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Review

New insights into cirrhotic cardiomyopathy

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ABSTRACT

Cirrhotic cardiomyopathy designates a cardiac dysfunction, which includes reduced cardiac contractility with systolic and diastolic dysfunction, and presence of electrophysiological abnormalities in particular prolongation of the QT interval. Several pathophysiological mechanisms including reduced beta-receptor function seem involved in the autonomic and cardiac dysfunction. Cirrhotic cardiomyopathy can be revealed by tissue Doppler imaging but is best demasked by physical or pharmacological stress. Liver transplantation may revert cardiac dysfunction but surgery and shunt insertion may also aggravate the condition. Moreover, cirrhotic cardiomyopathy may contribute to heart failure after invasive procedures and to development of hepatic nephropathy as part of a cardiorenal syndrome. Whether beta-blockers have a deleterious effect in this clinical situation remains to be settled.

1. Introduction

Alterations in systemic haemodynamics in chronic liver disease have been known since 1953 [1]. Since then it became apparent that apart from portal and splanchnic haemodynamic changes, patients with cirrhosis also present with characteristic systemic circulatory and cardiac changes [2]. These changes include a hyperdynamic circulation with increased cardiac output and heart rate and progressively reduced systemic vascular resistance owing to a splanchnic arterial vasodilatation [2,3]. Arterial underfilling with reduced central blood volume due to arterial vasodilatation activates several neurohumeral axes leading to ascites and oedema. The pathogenesis of development of sodium and water retention may share pathophysiology with other oedematous conditions such as cardiac and renal failure and pregnancy [4]. In the recent years an increasing amount of evidence of a specific heart disease associated with cirrhosis has led to the definition of the entity cirrhotic cardiomyopathy [5–7]. This condition, which is seen in 40–50% of the patients, includes a systolic and diastolic dysfunction, and electrical mechanical abnormalities [8–10]. Even in children with biliary atresia, structural and functional alterations in the heart indicate a cirrhotic cardiomyopathy [11]. Cirrhotic cardiomyopathy is primarily observed in stress-situations, but recent research has revealed that systolic dysfunction can also be quantified using modern echocardiographic techniques [12]. Recent post-mortem analyses of a large group of cirrhotic patients have revealed a high rate of cardiac abnormalities such as for example left and right ventricular chamber dilatations which is seen in approximately one-third of the patients [13]. The results from this preliminary abstract should however be cautiously interpreted. In this paper we review the present knowledge on mechanisms, impact, and therapeutic aspects of cirrhotic cardiomyopathy.

2. The systemic circulation in cirrhosis

According to the “arterial vasodilatation hypothesis”, splanchnic arteriolar vasodilatation in cirrhosis leads to development of a hyperdynamic syndrome with increased cardiac output and heart rate and low arterial blood pressure and systemic vascular resistance [14,15], see Fig. 1. Redistribution of the circulating blood volume with pooling in the splanchnic bed results in a reduced central blood volume with central or “effective” hypovolaemia [15]. Low effective blood volume (central and arterial volume) in combination with arterial hypotension leads to volume- and baroreceptor activation of potent vasoconstricting systems such as for example the sympathetic nervous system [16]. In addition, the circulating plasma and blood volumes are abnormally distributed with expanded peripheral volumes and contracted central or “effective blood volume” which is identical to the volume that is sensed by baroreceptors [15,17]. A reduced effective blood volume activates vasoconstrictor systems and

