–5%, which is similar to the rate of PE after other major surgical procedures [79,80]. In one report [81], 28 of 999 patients (2.8%) developed post-transplant deep vein thrombosis (DVT) or PE either during their initial hospital stay or within the first 30 days after their transplant procedure. The risk of PE early after LT is not clear. Reports vary greatly from one hospital to another. PE is associated with the unpredictable balance between coagulation/anticoagulation and fibrinolytic mechanisms, and it is influenced by prior liver disease etiology and severity, characteristics of the surgical procedure, quality of graft recovery, and therapeutic interventions. Recognized risk factors for post-transplant DVT include a history of DVT, diabetes, end-stage renal disease, the intraoperative administration of large amounts of cryoprecipitate or FFP, prolonged vascular clamping, venous stasis, hemodynamic instability, tissue injury/ischemia, and anti-fibrinolytic drugs [81,82]. High pulmonary artery pressures, the use of veno-venous bypass, ischemic insults to the intestine, pelvic and deep leg vein thrombosis, factor V Leiden (activated protein C) resistance, and increased levels of serum lactate have also been recognized as perioperative factors predisposing to thrombotic complications [83] Patients may be hypercoagulable soon after LT, and those with a complicated postoperative course and cardiocirculatory instability are particularly at risk. Omitting venous thromboembolism prophylaxis exposes them to a higher incidence of DVT and/or PE. Pulmonary emboli may originate from both upper and lower extremities. Upper-extremity DVT is a substantial risk factor for PE, comparable with that of lower-extremity DVT, and with a similar mortality [84]. Clinical signs of PE include acute-onset hypotension associated with an increased PAP, elevated CVP, or persistent hemodynamic instability refractory to supportive therapy. Cardiac arrest may occur before PE is diagnosed. The combination of hemodynamic impairment and transesophageal echocardiography (TEE) imaging (showing acute right heart pressure overload with dilated RV and atrium, and emptied LV) enables a correct diagnosis. Thrombolytic therapy with recombinant tissue plasminogen activator (rTPA) may reduce the mortality of patients with massive PE embolism: despite raising the risk of significant hemorrhage, it is associated with a better survival rate (77%) than embolectomy (53%) or heparin [85].

5.9. Post-transplant coagulopathy and bleeding complications

Postoperative intra-abdominal bleeding is often secondary to difficulties with hemostasis during surgery, technical errors in vascular anastomosis, persistent coagulopathy, and portal hypertension [86]. It is not uncommon for the severely-deteriorated coagulation in LT recipients with ESLD to combine with a potentially poor 'functional' recovery of their new liver and the negative effects of multiple transfusions to give rise to complex hemostatic system abnormalities, which can often cause uncontrolled postoperative hemorrhage. Coagulation defects after LT may involve an impaired coagulation factor synthesis, an increased consumption of coagulation factors, fibrinolysis and dysfunction of coagulation factors. Thrombocytopenia and platelet dysfunction are also common. Loss of antifibrinolytic factors, platelet entrapment in the sinusoids of the donor liver, and hemodilution due to fluid administration can aggravate any existing coagulopathy and inevitably raise the risk of needing hemotransfusion. Ischemia/reperfusion of the liver graft and gastrointestinal viscera, in concert with tissue trauma, can also alter hemostasis, and further contribute to prolonged blood loss [87,88]. Although considerable progress has been made in the management of surgical hemostasis, thanks to the proper administration of intraoperative fluids, the prevention and treatment of clotting abnormalities, the functional assessment of clot formation and fibrinolysis on the thromboelastogram (TEG), and the use of 'personalized' transfusion triggers, early post-transplant bleeding remains the most frequent and serious complication of LT surgery. Postoperative hemorrhage and reoperation for bleeding are frequently associated with substantial hemodynamic instability, a higher risk of systemic complications, longer hospital stays, and a higher mortality [89].

5.10. Massive ascites after LT

Another potential cause of postoperative hypovolemia lies in the exudation of considerable quantities of proteinaceous fluid from inflamed abdominal serosal surfaces. Massive ascites after LT may be due to the free exudation of lymph into the abdominal cavity as a result of lymphatic channel transection, aggressive surgical manipulation of splanchnic viscera, and tissue injury. Other major causes of massive post-transplant ascites include stenosis of the inferior caval anastomosis, abnormal 'piggyback' technique, absent or inadequate portal vein blood flow (thrombosis, anastomotic stricture, or kinking if the vein is too long), and obstruction of the liver vein outflow tract. Minor causes include disparity between the sizes of the donor's and recipient's livers or vessels, and microvascular changes during acute rejection [90].

