Review

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Cirrhotic cardiomyopathy

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Increased cardiac output was first described in patients with cirrhosis more than fifty years ago. Later, various observations have indicated the presence of a latent cardiac dysfunction, which includes a combination of reduced cardiac contractility with systolic and diastolic dysfunction and electrophysiological abnormalities. This syndrome is termed cirrhotic cardiomyopathy. Results of experimental studies indicate the involvement of several mechanisms in the pathophysiology, such as reduced β-adrenergic receptor signal transduction, altered transmembrane currents and electromechanical coupling, nitric oxide overproduction, and cannabinoid receptor activation. Systolic incompetence in patients can be revealed by pharmacological or physical strain and during stressful procedures, such as transjugular intrahepatic portosystemic shunt insertion and liver transplantation. Systolic dysfunction has recently been implicated in development of renal failure in advanced disease. Diastolic dysfunction reflects delayed left ventricular filling and is partly attributed to ventricular hypertrophy, subendocardial oedema, and altered collagen structure. The QT interval is prolonged in about half of the cirrhotic patients and it may be normalised by β-blockers. No specific therapy for cirrhotic cardiomyopathy can be recommended, but treatment should be supportive and directed against the cardiac dysfunction. Future research should better describe the prevalence, impact on morbidity and survival, and look for potential treatments.

Keywords: Cardiac failure; Portal hypertension; Cirrhotic cardiomyopathy; Hyperdynamic circulation; Myocardial dysfunction.

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Abbreviations: ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CO, carbon monoxide; CB1, cannabinoid-1-receptor; $G_{\alpha i}$, inhibitory G-protein; $G_{\alpha s}$, stimulatory G-protein; HO, haemoxygenase; HRS, hepatorenal syndrome; L-NAME, L-nitro-arginine-methyl-ester; NO, nitric oxide; NOS, nitric oxide synthase; PDE, phosphodiestrase; RAAS, renin-angiotensin-aldosterone system; RGS, regulator of G-protein signalling; SNS, sympathetic nervous system; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt; TNF-α, tumour necrosis factor-α.

Introduction

Deterioration of liver function was first associated with the function of the cardio-vascular system via a hyperdynamic circulation that was described in these patients more than fifty years ago [1]. Later it became clear that cirrhotic patients exhibit a circulatory and cardiac dysfunction predominantly governed by peripheral vasodilatation [2,3]. There is now substantial evidence that impaired liver function and portal hypertension with splanchnic vasodilatation lead to the development of a hyperdynamic syndrome [3,4]. Redistribution of the circulating blood volume results in a reduced central blood volume with central or "effective" hypovolaemia [3]. Low effective blood volume (central and arterial volume) in combination with arterial hypotension, lead to volume- and baroreceptor activation of potent vasoconstricting systems, such as for example the sympathetic nervous system [5]. This further aggravates the hyperdynamic circulation and cardiac strain. Results of experimental and clinical studies have shown impaired myocardial contractility as well as electrophysiological abnormalities in cirrhosis, which have led to a clinical entity called "cirrhotic cardiomyopathy" [6,7]. This term denotes a chronic cardiac dysfunction, characterised by blunted contractile responsiveness to stress and altered diastolic relaxation with electrophysiological abnormalities, such as prolongation of the QT interval, all occurring in the absence of any other cardiac disease [8,9]. This cardiac dysfunction may affect the prognosis of the patients and aggravate the course during invasive procedures such as surgery, insertion of a transjugular intrahepatic portosystemic shunts (TIPS), and liver transplantation [10,11]. On the other hand, liver transplantation has also been shown to ameliorate the cardiac and circulatory disturbances [12].

This review seeks to describe the elements of the cirrhotic cardiomyopathy, the pathophysiological background, the impact on the course of the disease, aspects of treatment, and future strategies.

Experimental evidence of cirrhotic cardiomyopathy

Physiological and biochemical abnormalities in cirrhotic models may differentially affect cardiac function with respect to the control of heart rate, contractility, conduction, and repolarisation. Arterial vasodilatation, increased cardiac output, and increased heart rate characterise the circulation in cirrhotic animal models [13]. Effective hypovolaemia activates the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) both of which significantly contribute to the hyperdynamic

circulatory state in cirrhosis [14–16]. In addition to being hyperdynamic, the circulation in cirrhosis is also hyporeactive with reduced vascular reactivity to adrenaline and angiotensin-II most likely because of increased release of nitric oxide (NO) [17–21]. An autonomic dysfunction that involves the sympathetic as well as the parasympathetic branch also seems to play a role [22–24]. This has been verified in cirrhotic patients by applying standard cardiovascular reflex tests, for example to measure heart rate variability, response to head-up tilt, and baroreflex-sensitivity [5,25,26]. Most of the results of these tests are impaired in cirrhosis and the autonomic dysfunction may therefore interact with the cardiac performance.

Results of many experimental studies in cirrhotic models have shown reduced cardiac performance with impaired cardiac contractility and limited preload reserve, but of different pathophysiological mechanisms (Fig. 1).

In the face of an activated SNS, Gerbes et al. found a decreased density of β-adrenoceptors in leucocytes from cirrhotic patients as evidence of the down-regulation of β-adrenoceptors [27]. Lee et al. expanded these results in a cirrhotic rat model by showing evidence of desensitisation of myocardial β-adrenergic receptors, indicating that down-regulation of β-adrenergic receptors could be responsible for the myocardial hyporesponsiveness to catecholamines [28]. Another important mechanism to be considered is the nitration of proteins, which may be harmful to their function. Thus, Mani et al. recently showed that nitration of cardiac proteins led to an abnormal cardiac chronotropic function and thereby impairment of control of heart rate in cirrhotic cardiomyopathy [29].

