Cardiac involvement in patients with cirrhosis: a focus on clinical features and diagnosis

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Cirrhotic heart has been traditionally considered protected from cardiovascular disease, even if a large amount of literature has recently shown that patients affected by chronic liver disease are exposed to cardiovascular events, as well. Since the first recognition of cardiac involvement in cirrhosis, all published studies explain that decompensated cirrhotic patients suffer from haemodynamic changes, currently known as hyperdynamic syndrome, which finally lead to cirrhotic cardiomyopathy. This is defined by the presence of a subclinical systolic dysfunction unmasked under stress conditions, impaired diastolic function and electrophysiological abnormalities, in the absence of any known cardiac disease. In this review, we will discuss the clinical and diagnostic features of this condition, the prevalence of associated comorbidities, echocardiographic, electrocardiographic and cardiac magnetic resonance hallmarks and the possible diagnostic role of serum biomarkers.

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Introduction

Along with haemodymanic changes usual of cirrhosis, vasodilatation is the vascular modification finally leading to multiorgan involvement, including the heart.[1] In fact, splanchnic vasodilatation is the first pathophysiological stage of clinical complications of cirrhosis, while portal hypertension and its sequelae (oesophageal or gastric varices, ascites, spontaneous bacterial peritonitis) are causes of admission to the hospital, worsening of clinical conditions and death.[2] Some other complications, involving more organs and systems, such as hepatic encephalopathy, hepato-renal syndrome and pulmonary involvement, which represent widespread functional consequences of hyperdynamic syndrome, have been deeply examined in a comprehensive review,[2,3] and thus will not be debated here, also considering that specific guidelines have been already developed for their diagnosis and management.[4] Cardiovascular dysfunction in cirrhotic patients has been revealed since 1953, when Kowalsky and Abelmann[5] described an impaired contractility function in patients with alcoholic cirrhosis. However, about 50 years later, the cardiac involvement of cirrhosis has been characterized and defined as cirrhotic cardiomyopathy.[6] Commonly, cardiac dysfunction develops as a subclinical condition, being evident only in certain situations or during stressing procedures, such as large volume paracentesis, transjugular intrahepatic portal shunt (TIPS) insertion and liver transplantation. Recently, different cohort studies have shown a high incidence of cardiovascular mortality and morbidity in cirrhotic patients,[7–9] and moreover, a high prevalence of asymptomatic coronary artery disease (CAD) has been displayed by cirrhotic patient candidates for transplantation.[10] Therefore, in this review, we aimed to clearly define the clinical features and diagnosis of cardiovascular dysfunction occurring in cirrhotic patients, the prevalence of associated comorbidities, echocardiographic, electrocardiographic and cardiac magnetic resonance hallmarks and the possible diagnostic role of serum biomarkers.

Cirrhotic cardiomyopathy

Patients with advanced cirrhosis are characterized by a hyperdynamic circulatory state, revealed by raised cardiac output (CO), heart rate (HR) and blood volume, reduced systemic vascular resistance and low, normal or decreased blood arterial pressure.[1,5,11] The hyperdynamic syndrome defined above is responsible of the cardiovascular complications finally leading to cirrhotic cardiomyopathy. Prevalence of cirrhotic cardiomyopathy is unknown, because diagnosis is difficult and cardiac function at rest is usually normal. Most patients are diagnosed during the ascitic phase of the liver disease; when following the splanchnic vasodilation and low vascular resistance, the CO is increased. Patients remain asymptomatic for a long time (many years), because the arterial vasodilation due to reduced vascular peripheral resistances determines afterload reduction, masking

the cardiac dysfunction. Baseline CO is maximally increased and it cannot further improve during stress conditions. Therefore, during stressing procedures that acutely increase the cardiac preload, cirrhotic heart is unable to improve systolic function and cardiac failure becomes evident. Worsening of cardiac function after liver transplantation, however, resolves briefly within 6 months, and hyperdynamic circulation disappears.[6,12] Until now, there are no standardized criteria for the diagnosis of cirrhotic cardiomyopathy. It should be suspected in patients with end-stage liver disease, and the clinical suspicion can be confirmed by physical stress (physical exercise) or pharmacological test (dobutamine stress echocardiography). Echocardiography is a useful diagnostic tool to detect diastolic dysfunction and subclinical impairment of systolic function. Common diagnostic features are also electrophysiological abnormalities such as long QT, usually revealed at 12-lead ECG. Finally, cardiovascular magnetic nuclear resonance (CMNR) is a promising method to screen cirrhotic patients at risk of developing congestive heart failure, in addition to the use of cardiac serum biomarkers.