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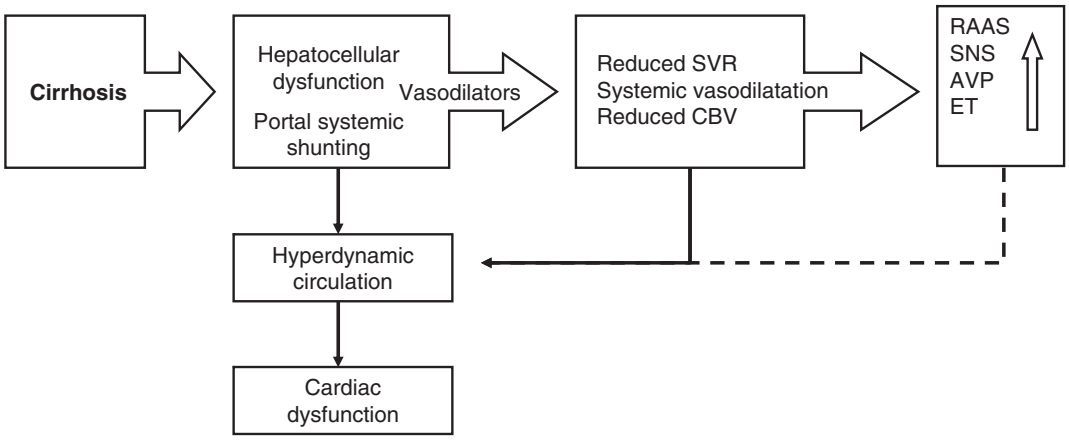

Fig. 1. Role of hepatocellular dysfunction and portosystemic shunting in the development of extrahepatic vasodilatation in cirrhosis. Arterial vasodilatation leads to redistribution of the blood volume with development of central hypovolaemia, hyperdynamic circulation, and cardiac dysfunction. AVP: vasopressin, CBV: central blood volume, ET: endothelin, RAAS: renin–angiotensin–aldosterone system, SNS: sympathetic nervous system, SVR: systemic vascular resistance.

secondary sodium–water retention. In humans, vasodilatation may be accomplished by a surplus of circulating vasodilators such as nitric oxide (NO) and calcitonin gene-related peptide (CGRP) [3,4,18]. The consequences of the splanchnic vasodilatation: the low arterial blood pressure and systemic vascular resistance and the systolic cardiac incompetence may play a role for the development of the progression of for example renal, pulmonary, and cerebral complications in cirrhosis [19–21]. Table 1 summarises the circulatory changes in patients with cirrhosis. The systemic haemodynamic changes in cirrhosis seem mainly to be determined by changes in portal pressure and hepatic blood flow [22]. However, the relations between the changes in organ-related perfusion and function are complex and future prospective studies should reveal how and in which order the simultaneous changes occur [23].

Table 1
Circulatory changes in patients with cirrhosis.

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 ↓
Heart
Left atrial volume ↑
Left ventricular volume →
Right atrial volume ↑
Right ventricular volume →
Right atrial pressure ↑
Right ventricular end-diastolic pressure →
Pulmonary artery pressure ↑
Pulmonary capillary wedge pressure →
Left ventricular end-diastolic pressure →
Pulmonary circulation
Pulmonary blood flow ↑
Pulmonary vascular resistance ↓
Renal circulation
Renal blood flow ↓
Renal vascular resistance ↑
Cerebral circulation
Cerebral blood flow ↓
Cutaneous and skeletal muscle circulation
Cutaneous blood flow ↑
Skeletal muscular blood flow ↑

↑ Denotes an increase, → denotes no change, and ↓ denotes a decrease.

3. Experimental and molecular studies on cirrhotic cardiomyopathy

Results of many experimental studies in cirrhotic models have shown reduced cardiac performance with impaired cardiac contractility with limited preload reserve, but of different pathophysiological mechanisms [5,24]. The contractility of the heart muscle cell can be disturbed in different ways. For example there is evidence of down-regulation of β-adrenoceptors and desensitisation of myocardial β-adrenergic receptors and changes in calcium and potassium channels may be responsible for myocardial hyporesponsiveness to catecholamines [25,26]. In addition, altered fluidity of the cardiac membrane may affect beta-adrenergic receptor signalling [27]. Other important mechanisms include nitration of proteins, increased fluidity of the cardiomyocyte plasma membrane with increased cholesterol/phospholipids ratio, and over-expression of regulators of G-protein signalling [5,28–30], see Table 2. The endogenous and exogenous cannabinoids (CB) belong to a system of cellular signalling pathways acting via CB1 receptors, whose activation induces arterial hypotension [31]. 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 improvement in the contractile function in cirrhotic cardiomyopathy [32]. Moreover, there is experimental evidence of

Table 2
Potential mechanisms involved in the impaired contractile function of the cardiomyocyte in cirrhotic cardiomyopathy.

