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Review

Cirrhotic cardiomyopathy in the pre- and post-liver transplantation phase

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ABSTRACT

Patients with advanced liver cirrhosis may develop a clinical syndrome characterized by a blunted contractile responsiveness to stress and/or altered diastolic relaxation, called "cirrhotic cardiomyopathy." This syndrome, which is initially asymptomatic, is often misdiagnosed due to the presence of symptoms that characterize other disorders present in patients with advanced liver cirrhosis, such as exercise intolerance, fatigue, and dyspnea. Stress and other conditions such as liver transplantation and transjugular intrahepatic portosystemic shunt (TIPS) may unmask this syndrome. Liver transplantation in this group of patients results in a clinical improvement and can be a cure for the cardiomyopathy. However, post-transplant prognosis depends on the identification of cirrhotics with cardiomyopathy in the pre-transplant phase; an early diagnosis of cirrhotic cardiomyopathy in the pre-transplant phase may avoid an acute onset or worsening of cardiac failure after liver transplantation. Since a preserved left ventricular ejection fraction may mask the presence of cirrhotic cardiomyopathy, the use of newer noninvasive diagnostic techniques (i.e. tissue Doppler, myocardial strain) is necessary to identify cirrhotics with this syndrome, in the pre-transplant phase. A pre-transplant treatment of heart failure in cirrhotics with cardiomyopathy improves the quality of life in this phase and reduces the complications during and immediately after liver transplantation. Since specific therapies for cirrhotic cardiomyopathy are lacking, due to the absence of a clear understanding of the pathophysiology of the cardiomyopathy, further research in this field is required.

Contents

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Introduction

Fifty years ago, after studies on a group of alcoholic cirrhotics affected by increased cardiac output and other electrocardiographic abnormalities, the profiles of a new nosological entity that, at the workshop of Montreal (2005) was termed cirrhotic cardiomyopathy, began to take shape [1]. This syndrome was originally defined as a "chronic cardiac dysfunction in patients with cirrhosis, characterized by a blunted contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities, in the absence of known cardiac disease." Cirrhotic cardiomyopathy affects both patients with portal hypertension and cirrhosis and is characterized by intrinsic alterations in myocardial function [2].

The clinical consequence is the presence of a blunted cardiac response which is initially evident only in stress conditions. Knowing whether cirrhotics awaiting liver transplant are affected by this syndrome is essential for the post-transplant prognosis. Cardiologists may be asked to help hepatologists and surgeons in the diagnosis and treatment of this syndrome before and after liver transplantation.

In this paper, we want to emphasize the importance of an early diagnosis of this syndrome in cirrhotics especially in those awaiting liver transplant, in order to avoid acute onset or worsening of cardiac failure after liver transplantation.

Epidemiology

Symptoms and signs of cirrhotic cardiomyopathy are difficult to identify since this syndrome is clinically silent until intercurrent changes in demand occur (i.e. infection, transjugular intrahepatic portosystemic shunt, transplantation). Therefore, the exact prevalence cannot be defined.

However, some information might derive from the data on the prevalence of QT interval prolongation in cirrhotics (25% in cirrhosis Child Pugh class A vs 51% in Child Pugh class B, vs 60% in Child Pugh class C); indeed, QT interval prolongation is considered to be the earliest sign of cirrhotic cardiomyopathy [1,3].

Natural history

The natural history of this syndrome is not entirely characterized and the lack of symptoms, especially in the early phase of cirrhosis, masks and delays its diagnosis that may only unmask itself during the decompensation phase [1–3].

Delaying the diagnosis of this syndrome carries unfavorable prognostic implications; therefore, an improvement in the diagnostic methods in order to early identify those patients at risk of developing this syndrome is desirable.

The presence of splanchnic arterial vasodilation, a characteristic finding of cirrhotics, offloading the left ventricle, may mask the presence of a blunted cardiac response in the initial phase of the cardiomyopathy [1].

At present there are no therapeutic guidelines with regards to the management of cirrhotic cardiomyopathy and the natural history of the disease is unknown [4]. Moreover, the treatment of cirrhosis complications, including ascites, hepatic encephalopathy, and esophageal varices, has not modified the natural history of this syndrome, whereas a significant clinical difference has been shown by transjugular intrahepatic portosystemic shunt (TIPS) and liver transplantation, as they both cause a rapid increase in venous return; which in turn favors the onset of heart failure and pulmonary hypertension that unmasks the presence of cirrhotic cardiomyopathy [1].