Pathogenesis

It has been hypothesized that several mechanisms may be responsible for the specific cardiac dysfunction observed in cirrhosis: autonomic dysfunction, nitric oxide, carbon monoxide and endocannabinoids. In patients with cirrhosis, a reduced response to beta-adrenergic stimulation and consequently a blunted inotropic and chronotropic response has been clearly documented. In fact, HR does not properly increase under stimulation (stress, drugs and so on) and the baroreflex function is altered, with a tendency to orthostatic hypotension.[12] A possible explanation could be the downregulation of the β-adrenergic receptors secondary to long-term exposure to increased circulating catecholamine levels.[13] Another explanation could be the impaired cell membrane fluidity, observed in cirrhotic patients, which could interfere with a correct function of receptors and signal transduction pathway.[14] The production of nitric oxide is increased in cirrhotic patients, probably due to elevated level of proinflammatory cytokine and gut-derived bacterial endotoxins. This is a potent vasodilator and plays a key role in the peripheral vasodilation and hyperdynamic state proper of cirrhosis.[15,16] Moreover, nitric oxide is able to reduce cardiac contractility, inhibiting the β-adrenergic stimulation of cAMP and activating the guanylate–cyclase mediated cGMP production, which is able to block the extracellular calcium influx.[12,17] Carbon monoxide, a degradation product of heme, also has a role in cardiac dysfunction, in cirrhosis, via activation of guanylate–cyclase and production of cGMP.[18,19] Production of endogenous cannabinoids (such as anandamide) is increased in experimental models of cirrhotic rats, probably as a result of bacterial endotoxins.[20,21] Endogenous cannabinoids are involved in vasodilation, induction of portal hypertension and reduction of cardiac contraction. Endocannabinoids may induce systemic vasodilation probably activating the G-protein coupled inhibitory receptors (CB1 and CB2) in the vascular endothelium.[22,23] Moreover, they can impair microcirculation of the liver and favour the development of portal hypertension and hyperdynamic circulation through the induction of apoptosis in hepatic stellate cells.[24] Finally, the negative inotropic effect on cardiac contractility could be related to interference with the G-protein coupled inhibitory receptors CB1.[25] Figure 1 summarizes mechanisms of cardiovascular dysfunction in cirrhosis.

Associated comorbidities in cirrhotic patients

For many years, it has been believed that cirrhotic patients could be protected against cardiovascular disease, thanks to haemostatic defects, such as coagulation impairment and low platelet count, low cholesterol levels and low blood pressure. However, two recent published cohort studies carried out in cirrhotic patients undergoing evaluation for liver transplantation reported a high prevalence of asymptomatic CAD and coronary artery calcification.[26,27] Moreover, traditional risk factors have become common in patients suffering from cirrhosis because of increased survival rates and this probably might explain the reported prevalence of CAD in this clinical setting. Actually, age, male sex, dyslipidemia, smoking habits and diabetes are independent risk factors for CAD in cirrhotic patients candidates for liver transplant.[28] In a large retrospective study of 1183 individuals with cirrhosis of different causes, without any history of chest pain or CAD, who underwent computerized angiography as part of a preliver transplant cardiac work-up, the prevalence of silent CAD was around 8%, and conventional risk factors were reported as follows: 33.5% hypertension, 24.2% diabetes and 1.1% hyperlipidemia; BMI and cholesterol levels are usually lower in patients with cirrhosis than in those without.[10]

However, it is not easy to understand the amount of cardiac dysfunction really attributable to haemodynamic changes of cirrhosis and that induced by coexisting and interfering conditions. In fact, chronic liver disease patients usually present some condition, such as smoking, hypertension or diabetes, and it is well known that all the above-mentioned disorders represent cardiovascular risk factors. Nevertheless, the cause of chronic liver disease *per se* could be the cause of cardiomyopathy (e.g. alcohol), and accordingly, heavy drinkers may suffer from heart failure before a significant liver damage has occurred. In this regard, in the study by An *et al.*,[10] subgroup analysis showed that alcoholic cirrhosis was an independent risk factor, unlike hepatitis virus related disease. Therefore, the real impact of cardiovascular risk in cirrhosis is still undefined; at this time, no specific guidelines have been developed in this clinical setting and physicians follow the general rules for the preoperative assessment of