Changes in receptor affinity
Down regulation and desensitisation of myocardial β-adrenergic receptors [25]
Upregulation of cannabinoid 1-receptor stimulation [32]
Changes in intracellular signalling
Changed expression of regulators of G-protein signalling [24,30]
Changed adenylcyclase inhibition or stimulation [29]
Over-expression of regulators of G-protein signalling [36]
Changes in ion fluxes
Altered function and reduced conductance of potassium channels [66]
Inhibition of L-type calcium channels [26]
Contractility defects
Overexpression of the β-myosin heavy chain [29]
Altered ratio of collagens and titans [24]
Biochemical changes
Increased inhibitory effects of haemeoxygenase and carbon monoxide [5]
Nitration of proteins [28]
Increased nitric oxide synthase-induced nitric oxide release [33]
Increased tumour necrosis factor-α release [5]
Increased fluidity of the plasma membrane [27]
Increased cholesterol/phospholipid ratio [5,29]

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enhanced NO-synthesis expression in cirrhotic rat hearts since inhibition of the NO synthesis reverses the impaired cardiac contractility [33]. Defects in contractile and connective proteins in the heart may play a role in the impaired systolic and diastolic function. Glenn et al. have demonstrated a link between diastolic dysfunction in experimental cirrhosis and alterations in modulation of cardiac myofilament proteins titin and collagen, and an altered ratio of the stiffer collagen I and the more compliant collagen III. These biochemical changes in the cardiomyocyte may affect compliance and passive tension and thereby diastolic function in the cirrhotic heart [24].

Several mechanisms seem to contribute to the reduced contractility in cirrhotic cardiomyopathy such as down-regulation of β-receptors with impaired β-adrenergic signalling, changed plasma membrane fluidity with altered potassium and calcium channels, and electrophysiological abnormalities; activation of the cannabinoids, NO and cytokine systems and abnormal myofilaments have contributed to elucidate the pathophysiological background of cirrhotic cardiomyopathy.

4. Pathophysiology of cirrhotic cardiomyopathy

4.1. Systolic dysfunction

Systolic function relates to the potential of the heart to generate an adequate arterial pressure and cardiac output. In cirrhosis, the circulatory dysfunction has been expressed as a hyperdynamic unloaded failure of the heart [2,34]. Despite the characteristic high cardiac output, a systolic dysfunction is included in the working definition of the cirrhotic cardiomyopathy (see Table 3) [2]. However, at rest the cardiac pressures are normal in the majority of cirrhotic patients partly because the reduced after-load and low systemic vascular resistance protect the systolic function. Physical exercise, however, increases left ventricular pressures in some patients and induces a relatively smaller increase in the left ventricular ejection fraction and heart rate [5,35,36]. Administration of vasoconstrictors, such as angiotensin II and terlipressin, increases the systemic vascular resistance and thereby the left ventricular afterload [2,37–39]. 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 [39], Fig. 2. However, a reduction in heart rate following terlipressin-infusion can also be considered as an adaptive reaction on an improved (increased) arterial blood pressure in these patients. Thus, in cirrhosis, terlipressin may improve the hyperdynamic circulation and systolic function, but at the same time, aggravate diastolic function and myocardial perfusion.

