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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (7): Liver transplant

Role of cardiovascular intervention as a bridge to liver transplantation

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Abstract

End stage liver disease (ESLD) is associated with many specific derangements in cardiovascular physiology, which influence perioperative outcomes and may profoundly influence diagnostic and management strategies in the preoperative period. This review focuses on evidence-based diagnosis and management of coronary, hemodynamic and pulmonary vascular disease in this population with an emphasis on specific strategies that may provide a bridge to transplantation. Specifically, we address the underlying prevalence of cardiovascular disease states in the ESLD population, and relevant diagnostic criteria thereof. We highlight traditional and non-traditional predictors of cardiovascular outcomes following liver transplant, as well as data to guide risk-factor based diagnostic strategies. We go on to discuss the alterations in cardiovascular physiology which influence positive- and negative-predictive values of standard noninvasive testing modalities in the ESLD population, and review the data regarding the safety and efficacy of invasive testing in the face of ESLD and its co-morbidities. Finally, based upon the totality of available data, we outline an evidence-based approach for the management of ischemia, heart failure and pulmonary vascular disease in this population. It is our hope that such evidence-driven strategies can be employed to more safely bridge appropriate candidates to liver transplant, and to improve their cardiovascular health and outcomes in the peri-operative period.

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Key words: Perioperative management; Liver transplantation; Coronary heart disease; Cirrhotic cardiomyopathy; Heart failure; Pulmonary vascular disease

Core tip: The population of liver transplant candidates is rapidly evolving with respect to advanced age, etiology and co-morbidities. Consequently, the cardiovascular risk profiles of these candidates have increased. At the same time, the availability of interventions, both mechanical and pharmacologic, for cardiovascular conditions has allowed previously unsuitable candidates to go on to liver transplantation. Therefore, it is imperative to understand how to define the cardiovacular risk profile of liver transplant candidates and the pre-transplant treatment options available to them.

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CORONARY ARTERY DISEASE

In light of the rising prevalence of coronary artery disease (CAD) among the general population, and the

increasing age and co-morbidities among present-day liver transplant candidates, special care must be given to coronary evaluation and management prior to liver transplantation (LT)[1]. It has been estimated that more than one in four LT candidates with traditional coronary risk factors (Table 1) may have developed moderate coronary stenosis by the time of LT consideration even while asymptomatic and that the likelihood of obstructive CAD (> 70% coronary stenosis or > 50% left main stenosis) is greatest among candidates with ≥ 2 traditional cardiac risk factors[2-4]. In particular, age > 50 years and diabetes mellitus (DM) seem predictive of cardiac ischemia post-LT[5-9]. In one analysis, LT recipients with known CAD or DM had approximately 40% greater 5-year mortality than those without CAD or DM[10]. In a retrospective analysis of ESLD patients who underwent invasive angiography prior to LT, multi-vessel CAD of any severity was associated with increased mortality and postoperative hemodynamic instability[11]. It is therefore important to identify and treat patients at risk for coronary disease prior to liver transplantation given their elevated risk of postoperative ischemic complications[9,12,13].

Ischemic evaluation with exercise or pharmacologic stress testing (utilizing either echocardiographic or perfusion imaging) has been shown to have decreased predictive value in LT candidates when compared to the general population. (Table 2) Stress testing should be pursued based on careful, individualized evaluation of the candidate's pretest probability for having CAD. In general, the ability to exercise to target heart rate is blunted in LT candidates, likely due to decreased beta-agonist transduction, and pharmacologic stress testing is usually favored[14]. For the same reason, LT candidates may not achieve desired chronotropy on dobutamine stress echocardiography (DSE). Indeed, those who do not achieve target heart rate or peak double product (heart rate × blood pressure) are felt to be at elevated risk of postoperative cardiovascular events[15]. DSE may have poor sensitivity (reported as low as 13%) and low negative predictive value (reported as low as 75%) among LT candidates[16-18]. Vasodilator perfusion imaging with nuclear SPECT (single photon emission computed tomography) may also have limited utility in the setting of the chronically vasodilated states seen in advanced liver disease[19]. Resting microvascular vasodilation in ESLD may effectively "decrease" available coronary flow reserve, which may in turn lead to apparent perfusion defects having lower-than-expected specificity for obstructive epicardial coronary disease (*i.e.*, false-positive vasodilator stress test results)[20-24] (Table 2).

