Pathophysiological and Clinical Approach to Cirrhotic Cardiomyopathy

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ABSTRACT

Hyperdynamic circulation, systolic and diastolic left ventricular dysfunction and certain electrophysiological abnormalities have been associated with cirrhosis and known for a long time. These clinical features have been introduced as cirrhotic cardiomyopathy (CCM), which is characterized by blunted myocardial contractile responsiveness to physical, physiological and pharmacological stress. Importantly, cardiac dysfunction can be reversible and can improve due to effective medical treatment and also after liver transplantation. Echocardiography and electrocardiography are essential tools for recognizing the characteristic changes in the myocardial function and also the alterations in the electrophysiological properties of the heart. Laboratory markers are auxiliary modalities further aiding the establishment of the correct diagnosis. In this review, we aimed to collect the pathophysiological background and clinical characteristics of CCM with the intention of summarizing the current possibilities for the diagnosis establishment and treatment of this cardio-hepatic disorder.

INTRODUCTION

Cirrhosis is associated with an increased risk for the development of cardiovascular diseases. Decreased systemic vascular resistance, increased cardiac output and abnormal myocardial contractile function are the characteristic features and likely to appear as consequences of cirrhosis. The functional and structural changes of the myocardium have been referred as cirrhotic cardiomyopathy (CCM), a slow progression myocardial dysfunction associated with cirrhosis [1]. Most importantly, this condition should not be confused with alcoholic cardiomyopathy where the underlying mechanism responsible for the structural and functional cardiac abnormalities is well defined [2]. In contrast to alcoholic cardiac disease, in the case of CCM any well-defined underlying provoking factor(s) can be identified; however, sometimes iron overload or alcohol consumption may worsen the already hampered structural and functional condition of the myocardium [3]. In CCM, left and right ventricular contractile function may decrease resulting in an altered responsiveness to physical, physiological and pharmacological activity, leading to the characteristic symptoms of heart failure [4]. Moreover, the disturbed ability for relaxation may lead to diastolic myocardial dysfunction or even diastolic heart failure. It is important to note that, based on the severity of diastolic heart

function, patients are relatively asymptomatic. Nevertheless, regardless of clinical manifestation, diastolic heart failure is an independent risk factor for cardiovascular mortality in both symptomatic and asymptomatic patients [5]. Furthermore, diastolic dysfunction is an important underlying factor in the development of certain arrhythmias, especially in the genesis of atrial fibrillation [6]. In the case of CCM, appearance of electrophysiological abnormalities may result in an increased risk for the development of both atrial and ventricular rhythm disturbances. Fortunately, these abnormalities may be reversible after liver transplantation [7]. Cardiac dysfunction is considered to be multifactorial in chronic liver diseases. In the present review, we aimed to collect all the pathophysiological and clinical evidence that may help to understand the core of CCM in order to assist clinicians to come to a more exact diagnosis and establish a better treatment and care strategy for patients suffering from CCM in everyday clinical practice, surmounting complications, delaying progression and diminishing mortality.