Analogously to the normal resting cardiac pressures in cirrhosis, changes in the size of the myocardial mass and cardiac volumes are only modest [40]. As assessed by magnetic resonance imaging, there seems to be a trend towards slightly increased left ventricular end-diastolic and left atrial volumes [2,41]. Recently, an increased left ventricular end-diastolic diameter and systolic myocardial velocity have been related to the presence of the hepatopulmonary syndrome in cirrhosis [42]. This points to a relation between the hepatopulmonary syndrome and the hyperdynamic circulation and systolic dysfunction. However, increased left ventricular end-diastolic diameter as an indicator of the hepatopulmonary syndrome needs to be validated in other studies. In a new study of autopsy records in 135 cirrhotic patients, 43% had macroscopical anatomic cardiac abnormalities, in particular cardiomegaly and left ventricular hypertrophy [43]. Recent studies using contemporary echocardiographic techniques, however, have shown reduced peak systolic tissue velocity and increased peak systolic strain rate in cirrhotic patients compared with controls [12]. These results indicate that systolic dysfunction may not only be revealed during stress, but also at rest. There exist some controversies as to the relation between the degree of liver dysfunction and cirrhotic cardiomyopathy. Thus, some studies show no direct relation between the aetiology or severity of the liver dysfunction and cardiac dysfunction, whereas others have reported the most severe cardiac dysfunction in patients with decompensated cirrhosis [9,42,44–47].

The reduced systolic function may have an impact on the development of complications, such as sodium and water-retention and ascites formation, and development of renal dysfunction, and prognosis [2,29,36,48].

4.2. Diastolic dysfunction

The transmitral blood flow is changed in about half of the patients with cirrhosis, with an increased atrial contribution to the late ventricular filling [2,9,12]. 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 [13,29,49]. 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 [2,36]. Left atrial volume can be estimated by the area–length method and indexed to the body surface area [50]. As assessed by tissue Doppler imaging there seems to be an association between diastolic dysfunction and circulatory dysfunction, development of ascites, hepatorenal syndrome, and survival [9]. Activation of the RAAS contributes to volume regulation and compliance, and seems to be associated with diastolic dysfunction in cirrhotic, as well as in non-cirrhotic portal fibrosis [51]. Since activation of RAAS may induce fibrosis and there is evidence of relations between plasma aldosterone and E/A-ratio, RAAS may be directly as well as indirectly involved in diastolic dysfunction in cirrhosis [52]. 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 represent an essential element in the cirrhotic cardiomyopathy [9,36]. An E/A ratio below 1 is associated with a high mortality rate during the first year after TIPS treatment and reduced ascites mobilisation [53,54]. Furthermore, the low E/A ratio seems associated with an increased need for liver transplantation or death

Table 3
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 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 CO with exercise, volume challenge or pharmacological stimuli
•Resting EF <55%
Diastolic dysfunction
•E/A ratio <1.0 (age-corrected)
•Prolonged deceleration time (>200 ms)
•Prolonged isovolumetric relaxation time (>80 ms)
Supportive criteria
•Electrophysiological abnormalities
•Abnormal chronotropic response
•Electromechanical uncoupling/dyssynchrony
•Prolonged Q-Tc interval
•Enlarged left atrium
•Increased myocardial mass
•Increased BNP and pro-BNP
•Increased troponin I

BNP: brain natriuretic peptide; CO: cardiac output; E/A: early diastolic/atrial filling ratio; EF: left ventricular ejection fraction.

