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

The heart in liver transplantation

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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
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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].

Frontiers in Liver Transplantation

Table 1. Relationship between different cardiac diseases present previous to LT and outcome after LT. *Post-transplant outcome also depends on management of the primary cause of liver disease. Data regarding mortality is orientative, as multiple factors are likely to be involved. No information regarding relationship between LT and cardiac arrythmias, or alcoholic cardiomyopathy has been reported. No data was available regarding prevalence of alcoholic cardiomyopathy in liver transplant candidates nor its effect on LT.

	Pretransplant	During Transplant	Post-transplant
Coronary artery disease	Prevalence 6-26% [68-70]	Mortality 50% Morbidity among survivors 81% [136]	
Valvular heart disease	27.5% valvular dysfunction [83]	Valvular dysfunction associated to greater vasoactive drug and blood transfusion requirements [83]	Valvular dysfunction no differences in mortality rates [83]
Asymptomatic patent foramen ovale	Prevalence 4% [82]	Non significant trend to greater incidence of reperfusion syndrome [82]	Longer stay in ICU, no difference in morbidity or mortality [82]
Cirrhotic Cardiomyopathy increased baseline CO chronotropic abnormalities systolic and diastolic dysfunction	Greater prevalence with more severe disease 40-90% prevalence prolonged cQT [41, 46, 149]	23% abnormal cardiac response [6]	- 3.3-7% severe left heart failure [34, 87] - 45% mortality in those with severe left heart failure [127] - Progressive improvement of all abnormalities, although possible initial worsening of diastolic function [40, 50, 132]
Portopulmonary hypertension	Prevalence 2-14% [52-56]	MPAP >50mmHg 100% mortality MPAP 35-50mmHg 50% mortality MPAP <35 mmHg no disease related increase in mortality [57]	
Specific cardiac disease			
hemocromatosis*	EKG abnormalities 46% [14]	Complicated intraoperative management [19]	- 15-25% of deaths caused by cardiac events in post LT [19, 20, 140]
amyloidosis			- No improvement of sympathetic cardiac denervation, progression of cardiac amyloid infiltration [26, 128, 129]

However, sudden death is not a frequent event in patients with cirrhosis despite 60% of Child-Pugh class C patients have a prolonged QT interval [41]. Interestingly, it has also been associated to survival in Child-Pugh class A patients [41], and has been more frequently observed in patients who died after LT than in survivors [46]. Special care should be taken with drugs that can

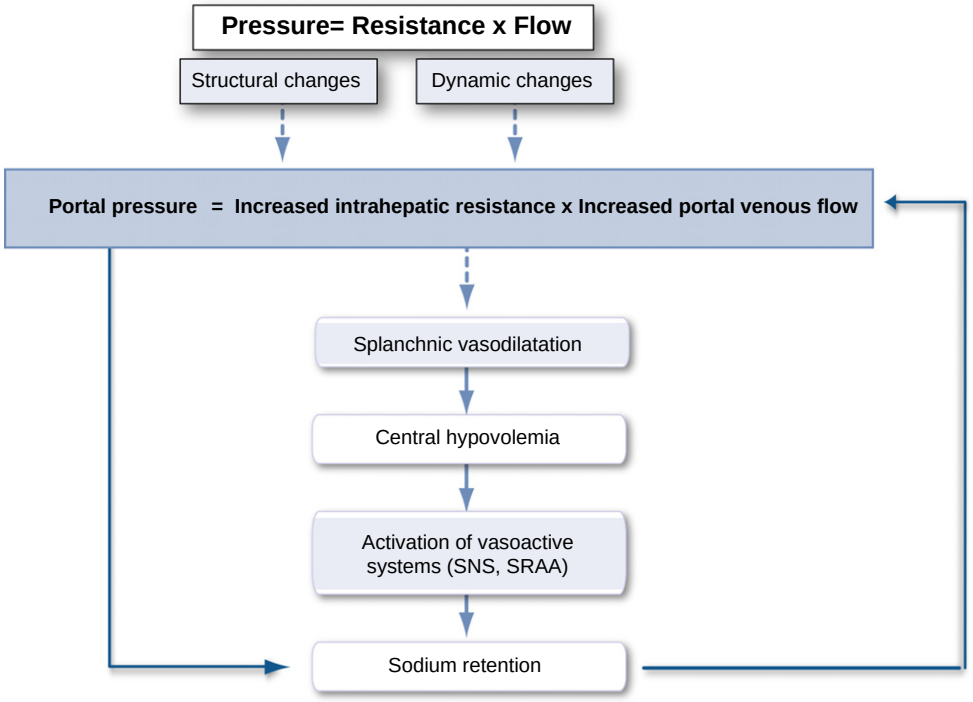

Fig. 1. Diagram of pathophysiology of portal hypertension. The increase in portal pressure is defined by Ohm's law, that states that pressure depends on resistance and flow. In cirrhosis there is an initial increase in intrahepatic resistance. This increase in intrahepatic resistance leads to splanchnic vasodilation which in turn leads to central hypovolemia and activation of vasoactive mechanisms that increase cardiac output and kidney sodium retention. This leads to an increase in portal venous flow. The combination of both mechanisms leads to an increase in portal pressure. Furthermore, increased intrahepatic resistance also leads to an independent increase in kidney sodium retention and further increases portal venous flow.

