Brief Report

Physiologic Adaptation or Cirrhotic Cardiomyopathy: It Is Time for New Definitions!

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Cardiovascular diseases, including heart failure, have become the leading cause of postoperative mortality in patients undergoing liver transplantation (LT).[1] Consequently, liver transplant programs include a strict cardiac evaluation to identify and optimize cardiovascular diseases before listing a patient for LT. The identification of well defined predictors of post-LT cardiovascular events would allow for optimization of the selection process and care around LT.

In this issue of the *Journal of Cardiac Failure*, Eyvazian et al used an organ transplant database to conduct a retrospective cohort study to evaluate the incidence and predictors of new-onset post-LT left ventricular systolic dysfunction (LVSD).[2] Their cohort included patients with normal LV systolic function before LT, defined as a left ventricular ejection fraction (LVEF) >50% on transthoracic echocardiography (TTE). Their main outcome of interest was the occurrence of LVSD, defined as LVEF <40%, within 6 months after LT. Out of the 1,760 included patients, 601 had a TTE study after LT. Of those, ~11% (69/601) developed post-LT LVSD, of which one-half (34 patients) recovered their LVEF to >50% within 30 days. Patients who developed post-LT LVSD tended to have systolic wall motion abnormalities and low-normal LVEF on pre-LT TTE compared with those who did not.

Previous observational studies have shown that various pre-LT echocardiographic abnormalities may predict post-LT heart failure.[3–6] However, one limitation of all the studies in this field is that TTE was, understandably, performed only in the presence of symptomatology and not routinely after LT. In the work of Eyvazian et al, only a third of patients underwent TTE within 6 months after LT. Those patients had worse survival after LT, regardless of the presence of LVSD, indicating that they were probably sicker than those who did not have an indication for TTE. Thus, the true incidence of post-LT LVSD remains unclear, because post-LT TTE was not done for the entire cohort.

Patients with liver cirrhosis, particularly those with decompensated disease, have significant physiologic interactions with the heart and circulatory system. Individuals with cirrhosis and portal hypertension frequently develop hyperdynamic circulation, a well known physiologic adjustment. In early stages of cirrhosis, portal hypertension is driven mainly by increased intrahepatic vascular resistance due to fibrogenesis. As hepatocellular function worsens, decreased metabolism of vasodilators leads to splanchnic vasodilation, mediated mainly by nitric oxide, with increased portal blood flow, as well as systemic vasodilation, decreased systemic vascular resistance and cardiac afterload, and hypotension. These events promote activation of compensatory mechanisms, including the sympathetic nervous system, the renin-angiotensin-aldosterone system, and the vasopressin system, leading to an increase in heart rate and stroke volume. Increased intrahepatic vascular resistance in combination with increased portal blood flow leads to the development of portal hypertension and portosystemic shunts, which further increase cardiac preload. The combination of increased preload, decreased afterload, and activation of humoral compensatory mechanisms leads to increased cardiac output and heart rate, which are well characterized features of hyperdynamic circulation. These physiologic changes are echocardiographically manifested as an increased LVEF.[7]

In addition to the hyperdynamic circulatory alterations, a form of myocardial dysfunction known as cirrhotic cardiomyopathy may develop in patients with cirrhosis. It is characterized by a blunted cardiac contractile response to stress or altered diastolic relaxation with electrophysiologic abnormalities in an otherwise normal heart. The pathophysiology underlying cirrhotic cardiomyopathy involves hemodynamic, humoral, endocrine, electrophysiologic, and autonomic mechanisms. It is often asymptomatic until the heart is challenged by changes in preload or afterload, such

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as deploying a transjugular intrahepatic portosystemic shunt or reperfusion after LT.[8]

It is unclear if cirrhotic cardiomyopathy represents a bona fide cardiomyopathy or a reversible physiologic adjustment. Postmortem studies have shown anatomic abnormalities in patients with liver cirrhosis, including cardiomegaly and ventricular hypertrophy, implying a true cardiomyopathy.[9,10] These abnormalities were more frequent in patients with ascites than in those without ascites, demonstrating a direct correlation between the cardiac changes and the progression of cirrhosis to decompensation.[9] However, studies that attempted to evaluate the effect of LT on cirrhotic cardiomyopathy have shown a wide range of effects that varied from improvement to worsening of heart function, indicating a spectrum of cirrhosis-related cardiac changes.[11−14] On one end is the reversible adaptation related to hyperdynamic circulation that resolves with LT, and on the other end are irreversible modifications related to an authentic cardiomyopathy that persists after LT.

To further complicate the problem, acute worsening in cardiac function after LT might also be related to stress-induced cardiomyopathy (SIC) secondary to the transplantation surgery and the reversal of the hyperdynamic circulation. However, SIC usually resolves within 4−12 weeks after the inciting event.[15,16] Other possible confounding factors include preexisting cardiac dysfunction related to an increasing number of older LT recipients and the specific etiology of cirrhosis, as in alcoholic liver disease and hemochromatosis.[17,18]

The current diagnostic criteria for cirrhotic cardiomyopathy proposed almost 15 years ago (Table 1) are up for revision. Consideration should be given to the increase in LVEF that develops as cirrhosis progresses to decompensation.[8,19] The current criteria ignore the dynamic nature of LVEF, which is influenced by the preload, afterload, and sympathetic tone that are affected in cirrhosis.[20] Eyvazian et al showed that low-normal LVEF before LT was predictive of post-LT LVSD, suggesting preexisting subclinical LV dysfunction. Therefore, although LVEF of 55% reflects normal systolic function in patients with compensated cirrhosis, in those with decompensated cirrhosis and hyperdynamic circulation, this percentage does not assure normal ventricular function. New diagnostic criteria should also address the potential reversibility of the process and define differences related to the distinct etiologies of cirrhosis. Finally, the understanding and assessment of diastolic dysfunction has evolved significantly since 2005 and should be included in a new definition. Recent advances in imaging modalities, including tissue Doppler imaging and ventricular strain imaging, might provide more accurate assessment of cardiac function in cirrhotic patients.[21,22]

Table 1. Diagnostic Criteria of Cirrhotic Cardiomyopathy

Systolic dysfunction	• Blunted increase in cardiac output on exercise, volume challenge, or pharmacologic stimuli • Left ventricular ejection fraction <55%
Diastolic dysfunction	• Age-corrected early/late diastolic filling velocities (E/A) ratio <1.0 • Prolonged deceleration time (>200 ms) • Prolonged isovolumetric relaxation time (>80 ms)
Supportive criteria	• Electrophysiologic abnormalities (abnormal chronotropic response, electromechanical uncoupling/dysynchrony, prolonged QTc interval) • Structural changes (enlarged left atrium, increased myocardial mass) • Increase in cardiac biochemical markers (B-type natriuretic peptide [BNP], pro-BNP, troponin I)

Modified from Moller S, Henriksen JH. Cardiovascular complications of cirrhosis. Gut 2008;57:274.[8]

Eyvazian et al clearly demonstrated that post-LT LVSD is a significant problem. However, the literature has been limited by small size and retrospective studies and by outdated diagnostic criteria for cirrhotic cardiomyopathy. It is time to better define the natural history of cirrhosis-related cardiac interactions by designing longitudinal prospective cohort studies with serial assessment of cardiac geometry and function, revising the current diagnostic criteria of cirrhotic cardiomyopathy, and using new advances in cardiac diagnostics. Our knowledge about cardiac changes in the setting of cirrhosis and after liver transplantation is evolving. For now, clinicians should use the current criteria with caution.

Disclosures

None.

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