As the ascitic compartment is known to be in equilibrium with plasma, continuous loss of ascitic fluid will lead to depletion of albumin and low-molecular-weight plasma proteins, which pass freely across the peritoneal membrane. Marked hypoalbuminemia and a drop in oncotic pressure contribute to fluid accumulation in the interstitial space, lung and serosal cavities. Refractory post-transplant ascites leads to hypovolemia and organ hypoperfusion.

6. Early post-transplant cardiocirculatory instability and multisystem derangements

It has long been known that perioperative blood pressure instability is frequently associated with major acute and chronic adverse outcomes. Apart from their primary harmful effects on graft perfusion, impaired postoperative hemodynamics also predispose to systemic complications and multi-organ dysfunction. Periods of blood pressure instability and fluctuations are most likely to affect the more vulnerable patients, such as those suffering preoperatively from cardiac disease, diabetes, kidney dysfunction, hypertension and vascular disease, and those with a history of smoking. Because of their underlying conditions, such patients require tighter perioperative blood pressure control, and they are unable to tolerate prolonged episodes of hypotension. Sustained hypotension induces a prolonged increase in catecholamine release; and persistent catecholamine-induced peripheral and splanchnic vasoconstriction eventually exacerbates vital organ injuries.

6.1. Hemodynamic instability and liver graft function

Optimal hemodynamics are essential for an adequate portal venous blood flow. Poor graft perfusion due to significant systemic or portal vein hypotension is always associated with graft dysfunction. Hypotensive episodes are accompanied by activation of the sympathetic nervous system and renin-angiotensin/aldosterone-system. The resulting excessive vasoconstriction is deleterious in the post-transplant setting, when preserving microvascular flow and preventing graft damage are major challenges. Even a mild systemic circulatory disorder can strongly affect splanchnic circulation and have a major negative impact on local graft circulation. Passive venous congestion due to low cardiac output, or a reduced hepatic arterial and/or portal vein blood flow can cause hepatocyte hypoxia. Even a small reduction in CO and effective volemia can prompt a critical drop in portal vein flow, which is more vulnerable to impairment than hepatic arterial flow [91]. Liver ischemia due to hypoperfusion with active compensatory vasoconstriction gives rise to an inadequate or delayed graft recovery. Hepatic hypoxia is a serious cause of liver cell injury, which manifests with ultrastructural changes in the centrilobular region of the hepatic acinus (the area with the lowest oxygen concentration). Hepatocellular and bile duct injuries are typical features of graft ischemia [92]. In human and animal studies, hypoxia-induced liver cell toxicity is characterized by activation of oxidative stress, ATP depletion, excessive glycogen accumulation, and high serum levels of hepatic enzymes [92,93]. A decrease in albumin and coagulation factors, together with an increase in liver enzymes and bilirubin, are characteristic laboratory findings of ongoing overall liver dysfunction. Critical laboratory and clinical data can improve within days of restoring optimal systemic hemodynamics and graft microcirculatory failure [94].

6.2. Postoperative hypotension and hyperinflammatory state

Shock of hypovolemic-hemorrhagic or other types may trigger a systemic inflammatory pathway, potentially contributing to multi-organ dysfunction. The endothelium is the main target of inflammatory reactions induced by serious blood pressure instability. Endothelial cells are significantly altered after hypovolemic shock, due primarily to a critical reduction in blood flow, and also after 'resuscitation' maneuvers leading to reperfusion. Many vasoactive substances (nitric oxide, prostacyclin, platelet-activating factor, endothelin, mitochondrial N-formyl peptide) and mediators of inflammation (tumor necrosis factor, interleukins, interferon) are released when endothelial cells are activated by ischemia/reperfusion. Severe damage to the structure of the endothelial glycocalyx and cell apoptosis are among the many changes seen in cases of prolonged heart failure or inadequate circulating blood volumes [95]. The lack of any protective effect of the normal endothelial barrier as a result of inflammatory damage may give rise to a greater permeability and widespread leakage of fluids and cells into tissues. Extravasation of cells, albumin, neutrophils and macrophages into the interstitial spaces not only threatens the vitality of the organs affected, but also facilitates the spread of inflammatory processes.