The contractility of the heart muscle cell can be disturbed in different ways, but the molecular mechanisms of the decreased contractility are not completely understood. There is however, experimental evidence of decreased responsiveness of cardiomyocytes to β-adrenergic agonists. The β-adrenergic receptors are located in the cell membrane, and altered physical properties with increased fluidity of the cardiomyocyte plasma membrane may be associated with the decreased β-adrenoceptor function [30]. Thus, changes in the cardiomyocyte plasma membrane

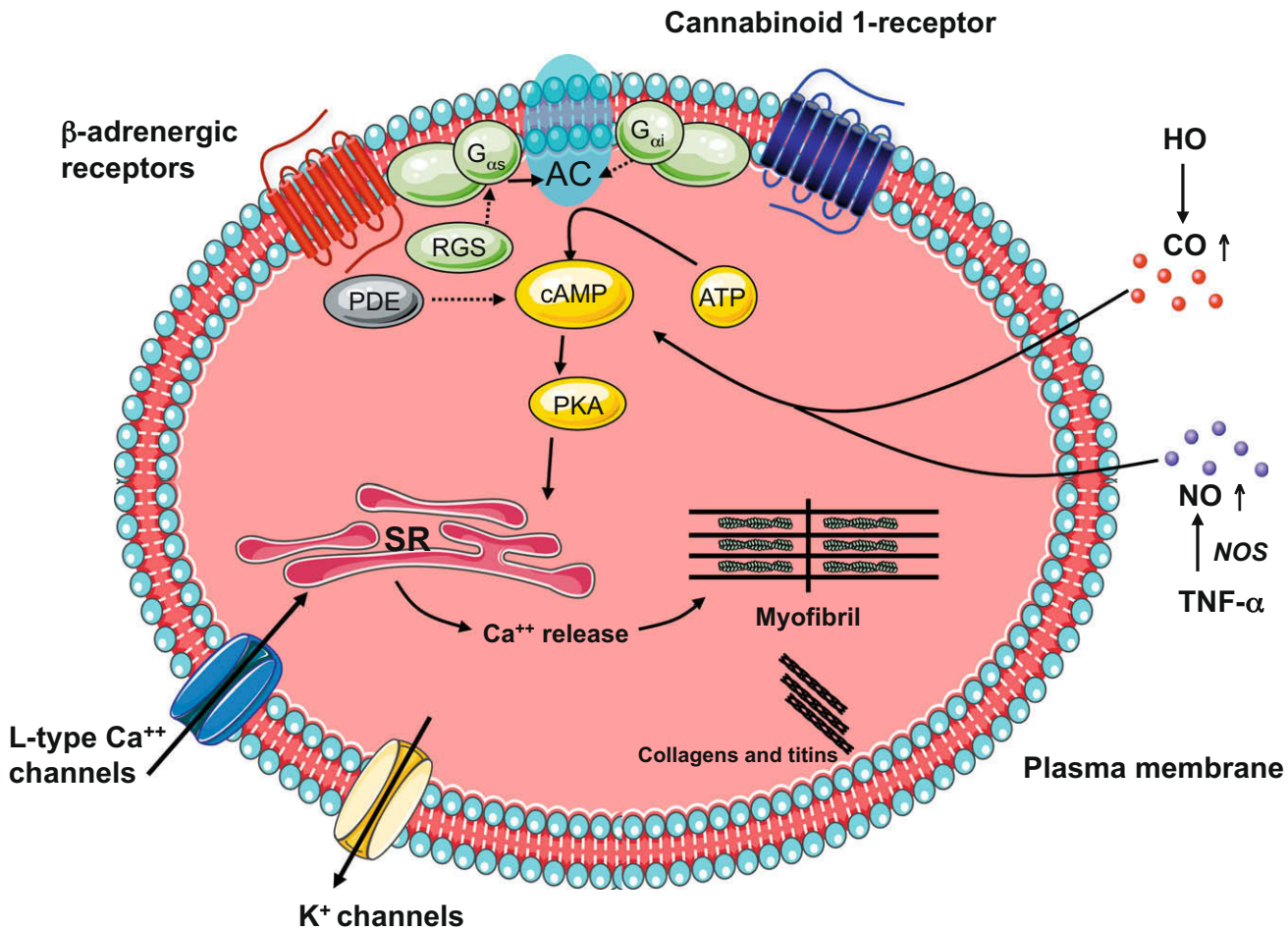

Fig. 1. Potential mechanisms involved in the impaired contractile function of the cardiomyocyte in cirrhotic cardiomyopathy: Down-regulation of β-adrenergic receptors with decreased content of G-protein ($G_{\alpha i}$: inhibitory G-protein; $G_{\alpha s}$: stimulatory G-protein); up-regulation of cannabinoid 1-receptor stimulation; increased inhibitory effects of cardiodepressant substances such as haemoxygenase (HO), carbon monoxide (CO), nitric oxide synthase (NOS)-induced nitric oxide (NO) release, and tumour necrosis factor-α (TNF-α). Many post-receptor effects are mediated by adenylcyclase (AC) inhibition or stimulation. (RGS: regulator of G-protein signalling; PDE: phosphodiesterase; PKA: protein kinase A). Sarcoplasmatic reticulum (SR), Altered function and reduced conductance of potassium channels, inhibition of L-type calcium channels, and increased fluidity of the plasma membrane (increased cholesterol/phospholipid ratio) also contribute to reduced calcium release and contractility together with altered ratio of collagens and titins.

may affect β-adrenergic receptors, signalling function, and cardiac contractility [31,32]. Recently, Ceolotto and co-workers demonstrated that the reduced β-adrenergic-dependent inotropic effect could partly be attributed to an over-expression of proteins such as inhibitory G-protein ($G_{\alpha i}$) and regulators of G-protein signalling (RGS2) that inhibit the adenylate cyclase and those that accelerate degradation of cAMP such as phosphodiesterase (PDE2) [33], Fig. 1. Thus, abnormal gene expression of the β-adrenergic system may be involved in the abnormal signal transduction and altered myocardial contractility in cirrhotic cardiomyopathy [33]. In addition, there is experimental evidence for the involvement of the parasympathetic nervous system, although parasympathetic dysfunction appears somewhat complex. The myocardial contractile responsiveness to muscarinic stimulation is attenuated in cirrhotic rats but the changes are likely compensatory, suggesting post-receptor factors [34]. Thus, it is less likely that the muscarinic over-activity is directly involved in the cirrhotic cardiomyopathy.

The endogenous and exogenous cannabinoids (CB) belong to a system of cellular signalling pathways acting via CB1 receptors, whose activation induces arterial hypotension. The endocannabinoids influence the vascular tone by a vasodilatory effect that activates G-proteins; an effect that is amplified by the ability of endocannabinoids to induce apoptosis of hepatic stellate cells, thus favouring the development of portal hypertension and hyperdynamic circulation [35,36]. There is evidence of increased local ventricular endocannabinoid production in cirrhosis and that activation of CB1 receptors by endogenous anandamide contributes to the reduced cardiac contractility in cirrhosis [37]. Antagonist blockade of the CB1 receptors may reverse the impaired cardiac contractility, and studies in a model of CCl_4-induced cirrhotic rats by the use of CB1 receptor antagonists have shown an improvement in the contractile function in cirrhotic cardiomyopathy [37,38]. Future clinical studies should focus on the potential therapeutic benefits of CB1 antagonism.