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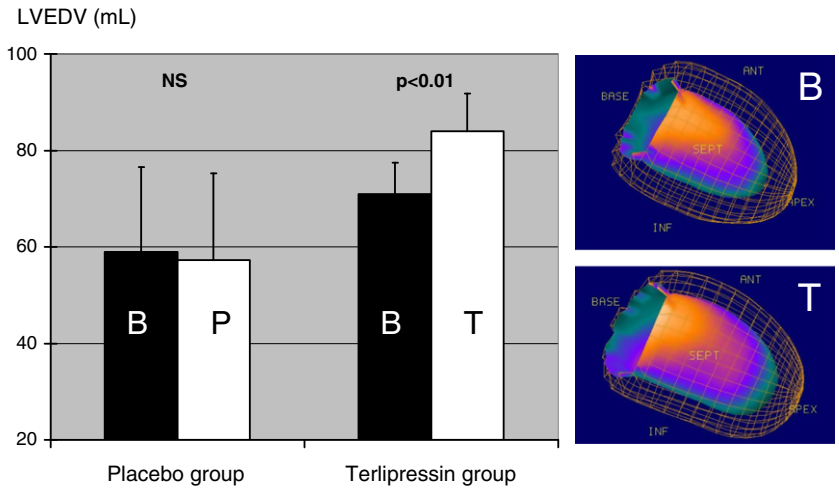

Fig. 2. Effects of the vasoconstrictor terlipressin or placebo on left ventricular end-diastolic volume (LVEDV). Representative myocardial perfusion images are shown to the right in the figure.
From Krag et al. [39].

over a 5-year follow-up period [55]. In these patients, assessment of the diastolic function may help identify patients at highest risk of death. After liver transplantation, diastolic function seems to improve in some patients, but the results are sparse [56,57].

Taken together, there is evidence that the diastolic function is impaired particularly in patients with advanced cirrhosis, large ascites, and hepatorenal syndrome and that diastolic dysfunction affects survival.

4.3. Assessment of cardiac function

Echocardiography is essential in the evaluation of contractile reserve using stress echocardiography, which may provide important prognostic information in conditions with cardiac failure [58], but its role in routine screening for left ventricular (LV) dysfunction in cirrhotic cardiomyopathy patients remains unclear. Newer techniques such as strain imaging with 2D echocardiography have been used to detect subclinical LV dysfunction and have demonstrated predictive value in disease states such as cardiac amyloidosis and hypertrophic cardiomyopathy, as well as to determine viability prior to revascularization in patients with coronary artery disease. Diastolic dysfunction is most easily diagnosed by Doppler echocardiography that reveals impaired left ventricular relaxation, decreased E/A ratio, and delayed early diastolic transmitral filling in cirrhosis. These changes are most pronounced in patients with ascites [57]. Tissue Doppler imaging (TDI) is a relatively new echocardiographic technique that allows assessment of the longitudinal function of the myocardium. From velocity curves in particular regions of interest at the mitral annular level, regional peak velocities during systole, early diastole and late diastole can be measured as s′, e′ and a′, respectively, which detect light degrees of systolic and diastolic left ventricular dysfunction. The diastolic dysfunction evaluated from TDI has been related to hypertension, diabetes, ischaemic heart disease and worse prognosis. Combining the E from the pulsed wave Doppler of the left ventricular inflow curve and the e′ from the TDI, E/e′ can be calculated. Increased E/e′ as marker of diastolic dysfunction has been related to the presence and the extent of ischemic heart disease [59].

Cardiac magnetic resonance imaging (*CMR*) has some potential advantages compared to echocardiography particularly in obese patients where echocardiography is suboptimal. CMR is an excellent modality for obtaining accurate serial measurements of LV function, and is considered the gold standard for measuring LV function [60], but may also be used for strain imaging [61].

CMR has the potential to demonstrate subclinical myocardial changes prior to the onset of LV dysfunction, and also has the unique ability to detect myocardial oedema, which may be seen in acute myocardial injury. Increased signal in the myocardium on T2-weighted (T2-W) images has been described in the presence of acute myocardial inflammation and injury, as in myocarditis.

Myocardial T1 mapping is a new technique that uses T1 relaxation times to calculate the volume of distribution of gadolinium contrast in myocardium. It is increased in the presence of diffuse myocardial fibrosis or infiltrative disease [62]. T1 mapping may prove to be a useful method to identify patients at risk for cardiomyopathy.

