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iREVIEWS

STATE-OF-THE-ART PAPER

Echocardiography in Liver Transplant Candidates

Anubhav Garg, MD, William F. Armstrong, MD
Ann Arbor, Michigan

Involvement of the cardiovascular system in patients with end-stage liver disease (ESLD) is well recognized and may be seen in several scenarios in adult liver transplantation (LT) candidates. The hemodynamic effects of ESLD may result in apparent heart disease, or in some instances may mask cardiac disease. Alternatively, cardiac disease can occasionally be the underlying etiology of ESLD. LT imposes significant hemodynamic stresses, with cardiovascular complications accounting for considerable perioperative mortality and morbidity. Pre-operative assessment of the cardiac status of LT candidates is thus critically important for risk stratification and management. Cardiac imaging plays an integral role in the assessment of LT candidates. In this review, we discuss the role of cardiac imaging, including transthoracic echocardiography with Doppler and contrast enhancement, noninvasive functional assessment for routine pre-operative assessment of coronary artery disease, and transesophageal echocardiography in select cases to aid in intra-operative fluid management and monitoring in LT candidates. (J Am Coll Cardiol Img 2013;6: 105–19) © 2013 by the American College of Cardiology Foundation

Involvement of the cardiovascular system in end-stage liver disease (ESLD) is well recognized and results in several distinct clinical scenarios. The hemodynamic effects of ESLD may result in apparent heart disease or in some instances may mask cardiac disease. ESLD results in a constellation of secondary cardiovascular effects referred to as "cirrhotic cardiomyopathy"—a form of cardiac dysfunction characterized by cardiac structural changes, diastolic dysfunction, and baseline supernormal cardiac output with impaired contractile reserve in response to stress (1). Liver transplantation (LT) imposes significant hemodynamic stresses with cardiovascular events reported in up to 70% of LT recipients (2). Less common cardiovascular abnormalities in LT candidates include pulmonary heart disease, pericardial effusions, and intracardiac shunts (1). Occasionally, pre-operative evaluation of the LT candidate reveals evidence of cardiac disease as the underlying etiology of ESLD.

Cardiac imaging plays an integral role in the assessment of LT candidates. While computed tomography (CT), cardiac magnetic resonance (CMR), and angiography have all been used for the characterization of cardiac disease in ESLD, echocardiography remains the most commonly utilized technique. In this review, we discuss the role of cardiac imaging including transthoracic echocardiography (TTE) with Doppler and contrast enhancement, noninvasive functional assessment for pre-operative assessment of coronary artery disease (CAD), and transesophageal echocardiography (TEE) in select cases to aid in intraoperative fluid management.

From the Department of Internal Medicine, Division of Cardiovascular Disease, University of Michigan Medical Center, Ann Arbor, Michigan. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Cardiovascular Hemodynamics and Disease in ESLD

Hemodynamics of ESLD cirrhotic cardiomyopathy. Patients with ESLD have decreased sinusoidal, but increased peripheral, nitric oxide production, leading to portal hypertension and splanchnic and peripheral vasodilatation (3,4). ESLD is also characterized by an expansion and redistribution of circulating blood volume, resulting in relative splanchnic hypervolemia and effective central hypovolemia (3,5). The combination of decreased systemic vascular resistance with central hypovolemia leads to a hyperdynamic circulatory state that is unique to patients with ESLD (4–9). This hemodynamic state results in increased pulmonary and systemic flows at baseline with high normal or elevated right ventricular (RV), pulmonary artery, and left-atrial (LA) or pulmonary capillary wedge pressures (Table 1) (4,5). This hemodynamic profile is noted in patients with ESLD not complicated by pulmonary vascular disease or primary cardiac disease (Figs. 1, 2, and 3; Online Videos 1 and 2).

ABBREVIATIONS AND ACRONYMS

AASLD = American Association for the Study of Liver Diseases

ACCF = American College of Cardiology Foundation

AHA = American Heart Association

CAD = coronary artery disease

DSE = dobutamine stress echocardiography

ESLD = end-stage liver disease

HPS = hepatopulmonary syndrome

LT = liver transplantation

LV = left ventricle/ventricular

LVH = left-ventricular hypertrophy

LVOTO = left-ventricular outflow tract obstruction

PPH = portopulmonary hypertension

TTE = transthoracic echocardiography

In the LT candidate, pre-operative cardiac compromise and overt heart failure is rarely present as left-ventricular (LV) dysfunction is masked by the peripheral vasodilatation associated with ESLD (7). However, an impaired cardiac ventricular response to physiological or pharmacological stress may be present despite the increase in baseline cardiac output (8,9). This impaired hemodynamic response to stress in the absence of primary cardiac disease is the hallmark of cirrhotic cardiomyopathy (8,9). This latent LV systolic dysfunction results from a combination of the following: 1) decreased beta-adrenergic receptor density and function; and 2) negative inotropic effect of endocannabinoids and nitric oxide, both of which are upregulated in the setting of cirrhosis (1,3). The prevalence of cirrhotic cardiomyopathy is unknown as it is often difficult to establish the diagnosis due to the normal or hyperdynamic cardiac function at rest and the presence of concurrent primary cardiac disease (3,10).

In addition to masked systolic dysfunction, cirrhotic cardiomyopathy may be accompanied by diastolic dysfunction and structural and electrical cardiac abnormalities (8,9,11). The increased myocardial stiffness found in patients with cirrhosis is thought to reflect a combination of LV hypertrophy (LVH), myocardial fibrosis, and subendothelial edema secondary to ESLD (4,5,9). Several studies have documented impaired ventricular relaxation in cirrhotic patients noted as a nonsignificant increase in the E-wave velocity, significantly increased A-wave velocity, increased deceleration time, and decreased E/A ratio when compared to controls (6,11,12) (Fig. 4). Patients with ascites have more pronounced diastolic dysfunction than patients without ascites (6,13).

A recent autopsy study of 133 patients with cirrhosis and no known history of heart disease revealed significant cardiac abnormalities in 43%, with cardiomegaly and LVH the most common

Table 1. Baseline Hemodynamic Changes in Patients With ESLD

Hemodynamic Parameter	Changes
Systemic circulation	Plasma volume ↑, total blood volume ↑, noncentral blood volume ↑, central blood volume ↓ ↔, arterial blood pressure ↔ ↓, systemic vascular resistance ↓, heart rate ↑, cardiac output ↑
Cardiac hemodynamics	LA volume ↑, LV volume ↑ ↔, right atrial volume ↔ ↑ ↓, RV volume ↔ ↑ ↓, RA pressure ↔ ↑, RV end-diastolic pressure ↔, pulmonary capillary wedge pressure ↔, LV end-diastolic pressure ↑ ↔
Pulmonary circulation	Pulmonary blood flow ↑, pulmonary artery pressure ↔ ↑, pulmonary vascular resistance ↔ ↑ ↓

↔ = No change; ↑ = increase; ↓ = decrease; ESLD = end-stage liver disease; LA = left-atrial; LV = left-ventricular; RA = right-atrial; RV = right ventricular.