As mentioned above, there is experimental evidence that NO is involved in the vascular hyporesponsiveness to vasoconstrictors [18,19]. Furthermore, NO has been shown to modify cardiac performance with significant impairment of the cardiac contractility in bile duct-ligated cirrhotic rats [39,40]. Results of additional experimental studies have indicated that the cytokine–NO pathway occurs in cirrhotic rat hearts with enhanced expression of the NO synthase [20,41] and that inhibition of the NO synthesis by the NO inhibitor L-NAME reverses the impaired cardiac contractility [39,41]. In a model of chronic bile duct ligation-induced cirrhosis, portal hypertension induced a marked left ventricular hypertrophy with increased myocardial NO synthesis, but in this model without any functional impairment [42]. Defects in contractile and connective proteins may play a role in the impaired systolic and diastolic function. In bile duct-ligated rats, over-expression of the β-myosin heavy chain in the cirrhotic heart seems to play a role in the impaired systolic function [43], and an altered ratio of the stiffer collagen I and the more compliant collagen III along with titins could play a role in the decreased compliance in the cirrhotic heart and the diastolic dysfunction [44]. Activation of the haemoxygenase-carbon monoxide pathway may also occur in cirrhotic rat hearts with expression of haemoxygenase-1 [45]. Inhibition of the effects of carbon monoxide improves cardiac contractility and may play an important role in the pathogenesis of cirrhotic cardiomyopathy [40,45]. Nuclear factor-κB regulates different cytokines such as tumour necrosis factor-α (TNF-α) and seems activated in cirrhotic rat hearts [46]. Activation of nuclear factor-κB, a transcription factor that regulates inflammatory processes, suppresses cardiac contractility and its inhibition improves systolic and diastolic contractility, which emphasises a role of cytokine expression in cirrhotic cardiomyopathy [46].

Abnormalities in the properties of the plasma membrane affect repolarisation and conduction. The plasma membrane fluidity of the cardiomyocyte is changed in models of cirrhotic cardiomyopathy and the membrane lipid content is abnormal with an increased cholesterol and thereby an increased cholesterol/phospholipid ratio [47]. As this determines the characteristics of the membrane and its membrane-bound proteins, the function of ion channels, for instance, may be significantly changed. Thus, Ward et al. found a decreased density of potassium currents in ventricular myocytes, which may contribute to prolong the QT interval [48]. In the same model of bile duct-ligated rats, the same group found a reduced expression and density of L-type Ca^{++} channels and of inward cellular calcium current; therefore modifications of the cellular calcium regulatory system with reduced calcium influx contributes to the reduced cardiac contractility (Fig. 1) [49]. In a model of portal vein-ligated rats, Zavecz et al. similarly reported a reduction of the density of L-type Ca^{++} channels and the sarcoplasmic reticulum Ca^{++} pool as a cause of changed excitation–contraction coupling [50]. Changes in the calcium channels also contribute to the prolonged QT interval, which has an arrythmogenic effect. However, in different rat models, NO reduces the susceptibility to adrenaline-induced arrhythmia, which could counteract the pro-arrythmogenic effect of a QT prolongation [51].

In conclusion, cirrhotic models supply a considerable amount of experimental evidence for the reduced cardiac contractility. The pathophysiology behind the reduced contractility is complex, but different findings have contributed towards a better understanding of the pathophysiological background of cirrhotic cardiomyopathy, such as the down-regulation of β-receptors along with an impaired β-adrenergic signalling, changed plasma membrane fluidity with altered potassium, calcium channels and electrophysiological abnormalities, activation of the cannabinoid, NO and cytokine systems, as well as abnormal myofilaments.

Cirrhotic cardiomyopathy in patients

Systolic dysfunction

The systolic function closely relates to the size of the stroke volume, heart rate, and cardiac output. In cirrhosis, the circulatory dysfunction has been expressed as a hyperdynamic unloaded failure of the heart [52]. Despite the characteristic high cardiac output, a systolic dysfunction is included in the working definition of the cirrhotic cardiomyopathy (Table 1) [9]. However, at rest, the cardiac pressures are normal in the majority of cirrhotic patients [52,53]. Physical exercise, however, increases left ventricular pressures in some patients [54,55] and induces a relatively smaller increase in the left-ventricular ejection fraction and heart rate, Table 2 [56]. Although sympathetic nervous tone is increased during exercise, cardiac performance is reduced because of reduced cardiovascular reactivity [57].

Administration of vasoconstrictors, such as angiotensin II and terlipressin, increases the systemic vascular resistance

Table 1. Proposal for diagnostic and supportive criteria for cirrhotic cardiomyopathy agreed upon at a working party held at the 2005 World Congress of Gastroenterology in Montreal.

A working definition of cirrhotic cardiomyopathy
A cardiac dysfunction in patients with cirrhosis characterised by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease
Diagnostic criteria
Systolic dysfunction
• Blunted increase in cardiac output with exercise, volume challenge or pharmacological stimuli
• Resting EF <55%
Diastolic dysfunction
• E/A ratio <1.0 (age-corrected)
• Prolonged deceleration time (>200 msec)
• Prolonged isovolumetric relaxation time (>80 msec)
Supportive criteria
• Electrophysiological abnormalities
• Abnormal chronotropic response
• Electromechanical uncoupling/dyssynchrony
• Prolonged QTc interval
• Enlarged left atrium
• Increased myocardial mass
• Increased BNP and pro-BNP
• Increased troponin I

BNP, brain natriuretic peptide; E/A, early diastolic/atrial filling ratio; EF, left-ventricular ejection fraction.

and thereby the left ventricular afterload [3,58–60]. Pharmacological or physical stress may unmask a latent left ventricular dysfunction in patients with cirrhosis, as evidenced by an increase in left ventricular end-diastolic volume and a decrease in left-ventricular ejection fraction (Table 2) [61]. Infusion of angiotensin II in cirrhotic patients elicits an abnormal response in terms of a 30% increase in the left ventricular afterload and results in a doubling of the pulmonary capillary wedge pressure without changes in the cardiac output [58]. Dobutamine infusion increases the cardiac work by elevating the cardiac output and heart rate but with smaller changes in cardiac pressures [59]. In cirrhotic patients, a dobutamine stress test could be used to reveal a cardiac dysfunction [62]. In the preoperative assessment of patients with end-stage liver disease, a dobutamine stress echocardiography revealed ventricular dysfunction in fewer than 10% of the patients, but the predictive values of this test are not known [60]. In accordance with these findings, recent data from our group indicate that cirrhotic cardiomyopathy may be less frequently revealed by dobutamine, at least in patients with mild disease [63]. Therefore, at present the dobutamine test cannot be recommended for the diagnosis of cirrhotic cardiomyopathy, but should be reserved for severe ischaemic heart disease before transplantation.