Clinical presentation

It is well established that cardiac function is modulated by preload and afterload. Cirrhotics are clinically volume overloaded but the concomitant splanchnic vasodilation leads to reduced vascular resistances, reduced afterload, and consequent impaired venous return. Indeed, cirrhotics are affected by low arterial pressure and impaired exercise tolerance and fatigue. To compensate for the reduced vascular resistance, a sympathetic activation occurs; this increases cardiac contractility but also stimulates renal sodium and water retention through the activation of the renin–angiotensin–aldosterone system [1]. In cirrhotics without cardiomyopathy, cardiac output is generally increased whereas, in cirrhotics with cardiomyopathy, the presence of a blunted cardiac response due to an impaired cardiac function causes a further reduction in the mean arterial pressure [1].

This effect is particularly evident during exertion in which an increased demand leads to a further reduction of the mean arterial pressure and a reduction in exercise intolerance and increased fatigue (Fig. 1).

The amount that a further reduction in systemic vascular resistance and the subsequent reduction in the cardiac response that each one contributes to worsen the symptoms is, however, difficult to establish.

An ensuing cardiomyopathy may aggravate renal hypoperfusion thus contributing to further volume overload and pulmonary congestion, a condition that severely worsens in cirrhotics following TIPS or liver transplantation.

Indeed, heart failure symptoms develop only after TIPS or liver transplantation, although most cirrhotics with advanced liver disease are already affected by the cardiomyopathy.

Cardiomyopathy affecting cirrhotics has similar but also different aspects from the common dilated cardiomyopathy that is always characterized by a low cardiac output.

In cirrhotics affected by cardiomyopathy, in the initial phases, a high-output heart failure may be also present [5,6].

Therefore, diagnostic methods may fail to reveal cardiac abnormalities in physiological conditions. A normal cardiac output on echocardiography in decompensated cirrhotics should not rule out the diagnosis of cardiomyopathy but maybe make it more likely.

Pathophysiology

A broad spectrum of cardiac abnormalities characterizes the development of cardiomyopathy in cirrhotics and, although a precise chronological sequence in which these impact on the cardiomyocytes is lacking, a pivotal role may surely be attributed to electrical abnormalities (QT-interval abnormalities, electrical and mechanical dissociation, chronotropic incompetence) due to defective K-channel function in ventricular cardiomyocytes as a result of decreased K-current density and also due to autonomic dysfunction, such as defects in the sympathetic nervous system and vagal impairment [1,7].

All these alterations, although associated with a direct impairment of cardiomyocyte function (see Table 1), are not free from the profound alterations involving the liver and its principal effector (hepatic stellate cell) during cirrhosis; this causes an exaggerated production of extracellular matrix components and vasoconstrictive mediators thus favoring mechanic and dynamic portal hypertension [8,9]. In portal hypertension conditions, the intestinal recruitment of leucocytes is delayed, the local immune response may not be able to prevent the passage of bacteria from intestinal lumen to the systemic circulation, and mesenteric lymph nodes are deranged to retain and destroy bacteria [10–12]. The logical consequence is that endotoxin or bacterial DNA may easily reach the systemic circulation, causing liver endothelial dysfunction, imbalance of the intrahepatic circulation, worsening of portal hypertension, and hemodynamic complications, as those observed in studies on cirrhotics in normal conditions and post-prandial phase [13–15].