ROLE OF THE VASCULAR TONE IN THE GENESIS OF CIRRHOTIC CARDIOMYOPATHY

Portal hypertension and altered liver function may play an important role in the change of intracardiac volume and pressure conditions in cirrhosis [8, 9]. Variceal bleeding, concomitant anemia and the appearance of ascites are among the most important factors that contribute to the decreased right and left ventricular preload and afterload [10]. Reduction of central and arterial blood volumes in combination with arterial hypotension can lead to volume- and baroreceptor activation resulting in sodium-water retention [11]. The triad of systolic and diastolic dysfunction, hyperdynamic circulation and electrophysiological abnormalities are important clinical features of CCM. Arteriolar vasodilatation with increased cardiac output, low arterial blood pressure and decreased systemic vascular resistance eventuate the development of hyperdynamic syndrome in cirrhosis. Vasodilatation appears in the splanchnic area while vasoconstriction is present in the kidneys. These conditions are responsible for the decreased effective central blood volume [9, 12]. High concentration of vasodilators and reduced sensitivity to vasoconstrictors play an important role in the genesis of vasodilatation in patients with cirrhosis known to be caused by various substances. Nitric oxide (NO), tumor necrosis factor-alfa (TNF-α), endocannabinoids, adrenomedullin, calcitonin gene-related peptide (CGRP), and carbon monoxide (CO) are the most important mediators in this field [13, 14]. On the contrary, a concomitant activation of the sympathetic nervous system and the renin-angiotensin aldosterone system (RAAS) (noradrenaline, neuropeptide-Y, endothelin-1, angiotensin II, and vasopressin) has been observed [15, 16] (Fig. 1).
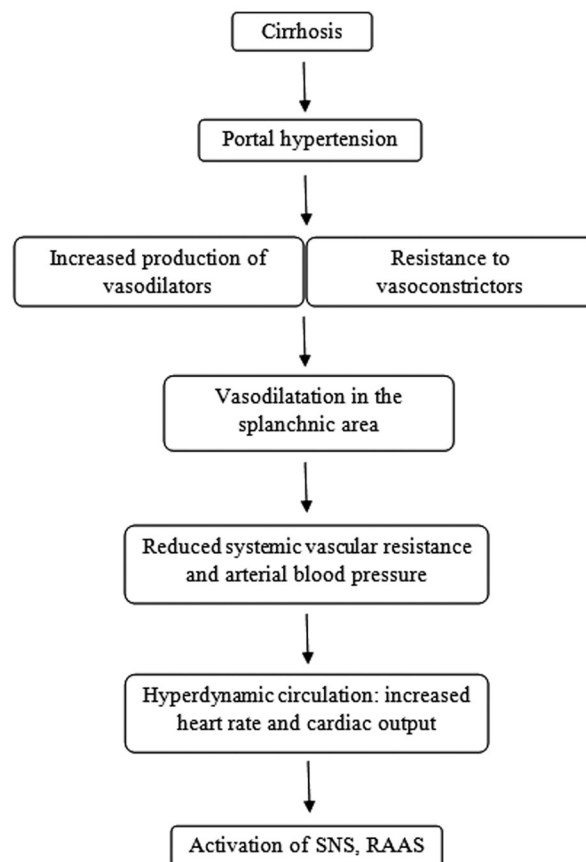
Fig. 1. Hyperdynamic circulation is caused by a pathophysiological cascade in patients with cirrhosis.
SNS: sympathetic nervous system; RAAS: renin angiotensin aldosterone system

MECHANISMS FOR ALTERED MYOCARDIAL FUNCTION

Systolic function

In cirrhosis, myocardial dysfunction was found to be associated with the severity of liver disease. Systolic dysfunction, however, is mostly latent in this patient population. The circulatory dysfunction manifests itself as a hyperdynamic unloaded heart failure and cardiac output proves to be normal or increased at rest in most cases [17]. Reduction in myocardial function becomes overt under conditions of physical or pharmacological stress [18]. Latent systolic dysfunction becomes manifest during the normalization of arterial blood pressure [19]. Accordingly, clinical symptoms of systolic heart failure may evolve after liver transplantation or the placement of a transjugular intrahepatic portosystemic shunt (TIPS) [20]. Reduced left ventricular ejection fraction was found to be an important determinant for the development of the hepatorenal syndrome as well [21, 22]. Several molecular abnormalities were identified as the background of systolic dysfunction in patients with cirrhosis. Alterations in the beta (β)-adrenergic signaling pathway result in a decreased density of β-receptors, reduction in G-proteins and consequently a decrease in the production of cyclic adenosine monophosphate (cAMP) [23]. Furthermore, due to the increased cholesterol content the fluidity of the myocardial cell membrane may alter and can impair the ion channel functions [24, 25]. Moreover, enhanced endocannabinoid signaling has a negative inotropic effect [14]. Additionally, NO overproduction exerts a toxic effect on the myocardium due to suppressed contractility and induced apoptosis [26]. As TNF-α is a major trigger mechanism of NO production, high level of this cytokine worsens the pathophysiological and clinical status [27].