Fig. 1
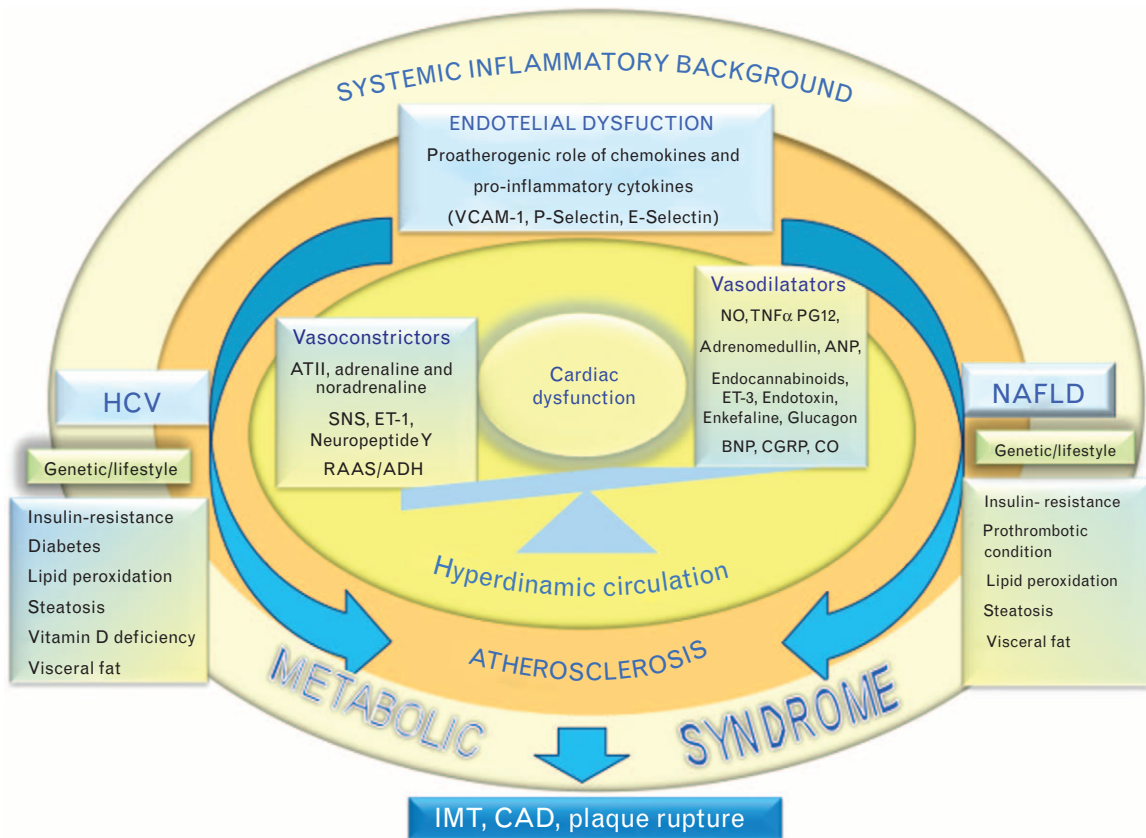
Main pathogenetic mechanisms of cardiovascular dysfunction in cirrhosis. ADH, vasopressin; ANP, atrial natriuretic peptide; ATII, angiotensin II; BNP, brain natriuretic peptide; CGRP, calcitonin gene related peptide; CO, carbon monoxide; ET-1, endothelin-1; ET-3, endothelin-3; NAFLD, nonalcholic fatty liver disease; NO, nitric oxide; PGI2, prostaglandin I2; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system; TNF-α, tumour necrosis factor alpha; VCAM, vascular cell adhesion molecule.

noncardiac surgery,[29] always becoming more important to identify novel and accurate scores to evaluate cirrhotic patients, with cardiovascular risk factors or presence of CAD.

Another question considers the hepatitis C virus (HCV)-related cirrhosis. It has been shown that there are different potential mechanisms linking HCV infection to cardiovascular alteration. The question raised is whether the HCV *per se* or through induction of metabolic disorders such as insulin resistance, liver steatosis and diabetes[30] and/or inflammatory conditions [releasing of toxic free fatty acids and proinflammatory cytokines, such as tumour necrosis factor-a (TNF-*a*) and interleukin (IL)-6] could be associated with increased cardiovascular risk.[31] In fact, the HCV chronically infected patients, although they are usually characterized by a favourable lipoprotein profile (reduced levels of very low density lipoprotein and very low density lipoprotein cholesterol), show a higher prevalence of carotid atherosclerosis.[32] In addition to the conventional cardiovascular risks factors, other metabolic alterations can contribute to the high

cardiovascular mortality in this clinical setting: vitamin D deficiency and high industrial fructose consumption.[33–35] Therefore, according to a recently published review, HCV is able to directly and indirectly interfere with glucose and lipid metabolism, resulting in a high prevalence of insulin resistance, hyperglycaemia and diabetes; these factors, together with genetic background and lifestyle, work synergically in increasing cardiovascular risk of HCV-infected patients.[36]

Atherosclerotic plaque is the final step of inflammatory process, whose initial phases are expressed by 'endothelial dysfunction', which is considered one of the earliest steps of atherogenesis. Several studies suggested that non inflammatory liver disease (NAFLD), the common cause of liver disease in Western countries, could be considered the hepatic manifestation of metabolic syndrome.[37] Metabolic syndrome represents a condition notoriously associated with atherosclerosis and some authors reported a precise relationship between NAFLD and cardiovascular risk especially among patients with metabolic syndrome.[38] In a recent review, Ciccone *et al.*[39] stressed the link between

liver disease and endothelial dysfunction on the basis of the common inflammatory nature of both diseases. Particularly, NAFLD is associated with increased CAD prevalence[40,41] and a worse prognosis.[42] Furthermore, the likelihood of coronary multivessel involvement is higher in patients with NAFLD than in controls and the Gensini score is higher in patients with NAFLD.[43] Finally, it could be interesting to exclude the presence of anatomical variation in internal carotid artery (i.e. dolichocarotid) linked to aging or chronic disease such as atherosclerosis and hypertension[44] and potential causes of cerebrovascular or cardiovascular events. However, literature data suggest that NAFLD is linked to cardiovascular risk independently of metabolic syndrome, and therefore, NAFLD is involved in the pathogenesis of cardiovascular disease.[45–47] Patient's comorbidity burden has been recently quantified in a single number by a comorbidity score system, the Cir-Com score.[48] It is considered simpler than the Charlson Index, because it takes into account only nine items. Thus, as comorbidities (diabetes, cardiovascular disease, lung or kidney disease, smoking and so on) are common in these patients, a better understanding of interaction between a single comorbidity and cirrhosis will improve our knowledge.

Echocardiographic characteristics

Systolic function in the majority of cirrhotic patients has been traditionally considered normal at rest. Left ventricular ejection fraction (LVEF), measured by conventional two-dimensional (2D) echocardiography, is the most common method for quantifying left ventricular function. However, this method is not sensitive enough to detect latent myocardial dysfunction. Moreover, in the presence of volume overload, LVEF does not reliably express contractility.