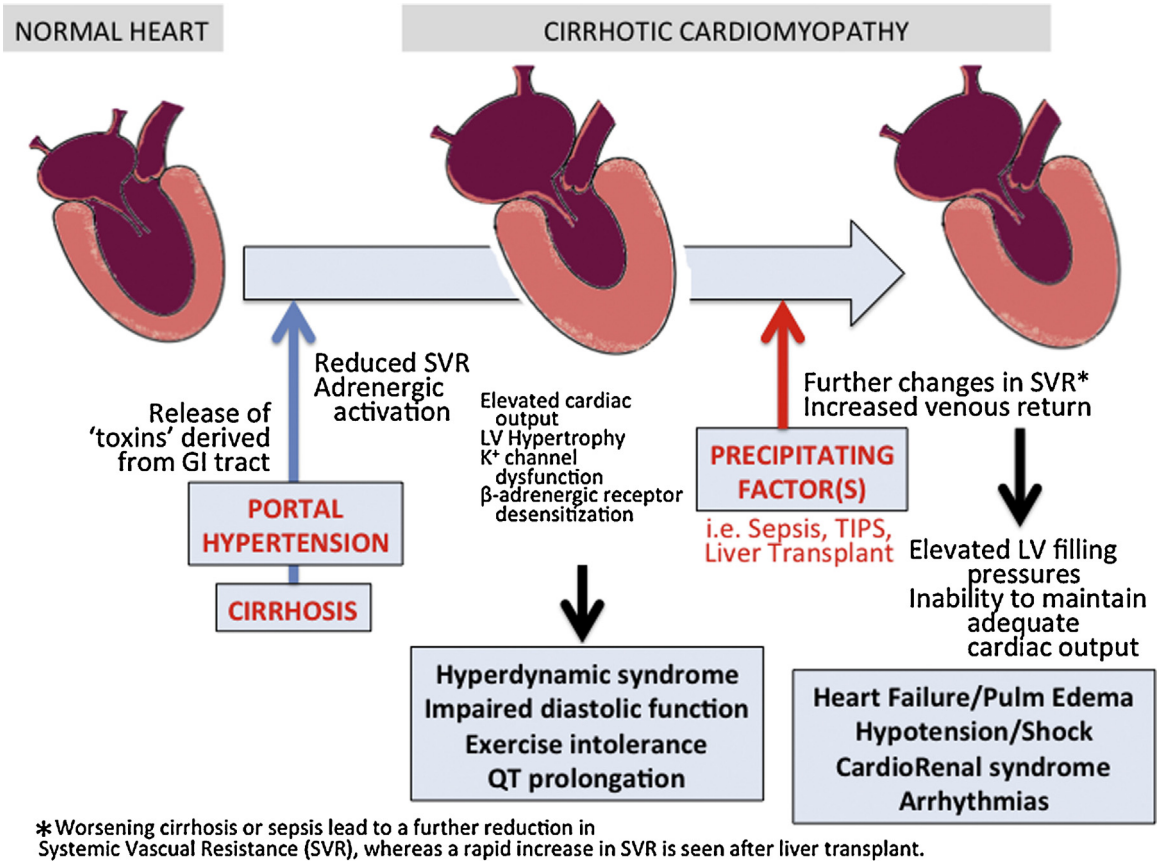

Fig. 1. Clinical pathophysiology of cirrhotic cardiomyopathy. GI, gastrointestinal; LV, left ventricular; SVR, systemic vascular resistance; TIPS, transjugular intrahepatic portosystemic shunt.

The subsequent marked peripheral arterial vasodilation produced by these alterations may be initially compensated by an increase in heart rate and cardiac output (hyperdynamic circulation through the activation of sympathetic nervous system and the renin–angiotensin–aldosterone system) but, in the late stages, this compensation may be lost by favoring a reduction of the preload (relative hypovolemia) [16,17]. As a result, the blunted cardiac response reduces renal perfusion favoring the development of hepatorenal syndrome [18].

Indeed, although short-term sympathetic overdrive increases cardiac performance, prolonged stimulation leads to the occurrence of cardiomyopathy [1].

Table 1
Pathophysiology of cardiac abnormalities in cirrhotics with cardiomyopathy.

Cardiac abnormalities	Pathophysiology
QT-interval prolongation	– K+ channel abnormalities – Sympatho adrenergic hyperactivity
Electrical and mechanical dissociation	– K+ channel abnormalities – Sympatho adrenergic hyperactivity
Diastolic dysfunction	– Increased myocardial stiffness – Left ventricular hypertrophy – Myocardial fibrosis – Changes in cardiomyocyte plasma membrane fluidity – Impaired calcium signaling in cardiomyocytes
Systolic dysfunction	– Reduced myocardial reserve – Impaired oxygen extraction (local imbalance of nitric oxide) – Alterations in cardiac energy metabolism – Negative inotropic effects of endocannabinoids – Peroxynitrite impairment production – Changes in ventricular β-adrenoceptor – Changes in ventricular muscarinic receptors

However, vascular remodeling in the conductive vessels, consisting of a decrease in the thickness and the total area of the vascular wall and in a reduction in the vessel ability to contract, may reduce the afterload, thus masking a blunted cardiac response; in this way the diagnosis of cirrhotic cardiomyopathy may be delayed [1].

