The Patient with Severe Comorbidities: Cardiac Disease

21

Shahriar Shayan and Andre M. De Wolf

Introduction

In order to properly discuss the anesthetic management of patients with cardiac comorbidities undergoing liver transplantation (LTx), we will first briefly describe the cardiovascular changes that occur as a result of liver failure, including hemodynamic changes and cirrhotic cardiomyopathy. We will then concentrate on the following comorbidities: coronary artery disease (CAD), valvular heart disease, and hypertrophic obstructive cardiomyopathy (HOCM). Preoperative diagnosis of cardiac comorbidities is essential to ensure preoperative optimization and proper intraoperative management and helps in determining the potential need for combined cardiac surgery and LTx. Poor left ventricular function (ejection fraction <35%) or severe cardiac disease that cannot be improved or corrected is considered to be contraindication for LTx, and only rarely can a patient with these conditions be considered for combined heart Tx/LTx [1].

S. Shayan • A.M. De Wolf (✉)
Department of Anesthesiology, Northwestern University Feinberg School of Medicine, 251 East Huron Street, F5-704, Chicago, IL 60611, USA
e-mail: a-dewolf@northwestern.edu

The Cardiovascular Changes in End-Stage Liver Disease

Severe liver disease results in significant changes in the circulation and cardiac function, which can be summarized as a hyperdynamic circulation; this is characterized by increased cardiac output, heart rate, and blood volume; peripheral vasodilation; and low systemic blood pressure [2]. With mild liver dysfunction, the cardiovascular changes may be nearly imperceptible clinically; however, the circulatory effects may already have well progressed. The arterial compliance increases, and the overall systemic vascular resistance (SVR) decreases incrementally, corresponding to the degree of liver failure. As liver dysfunction progresses, the circulatory burden of biologically active compounds such as estrogen, bradykinin, prostacyclin, nitric oxide (NO), and vasoactive intestinal peptide exerts a predominantly vasodilator effect on the vascular smooth muscle. These and other vasodilating substances are overproduced or cleared less (as a result of reduced metabolism in the diseased liver or due to bypassing the liver); furthermore, there may be an increased sensitivity to their vasodilatory effects. In addition, peripheral arteriovenous communications form, and the sensitivity to vasoconstrictors such as norepinephrine, vasopressin, and endothelin-1 decreases due to a reduced number of receptors in combination with post-receptor defects.

Although SVR decreases in patients with severe liver disease, not all vascular beds are

G. Wagener (ed.), *Liver Anesthesiology and Critical Care Medicine*,
DOI 10.1007/978-1-4614-5167-9_21,

affected in the same way. As the primary disturbance in end-stage liver disease (ESLD), portal hypertension develops as a result of increased hepatic vascular resistance at the level of the sinusoids and is a direct consequence of local structural changes (fibrosis and regeneration nodules) and sinusoidal vasoconstriction (locally decreased NO production and increased local release of and sensitivity to vasoconstrictors such as endothelin, angiotensin II, catecholamines, and leukotrienes). The spanchnic circulatory response to portal hypertension is characterized by a massively increased local production of NO resulting in severe vasodilation of the splanchnic circulation. In addition, splanchnic vessels are less responsive to vasoconstrictors and release of substances such as vascular endothelial growth factor result in the creation of portosystemic collaterals. Other vascular beds, however, undergo vasoconstriction as a result of activation of compensatory mechanisms (see below).

The severe splanchnic vasodilatation leads to intravascular volume redistribution, which results in a reduction in central and arterial blood volume and an increase in noncentral blood volume (mainly splanchnic system) (Fig. 21.1) [3]. This is detected by central baroreceptors and leads to an activation of compensatory mechanisms, mainly the sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS). There is also an initial increased release of vasopressin by the pituitary gland and an increased concentration of circulatory endothelins. In combination with the reduction in SVR, the stimulation of the SNS and RAAS results in a large increase in stroke volume and cardiac output. Eventually, with progressive liver failure, the SNS and RAAS become maximally stimulated, and the increase in cardiac output and vasoconstriction in certain vascular beds is insufficient to maintain an effective circulatory volume and compensate for the massive vasodilation of the splanchnic system. As a consequence, blood pressure gradually decreases and progressive autonomic dysfunction and baroreceptor insensitivity will further exacerbate this inadequate compensation.

Activation of the SNS and RAAS can be detrimental to the function of other organs. Indeed, the persistent sympathetic stimulation results in vasoconstriction of coronary, cerebral, and renal vessels. This is most apparent in the kidneys, where reduction of blood flow in addition to a reduced circulatory volume may result in the progression to hepatorenal syndrome with fluid retention, hyponatremia, and ascites formation.

Although activation of the SNS results in a persistent state of sympathetic stimulation, it does not necessarily lead to a better myocardial performance. On the contrary, ESLD may cause progressive myocardial dysfunction called cirrhotic cardiomyopathy. Cardiac dysfunction in liver disease unrelated to alcohol was first described by Ma in 1996 and consists of systolic dysfunction, diastolic dysfunction, and electrophysiologic abnormalities [4]. Despite increased cardiac output in ESLD, the systolic contractility and diastolic relaxation are attenuated. Furthermore, repolarization changes such as prolonged QT interval (which may improve after β-blocker therapy) and reduced inotropic and chronotropic response to β-adrenergic stimulation may occur. Although cirrhotic cardiomyopathy is usually not apparent at rest, it becomes noticeable during cardiac stress (increase in preload or afterload). For example, cardiac dysfunction may become clinically relevant for the first time after transjugular intrahepatic portosystemic shunt (TIPS) placement or in the early postoperative period after LTx. The cause of cirrhotic cardiomyopathy is multifactorial; this includes circulating myocardial depressant substances (tumor necrosis factor-α, bile acids, endotoxins, cytokines, carbon monoxide, endogenous cannabinoids, etc.) and downregulation of β-receptors (reduced β-receptor density, desensitization of β-receptors, and abnormal excitation–contraction coupling). Furthermore, morphologic changes in the heart such as cardiac hypertrophy and patchy areas of fibrosis and subendothelial edema may occur and further contribute to the systolic and diastolic dysfunction. One of the early indicators of cirrhotic cardiomyopathy is diastolic dysfunction, which can be seen in many patients with ESLD. Typically there is a decreased E/A ratio on Doppler echocardiographic examination of the blood flow through the mitral valve; the E wave represents early passive transmitral flow, while the A wave represents

