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EDITORIAL

Assessing the liver to predict outcomes in heart transplantation

Michael M. Givertz, MD

From the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

Is life worth living? It all depends on the liver.
William James (1842–1910)
American philosopher and psychologist

For highly selected patients with progressive heart failure symptoms and worsening clinical status, cardiac transplantation remains the standard of care for treatment of advanced heart disease.[1] Guidelines for selecting patients for heart transplant include absolute and relative contraindications,[2,3] which may vary from center to center and across regions and countries. Definitions of severe or irreversible organ dysfunction have been proposed (Table 1), but specific criteria must be evaluated in the context of individual patient disease trajectory, including the presence or absence of inotropic or mechanical circulatory support. Much is known about the prevalence and effect of renal dysfunction in the setting of advanced heart failure,[4] but the understanding of cardiohepatic interactions remains less clear.

In the setting of cardiogenic shock, Samsky et al[5] postulate that acute cardiogenic liver injury is linked to a combination of hepatic congestion from elevated hepatic venous pressure and impaired perfusion (i.e., both are required). Chronic passive congestion (or "congestive hepatopathy"), however, may be associated with advanced biventricular heart failure, restrictive cardiomyopathy, and/or severe tricuspid regurgitation and presents with more subtle signs and symptoms. In the middle are patients admitted with acute decompensated heart failure in whom symptoms and laboratory abnormalities may be confused with primary gastrointestinal or hepatobiliary conditions. Cardiohepatic interactions, whatever the cause, may have overlapping pathology that may be silent with current imaging (Table 2).

During the past 10 years, the prognostic importance of acute and chronic liver dysfunction in patients with advanced heart disease has been illuminated. Most of the studies, however, have focused on easily accessible, routine

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laboratory investigations. In the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study, total bilirubin was a strong independent predictor of worsening heart failure and all-cause mortality.[6] More recent data from Poelzl et al[7] demonstrate that other markers of cholestasis (e.g., alkaline phosphatase and γ-glutamyl transferase), but not transaminases, predict transplant-free survival in ambulatory heart failure patients. In patients with acute heart failure, baseline, and in-hospital changes in albumin (decrease) and total bilirubin (increase) provide additional prognostic information.[8] Similarly, hyperbilirubinemia and hypoalbuminemia predict right ventricular failure after left ventricular assist device (VAD) implantation and adverse outcomes after transplant.

Several investigators have assessed the effect of the Model for End-Stage Liver Disease (MELD) and MELD without international normalized ratio (MELD-XI) scores on heart failure, VAD, and post-transplant outcomes. This scoring system, originally developed in patients with hepatic cirrhosis waiting for a liver transplant, incorporates hepatic, renal, systemic inflammatory, and nutritional data. Not surprisingly, this multimarker approach independently predicts adverse outcomes in patients with chronic heart failure[9] as well as peri-operative bleeding and post-operative morbidity and mortality in VAD[10] and transplant patients.[11] Moreover, improved MELD scores may be observed during VAD support or after transplant and indicate enhanced prognosis.

Unfortunately, none of these laboratory parameters takes into account structural abnormalities of the liver, including the extent and severity of fibrosis. Although static or functional imaging studies, such as ultrasound, computed tomography, and liver-spleen scan, may identify hepatic cirrhosis in some patients, the overall sensitivity of non-invasive imaging is poor. Analysis of a specimen from a

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Table 1 Definitions of Severe or Irreversible Organ Dysfunction[a]

Organ system	Absolute contraindications	Relative contraindications
Renal	Stage 4 or 5 chronic kidney disease Significant proteinuria	Creatinine clearance between 20 and 30 ml/min
Pulmonary	FEV_1 < 1.0 liter	FVC, TLC, or D_{LCO} < 40% to 50% predicted Recent pulmonary embolism
Hepatic	Cirrhosis proven on biopsy specimen	Total bilirubin >2.5 to 3.0 mg/dl Chronic active HBV or HCV infection
Neurologic	Multi-infarct dementia	Muscular dystrophy Non-disabling stroke or recent seizures
Gastroenterologic		Active peptic ulcer disease or gastrointestinal bleeding

D_{LCO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HBV, hepatitis B virus; HCV, hepatitis C virus; TLC, total lung capacity.