prolong ventricular repolarization, i.e. anti-arrythmics such as amiodarone, or antibiotics such as erythromycin [47]. Use of betablockers has been associated to shortening of the QT interval [48,49], a finding which may partly explain the low incidence of sudden death in this population.

A more detailed description of the abnormalities associated with cirrhotic cardiomyopathy is shown in Table 2. Although there have been reports suggesting that alterations in cardiac structure associated with cirrhotic cardiomyopathy may be modifiable with pharmacological treatment [50,51], further studies

Table 2. Summary of abnormalities associated cirrhotic cardiomyopathy in baseline and in stress conditions with modification only of preload or afterload or mixed stress. (See below-mentioned references for further information.)

	Baseline	Modification of preload or afterload	Mixed stress (modification of pre and afterload)
Structural changes	- Increase in diameter of atrium and ventricle or LVEDV [91, 93, 94, 120, 141-143] - Increase in LVWT [51, 94, 120, 132, 141]		- Increase in LVEDV with exercise [144] - Increase in left atrial diameter and left ventricle diameter or LVEDV after TIPS [142, 160, 161] - Increase in LVEDV after TIPS in patients with central underfilling [145]
Functional changes			
systolic	- Normal or increased LVEF, SV and/or CI at rest [2, 3, 93, 95, 120, 132, 153, 159] - Reduced LVEF in ascites [141] - Lower LVESVI [95, 159] - Lower CI or CO in patients with ascites who develop HRS [37, 38]	- Increase in PWCP without increase in CO with terlipressin [156] - Increase in PWCP without increase in CO with angiotensin [146]	- Lower CO in patients with SBP that develop HRS [36] - Inadequate or absent increase of cardiac stroke index, CO, LVEF and/or LVEDP with exercise [91, 120, 132, 144, 147, 148] - Reduced maximal work capacity [132, 148]
diastolic	- Decrease of E/A ratio [51, 93, 141, 158] - Decrease E/A ratio in ascites [143] - E/A <1 associated to survival and slower ascites mobilization [157] - Prolonged IVRT and DT [93, 120]		- Lower PFR with exercise, especially with ascites [132] - E/A <1 after TIPS placement associated to 1 yr survival [35]
Electrophysiologic abnormalities	- Prolonged QT [2, 43, 45, 149, 151] - Prolonged QT interval associated to Child-Pugh [41, 42, 44, 46, 153-155]		- Chronotropic incompetence with exercise [119, 132, 144, 152] - Abnormal autonomic reflex with exercise [144] - Further prolongation QT interval and increase QT dispersion after TIPS [151]

CO: cardiac output
CI: cardiac index
SV: stroke volume
SVI: stroke volume index
PWCP: pulmonary wedged capillary pressure
LVEDV: left ventricle end diastolic volume
LVESVI: left ventricle end systolic volume index
LVEF: Left ventricle ejection fraction
LVWT: left ventricle wall thickness
LVEDP: left ventricle end diastolic pressure
IVRT: isovolumetric relaxation time
DT: deceleration time
PFR: peak filling rate
LF/HF: low frequency/high frequency heart rate ratio
QTc: corrected QT interval

are needed. Further insight on cirrhotic cardiomyopathy is offered in a recently published review [29].

Portopulmonary hypertension

Portopulmonary hypertension is a liver disease-specific cause of primary pulmonary hypertension. The diagnosis is based on hemodynamic characterization including the evaluation of cardiac output and pulmonary vascular resistance on right heart catheterization. This disease has prognostic relevance for LT and is detected between 2% and 14% of patients with cirrhosis [52–56]. Based on the mean pulmonary artery pressure, portopulmonary hypertension can be graded into mild (MPAP $\geqslant$25 to <35 mm Hg), moderate (MPAP $\geqslant$35 to <45 mm Hg), and severe (MPAP $\geqslant$45–50 mm Hg). Patients with moderate or severe portopulmonary hypertension have increased transplantation related mortality [57], and, for this reason, LT is contraindicated in these patients if they do not respond to medical therapy [58]. Patients with moderate and severe portopulmonary hypertension may benefit from treatment [59–65], although randomized clinical trials are lacking. The benefit of administering prophylactic beta-blockers to prevent portal hypertension related bleeding should be evaluated on an individual basis, as suggested by one study that showed that the removal of betablockers leads to a decrease in pulmonary vascular resistance and an increase in exercise capacity [66].

