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Common cardiac comorbidities and perioperative assessment modalities for liver transplant candidates – an update

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Cardiac complications are currently the leading cause of early mortality following liver transplantation. Guidelines for the cardiac workup prior liver transplantation are limited. In this review we are discussing commonly modalities used for cardiovascular evaluation of liver transplant candidates.

Keywords: liver transplantation, cardiovascular complications, preoperative preparation

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Наиболее часто встречающиеся сопутствующие заболевания сердечно-сосудистой системы и методы их периоперационной оценки у кандидатов на трансплантацию печени

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В настоящее время осложнения со стороны сердечно-сосудистой системы являются основной причиной ранней летальности после трансплантации печени. Рекомендации по кардиологическому обследованию перед трансплантацией печени представлены в ограниченном объеме. В данном обзоре мы рассматриваем общие методы, используемые для оценки сердечно-сосудистой системы у кандидатов на пересадку печени.

Ключевые слова: трансплантация печени, сердечно-сосудистые осложнения, предоперационная подготовка

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AASLD/AST, American Association for the Study of Liver Diseases and the American Society for Transplantation
ACC/AHA, American College of Cardiology/American Heart Association
AF, Atrial fibrillation
ALD, alcohol-related liver disease
AS, Aortic stenosis
AT, anaerobic threshold
AVR, aortic valve replacement
BMI, Body Mass Index
CAD, coronary artery disease
CCM, cirrhotic cardiomyopathy
CPET, Cardiopulmonary exercise stress testing
DAPT, dual antiplatelet therapy
DSE, Dobutamine Stress Echocardiogram
EKG, electrocardiogram
ESLD, end stage liver disease
FFR, fractional flow reserve
HF, heart failure
LA, left atrial
LHC, Left heart catheterization
LT, liver transplantation
LV, left ventricular
LVEF, left ventricular ejection fraction
LVH, Left ventricular hypertrophy
MACE, major adverse cardiovascular events
MELD, model for end-stage liver disease
MI, myocardial infarction
MPS, myocardial perfusion scanning
MPI, myocardial perfusion imaging
MR, mitral regurgitation
NAFLD, non-alcoholic fatty liver disease
NASH, nonalcoholic steatohepatitis
NPV, Negative predictive value
PCI, Percutaneous Coronary Intervention
PPV, positive predictive value
QTc, corrected QT interval
SPECT, Single-photon emission computed tomography
TR, tricuspid regurgitation
TAVR, Transcatheter aortic valve replacement
TEE, Transesophageal echocardiography
TTE, Transthoracic echocardiography
UNOS, United Network for Organ Sharing

Introduction

Patients undergoing evaluation for liver transplantation (LT) represent a unique patient population with a specific set of comorbidities secondary to end stage liver disease (ESLD) [1]. One of the responsibilities of the anesthesiologist, as an integral member of a multidisciplinary transplant program, is to ensure that patients are adequately screened and prepared prior to being listed for transplantation in order to determine meaningful postoperative survival and optimal organ allocation [2]. It has been shown previously that a dedicated transplant anesthesia team results in improved outcomes [3].

The need for donor organs continues to by far exceed the organ supply. In 2013, more than 25,000 liver transplantations were performed worldwide, while the donor organ pool remains stagnant. Currently, about 7,000 liver transplantations are performed each year in the Unites States, however more than 14,000 patients remain on the waitlist, and 22 patients will die every day waiting for a donor organ. Despite advances in surgical technique, anesthesia, postoperative care and immunosuppression, liver transplantation is still considered a high risk surgery with an overall 1-year mortality rate of almost 10% [4], highlighting the importance of diligent preoperative screening and stratification. Early morbidity and mortality after LT are commonly due to cardiac causes [5]. Cardiovascular disease is the leading cause of non-graft related short term (<1 year) and the third common cause of late (>1year) mortality [5-7]. Stresses on the cardiovascular system include hemodynamic instability and a likelihood of vasodilatory shock during reperfusion of the graft. Prolonged cardiovascular stress may adversely impact and exacerbate pre-existing cardiac dysfunction.

This review discusses common cardiac abnormalities associated with ESLD and an update on the most commonly used evaluation modalities including their ability to predict morbidity and mortality in patients presenting for LT evaluation.