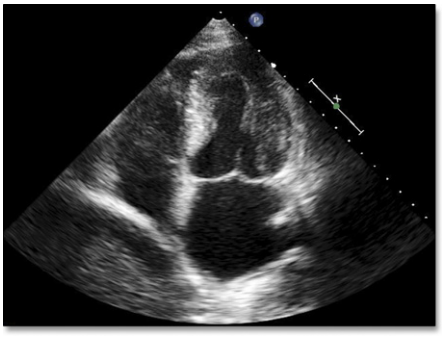

Figure 1. Apical 4-Chamber View Recorded in a Patient With ESLD

Note the left atrial (LA) dilation (LA area, 25.5 cm^2) and hyperdynamic left ventricular (LV) function (LV ejection fraction, 72%). (See Online Video 1). ESLD = end-stage liver disease.

findings (14). Numerous studies have evaluated cardiac chamber sizes in patients with ESLD although with conflicting results. Using echocardiography, Pozzi et al. (6) and Abd-El-Aziz et al. (11) found that LA size was significantly larger but LV size was similar in cirrhotic patients as compared to controls. In contrast, Finucci et al. (12) found significantly increased left atrial volumes, LV end diastolic volumes, and stroke volumes in cirrhotic patients compared to controls. In contrast, right-sided cardiac chamber sizes can be reduced, normal in size, or enlarged, likely depending on the presence of accompanying pulmonary vascular disease (5). Mild LVH is a common finding in cirrhotic cardiomyopathy (6,11,12). Although the mechanism of LVH is not completely understood, it is presumed to result from a combination of mechanical overload in the setting of chronically increased cardiac output and activation of the neuroendocrine system, especially in the setting of ascites (6,13).

Coronary Artery Disease

The prevalence of CAD in ESLD previously was thought to be lower than in the general population related to abnormal synthetic liver function resulting in lower cholesterol, lower blood pressure, and higher levels of circulating estrogens (15,16). More recent studies have demonstrated that LT candidates have a significantly greater prevalence of CAD than previously thought (15). In studies utilizing cardiac catheterization for all enrolled patients, the prevalence of CAD has ranged from 18% to 27% (Table 2) (17–19). Risk factors for the presence of CAD included older age, male gender, hypertension or diabetes, and non–alcohol-related etiology of cirrhosis (17–19). Studies have also revealed a significant burden of unrecognized, asymptomatic CAD (1,15). Carey et al. (17) reported that 13.3% of LT candidates with moderate or severe coronary stenosis were asymptomatic, presumably due to the masking effect of poor functional status.

ESLD patients with CAD have worse outcomes than patients without CAD (20). In patients with known CAD who underwent LT, Plotkin et al. (20) reported a 30-day 25% mortality rate, an overall mortality rate of 50%, and morbidity rate of 81%. Cardiovascular disease continues to contribute to late mortality after transplantation due to the secondary development of hypertension, hyperlipidemia, diabetes, and obesity from chronic immunosuppression (15,16). Cardiovascular disease is the second most common cause of death (21%) 1 year after transplantation (21) and the third most common cause (21%) 3 years after transplantation (22). With greater emphasis on improved assessment and revascularization of CAD pre-operatively, Diedrich et al. (23) recently showed an improvement in the overall mortality rate to 26% and morbidity rate to 38%.

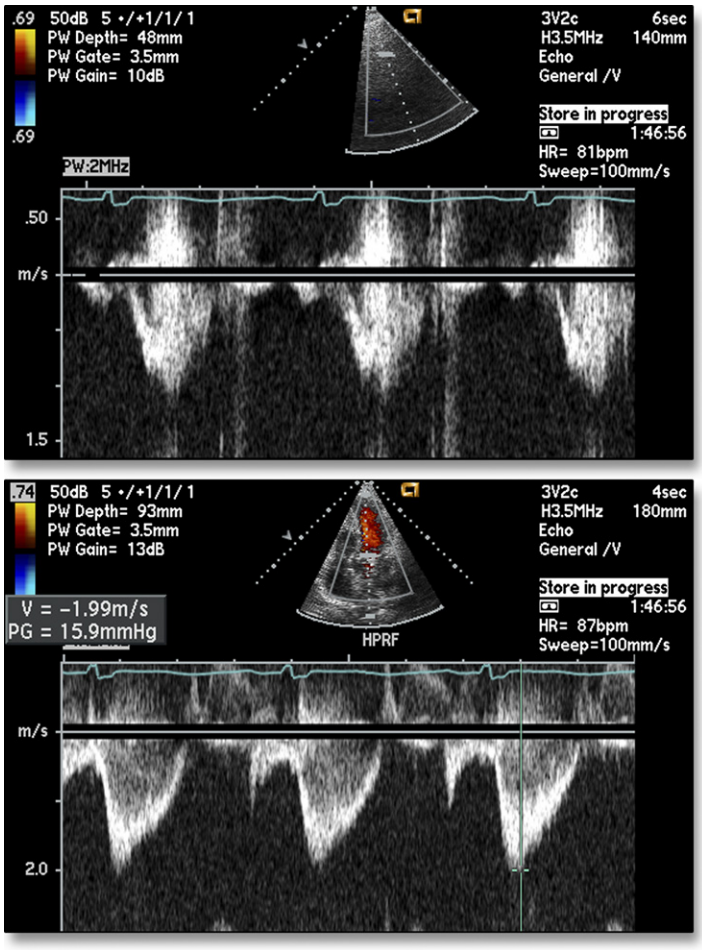

Figure 2. TVIs Recorded in a Patient With ESLD

Note the upper normal to elevated time-velocity integrals (TVIs) of the right ventricular outflow track of 27 cm **(top panel)** and LV outflow track of 39 cm **(bottom panel)** indicative of the high-flow state. Abbreviations as in Figure 1.

Noninvasive assessment of the liver transplant candidate. Currently, the American Association for the Study of Liver Diseases (AASLD) recommends routine TTE for all LT candidates for the assessment of chamber sizes, hypertrophy, systolic and diastolic function, valvular function, and LV outflow tract obstruction (LVOTO) (24). In patients with ESLD, TTE should reveal normal or super-

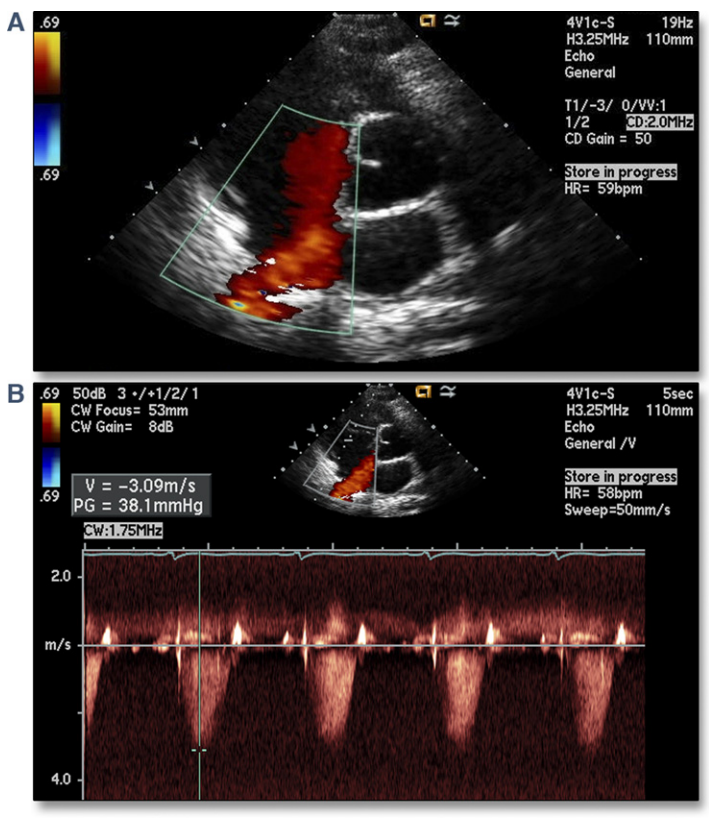

Figure 3. Flow Related Elevation of Right Ventricular Systolic Pressure in a Patient With End Stage Liver Disease

(A) Right ventricular inflow track view revealing high-velocity inflow from the inferior vena cava consistent with a high flow state. **(B)** Tricuspid regurgitation jet revealing a peak gradient of 3.09 m/s corresponding to a right ventricular to right-atrial pressure gradient of 38 mm Hg consistent with mild elevation of pulmonary artery pressures. (See Online Video 2.)

normal LV systolic function at rest; the finding of "normal" or reduced ejection fraction should raise suspicion of an underlying cardiomyopathy or CAD and merits further evaluation. Other imaging modalities have been utilized, including single photon emission computed tomography (SPECT), computed tomography angiography (CTA), and CMR, although the bulk of the available data are with echocardiography.