6.3. Blood pressure instability and coagulation disorders

The combined negative effects of inflammatory endothelial activation and a persistently low blood flow may lead to a dysregulated blood coagulation. The coagulation profile after LT is on a continuum involving a delicate balance between the new graft's capacity for synthesis and the consumption of coagulant factors (due to unrecognized minimal bleeding, fibrinogen and platelet consumption, and hyperfibrinolysis). Graft and tissue hypoperfusion may unexpectedly interfere with this balance, with rapidly-evolving changes from an initially anticoagulant to a potentially procoagulant state, or vice versa, within hours to days [96].

Ischemia of several hepatic segments may theoretically reduce the hepatic clearance of procoagulant factors and prompt the release of thromboplastic material from the graft, also triggering *disseminated intravascular coagulation*.

The competing effects of acute inflammation, coagulation and fibrinolysis may elicit a systemic inflammatory response syndrome and lead to thrombotic microangiopathy [97]. The formation of disseminated intravascular clots due to systemic activation of blood coagulation and derangement of the fibrinolytic system have been described after ischemia and necrosis of some regions of transplanted grafts. Though rare, this dramatic systemic disorder seems to be mediated by high-mobility group box 1 (HMGB1) protein, a procoagulant and proinflammatory protein of hepatocyte nuclei released into the blood in the event of low blood flow, sepsis, severe IRI and necrosis [98]. Simultaneously-occurring thrombotic and bleeding problems (with coagulation and fibrinolysis markedly impaired at the same time) may complicate the post-transplant course, further exacerbating a low blood flow state. This can give rise to multiple organ dysfunction and seriously affect patient outcomes [99].

6.4. Postoperative hypotension and mesenteric ischemia

Acute mesenteric circulatory disorders - induced not by organic blood vessel occlusion but by spasm and narrowing of the superior mesenteric artery - can be a consequence of persistent low perfusion due to a reduced cardiac output and blood pressure. Intense compensatory activation of the renin-angiotensin system, and the effect of high-dose

vasopressors may significantly lessen mesenteric blood flow, especially in marginal arteries and diseased vessels [100]. Overt mesenteric ischemia begins with mild abdominal pain, nausea, vomiting or an unpleasant feeling in the abdomen. Symptoms gradually worsen unless an acceptable mesenteric perfusion is restored, and ileus with an enlarged abdomen eventually becomes manifest. Laboratory data may show rising levels of creatine phosphokinase, GOT, GPT and LDH; and lactic acidosis is a typical marker of intestinal ischemia.

6.5. Acute renal injury

Unstable perioperative hemodynamics are unanimously considered the most important risk factor for the onset of acute kidney injury (AKI), which is characterized by a deterioration in renal function ranging from a mild increase in serum creatinine to anuric renal failure [101]. The reported incidence of AKI after LT is in the range of 11–57%, and varies considerably among centers [102]. The etiology of post-LT early AKI is multifactorial, with prolonged hypotension, preoperative renal insufficiency, graft dysfunction, the use of immunosuppressive and nephrotoxic drugs, an elevation in intra-abdominal pressure, retransplantation and sepsis as prevailing causes. Massive intra- and postoperative blood loss and large amounts of blood transfusions are other important causes of postoperative AKI. Several studies have demonstrated an association between post-LT AKI and the number of perioperative RBC transfusions, which is frequently used as a surrogate marker of blood loss [103,104].

Serious early cardiocirculatory complications after LT result not only in a persistently precarious hemodynamic status, but also give rise to a redistribution of blood flow away from the kidneys. As a consequence of intense activation of the renin-angiotensin and sympathetic nervous systems, renal vascular resistance increases, with a rapid decline in glomerular filtration rate. A postoperative increase in renal oxygen consumption is a common feature of LT due to activation of the new liver's metabolic processes and the increased post-transplant demand for blood 'purification'. When an appropriate balance in the renal oxygen supply and demand is no longer guaranteed, a greater renal oxygen consumption can no longer be covered by a proportional increase in renal oxygen delivery, and tubular ischemic damage ensues [105]. Impaired renal oxygenation induces tubular injury, particularly in the renal medulla, where tissue oxygen tension is already low in normal conditions. Tubular dysfunction in turn exacerbates pre-existing afferent arteriolar vasoconstriction (with activation of the tubuloglomerular feedback mechanism), with a further decrease in both renal and glomerular blood flow [106]. Volume overload, metabolic acidosis and electrolyte disturbances are features of the immediate systemic complications of postoperative AKI. Although early AKI is eventually reversible in most patients, it remains a complicating factor associated with a higher morbidity and longer stays in the ICU or in hospital [107] In some studies [108,109] AKI developing within the first 72 h after LT is also associated with worse liver graft survival rates. Patients requiring renal replacement therapy for early severe postoperative renal dysfunction have more complications and 50% higher mortality rates.