[a]Adapted from Givertz MM, Heart transplantation. In: Nabel EG, editor. Scientific American Medicine. Hamilton, Ontario: Decker Intellectual Properties, 2014. See also, Scientific American Medicine, available at: http://www.sciammedicine.com; accessed March 29, 2015.

liver biopsy, whether performed by the transvenous, transcutaneous, or open route, remains the gold standard.

To determine the clinical predictors of hepatic fibrosis in patients with advanced heart failure, Gelow et al[12] identified 59 patients from whom liver tissue was obtained during evaluation for VAD or transplant. Nearly 80% had some degree of fibrosis on blinded pathologic review, with approximately 50% meeting criteria for severe (grade 3 or 4) fibrosis. Notably, advanced heart failure patients with hepatic fibrosis had worse renal function, more severe tricuspid regurgitation, and greater obstructive or mixed liver function test abnormalities. Abnormal abdominal imaging was inadequate to identify or rule out fibrosis, with a sensitivity of 30% and negative predictive value of 21%, respectively. No outcomes information was provided.

In the current issue of *The Journal of Heart and Lung Transplantation,* Farr et al[13] extend these data by determining the prognostic value of liver biopsy in patients evaluated for heart transplant. During a 13-year period, approximately 1,200 patients underwent cardiac transplantation at Columbia University. Advanced liver disease was suspected in 68 of these patients (5.3%), and they underwent liver biopsy. Retrospectively, they were assigned a standard fibrosis score (0–4) along with a novel liver risk score [(fibrosis + 1) × MELD-XI]. This highly-selected biopsy group was more than 40% non-Caucasian, with nearly 50% having "other" etiologies of heart failure, including congenital heart disease and restrictive or infiltrative cardiomyopathies.

Of the study cohort, 52 patients were listed for transplant and 36 received an allograft, with 27 (75%) surviving longer than 1 year. Post-transplant survivors had lower MELD-XI and liver risk scores, whereas patients who died after transplant had more allograft dysfunction, longer ventilator times, and more severe bleeding. In a multivariable analysis, the MELD-XI score before transplant and the liver risk score during evaluation were independent predictors of 1-year death. The novelty of the liver risk score is its ability to combine structural (e.g., fibrosis) and functional (e.g., total bilirubin, creatinine) abnormalities of advanced heart disease associated with end-organ dysfunction. Similar to previous findings,[12] other liver function tests and imaging studies were not able to differentiate patients with no to mild vs moderate to severe fibrosis.

Table 2 Clinicopathologic Correlations in Advanced Heart and Liver Disease

Hepatic injury	Signs and symptoms	Laboratory assessments	Pathology
Acute cardiogenic liver injury	Weakness and apathy Confusion Tremor	Markedly elevated LDH, followed by ALT/AST Elevated bilirubin Elevated INR	Hemorrhagic centrilobular necrosis Mild biliary stasis Lack of regenerative activity or fibrosis
Acute decompensated heart failure	Abdominal bloating Nausea and anorexia	Elevated alkaline phosphatase Mild-moderately elevated ALT/AST	Cholestasis Sinusoidal dilation Bridging fibrosis or cirrhosis[a]
Chronic passive congestion	Abdominal bloating Ascites and lower extremity edema[b]	Mildly elevated ALT/AST Elevated alkaline phosphatase, bilirubin and GGT Decreased albumin	Centrilobular necrosis Cholestasis Minimal portal inflammation Bridging fibrosis or cirrhosis[a]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; INR, international normalized ratio; LDH, lactate dehydrogenase.

[a]In advanced cases.

[b]May be absent, especially in younger patients.