ESLD, especially if complicated by hepatomegaly and ascites, may pose distinct problems with imaging. These issues may include technical difficulty with acquisition of high-quality images and issues relating to accurate diagnoses, which are specific to the pathophysiology of ESLD. In general, with CTA or CMR, the only technical issues include control of respiratory rate and/or breath holding in patients with ascites who may have respiratory compromise while supine. Other than this, the relative and absolute contraindications are the same in the ESLD patient as in the general population. When utilizing SPECT for assessment of CAD, diaphragmatic attenuation may be noted related to elevation of the diaphragm and/or hepatomegaly shadowing the inferior port of the heart and thus mimicking an inferior perfusion defect.

Echocardiographic imaging of the patient with ESLD may be complicated by ascites, which limits the ability to image from the subcostal position and may alter the orientation of the heart within the thorax such that off-axis views and unconventional imaging windows are necessary. In general, acquisition of clinical quality images is feasible in the majority of patients. The echocardiographer must recognize the anticipated physiological changes in ESLD, including high volume flow and mild degrees of chamber enlargement. On occasion, ascites may distort the contour of the LV and result in artifactual pseudodyskinesis of the posterior wall (Fig. 5; Online Video 3).

Assessment for underlying CAD is often accomplished with dobutamine stress echocardiography (DSE), which is presumed to mimic the hemodynamic stress of LT (15). Initial studies evaluating DSE in the LT candidate were promising (Table 3). Donovan et al. (25) compared DSE to coronary angiography in a limited subset of 18 patients and found a sensitivity of 75% and specificity of 57%. Subsequently, Plotkin et al. (26) evaluated a higher risk group of patients with ESLD and found a sensitivity of 100% and specificity of 100% for significant CAD (coronary stenosis ≥70%). More recent studies have cast a doubt on the utility of DSE as a screening tool for CAD in this patient population (Table 3). In evaluating 64 patients for obstructive CAD (stenosis ≥50%) with DSE, Harinstein et al. (27) found a sensitivity of 17% and specificity of 88%. Similarly, Patel et al. (19) evaluated 205 patients for severe CAD (stenosis >70%) with DSE and found a sensitivity of 60% and specificity of 69% (Fig. 6; Online Video 4).

The prognostic value of DSE in predicting intraoperative cardiac events has also been examined. Umphrey et al. (28) found that maximum heart rate achieved during DSE may be a predictor of adverse cardiovascular events in the perioperative setting. However, both Williams et al. (29) and Findlay et al. (30) demonstrated poor correlation between a positive DSE and significant intraoperative cardiac events (Table 4). It has been suggested that the conflicting diagnostic performance of DSE may be due to the differing study definitions of CAD,

retrospective analysis, lack of identification of multivessel disease and a high rate of nondiagnostic studies related to inadequate heart rate response (15). Finally the low accuracy for predicting events may be related to an etiology for events not dependent on obstructive CAD.

SPECT has been evaluated as a screening tool for CAD in LT candidates, likewise with variable results (Table 3). Davidson et al. (31) evaluated stress myocardial perfusion imaging in LT candidates without known CAD and found a sensitivity of 37% and specificity of 63% when compared to coronary angiography. Defining only reversible perfusion abnormalities as indicative of a positive SPECT study, Aydinalp et al. (32) revealed a sensitivity of 100% and specificity of 61% when compared to coronary angiography. In this study, however, fixed perfusion defects were classified as normal or minimal CAD (32). Zoghbi et al. (33) examined the usefulness of SPECT to predict cardiovascular complications and found that a normal SPECT study had a 99% negative predictive value for perioperative cardiac events, although this was in a low-risk cohort of patients. A more recent study found a low proportion of positive stress myocardial perfusion imaging results (7%) in a population of 772 consecutive adult LT candidates—a finding that is incongruous with the reported prevalence of CAD in this patient population (34). This study also reported a substantially lower rate of cardiovascular complications which were not well predicted by pre-transplant imaging.

Several newer modalities are being evaluated for the noninvasive assessment of CAD in LT candidates. Coronary artery calcification scoring has been well validated as an independent risk factor for CAD in the general population (35), but currently, there are only limited data utilizing this modality in LT candidates (36,37). Cardiac CTA is emerging as a potential noninvasive alternative for preoperative evaluation. Keeling et al. (38) reported a prevalence of CAD of 90.8% in LT candidates using CTA, although without confirmation with coronary angiography. Cassagneau et al. (39) recently compared the prognostic value of CTA with DSE and found a comparably high negative predictive value for major cardiac adverse events with CTA and DSE. Although CTA appears promising, several limitations exist for this patient population including the need for tight heart-rate control, breath-holding during the test, and the potential for contrast-induced renal impairment (15). Keeling et al. (38) revealed that over a quarter of patients had poor image quality due to these limitations. CMR is a developing technology that would allow for a complete noninvasive assessment of the LT candidate but has not been studied in this patient population and shares many of the limitations as CTA (15).

Coronary angiography remains the gold standard for the diagnosis of CAD. It has been suggested that coronary angiography should be used in all LT candidates with known CAD due to the high rates of morbidity and mortality in this subset of LT candidates (1,16). However, coronary angiography should not be used as the initial screening test as it is invasive, carries increased risk in ESLD patients who may be coagulopathic, and can lead to contrast-induced renal failure (38).