Cardiac comorbidities in patients with end stage liver disease

Cardiovascular complications are a major cause of long-term morbidity and mortality in patients with ESLD, especially after LT [8]. A large study showed that major adverse cardiovascular events (MACE) and associated hospitalizations occurred in 8% and 11% of patients at 30 and 90 days post-transplantation, respectively. An increased number of MACE was also associated with a prior history of NASH, alcoholic cirrhosis, myocardial infarction (MI), heart failure (HF), stroke, atrial fibrillation, and chronic renal disease [7].

Cardiovascular changes associated with cirrhosis were recognized over 50 years ago, and since then a large body of research has been directed toward a greater understanding of the effects of liver failure on the heart and circulatory system [9].

Coronary artery disease

The prevalence for coronary artery disease (CAD) in patients with ESLD was previously thought to be lower when compared to the general population; however, evidence has shown that this patient population instead represents a high risk group [10]. A relation was found with the current

change in demographics. Increasing age resulting in higher rates of traditional risk factors for atherosclerosis combined with immunosuppression-related acceleration of atherosclerosis, a steadily increasing incidence of NASH and a state of chronic inflammation increases the risk of plaque rupture [11]. The overall prevalence of CAD in patients with chronic liver disease has been described from 3 to 36.8%. The wide range is likely as a result of inconsistent definitions, screening methods and sample population [10].

In a study in 161 patients aged over 45 years without known CAD, Tiukinhoy-Laing et al [12] used coronary angiography as the gold standard test to evaluate for CAD, in addition to transthoracic echocardiography, and found that 60% of patients had CAD, with 24% of them having moderate to severe disease. In this cohort, 50% of patients had two or more risk factors for CAD; and the presence of CAD was associated with male gender, hypertension, and type 2 diabetes mellitus. Patients over the age of 50 had higher rates of significant CAD, with 27% moderate and 16.2% severe CAD. Of 17,482 recipients assessed from the US Organ Procurement and Transplantation Network (UNOS) database between 2004 and 2006, the incidence of CAD was 7.4% in non-alcoholic fatty liver disease (NAFLD) patients, 2.7% in chronic hepatitis C patients, and 2.9% in patients with alcohol-related liver disease (ALD) [13]. In another study in 420 patients with ESLD, severe CAD (more than 70% stenosis) was found in 2% of the ALD and 13% of the NAFLD group. The absence of risk factors was highly predictive of the absence of significant CAD in both study groups with 97% sensitivity in NAFLD group and 100% in ALD group [10]. The steadily increasing incidence of NASH [14-16], which is now considered an independent risk factor for cardiovascular disease [15, 17], accounts for over 75% of all chronic liver diseases and is the second leading cause among patients awaiting LT in the United States [18]. Patel et al showed that critical CAD, defined as more than 70% stenosis, was present in 52.8% of patients with decompensated NASH undergoing elective coronary angiography as part of the LT evaluation [19].

LT candidates with pre-transplant CAD have demonstrated worse outcomes when compared to patients without CAD [9, 20, 21], with a one year mortality rate reported to be as high as 40% [22]. Cardiovascular disease accounted for 21% of deaths and was the third most common cause of mortality after recurrent liver disease (24%) and malignancy (24%) in LT recipients surviving more than three years following transplantation [20]. The 10-year risk of developing a cardiac event in LT recipients was estimated at 14%, which represents a 64% increase in the post-transplant cohort compared to the control population [5]. Another single-center study in 775 LT recipients reported a 10% incidence of cardiac events over a 3-year follow-up period [5]. Balogh et al have shown that 16% of LT candidates had a pre-transplant diagnosis of CAD (single vessel more than 50% or multi-vessel disease, history of MI, stenting, or coronary artery bypass grafting). Patients with CAD were older and had greater incidence of obesity (BMI more than 30), diabetes, hypertension, and renal insufficiency. No significant difference was shown in 1-, 3- and 5-year survival of LT recipients with CAD (91.6%, 88.1%, and 64.1%, respectively) compared to those without CAD (90.3%, 83.3%, and 73.7%) [21].

In the post-transplantation phase, the effects of immunosuppression have shown to contribute to the development of new or worsening diabetes, hypertension, hypercholesterolemia, and an increase in body mass index, resulting in an increased risk for cardiovascular complications [23]. Metabolic syndrome has a prevalence of up to 60% post-LT and is associated with significant cardiovascular risk [24]. It has been shown that the incidence of hypertension increased from 5% pre-transplantation to 77% post-LT, hypercholesterolemia increased from 16% to 60%, and diabetes increased from 9% to 13% [24].