Cardiac disease in LT candidates: coronary artery disease (CAD)

Historically, patients with end-stage liver disease were considered to be relatively well protected from CAD due to their characteristic hemodynamic profile and decreased cholesterol levels [67]. However, recent studies suggest that CAD is possibly more frequent in cirrhotic patients than in the general population. The prevalence of CAD in LT candidates over the age of 45–50 years ranges between 6% and 26% [68–70], depending on the selection criteria. Silent moderate to severe CAD has been detected in 13.3% in a large study [68], and therefore, it should be actively screened for in high-risk patients. Patients with more than one cardiovascular disease risk factor such as male sex, age >50 years, smoking, hypercholesterolemia, and diabetes mellitus, have a greater probability of concomitant significant CAD [70]. Special care should be taken in patients with diabetes mellitus, as this disease has been associated with the presence of asymptomatic CAD [68], and the combination of diabetes and CAD has a very poor prognosis after LT [71]. Furthermore, as previously mentioned, patients with cirrhosis due to NAFLD or alcoholic liver disease may have an increased risk of CAD [12,13,21–24] and perhaps should also be screened. Although the efficacy of CAD screening in LT candidates has been questioned, taking into account the clinical burden this implies [72] most specialists and the present guidelines recommend CAD screening in selected patients [58].

Management of detected coronary lesions in the pre-transplant period is an unsolved issue. General recommendations [73,74] include counseling about weight control, regular physical activity, smoking cessation, and use of aspirin as well as optimization of blood pressure, LDL lipoprotein levels (<100 mg/dl), and diabetes (hemoglobin A1c approximately 7%). However, in the context of liver cirrhosis some of these recommendations are difficult to apply or are not applicable. Patients with end-stage liver disease generally do not have hypertension or elevated LDL-cholesterol levels, and the use of aspirin can be hampered by thrombocytopenia and potential renal toxicity. If indicated, statins can be used safely and have shown to have beneficial effects on portal pressure in hemodynamic studies [75]. Percutaneous revascularization can be performed, but it is unclear whether this intervention may improve clinical outcome in low-risk asymptomatic patients. Dual antiplatelet therapy with aspirin and a thienopyridine such as clopidogrel is always prescribed after coronary stenting. In the setting of cirrhosis, with thrombopenia and coagulopathy, the risk of life-threatening hemorrhage related to dual antiplatelet therapy is a significant concern. Furthermore, it is generally recommended that patients on dual antiplatelet therapy should avoid surgical procedures, as there is a greater risk for post-operative bleeding. For these reasons, in the setting of LT candidates, perhaps bare metal stents are the ideal, as dual antiplatelet therapy should be administered for a shorter period of time than with drug-eluting stents. Normally, although a minimum of 1 month of dual antiplatelet therapy is recommended for bare stents, only 2 weeks of clopidogrel can be given if there is a significant increase in the risk of bleeding [74]. Finally, surgical revascularization has a very high morbidity and mortality in patients with cirrhosis [76–80], although some successful cases have been reported [81].

There are relatively fewer reports regarding the relevance of other common cardiac diseases in liver transplant recipients such as patent foramen ovale, arrythmias and valvular disease. A small retrospective study evaluating the influence of aymptomatic patent foramen ovale in liver transplant recipients observed a non-significant greater incidence of reperfusion syndrome, and a slightly longer stay in ICU in these patients compared to age, gender and cause of liver disease matched controls. Neither differences in morbidity nor mortality was observed [82]. The presence of valvular dysfunction has been associated to a greater requirement of vasoactive drugs and blood transfusion in the perioperative period [83]. Patients with end-stage liver disease who require cardiac valvular surgery are challenging as preLT cardiac surgery has high morbidity and mortality [80]. Some cases of successful simultaneous cardiac surgery and liver transplant have been reported [84,85], although morbidity and mortality of this double surgical procedure is most likely increased.

Cardiac evaluation in LT candidates

The outcome of liver transplant depends partially on the co-morbid conditions of the receptor, including the presence of heart disease [86]. The evaluation of the heart function in the LT candidate and the identification of high risk patients are both of utmost importance as cardiovascular complications are a leading cause of non-graft related death in the post-transplant period [34,87]. Symptoms of heart disease may be evident in some cases with florid clinical expression including pulmonary and peripheral edema, although these findings are not pathognomonic, particularly in the context of cirrhosis. However, other more subtle symptoms can also reflect chronic heart failure such as a decrease in exercise capacity or in oxygen consumption. Several tools such as the New York Heart Association (NYHA) or Framingham score [88] may be useful to identify patients with heart failure, although the clinical applicability in patients with cirrhosis may be reduced. Cardiac evaluation with electrocardiography (EKG) and echocardiography is done on a routine basis in most centers [58]. The decision for further evaluation depends on the individual characteristics and the LT center. A simplified algorithm for cardiac evaluation is shown in Fig. 2.