7. Preventing and managing hemodynamic instability after liver transplantation

LT is a major surgical procedure performed in patients with prior liver failure and multisystem derangements. The potential for hemodynamic instability, complex coagulopathy and metabolic disturbances (as well as other unexpected and serious complications) developing soon after LT is consequently very high. A skilled and complex management of myocardial dysfunction and systemic hemodynamics is needed to ensure the optimal functioning of all organs. A detailed description of all preventive and therapeutic measures conventionally adopted to manage postoperative circulatory derangement is beyond the scope of this paper, but it is worth including a few comments on the commonly-implemented strategies. Maintaining a high cardiac output and restoring optimal volemia are the basic principles of postoperative hemodynamic management. Given the pathophysiological circulatory features of ESLD, however - which include a higher venous capacitance due to arterio-venous and porto-systemic shunts, newly-formed and dilated splanchnic vessels capable of sequestering substantial volumes of plasma, and arterial vasodilation – it is crucial to ensure optimal postoperative volemia and maintain contractility in a complicated LT. Appropriate adjustments to fluid administration in the setting of variable hyper-hypovolemia and vasodilation demand 'extensive' and invasive cardiovascular monitoring. Pulmonary artery catheters (PACs) are still routinely used in many hospitals, but the transthoracic thermodilution methods of volumetric monitoring (PiCCO system: [Pulsion Medical System, Munich, Germany; LiDCO Plus [LiDCO Plus, Ltd., London, United Kingdom) are becoming increasingly popular [110]. Another device that derives cardiac output from arterial waveforms, the Flotrac-Vigileo (FloTrac Sensor, Edwards Lifesciences), has also been used in the setting of LT, but with inconclusive results [111]. TEE is mainly reserved for intraoperative use, and performed postoperatively only in particular circumstances. In clinical practice, postoperative hemodynamic monitoring still relies on conventional approaches, physicians' preferences and attitudes, and in-hospital availability. The existing literature does not say how best to monitor postoperative hemodynamics, nor does it provide reliable answers as to which single device is superior in terms of accuracy and validity [112]. Conventional estimates of intravascular volume status and cardiac filling pressures have not been found to correlate well with changes in cardiac output [113,114], and the more recently adopted dynamic parameters of fluid responsiveness have revealed several limitations as well [115].

Regardless of the device used, the absolute values of single parameters such as CO, PAP, MAP, PCWP, intrathoracic blood volume, stroke volume variations, and so on, are unsatisfactory and unsuitable for detecting the subtle instabilities of an LT recipient's peculiar hyperdynamic state. In specific circumstances, associating volumetric monitoring with conventional pressure-based hemodynamic monitoring, and performing 'temporary' TEE may sound reasonable. 'Judiciously' combining multiple sources of information may help physicians to better interpret serious and otherwise incomprehensible impairments of cardiovascular performance and volemic status, and possibly avoid some conceptual and physiological pitfalls [116]. The prevention of hypotension and blood pressure fluctuations relies on adequately matching cardiac performance and fluid management. Given the substantial fluid shifts occurring perioperatively, and the variations in central blood volume, considering a set of parameters may best elucidate fluid needs, help optimize preloading, and avoid pulmonary and graft edema [117]. Maintaining a high cardiac output is mandatory, and can be achieved not only by restoring adequate preloads, but also (as mentioned earlier) by avoiding sudden increases in afterload or conditions affecting myocardial contractility. In cases of persistent refractory postoperative vasodilation, vascular response to both endogenous catecholamines and administered vasopressors may be impaired. If so, the LT recipient's intrinsic myocardial contractility could result in a cardiac output that, though high, is not enough to meet graft and distant organ perfusion requirements. Apart from the treatment of some cardiac issues (arrhythmias, Q-T prolongation, Takotsubo cardiomyopathy and cardiac tamponade, for instance) that require specific and personalized measures, heart failure in the post-LT period is treated in much the same way as usual. Inotropic drugs, such as dopamine, dobutamine and adrenaline (sometimes in combination), and vasopressors such as norepinephrine, vasopressin and terlipressin, are the mainstays of treatment. Diuretics and continuous veno-venous hemofiltration (CVVH) are useful for congestive HF. Methylene blue has also been administered for refractory vasoplegia. As in other situations, when conventional therapies prove ineffective, using veno-arterial ECMO or counterpulsation pumps is also reportedly a viable option for treating post-LT