Revascularization is appropriate in cases where the burden of obstructive CAD would be prohibitive for LT in an otherwise appropriate surgical candidate. Revascularization, necessitating the need for dual antiplatelet therapy (DAPT), can be performed safely and can improve post-LT outcomes similar to those LT candidates without significant CAD. In patients requiring non-cardiac surgery, such as LT, the current recommendation is to delay surgery a minimum of 1 month after bare metal stent placement and 6 months after drug eluting stent placement. Bare metal stents are preferred in LT candidates to minimize the duration of DAPT. Non-vascularized obstructive severe multivessel CAD remains an absolute contraindication for LT [25].

Cirrhotic cardiomyopathy

A hyperdynamic circulation in combination with an elevated cardiac output and decreased SVR are hallmark findings in patients with ESLD. These

hemodynamic findings are the consequence of abnormal liver function, portal hypertension, and splanchnic vasodilatation [26]. These pathophysiological cardiac changes associated with ESLD are referred to as cirrhotic cardiomyopathy (CCM) [27] and have been shown to be present in 40-50% of patients with ESLD [28]. Systolic function is often normal or increased at rest; however, cardiac dysfunction is often unmasked when exposed to physical or surgical stress, hemorrhage and infection. The original criteria for CCM, established by the 2005 World Congress of Gastroenterology, include LV systolic dysfunction, defined as LVEF less than 55% at rest and/or failure of LVEF to increase on stress testing by more than 5% [29], additionally, diastolic dysfunction, defined as an E/A ratio less than 1 and/or a prolonged mitral deceleration time more than 200 ms. Those findings in the absence of cardiopulmonary disease were defined as CCM. More recently, in 2019, the Cirrhotic Cardiomyopathy Consortium proposed an update on these criteria because an assessment of impaired contractile response to stress testing is often impaired in ESLD patients [29]. The Consortium proposes to include echocardiographic assessment of global longitudinal strain (GLS) in order to more objectively quantify the regional myocardial contractile function and values of less than -18% or more than -22% are considered abnormal. In order to evaluate a diastolic dysfunction, it was recommended to apply criteria suggested by the American Society of Echocardiography, namely a septal e' velocity less than 7 cm/sec, E/e' ratio more than 15, LA Volume Index more than 34 mL/m^2 and TR velocity more than 2.8 m/sec. The presence of more than 3 of these parameters was considered diagnostic [29].

Mortality from HF after LT is estimated to be as high as 15%, and there is clinical or radiographic evidence of pulmonary edema in as many as 56% of patients within the first postoperative week [30]. In a large recent analysis of over 32,000 LT recipients in the United States, HF contributed to nearly 25% of hospital admissions, within 90 days after liver transplantation [7].

Treatment of CCM is challenging as it remains silent for a long time under stable conditions. It should, however, be suspected in cirrhotic patients without known cardiac disease and exercise intolerance. Once the cardiac failure becomes evident, management should follow similar guidelines as in non-cirrhotic patients, although the treatments to reduce cardiac afterload are poorly tolerated by ESLD patients being often significantly vasodilated and should be avoided. To date there are no clinical studies available on the management of CCM [31]. Non-selective beta-blockers have shown to reduce the prolonged QT interval and also decrease the hyperdynamic load; however, a positive long term effect has not been shown, and the use of beta blockers in patients with refractory ascites has a risk of increased mortality [32]. Liver transplantation has shown to reverse systolic and diastolic dysfunction and the prolonged QT interval and is therefore considered the definitive treatment [33].

Cardiac dysrhythmias

Atrial fibrillation (AF) is the most common cardiac dysrhythmia in patients presenting for liver transplantation with a prevalence of about 5.6% [34-36], which is higher than 2.5% in the general population [34]. Following LT, AF has been shown to increase the likelihood of an elevated central venous pressure potentially resulting in poor graft venous outflow [35]. AF has also been shown to increase post-operative cardiac morbidity and is associated with worse long term outcomes [7, 35]. In a single-center series of 757 LT candidates, a one-year post-transplant survival in patients with AF was lower when compared to patients without AF (68.4% vs. 90.4%). Postoperative AF is associated with increased mortality, renal failure, infection, and cognitive dysfunction in the general population [36]. In a single-center study of LT recipients, the incidence of a new-onset AF was 7.4% in the first month after LT with its peak within the first week. Preoperative risk factors for the development of postoperative AF included a history of preoperative paroxysmal AF, increased age, increased body weight, high MELD, and the need for preoperative dialysis and vasopressors. A new-onset of AF in LT recipients likely represents a manifestation of advanced CCM and a lack of cardiac reserve [7, 25]. The preoperative development of a new-onset AF in LT candidates is a significant risk factor for decreased survival following LT.