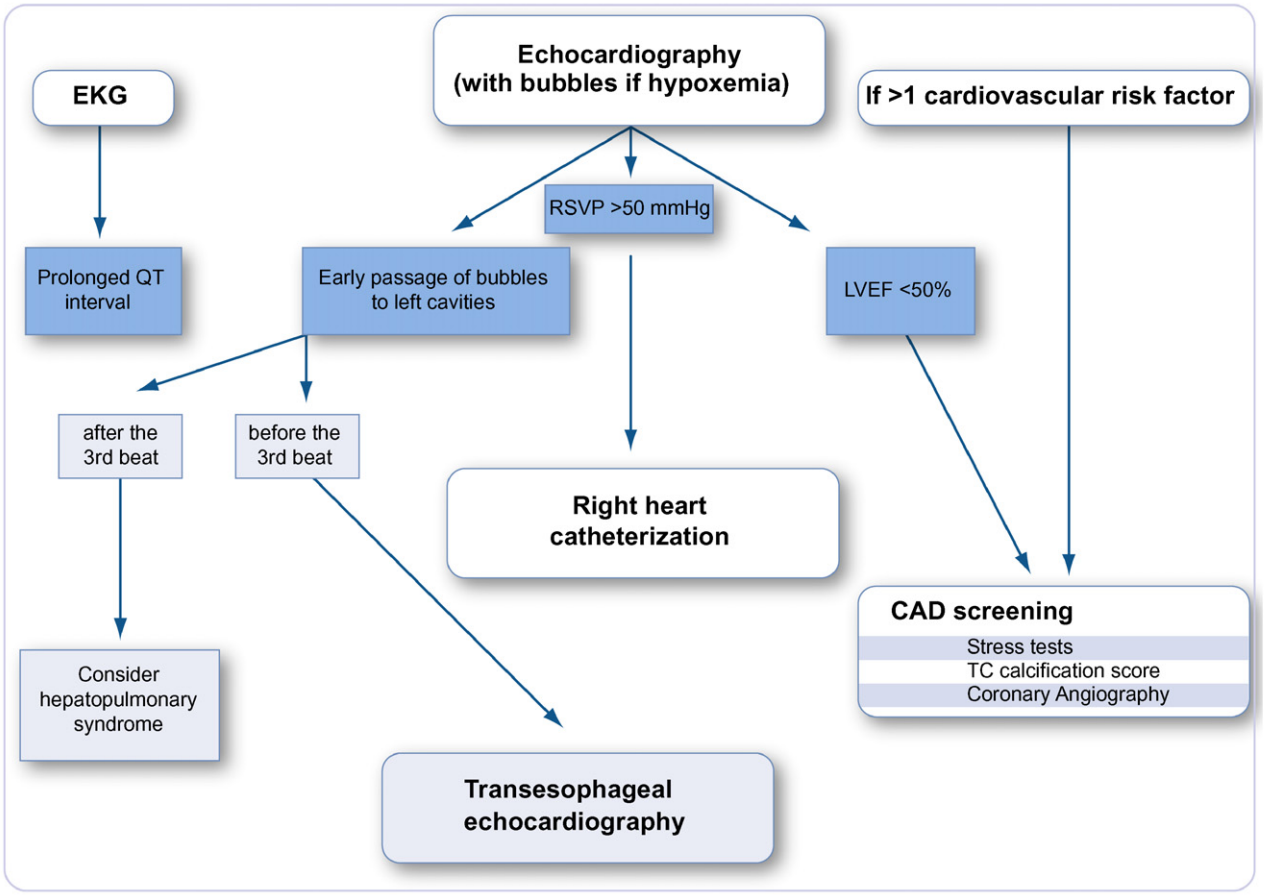

Fig. 2. Algorithm for pretransplant cardiac evaluation, taking into account the most frequently identified problem in LT candidates. Most centers perform EKG and echocardiography on a routine basis. Screening of patients with risk factors for CAD is also recommended. According to the findings in these initial examinations, further tests will be performed.

Absolute and relative cardiac contraindications for LT are difficult to establish as clinical practice varies between centers and as this decision is taken on an individual basis. When evaluating a patient, both the perioperative risk attributable to pre-existing cardiac disease and the risk associated with the long-term outcome of this disease must be considered. Patients with overt heart failure due to cardiac disease will most likely not benefit from LT. Also, there is general agreement that patients who have moderate or severe portopulmonary hypertension should not be considered for LT unless a clinical and hemodynamic response is achieved after vasodilator therapy [59,62–64]. Prognostic significance of cirrhotic cardiomyopathy remains to be determined. There are no clear recommendations about the management of CAD in LT candidates. It has been suggested that diabetic patients with CAD that is not amenable to revascularization or those patients with left ventricular dysfunction should be denied LT [89]. Patients who are finally accepted as LT candidates will benefit from a healthy lifestyle including a healthy diet and regular physical exercise.