Non-alcoholic steatohepatitis (NASH) cirrhotic patients more commonly exhibit traditional coronary risk factors and associated CAD compared to patients with other etiologies of cirrhosis[25-29]. In addition, cirrhotic patients with concomitant renal dysfunction are also at elevated risk for coronary disease[30].

A direct visual assessment of the coronary artery anatomy should be considered for LT candidates with high pretest probability of CAD (≥ 2 traditional coronary risk factors, especially DM) in addition to those with ischemia on stress imaging. In one study of LT candidates without known CAD, greater than 30% were found to have at least moderate CAD on cardiac CT angiography[4]. CT angiography offers an attractive balance of safely and accuracy for this purpose. It can be offered to patients of normal habitus who are able to lie still, perform required breath holding maneuvers and who have a regular non-tachycardic rhythm[4,31,32]. Negative predictive value of normal or nonobstructive findings on coronary CT angiography can approach 95%[33]. Invasive coronary angiography can also be performed safely in LT candidates even in the face of renal dysfunction and elevated bleeding risk[34-36]. Invasive angiography *via* a transradial approach has been advocated in LT candidates, if possible, to promote more reliable hemostasis in the setting of the often-profound coagulopathies and cytopenias seen with ESLD[37,38]. Revascularization of obstructive coronary disease may be pursued to improve symptom burden and cardiovascular mortality per ACC/AHA guidelines, and in cases where the burden of obstructive CAD would prohibit LT in an otherwise appropriate surgical candidate[24,39,40].

Revascularization if clinically indicated is felt to be safe, especially in the absence of significant varices, and can improve post-LT outcomes similar to those in LT candidates without significant CAD[41,42]. Treatment of thrombocytopenia and coagulopathy as well as minimal adequate sheath sizing may reduce vascular and bleeding complication rates to those observed patients without ESLD[43]. In general, bare metal stents are usually favored in this population to minimize duration of dual antiplatelet therapy and intendant bleeding risks. In select patients, coronary artery bypass grafting may also be performed prior to LT[44]. It has been suggested that advanced age, female gender, and the presence of clinical heart failure or ascites are predictors of mortality after coronary bypass, however these data must be interpreted with caution given low representation of cirrhotic patients in surgical study cohorts[45].

Table 1 Traditional cardiac risk factors

Positive risk factors
Age: male ≥ 45 yr, female ≥ 55 yr or premature menopause without estrogen replacement therapy
Family history of premature coronary disease: definite myocardial infarction or sudden death before age 55 yr in male first-degree relative and before age 65 yr in female first-degree relative
Current cigarette smoking
Hypertension: blood pressure > 140/90 mmHg, or an antihypertensive medication
HDL cholesterol < 40 mg/dL (1.03 mmol/L)
Negative risk factors (subtract one risk factor if present)
HDL cholesterol ≥ 60 mg/dL (1.55 mmol/L)

Data from Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel Ⅲ). *JAMA* 2001; 285: 2486.

Table 2 Utility of non-invasive testing for coronary artery disease detection in liver transplant candidates (using coronary angiography as the gold standard)

Ref.	Screening modality	Positive predictive value	Negative predictive value
Harinstein *et al*[16]	DSE	22	75
Donovan *et al*[18]	DSE	33	100
Williams *et al*[17]	DSE	0	86
Davidson *et al*[19]	SPECT	22	77
Aydinalp *et al*[20]	SPECT	15	100
Bhutani *et al*[23]	SPECT	23	93

DSE: Dobutamine stress echocardiography; SPECT: Single photon emission computed tomography.