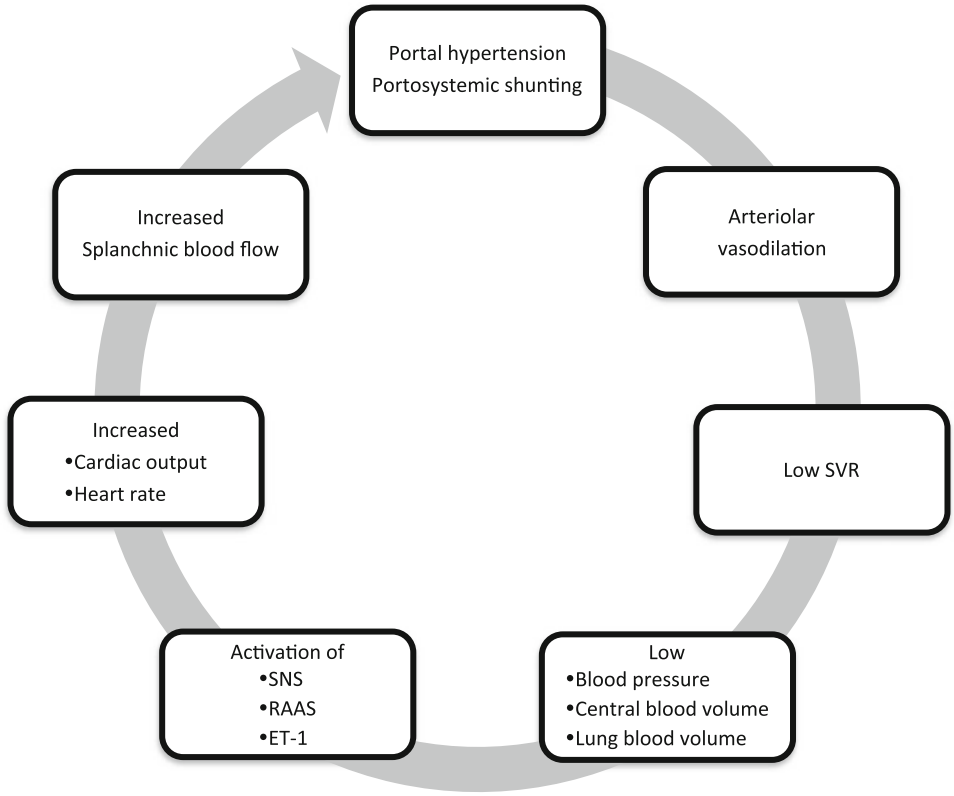

Fig. 21.1 Pathophysiology of hemodynamic changes in cirrhosis: Systemic overproduction of vasodilators results in arteriolar vasodilation and low systemic vascular resistance (SVR), resulting in low blood pressure. Redistribution of blood results in a reduction in central blood volume and lung blood volume. Consequently, there is activation of sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS) and increased plasma concentrations of endothelin-1 (ET-1). This leads to increases in cardiac output, heart rate, plasma volume (fluid and water retention), and splanchnic blood flow

transmitral flow as a result of atrial contraction. It is unclear whether diastolic dysfunction is a good marker for the degree of cirrhotic cardiomyopathy or whether it correlates well with systolic dysfunction; however, there is evidence that diastolic dysfunction precedes systolic dysfunction [5].

Coronary Artery Disease

CAD Does Occur in Patients with ESLD

In the 1960s and 1970s, it was thought that patients with severe liver disease had a low incidence of CAD, based on a lower incidence of hypercholesterolemia, increased levels of circulating estrogen (resulting in protection against atherosclerosis), and decreased SVR thereby eliminating, at least in theory, hypertension as risks factors for CAD [6]. However, there is increasing evidence that the prevalence of CAD in patients with ESLD is higher than previously thought and maybe even higher than in the general population (20% vs. 12%, respectively) [7, 8]. Obesity, nonalcoholic steatohepatitis (NASH) and other inflammatory liver conditions, and advancing age of the LTx candidate have lead to an increasing prevalence of atherosclerosis [9, 10]. Interestingly, the prevalence of CAD is much higher in patients with alcoholic liver disease (31%) and NASH (27%) than in patients with cirrhosis due to other causes (2.4%) [11]. This could be related to a higher incidence of smoking, diabetes mellitus, older age, and hypertension in

patient with alcoholic liver disease and NASH, but it is unlikely that these risk factors by themselves can account for the higher incidence of CAD. There is also evidence that while light to moderate alcohol intake reduces the risk for CAD, heavy episodic alcohol drinking may actually increase its risk [12]. The prevalence of CAD in patients with viral cirrhosis, however, is lower than in patients without cirrhosis [13, 14]. Although there is limited comparative data about the prevalence of CAD in patients with cirrhosis with different etiologies, one must assume that CAD has a higher overall incidence in patients with ESLD than in the general population, mainly due to the high incidence of CAD in patients with alcoholic liver disease and NASH.