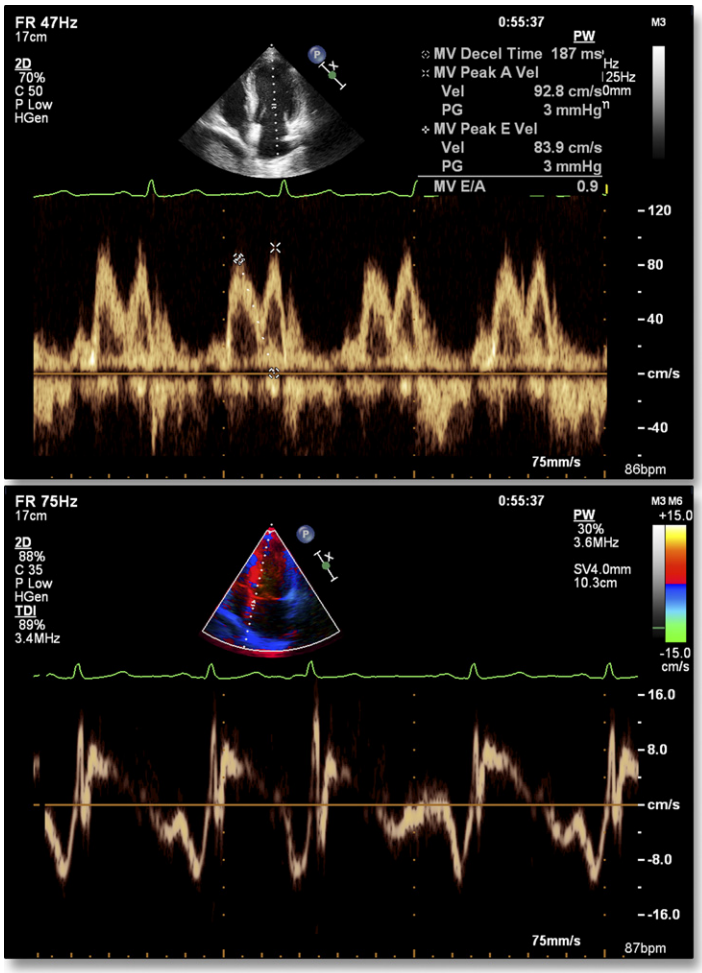

Figure 4. Doppler Evidence of Diastolic Dysfunction

Transmitral Doppler inflow and annular velocity in a patient with ESLD documenting abnormal mitral inflow and annular tissue velocities consistent with diastolic dysfunction. This patient also appears in Figure 1. Abbreviation as in Figure 1.

Table 2. Prevalence of CAD in LT Candidates

Author (Year) (Ref. #)	No. of Patients	Patient Age, yrs	Prevalence of CAD, %
Carey et al. (1995) (17)	37	50–71	27*
Tiukinhoy-Laing et al. (2006) (18)	161	57 ± 7	26†
Patel et al. (2011) (19)	420	56 ± 8	18*

*Defined as coronary stenosis ≥30% on coronary angiography. †Defined as coronary stenosis ≥50% on coronary angiography.
CAD = coronary artery disease; LT = liver transplant.

Based on existing evidence, the AASLD, the American Heart Association (AHA), and the American College of Cardiology Foundation (ACCF) have established guidelines for pre-operative CAD assessment in LT candidates (24,40). These guidelines agree that LT candidates should undergo an evaluation for CAD based on the presence of risk factors. Depending on the committee, these risk factors include a history of smoking, diabetes mellitus, hypertension, hyperlipidemia, clinical or family history of heart disease, LVH, or age >50 years versus >60 years (24,40). The AASLD also states that DSE *appears* to be an effective screening test in this setting with coronary angiography recommended for all positive results. It should be emphasized that the recommendation for use of DSE is a consensus opinion and not one based on robust comparative trials. In clinical practice, multiple modalities have found reasonable success, and in the absence of more robust data, the choice of provocative testing in LT candidates is probably best determined by local expertise.

Other Cardiovascular Considerations

LVOTO and hypertrophic cardiomyopathy. The baseline hyperdynamic systolic function and low peripheral vascular resistance in the setting of LVH predisposes LT candidates to hypotension or to development of LVOTO during DSE or in the setting of decreased intraoperative preload. Maraj et al. (41) found that 43% of patients had inducible LVOTO on pre-operative DSE, defined as an outflow tract gradient of >36 mm Hg (Fig. 7; Online Video 5). These patients had a significantly increased risk of intraoperative hypotension but no significant increase in post-operative mortality (41). In rare cases, the LT candidate may have LVOTO secondary to concomitant hypertrophic cardiomyopathy (42,43). The finding of LVOTO necessitates careful intraoperative monitoring with avoidance of hypovolemia, tachycardia, and inotropic agents. Furthermore, in the setting of LVOTO and diastolic dysfunction, invasive measurement of cardiac filling pressures may provide erroneous information for assessment of ventricular volume, especially in the post-reperfusion period (42). Intraoperative TEE can play a critical role for continuous monitoring of ventricular volumes and dynamic LVOTO, guiding the use of volume resuscitation and vasopressor therapy (42,43).

Valvular heart disease. Limited data exist on the incidence and relevance of valve dysfunction in LT candidates. In a retrospective study, Alper et al. (44) reported that 27.5% of LT candidates had evidence of either mitral regurgitation, tricuspid regurgitation, or both. Furthermore, systemic vascular resistance was significantly decreased in patients with mitral regurgitation, and cardiac output was significantly increased in patients with isolated mitral regurgitation or mitral and tricuspid regurgitation as compared to controls (44). Although these hemodynamic changes did not affect overall mortality, more patients with either isolated mitral regurgitation or mitral and tricuspid regurgitation experienced intraoperative hypotension requiring vasopressor therapy (44).

Aortic stenosis results in LV pressure overload with compensatory ventricular hypertrophy and decreased LV compliance. These hemodynamics are exaggerated during LT due to profound fluid shifts resulting in a sudden decrease in preload during

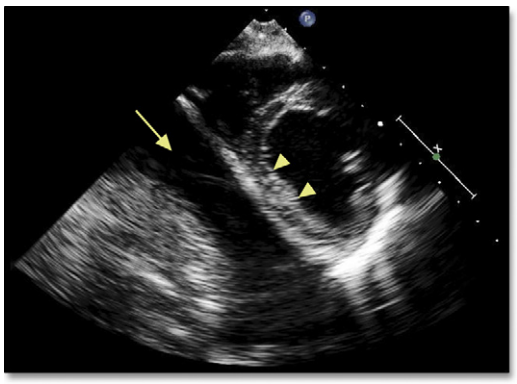

Figure 5. Parasternal Short-Axis View Recording in a Patient With ESLD

Note the posterior compression of the LV by the ascites (**long arrow**) resulting in a D-shaped LV with flattening of the posterior wall in diastole (**arrowheads**). In the real-time clip, note the restitution of circular LV geometry in systole resulting in posterior wall pseudodyskinesis. Abbreviations as in Figure 1. (See Online Video 3.)

Table 3. Accuracy of DSE and SPECT Imaging in the Detection of CAD in LT Candidates

Type of Stress Testing/Author (Year) (Ref. #)	No. of Patients	Sensitivity, %	Specificity, %	PPV, %	NPV %
DSE					
Donovan et al. (1996)* (25)	18	75.0	57.1	33.3	88.9
Plotkin et al. (1998)† (26)	40	100.0	100.0	100.0	100.0
Harinstein et al. (2008)* (27)	64	16.7	87.5	44.4	63.6
Harinstein et al. (2008)† (27)	64	12.5	85.4	22.2	74.5
Patel et al. (2011)‡ (19)	205	60	68.9	21.1	92.5
SPECT imaging					
Davidson et al. (2002)† (31)	83	36.8	62.5	22.6	76.9
Aydinalp et al. (2009)‡§ (32)	93	100.0	60.9	15.0	100.0

*CAD defined as coronary stenosis ≥50% in 1 or more arteries. †CAD defined as coronary stenosis ≥70% in 1 or more arteries. ‡CAD defined as coronary stenosis >70% in 1 or more arteries. §SPECT imaging considered non-ischemic if normal perfusion or fixed defects.
DSE = dobutamine stress echocardiography; NPV = negative predictive value; PPV = positive predictive value; SPECT = single photon emission computed tomography; other abbreviations as in Table 2.