Pulsed Doppler analysis can help to identify subtle systolic alteration, even at rest. In fact, in cirrhotic patients, preejection period (PEP) is decreased and left ventricular ejection time (LVET) is prolonged; consequently, the ratio between PEP and LVET is decreased. In this way, the duration of mechanical systole remains constant, but left ventricular ejection period takes a larger percentage of the time interval. This observation suggests, in patients with chronic liver disease,[49] the existence of an abnormal electromechanical coupling rather than a true ventricular mechanical failure.[50] In addition, reduction of peripheral resistance and, thus decrease of arterial elastance, in cirrhotic patients involves an abnormal ventricular arterial coupling and reduced cardiac efficiency.

Tissue Doppler echocardiography enables the assessment of the deformation of longitudinal fibres revealing early alterations of myocardial function in cirrhosis even in the absence of a significant overload for the heart. Kazankov et al.[51] found, compared with healthy controls, reduced S wave value at Tissue Doppler analysis in cirrhotic patients that is suggestive of reduced systolic longitudinal function (see Fig. 2).

Speckle tracking echocardiography, which objectively measures intrinsic deformation of myocardial fibres, is not influenced by volume load condition and is more sensitive and accurate to detect subtle systolic dysfunction. Peak systolic longitudinal strain is reduced at rest, in cirrhotic patients compared with controls with similar ejection fraction. Conversely, circumferential shortening, during the ventricular systole, is augmented as a compensatory mechanism.[52,53]

Systolic dysfunction becomes evident in cirrhotics, during exercise or stress. In fact, under these conditions, ejection fraction, CO and HR do not rise as expected. This could explain the possible occurrence of acute pulmonary oedema and congestive heart failure following stressing procedures that suddenly increase blood flow to the heart chambers. A pharmacological (dobutamine) stress test can unmask a latent cardiac dysfunction in cirrhotic patients.[54] Latent cardiac dysfunction was defined as a decrease of less than 10% in left ventricular end-diastolic volume, a decrease of less than 20% in end-systolic volume and an increase of less than 10% in LVEF at peak dobutamine infusion (40 μg/kg/min). Donovan et al.[55] reported that a preoperative dobutamine stress echocardiography revealed ischemia in 11 out of 165 patients (7%), five of whom had resting wall motion abnormalities, while 148 patients (89%) had normal resting studies and no ischemia with dobutamine. A negative dobutamine stress echocardiogram was useful in excluding patients at risk for perioperative cardiac events related to obstructive CAD.[55]

Diastolic dysfunction is proper of cirrhotic cardiomyopathy as it has been documented by several studies.[56,57] The most frequent diastolic alteration is first-degree diastolic dysfunction, characterized by reduced early diastolic ventricular filling and increased atrial filling (E/A <1), prolonged isovolumic relaxation time (IVRT >80 ms) and deceleration time (>200 ms), which represent increased resistance to ventricular inflow (Fig. 2). The presence of enlarged left atrium (volume >34 ml/mq) is not a diagnostic criterion per se, but rather a supportive one, due to the presence of volume overload in cirrhotic patients.[58] Many studies documented left atrium enlargement in cirrhotic cardiomyopathy, as well as mild dilatation of end-diastolic and end-systolic left ventricle volumes.[59]

A key element to diagnose diastolic dysfunction is the measurement of a reduced E' velocity, at the site of mitral annulus, by Tissue Doppler (septal <8 cm/s, lateral <10 cm/s)[60] (see Fig. 2). Diastolic filling pressure may be esteemed by the E/E' ratio (E wave measured by pulsed Doppler of mitral inflow and E' wave measured with Tissue Doppler at the site of mitral annulus).[60] Kazankov et al.[51] reported substantial diastolic myocardial

