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Severe Cardiovascular Complications Following Liver Transplantation in Patients With Iron Overload

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ABSTRACT

We report 4 cases of our institutional experience with liver transplantation that illustrate the high risk of heart failure and cardiogenic shock in the setting of cardiac iron overload. We then discuss a pragmatic approach to assess the cardiovascular risk in liver transplantation candidates with cardiac iron overload. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2022;4:677-681) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

INTRODUCTION

Patients with myocardial iron overload are at an increased risk of cardiovascular complications following liver transplantation (LT).[1,2] There is currently no clear guideline to determine who should be considered too high risk for LT from a heart failure (HF) standpoint, given the insufficient case experience and incomplete understanding of pathophysiological changes in the patient with hemochromatosis who has undergone LT. We present 4 cases of patients with suspected iron overload–induced cardiovascular complications following LT. We then discuss preoperative clinical evaluation of LT recipients with evidence of myocardial iron overload.

LEARNING OBJECTIVES

- To review the dynamic change in cardiovascular physiology after LT.
- To be able to assess the significance of cardiac iron overload in patients undergoing LT.

CASE DESCRIPTIONS

We describe 4 cases of acute HF following LT in patients with cardiac iron overload documented on cardiac magnetic resonance (CMR) and/or endomyocardial biopsy. Details are summarized in **Table 1**.

Patient 1 had a history of alcoholic cirrhosis and biopsy-confirmed cardiac siderosis, with CMR showing T2* of 12.8 milliseconds, a finding suggesting moderate iron deposition. His echocardiogram and hemodynamic assessment revealed borderline left ventricular (LV) dysfunction. Following LT, cardiogenic shock developed, requiring temporary mechanical circulatory support. He was able to be weaned from cardiorespiratory support, but he later died of post-transplant lymphoproliferative disorder.

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

ESLD = end-stage liver disease

HF = heart failure

LT = liver transplantation

LV = left ventricular

LVEF = left ventricular ejection fraction

Patient 2 had a history of nonalcoholic steatohepatitis and suspected primary hemochromatosis (explanted liver with severe iron deposition). Pre-LT, she had mild LV dysfunction with normal hemodynamics and CMR evidence of mild to moderate myocardial iron deposition (T2* of 15-16 milliseconds). Post-LT, severe cardiogenic shock developed in response to biventricular failure in the setting of concurrent distributive shock, and she died of multiorgan failure.

Patient 3 had a history of primary biliary cirrhosis, autoimmune hepatitis, and Evans syndrome requiring frequent transfusion. She had an unremarkable cardiac work-up except for mild diastolic dysfunction on the echocardiogram, and iron overload was not assessed preoperatively. Postoperatively, she developed refractory arrhythmia and cardiogenic shock with marked LV dysfunction on the echocardiogram. Autopsy revealed severe cardiac iron deposition and an HFE variant of unknown significance.

Finally, Patient 4 had a history of alcoholic cirrhosis with a normal echocardiogram and hemodynamics. However, his CMR showed evidence of moderate iron deposition (CMR T2* 14 milliseconds). Post-LT, he had a prolonged hospital course as a result of multiorgan failure with progressive LV dysfunction, with an LV ejection fraction (LVEF) as low as 28% at 3 months postoperatively. Following guideline-directed therapy for HF, his LVEF gradually improved to 55% at 1-year post-LT.

DISCUSSION

Pre-LT evaluation of cardiac risk involves deeper assessment of myocardial function in addition to routine ischemia evaluation; cirrhosis itself, as well as associated comorbidities (eg, alcohol, iron overload), can directly affect myocardial function.[3] Currently, however, there are no clear guidelines regarding pre-LT cardiovascular evaluation, given the scarcity of data in this specific group of patients and the heterogeneous definition and reporting of cardiovascular outcomes in published reports of LT; these issues make it difficult to assess the true incidence and prevalence of post-LT cardiovascular complications.[1] Various cardiovascular tests have been proposed to stratify cardiovascular risk following LT,[1,3] including 12-lead electrocardiography, comprehensive echocardiography, stress echocardiography, coronary computed tomography angiography, right-sided heart catheterization, and invasive coronary angiography, depending on the individual patients and institutional experience and preference. The presence of systolic and diastolic dysfunction, electrophysiological abnormalities such as QTc prolongation, and autonomic dysfunction with inadequate catecholamine response have all been implicated in the pathogenesis of cirrhotic cardiomyopathy, which portends a poor outcome following LT.[3] Although there are no established LVEF cutoffs to preclude LT, an LVEF <40% is generally considered an absolute contraindication, and an LVEF <50% is a relative contraindication to LT.[1]