Electrocardiography

EKG is part of the routine evaluation of the heart in LT candidates [58]. QT interval prolongation is a characteristic EKG abnormality in patients with end-stage liver disease [41–45,90]. As discussed previously, this electrophysiological abnormality is one of the typical features of cirrhotic cardiomyopathy.

Ultrasonography

(1) Echocardiography: this technique is helpful to detect structural and functional heart abnormalities that could influence the outcome of the LT and should be done on a routine basis. Many subtle changes in cardiac morphology have been described using this technique, including an increase in left and right ventricular cavity size, as well as an increased thickness of the left ventricle wall [91–95]. Additionally, if tricuspid regurgitation is detected, right ventricle systolic pressure or pulmonary artery pressure can be estimated with Doppler echocardiography. Patients who have a RVSP $\geqslant$ 50 mm Hg (an arbitrary standard cut-off) will require further tests to characterize pulmonary pressure. Although estimation of pulmonary pressure is less precise with higher values of mean pulmonary artery pressure [56,96], this technique can identify patients with moderate or severe portopulmonary hypertension with relative accuracy [56] as it has a high negative predictive value [55]. Finally, although not specifically a cardiac disease, the presence of hepatopulmonary syndrome is also evaluated by echocardiography in patients with clinical suspicion due to the presence of hypoxemia [97]. If there are doubts regarding the possible presence of intra-atrial com-

munication, transesophageal echocardiography should be performed. Although no studies have evaluated this specifically, once the patient is on the waiting list, it seems reasonable to repeat an echocardiogram on a yearly basis or whenever indicated if novel symptoms develop.

(2) *Carotid intima-media thickness:* the measurement of carotid intima-media thickness by ultrasound has been proposed as a safe and easy-to perform alternative to predict cardiovascular disease; however, it is mainly used in the research field as no studies have evaluated this measurement in pre-transplant patients [98].

Cardiac magnetic resonance imaging (MRI)

Cardiac MRI provides a detailed structural and functional evaluation of the heart, as well as tissue characterization. In the setting of hemochromatosis, cardiac MRI may be useful to evaluate the degree of iron overload [16]. In patients with familial amyloidosis, cardiac involvement can be detected by gadolinium enhanced cardiac MRI with high accuracy [99]. Furthermore, in patients with known or suspected CAD it can be used to evaluate the presence of myocardial scars and to identify viable myocardium susceptible for functional recovery after an eventual revascularization [100]. Further studies are needed to evaluate the role of cardiac MRI in the pre-transplant evaluation.

Computed tomography

The coronary artery calcification score (CACS) as measured by computerized tomography, has been proposed as an independent risk factor for CAD in non-cirrhotic patients. A recent study [101] of 101 cirrhotic patients showed a strong relationship between the CACS and a number of specific cardiovascular risk factors. In this study, the CACS revealed a high prevalence of occult coronary artery disease in patients undergoing LT assessment. However, further studies are needed in order to establish the clinical relevance of this score and its safety in patients with end stage liver disease, especially taking into account that a significant proportion of patients have impaired renal function. CACS predicts better cardiovascular disease than measurement of carotid intima media thickness by ultrasound in non-cirrhotic patients [102]. There is no data regarding the value of computed tomography coronary angiography in pre-transplant patients with suspected CAD.

Stress tests

Different stress tests have been used as part of the pre-transplant cardiac work-up (Table 3). By increasing myocardial oxygen requirements, these tests aim to unveil any subclinical imbalances between supply and demand. When the supply of oxygen is inadequate, normally due to a stenosis in the coronary arteries, ischemia will initially be detected with hypoperfusion of the myocardial tissue and lastly with wall motion abnormalities. Such alterations are detected with perfusion imaging and echocardiography, respectively. When performing stress tests, it is important to achieve the target heart rate or heart rate-blood pressure product in order to obtain conclusive results. Tests that are used in clinical practice are discussed. Other stress tests with other drugs (such as terlipressin and metariminol) or volume challenge still remain in the research field.

Exercise stress test

Exercise tests have not been extensively evaluated specifically in patients with cirrhosis. As patients with decompensated disease have a poor functional and exercise capacity, achieving target heart rates in order to have conclusive results is particularly difficult.