Valvular heart disease

Abnormalities in the cardiac valves, especially mitral regurgitation (MR) and tricuspid regurgitation (TR), are present in 27.5% of LT candidates and may significantly impact the peri- and intraoperative management and postoperative outcomes [25, 37]. MR and TR are commonly due to increased loading conditions especially in the setting of portal hypertension and hepatorenal syndrome. Severe

TR should raise high suspicion for underlying portopulmonary hypertension and potential right ventricle failure.

Severe AS is associated with significant perioperative morbidity and mortality in noncardiac surgery in all patients. The hemodynamics of cirrhosis, underlying CCM, and perioperative stress associated with LT are detrimental in patients with severe AS and all those remain an absolute contraindication for liver transplantation.

Preoperative detection of AS and quantification of its severity is critical in LT candidates. Definitive correction of AS before LT remains a clinical challenge. Cardiac surgery in ESLD patients is associated with an operative morbidity between 50% and 100% [37] and mortality rates as high as 29% [38]. In a single-center case series, the success of AVR in high MELD patients was limited [39]. However, a successful valve repair before LT has been described in a small case series [40]. Evidence suggests that pre-transplant aortic valve replacement (AVR) may only be a viable approach in the candidate with an MELD score less than 13 [41]. Simultaneous AVR and LT is very rare and has been described in case reports [42]. Transcatheter aortic valve replacement (TAVR) is an emerging technique for patients who are not candidates for open heart surgery. TAVR may have a role in the management of AS in LT candidates, with early promising results shown in selected patients [43-45]. As mentioned above, the presence of severe AS remains an absolute contraindication for LT; however, the determination of candidacy for LT in patients with asymptomatic mild to moderate AS (aortic valve area >1cm^2) remains controversial and must be managed by multidisciplinary transplant teams on a case-by-case basis.

Intraoperative TEE is becoming the standard of care in the management of patients with valvular heart disease undergoing LT [25].

Preoperative cardiac evaluation of the liver transplant candidate

Preoperative cardiac screening is performed to ultimately minimize postoperative morbidity and mortality and therefore improve organ allocation. A recent large retrospective analysis of 64,977 LT recipients showed a 90-day and 1-year mortality of 5% and 10%, respectively. The most common cause of death during the first week after transplantation was cardiovascular (18.5%), followed by infectious complications (12.9%), and graft failure (5%) [46]. A study evaluating data from LT recipients in the UK demonstrated that patients with congestive heart failure had the highest 90-day mortality rate with 20.2% and a 5-year mortality rate of 37.5% [47]. More recently, Khurmi et al have shown that LT recipients admitted to the hospital for a cardiovascular event had a mortality rate of 3.9% [8]. When compared to the general population, the risk for a cardiovascular event is increased by 64% in LT recipients [48].

Standardized guidelines that outline the optimal cardiovascular risk stratification for LT candidates are limited, especially in asymptomatic patients [11]. The American College of Cardiology/American Heart Association (ACC/AHA) issued a recommendation to evaluate all LT candidates for any active cardiac condition by performing a detailed history and physical examination [49]. Non-invasive testing should be considered in LT candidates without active cardiac conditions based on the presence of more than three risk factors for CAD (diabetes mellitus, cardiovascular disease, left ventricular hypertrophy, age more than 60 years, smoking, hypertension and hyperlipidemia), regardless of functional status [50]. The American Association for the Study of Liver Diseases and the American Society for Transplantation (AASLD/AST) recommended in their 2013 practice guidelines to perform non-invasive cardiac testing (exercise stress testing or pharmacological stress testing) for all adults undergoing evaluation for LT [49]. Abnormalities on non-invasive testing requiring further investigations are usually performed on a case-to-case basis and per individual institutional protocol.