4.4. Prolongation of the QT interval

Prolongation of the QT interval is seen in up to 50% of the patients with cirrhosis and is associated with an increased risk of sudden cardiac death but unrelated to the aetiology of the liver disease [63,64]. The duration of the QT interval is however associated with indicators of autonomic dysfunction and is partly reversible after liver transplantation [64]. Interestingly, the QTc interval progressively increases during liver transplantation from the prehepatic stage, through the anhepatic stage to the neohepatic stage where it returns to the baseline level [65]. In a study of 107 cirrhotic patients, Bernardi et al. showed that the prolonged QT interval correlated with the degree of liver dysfunction and circulating plasma noradrenaline [63]. In that study, the QT interval was also related to survival. In addition, the QT interval during Holter monitoring was related to the degree of portal hypertension [66]. 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 QT interval and a normal dispersion suggests a delayed cardiomyocyte repolarisation in cirrhosis [67]. Electromechanical uncoupling is a functional disturbance between the electrical and mechanical coupling, and has been variably found both in experimental and clinical cirrhosis with a direct relation between the QT interval and the duration of the mechanical systole [68,69]. The underlying mechanisms most likely relate to impaired function of potassium channels prolonging the action potential and the QT interval [36]. In addition increased levels of cytokines seen during infections and bleeding episodes may harmfully affect cardiac contractility and excitability [70]. This suggests an altered cardiac excitation–contraction coupling with a compromised association between the electrical and mechanical function of the cirrhotic heart [71].

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There is thus significant evidence of prolonged QT-interval 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 [64,72].

4.5. Cardiac autonomic dysfunction

Reduced baroreflex sensitivity has been shown to occur in cirrhosis as part of a general cardiovascular autonomic dysfunction [15,66]. In a study of 105 patients with cirrhosis, we found a reduced baroreflex sensitivity, which was significantly related to central haemodynamics and biochemical characteristics such as blood haemoglobin and serum sodium [16]. These results suggest that a reduced baroreflex sensitivity owing to the severity of the liver disease, is associated with the cardiac dysfunction in cirrhosis [16]. Since regulation of the arterial blood pressure plays an important role in the development of fluid retention and renal function, reduced baroreflex sensitivity will further impair renal sodium and water excretion in these patients. 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 [67,73]. Therefore, impaired baroreflex sensitivity as well as impaired cardiac conductance and contractility may all contribute to the defect in cardiovascular regulation in cirrhosis.

4.6. Biomarkers of cardiac dysfunction

Cardiac biomarkers are substances produced in the heart reflecting myocardial injury and function. The ventricular myocardial mass is increased in some patients in particular with septal hypertrophy [36]. Troponin I is a thin filament-associated protein of the myocyte and its extracellular presence reflects cardiac injury. This marker is elevated in patients with myocardial ischaemia and in some patients with cirrhosis who show increased serum concentrations [74]. These patients have a significantly lower ventricular stroke volume and left ventricular mass index, indicating subclinical myocardial injury [74].

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. ANP is regarded as a marker of volume overload and is found increased in decompensated cirrhosis [15,36]. ANP is released by stretch of the atrial fibres such as in patients with ascites where the right atrium has been reported increased partly because of volume overload with expanded blood volume [15]. However, the interpretation of increased ANP in patients who from a functional point of view suffer from effective hypovolaemia is complex.

BNP and its prohormone, pro-BNP, are sensitive markers of even mild myocardial dysfunction, and have been found elevated in both compensated and decompensated cirrhosis [36,45,49]. These peptides seem to correlate with the severity of cirrhosis, degree of cardiac dysfunction and myocardiac hypertrophy, and survival [45]. Since BNP and pro-BNP reflect the presence of myocardial hypertrophy and cardiac dysfunction these peptides may be useful in screening patients for the presence of cirrhotic cardiomyopathy [36,75]. There is a need of more precise biomarkers for a more accurate diagnosis and prediction of the development of complications and survival.