Table 2. Potential cardiovascular changes in cirrhotic cardiomyopathy at rest and during pharmacological or physical stress.

At rest
Heart
Heart rate ↑
Cardiac output ↑
Left atrial volume ↑
Left ventricular volume → (↑)
Right atrial volume→ ↑ ↓
Right atrial pressure → ↑
Right ventricular end-diastolic pressure →
Pulmonary artery pressure → ↑
Pulmonary capillary wedge pressure →
Left atrial pressure →
Left ventricular end-diastolic pressure →
Systemic circulation
Plasma volume ↑
Total blood volume ↑
Non-central blood volume ↑
Central and arterial blood volume → ↓
Cardiac output (→) ↑ (↓)
Arterial blood pressure → ↓
Heart rate ↑
Systemic vascular resistance ↓
During stress
Peak heart rate ↓
Peak work rate ↓
Peak exercise blood pressure ↓
Blood pressure • heart rate product ↓
Left atrial pressure ↑
Left ventricular volume ↑
Peak cardiac output ↓
Peak left-ventricular ejection fraction ↓

↑, →, ↓ denote increased, unchanged, and decreased values compared to controls. Arrows in parentheses describe less typical changes.

Analogously to the normal resting cardiac pressures in cirrhosis, changes in the size of the cardiac volumes are only modest. As assessed by magnetic resonance imaging, there seems to be a trend towards slightly increased left ventricular end-diastolic and left atrial volumes, probably in relation to the presence of diastolic dysfunction [64–66]. Increased atrial natriuretic peptide (ANP) in some patients with cirrhosis may reflect distension or distortion of the atria, a finding that may coexist with effective hypovolaemia [67,68].

The ventricular myocardial mass is increased in some patients in particular with septal hypertrophy [69]. Troponin I is a thin filament-associated protein of the myocyte, which reflects cardiac injury. This marker is elevated in patients with myocardial ischaemia and in some patients with cirrhosis who show increased serum concentrations [70]. These patients have a significantly lower ventricular stroke volume and left ventricular mass index, indicating subclinical myocardial injury [70].

ANP and B-type natriuretic peptide (BNP) are secreted from the cardiac atria and ventricles, respectively. ANP signals to decrease blood pressure and BNP to decrease hypertrophy and locally reduce ventricular fibrosis [71]. BNP and its pro-hormone, pro-BNP, are sensitive markers of even mild myocardial injury, and have been found elevated in both compensated and decompensated cirrhosis [72]. These peptides seem to correlate with the severity of cirrhosis, degree of cardiac dysfunction and myocardiac hypertrophy, but not to the degree of hyperdynamic circulation [73] (Fig. 2) [74,75]. Since BNP and pro-BNP reflect the presence of myocardial hypertrophy and cardiac dysfunction these peptides may be useful for screening patients for the presence of cirrhotic cardiomyopathy [72,76].

The exercise capacity is reduced in a considerable number of cirrhotic patients with a particularly low peak rate of work [77] (Table 2). Together with the impaired cardiovascular response to exercise, this is significantly associated with a chronotropic incompetence and failure to enhance systolic function [78]. The normal stepwise increase in cardiac output following graded exercise testing by upright bicycle ergometry is significantly suppressed in patients with cirrhosis compared with controls, and the inability to increased cardiac performance seems most pronounced in decompensated patients [79].

In advanced cirrhosis with pronounced vasodilatation, effective hypovolaemia, and arterial hypotension, the RAAS is highly