Diastolic function

Decreased left ventricular relaxation is characterized by abnormal trans-mitral ventricular filling, increased atrial pressure and prolonged isovolumic relaxation [28]. The pathophysiological background of the diastolic dysfunction in cirrhosis is the increased stiffness of the myocardial wall, which is often caused by myocardial hypertrophy and fibrosis due to activation of the RAAS [29]. Subendothelial edema and increased interstitial collagen deposition play a further role in the decreased ability for relaxation [2, 8]. Based on the severity of diastolic heart function, patients may be relatively asymptomatic. Diastolic dysfunction is an underlying factor in the development of atrial fibrillation where the pathomechanism is postulated to be due to an increased atrial volume load [6]. Despite these pathomechanisms, no convenient evidence can be evaluated on the relationship between cirrhosis and atrial fibrillation. Previously, Gundling et al reported the increased prevalence of atrial fibrillation in their cirrhotic cohort compared to the average population [30].

Nevertheless, regardless of clinical manifestation, diastolic heart failure is an independent risk factor for cardiovascular mortality in both symptomatic and asymptomatic patients [31].

ELECTROPHYSIOLOGICAL ABNORMALITIES IN CIRRHOTIC CARDIOMYOPATHY

Electrophysiological abnormalities occurring in cirrhosis comprise chronotropic incompetence, electromechanical uncoupling, and prolonged QT interval [32–34].

Chronotropic incompetence

In patients with chronotropic incompetence the sinus node is not able to respond to physiological and pharmacological stimuli. Furthermore, sympathetic overdrive conditions do not result in an adequate acceleration of atrial and ventricular rate. This is true even in the case of elevated plasma norepinephrine concentrations. This phenomenon may appear both in patients with alcoholic and non-alcoholic liver disease and correlates with the severity of cirrhosis [2, 35, 36].

Electromechanical uncoupling

In the case of electromechanical uncoupling there is an asynchrony between electrical and mechanical systole that can lead to an altered contractile function of the ventricular myocardium resulting in congestive heart failure [33, 37]. Furthermore, the prevalence of electromechanical uncoupling is associated with the severity of liver disease depicted by Child-Pugh classification [32]. This abnormality has been demonstrated to be caused by receptor and post-receptor defects [34].

QT interval and dispersion

The QT interval represents the electrical depolarization and repolarization of the ventricular myocardium and it depends on the ventricular rate: the faster the heart rate the shorter it is [38]. Determination of the QT interval can aid the selection of the patient population with increased risk for the development of life threatening ventricular dysrhythmias [39]. The QT interval duration varies between leads on the standard surface electrocardiogram. The interlead difference of QT intervals is defined as QT dispersion, which is an index of the spatial dispersion of the ventricular recovery times, and can distinguish between myocardium that is homogeneous from myocardium that displays increased prolongation of repolarization [40]. Since these electrocardiographic markers can predict ventricular arrhythmias and sudden cardiac death they are considered to be among the most significant non-invasive parameters [41].

In patients with cirrhosis, the lengthening of the QT interval does not seem to be related to the etiology of the liver disease, and appears both in alcoholic and non-alcoholic subjects [35, 36]. The prevalence of QT prolongation is high in patients with cirrhosis and increases with the severity of the liver disease. Accordingly, at least 60% of patients with end-stage liver disease show this electrocardiographic abnormality [32]. Contraversely, Baik et al reported that sudden cardiac death is rare in cirrhosis, and torsades de pointes was described only in a few patients. Therefore, the clinical significance

of QT prolongation in cirrhosis still remains to be clarified [42]. Prolongation of the QT interval may also worsen after TIPS insertion both in cirrhotic and non-cirrhotic portal hypertensive patients. Moreover, TIPS insertion was shown to be associated with an increased risk of heart failure [43]. The aforementioned electrophysiological changes appeared as a result of a combination of ion-channel dysfunction, plasma membrane abnormalities and β-adrenoceptor and post-receptor pathway defects.