life-threatening myocardial dysfunction. Moguilevitch et al. successfully applied a biventricular assist device (BIVAD) in a patient with congestive HF after LT as a bridge to the recovery of myocardial contractility (after ECMO had failed) [118]. Postoperative coagulopathy is one of the most important factors contributing to overall blood loss, and thereby raising the risk of hemodynamic instability. Providing surgical hemostasis has been adequate, correcting coagulation defects is a crucial aspect of perioperative care. Despite notable improvements in the handling of blood loss and transfusions, there is still a marked variability in the way perioperative bleeding is managed [119,120]. FFP, platelets and antihyperfibrinolytics 'on demand' have always been the mainstays of coagulation defect management. In earlier times, the amounts of FFP and platelets to be administered were entirely at the physician's discretion, and there were no specific protocols available. The optimal plasma/RBC ratio to aim for when dealing with massive hemorrhage or substantial coagulopathy in the setting of LT has never been reported. In traditional transfusion practice, applying a high FFP/RBC ratio was assumed to be beneficial, but the currently-available literature tells us nothing about whether LT recipients treated with a high plasma/RBC ratio had significantly reduced morbidity or better survival rates. In actual fact, given the rebalanced hemostatic system of end-stage cirrhotic patients, it is unnecessary and may even be harmful to correct hemostatic abnormalities after surgery with excessive amounts of FFP. Overfilling patients with blood products can raise the pressure in the portal system and venous collaterals, and this volume overload may exacerbate their tendency to bleed [121].

'Liberal' perioperative platelet transfusions have been found associated with a greater risk of immunosuppression and infection, and higher morbidity and mortality rates [122]. Current strategies focus mainly on identifying the specific coagulation pathway(s) to restore, and on strict (continuous, bedside) monitoring of any deficit. TEG or rotational thromboelastometry (ROTEM®) enable a quick and easy graphic assessment of functional clotting status (characteristic changes due to hypofibrinogenemia, thrombocytopenia, hyperfibrinolysis) and any residual heparin effect. Dilutional coagulopathy (often responsible for persistent bleeding and circulatory instability) is another important 'inadvertent' adverse effect of massive fluid infusions given to restore euvolemia and blood pressure. In point-of-care (POC) coagulation monitoring, it appears mainly as a reduction in clot firmness, an effect that is immediately visible without any need for a central laboratory. FFP, fibrinogen, cryoprecipitates, antihyperfibrinolytic agents and platelets can be administered properly with the aid of TEG monitoring, instead of taking the conventional 'clinician-directed' transfusion management approach [87]. The importance of fibrinogen has recently come to light again: fibrinogen is the first factor to drop to critical levels as a result of massive bleeding or hemodilution. With POC monitoring, the action of fibrinogen during coagulation is easy to estimate, and its trends after fibrinogen replacement can be monitored too. Visco-elastic hemostatic assays of low levels of fibrinogen result in severely reduced maximum clot firmness. Recent data have emphasized how low perioperative levels of fibrinogen are associated with a significantly higher demand for blood products, and that fibrinogen supplements improve clotting and reduce blood loss in surgical patients who are bleeding [123,124]. Administering fibrinogen has also proved more effective than FFP in restoring coagulation. The appreciable advantages are not only lower rates of pathogen transmission, but also a lower risk of hypervolemia. Prothrombin complex concentrate (PCC) has also been administered for complex perioperative coagulopathy. There are three-factor (II, IX and X) and four-factor (II, VII, IX and X) PCCs available for clinical use. The four-factor PCC also contains the anticoagulant factors protein S and protein C [125]. The administration of PCC (alone or in addition to fibrinogen) to treat post-LT coagulopathy is often indicated as a rescue therapy to improve thrombin generation during massive bleeding [126]. Although data on the safety of PCC in the setting of LT are still scarce, no increased risk of thrombotic, thrombo-embolic or ischemic events has been associated with their use as yet [127,128]. The adoption of POC algorithms, which include the first-line use of factor concentrates, in transplant procedures and other clinical contexts has been associated with a marked reduction in the use of FFP, platelets and RBC, together with a 50% reduction in the incidence of massive transfusions. Recombinant activated factor VII has also been used as a 'rescue/life-threatening therapy' to control refractory hemorrhage [129]. The prevention and treatment of kidney injury due to early post-transplant circulatory derangement is complex and challenging, and sometimes an impossible task. Well-known protective strategies focus on promoting hemodynamic stability throughout the perioperative period. Maintaining ideal volemia and cardiac output (as noted earlier) is one of the best ways to preserve renal blood flow because not only hypovolemia but also large fluid infusions may be detrimental to renal function [130]. An abnormally vasodilated state is an important cause of blood pressure instability and can take hours or days to revert to near normal. Failure to recover vascular tone is a sign of poor graft function and carries a poor prognosis.