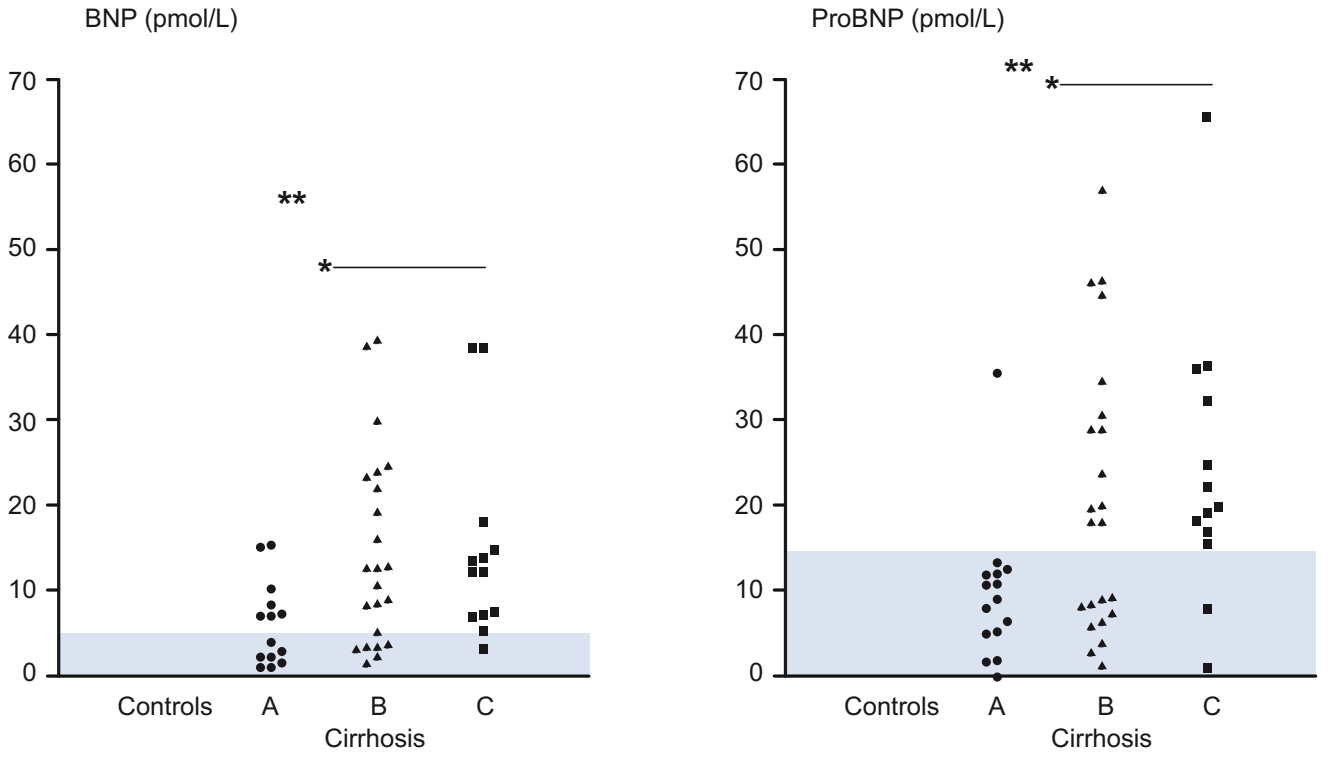

Fig. 2. Brain natriuretic peptide (BNP) and its pro-peptide (pro-BNP) in controls and in patients with cirrhosis, according to the Child–Turcotte classification. BNP and pro-BNP are significantly increased in cirrhosis and correlate with the prolonged QT interval, indicating that the cardiac generation of BNPs reflects cardiac dysfunction in cirrhosis. Data from Henriksen et al. [73].

activated and such patients often develop a hepatorenal syndrome (HRS) [15]. Patients with HRS have a low renal blood flow, glomerular filtration rate, and sodium excretion that appear to be related to a reduced systolic function. Thus, Ruiz-Del-Arbol et al. recently reported lower cardiac output and arterial blood pressure in patients with HRS, and a higher risk of developing HRS in patients with a cardiac output lower than 6 L/min [80]. Maintenance of cardiac contractility thus seems to be an important factor in the prevention of renal dysfunction and HRS. Krag et al. recently demonstrated a significant relation between the degree of systolic and renal dysfunction and survival in patients with decompensated cirrhosis [81]. These studies indicate that systolic dysfunction contributes to sodium and water-retention but on the other hand sodium retention may also be involved in the pathophysiology of systolic as well as diastolic dysfunction [82]. However, these relations need to be more carefully studied in the future. Release of inflammatory mediators such as tumour necrosis factor-α (TNF-α) and interleukins may also play a role in the systolic dysfunction. In patients with spontaneous bacterial peritonitis (SBP), cardiac output seems lower in patients who develop renal failure both before and after resolution of the infection [83].

In conclusion, systolic dysfunction is often latent in cirrhotic patients, but is unmasked by physical or pharmacological strain. The reduced systolic function may have an impact on the development of complications, such as sodium and water-retention as well as ascites formation, the development of renal dysfunction and prognosis (see Box) [9,69].

Diastolic dysfunction

Abnormal left ventricular diastolic function, caused by decreased left ventricular compliance and relaxation, implies an abnormal filling pattern of the ventricles. The transmitral blood flow is changed, with an increased atrial contribution to the late ventricular filling [55] (Fig. 3). The pathophysiological background of the diastolic dysfunction in cirrhosis is an increased stiffness of the myocardial wall, most likely because of a combination of mild myocardial hypertrophy, fibrosis, and subendothelial oedema [84]. There is experimental as well as clinical evidence that increased sodium intake may lead to the development of myocardial hypertrophy [82,85]. Therefore sodium retention *per se* may contribute to diastolic dysfunction in cirrhosis. The increase in myocardial stiffness is also reflected by other parameters of diastolic dysfunction, such as a prolonged time for the ventricles to relax after diastolic filling at a specific end-diastolic volume, which reflects an increased resistance to the ventricular inflow, Fig. 3 [55,65,69]. With Doppler echocardiography, Finucci et al. found impaired left ventricular relaxation, decreased E/A ratio, and delayed early diastolic transmittal filling in patients with cirrhosis compared with controls [65]. This was later confirmed by Pozzi et al. and Torregrosa et al., who revealed a complex pattern of diastolic dysfunction in cirrhosis which was most pronounced in patients with ascites [12,86].

ANP is regarded as a marker of volume overload and is found increased in decompensated cirrhosis [87]. ANP is released by stretch of the atrial fibers such as in patients with ascites where the right atrium has been reported increased partly because of

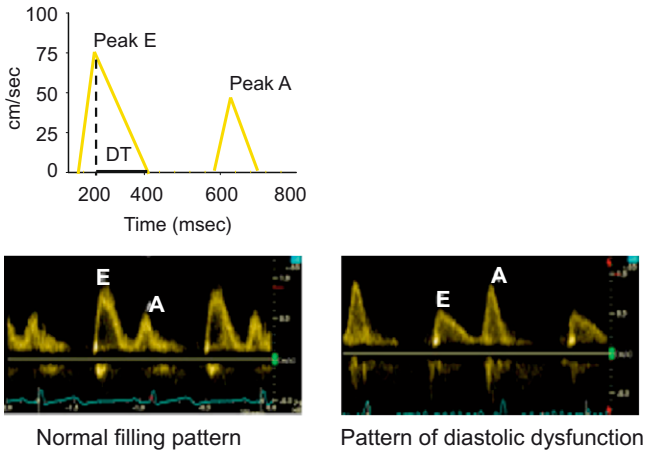

Fig. 3. Schematic illustration of the transmitral Doppler flow profile. Peak E denotes the early filling of the ventricle and peak A the late atrial contribution. Diastolic dysfunction induces characteristic changes in the flow pattern, including increased E/A ratio and prolonged deceleration time (DT). The lower diagrams show a normal filling pattern (left) and a filling pattern indicating diastolic dysfunction (right).