The reported prevalence of significant CAD (defined as at least one coronary artery stenosis ≥50%) in patients with ESLD varies widely from 2.5 to 27%. There are several reasons for this variability. First, most studies have looked at a relatively small number of patients and second some studies based the diagnosis of significant CAD on abnormal screening tests such as positive dobutamine stress echocardiography (DSE). Third, the only method to determine the true incidence of CAD is by coronary angiography, and in most studies, coronary angiography was only performed in the subgroup of patients with abnormal screening tests or with multiple risk factors for CAD [15–17]. Interestingly, Carey found an incidence of CAD of 27% in 37 LTx candidates older than 45 years who underwent coronary angiography without consideration of other risk factor [18]; these results raise doubt on the appropriateness of risk stratification of patients that were referred to coronary angiography in other studies; however, this study was limited due to its small sample size (37 patients). Therefore, the true incidence of CAD in patients with ESLD remains unknown.

Consequence of CAD in Patients Undergoing LTx

Why is there so much emphasis on the preoperative diagnosis of CAD? LTx is a procedure that creates a substantial stress for the heart with virtually unavoidable episodes of often severe tachycardia and hypotension. Furthermore, plaque rupture resulting in acute coronary artery thrombosis and myocardial infarction may be related to a chronic inflammatory state. Episodes of hypercoagulability further increase the perioperative risk through intracoronary thrombus formation triggered by an area of coronary atherosclerosis. Therefore, CAD is considered to increase the peri- and postoperative risk. In 1996, Plotkin et al. reported a 50% 3-year mortality rate after LTx in patients with CAD, irrespective of whether the management of CAD was medical or surgical [19]. Management options for CAD have evolved since then and we can now choose among medical management, percutaneous transluminal coronary angioplasty (PCTA), coronary stenting with bare metal or drug eluting stents, coronary artery bypass surgery (CABG), and off-pump CABG (OPCAB), with cardiac surgery being performed before LTx or as a combined procedure. As a result, a more recent study demonstrated an improved outcome, although the mortality rates were still higher than in the general LTx population: 1-year mortality rate of 12.9% vs. 2.4% and 3-year mortality rate of 26.2% vs. 7.1%, respectively [20]. Postoperatively, CAD continues to be a significant cause of mortality after otherwise successful LTx [21].

Preoperative Evaluation

Preoperative risk stratification is guided by traditional CAD risk factors that include age >50 years, diabetes mellitus, peripheral vascular disease, and history of CAD [22]. Interestingly, acute renal failure also increases cardiovascular risk in LTx patients [23]. Patients with no prior screening tests but several risk factors for CAD had a 26% incidence of moderate or severe CAD during coronary angiography, suggesting that CAD is quite common in patients with ESLD [17]. However, not all LTx candidates can or should undergo coronary angiography as the procedure is associated with significant risks such as femoral artery and renal injury [24, 25]. However, LTx candidates often present with a poor

functional status and hepatic encephalopathy, making the clinical diagnosis of significant CAD through eliciting signs and symptoms or exercise tolerance challenging and nearly impossible. For the same reasons, exercise testing is rarely feasible. Therefore, there is a real need for improved understanding who should receive what screening test and who should then undergo coronary angiography.

Dobutamine Stress Echocardiography

DSE is the most frequently used screening test for CAD in LTx candidates. Dobutamine is administered at an increasing dose in an attempt to achieve 85% of the predicted maximal heart rate. The associated increase in myocardial oxygen demand attempts to mimic the physiologic stress that the myocardium undergoes in the perioperative period. Obstructive CAD is detected by regional wall motion abnormalities in the myocardial territories at maximal heart rate. Several studies show that a negative DSE is highly predictive of a myocardial injury-free perioperative course [15, 16, 26–28], and thus, a normal DSE has a good negative predictive value (range 89–100%). The negative predictive value, however, is reduced from 86 to 80% when non-diagnostic tests (due to inability of up to 50% of patients to reach the target heart rate) are included [29]. Others found an even lower negative predictive value (75% and 79%) [30, 31]. Another interesting finding is that patients who did not reach the target heart rate during DSE ("chronotropic incompetence") had a higher incidence of cardiac complications up to 4 months after LTx [27]. The positive predictive value of DSE is not nearly as good, ranging from 22 to 44% [15, 16, 26, 28, 30, 31]. Therefore, an abnormal DSE is not necessarily caused by significant CAD. It has been suggested that the positive predictive value may be improved by the use of real-time contrast myocardial echocardiography for patients with intermediate risk factors for CAD [31]. The wide variability among various studies likely arises from differences in institutional protocols in selecting patients for DSE, coronary angiography, and definitions of outcomes. For example, CAD can be defined as coronary obstruction >50% vs. >70%, perioperative myocardial infarction can be diagnosed based on different troponin cutoffs, and end point could be cardiac mortality or any-cause mortality. In addition, many patients failed to achieve the predicted maximal heart rate, rendering the ability of interpreting the DSE rather marginal [27, 30]. This may be the result of the use of β-blockers as part of medical management of portal hypertension, in addition to downregulation of β-receptors in ESLD (see above). Withholding β-blockers before the test and the administration of atropine has been recommended to reduce the number of inconclusive tests due to submaximal heart rates [27], but withholding β-blockers may increase the risk of variceal bleeding [32]. Because of the relatively poor predictive value of DSE in predicting perioperative cardiac events or early mortality, some clinicians deem alternative or additional screening tests for CAD necessary in order to avoid unnecessary coronary angiographies. However, in our opinion, it is still much better to obtain some false-positive screening test results (resulting in unnecessary coronary angiographies) than too many false-negative results resulting in patients accepted for LTx with unrecognized significant CAD. Also, no other screening test has a better positive predictive value than DSE at this time.