4.7. Relation to renal function

A considerable number of patients with advanced cirrhosis develop renal disturbances. The pathogenesis involves liver dysfunction, splanchnic vasodilatation, and activation of vasoconstrictive systems. In advanced cirrhosis with pronounced vasodilatation, effective hypovolaemia, and arterial hypotension, the RAAS is highly activated and such patients often develop a hepatorenal syndrome (HRS) [48]. Patients with HRS have a reduced 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 [46]. 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 [76]. 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 since fluid retention and subendothelial oedema may further compromise cardiac function. Release of inflammatory mediators such as NO, tumour necrosis factor-α (TNF-α) and other cytokines may also play a role in the systolic dysfunction. Increased concentrations of these vasodilating cytokines termed as a “cytokine storm” may have potential toxic and suppressive effects on the myocardial contractility and thereby impair systolic function [32,77–79]. 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 [80]. The temporal relationship between the development of renal failure on the one hand and decreased systemic vascular resistance, effective blood volume, and cardiac output on the other indicates a causal effect of arterial vasodilatation as well as cardiac systolic dysfunction on renal function. This cardiorenal relation in decompensated cirrhosis may be a result of an acute-on-chronic circulatory stress. Therefore several observations now indicate a relation between the impaired renal function and impaired cardiac systolic function in patients with advanced cirrhosis and ascites. We have recently hypothesised that in cirrhosis, a cardiorenal syndrome could refer to a condition where a cardiac dysfunction in cirrhosis is a major determinant of kidney function and survival in patients with advanced cirrhosis and renal insufficiency [81]. Thus, the relation between the cardiac dysfunction and the renal insufficiency should be the target for future studies and new treatments should focus on ameliorating the cardiac dysfunction.

4.8. Cardiac performance after shunt insertion

Insertion of a transjugular intrahepatic portosystemic shunt (TIPS) may lead to an acute increase in the right cardiac preload and worsening of the hyperdynamic state with increased stroke volume and left and right end diastolic volumes [82]. Short-term as well as long term changes (>6 months) have been reported [36] and a sustained rise in cardiac output may persist as long as 1 year post-TIPS. In a few patients, TIPS insertion can lead to high-output congestive heart failure with rises in pulmonary arterial and capillary pulmonary wedge pressures [83]. Despite continuously high portosystemic shunting, the cardiac output normally tends to normalise after 6–12 months [82]. But the combined increase in left atrial diameter, the pulmonary capillary wedge pressure and total pulmonary resistance can be a sign of a diastolic dysfunction of the left ventricle and unmask a cirrhotic cardiomyopathy. Such patients are particularly sensitive to volume changes that occur, for example, in relation to portal decompression with a shunt. A TIPS may further increase the left atrial diameter, left myocardial mass, and pulmonary capillary wedged pressure, which indicates that the cirrhotic heart is unable to adjust to an increased preload [82]. Recently, it has been shown that the occurrence of diastolic dysfunction after TIPS insertion is associated with reduced survival and slower mobilisation of ascites [54]. Moreover, diastolic dysfunction diagnosed within 6 months prior to TIPS insertion predicts 3 months post-TIPS mortality [53]. In summary, TIPS insertion may acutely worsen the hyperdynamic circulation, but these changes seem to attenuate over time. TIPS insertion is in predisposed patients associated with an increased risk of decompensated heart failure and mortality.

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4.9. Cardiac function and liver transplantation