volume overload with expanded blood volume [71,87]. However, the interpretation of the increased ANP in patients who from a functional point of view suffer from effective hypovolaemia is complex. Nazar et al. recently reported a prevalence of 57% among 102 patients with cirrhosis, with a higher degree of liver failure and circulatory dysfunction and higher concentrations of ANP [88]. The RAAS and ANP both contribute to volume regulation and compliance, and seem to be associated with the degree of diastolic dysfunction in cirrhotic, as well as in non-cirrhotic, portal fibrosis [89]. On the other hand, volume and pressure overload stretches myocardial fibres and activates the intracardiac renin-angiotensin-system [90]. Therefore, the RAAS may be directly as well as indirectly involved in diastolic dysfunction in cirrhosis. Patients with diastolic dysfunction are particularly sensitive to volume changes that occur, for example, in relation to insertion of a TIPS. Portal decompression with a TIPS may lead to a further increase in the left atrial diameter and pulmonary capillary wedged pressure, which indicates that the cirrhotic heart is unable to receive an adequate increased preload [91–93]. Thus, Cazzaniga et al. investigated the diastolic function in 32 cirrhotic patients after TIPS insertion and found that it predicted death after TIPS [94]. Changes in diastolic function appear most prominent in patients with severe decompensation, and in these patients the combination of myocardial hypertrophy, contractile dysfunction, changes in heart volumes, and diastolic dysfunction may add to a cirrhotic cardiomyopathy [66,69,79,95]. The increase in diastolic volumes after TIPS seems, however, to normalise after months but with persistence of a mild left ventricular hypertrophy [93]. Moreover, reduced diastolic function seems to be associated with slower mobilisation of ascites [11]. After liver transplantation, diastolic function seems to improve in some patients, but the results are sparse [12,96]. Pozzi et al. recently demonstrated that anti-aldosterone treatment with K-canrenoate in cirrhosis ameliorated cardiac structure by reducing left ventricular wall thickness and volume, but this treatment had almost no effects on systolic and diastolic function [97].

In conclusion, there is evidence that the diastolic function is impaired particularly in patients with advanced cirrhosis and large ascites, and that indicators of diastolic dysfunction may contain prognostic information on the course of procedures that may affect filling of the ventricles such as TIPS insertion.

Prolongation of the QT interval

The main electrocardiographic change in cirrhosis is a prolongation of the QT interval adjusted for heart rate. It has been known for a long time that it is prolonged in up to 50% of patients with cirrhosis [1]. In alcoholic patients, prolonged QT interval is associated with an increased risk of sudden cardiac death [98]. In patients with cirrhosis, the prolonged QT interval is unrelated to the aetiology of the liver disease, and it is seen in both alcoholic and non-alcoholic liver diseases [98–100]. However, in cirrhosis, the duration of the QT interval is associated with indicators of autonomic dysfunction and is partly reversible after liver transplantation [101–103]. In a minority of the patients, the QT interval may worsen after liver transplantation [104,105]. In their study of 107 cirrhotic patients, Bernardi et al. showed that the prolonged QT interval was correlated with the degree of liver dysfunction and circulating plasma noradrenaline [10]. In that study, the QT interval was also related to survival, but others have been unable to confirm an effect on mortality [106]. The QT interval is prolonged in both non-cirrhotic and cirrhotic portal hypertension, and the observation of a further increase after TIPS insertion suggests that portosystemic shunting may be responsible for the altered ventricular repolarisation [107,108]. The finding that the QT interval is also prolonged in patients with only mild portal hypertension adds to the assumption that the portosystemic shunting *per se* is of importance [109]. Acute non-selective β-blockade has been shown to reduce the prolonged QT interval towards normal values in patients with cirrhosis [110]; it could therefore constitute a future indication for β-blocker treatment. Recently, Zambruni et al. showed that chronic β-blockade shortened the QT interval but only in patients with a prolonged interval before treatment [111]. Life-threatening arrythmias are, however, uncommon in cirrhosis and until now there is little evidence that treatment with β-blockers prevent their occurrence. At present, QT interval prolongation *per se* in patients with cirrhosis is therefore not an indication for treatment with β-blockers. Studies on the dispersion of the QT interval (i.e. difference between the longest and shortest interval) have shown a normal diurnal variation, and the combination of a prolonged interval and a normal dispersion suggests a delayed myocyte repolarisation in cirrhosis [112]. Electromechanical uncoupling is a functional disturbance between the electrical and mechanical coupling, and has been found in experimental cirrhosis [31,50]. Bernardi et al. measured systolic time intervals and reported a reduced cardiovascular responsiveness to exercise, despite enhanced sympathetic nervous activity [57]. These findings indicate that the impairment of cardiac contractility is partly based on an abnormal electromechanical coupling. Among 48 cirrhotic patients and 17 controls, we found a significant difference between the electrical and mechanical systole, the latter being significantly longer in patients with cirrhosis, whereas, as expected, there was a direct relation between the QT interval and the duration of the mechanical systole in the controls [113] (Fig. 4). This suggests an altered cardiac excitation–contraction coupling with a compromised association between the electrical and mechanical function of the cirrhotic heart [8].