Electrocardiography

A 12 lead EKG is part of a routine cardiac evaluation in candidates for liver transplantation. Prolonged QTc interval (more than 440 ms) is the common abnormality found in 30-60% of cirrhotic patients [9, 51] and has previously been considered one of the supportive criteria for CCM [29]. Prolongation of QTc may lead to electromechanical uncoupling, which in turn may lead to sudden cardiac death in the setting of surgical stress [52]. QTc prolongation however, improves in 50% of patients after liver transplantation [51]. The interval from peak T wave to end T wave (less than 50 ms) reflecting ventricular repolarization has previously been associated with poor outcomes [53].

Echocardiography

Transthoracic echocardiography (TTE) is a helpful, non-invasive risk assessment tool in detecting structural and functional abnormalities in the heart, such as chamber sizes, hypertrophy, systolic and diastolic function, valvular function and LV outflow tract obstruction. Right ventricular systolic pressure and pulmonary artery pressure can be measured as well as the presence of hepatopulmonary syndrome using bubble contrast [54]. TTE should be part of the routine cardiac evaluation in every LT candidate as recommended by the AASLD. However specific TTE variables that predict poor outcomes following LT have not been definitely identified [55]. TTE in patients with ESLD may be complicated by large volume ascites, limiting the ability to image from a subcostal position [56].

Cardiac stress testing

LT candidates are often deconditioned and unable tolerate exercise stress testing, making pharmacological stress testing the more commonly used modality. Dobutamine Stress Echocardiogram (DSE) does not test for the presence of CAD, but for the presence of wall motion abnormalities in the setting of increased oxygen demand. Questions remain about the severity of coronary disease that requires treatment and what type of treatment is best.

Conflicting results on sensitivity and specificity of DSE in predicting CAD in LT candidates have been reported in the literature [57]. A negative DSE appears useful in excluding the patients at risk for perioperative cardiac events related to obstructive CAD in patients undergoing evaluation for LT [30].

A study in 80 LT candidates with known or suspected CAD, with half of the patients undergoing coronary angiography, demonstrated a 5% prevalence of CAD, with a primary association with diabetes [58]. The positive predictive value (PPV) of DSE for CAD detection was 100%. Several subsequent studies could not show a similar correlation. In a study of 165 LT candidates [30], DSE had a sensitivity of 75% and specificity of 57%. Inducible ischemia was present in 7% of DSE studies. Nine of the 11 patients with ischemia had undergone left heart catheterization, with 3 of them showing CAD, translating in a PPV of 33%. Subsequently 5.6% of patients who were transplanted showed global dysfunction. None of these events were predicted by DSE [57]. Another study correlated post-LT troponin T elevations with preoperative DSE results and found no difference in the prevalence of elevated troponin in patients with abnormal versus normal DSE findings; however, the NPV of DSE was high. In this study troponin elevations were associated with intraoperative hemodynamic instability, but hemodynamic instability was not associated with a positive DSE [59]. In a study of 105 LT candidates who underwent DSE and LHC, DSE had a low sensitivity (13%), high specificity (85%), and low PPV (22%). The low sensitivity of DSE may be due to an inability to reach target heart rate, particularly in patients on beta blockers for the prophylaxis of esophageal bleeding from varices. However, non-invasive stress testing should be considered in asymptomatic candidates with multiple cardiac risk factors. Although the exact number of risk factors that warrants testing is unknown, the presence of three or more seems reasonable. Patients with evidence of ischemic wall motion abnormalities are commonly referred for coronary angiography and consideration of percutaneous revascularization prior to transplantation.

SPECT myocardial perfusion imaging

LT candidates who cannot achieve a target heart rate with DSE are often further evaluated with myocardial perfusion scanning (MPS), utilizing various radiotracers. The uptake of the radiotracer indicates areas of perfusion and viable tissue during stress and rest. MPS when compared to coronary angiography for cardiovascular screening of LT candidates demonstrated a high sensitivity, however low specificity [60, 61]. Davidson et al showed that 39% of LT candidates produced false positive MPS scans, with subsequent coronary angiography showing no obstructive coronary artery disease [60].

Another study showed that SPECT after dipyridamole administration can be positive in 12.5% of LT candidates. Microvascular tone changes are presumed to be the reason for false positive results [62]. A normal dipyridamole, adenosine, or exercise stress SPECT imaging study has 99% NPV for cardiovascular events in patients undergoing LT. The presence of ascites and splenomegaly can produce false positive results. A two-year post-LT survival did not differ in patients evaluated with SPECT when compared to patients who did not undergo SPECT evaluation pre-operatively [63].