Dobutamine stress test

The value of the dobutamine stress test has been assessed in several studies with controversial results. With this technique, a stress is induced by the administration of the beta-1-agonist dobutamine and wall motion abnormalities were detected with

Table 3. Advantages and disadvantages of different CAD detecting tests in the context of LT candidate screening. Patients who have at least 2 risk factors for CAD should be screened. All diabetic patients with evidence of end-organ damage should be screened.

	Advantages	Disadvantages
Conventional coronary angiography	Gold standard. Possibility to treat significant lesions during the procedure.	-Difficult to establish relevance of asymptomatic moderate lesions. -Invasive procedure with arterial puncture and contrast media
Dobutamine stress echocardiography	- Does not require sophisticated equipment - Not invasive - High NPV (when the study is conclusive)	-26 to 56% studies are inconclusive as target heart rate is not achieved, due to the particularities of patients with cirrhosis
Dipiridamole or Adenosine nuclear myocardial perfusion imaging	- Detects perfusion abnormalities before wall motion abnormalities	-Requires more sophisticated equipment -Many inconclusive studies as it is difficult to achieve further vasodilation in patients with cirrhosis
Computed tomography coronary arteriography. Coronary Artery Calcification score	- Easily performed with CT - Associated to CV risk factors in cirrhosis	-Not yet validated its use in cirrhotics for identification of clinically relevant CAD

echocardiography. Although one study suggested that the dobutamine stress test was a very useful tool for the detection of CAD [69], other studies have suggested that this method is not sensitive enough to detect inducible ischemia in this group of patients [103–107]. In a prospective study [103] including 165 LT candidates undergoing dobutamine echocardiography, inducible ischemia, left ventricle (LV) dysfunction or significant valvular regurgitation was demonstrated in less than 10%; furthermore, 7% of the patients that finally underwent LT ($n = 71$) had cardiac events, that were not previously predicted. Similarly, another study showed that previous dobutamine stress echocardiography did not predict cardiovascular events in patients undergoing LT [107]. However, in this study the independent predictors for cardiovascular events were MELD score and an inconclusive dobutamine stress test (inability to achieve more than 85% of the maximum predicted heart rate). On the contrary, a conclusive negative dobutamine stress test (no inducible ischemia observed despite achieving an appropriate heart rate or heart rate-blood pressure product) had a high negative predictive value [107].

Due to chronotropic incompetence and frequent use of betablockers, between 26% and 56% of dobutamine stress test studies in patients with cirrhosis are inconclusive studies because target heart rates and/or heart rate-blood pressure products were not achieved [105–108]. One study using dobutamine stress myocardial contrast perfusion echocardiography suggested that this tool may be more useful in the evaluation of patients with advanced liver disease [109], but currently this technique remains only in the research field.

Nuclear myocardial perfusion imaging

Nuclear myocardial perfusion imaging with the administration of vasodilator drugs (such as adenosine or dipyridamole) has also demonstrated controversial results. This is possibly related to the challenges of achieving further vasodilatation in patients with a very low systemic vascular resistance at baseline [104,110–112].

Cardiac catheterization

Right heart catheterization

According to current guidelines, when pulmonary hypertension is suspected (RVSP >50 mm Hg) right heart catheterization should be performed in order to confirm the diagnosis and characterize the pressure-resistance relationship in the pulmonary artery [56,97]. Diagnosis of portopulmonary hypertension is established by the measurement of mean pulmonary artery pressure (MPAP >25 mm Hg) and pulmonary vascular resistance (>240 dyn·sec·cm^{-5}) and/or pulmonary capillary wedged pressure (<15 mm Hg). Hemodynamic characterization of pulmonary hypertension will allow one to distinguish portopulmonary hypertension from pulmonary venous hypertension. According to mean pulmonary artery pressure, portopulmonary hypertension is graded as has been previously described. Acute response to inhaled or intravenous vasodilators may help identify patients who could benefit from treatment and thereafter proceed to LT, although this strategy has not been specifically evaluated [113–116].

Coronary angiography

There is consensus about the need to perform additional testing to evaluate the presence of significant CAD in patients who have more than one cardiovascular risk factor [58], however there are no recommendations about which test should be done. Coronary angiography is the gold standard technique to evaluate the presence of CAD. Although it has a low rate of complications [117] and can allow therapeutic management of the coronary lesion, it is an invasive test, that requires potentially nephrotoxic contrast media, and no information regarding the functional behavior of the coronary artery stenosis is obtained.

Cardiopulmonary exercise testing

Several studies have demonstrated that patients with cirrhosis have a reduced aerobic capacity, which has been partially attributed to cirrhotic cardiomyopathy [118–120]. A study has described an association between aerobic capacity and 100-day survival after liver transplantation [121]. Although, it may provide interesting information, most centers do not use this method on a regular basis for evaluation of LT candidates.