Myocardial Perfusion Scan

Single photon emission computed tomography (SPECT) myocardial perfusion scintigraphy is another screening test for CAD. It uses exercise, dobutamine, or vasodilators such as adenosine or dipyridamole to stress the myocardium and determines the relative blood flow to different areas of the myocardium. Defects in perfusion can be classified as fixed (scar) or reversible (presumably ischemia), and defects in at least three segments (out of 17 or 20) are indicative of at least moderate risk for CAD [33]. Overall, the positive predictive value (range: 15–50%) and the negative predictive value (range: 77–99%) are

worse than for DSE [34–37]. These results are worse than those in patients without liver disease; this can be attributed to the decreased baseline arterial vascular resistance in patients with ESLD, as the typical response of the coronary arteries to vasodilators may not be achieved [35]. In addition, false-positive tests could be the result of abnormal coronary microvascular tone [38], which has also been observed in patients without severe liver disease [39]. This abnormal microvascular (coronary) blood flow (in the presence of normal coronary angiography) may be associated with a higher perioperative morbidity and mortality rate, sepsis, and graft failure [40]. Furthermore, ascites may result in attenuation artifacts in the inferior wall that may mimic ischemia or scar tissue [36]. Therefore, a high number of false-positive results makes this test less accurate [37], and myocardial perfusion scan may be only indicated as a screening test in patients with several risk factors for CAD who do not tolerate or have an inconclusive DSE.

Computerized Tomography (CT) Coronary Angiography and Coronary Artery Calcification

Coronary artery calcification (CAC) determined by multisection CT reflects the degree of calcification of coronary atherosclerotic lesions and may be an indicator of the degree of coronary obstruction. There is a good correlation between the CAC score and the presence of risk factors for CAD [41, 42], but currently, no studies compare the CAC scores to traditional contrast coronary angiography in the catheterization laboratory, nor are there any outcome studies. However, not all plaques are calcified and using the same test CT coronary angiography theoretically allows the detection of noncalcified plaques [41]. Again, there are no studies that compare abnormal CT coronary angiography tests with traditional contrast coronary angiography, and therefore, the usefulness of CT coronary angiography in patients with ESLD remains to be determined.

In conclusion, the currently available screening tests for CAD are not very good. Both DSE and myocardial perfusion scan have a good negative predictive value, but the positive predictive value is not nearly as good, although slightly better for DSE than for MPS. There is little experience with CT coronary angiography, and it is therefore difficult to estimate its ability as a screening test for CAD in LTx candidates. Since DSE gives additional information about cardiac function, valvular disease, hypertrophic cardiomyopathy, peak right ventricular pressure, and hepatopulmonary syndrome, it seems to be the preferred screening test at this time [8]. An excellent algorithm to screen for CAD has recently been presented by Ehtisham et al. [8] (Fig. 21.2).

Invasive Evaluation of CAD (Diagnosis)

Coronary angiography using the standard dye technique in the catheterization laboratory is considered the gold standard for detection of CAD. A positive screening test for CAD should be followed by coronary angiography to confirm the presence of CAD considering the relatively low positive predictive value of these screening tests. Infrequently, coronary angiography is performed in candidates with several cardiac risk factors (e.g., diabetes, age >50 years, hypertension, smoking, family history of CAD, and hypercholesterolemia) even in the presence of a normal screening tests. This may be justified in patients with >2 risk factors for CAD [17], especially in patients with alcoholic liver disease and NASH, as the incidence of CAD is significantly higher in these patients.

Cardiac catheterization and coronary angiography are associated with a higher number of complications in patients with ESLD compared to patients without ESLD: patients with ESLD may have less renal function reserve, resulting in a higher incidence of renal dysfunction, and there is an increased incidence of bleeding complications at the site of vascular access [25]. Using the radial artery for vascular access is becoming more popular as it may have a reduced complication rate.

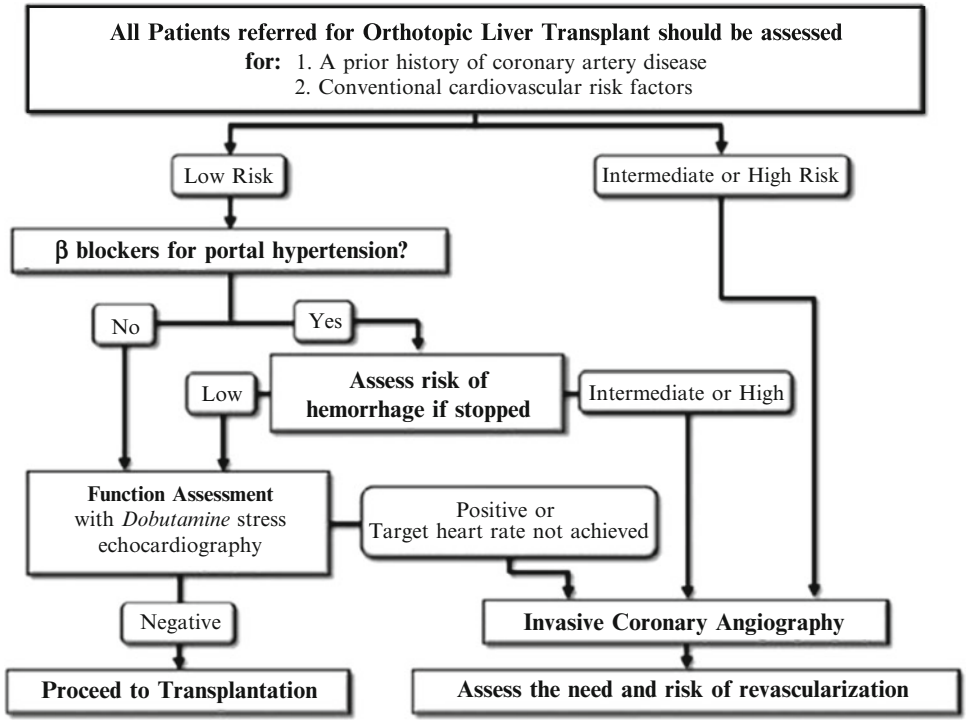

Fig. 21.2 Coronary artery disease in orthotopic liver transplantation: Pretransplant assessment and management (from Ehtisham et al. [8]; with permission)