Various ion channel defects in cirrhosis are now associated with the prolongation of the action potential of the myocardial cells, which results in the extension of ventricular systole or a prolonged QT interval [44, 45]. The electrical properties of the myocardial cells largely depend on the duration of the monophasic action potentials, which are generated by special types of voltage gated ion channels placed in the myocardial cells' plasma membrane. These channels begin to open when the membrane potential passes a threshold value. During depolarization an inward flow of sodium ions appear, which results in a further rise in the membrane potential. Consequently, more channels will open (calcium channels), leading to a greater electric current across the myocardial cells' membrane. The polarity of the plasma membrane then turns to be reversed and the ion channels will rapidly become inactivated. Afterwards, an outward current of potassium ions (outward rectifier) will return the electrical transmembrane gradient to the resting state (repolarization) (Fig. 2). The plateau phase of the action potential depends on the balance between the efflux of potassium and the influx of calcium currents determining the repolarization time of the myocardial cell [46]. Impaired function of potassium channels in animal models of cirrhosis has been reported leading to a prolongation of the action potential, suggesting an increase in the transmural heterogeneity of repolarization [47].

Bacterial infections commonly appear in patients with cirrhosis. As the inflammation progresses cardio-depressant substances such as cytokines, endogenous cannabinoids, and nitric oxide are released [48]. The urokinase-type plasminogen activator receptor (suPAR) has recently been suggested to bear prognostic information [49]. These mediators may influence the activation of the inward calcium current leading to an increase in the duration of the monophasic action potential. Moreover, endothelin (which is elevated in cirrhosis) was shown to induce alterations in ion currents of myocardial cell preparations [50]. Also, increased bile acid levels (biliary cirrhosis) may modulate membrane fluidity causing the changes in ion channel activity and the alterations of β-adrenoceptor and G-protein function. Increased sympathetic nervous system activity in the presence of potassium channel defects may play a role in the genesis of inhomogeneous repolarization. Non-selective β-blockade may have a favorable effect on QT interval duration in patients with cirrhosis, which can be secondary to the improvement in hyperdynamic circulation and decreased portal pressure. In addition, the enhanced role of sympathetic activity in the genesis of myocardial dysfunction in cirrhosis was shown by Bernardi et al: a direct correlation between QTc and plasma norepinephrine was found that was absent during β-adrenergic blockade [32, 51].

However, Zambruni et al reported that chronic administration of a non-selective β-blocker was effective in reducing the QT interval only in patients with a prolonged baseline value. In patients with normal baseline values, the QT interval was not found to be changed by β-blockade. Accordingly, the exact role of chronic β-adrenoceptor blockade in the arrhythmogenesis in cirrhotic patients is not fully elucidated and needs further investigation [52].

DIAGNOSIS

Clinical symptoms

Since cardiac function is nearly normal at rest, the diagnosis of this disorder is not easy. In most cases this condition is well tolerated and may be asymptomatic for a long period of time, and it is often impossible to distinguish the clinical signs and complaints from those of the underlying disease. Most of the patients are diagnosed during the worsening of the liver disease
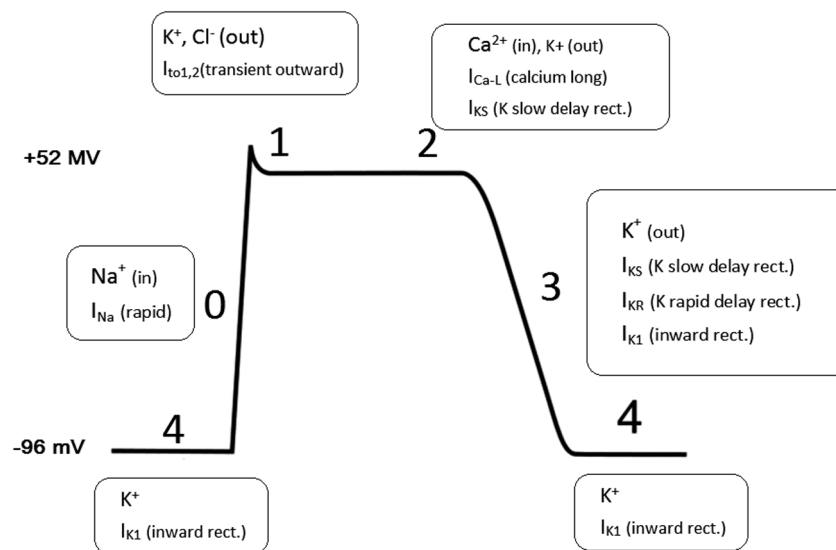
Fig. 2. The monophasic action potential of the myocardial cell is shown. The plateau phase largely depends on the potassium and the calcium ion channel activity. The longer the plateau phase, the more increased the myocardial cell's repolarization.

when the main clinical characteristics of diastolic heart failure and high-output heart failure usually appear. The decrease of systolic ventricular competence may enhance the development of complications, such as sodium and water-retention, ascites formation and worsening of the kidney function [53].