Fig. 2
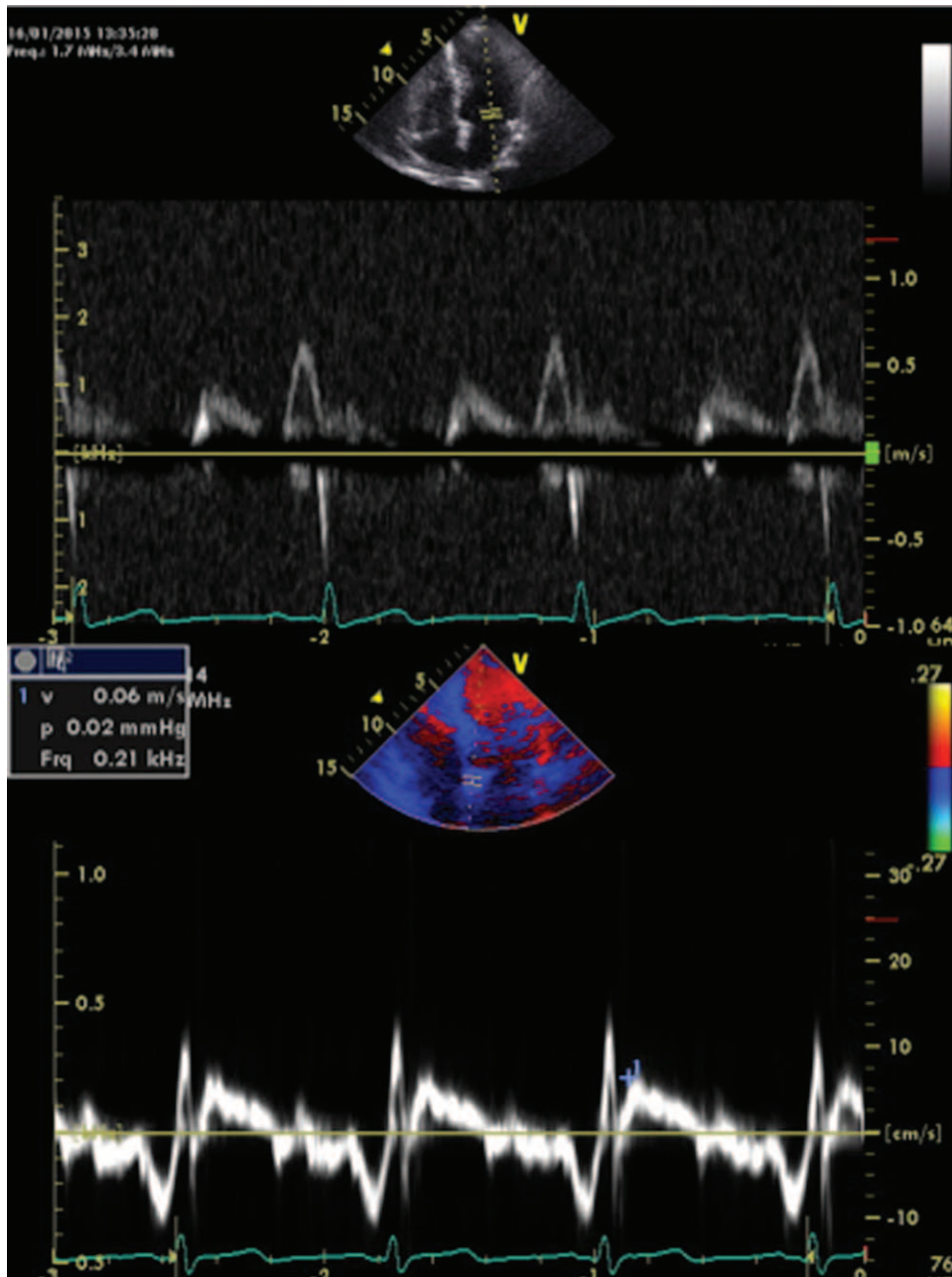
Echocardiographic study. Transmitral flow pattern (upper panel) showing E/A ratio <1 and Tissue Doppler recorded at the site of mitral annulus (lower panel) showing reduction of E' and S wave (<8 cm/s), in a patient with cirrhotic cardiomyopathy.

dysfunction during rest, by Tissue Doppler imaging, in cirrhotic patients. Woo *et al.*[61] reported increased E/E' ratio in cirrhotic patients. The pathophysiological background of the diastolic dysfunction in cirrhosis is an increased stiffness of the myocardial wall, most likely caused by histological alteration such as mild myocardial hypertrophy, fibrosis and subendothelial oedema.[62]

There is experimental as well as clinical evidence that increased sodium retention can modulate cardiac mass,

leading mainly to concentric hypertrophy; however, the mechanism by which it occurs is not clear, probably interfering with cardiac sympathetic activity and renin angiotensin system (RAS).[63,64] Sodium induces changes in cardiac norepinephrine and receptor characteristics, thus leading to the hypothesis that it can influence cardiac sympathetic activity. However, in experimental studies, the lack of an increase in left ventricular norepinephrine turnover and tyrosine hydroxylase activity suggests that the hypertrophy is not mediated through

Table 1 Diagnostic features of cirrhotic cardiomyopathy

Echocardiography	Systolic function:
	Nearly normal EF
	↓PEP; ↑LVET; ↓PEP/LVET
	Tissue Doppler: ↓ S wave
	Diastolic function:
	↓E/A (<1)
	↑IVRT (>80 ms), ↑ DT (>200 ms)
	(rarely possible higher degree of diastolic dysfunction)
	↑E/E'
	2D: LA enlargement
	Possible: ↑ wall thickness
	and mild LV dilation
	Stress echo: little increase of CO, and EF
ECG	Prolonged QTc
	fragmentation of QRS
CMR	LGE patchy distribution
Biomarkers	↑ BNP and NT-proBNP
	Possible ↑ cTNI

↑, Increased; ↓, Reduction; BNP, brain natriuretic peptide; CO, cardiac output; cTNI, cardiac troponin; DT, deceleration time; EF, ejection fraction; IVRT, isovolumic relaxation time; LA, left atrium; LV, left ventricle; LVET, left ventricular ejection time; PEP, pre-ejection period.