Relationship between the heart and the liver during LT

LT is a significant cardiovascular stressor for the patient with cirrhosis, as it results in important changes in preload and afterload, and the sudden release of cytokines and vasoactive mediators into the systemic circulation. The greatest impairment of hemodynamic stability occurs during the clamping of the hepatic vein (which involves a considerable reduction of the amount of blood that reaches the heart) and, especially, at the time of reperfusion [5]. Post-reperfusion syndrome is defined by a drop of mean arterial blood pressure at least 30% from baseline for at least 1 min in the first 5 min after reperfusion [5]. Although the mechanisms involved in the development of this syndrome have not been fully characterized, it is attributed to the liberation of cytokines and cardiodepressive substances [122], and has been associated with high baseline levels of proinflammatory cytokines such as IL-6 [4]. It is not well established whether or not previous heart function has a role in its development.

A number of studies have suggested that a subset of patients show an abnormal cardiac response during LT. The intraoperative hemodynamic behavior of 209 patients undergoing LT for end-stage liver disease or hepatocellular carcinoma was recently evaluated by continuous monitoring of right-heart pressure [6]. Twenty-three percent of the patients had an abnormal cardiac response defined by a decrease in stroke work despite an increase in preload, measured by the pulmonary wedge capillary pressure. Patients who developed this behavior seemed to have a greater circulatory dysfunction, with lower central venous pressure and hyponatremia. Additionally, this abnormal cardiac response during LT was associated with a longer post-operative tracheal intubation time [6] Similarly, abnormal hemodynamic behavior defined by low MAP (<40 mm Hg) or high MPAP (>40 mm Hg) has been associated to negative surgical outcome defined by the presence of poor early graft function, primary graft nonfunction and death due to hemodynamic causes [123]. On the other hand, other studies that evaluated parameters obtained by transesophageal echocardiography suggest that alterations in cardiac contractility play only a minor role in the hemodynamics of LT [124,125].

Frontiers in Liver Transplantation

Relationship between the heart and the liver in the postransplantation period

Incidence of cardiovascular events in the post-transplant period

Different retrospective studies have evaluated the incidence of cardiovascular events in the post-transplant period. A retrospective study [87] of 146 liver transplants demonstrated a 3.4% rate of major cardiovascular events (defined by the presence of myocardial infarction, reversible ischemia, pulmonary edema, cardiogenic shock, symptomatic rhythm disturbances and pulmonary embolism) intra-operatively and a 23% rate during the first 6 months. Interestingly, the presence of major cardiac events was associated with a lower 5-year survival rate. Another retrospective study [34] which included 86 patients in whom pre-transplant heart disease was ruled out, detected a 7% prevalence of heart failure after LT. However, it should be underlined that pulmonary oedema may be secondary to volume overload and renal failure. Similarly, a 10% incidence of severe adverse cardiovascular events (myocardial infarction, new heart failure, asystole or unstable ventricular arrhythmia requiring acute treatment) during surgery and up to the first 4 months was described in a non-selected group of LT recipients [107]. A recent retrospective study evaluated 403 patients to identify the risk factors that predict cardiac outcomes (defined by a composite end-point of myocardial infarction or death) in the first 30 days after LT surgery. Forty-eight patients (12%) developed the end-point, and the independent risk factors that were identified were previous history of stroke, CAD, post-operative sepsis and increased interventricular septal thickness, while perioperative use of beta-blockers was a protective factor of this outcome [126]. Lastly, a case-control study evaluating the factors associated with severe left heart failure after LT has shown that the characteristics of this entity were different according to time of presentation [127]. Immediate post-operative left heart failure had no association with previous or concurrent events, while a later onset was associated with MELD score and the presence of infection. The mortality rate in these patients was very high (45%).

The incidence of post-transplant cardiac events has only been determined prospectively in one small study in which 10 out of 40 patients suffered a cardiac event (two intra-operative arrests and eight clinically significant episodes of pulmonary edema) [50]. The difference in the incidence of these cardiac events may be due to heterogeneous study populations (Table 1).

Clinical outcome of pre-transplant cardiac disease after LT

Systemic diseases can lead to cirrhosis and heart disease. The presence of previous cardiovascular disease increases the incidence of major cardiovascular events in the post-transplant setting. Although there are no studies that specifically address the natural history of cardiac disease associated with alcoholic cardiac disease or hemochromatosis after LT, presumably the prognosis will depend on the control of the original cause of both the heart and liver disease. Special effort should be made in order to provide alcoholic patients the support they need to maintain abstinence. Patients with hemochromatosis have a lower survival rate than other etiologies of liver disease, attributed to cardiac complications and infections [20]. Iron overload may recur in the postransplant period [19]. In this situation, in absence of specific studies, it seems reasonable to initiate iron depletion therapy. The metabolic syndrome is a relevant problem in the post LT setting, and this problem is enhanced in patients with pre-existing disease. These patients will require additional support and treatment in order to minimize their cardiovascular risk. Finally, after LT in familial amyloid polyneuropathy, once the metabolic defect is solved, the patient's neurological condition should at least stabilize. In studies that evaluated the cardiac outcome in patients who were transplanted for this disease, sympathetic cardiac denervation remained stable, but cardiac amyloid infiltration progressed [26,128,129].

