EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

The heart in liver transplantation

Cristina Ripoll[1], Raquel Yotti[2], Javier Bermejo[2], Rafael Bañares[1,*]

[1]*Hepatology and Liver Transplant Unit, Department of Digestive Disease, Ciber EHD Hospital General Universitario Gregorio Marañón, Dr Esquerdo 46, Madrid 28007, Spain;* [2]*Department of Cardiology, Hospital General Universitario Gregorio Marañón, Dr Esquerdo 46, Madrid 28007, Spain*

The heart and liver are organs that are closely related in both health and disease. Patients who undergo liver transplantation may suffer from heart disease that is: (a) related to the original cause of the liver disease such as hemochromatosis, (b) related to the liver disease itself, or (c) related to other associated conditions. Furthermore, liver transplantation is one of the most cardiovascular stressful events that a patient with cirrhosis may undergo. After liver transplantation, the progression of pre-existing or the development of new-onset cardiac disease may occur. This article reviews the relationship between the heart and liver transplantation in the pre-transplant, intra-operative, and post-transplant periods.

Introduction

The mutual interaction between the heart and the liver in health and disease states has been established for some time. Patients with chronic heart failure may have liver damage, even cirrhosis, due to liver congestion [1], while patients with liver disease have cardiovascular abnormalities [2,3]. In patients with cirrhosis, cardiac disease can be related to (1) systemic diseases that affect both the heart and the liver, such as chronic excessive consumption of alcohol, and hemochromatosis, (2) specific cardiac diseases of cirrhosis and (3) common cardiac diseases that also occur in general population that can influence the outcomes of liver transplantation (LT).

LT is an important event that completely changes the natural history of liver disease and also influences cardiac performance and disease. Previous cardiac conditions may influence the outcomes of transplant, so thorough evaluation prior to LT is recommended. Furthermore, the surgical procedure on its own, which involves acute changes in loading conditions and the liberation of cytokines and toxins associated with reperfusion, has a documented influence on heart function [4–6]. Lastly, after LT there is an increased risk of cardiac events associated with life-long immunosuppression and its secondary effects.

This review aims to summarize the present state of knowledge regarding the interaction between the heart and the liver in the pre-transplant period, during LT, and in the post-transplant period, focusing specifically on patients with cirrhosis who undergo LT due to end-stage liver disease or hepatocellular carcinoma. Table 1 shows the most frequent cardiac conditions including their prevalence and outcome after LT.

Cardiac diseases in the pre-transplant period

Systemic diseases that can affect both the heart and the liver

Several systemic diseases that cause cirrhosis may also induce specific cardiac diseases. The most relevant etiologies are alcoholic disease and hemochromatosis. Non-alcoholic fatty liver disease (NAFLD) is frequently considered as a component of the metabolic syndrome that can also lead to cardiovascular disease. Finally, familial amyloid polyneuropathy is an infrequent systemic disease that may lead to cardiac disease.

Chronic alcoholism

Excessive alcohol consumption may lead to cirrhosis and alcoholic cardiomyopathy, which is the main cause of secondary non-ischemic dilated cardiomyopathy in the western world [7–9]. It is characterized by the presence of left ventricular dilatation, impaired systolic function, myocardial fibrosis, and disruption of the myofibrillary structure. Although overt alcoholic liver disease and cardiac involvement usually do not occur together, patients with alcoholic cirrhosis without signs or symptoms of heart disease may have demonstrable evidence of asymptomatic myocardial disease [9]. Abstinence from alcohol in the early stages of the cardiac disease may lead to significant improvement in most patients [10,11].

On the other hand, alcoholic liver cirrhosis patients may be at increased risk of coronary artery disease (CAD). Although mild to moderate chronic consumption of alcohol has been suggested to

Keywords: Liver transplantation; Heart function; Liver cirrhosis; Coronary artery disease; Cirrhotic cardiomyopathy; Portopulmonary hypertension.
Received 16 February 2010; received in revised form 27 September 2010; accepted 4 November 2010
* Corresponding author. Address: Sección de Hepatología, Servicio de Aparato Digestivo, Hospital General Universitario Gregorio Marañón, Dr Esquerdo 46, Madrid 28007, Spain. Tel.: +34 915866687; fax: +34 914265164.
E-mail address: rbanares@telefonica.net (R. Bañares).
Abbreviations: LT, liver transplantation; NYHA, New York Heart Association; EKG, electrocardiogram; TIPS, transjugular intrahepatic portosystemic shunt; MPAP, mean pulmonary artery pressure; CAD, coronary artery disease; LV, left ventricle; MELD, Model for end-stage liver disease; HRS, hepatorenal syndrome; NAFLD, non-alcoholic fatty liver disease; LDL, low density lipoprotein; RVSP, right ventricle systolic pressure; ICU, intensive care unit; CACS, coronary artery calcification score; MRI, magnetic resonance imaging.

have a protective effect, high average chronic consumption of alcohol (as is common in patients with alcohol induced cirrhosis) has been shown to increase the risk for CAD in comparison to teetotalers [12,13].