increased cardiac neuronal sympathetic activity.[63] The mechanical stretch due to volume overload activates the intracardiac RAS and this can trigger the intracardiac production of angiotensin II (Ang II).[65] Binding of Ang II to its angiotensin type1 (AT1) receptors, in the myocardium, activates a cascade of intracellular events promoting cardiomyocytes hypertrophy, via the protein kinase cascade and extracellular matrix production.[66] Moreover, growth hormones for cardiomyocytes, such as endothelin and norepinephrine, which are hugely present, especially in decompensated cirrhosis, can cause cardiac hypertrophy even in the absence of stretch.[67,68] A recent study assessing the role of NF-kB in mediating systolic dysfunction in cirrhosis also showed an improvement of diastolic relaxation in cardiomyocytes when its inhibitors blocked NF-kB activity, with a reduction in TNF-α expression.[69] This suggests that an inflammatory micro-environment could be partly responsible for the diastolic dysfunction in cirrhosis, but the exact mechanism with which TNF-α affects diastolic dysfunction has not been yet elucidated. However, Merli et al.[70] did not identify an association between severity of liver disease and cardiac dysfunction. On the other side, individuals with a thicker ventricle and more severe diastolic dysfunction were more likely to have heart failure after liver transplantation.[57] Diastolic function tends to return to normal 6–12 months after a liver transplant.[71,72] Table 1 summarizes the main echocardiographic abnormalities in cirrhotic cardiomyopathy.

## Electrical abnormalities

Electrocardiographic abnormalities may represent an early manifestation of cardiac involvement in patients with liver cirrhosis. Many studies report an impairment of electric ventricular recovery, which can be easily revealed by measuring QT interval. The QT interval prolongation is traditionally considered a marker of arrhythmic risk in the general population.[73–75] Although QT interval prolongation is the most frequent ECG abnormality in the cirrhotic heart, life-threatening arrhythmias are generally uncommon.[12] Patient with cirrhotic cardiomyopathy may have a prolonged QTc (QT corrected for HR); the magnitude of QT interval prolongation could be related to the severity of liver disease.[12,76] Nowadays, the prolongation of QT interval is one of the diagnostic criteria of cirrhotic cardiomyopathy. Figure 3 shows an ECG with QTc lengthening in a patient with cirrhosis.

Several pathogenic mechanisms are responsible for the ventricular recovery impairment observed in cirrhotic patients, such as electrolyte imbalance or changes in sympathetic activity. Altered cardiomyocyte membrane fluidity, increased myocardial fibrosis, cardiomyocyte hypertrophy and ion channel defects are also responsible for the ventricular recovery impairment. In this regard, some authors reported alterations of conductance properties of K+ and Ca++ channels and abnormalities of ionic currents in various cells in experimental and human cirrhosis.[77–79] Moreover, various toxins that are elevated in cirrhosis can contribute to ion channel disturbance, widening of the QRS complex and consequently prolonging QT intervals.[6,12] Some authors[80,81] evaluated the influence of vasoactive peptides on prolonged QT interval. They reported that the prolonged QT is related to liver dysfunction and presence of portal hypertension, but not to the amount of vasoconstrictor (ET-1) or vasodilator (CGRP, ET-3) circulating peptides. However, the QT interval has been found prolonged after TIPS insertion, which means that porto-systemic shunting may play a role in its determinism.[82] QT prolongation is present either in alcoholic or nonalcoholic cirrhosis. The impact of the specific cirrhosis cause in the genesis of ventricular repolarization alterations is controversial. In the study of Bernardi et al.,[83] the prevalence of QT interval prolongation did not differ between patients with alcohol-related cirrhosis and those with the postviral liver disease. By contrast, Bal and Thuluvath[76] reported that the prolonged QTc was a more common finding in patients with alcoholic cirrhosis (60%) than in nonalcoholic ones (35%), and that alcoholic cirrhosis was an independent predictor of QT interval prolongation. Other studies emphasize the role of drugs potentially linked to QT interval lengthening, showing a higher risk of sudden cardiac death in individuals with cirrhosis during treatment with drugs, such as neuroleptics.[84] More recently, Genovesi et al.[82] carried out a study aiming to assess the determinants of QT interval prolongation in cirrhotic patients, evaluating the 24-h mean QTc intervals, the slope of the regression line QT/RR, HR variability (HRVHR variability), plasma calcium and potassium concentration and hepatic venous pressure gradient (HVPG). They showed that there was a significant correlation between QTc and hepatic venous pressure gradient. Further, they also showed that patients