A study by Aydinalp et al confirmed that reversible perfusion defects on MPS have low specificity (61%), however a high sensitivity (more than 90%) for severe CAD, when compared to

coronary angiography. About 68.8% of MPS scans showed abnormal results with 37.5% fixed defects and 62.5% reversible defects. Only 9.4% of abnormal MPS studies could demonstrate severe CAD by coronary angiography. Patients with fixed defects or normal MPI generally do not show severe CAD on coronary angiography [61]. In a different study, Bhutani et al concluded that both adenosine and regadenoson had low sensitivity and high specificity for diagnosing CAD. The group stated that a standard risk factor analysis as a predictor for CAD in patients with ESLD is less expensive, has no radiation exposure, and is as accurate as SPECT imaging study [64].

Bradley et al showed in a population of 772 LT candidates that when dipyrimadole stress test is used, approximately 93% of patients showed low risk MPS, 5% have an intermediate-risk MPS, and 2% have a high risk MPS study [65], a finding that is incongruous with the prevalence of CAD demonstrated in other studies. In addition, they reported a significantly lower rate of cardiovascular complications, which was not well predicted by pre-transplant imaging. Zoghbi et al examined the usefulness of SPECT to predict cardiovascular complications and found that a normal study had a 99% NPV for perioperative cardiac events in a low risk cohort of patients [63].

More recently, in a study evaluating 389 patients for early cardiac events predicted by either DSE or SPECT showed respective sensitivities of 9% vs 57%, specificities of 98% vs 75%, and PPV of 33% vs 28% [66]. A recent retrospective study by Duvall et al [67] in 2,500 LT candidates showed abnormal perfusion results on MPS in 7.8% of LT candidates compared to 34% of all other patients. Moreover, they concluded that repeat testing in LT candidates after initial normal results might be of limited value.

An increased incidence of 1-year all-cause mortality after orthotopic liver transplantation was found in a study by Oprea-Lager et al, associated with the presence of a single reversible perfusion defect.

Coronary angiography

The definitive test of diagnosing CAD is coronary angiography. However, its invasive nature and the perceived risk of renal failure, coagulopathy and infectious complications make this test less suitable as an initial diagnostic test and is often deferred in patients with decompensated liver cirrhosis [68-70]. The PPV is higher for coronary angiography when compared to coronary computed tomography angiography or chemical stress test [19]. Percutaneous interventions are typically performed for severe stenosis (more than 70%), whereas moderate (50% to 70%) stenosis is managed based upon individual center protocol. The prevalence of severe stenosis in LT candidates undergoing screening for CAD has been reported to range from 4% to 15% [12, 43, 70]. A recent study by Pang et al has shown that diabetes, dyslipidemia, ischemic heart disease, age more than 65 years, and LVH are risk factors of abnormal coronary angiography in LT candidates [71].

Some centers obtain fractional flow reserve (FFR, the ratio of distal to proximal coronary pressure; abnormal <0.75 to 0.80) during angiography to determine the significance of each individual lesions. This technique is considered the gold standard for the diagnosis of CAD during angiography. When PCI is performed, bare-metal stents and limited dual antiplatelet therapy are commonly used. In lesions not amenable to PCI, simultaneous cardiac surgery and liver transplantation has been reported. Experience is limited to case reports and small series. Cardiac surgery after LT appears to be safe with similar 5-year survival when compared to a general population undergoing cardiac surgery. A case series of PCI in LT candidates showed that 16 patients safely underwent PCI without in-house mortality or MI [72]. Bare-metal stents were placed in 15 and angioplasty alone was performed in 1 patient resulting in successful PCI in 94% and 3 of these patients subsequently underwent a successful LT [72].

Cardiopulmonary exercise testing

Cardiopulmonary exercise stress testing (CPET) simultaneously evaluates the cardiovascular and respiratory system during exercise. The diagnostic and prognostic information provided can identify patients who might benefit from pre-habilitation or perioperative optimization and predict short- and long-term surgical outcomes. CPET is considered a functional assessment that measures maximum aerobic capacity (VO_2max) defined as the ability of the body to consume and use oxygen during exercise [73] and ultimately indicates the ability of the cardiopulmonary system to deliver oxygen to the peripheral tissues. Another parameter evaluated is the anaerobic threshold (AT), which is the physiological point at which oxygen supply to muscle does not meet demand causing a switch to anaerobic glycolysis [74]. CPET involves measurements of

respiratory oxygen uptake (VO_2), carbon dioxide production (VCO_2) and ventilator measures during symptom-limited exercise test [75].