Hemocromatosis

Iron overload is associated with the deposition of iron in the myocardium and conducting system that can lead to electrocardiographic abnormalities and heart failure. Although electrocardiographic abnormalities are frequent in patients with cirrhosis due to hemochromatosis [14], heart failure is unusual. Increases in left ventricular mass, end-diastolic and end-systolic diameters of the left ventricle, and left atrium diameters may be observed, as well as significant changes of systolic function indices. Patients without overt symptoms of heart disease may have an augmentation of atrial contraction as an early manifestation of abnormal diastolic function [15]. At early stages of heart involvement, asymptomatic disease may be unmasked by cardiac magnetic resonance imaging [16]. Functional and structural cardiac changes can improve with iron removal therapy [17,18], although it may not be feasible in patients with decompensated cirrhosis. Patients with hemochromatosis have a 14-fold increase in mortality due to heart disease compared to an age and sex matched population [14] and increased mortality after LT compared to other etiologies [19,20]. Careful pre-transplant cardiac evaluation is essential in these patients.

Non-alcoholic fatty liver disease (NAFLD)

NAFLD is associated with the metabolic syndrome, which, in turn, is clearly associated to CAD. Several studies suggest that patients with NAFLD have higher incidence of CAD [21–24]. However, the association between hepatic steatosis and cardiovascular disease has recently been questioned [25].

Familial amyloid polyneuropathy

Although familial amyloid polyneuropathy does not specifically induce liver damage, since the enzymatic defect that leads to this disease is found in the liver, LT is the main therapeutic approach. One should keep in mind that this condition may induce heart disease associated with amyloid deposition, which may lead to cardiac denervation, restrictive cardiomyopathy, conduction disturbances and death. Echocardiography and autonomic function testing are important for the evaluation of these patients when considering LT [26].

Cardiac abnormalities specific to cirrhosis

Hemodynamic changes in cirrhosis

Cirrhosis induces characteristic hemodynamic changes that influence cardiac evaluation (Fig. 1). An increase in portal pressure causes an intense splanchnic vasodilation, which leads to a reduction in the systemic vascular resistance and afterload [27,28]. Initially, this decrease can be overcome by activation of compensatory mechanisms in order to maintain a normal central volemia or preload. However, with further progression of the disease, these mechanisms fail, and there is a decrease not only in afterload, but also in preload. The hemodynamic abnormalities observed in cirrhosis progress as the liver disease progresses, so Child-Pugh class A patients have a lesser degree of hemodynamic derangement than Child-Pugh class C patients [28].

Key points

- Heart and liver are closely related and influence each other in health and disease states.
- In pre-transplant patients with liver disease, attention should be placed on identification of subclinical cardiac disease that influences surgical risk and long term outcome.
- Portopulmonary hypertension identified on screening test should be further characterized with right heart catheterization. Treatment with vasodilators in patients with moderate or severe portal hypertension can be attempted.
- Screening for coronary artery disease is recommended in high risk patients, although clear recommendations regarding management of these patients remain to be elucidated.
- During LT, close surveillance of hemodynamic factors can improve outcome. Patients with greatest hemodynamic derangement (Child-Pugh class C), portopulmonary hypertension and familial amyloid polyneuropathy have the greatest difficulties of intraoperative management.
- Cardiovascular events are an important cause of morbidity and mortality in the post-LT period.
  Special care of previous disease and effort to control newly developed risk factors should be attempted.

Cirrhotic cardiomyopathy

In recent years, researchers have suggested that there is a specific heart disease associated with cirrhosis, termed cirrhotic cardiomyopathy. This condition is closely related to the hemodynamic alterations that occur in cirrhosis and is characterized by the presence of: (1) increased baseline cardiac output, with blunted ventricular response to stimuli, (2) systolic and diastolic dysfunction which are best observed in stress situations, and (3) electrophysiological abnormalities [29]. Brain natriuretic peptide has been proposed as a marker of cirrhotic cardiomyopathy [30,31].

In patients with cirrhosis, the characteristic hemodynamic changes associated with portal hypertension previously described [27,28] make the accurate evaluation of heart function very difficult. Standard echocardiographic indices of systolic and diastolic function are deeply affected by changes in load [32,33]. Therefore, in the context of cirrhosis, interpretation of these imaging tests can be challenging, because of the progressive hemodynamic changes that lead to different loading conditions.

However, there is evidence that supports that patients with end-stage liver disease have an impaired cardiac function. Abnormal cardiac function is more easily observed in stress situations such as LT [34], TIPS placement [35], and infections like spontaneous bacterial peritonitis [36]. It is also hypothesized that hepatorenal syndrome may be a manifestation of cardiac impairment, causing the organ to deliver insufficient perfusion to the kidney [37–40].

A prolonged QT interval is an easily evaluated electrophysiological abnormality associated with cirrhotic cardiomyopathy. It has been related to the severity of the liver disease and the degree of portal hypertension [41–44] and mortality [41,45].