liver resection and impaired myocardial contractility during the post-reperfusion syndrome. The presence of severe aortic stenosis in the LT candidate requires a collaborative approach, and only case reports have documented successful LT in these patients (45,46). Although TTE is an important noninvasive method for evaluating the severity of aortic stenosis, it requires careful interpretation in ESLD. As a result of high transvalvular flows, reliance on aortic valve gradients alone may result in overestimation of the degree of obstruction and calculation of aortic valve area is thus essential (45). Although additional echocardiographic findings such as LVH can support the diagnosis of advanced aortic stenosis, it can be present in cirrhotic cardiomyopathy alone (45). When echo-

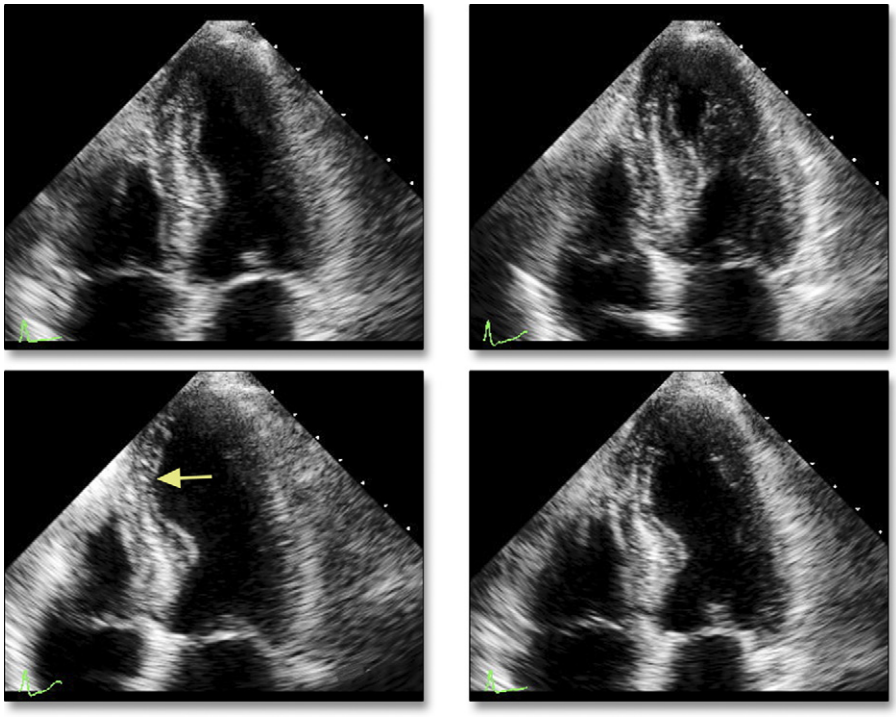

Figure 6. DSE Performed 6 Months Following Liver Transplantation

Pre-operative dobutamine stress echocardiography (DSE) had revealed a normal hyperdynamic response and suggested the absence of coronary artery disease (CAD). The patient subsequently developed chest discomfort following transplant and a repeat study revealed findings consistent with left anterior descending coronary artery ischemia with dyskinesis of the distal septum **(arrow)** at peak dobutamine. **(Upper left:** rest, **upper right:** low dose, **lower left:** peak dose, **lower right:** recovery.) (See Online Video 4.)

Table 4. Prognostic Value of DSE for Significant Intraoperative Cardiac Events

Author, Year, (Ref. #)	Number of Patients	Sensitivity	Specificity	PPV	NPV
Williams et al. (2000)* (29)	71	0.0%	96.2%	0.0%	86.4%
Findlay et al. (2005)† (30)	73	20.0%	90.5%	25.0%	87.7%

**Significant intraoperative cardiac event* defined as arrhythmia, cardiac arrest, or death. †*significant intraoperative cardiac event* defined as elevation of cardiac troponin T measured after transplantation.
Abbreviations as in Table 3.

cardiographic data are in question, cardiac catheterization should be performed to assess the hemodynamic severity.

Hepatopulmonary syndrome. Hepatopulmonary syndrome (HPS) is characterized by the presence of abnormal intrapulmonary vascular dilatations resulting in a compromise of pulmonary gas exchange in patients with advanced liver disease (47,48). The prevalence of HPS is approximately 20% in LT candidates but clinically significant HPS with arterial hypoxemia is identified in <5% (47). The pathogenesis of HPS is linked to an imbalance between vasoconstrictors and vasodilators leading to pulmonary vascular dilatation at the pre-capillary and capillary level (47,49). This results in intrapulmonary shunting, ventilation–perfusion mismatch, and hypoxemia with clinical presentation of progressive hypoxia, dyspnea, and cyanosis (48,50). LT may be curative in some patients with mild to moderate HPS (48). The diagnosis of HPS is established based on 3 criteria: evidence of chronic liver disease, hypoxemia at rest, and evidence of intrapulmonary vascular shunting (49,50). The gold standard for demonstration of intrapulmonary shunting is saline contrast echocardiography (49,50) (Fig. 8; Online Video 6). Appearance of agitated saline on the left side of the heart in HPS is dependent on the time it takes for transpulmonary blood flow and can occur within 4 to 5 beats in patients with increased cardiac output or be delayed by 8 to 10 beats if the cardiac output is depressed. With intrapulmonary shunting, contrast will be visualized in the pulmonary veins and may continue to appear in the left side of the heart even after there has been clearance of saline from the right side of the heart. This is in contrast to intracardiac shunts where appearance of contrast in the left heart is dependent on the pressure gradient between the RA and LA and is thus respiratory dependent and phasic in appearance (Table 5) (49,50). Detection of intrapulmonary shunts may also be improved by performing contrast-enhanced echocardiography in the standing position (51). Alternatively, technetium-99m–labeled macroaggregated albumin perfusion scanning can be utilized to diagnose HPS. Under normal conditions, the majority of labeled albumin is trapped within the pulmonary circulation. In the presence of intrapulmonary shunting, the albumin is not completely trapped in the lungs and the degree of shunted radioisotope can be

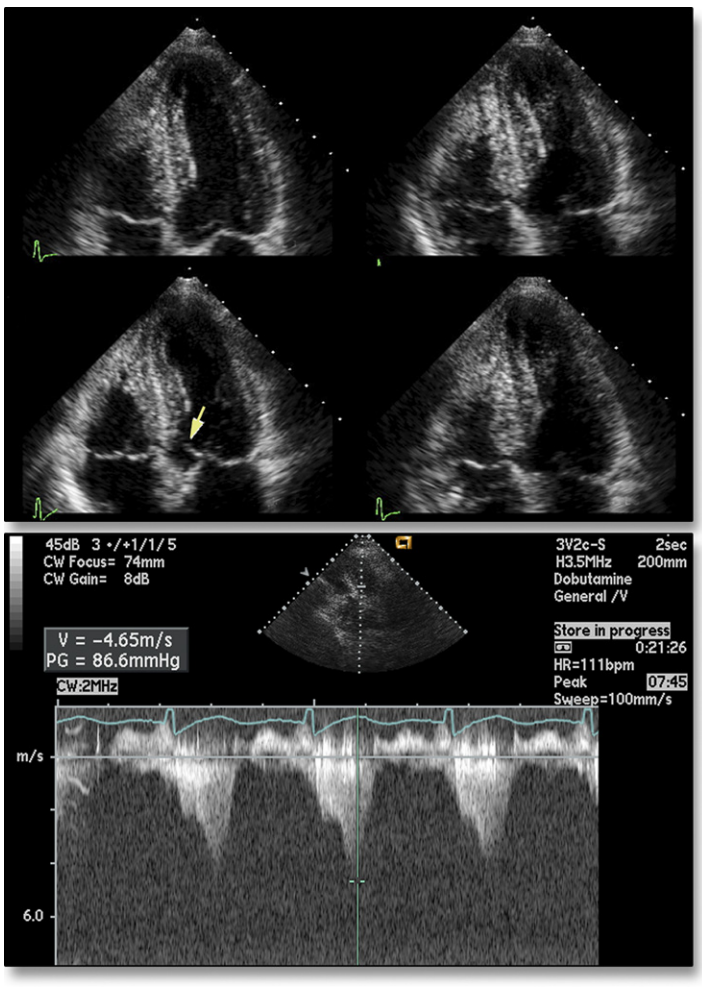

Figure 7. DSE Revealing a Normal Hyperdynamic Response and Evidence of Dynamic Outflow Tract Obstruction

At peak dobutamine, note the systolic anterior motion of the mitral valve **(arrow)** and the late peaking dynamic LV outflow track gradient of 86.6 mm Hg. Abbreviations as in Figures 1 and 6. (See Online Video 5.)