Prognosis, treatment, and screening

Since cirrhosis has an overall unfavorable prognosis, only liver transplant may be the cure for cirrhosis and the associated cardiomyopathy [1].

Cirrhotics with cardiomyopathy have an impaired cardiac function and this further worsens the prognosis. Furthermore, cirrhotic cardiomyopathy is an important cause of perioperative morbidity and mortality for liver transplant recipients [4].

Initially, it may seem that medical treatment used for heart failure can be adopted also in cirrhotic cardiomyopathy; however, evidence has shown that the treatment used for common heart failure is not useful for curing cirrhotic cardiomyopathy. Angiotensin-converting enzyme inhibitors (and vasodilators in general) are not useful in conditions of severe systemic vasodilation such as those observed in cirrhotics with cardiomyopathy. However, low-dose angiotensin II receptor antagonists have demonstrated an acceptable safety profile and a positive effect on portal pressures, in patients with compensated or decompensated liver cirrhosis [19].

Beta-adrenergic blockers are usually given to cirrhotics for the prevention of recurrent variceal bleed but data on their utility in cirrhotic cardiomyopathy are lacking. However, the clear rationale for using these drugs in cirrhotics with cardiomyopathy might be their sympathetic overdrive, a key feature of the disease process. In

this way, selective beta-blockers (beta1 and beta2) without alpha-blocking activity would appear better than non-selective alpha-beta1/2 blockers, due to their ability to avoid further vasodilation. However, recent studies showed that carvedilol, a non-selective blocker that possess α-blocking activity on top of β1/β2 blockade, is well tolerated and as effective, or even more effective, than selective propranolol (selective β1/β2 blocker) in reducing portal hypertension [20,21]. As for diuretics (loop-diuretics and aldosterone antagonists) that are often given to cirrhotics with and without cardiomyopathy to treat hypervolemia, insufficient data are available on whether such treatments affect the outcome in cirrhotics with cardiomyopathy.

Despite the difficulty of diagnosing cirrhotic cardiomyopathy and obtaining results from medical treatment, there would be the need for screening cirrhotics and treating potential heart failure signs, especially prior to liver transplantation.

Indeed, after liver transplantation, rapid hemodynamic changes due to increased filling pressures may worsen a pre-existing congestive heart failure. Almost 25% of patients undergoing liver transplant have cardiovascular complications and a higher risk for postoperative pulmonary edema [22,23]. In the pre-transplant phase, screening of cirrhotic cardiomyopathy should be made in all cirrhotics, independently of their Child-Pugh-Turcotte or Model for End-Stage Liver Disease (MELD) classifications.

The investigation of cardiac function in cirrhotics awaiting liver transplant is necessary to better plan the management of heart failure immediately after transplantation. Indeed, cirrhotic cardiomyopathy is a syndrome deeply linked to the chronic liver disease as demonstrated by the fact that cardiac function improves after liver transplant [24].

Pre-transplant investigative methods

The basic concept is to persist in monitoring cardiac function in cirrhotics awaiting liver transplant since, in conditions of marked vasodilation (hyperdynamic syndrome), only the ability to increase cardiac output may avoid the post-transplant development of heart failure [25].

Unfortunately, specific recommendations for the pre-transplant assessment of liver transplant candidates are not provided by the New York Heart and the American Heart Associations, although their scores are useful means to classify heart failure in these patients; however, both have established that cirrhotics with cardiac risk factors selected for liver transplant should undergo an evaluation for cardiovascular disease [26]. Furthermore, the American Association for the Study of Liver Diseases recommends that all liver transplant candidates must undergo transthoracic echocardiography. Since, cardiac dysfunction in cirrhosis seems not to be associated with the severity of liver disease [27], both an accurate patient selection for liver transplant [28,29] and a precise investigation for cirrhotic cardiomyopathy are mandatory. Indeed, cirrhotic cardiomyopathy may influence the outcome after liver transplantation [30–32]; moreover, liver transplantation may be responsible for additional intra- and postoperative short- and long-term cardiac morbidity [33].