Specific cardiac diseases in cirrhosis

(1) Hemodynamic changes in cirrhosis: 2 weeks after LT, cardiac output was reported to decrease in parallel with an increase in systemic vascular resistance and the normalization of portal hypertension [130,131]. Furthermore, at 2 months after LT, a further increase of systemic vascular resistance has been observed without changes in cardiac output [131]. Pre-transplant hemodynamic changes in Child-Pugh class A patients are less pronounced, so the normalization of hemodynamic parameters could be achieved earlier in these patients.

(2) Cirrhotic cardiomyopathy: two prospective studies have evaluated the natural history of cirrhotic cardiomyopathy after LT. In the first study, 40 patients were followed up for 3 months after LT [50] and the deterioration of diastolic function as measured by echocardiography was observed. The second study also evaluated 40 patients with echocardiography and stress radionuclide ventriculography [132], with repeat measurements 6 months after transplantation in 15 patients, and showed an improvement in wall thickness, in diastolic function and in systolic response and exercise capacity during stress. These divergent results may simply be due to the different time frame in which they were performed [133]. In addition, echocardiographic indices may be difficult to interpret given the changes in load after LT [32,33]. Improvement of electrophysiological abnormalities with a decrease in QT interval has been observed at 3 months after LT [46]. Far from being solved, the debate remains open. A recent case report describes an immediate intra-operative recovery of diastolic function suggesting underlying a metabolic inhibition of myocardial metabolism [134]. Further studies will be needed to establish the natural history of this entity.

(3) Portopulmonary hypertension: in most LT centers, patients with moderate or severe portopulmonary hypertension are not transplanted, unless they achieve an appropriate hemodynamic response with treatment. Observational studies have reported satisfactory outcomes with this approach [60]. Vasodilators should be maintained until hemodynamic impairment is resolved; normally approximately 6 months after LT. Patients with portopulmonary hypertension have a trend to have an increased requirement for ventilation and longer ICU stay [135].

(4) Cardiac disease in LT candidates: coronary artery disease (CAD): a retrospective review of the outcomes after LT has been reported in 32 patients with pre-existing CAD [136]. Of these 32 patients, CAD was managed medically in 9 patients, by percutaneous coronary intervention in one patient and surgically in 22 patients. Both the medically and surgically managed patients had approximately a 50% mortality rate at 3 years after LT. The patient who had been managed with angioplasty was alive at the end of follow-up. Currently, patients with pre-existing coronary artery disease should be evaluated on an individual basis while further studies are awaited.

De novo presentation of cardiac disease in the post-transplant period.

One of the most relevant problems in the post-transplant period is the increased cardiovascular disease risk. With improvement in long-term survival of LT recipients, the long-term effects of immunosuppression, such as hypertension, type 2 diabetes, dyslipemia, and obesity, increases the risk of cardiovascular disease. Interestingly, the prevalence of metabolic syndrome in LT recipients has been recently reported between 43% and 58%, which is far greater than the expected 24% estimated for the age and gender matched population [137]. Acute coronary syndrome and myocardial infarction in patients who had received LT ($n = 118$) has an incidence of almost 5% per year (mean follow-up 58 month), and is more frequent in patients with metabolic syndrome [138]. Another study, observed a 3-fold increase in the risk of ischemic cardiac events and a 2.5-fold increase in the risk of cardiovascular death compared to an age-matched population [139]. Cardiac muscle protectors, which are commonly used in postLT such as ACE inhibitors, spirinolactone, beta-blockers and statins may have a beneficial role in this setting.

Conclusions

The heart and the liver have a reciprocal influence in all phases of LT. In the pre-transplant period, it is of utmost relevance to evaluate the heart function of the LT candidate in order to determine the surgical risks; severe cardiac problems associated with cardiovascular risk factors should be identified, along with the etiology of the liver disease, or with the liver disease on its own. Furthermore, although the recognition of patients with silent coronary artery disease is necessary, studies are required to guide an evidence-based management of these patients. Identification of high-risk patients will help to establish the best approach for the management of their liver disease, taking into account cardiovascular risk during the LT surgery and in the post-transplant period. Even despite a careful selection of patients, cardiovascular events in the post-transplant period are frequent. Strict control of cardiovascular risk factors is encouraged.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Acknowledgements

CiberEHD is funded by the Fondo de Investigaciones Sanitarias. Funded in part by the Fundación de Investigación Médica Mutua Madrileña PI 0264/2005.

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