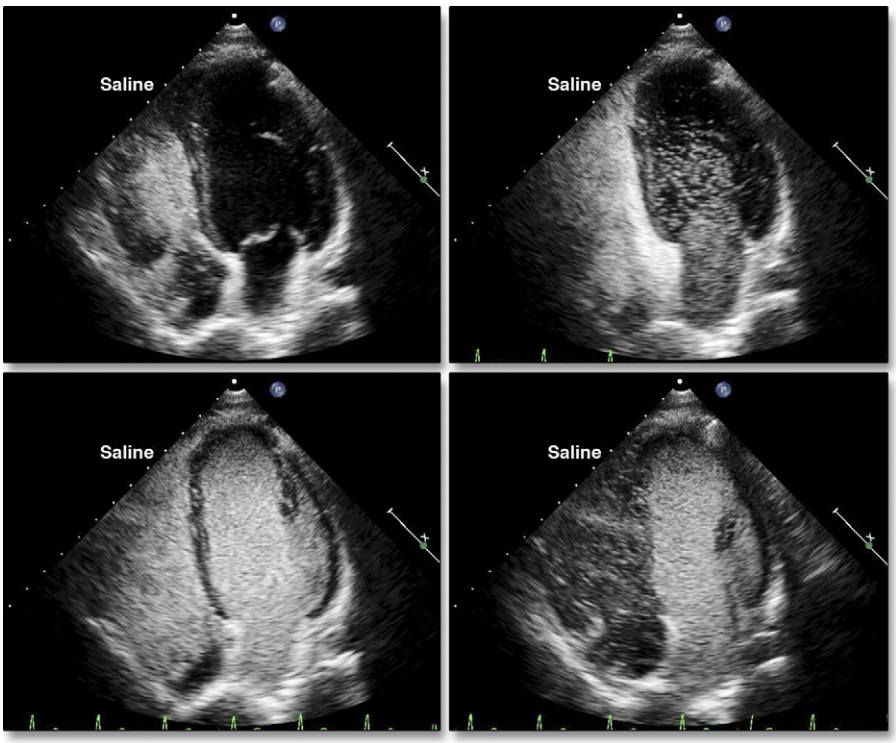

Figure 8. Saline Contrast Echocardiography Performed in a Patient With ESLD Revealing Marked Right-to-Left Shunt Through Pulmonary AVM

The **upper left panel** is immediately after appearance of contrast in right heart. The **upper right panel** is 5 beats following appearance and reveals nearly continuous flow into the LA and LV. The lower left panel is approximately 10 s after injection of contrast and reveals equal contrast in both the right and left ventricles and the lower right panel is recorded 15 s following injection of contrast and reveals continued appearance of contrast into the LV when contrast is diminishing in the right ventricle. AVM = arteriovenous malformation; other abbreviations as in Figure 1. (See Online Video 6.)

quantified by its appearance in other organs, including the brain, liver, and spleen (49,50). Obviously, atrial septal defect needs to be excluded as it will also result in isotope appearance in the liver. Pulmonary angiography is not commonly used for the diagnosis of HPS but allows for the direct visualization of intrapulmonary vascular malformations (49,50).

Table 5. Characteristics of Intrapulmonary Shunts and Intra-Cardiac Shunts on Saline Contrast Echocardiography

Shunt Type	Contrast Appearance on Left Side of Heart
Intrapulmonary	Dependent on time necessary for transpulmonary blood flow; contrast visualized in pulmonary veins; continuous appearance; can appear after clearance of contrast from right side of heart
Intracardiac	Dependent on interatrial pressure gradient; occurs when RAP exceeds LAP; respiratory dependent; phasic appearance

LA = left atrium; LAP = left atrial pressure; RA = right atrium; RAP = right atrial pressure.

Portopulmonary hypertension. Portopulmonary hypertension (PPH) is a form of pulmonary arterial hypertension associated with portal hypertension with or without accompanying cirrhosis (52,53). PPH is hypothesized to occur: 1) as a result of increased vascular wall shear stress resulting in endothelial dysfunction; and 2) due to the portosystemic shunting of vasoactive substances from the splanchnic circulation to the pulmonary circulation, leading to progressive pulmonary vascular vasoconstriction and remodeling (52,53). Hemodynamically, the diagnostic criteria for PPH includes a mean pulmonary artery pressure (mPAP) >25 mm Hg at rest, mean pulmonary capillary wedge pressure <15 mm Hg, and pulmonary vascular resistance >240 dynes/s/cm^{-5} (50,53). Risk factors for the development of PPH include female sex and autoimmune hepatitis, while ESLD secondary to hepatitis C is associated with a decreased risk of PPH (54). Clinically, patients with PPH are asymptomatic for months to years with development of dyspnea on exertion,

syncope, and chest pain later in the disease course (49,53). Small studies have demonstrated that pre-operative mPAP <35 mm Hg is associated with no significant increased mortality, pre-operative mPAP between 35 and 50 mm Hg is associated with a 50% mortality, and pre-operative mPAP >50 mm Hg is associated with mortality approaching 100% after LT (55). Many transplant centers consider PPH with a pre-operative mPAP >50 mm Hg a contraindication to LT due to the increased risk, uncontrollable intraoperative bleeding, and reduced transplant organ perfusion post-transplantation (56).

The AASLD and the AHA/ACCF recommend screening for elevated pulmonary pressures in all LT candidates with Doppler echocardiography (24,40) (Fig. 9; Online Video 7). Utilizing the peak tricuspid regurgitant velocity (TRV), the estimated RA pressure (RAP), and the modified Bernoulli equation, the RV systolic pressure (RVSP) can be calculated as: $4(TRV)^2$ + RAP (49,52). In the absence of pulmonic stenosis, the pulmonary systolic pressure is equivalent to the RVSP. In LT candidates undergoing screening for PPH, TTE has a sensitivity of 97% and a specificity of 77% for diagnosing elevated pulmonary pressures (57). These pressures must be interpreted carefully as up to 20% of LT candidates show moderately increased pulmonary pressures attributable to the hyperdynamic state of cirrhotic cardiomyopathy, volume overload, or LV dysfunction (53,58), while only 5% to 10% of LT candidates have elevated pulmonary pressures due to PPH (59). This distinction is critical as patients with elevated pulmonary pressures for etiologies other than PPH do not have an increased rate of adverse events with LT (58). The AASLD and AHA/ACCF recommend right heart catheterization with calculation of pulmonary vascular resistance for confirming the diagnosis of PPH when an RVSP of 45 to 60 mm Hg is found (24,40). Recent case series and retrospective analyses have shown that successful LT can be facilitated in patients after reduction in pulmonary pressures with pharmacotherapy (55,60).