CARDIOMYOPATHY AND HEART FAILURE

Changes in cardiac morphology, chronotropy, systolic/diastolic performance and vascular resistance that are commonly seen in the setting of cirrhosis can compromise a patient's ability to handle the hemodynamic stresses of LT. Specifically, ELSD has been associated with chamber enlargement and hypertrophy, decreased beta-agonist transduction with bradycardia and decreased chronotropic competence, high cardiac output +/- left ventricular outflow tract obstruction, and a milieu of circulating inflammatory mediators with cardiodepressant and systemic vasodilatory properties (low SVR)[46-52]. The term cirrhotic cardiomyopathy has been applied to these alterations in normal cardiovascular physiology, and such derangements can influence ventricular response to the sudden increase in preload that immediately follows transplant graft reperfusion[53-55]. Close monitoring and optimization of cardiac function is imperative to minimize post-transplant congestion and heart failure.

Common echocardiographic features of cirrhotic cardiomyopathy include hypertrophy out of proportion to hemodynamic load, impaired diastolic relaxation, and decreased contractile reserve[56-58]. Sudden increase in preload and gradual normalization of afterload post-transplant can unmask these cardiomyopathic features to produce overt heart failure[59-62]. Preoperative features predictive of clinically significant systolic heart failure after LT include elevated right-heart and pulmonary artery pressures prior to transplant[63]. In addition, the magnitude of early hemodynamic compromise (as measured by cardiac index and oxygen delivery within the first 12 h of transplant) has been correlated with risk of multiorgan failure and mortality[64]. With aggressive supportive management, the pathophysiologic features of cirrhotic cardiomyopathy may improve with LT over time[65]. Preoperative evaluation with transthoracic Doppler echocardiography can help identify those LT candidates at greatest risk for developing clinically significant heart failure syndromes postoperatively, in order to allow optimization of volume status and heart failure symptoms prior to LT, as well as planned aggressive management of heart failure after transplantation. Beta blockers, angiotensin converting enzyme inhibitors (ACE-i) and aldosterone antagonists are generally well tolerated post-LT, and should be continued in the absence of contraindications[66]. Study of beta blockers in cirrhosis suggests that carvedilol may best improve portal hypertension and hepatic venous pressure gradients *via* decreased splanchnic blood flow and decreased portocollateral resistance[67-69]. Dose adjustments of ACE-i and aldosterone antagonists may be required in the face of renal dysfunction with calcineurin inhibitors.

Resting transthoracic echocardiography is also useful for the identification and quantification of left ventricular outflow tract obstruction (LVOTO). LVOTO may be primarily functional (secondary to the high-flow state of ESLD) or primarily mechanical (secondary to obstructive hypertrophy). In either case, the risk for intraoperative hypotension is increased, especially in those LT candidates with resting LVOTO > 36 mmHg[70]. Careful preoperative evaluation is required to allow appropriate adjustment of anesthetic strategy in those at risk. Anesthetic strategies that avoid tachycardia, minimize preload depletion and limit inotropy are preferred in the setting of hemodynamically significant LVOTO[71-74]. Marked septal hypertrophy leading to symptomatic primary mechanical LVOTO may require invasive management for alcohol septal ablation if the degree of LVOTO would prohibit LT in an otherwise appropriate surgical candidate[75,76].

PULMONARY HEART DISEASE

Pulmonary heart disease is prevalent in LT candidates and is prognostic of postoperative outcomes. Vascular dilation in the pulmonary bed with intrapulmonary right-to-left shunting, ventilation-perfusion mismatch and hypoxemia is common in ESLD (termed hepatopulmonary syndrome), and does not portend worse outcomes with LT[77]. Pulmonary pressures and pulmonary vascular resistance are not markedly elevated in hepatopulmonary syndrome, and its pathophysiologic features may in fact correct post-LT. In contrast, some LT candidates with portal hypertension can develop progressive pulmonary vascular constriction and remodeling with elevated pulmonary vascular resistance, a condition termed portopulmonary hypertension (POPH)[77,78]. POPH is estimated to be present in approximately 5%-10% of all LT candidates[79]. Extent of vascular remodeling in POPH is associated with increased mortality post-LT, with 50% mortality among those with POPH and mean pulmonary artery pressure (mPAP) 35-50 mmHg and near 100% mortality among those with POPH and mPAP > 50 mmHg[80,81]. Advanced untreated POPH with mPAP ⩾ 35 mmHg, therefore, is considered a contraindication for LT. Aggressive screening and early referral to pulmonary hypertension specialists, ideally when right ventricular function is still preserved, may allow sufficient lowering of pulmonary pressures to allow LT[82-85].