To date most transplant liver centers screen for cardiac characteristics required to receive a liver transplant in cirrhotics by means of electrocardiography and echocardiography.

Indeed, decompensated cirrhotics with a high degree of portal hypertension have a prolonged QT interval, due to electrolyte disturbances or the use of QT interval-prolonging drugs, that need correction [34]. Although, in normal hemodynamic conditions, echocardiography is an excellent tool to assess the presence of systolic or diastolic dysfunction, generally cirrhotics are affected by a hyperdynamic syndrome; this hemodynamic disturbance influences the cardiac load and makes an accurate evaluation of cardiac function through conventional echocardiography more difficult [34].

Although, tissue Doppler imaging (TDI) may overcome this problem by directly measuring the velocity of myocardial displacement, and assessing left ventricular filling dynamics [35], other diagnostic tools and indices may give useful information about the presence of cirrhotic cardiomyopathy, helping to stage the degree of cardiac dysfunction [36].

In Table 2, we summarize the role of diagnostic tools in the pre-transplant investigation of cirrhotic cardiomyopathy.

Special attention should be given to cirrhotics with preoperative elevated right-sided cardiac pressures, as well as older patients, that have shown a greater risk for developing heart failure after liver transplantation [37].

Optimization of therapy, using beta-blockers and diuretics (including aldosterone-antagonists), should be done in all cirrhotics with heart failure signs.

Table 2
Diagnostic methods for investigating cirrhotic cardiomyopathy.

Methods	Signs
Electrocardiogram	– Prolonged QT interval
Exercise test	– Reduced exercise tolerance
Cardiopulmonary exercise test	– Alteration of aerobic capacity (peak VO_2) or ventilatory efficiency (VE/VCO_2 or OUES)
Six-minute walk test	– Reduced tolerance
Echocardiography	– Systolic dysfunction (LVEF < 55%) – Diastolic dysfunction – Left ventricular hypertrophy – Diastolic dysfunction (mean E/E' index > 10)
Exercise or dobutamine stress echocardiography	– Reduced contractile reserve
Magnetic resonance	– Systolic dysfunction (LVEF < 55%) – Diastolic dysfunction (peak filling rate) – Left ventricular hypertrophy
BNP/NT-proBNP	– Elevated levels

A wave, peak late atrial filling velocity (A, $cm\,s^{-1}$); BNP, brain natriuretic peptide; EDT, E wave deceleration time (m/s); E wave, peak early filling velocity (E, $cm\,s^{-1}$); LVEF, left ventricular ejection fraction; OUES, oxygen uptake efficiency slope; proBNP, prohormone brain natriuretic peptide; VE, ventilator efficiency; VE/VCO_2, minute ventilation/carbon dioxide production; VO_2, oxygen volume (oxygen consumption); VCO_2, carbon dioxide production.

Post-transplant phase

Immediately after liver transplantation, there is a significant stress on the cardiovascular system, with changes in preload and afterload due to fluid infusion and clamping of the hepatic vein [38]. The heart of patients with cirrhotic cardiomyopathy is unable to manage this situation, thus unmasking an underlying myocardial contractile responsiveness.

In this situation, prompt fluid management and cardiac monitoring through transesophageal echocardiography and/or pulmonary artery catheterization, are needed. Due to liver denervation, transplant cirrhotics have been demonstrated to have a different response to propranolol administration compared to that of nontransplant cirrhotics [39]. Indeed, they showed lower baseline hepatic vein pressure gradient (HVPG) values but similar HVPG responses to propranolol infusions compared to nontransplant cirrhotics [39]. Conversely to nontransplant cirrhotics, in transplant cirrhotics, propranolol increased the systemic vascular resistance and arterial pressure [39].

Conflicting results emerge on the time necessary to restore hemodynamics in the post-transplant phase, but general accordance exists on the fact that liver transplantation results in correction of portal hypertension and reversal of hyperdynamic syndrome [40,41].