Management of CAD

If significant CAD is diagnosed preoperatively, the coronary status of these patients should be optimized prior to LTx because if left untreated the perioperative mortality is excessively high [43]. The best strategy to accomplish this has not been determined, since no randomized controlled trials have compared percutaneous revascularization to surgical techniques in this population. The main therapeutic options besides medical management are placement of coronary stents, coronary artery bypass grafting (CABG), and off-pump coronary artery bypass (OPCAB).

Coronary Stent Placement

Although coronary stent placement is an effective method of revascularization it is not without risks in patients with ESLD. Antiplatelet therapy is required after stent placement in order to maintain patency and this further increases the risk of bleeding complications. However, the potential for clot formation is not as abnormal in patients with ESLD as previously thought [44], at least in part due to increased concentration of von Willebrand factor [45]. Most commonly bare metal stents are used instead of drug eluting stents because bare metal stents are covered faster by an endothelial layer and therefore do not require prolonged dual antiplatelet therapy (1 month vs. 12 months). The disadvantage of bare metal stents is the higher long-term restenosis rate, but this may not result in a higher incidence of acute myocardial infarction or death. Just like with coronary angiography, there are similar risks associated with arterial vascular access.

CABG

Coronary artery bypass grafting (CABG) may be the only option in patients with significant CAD

that cannot be corrected by coronary stent placement. However, CABG in patients with ESLD and CAD prior to LTx is associated with a high mortality, mainly as the result of postoperative liver failure [46–49]. Other complications include renal failure, infections, and bleeding [46, 47, 49, 50]. Patients with mild cirrhosis (Childs A) have up to 25% morbidity (usually late postoperative liver failure and wound infections) but a low incidence of mortality [51]. Patients with moderate cirrhosis (Childs B) have a morbidity of almost 100% and mortality of up to 30%. Non-pulsatile blood flow during cardiopulmonary bypass results in systemic inflammattion further contributing to liver dysfunction or liver failure. CABG is therefore an unattractive option for myocardial revascularization in patients with ESLD awaiting LTx. A better alternative may be simultaneous CABG/LTx, with the cardiac procedure performed first, resulting in excellent results, although it requires significant multidisciplinary coordination and cooperation from the cardiac surgical team [52].

OPCAB

Off-pump coronary artery bypass (OPCAB) offers several theoretical advantages over CABG: no need for cardiopulmonary bypass and therefore less requirement for anticoagulation and better pulsatile organ perfusion. Therefore, if CAD is the only cardiac lesion to be corrected, then OPCAB would theoretically offer significant advantages, especially in patients with ESLD [47]. While some studies confirmed this [48, 53, 54], others found no improvement in incidence of hepatic dysfunction and overall mortality when OPCAB was used [55].

Valvular Disease

Mild or moderate valvular disease in patients with ESLD is usually well tolerated. The incidence of mild or moderate tricuspid and mitral regurgitation is higher than in the general population [56] possibly due to cirrhotic cardiomyopathy and subsequent ventricular remodeling. These conditions require no special consideration perioperatively, although patients may require more blood transfusions and inotropic support [56]. Also, patients with severe valve disease with mild liver disease tolerate cardiac surgery better with a somewhat increased complication rate similar to patients with mild liver disease undergoing CABG [47, 50].

Perioperative management of patients with severe valvular disease and severe liver disease is very complex. If an attempt is made to surgically correct the valvular disease using cardiopulmonary bypass prior to LTx, the outcome will be as poor as the results of CABG in patients with ESLD [47, 48, 50]. Few patients underwent such an operation successfully [57, 58], and other options need to be explored. Percutaneous balloon valvuloplasty, avoiding cardiopulmonary bypass, could be used to correct severe mitral or aortic stenosis. Another option is a simultaneous valve replacement and LTx, although this requires a thoracoabdominal incision, cardiopulmonary bypass at the time of LTx, and initiation of immunosuppression [59].

Hypertrophic Obstructive Cardiomyopathy

HOCM is characterized by an asymmetrically hypertrophied non-dilated left ventricle, potentially causing left ventricular outflow tract (LVOT) obstruction. It has a genetic inheritance pattern, although it can be the result of de novo genetic mutation, and has an incidence of about 0.2% of the general population [60]. Although frequently asymptomatic, some patients develop anginal chest pain, dyspnea, or syncope, and it can progress to congestive heart failure or sudden death as a result of dynamic LVOT obstruction, mitral regurgitation, diastolic dysfunction, myocardial ischemia, or arrhythmias [60]. LVOT obstruction caused by septal hypertrophy becomes hemodynamically more significant in the presence of systolic anterior motion (SAM) of the anterior mitral leaflet that prevents complete ejection of the stroke volume and results in

a sudden drop in cardiac output. Echocardiography is the most useful method of diagnosing HOCM as it allows visualization of the HOCM, diagnosis of SAM, and estimation of the degree of obstruction [60]. Volume status, afterload, and myocardial contractility all affect the degree of LVOT obstruction and mitral regurgitation. Specifically, low SVR and a hyperdynamic left ventricle will worsen LVOT obstruction especially in hypovolemic patients. The hemodynamic goal is to prevent conditions that would result in obliteration of the LV cavity and ultimately LVOT obstruction. Such treatment modalities are focused on increasing LV cavity size by avoiding hypovolemia and reducing contractility with β-blockers. Myectomy and alcohol septal ablation are reserved for patients with drug-refractory heart failure symptoms [60].