Diagnosis of POPH should not be made on the basis of elevated pulmonary pressures alone. Baseline preoperative transthoracic echocardiography should be the initial screening strategy for the identification of PH in this population. A diagnosis of mild to moderate PH based on the estimation of the pulmonary artery systolic pressure on echocardiography has not been associated with worse outcomes. Thus for cases of worse PH, further assessment is warranted. Volume overload, left ventricular failure and high cardiac output can all contribute to elevated pulmonary pressures without conferring the same degree of perioperative risk. If there is evidence of right ventricular dysfunction or pulmonary hypertension on transthoracic echocardiography, the patient should be referred for invasive hemodynamics to differentiate pulmonary arterial from pulmonary venous hypertension. Accurate diagnosis of prohibitive POPH can only be made if mPAP is $\geqslant$ 35 mmHg and pulmonary vascular resistance is > 3 Woods units in the setting of a normal pulmonary capillary wedge pressure (PCWP) of < 15 mmHg. If PCWP is elevated, repeat invasive hemodynamics are warranted after appropriate diuresis or volume management as clinically tolerated. Finally, clinical management of underlying lung disease and other potentially reversible contributors to pulmonary hypertension should not be neglected.

Structural heart disease is prevalent in the general population, and atrial septal defects (ASD) or patent foramen ovalae (PFO) may also be found in LT candidates. ASD may be associated with shunt physiology and potential alterations in pulmonary vascular resistance over the long-term, theoretically contributing to risk of right-heart failure after transplant. The presence of PFO prior to LT has not been associated with worse outcomes in case series[86]. Existing data does not support excluding patients for transplant consideration based upon the presence of ASD or PFO[87].

CONCLUSION

CAD, cirrhotic cardiomyopathy and pulmonary heart disease are among the more common cardiovascular maladies affecting patients with ESLD. When epicardial coronary atherosclerosis is felt to prohibit LT, revascularization with either CABG surgery or PCI should be considered. In general, percutaneous revascularization is a safe and effective therapy for obstructive CAD among LT candidates, and is valuable in optimizing otherwise suitable surgical candidates to allow downstream transplantation. During PCI, bare metal stents are generally preferred to minimize duration of dual antiplatelet therapy and bleeding risk. The pathophysiologic features of cirrhotic cardiomyopathy may be unmasked by changes in preload and afterload with LT, and should therefore prompt aggressive volume and hemodynamic management as clinically tolerated prior to transplantation, with continued close monitoring and therapy throughout the perioperative period. The presence of LVOTO > 35 mmHg may warrant adjustment of anesthetic strategy to optimize intraoperative volume status to maintain preload, heart rate to maintain diastolic filling and to avoid excessive inotropy. Portopulmonary hypertension (pulmonary vascular remodeling with elevated resistance) is associated with risk of fulminant right-heart failure and increased perioperative mortality, especially with mPAP $\geqslant$ 35 mmHg. We recommend invasive hemodynamic assessment in all LT candidates with suggestion of right ventricular dysfunction and/or at least moderate pulmonary hypertension by echocardiography. Patients with volume overload (PCWP > 15 mmHg) and/or other reversible etiologies of pulmonary hypertension should be aggressively treated for these etiologies, with repeat assessment of pulmonary hemodynamics once euvolemic and better clinically compensated. Patients meeting hemodynamic criteria for moderate to severe POPH as detailed above should have early referral to a pulmonary hypertension specialist for advanced medical and intraoperative therapies to facilitate consideration for LT.

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