Laboratory markers

The determination of natriuretic peptides plays an important role in the diagnosis of heart failure. Atrial natriuretic peptide (ANP) is released from the atrial myocardium due to intracardiac volume overload. Consequently, atrial wall stretch is augmented resulting in higher serum levels of this biomarker. Since decompensated cirrhosis eventuates altered intracardiac volume and pressure conditions, ANP is likely to be elevated in these particular cases [54, 55]. Brain natriuretic peptide (BNP) and its pro-hormone (pro-BNP) are useful in the diagnosis of myocardial injury, and have been shown to be elevated in patients with cirrhosis. Moreover, these correlate with the stage of the liver disease and may show the severity of myocardial dysfunction and ventricular hypertrophy. Despite these favorable features BNP and pro-BNP may not be able to indicate the hyperdynamic circulation [56, 57]. These biomarkers have also been shown to be helpful in the screening of CCM [58]. Another laboratory marker, high sensitive troponin I seems to be valuable in the risk stratification of patients undergoing transjugular intrahepatic portosystemic shunts [59]. Recently, a novel plasma biomarker, the galectin-3 has been shown to mediate myocardial fibrosis and to be expressed in cirrhosis. Furthermore, galectin-3 binding protein concentrations have also been found to be increased in patients with cirrhosis [60].

Echocardiography
Assessment of systolic function

The left ventricular systolic performance highly depends upon its contractility. Additionally, ventricular pre- and afterload, and heart rate have an influence on the myocardial contractile power. The ejection fraction (EF) is known to be the best marker of the left ventricular systolic function. It is known to be a predictor of cardiovascular outcomes, including sudden cardiac death in patients with symptomatic heart failure [61]. For the evaluation of ejection fraction linear measurements (Teicholz or Quinones) can be performed by means of a two-dimensional echocardiography [62]. These methods require certain geometric assumptions, therefore they are not recommended to be used in the everyday clinical practice. Instead, the ejection fraction can be calculated more exactly from the difference between the end-diastolic and the end-systolic left ventricular volume, divided by the end-diastolic volume (Simpson's method) [63] (Fig. 3). Finally, speckle tracking, another echocardiographic method evaluates the frame-to frame tracking of the ventricular myocardium in radial, circumferential and longitudinal axis. This can provide a sensitive description of left ventricular systolic function [64]. Furthermore, new research is going on with the development of new techniques related to echocardiography, which in the future will improve this diagnostic method. Finally, radionuclide scintigraphy (MUGA - Multi Gated Acquisition Scan) can provide highly reliable values of left ventricular ejection fraction when echocardiography is uncertain [65].

Evaluation of diastolic function

Left ventricular relaxation abnormalities may be diagnosed with echocardiography, too. Even the asymptomatic diastolic dysfunction can be recognized at an early disease stage and therapy can be started without delay. Moreover, another echocardiographic entity, isolated diastolic dysfunction (heart failure with normal ejection fraction) can be recognized. For the evaluation of diastolic function the transmitral flow velocities are measured in early diastole and late diastole (presystole) with the help of a pulsed wave Doppler technique. The early diastolic transmitral peak flow velocity (E) can be determined from the apical four-chamber view. The peak flow velocity in the late diastolic period during the atrial contraction (A) is also determined. The time between the peak and the end of the E-wave deceleration slope is defined as deceleration time (DT) [66] (Fig. 4). Using Tissue Doppler Imaging (TDI) the
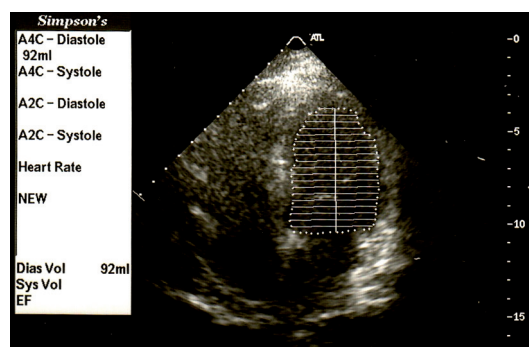