HOCM poses a particular difficulty for patients with ESLD as some of the circulatory abnormalities in ESLD promote LVOT obstruction. LVOT obstruction can be diagnosed by DSE, but the incidence seems to be quite variable ranging from low (two out of 157 patients developed high LVOT gradients during DSE) [27] up to 43% of all patients [61]. It is possible that the diagnosis of LVOT obstruction with DSE depends on if one is actually looking for LVOT obstruction. A LVOT gradient of >35 mmHg has resulted in denial for transplantation, even though the reported perioperative mortality is not increased [61]. Options for patients rejected for LTx because of a high LVOT obstruction include myectomy and alcohol septal ablation. Myectomy in patients with ESLD may be a poor choice with high mortality rate mainly resulting from the need for cardiopulmonary bypass [47], although a combined myectomy–LTx can be an option. Alcohol septal ablation is less invasive but may be associated with several complications as well [62], and currently, there are only a few case reports of patients with ESLD who received alcohol septal ablation prior to LTx [63, 64].

Although ESLD and LTx result in hemodynamic conditions that worsen LVOT obstruction, these patients can be transplanted safely when meticulous hemodynamic management is used, such as intraoperative avoidance of inotropic agents (epinephrine) and hypovolemia. TEE monitoring is essential in order to avoid hypovolemia and to closely follow the degree of LVOT obstruction and SAM [65–67]. During the anhepatic stage, venovenous bypass facilitates the avoidance of hypovolemia, while hypotension should be rapidly and aggressively treated with potent vasoconstrictors such as norepinephrine or vasopressin and volume. Also, calcium should be administered slowly in order to avoid a hypercontractile state [68].

References

1. Shaw Jr BW, Bahnson HT, Hardesty RL, Griffith BP, Starzl TE. Combined transplantation of the heart and liver. Ann Surg. 1985;202:667–72.
2. Møller S, Henriksen JH. Cardiopulmonary complications in chronic liver disease. World J Gastroenterol. 2006;12:526–38.
3. Schrier RW, Arroyo V, Bernardi M, Henriksen JH, Rodes J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology. 1988;8:1151–7.
4. Ma Z, Lee SS. Cirrhotic cardiomyopathy: getting to the heart of the matter. Hepatology. 1996;24:451–9.
5. Henriksen JH, Møller S. Cardiac and systemic hemodynamic complications of liver cirrhosis. Scand Cardiovasc J. 2009;43:218–25.
6. Howell WL, Manion WC. The low incidence of myocardial infarction in patients with portal cirrhosis of the liver: a review of 639 cases of cirrhosis of the liver from 17,731 autopsies. Am Heart J. 1960;60:341–4.
7. Kalaitzakis E, Rosengren A, Skommevik T, Björnsson E. Coronary artery disease in patients with liver cirrhosis. Dig Dis Sci. 2010;55:467–75.
8. Ehtisham J, Altieri M, Salamé E, Saloux E, Ollivier I, Hamon M. Coronary artery disease in orthotopic liver transplantation: pretransplant assessment and management. Liver Transpl. 2010;16:550–7.
9. Burke A, Lucey MR. Non-alcoholic fatty liver disease, non-alcoholic steatohepatitis and orthotopic liver transplantation. Am J Transplant. 2004;4:686–93.
10. Zetterman RK, Belle SH, Hoofnagle JH, Lawlor S, Wei Y, Everhart J, et al. Age and liver transplantation: a report of the Liver Transplantation Database. Transplantation. 1998;66:500–6.
11. Kalaitzakis E, Björnsson E. Coronary artery disease in liver cirrhosis: does the aetiology of liver disease matter? J Hepatol. 2009;51:962–3.
12. Murray RP, Connett JE, Tyas SL, Bond R, Ekuma O, Silversides CK, et al. Alcohol volume, drinking pattern, and cardiovascular disease morbidity and mortality: is there a U-shaped function? Am J Epidemiol. 2002;155:242–8.