Recently, it has been documented that diastolic dysfunction predicts liver transplantation or death in patients with cirrhosis [55]. Liver transplantation normalises hepatic metabolism and improves the hyperdynamic circulation. However, a persistent increase in cardiac output for up to two years after liver transplantation as well as an immediate attenuation of the hyperdynamic circulation has been reported [2,84]. The events occurring during the intraoperative period represent other challenges and should be separated from the immediate postoperative and more sustained events. At present there is no reliable method of identifying patients, who are susceptible to developing perioperative cardiac complications [84]. Recently, Therapondos et al. reported serum BNP as a predictor of cardiac failure in the early post transplantation period [56]. Having survived the first post-transplant period, there are, however, evidence of a significant improvement in cardiac performance and a reduction in myocardial mass between six and 12 months after the liver transplantation [57]. In particular, the systolic response to exercise capacity normalises during stress with significant increases in heart rate, ventricular ejection rate, stroke volume, and cardiac output (Fig. 3) [57]. Furthermore, diastolic and systolic function improves during this period and the prolonged QT interval reverses in about half of the patients [85]. At present we need a more sensitive and specific test to identify those patients who develop cardiac failure after liver transplantation. Postoperatively, cardiac function seems to normalise with improvements in cardiac hypertrophy, diastolic and systolic function, and QT interval.

5. Aspects of treatment

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 [6]. 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. We have shown that acute non-selective β-blockade reduces the prolonged QT interval towards normal values in patients with cirrhosis [86]. In this study, the size of the change in QTc interval correlated with the size of the reduction in cardiac output and the hepatic venous pressure gradient. Also chronic beta-blockade may shorten the QT interval but apparently only in patients with a prolonged QT interval before treatment [87]. Studies on cardiac control of heart rate variability in liver transplant candidates treated with propranolol have shown an improved vagal cardiac tone. Therefore, the effect of beta-blockers on the prolonged QT interval in cirrhosis may be due to a vagal cardiac modulation [88]. However, until now it is not known if correction of the prolonged QT interval by β-blockade in cirrhosis has any effect on the clinical outcome and the significance of QT prolongation remains elusive. In contrast the cardiodepressive effect of β-blockade may be responsible for an increased mortality among patients with refractory ascites who are treated with betablockers. Moreover, it may lead to an increased risk of paracentesis induced circulatory dysfunction in these patients [89].

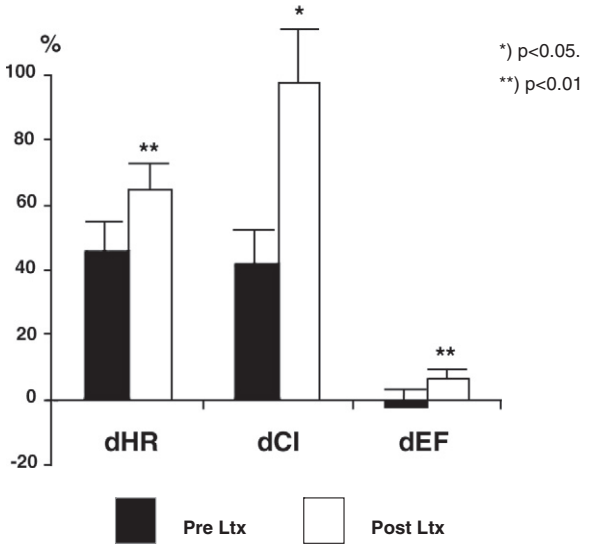

Fig. 3. Illustration of reversibility of systolic dysfunction in patients with cirrhosis and controls. Changes in heart rate (dHR), cardiac index (dEF), and left ventricular ejection fraction (dEF) after stress ventriculography improved significantly after liver transplantation (Ltx).
From Torregrosa et al. [57].

6. Conclusion

Cirrhotic cardiomyopathy denotes an impaired contractile responsiveness to stress, altered diastolic relaxation, and presence of electrophysiological abnormalities. It is independent of aetiology of cirrhosis, may be diagnosed at rest in some patients but demasked by physical or pharmacological stress. Diastolic dysfunction is detected by echocardiography or Doppler imaging with measurement of reduced E/A ratio. Liver transplantation may revert the cardiac dysfunction but surgery and TIPS insertion may also aggravate the condition. Moreover, cirrhotic cardiomyopathy contributes to heart failure after invasive procedures and is most likely an important factor in the development of the hepatorenal syndrome. Treatment is non-specific and directed towards the left ventricular heart failure.

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