Chronic vasodilation and resultant activation of sympathetic system are the hallmarks of cirrhotic hemodynamics (**Figures 1A and 1B**).[4] With restoration of hepatic function following LT, vascular tone normalizes, leading to increases in the afterload, and portal and splanchnic blood flow is restored, which increases the preload. These hemodynamic changes may be further amplified by the typical fluid shift and cross-clamping of the inferior vena cava during the surgical procedure.[4] The combined acute increases in afterload and preload following LT can significantly affect biventricular function. In addition, with the return of circulation to the grafted liver, a series of hemodynamic and metabolic changes may occur, resulting in hypotension, bradycardia, or arrhythmias; this condition is termed post-reperfusion syndrome.[3] Finally, any pre-existing myocardial conditions (eg, iron overload) can further increase the cardiovascular risk associated with LT.

Our cases describe acute myocardial dysfunction immediately post-LT in patients with myocardial iron overload. All 4 patients had relatively preserved LV function on echocardiograms, with evidence of mild to moderate myocardial iron overload confirmed during their pre-LT work-up or postmortem examination. Yet all these patients had acute cardiogenic shock post-LT, thus highlighting the challenges in using standard hemodynamic and echocardiographic assessment alone when evaluating the risk of cardiovascular compromise following LT.

Cardiac manifestations of iron overload typically start with diastolic dysfunction, which then progresses to systolic dysfunction when left untreated.[5] The presence of LV systolic dysfunction therefore implies advanced cardiotoxicity from iron overload increasing the risk of HF following LT. As seen in our cases, even when contractile function is preserved on gross imaging, underlying biochemical and cellular changes caused by iron overload may render the myocardium at higher risk for HF after LT. Therefore, dedicated evaluation of myocardial iron overload in high-risk

TABLE 1 Summary of Clinical Parameters for the 4 Cases Presented Pre- and Post-Liver Transplantation

	Patient 1 (Age 56 y, Male)	Patient 2 (Age 29 y, Female)	Patient 3 (Age 67 y, Female)	Patient 4 (Age 47 y, Male)
Pre-liver transplantation				
ESLD origin	EtOH	EtOH, NASH, iron	PBC, AIH	EtOH
Liver biopsy (iron deposition[a])	Severe	Moderate	N/A	N/A
Explanted liver (iron deposition[a])	Severe	Severe	Severe	Moderate
Endomyocardial biopsy (iron deposition[a])	Marked	N/A	N/A (severe on autopsy)	N/A
HFE genotypes	–	–	(HFE1 H63D VUS)	–
Laboratory results				
Ferritin, μg/L	1,853	2,574	3,327	1,775–4,917
Hemoglobin, g/dL	7.0-10.5	6.7-10.0	6.8-7.7	7.0-8.0
Echocardiographic parameters				
LVEDD, cm	4	4.9	3.8	4.7
LVEF, %	51	46-52	59	63
RV function	Borderline	Mildly reduced (FAC 34%)	Normal	Normal
Valvular disease	No significant disease	Mild-moderate MR/TR	No significant disease	No significant disease
Diastolic dysfunction	Borderline	Mild	Mild	N/A
Right-sided heart catheterization				
CO/cardiac index, L/min / L/min/m^2	N/A	7.8/4.1	5.2/3.0	No RHC done given normal diastolic function and RAP on echocardiogram
PAP, systolic/diastolic/mean, mm Hg	N/A	24/8/13	26/6/11	
LVEDP or PCWP, mm Hg	18	12	6	
PVR, WU	N/A	1.1	1.0	
MRI (T2-gated)[b]				
T2* liver, ms	5.7	5	N/A	10
T2* heart, ms	12.8	15-16	N/A	14
Coronary angiogram or coronary CTA	No significant disease	N/A	No significant disease	N/A
Stress test	N/A	N/A	No ischemia (DSE)	No ischemia (DSE)
Post-liver transplantation				
Echocardiographic parameters				
Lowest LVEF, %	18	20	32	28
RV function	Markedly reduced	Severely reduced	Moderately reduced	Moderately reduced
Cardiovascular outcome	Need for temporary LVAD, death from PTLD	Cardiogenic shock and death	Cardiogenic shock and death	Transient reduction in LV function, later normalized