13. Berzigotti A, Bonfiglioli A, Muscari A, Bianchi G, LiBassi S, Bernardi M, et al. Reduced prevalence of ischemic events and abnormal supraortic flow patterns in patients with liver cirrhosis. Liver Int. 2005;25:331–6.
14. Kadayifci A, Tan V, Ursell PC, Merriman RB, Bass NM. Clinical and pathologic risk factors for atherosclerosis in cirrhosis: a comparison between NASH-related cirrhosis and cirrhosis due to other aetiologies. J Hepatol. 2008;49:595–9.
15. Donovan CL, Marcovitz PA, Punch JD, Bach DS, Brown KA, Lucey MR, et al. Two-dimensional and dobutamine stress echocardiography in the preoperative assessment of patients with end-stage liver disease prior to orthotopic liver transplantation. Transplantation. 1996;61:1180–8.
16. Plotkin JS, Benitez M, Kuo PC, Njoku MJ, Ridge LA, Lim JW, et al. Dobutamine stress echocardiography for preoperative cardiac risk stratification in patients undergoing orthotopic liver transplantation. Liver Transpl Surg. 1998;4:253–7.
17. Tiukinhoy-Laing SD, Rossi JS, Bayram M, De Luca L, Gafoor S, Blei A, et al. Cardiac hemodynamic and coronary angiographic characteristics of patients being evaluated for liver transplantation. Am J Cardiol. 2006;98:178–81.
18. Carey WD, Dumot JA, Pimentel RR, Barnes DS, Hobbs RE, Henderson JM, et al. The prevalence of coronary artery disease in liver transplant candidates over age 50. Transplantation. 1995;27:859–64.
19. Plotkin JS, Scott VL, Pinna A, Dobsch BP, De Wolf AM, Kang Y. Morbidity and mortality in patients with coronary artery disease undergoing orthtotopic liver transplantation. Liver Transpl Surg. 1996;2:426–30.
20. Diedrich DA, Findlay JY, Harrison BA, Rosen CB. Influence of coronary artery disease on outcomes after libver transplantation. Transplant Proc. 2008;40:3554–7.
21. Johnston SD, Morris JK, Cramb R, Gunson BK, Neuberger J. Cardiovascular morbidity and mortality after orthotopic liver transplantation. Transplantation. 2002;73:901–6.
22. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof EL, Fleischmann KE, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. J Am Coll Cardiol. 2007;50:1707–32.
23. Cholongitas E, Senzolo M, Patch D, Shaw S, O'Beirne J, Burroughs AK. Cirrhotics admitted to intensive care unit: the impact of acute renal failure on mortality. Eur J Gastroenterol Hepatol. 2009;21:744–50.
24. Lester SJ, Hurst RT. Liver transplantation: do you have the heart for it? (editorial). Liver Transpl. 2006;12:520–2.
25. Sharma M, Yong C, Majure D, Zellner C, Roberts JP, Bass NM, et al. Safety of cardiac catheterization in patients with end-stage liver disease awaiting liver transplantation. Am J Cardiol. 2009;103:742–6.
26. Findlay JY, Keegan MT, Pellikka PP, Rosen CB, Plevak DJ. Preoperative dobutamine stress echocardiography, intraoperative events, and intraoperative myocardial injury in liver transplantation. Transplant Proc. 2005;37:2209–13.
27. Umphrey LG, Hurst RT, Eleid MF, Lee KS, Reuss CS, Hentz JG, et al. Preoperative dobutamine stress echocardiographic findings and subsequent short-term adverse cardiac events after orthotopic liver transplantation. Liver Transpl. 2008;14:886–92.
28. Safadi A, Homsi M, Maskoun W, Lane KA, Singh I, Sawada SG, et al. Perioperative risk predictors of cardiac outcomes in patients undergoing liver transplantation surgery. Circulation. 2009;120:1189–94.
29. Williams K, Lewis JF, Davis G, Geiser EA. Dobutamine stress echocardiography in patients undergoing liver transplantation evaluation. Transplantation. 2000;69:2354–6.
30. Harinstein ME, Flaherty JD, Ansari AH, Robin J, Davidson CJ, Rossi JS, et al. Predictive value of dobutamine stress echocardiography for coronary artery disease detection in liver transplant candidates. Am J Transplant. 2008;8:1523–8.
31. Tsutsui J, Mukherjee S, Elhendy A, Xie F, Lyden ER, O'Leary EO, et al. Value of dobutamine stress myocardial contrast perfusion echocardiography in patients with advanced liver disease. Liver Transpl. 2006;12:592–9.
32. Abraczinskas DR, Ookubo R, Grace ND, Groszmann RJ, Bosch J, Garcia-Tsao G, et al. Propranolol for the prevention of first esophageal variceal hemorrhage: a lifetime commitment? Hepatology. 2001;34:1096–102.
33. Berman DS, Abidov A, Kang X, Hayes SW, Friedman JD, Sciammarella MG, et al. Prognostic validation of a 17-segment score derived from a 20-segment score for myocardial perfusion SPECT interpretation. J Nucl Cardiol. 2004;11:414–23.
34. Kryzhanovski VA, Beller GA. Usefulness of preoperative noninvasive radionuclide testing for detecting coronary artery disease in candidates for liver transplantation. Am J Cardiol. 1997;79:986–8.
35. Davidson CJ, Gheorghiade M, Flaherty JD, Elliott MD, Reddy SP, Wang NC, et al. Predictive value of stress myocardial perfusion imaging in liver transplant candidates. Am J Cardiol. 2002;89:359–60.
36. Zoghbi GJ, Patel AD, Ershadi RE, Heo J, Bynon JS, Iskandrian AE. Usefulness of preoperative stress perfusion imaging in predicting prognosis after liver transplantation. Am J Cardiol. 2003;92:1066–71.
37. Aydinalp A, Bal U, Atar I, Ertan C, Aktas A, Yildirir A, et al. Value of stress myocardial perfusion scanning in diagnosis of severe coronary artery disease in liver transplantation candidates. Transplant Proc. 2009;41:3757–60.
38. Senzolo M, Bassanello M, Graziotto A, Zucchetta P, Cillo U, Maraglino G, et al. Microvascular autonomic dysfunction may justify false-positive stress myocardial perfusion imaging in patients with liver cirrhosis undergoing liver transplantation. Transplant Proc. 2008;40:1916–7.
39. Lanza GA, Crea P. Primary coronary microvascular dysfunction. Clinical presentation, pathophysiology, and management. Circulation. 2010;121:2317–25.
40. Guckelberger O, Byram A, Klupp J, Neumann UP, Glanemann M, Stockmann M, et al. Coronary event