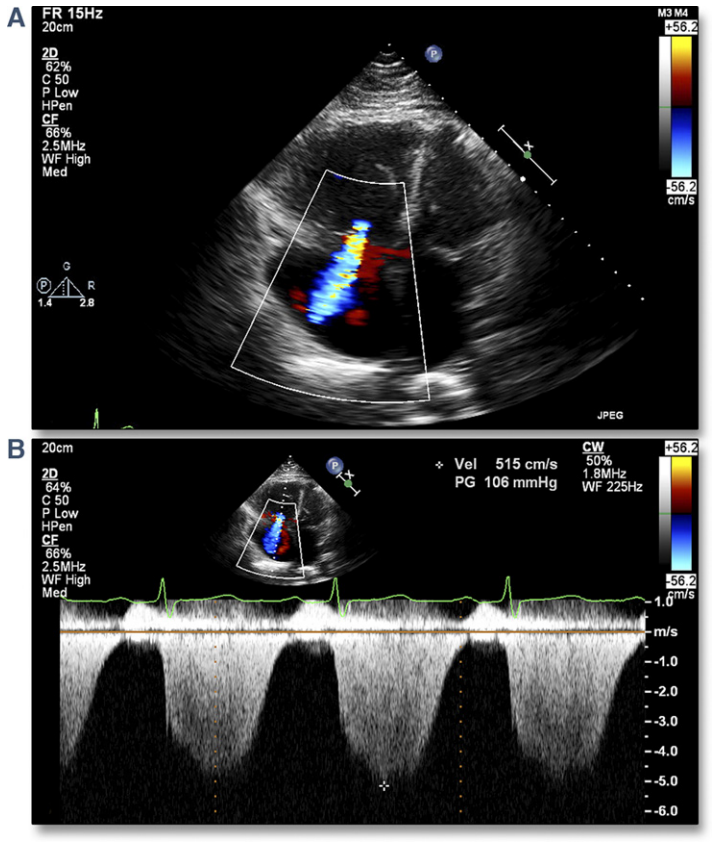

Figure 9. A 57-Year-Old Man With PPH Related to ESLD

(A) The apical 4-chamber view reveals a markedly dilated right ventricle and right atrium and moderate tricuspid regurgitation. **B:** Continuous wave Doppler documents a 106-mm Hg gradient between the right ventricle and the right atrium consistent with severe pulmonary hypertension. PPH = portopulmonary hypertension; other abbreviation as in Figure 1. (See Online Video 7.)

Pericardial effusions. LT candidates characteristically have fluid retention, manifest as a combination of peripheral edema, ascites, pleural effusions, and pericardial effusion (55,60). Pericardial effusions are reported in up to 63% of patients with ESLD, but are typically small in size and hemodynamically well tolerated (61). While the evaluation of a pericardial effusion should include determination of the size, circumferential extent, and presence or absence of hemodynamic compromise, the development of cardiac tamponade in the LT candidate is rare and has been reported only in isolated case reports (61,62).

Patent foramen ovale. Patent foramen ovale (PFO) is present in a quarter of the general population, and typically portends a benign course (63). Contrast-enhanced echocardiography or color Doppler imaging is recommended for the diagnosis of PFO. In the setting of LT, spontaneous echogenic contrast material representing air and/or microthrombi is seen in the right heart of all patients at the time of donor liver reperfusion (64). Hypothetically, changes in intracardiac pressure during the perioperative period can result in paradoxical emboli. Some studies have reported an increased risk of embolic events in patients with a PFO during LT (64), while a more recent retrospective study found

no significant difference in outcomes for patients with a PFO (65).

Assessing Risk of Specific Procedures

Risk of transjugular intrahepatic portosystemic shunt procedure. Insertion of a transjugular intrahepatic portosystemic shunt (TIPS) is standard treatment for refractory ascites and uncontrolled variceal bleeding (7,9,66,67). Placement of a TIPS results in an abrupt increase in cardiac preload due to a shift of portal venous blood into the systemic circulation, leading to an additional increase in cardiac output, increased LV and RV end-diastolic volumes, and further decrease in systemic vascular resistance (4). These acute hemodynamic effects in the setting of cirrhotic cardiomyopathy can result in high-output congestive heart failure, cardiac arrhythmias, and myocardial ischemia (4). In a study comparing outcomes of TIPS to repeated large-volume paracentesis, Ginès et al. (68) found that 12% of the TIPS group developed heart failure as compared to none in the paracentesis group. Similarly, Schwartz et al. (69) found that 13% of patients developed heart failure after TIPS placement. More recently, Cazzaniga et al. (67) reported that the presence of diastolic dysfunction (defined as E/A ratio ≤1) 4 weeks post-TIPS was the only independent predictor of overall survival following the procedure. Rabie et al. (66) revealed that the presence of diastolic dysfunction in the pre-TIPS period predisposed patients to both cardiac and noncardiac death post-procedure. Given these findings, it has been suggested that after TIPS insertion, patients with evidence of diastolic dysfunction should be preferentially considered for LT as compared to patients with normal diastolic function (67).

Acute effects of liver transplantation. LT imposes immediate stress on the heart. Intraoperatively, there is impaired myocardial contractility with an abrupt increase in peripheral vascular resistance and a sudden decrease in preload which can be further exacerbated by hemorrhage, third space fluid losses, and inadequate volume resuscitation, resulting in reduced cardiac output (4,8,9). Conversely aggressive fluid repletion or blood transfusion can result in volume overload and the development of pulmonary edema due to occult cardiac disease. Pulmonary edema occurs in 12% to 56% of LT candidates in the perioperative period (9,25). Metabolic derangements related to post-reperfusion syndrome can further impair cardiac contractility. The stress of LT can thus unmask the latent systolic dysfunction of cirrhotic cardiomyopathy, leading to overt heart failure (Fig. 10; Online Video 8) with heart failure and other cardiac complications accounting for 7% to 21% of mortality following LT (8,9). Unfortunately, there are no reliable diagnostic criteria to identify LT candidates with cirrhotic cardiomyopathy at risk of developing cardiac complications in the perioperative period. Kim et al. (10) evaluated the use of DSE for identifying patients with cirrhotic cardiomyopathy and found a blunted DSE response (defined as <10% reduction in LV end-diastolic volume, <20% decrease in end-systolic volume, and <10% increase in LV ejection fraction) in 25% of LT candidates. However, the prognostic value of a blunted DSE in predicting perioperative complications is unknown (4).

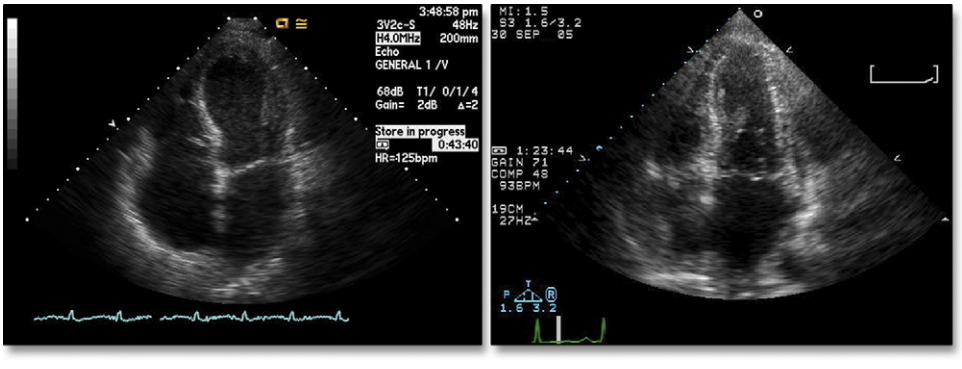

Figure 10. Serial Echocardiograms in a Patient With Acute Decompensation Following Liver Transplantation

End systolic apical 4-chamber view recorded 24 h after an otherwise successful liver transplant (LT) in a patient who developed acute severe systolic dysfunction and clinical congestive heart failure **(left panel)**. Pre-operative testing had revealed normal LV systolic function and there was full recovery of function 3 months later **(right panel)**. Abbreviation as in Figure 1. (See Online Video 8.)