Fig. 3. Evaluation of the left ventricular systolic function by means of echocardiography during volumetric measurements. The determination of the left ventricular diastolic volume from the four-chamber apical view (Simpson's method) is shown.
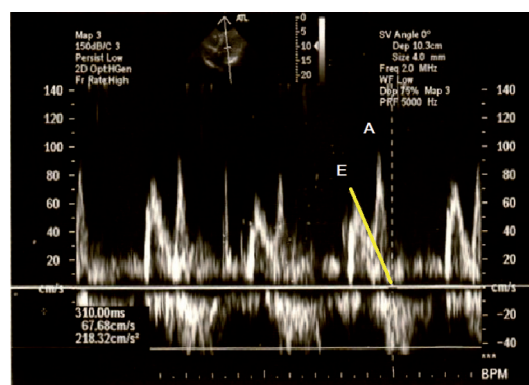
Fig. 4. Transmitral flow velocities measured with the help of a pulsed-wave Doppler technique. The ratio of early diastolic peak velocity (E) and late diastolic velocity (A) is less than 1. The deceleration time (DT) lasts from the peak till the end of the E-wave (shown in yellow). It is measured to be lengthened (310 msec). These data suggest a diastolic dysfunction (relaxation disorder). In patients with cirrhosis E/A ratio is usually markedly reduced (E/A < 1) and the deceleration time is prolonged (DT > 240 msec).

early diastolic velocity of the septal mitral annulus (Ea) from the apical approach can be examined. In order to estimate the left ventricular filling pressure the ratio of the E and Ea (E/Ea) is also calculated. First degree (mild) diastolic dysfunction (DD) is defined as: E/A < 0.8, E/Ea < 8, DT > 200 msec and second degree (medium) DD as: 0.8 < E/A < 1.5, 8 < E/Ea < 13 and the DT is 160-200 msec. The criteria for third degree (severe) DD are: E/A > 2, E/Ea > 13, DT < 160 msec [67, 68]. The diastolic dysfunction in cirrhosis is most pronounced in patients with ascites [28, 53].

Electrocardiography

The evaluation of the 12-lead surface electrocardiogram of patients with cirrhosis is useful in the recognition of pulse generation and/or conduction disturbances, and cardiac arrhythmia markers can also be examined. The QT interval is one of the most important electrocardiographic parameters for the description of ventricular repolarization in patients with cirrhosis. Numerous diseases may result in the prolongation of this arrhythmia marker (amyloidosis, sarcoidosis, carcinoid, hemochromatosis, diabetes mellitus, thyroid dysfunction or Parkinson's disease) [69–74]. In addition, the QT interval may be affected by genetic causes (long QT syndrome, short QT syndrome). The prolongation of the QT interval may be the consequence of drug interaction (e.g. haloperidol, methadone, amiodarone, sotalol, selective serotonin reuptake inhibitors, macrolide antibiotics, antifungal agents) [75]. Since this repolarization marker may be affected by various causes, the clarification of the patient's history is one of the key points in the arrhythmia risk determination.

Considering the required standards for precision, measurement of the QT interval still remains subjective because the end of the T wave cannot always be exactly defined [76]. QT interval may be measured manually by using the threshold method, where the end of the T wave is the point at which the T wave intercepts the isoelectric line. During the tangent method the end of the T wave is determined by the intersection of a line determined from the tangent line and the isoelectric line. The tangent line is defined as the terminal part of the T wave at the point of maximum downslope [77]. In order to get more exact data, three consecutive sections can be defined, then their average is calculated and the resulting value used as the QT interval in the given electrocardiographic lead (Fig. 5). The QT interval depends on the ventricular rate (the faster the heart rate the shorter the QT interval). Therefore the QT interval should be corrected to the heart rate (QTc). There are numerous methods that may provide the correction of this parameter. Bazett's formula is one of the most important in this field (QTc= QT/√RR) [78]. The QTc>450 msec value shows an increased risk of ventricular arrhythmias [79]. Interestingly, in patients with cirrhosis this formula does not clearly describe the relationship between the QT and heart rate. Therefore a specific 'cirrhosis formula' has been derived, which is similar to the Friderica's, and can be confidently used in this setting [80]. In order to eliminate the inter-observer variability, during the manual measurements values may be calculated with calipers by one examiner [40].