rates in liver transplant recipients reflect the increased prevalence of cardiovascular risk factors. Transpl Int. 2005;18:967–74.
41. Assy N, Djibre A, Farah R, Grosovski M, Marmor A. Presence of coronary plaques in patients with nonalcoholic fatty liver disease. Radiology. 2010;254:393–400.
42. McAvoy NC, Kochar N, McKillop G, Newby DE, Hayes PC. Prevalence of coronary artery calcification in patients undergoing assessment for orthotopic liver transplantation. Liver Transpl. 2008;14:1725–31.
43. Plotkin JS, Johnson LB, Rustgi V, Kuo PC. CAD and liver transplantation: the state of the art. Liver Transpl. 2000;6:S53–6.
44. Warnaar N, Lisman T, Porte RJ. The two tales of coagulation in liver transplantation. Curr Opin Organ Transplant. 2008;13:298–303.
45. Lisman T, Bongers TN, Adelmeijer J, Janssen HL, de Maat MP, de Groot PG, et al. Elevated levels of von Willebrand factor in cirrhosis support platelet adhesion despite reduced functional capacity. Hepatology. 2006;44:53–61.
46. Kaplan M, Cimen S, Kut MS, Demirtas MM. Cardiac operations for patients with chronic liver disease. Heart Surg Forum. 2002;5:60–5.
47. Hayashida N, Shoujima T, Teshima H, Yokokura Y, Takagi K, Tomoeda H, et al. Clinical outcome after cardiac operations in patients with cirrhosis. Ann Thorac Surg. 2004;77:500–5.
48. Filsoufi F, Salzberg SP, Rahmanian PB, Schiano TD, Elsiesy H, Squire A, et al. Early and late outcome of cardiac surgery in patients with liver cirrhosis. Liver Transpl. 2007;13:990–5.
49. Klemperer JD, Ko W, Krieger KH, Connolly M, Rosengart TK, Altorki NK, et al. Cardiac operations in patients with cirrhosis. Ann Thorac Surg. 1998;65:85–7.
50. An Y, Xiao YB, Zhong QJ. Open-heart surgery in patients with liver cirrhosis. Eur J Cardiothorac Surg. 2007;31:1094–8.
51. Bizouarn P, Ausseur A, Desseigne P, Le Teurnier Y, Nougarede B, Train M, et al. Early and late outcome after elective cardiac surgery in patients with cirrhosis. Ann Thorac Surg. 1999;67:1334–8.
52. Axelrod D, Koffron A, DeWolf A, Baker A, Fryer J, Baker T, et al. Safety and efficacy of combined orthotopic liver transplantation and coronary artery bypass grafting. Liver Transpl. 2004;10:1386–90.
53. Carr C, Desai J. OPCAB surgery in a cirrhotic hepatocellular carcinoma patient awaiting liver transplant. Ann Thorac Surg. 2004;78:1460–2.
54. Ben Ari A, Elinav E, Elami A, Matot I. Off-pump coronary artery bypass grafting in a patient with Child class C liver cirrhosis awaiting liver transplantation. Br J Anaesth. 2006;97:468–72.
55. Shaheen AA, Kaplan GG, Hubbard JN, Myers RP. Morbidity and mortality following coronary artery bypass graft surgery in patients with cirrhosis: a population-based study. Liver Int. 2009;29:1141–51.
56. Alper I, Ulukaya S, Demir F, Kilic M. Effects of cardiac valve dysfunction on perioperative management of liver transplantation. Transplant Proc. 2009;41:1722–6.
57. Pocar M, Passolunghi D, Moneta A, Donatelli F. Primary and redo valve replacement before and after liver transplantation. Eur J Cardiothorac Surg. 2007;32:674–5.
58. Iino K, Tomita S, Yamaguchi S, Watanabe G. Successful aortic valve replacement using dilutional ultrafiltration during cardiopulmonary bypass in a patient with Child-Pugh class C cirrhosis. Interact Cardiovasc Thorac Surg. 2008;7:331–2.
59. Eckhoff DE, Frenette L, Sellers MT, McGuire BM, Contreras JL, Bynon JS, et al. Combined cardiac surgery and liver transplantation. Liver Transpl. 2001;7:60–1.
60. Maron BJ. Hypertrophic cardiomyopathy: a systematic review [review]. JAMA. 2002;287:1308–20.
61. Maraj S, Jacobs LE, Maraj R, Contreras R, Rerkpattanapipat P, Malik TA, et al. Inducible left ventricular outflow tract gradient during dobutamine stress echocardiography: an association with intraoperative hypotension but not a contraindication to liver transplantation. Echocardiography. 2004;21:681–5.
62. Rigopoulos AG, Panou F, Kremastinos DT, Seggewiss H. Alcohol septal ablation in hypertrophic obstructive cardiomyopathy [review]. Hellenic J Cardiol. 2009;50:511–22.
63. Paramesh AS, Fairchild RB, Quinn TM, Leya F, George M, Van Thiel DH. Amelioration of hypertrophic cardiomyopathy using nonsurgical septal ablation in a cirrhotic patient prior to liver transplantation. Liver Transpl. 2005;11:236–8.
64. Hage FG, Bravo PE, Zoghbi GJ, Bynon JS, Aqel RA. Hypertrophic obstructive cardiomyopathy in liver transplant patients. Cardiol J. 2008;15:74–9.
65. Lim YC, Doblar DD, Frenette L, Fan PH, Poplawski S, Nanda NC. Intraoperative transesophageal echocardiography in orthotopic liver transplantation in a patient with hypertrophic cardiomyopathy. J Clin Anesth. 1995;7:245–9.
66. Harley ID, Jones EF, Liu G, McCall PR, McNicol PL. Orthotopic liver transplantation in two patients with hypertrophic obstructive cardiomyopathy. Br J Anaesth. 1996;77:675–7.
67. Cywinski JB, Argalious M, Marks TN, Parker BM. Dynamic left ventricular outflow tract obstruction in an orthotopic liver transplant recipient. Liver Transpl. 2005;11:692–5.
68. Chin JH, Kim YK, Choi DK, Shin WJ, Hwang GS. Aggravation of mitral regurgitation by calcium administration in a patient with hypertrophic cardiomyopathy during liver transplantation: a case report. Transplant Proc. 2009;41:1979–81.