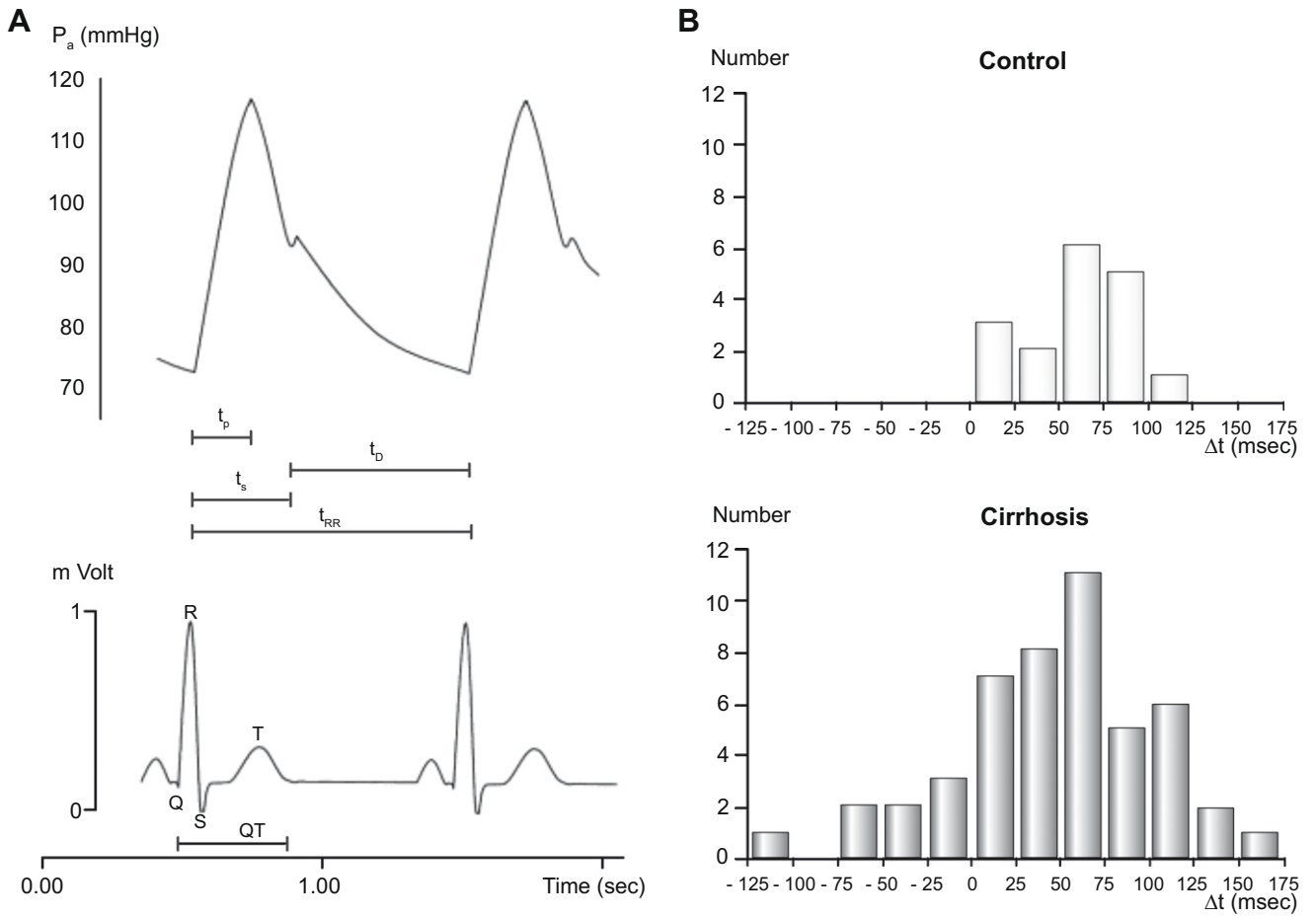

Fig. 4. Mechanical and electrical time intervals from the aortic pressure curve and electrocardiogram. (A) P_a, arterial pressure as a function of time; t_P, time to peak pressure; t_S, systolic time; t_D, diastolic time; t_{RR}, time of one heart cycle; QT interval, the time from the start of the Q wave to the end of the T wave. (B) Difference between electrical and mechanical systole time (Δt = QT – t_S) in controls and patients with cirrhosis. Data from Henriksen et al. [113].

In conclusion, there is a large body of evidence of cardiac conductance abnormalities in cirrhosis, which may increase the risk of cardiac events. The electromechanical changes may be aggravated after TIPS insertion and may be partly reversible after liver transplantation.

Cardiac autonomic dysfunction

Reduced baroreflex-sensitivity has been shown to occur in cirrhosis as part of a general cardiovascular autonomic dysfunction [3,24,25,100,112,114]. In a study of 105 patients with cirrhosis, we found a reduced baroreflex-sensitivity, which was significantly related to central haemodynamics and biochemical characteristics [5]. These results suggest that a reduced baroreceptor-sensitivity owing to the severity of the liver disease, is associated with the cardiac dysfunction in cirrhosis [5]. Since regulation of the arterial blood pressure plays an important role in the development of fluid retention and renal function, a reduced baroreflex-sensitivity will further impair renal sodium and water excretion in these patients. The baroreflex-sensitivity is reduced after exposure to hypoxia such as, for example, a sojourn at high altitude, but supply of oxygen to cirrhotic patients does not seem to ameliorate the low baroreflex-sensitivity [115]. A considerable number of cirrhotic patients show a reduced heart rate variability, which correlates with the severity of the disease, central hypovolaemia, and the degree of portal hypertension [26,108,112].

In conclusion, there are several indications that the reduced baroreflex-sensitivity and heart rate variability contribute to the cardiac dysfunction in cirrhosis.

Cardiac performance after TIPS

TIPS insertion leads to an acute increase in the right cardiac preload, because of acute translocation of portal venous blood into the systemic circulation. This results in a worsening of the hyperdynamic state with a further increase in cardiac output, stroke volume and left and right end-diastolic volumes and a decrease in the systemic vascular resistance [93,116–118]. It has been debated whether the effects of TIPS are transient or more sustained. Studies that describes short-term effects on the hyperdynamic circulation [91,119,120] as well as long-term effects (>6 months) have been published [92,121]. A sustained rise in cardiac output and a reduction in the systemic vascular resistance may persist for at least 1 year post-TIPS. Furthermore, TIPS insertion can lead to high-output congestive heart failure with rises in pulmonary arterial and capillary pulmonary wedge

pressures [122–124], although clinically significant heart failure occurs in relatively few patients [125]. The acute increase in cardiac output seems to attenuate, despite the persistence of increased pulmonary vascular resistances [119,126]. After 6–12 months, cardiac output and the systemic vascular resistance tend to normalise, despite an unchanged degree of portosystemic shunting [92,93,120]. The combined increase in left atrial diameter, the pulmonary capillary wedge pressure and total pulmonary resistance most likely reflect a diastolic dysfunction of the left ventricle, as mentioned earlier, and therefore TIPS may unmask a cirrhotic cardiomyopathy [91,92]. Prolongation of the QT interval as seen in patients with cirrhosis and portal hypertension, may also worsen after TIPS insertion in cirrhotic, as well as non-cirrhotic, portal hypertensive patients [107].

In conclusion, TIPS insertion may acutely worsen the hyperdynamic circulation, but it seems to attenuate over time. TIPS insertion is associated with an increased risk of heart failure and both haemodynamic and electrophysiological changes seem to be affected.

