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Review

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

Enrico Maria Zardi (MD, PhD)[a,*], Domenico Maria Zardi (MD)[b], Diana Chin (MD)[b], Chiara Sonnino (MD)[c], Aldo Dobrina (MD)[d], Antonio Abbate (MD)[c]

[a] Department of Clinical Medicine, University Campus Bio-Medico, Rome, Italy
[b] Department of Cardiology, II School of Medicine, University La Sapienza, Ospedale Sant'Andrea, Rome, Italy
[c] Virginia Commonwealth University-VCU Pauley Heart Center, Richmond, VA, USA
[d] Department of Physiology and Pathology, University of Trieste, Trieste, Italy

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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

* Corresponding author at: Department of Clinical Medicine, Alvaro del Portillo 200, 00128 Rome, Italy. Tel.: +39 06225411455; fax: +39 06225411456.
E-mail address: e.zardi@unicampus.it (E.M. Zardi).

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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].