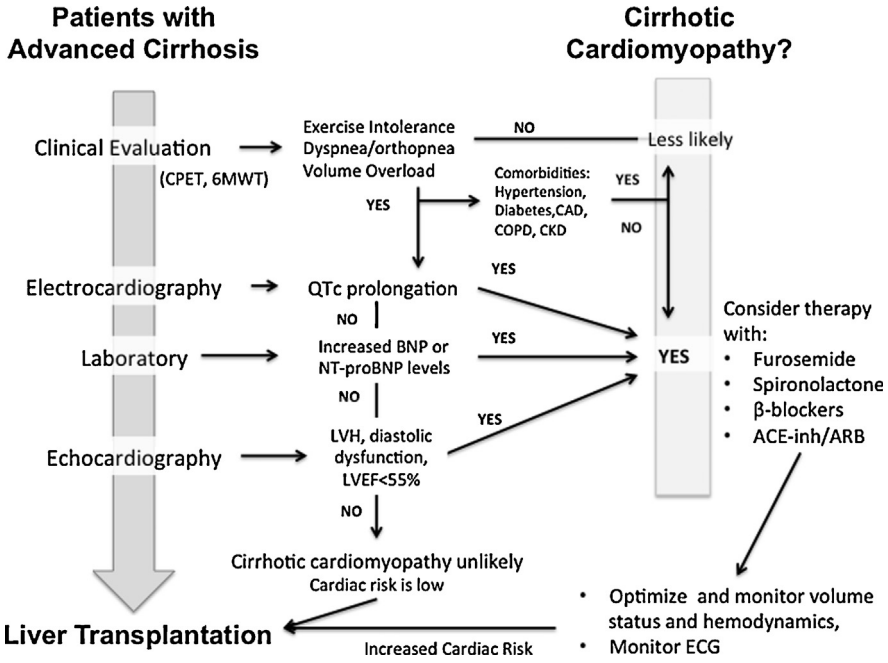

Fig. 2. Diagnostic algorithm and treatment for patients with cirrhotic cardiomyopathy awaiting liver transplantation. ACE-inh, angiotensin-converting enzyme inhibitors; BNP, brain natriuretic peptide; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPET, cardio pulmonary exercise test; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NT-proBNP, N terminal prohormone brain natriuretic peptide; 6MWT, six-minute walk test.

A high prevalence of subclinical complications in post-transplant phase is reported, due to the lack of accurate pretransplant investigations or to the fact that none of these would be able to sufficiently predict postoperative cardiac complications [42].

Two studies, investigating the cardiac function for up to 3 months after liver transplant in patients, demonstrated in the first case a diastolic function deterioration, and in the second case, a ventricular dysfunction [43,44].

Another study showed that increased B-type natriuretic peptide levels in the post-transplant phase returned to normal values after 1 week [45].

A further study demonstrated a restoration in the QT interval time after 3 months from liver transplantation [46]. A significant improvement in wall thickness, in diastolic function, in the systolic response, and exercise capacity during stress was observed after 6 months from liver transplant [24]. Of value, the current opinion is that cardiac dysfunction may last from a minimum of a few days until a period of 6 months [47]. Clinical management of cirrhotic cardiomyopathy in the pre-transplant phase, during, and after liver transplant is crucial to assure a good prognosis. Overall, these studies have their own limitations, but they all consistently demonstrate an improvement in cardiac performance after liver transplant, thus establishing that transplantation may be the cure for cirrhotic cardiomyopathy.

Conclusions

Early clinical and diagnostic investigations to identify signs of cardiomyopathy in cirrhotics undergoing liver transplant are mandatory to avoid the worsening of cardiovascular hemodynamics in the post-transplant phase.

Here, we propose a diagnostic algorithm to guide clinicians in their daily practice (Fig. 2).

Due to the reversal of the hyperdynamic syndrome following liver transplant, the prognosis may be good provided we prevent the development of heart failure, which remains the most common complication in patients receiving a liver transplant and is therefore a cause for prolonged hospitalization and death. Although the American College of Cardiology/American Heart Association has not given specific strategies to manage cirrhotic cardiomyopathy, we recommend to follow the heart failure guidelines for the treatment of cirrhotics affected by cardiomyopathy, with consideration for special conditions in patients with markedly reduced systemic vascular resistance [48].

Advances in research will hopefully envisage more specific therapeutic strategies, so that improved prognostic perspectives may be assured to cirrhotics, during and following liver transplantation.

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Disclosures

All authors declare that there is no personal or potential financial interest and no conflict of interest.

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