In such circumstances, sometimes even in spite of a high cardiac output, judicious filling will not restore blood pressure, and renal blood flow will remain insufficient for variable periods of time [131]. An inadequate response to measures to restore volume status justifies the use of vasoactive drugs well beyond the completion of the surgical procedure. Vasoconstriction therapy (a validated strategy for treating hepatorenal syndrome) seems to be the only way to reverse postoperative arterial dilation and a persistently low peripheral vascular resistance. Vasopressin, noradrenaline or terlipressin are generally used, but the concomitant use of two or more vasoactive agents is sometimes indicated to attain hemodynamic stability. Vasopressin increases SVR, reduces mean pulmonary artery pressure, normalizes CO, and maintains mean blood pressure, resulting in a better renal function, enhanced diuresis, and improved Na balance [132]. Vasopressin also has a dose-dependent constricting effect on the peripheral vasculature, with minimal effects on heart rate. Low-dose vasopressin infusion may be useful to reverse refractory hypotension, since it appears to selectively constrict the splanchnic vasculature without damaging the liver graft. Noradrenaline is as safe and effective as the vasopressin analog terlipressin in terms of achieving splanchnic vasoconstriction and increasing the effective arterial blood volume, and it is often used for the postoperative recovery of a vasodilated splanchnic circulation [133].

Pharmacological interventions to improve renal blood flow, with dopamine, fenoldopam or albumin supplementation, are acceptable, but cannot guarantee a genuine improvement in post-LT renal function [134,135].

Additional measures to attenuate hypotension-induced renal dysfunction include avoiding nephrotoxic drugs, iodinated contrast agents, nephrotoxic antibiotics, immunosuppressants like cyclosporine and tacrolimus, and any prolonged use of vasopressors. Non-nephrotoxic immunosuppressants such as sirolimus or everolimus, mTOR (mammalian target of rapamycin) inhibitors or IL-2 receptor antagonists, should be considered as a way to delay or replace calcineurin inhibitors until there are clear signs of renal recovery [136].

CVVH is essential for treating oliguric/anuric renal dysfunction associated with lung interstitial congestion, acidosis and electrolyte disorders in the setting of postoperative hemodynamic instability.

8. Conclusion

Although recent advances in our understanding of the pathophysiology of cardiovascular dysfunction and arterial tone abnormalities in ESLD have improved our management of complications, clear clinical signs of cardiac decompensation and organ perfusion anomalies may still arise after LT in stressful situations. The higher risk of adverse cardiac events after LT cannot be completely avoided, and it has important implications as the mortality rate among patients who experience cardiovascular events is high. Myocardial depression confined exclusively to the intraoperative period may be associated with minor morbidity,

but postoperative heart dysfunction and circulatory failure inevitably lead to organ impairment and injury, and may also affect long-term outcomes [14]. LT is one of the most stressful cardiovascular events for cirrhotic patients, so a careful preoperative assessment to rule out coronary artery disease or other occult cardiomyopathies is of the utmost importance. This is needed not only to assess perioperative risk, but also to improve the management of any postoperative circulatory disease of unknown origin. As it has become increasingly feasible to offer liver transplants to patients who are older and/or have various comorbidities and organ dysfunctions, great emphasis should be placed on preventing and correcting circulatory failure and cardiovascular complications. Extensive postoperative hemodynamic monitoring, aggressive hemodynamic interventions when needed, and timely organ support represent the essential targets of perioperative care.

Author contributions

FP designed the study, collected and analyzed the data, wrote the manuscript, and gave final approval of the manuscript.

BS, CU, CC, BA, GE, ME, and BA contributed to acquisition of data, drafting, revising, and editing the manuscript.

Declarations of Competing interest

The Authors declare no conflicts of interest.

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