[a]Iron deposition was assessed by Prussian blue staining according to a standard clinical pathology protocol. [b]A 1.5-T scanner was used for all 4 cases.

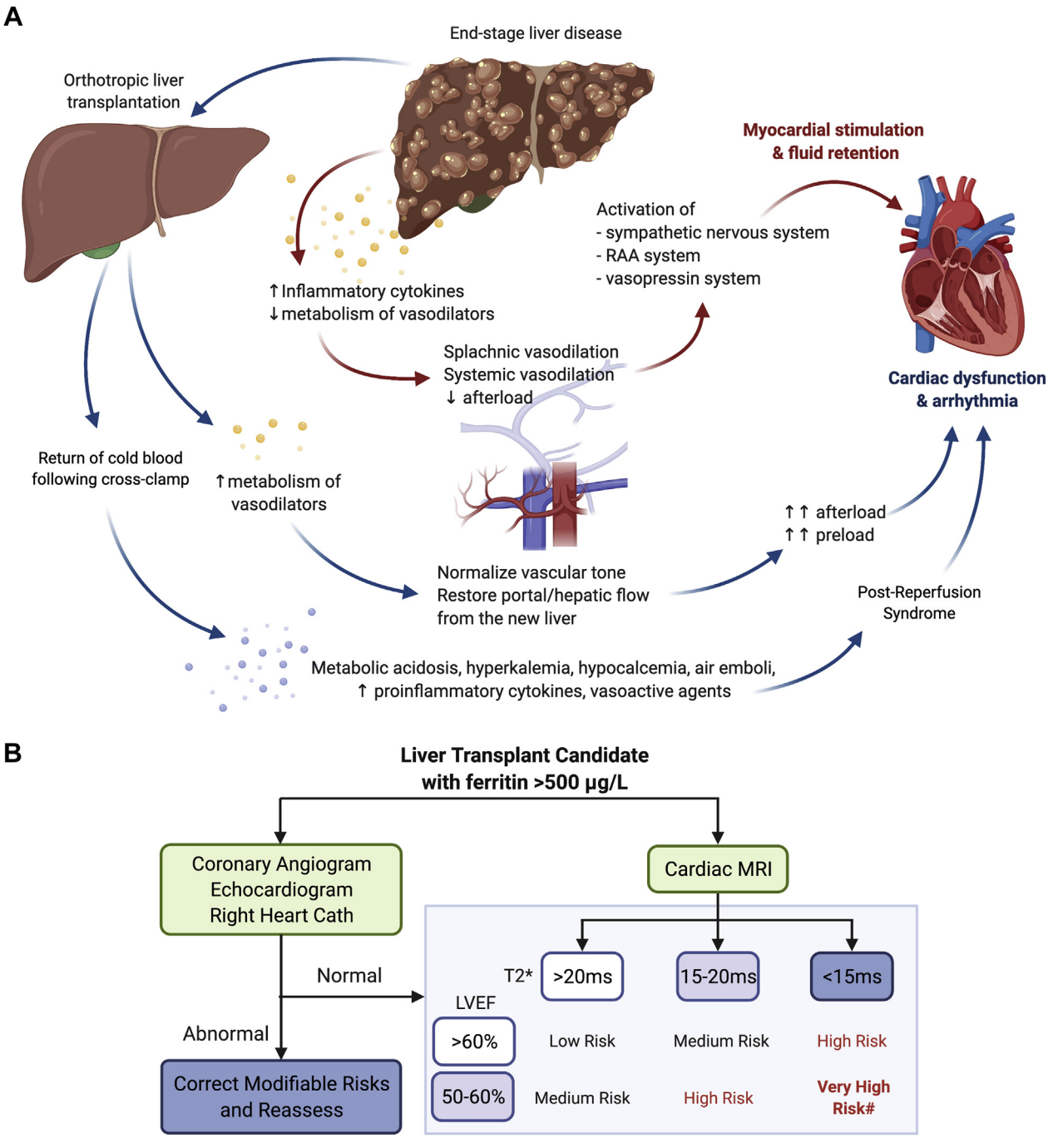
AIH = autoimmune hepatitis; CTA = computed tomography angiogram; CO = cardiac output; DSE = dobutamine stress echocardiography; EtOH = ethanol; FAC = fractional area change; LV = left ventricular; LVAD = left ventricular assist device; LVEDD = left ventricular end-diastolic dimension; LVEDP = left ventricular end-diastolic pressure; MR = mitral regurgitation; N/A = not applicable; NASH = nonalcoholic steatohepatitis; PAP = pulmonary artery pressure; PBC = primary biliary cirrhosis; PCWP = pulmonary capillary wedge pressure; PTLD = post-transplant lymphoproliferative disorder; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RHC = right-sided heart catheterizations; RV = right ventricular; TR = tricuspid regurgitation; TTE = transthoracic echocardiography; VUS = variant of unknown significance.