Cardiac function and liver transplantation

With implantation of a new liver, the circulating concentrations of cardiotoxic and vasoactive substances should be reduced and liver transplantation should therefore improve the circulatory changes, including the hyperdynamic circulation. However, some authors have seen persistence of the increased cardiac output for up to two years after liver transplantation, whereas others have reported an immediate attenuation of the hyperdynamic circulation [127–129]. Hence, the time course of the haemodynamic adaptation after liver transplantation is not yet completely understood. The events occurring during the intraoperative period should be separated from the immediate postoperative and more sustained events. The surgical procedure significantly stresses the heart by a sudden reduction in the cardiac preload, resulting in a decrease in cardiac output [130]. Bleeding and fluid losses during the operation can further reduce the cardiac output. Pulmonary oedema has been observed in a considerable number of patients partly because of excessive fluid administration [60,130]. Another critical period during the operation is that of reperfusion of the graft, which can result in the occurrence of a post-reperfusion syndrome with cardiac instability, reduced arterial blood pressure and heart rate [130]. However, at present there is no reliable method of identifying patients who are susceptible to developing these cardiac complications. Recently, Therapondos et al. reported serum BNP as a predictor of cardiac failure in the early post transplantation period [96]. However, Donovan et al. identified only a few patients with left ventricular dysfunction postoperatively, and all these patients had a normal preoperative cardiac function, and hence it was not possible to predict perioperative cardiac failure in this study [60]. Abnormal cardiac responses during transplantation have been related to a longer postoperative intubation time [131]. Interestingly, in that study, hyponatraemia and indicators of effective hypovolaemia predicted an abnormal cardiac response.

Postoperatively, there is a decrease in cardiac output, heart rate, pulmonary artery pressure, and an increase in arterial blood pressure and systemic vascular resistance [128,129,132]. Recently, Torregrosa et al. noted a significant improvement in cardiac performance and a reduction in myocardial mass between six and 12 months after liver transplantation [12]. Furthermore, diastolic and systolic function improved significantly during this period (Fig. 5).

More than 80% of patients with end-stage liver disease may have an autonomic dysfunction before liver transplantation [101]. About two-thirds of the patients with cirrhosis have an autonomic dysfunction and show improvement after liver transplantation [101,131,133]. The prolonged QT interval reverses in at about half of the patients after liver transplantation, probably as a result of diminished portosystemic shunting [101,102,105]. But in a minority of the patients, the QT interval may worsen after liver transplantation [104].

In conclusion, liver transplantation is the ultimate treatment for patients with end-stage liver disease, but perioperatively it exerts a considerable stress on the cirrhotic heart. Identification of patients at risk of developing cardiac failure is difficult. Dobutamine stress test has been applied to identify patients at risk of development cardiac complications but at present we need a more sensitive and specific test to identify those patients that develop cardiac failure after liver transplantation. Postoperatively, cardiac function seems to normalise with improvements in cardiac hypertrophy, diastolic and systolic function, and QT interval, but more studies on the cardiac effects are needed.

Summary and conclusion

There is considerable experimental evidence of a cirrhotic cardiomyopathy from *in vitro* and animal studies in cirrhotic models of cardiac dysfunction (see Box). Patients with advanced cirrhosis present with a circulatory hyperdynamic dysfunction as part of a multi-organ failure with impaired function and perfusion of kidneys, lungs, brain, skin, muscles, and the heart. While normal at rest, during stress the cardiac performance and systolic function are clearly impaired relative to the liver dysfunction. The impaired cardiac contractility in cirrhotic cardiomyopathy is different from that seen in alcoholic heart muscle disease. Among significant pathophysiological mechanisms are reduced β-adrenergic receptor signal transduction and a defective cardiac electro-

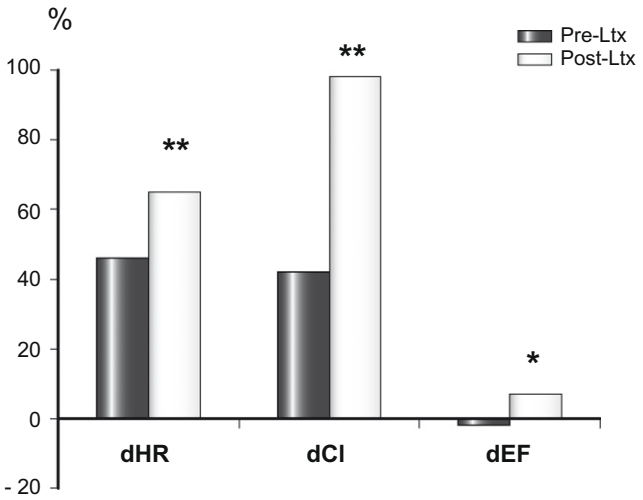

Fig. 5. Illustration of reversibility of systolic dysfunction in patients with cirrhosis and controls. The change in heart rate (dHR), cardiac index (dCI), and left-ventricular ejection fraction (dEF) after stress ventriculography significantly improved following liver transplantation (Ltx). *p <0.05. **p <0.01. Figure based on data from Torregrosa et al. [12].

mechanical coupling. The cirrhotic heart may be overloaded with a high-output failure and at the same time be hyperdynamic with a diastolic dysfunction; strain may unmask a latent congestive heart failure. No specific therapy can be recommended for this condition, and management of patients with cirrhotic cardiomyopathy should be directed against the congested heart failure and include conventional treatment for pulmonary stasis with diuretics. Vasodilators, like ACE-inhibitors, should not be used due to the risk of further aggravation of the systemic vasodilatory state. Aldosterone antagonists may have beneficial effects in terms of a reduction in left ventricular dilatation and wall thickness and improvement of diastolic function. Cardiac glycosides do not seem to improve cardiac contractility in cirrhotic cardiomyopathy. In addition to their lowering effect on portal pressure, β-blockers may reduce the hyperdynamic load and improve the prolonged QT interval, but future research should elucidate whether they also improve the contractile dysfunction, electromechanical abnormalities, and mortality. In addition, cirrhotic cardiomyopathy seems to play a role in the development of HRS. Lastly, liver transplantation improves most of the cardiac dysfunction.

Box: Key messages of cirrhotic cardiomyopathies

Key points

- Cirrhotic cardiomyopathy denotes an impaired contractile responsiveness to stress, altered diastolic
- Cirrhotic cardiomyopathy is independent of aetiology of cirrhosis and different from alcoholic heart muscle disease
- Systolic dysfunction can be demasked by physical or pharmacological stress
- Diastolic dysfunction is detected by echocardiography with measurement of reduced E/A ratio
- Measurement of Q-T interval prolongation should be adjusted for heart rate
- Liver transplantation may revert the cardia dysfunction but surgery and TIPS insertion may also aggravate this
- Cirrhotic cardiomyopathy contributes to hepatorenal syndrome
- Treatment is non-specific and directed towards the left ventricular heart failure

Conflicts 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.

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