Fig. 3
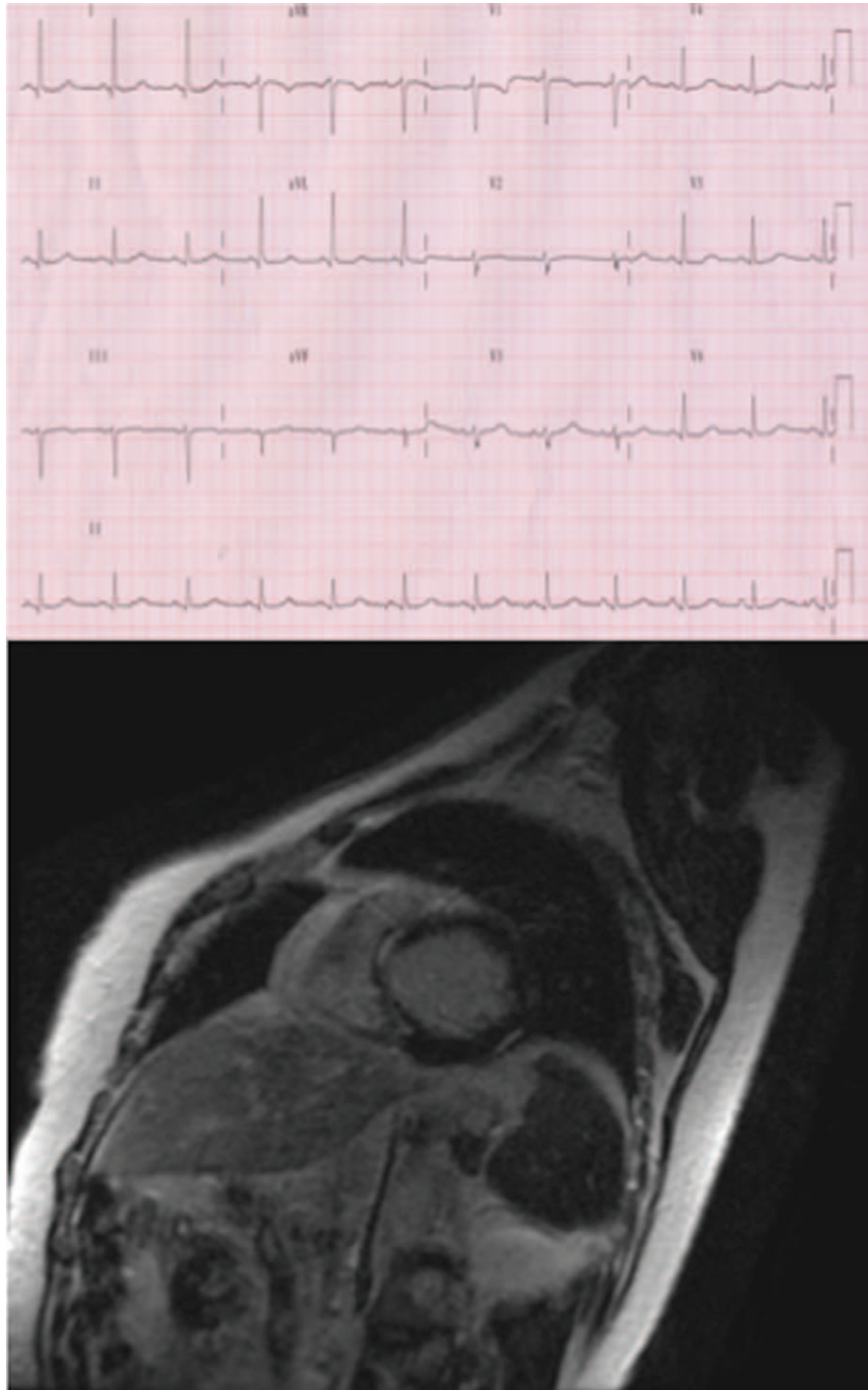
ECG and cardiac magnetic resonance. Upper panel: ECG showing mild QTc lengthening (447 ms). Lower panel: CMR study showing a case of LGE patchy distribution.

with alcohol-related cirrhosis presented QTc prolongation more frequently than those with postviral cirrhosis and that the plasma calcium concentration was inversely correlated with QTc. Furthermore, the presence of severe portal hypertension was associated with decreased HRV. Thus, it is possible to conclude that cirrhotic patients with a more severe disease, especially of alcoholic cause, who have greater HVPG and lower calcium plasma levels, are more likely to have abnormalities of ventricular repolarization.

Other authors[85] analysed QT variation with time and QT dispersion (QTdisp), defined as the interlead QT variability, in 23 patients with cirrhosis; they also evaluated a possible relationship between ECG markers and haemodynamic changes. They reported that mean QT(c) was above upper normal limit in 47% of cirrhotic patients, and that the minimum value of QT(c) (but not the maximum value) showed a significant diurnal variation and that QT(disp) was significantly related to indicators of liver dysfunction, central circulation time and arterial blood pressure. These findings could suggest that a combination of long QT(c) and normal QT(disp) may indicate delayed myocyte repolarization at the cellular level, rather than temporal and spatial heterogeneity in the myocardial wall.

Another possible issue to consider among the electrical abnormalities of cirrhotic cardiomyopathy is the evaluation of fragmentation of QRS (fQRS) complex, which is an easily accessible, noninvasive electrocardiographic parameter. Fragmentation of narrow QRS is defined as the presence of an additional R wave (R') or notching in the nadir of the S wave, or the presence of more than 1 R' in two contiguous leads.[86] The presence of fQRS has been associated with alternation of myocardial activation due to myocardial scar and myocardial fibrosis. Initial studies reported a higher sensitivity of fQRS than Q wave for detecting myocardial scar. Furthermore, they postulated that the presence of fQRS could be a good predictor of cardiac events among different types of patients, indicating its capability to evaluate electrocardiographic abnormalities of cirrhotic patients with cirrhotic cardiomyopathy. The main electrocardiographic abnormalities of cirrhotic cardiomyopathy are summarized in Table 1.