patients is necessary for appropriate pre-LT cardiovascular assessment.

Myocardial biopsy confirms the presence of iron, but the extent of iron deposition is best evaluated with CMR to assess T2*, which has been correlated with the degree of cardiac siderosis.[5] One report showed that the rate of HF following LT was higher in patients with lower T2* values.[2] The accumulating data suggest that in cases of preserved LV function, LT is reasonable if cardiac T2* is >20 milliseconds, whereas LT is relatively contraindicated if T2* is <15 milliseconds.

Taken together, it would be important for all patients to undergo routine iron studies during pre-transplant work-up irrespective of the reasons for the liver failure (Figures 1A and 1B). If the ferritin level is elevated (eg, >500 μg/L, the exact cutoff to be determined), obtaining CMR is critical to assess the extent of myocardial iron deposition because ferritin levels do not correlate with the degree of cardiac siderosis.[5] Other cardiac work-up testing, including echocardiography, right-sided heart catheterization, and coronary angiography, should be done to ensure normal hemodynamics and rule out significant valvular disease and ischemia. If there is any evidence of LV dysfunction in the setting of cardiac iron overload, as seen in patients 1 and 2, LT alone may present too high a risk, and simultaneous heart transplantation and LT may need to be considered in select cases.

FIGURE 1 Cardiovascular Complications of Liver Transplantation and Proposed Risk Assessment Strategy



(A) Pathophysiology of cardiovascular dysfunction in patients with end-stage liver disease and cardiovascular changes following orthotopic liver transplant. **(B)** Cardiovascular risk assessment algorithm on the basis of iron overload status. #A joint evaluation between the liver transplant and heart transplant teams should be considered for possible combined heart-liver transplantation; if the decision is to proceed with liver transplantation only, close coordination with cardiology is warranted, with a mechanical circulatory support team on standby at the time of liver transplantation. Created using BioRender. Cath = catheterization; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; RAA = renin-angiotensin-aldosterone.

CONCLUSIONS

Early identification of cardiac iron overload is critical in proper assessment of pre-LT cardiac risk. Less than normal cardiac function in the presence of any degree of iron deposition likely poses a significant cardiac risk to proceed with LT. Further compilation of experiences following LT in patients with varying degrees of iron deposition is warranted, along with an understanding of the mechanism underlying acute myocardial dysfunction in patients after LT.

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