Integration of respired gas analysis (oxygen and carbon dioxide concentrations) with ventilator flow measurements enables calculation of VO_2 and VCO_2, under conditions of progressively increasing physiological stress. The test is usually performed on a stationary bike or a treadmill [76] with continuous monitoring of heart rate, blood oxygen saturation (SpO_2), arterial blood pressure, and 12-lead EKG [74]. CPET testing has been shown to be safe, in patients with chronic liver disease, however it is costly and often not available outside of tertiary care centers [77].

In one study in a patient population with cirrhosis it was shown that only 32% of patients could achieve VO_2max, but nearly all could reach AT [78]. VO_2max and AT, have shown to be associated with 90-days and 100-days outcome following LT [73, 74]. Prentis et al were the first ones to show that low AT (less than 9 mL/min/kg) was significantly associated with a reduction in 90-day survival and increased requirement for postoperative critical care [77]. Another study noted that an AT of less than 9.2 mL/min/kg was associated with a significantly increased duration of post-transplant hospitalizations [73, 77]. In a meta-analysis by Ney et al, the group showed, that patients listed for liver transplantation have significant limitations in exertional tolerance. The mean peak baseline VO_2 across studies was 17.4 ml/kg/min, which correlates with expected VO_2 levels of a sedentary female in her 80's, and is below the 18 ml/kg/min threshold level required for full independent living. They conclude that CPET is a promising objective test for the prediction of pre- and post-transplant mortality [75]. A recent study by Wallen et al showed that poor cardiorespiratory fitness was evaluated with CPET as an independent risk factor for sepsis in LT candidates [79].

However, the value of CPET in the evaluation of LT candidates is often limited by deconditioning and lack of effort in sick patients.

Discussion

Preoperative cardiac evaluation of the LT candidate remains a crucial and equally controversial issue, since cardiac causes are the most common causes for early mortality and the third most common cause for late mortality. Standardizing the process to identify the patients at risk for perioperative cardiac event remains challenging, due to variations in the prevalence of cardiovascular disease, a large number of asymptomatic patients and often a prolonged period between listing and transplantation. Non-invasive testing such as cardiac echocardiography and pharmacologic stress testing have shown conflicting results in terms of sensitivity and specificity and CCM often does not present in its early stages and may only be revealed under stress conditions [80].

A large body of literature is available on a wide range of preoperative testing modalities used for cardiac evaluation of LT candidates, however universally accepted guidelines are limited. A document from the American Heart Association/American College of Cardiology (AHA/ACC) recognizes the challenges related to pre-transplant screening for cardiovascular disease. The absence of cardiac symptoms may have less predictive value in transplant candidates compared to the general population [50]. However, recommendations for CAD evaluation in non-cardiac surgery patients are focused on functional capacity and exercise tolerance [81]. Recommendations by the AASLD and the American Society of Transplantation however include assessment of cardiac risk factors with stress echocardiography as an initial screening test. Moreover, a consultation with a cardiologist and the cardiac revascularization should be considered in liver transplant candidates with significant coronary artery stenosis prior to transplantation [82]. Absolute contraindications for LT include symptomatic CAD, severe cardiac valvular abnormalities, severe ventricular dysfunction, severe pulmonary hypertension and cardiomyopathy, despite optimal medical, interventional, or surgical management [83].

CPET as a method for functional assessment is an emerging modality that is already part of routine evaluation for patients awaiting cardiac transplantation and thoracic surgery. It has been shown that VO_2max is superior in predicting postoperative survival than other clinical variables or even right heart catherization [76]. A number of studies have shown potential in predicting post-operative survival in LT, however, its utility is limited by its cost, availability, and the poor functional status of LT candidates who are often debilitated, and exercise tolerance may be difficult to assess. Larger multi-center trials are still needed.

Summary

An ideal non-invasive screening test with high sensitivity in asymptomatic patients with occult coronary artery disease is not available at this point and a vigilant multidisciplinary transplant team remains crucial in identifying liver transplantation candidates at risk.

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