Cardiovascular nuclear MRI

Cardiovascular magnetic resonance (CMR) has become the gold standard method for the assessment of cardiac morphology and function in various cardiomyopathies (CMPs).[87] Areas of high signal intensity appearing 10–15 min after injection of the intercellular contrast agent gadolinium were firstly described as late gadolinium enhancement (LGE) in regions of myocardial scarring after infarction.[88] Afterwards, it was shown that LGE could also be detected in nonischemic CMP, cardiac neoplasm, myocarditis, cardiomyopathy and storage diseases such as amyloidosis.[89] Typical LGE patterns have been defined for each of these diseases allowing differential diagnosis and etiological allocation.[90–92] Moreover, the presence and the extent of LGE was shown to be a prognostic indicator.[93]

CMR has been used for the evaluation of functional myocardial changes, noninvasive tissue characterization and the identification of specific cardiac lesions in cirrhotic patients listed for liver transplantation.[94,95] CMR and particularly the presence of LGE seems to be a promising tool to identify patients with end-stage liver disease at risk for cirrhotic cardiomyopathy. LGE can be detected regardless of the cause of liver disease, even if it is more pronounced in patients with alcoholic liver cirrhosis. LGE pattern in cirrhotic cardiomyopathy differs from other nonischemic CMP or myocardial infarction and shows a patchy distribution comparable to that found in acute myocarditis[96,97] (see Fig. 3).

LGE can be due to other causes beyond fibrosis, such as pathological deposits, causing local myocardial injury (e.g. cardiotoxic metabolites, oxygen supply/demand mismatch due to pulmonary arteriovenous shunts, inflammation); this can explain the focal, rather than diffuse, distribution of LGE found in cirrhotic patients. Accordingly, previous studies showed that cardiomyocytes and the trabecular network of the myocardium are changed in cirrhotic patients.[97] Inflammatory process and hyperdynamic circulation in portal hypertension may also play a role in the detection of LGE. Cardiac complications are a frequent cause of morbidity and mortality in patients undergoing liver transplantation and TIPS. Rates of pulmonary oedema have been reported to occur in up to 56% of liver transplant recipients following surgery, and haemodynamically significant arrhythmias in 27%, and congestive heart failure in as many as 5.6%.[98] In a more recent study, 82 out of 179 patients after liver transplantation suffered from cardiac decompensation and cardiac causes were the leading cause of death in these patients.[99] Liver transplant and TIPS pose a stress on the cardiocirculatory system and can lead to a decompensation of cardiac function. This occurs despite regular and careful previous cardiological evaluation.[100] For this reason, CMR could represent a useful tool, although expensive, for investigating patients before undergoing liver transplantation and TIPS.[101]

As previous studies demonstrated a normalization of the haemodynamic parameters after liver transplantation in end-stage liver disease patients,[55,101] further studies are needed, investigating the extent of a possible reversibility of these myocardial alterations.

Cardiac biomarkers

Troponin I, a thin filament associated protein of the myocytes cytoskeleton, is a specific and sensible marker of cardiac injury. It remarkably increases in patients with even very small myocardial infarction, but it is not specific of an ischemic cause. Therefore, it is also released when cellular death occurs for other reasons as well as in patients with cirrhosis.[102] atrial natriuretic peptide and B-type natriuretic peptide (BNP) are secreted from the cardiac atria and ventricles in response to increased cardiac preload. BNP and its pro-hormone, NT pro-BNP, are sensitive markers of myocardial injury. They have been found to be increased in both compensated and decompensated cirrhosis. In a recent study, we have shown that NT pro-BNP plasma levels are raised proportionally to the stage of chronic liver disease and are

significantly associated with increased left atrial volumes and with signs of cardiac diastolic dysfunction.[103] Overall, these peptides seem to correlate with the severity of cirrhosis (Child–Pugh score, HVPG and serum albumin), degree of cardiac dysfunction (plasma volume, HR and QT interval) and myocardial hypertrophy, but not with the degree of hyperdynamic circulation.[104,105] AS BNP and NT pro-BNP reflect the presence of myocardial hypertrophy and cardiac dysfunction in compensated cirrhosis, their evaluation may be useful in screening patients for the presence of cirrhotic cardiomyopathy.[106]

Therapeutic perspectives and prognostic implications

There is no specific therapy for patients with cirrhotic cardiomyopathy and they are usually asymptomatic unless undergoing stressful procedures. When symptoms develop, therapy is mainly aimed to treat heart failure. To reduce congestion, therapy with diuretics can be administered, including aldosterone antagonists, which can favour hypertrophy regression and improvement of diastolic function.[26] Vasodilators, such angiotensin-converting enzyme (ACE)-inhibitors should be used with caution, because they could aggravate the state of systemic vasodilation. Beta-blockers, which find an indication for reducing portal hypertension, can be also useful to reduce QT interval. Liver transplantation usually leads to regression of cardiac dysfunction.[6–12]

Conclusion

Cirrhotic cardiomyopathy is a relatively recent recognized condition. It is characterized by normal systolic function and mild diastolic dysfunction at rest, and inability to increase *CO* under stressful conditions such as TIPS insertion or liver transplantation, in the absence of known cardiac disease and irrespective of cirrhosis cause. Although recently the awareness of the syndrome increased, the real dimension of the problem remains unclear, because patients are asymptomatic at rest and they are usually diagnosed during end-stage liver disease.

However, nowadays, it is not easy to understand the amount of cardiac dysfunction really attributable to cirrhosis, due to the frequent coexistence of confounding conditions and/or comorbidities, such as smoking, hypertension, diabetes, CAD. Comorbidities of cirrhosis sometimes could antedate the onset of chronic liver disease, irrespective of cause, but influencing its pathophysiology.

More studies are needed to better investigate the underlying pathogenetic mechanisms of cardiac dysfunction in patients with cirrhosis and to improve diagnostic work-up and risk stratification.

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