Heart Diseases Causing Liver Disease

Occasionally, pre-operative evaluation of the LT candidate reveals cardiac disease as the etiology of ESLD. This syndrome termed cardiac cirrhosis is characterized by chronic right heart failure leading to elevated systemic venous pressures, passive hepatic venous congestion and subsequent sinusoidal collagen deposition and eventual cirrhosis (4,49). Cardiovascular diseases that may result in cardiac cirrhosis include dilated cardiomyopathy with secondary pulmonary hypertension, restrictive cardiomyopathy, constrictive pericarditis (Fig. 11; Online Video 9), primary pulmonary hypertension, or mitral stenosis with secondary pulmonary hypertension (4,49). The clinician should suspect cardiac cirrhosis when the triad of right heart failure, hepatomegaly, and ascites with a high protein content and high serum ascites albumin gradient is present (4,49). Ultimately, the combined use of liver vein catheterization with liver tissue sampling and right heart catheterization can help to discriminate between portal hypertension and right-sided heart failure (4). As the treatment of cardiac cirrhosis is based on treatment of the underlying cardiac disorder, there is no role for LT in this syndrome (49).

Recommendations

Cardiovascular complications account for considerable mortality and morbidity associated with LT. The AASLD and the AHA recommend TTE for all LT candidates to evaluate cardiac chamber sizes, systolic and diastolic function, valvular function, and pulmonary artery pressure and to exclude the presence of intracardiac shunts, significant LVOTO, or pericardial effusion (24,40). Additional noninvasive functional assessment for CAD is recommended for LT candidates based on the presence of risk factors (24,40). The cardiac imaging modality of choice for noninvasive screening of CAD remains unclear. As DSE appears to be an effective screening test and can provide a comprehensive cardiac assessment, it is currently recommended by the AASLD (24). Table 6 provides a summary of these recommendations based on the body of evidence reviewed. The role of cardiac imaging in the evaluation of the LT candidate continues to be in evolution. Further studies are necessary to develop an evidence-based approach to the diagnosis of underlying cardiac pathology (especially CAD) and identify the subset of patients at increased risk of cardiovascular complications.

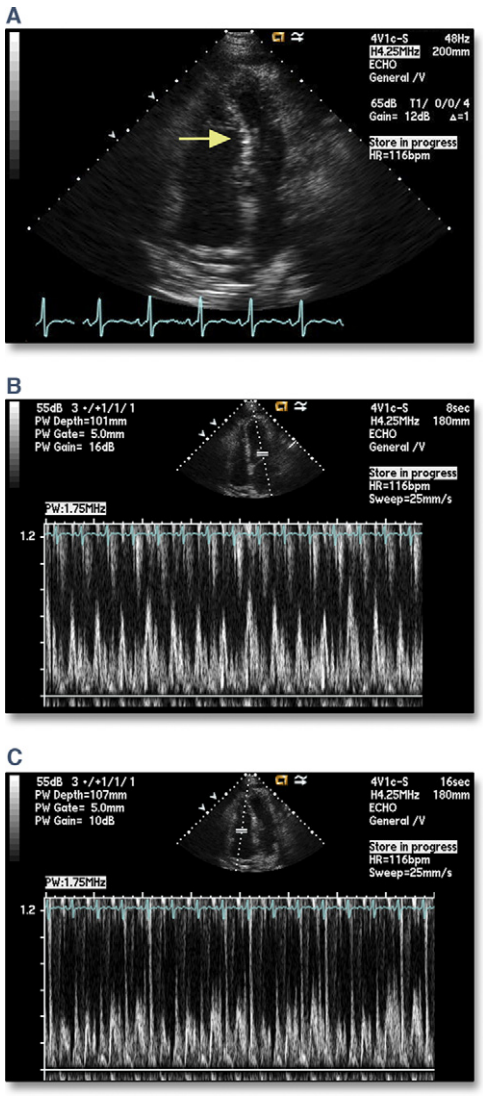

Figure 11. Two-Dimensional Echocardiogram Recorded in a 56-Year-Old Man With ESLD Related to "Cryptogenic Cirrhosis"

Echocardiography at the time of transplant evaluation revealed classic findings of pericardial constriction. In the apical 4-chamber view **(A)**, note the rightward shift of the ventricular septum **(arrows)** in this inspiratory still frame. In the real-time image, the respiratory variation of septal position is better appreciated. Transmitral **(B)** and transtricuspid **(C)** Doppler confirm exaggerated respiratory variation consistent with constriction. Abbreviation as in Figure 1. (See Online Video 9.)

Reprint requests and correspondence: Dr. William F. Armstrong, University of Michigan Medical Center, Department of Internal Medicine, Division of Cardiology, Cardiovascular Center Floor 2 Room 2161, 1500 East Medical Center Drive SPC 5853, Ann Arbor, Michigan 48109-5853. *E-mail: wfa@umich.edu.*

Table 6. Pre-Operative Cardiovascular Assessment

Cardiovascular Finding	Screening Recommendations	Limitations/Considerations
Coronary artery disease	DSE evaluation for all patients >50 yrs old, chronic smokers, diabetes, family or clinical history of heart disease	Low sensitivity and low NPV in some studies; frequent inability to reach target heart rate (study nondiagnostic); numerous proposed diagnostic algorithms; coronary angiography recommended for confirmation of positive studies
Cirrhotic cardiomyopathy	Echocardiography to assess systolic/diastolic function, LVH, cardiac chamber sizes	No diagnostic criteria available
LVOTO/HCM	Echocardiography	Diagnosis of HCM can be difficult in setting of underlying cirrhotic cardiomyopathy, LVOTO; intraoperative TEE monitoring to assess ventricular volumes and dynamic LVOTO
Valvular heart disease	Echocardiography	Hyperdynamic circulatory state with high transvalvular flow can overestimate degree of valve stenosis
Portopulmonary hypertension	Doppler echocardiography	Inability to distinguish between pulmonary arterial hypertension and pulmonary venous hypertension; right heart catheterization recommended for diagnosis confirmation
Hepatopulmonary syndrome	Contrast echocardiography	Must be differentiated from atrial septal defect and patent foramen ovale
Pericardial effusion	Echocardiography	Assessment for cardiac tamponade; frequent reaccumulation due to underlying ESLD
Patent foramen ovale	Contrast echocardiography	Significance of diagnosis unclear; intraoperative TEE monitoring for prevention of venous air emboli

HCM = hypertrophic cardiomyopathy; LVH = left-ventricular hypertrophy; LVOTO = left-ventricular outflow tract obstruction; TEE = transesophageal echocardiography.

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Key Words: cirrhosis ■ echocardiography ■ liver transplantation ■ pre-operative risk assessment.

APPENDIX

For supplemental videos, please see the online version of this article.