THERAPEUTIC APPROACH TO CIRRHOTIC CARDIOMYOPATHY

Impaired cardiac output in patients with CCM may result in an altered renal perfusion contributing to the pathogenesis of the hepatorenal syndrome.

In addition, due to the decrease in cardiac output, the sympathetic tone increases contributing to the activation of renal sodium and water retention, and also to the activation of the RAAS. Diastolic myocardial dysfunction can contribute to an elevated ventricular pressure. The consequently decreased circulatory volume can cause a further increase in sodium retention. Therefore, the increased sodium excretion mainly through aldosterone-blockers and diuretics can result in an improved cardiac function. As of now, no generally accepted protocol and clinical trials on the management of CCM are available. Consequently, patients should be treated following the guidelines for non-cirrhosis induced heart failure [2].

Angiotensin converting enzyme (ACE) inhibitors

Patients with cirrhosis on ACE inhibitor therapy could attain long term clinical benefits, but currently no studies are available to prove their efficacy in CCM. According to the latest
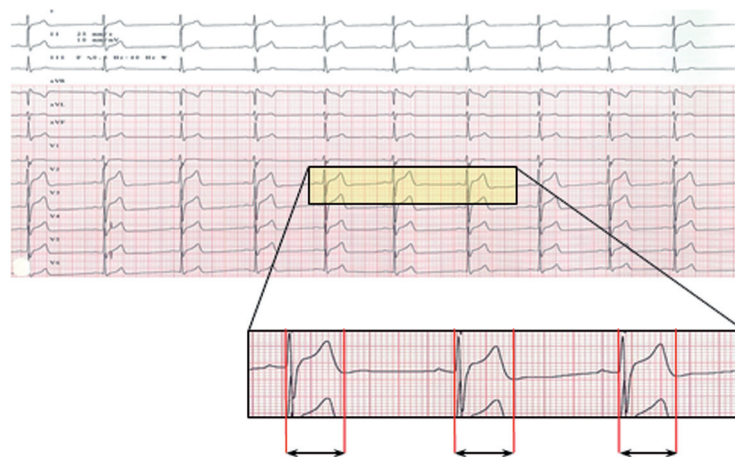
Fig. 5. The manual measurement of the QT interval of the 12-lead surface electrocardiogram. The calculation and averaging of three consecutive sections may provide a more accurate result in the given lead.

guideline, ACE inhibitors should be administered in patients with heart failure, unless contraindicated, in order to reduce morbidity and mortality. Data obtained from previous clinical investigations have shown no differences regarding clinical symptoms and survival among available ACE inhibitors. Management should be started at low doses, with gradual dose increments. Renal function and serum potassium should be monitored periodically especially in patients with renal impairment. It is also important to know that ACE inhibitor administration in patients with Child Pugh A cirrhosis is safe, but not in more severe stages, due to the reduction in glomerular filtration rate [81, 82].

Angiotensin-II receptor blockers

Though angiotensin receptor blockers (ARB) have been shown to increase sodium excretion without significantly affecting renal and systemic hemodynamics, they have not yielded beneficial clinical effects in long-term management of patients with cirrhosis [83].

Loop and thiazide diuretics

Only diuretics can effectively control the fluid retention of patients suffering from heart failure. Therefore, the appropriate administration of these drugs is one of the key elements of the treatment of these individuals, while inappropriately low doses will result in a fluid retention. On the other hand, the incautious use of high doses can lead to hypovolemia, hypotension and kidney failure. Loop diuretics (e.g. furosemide) are considered to be the diuretic agents for most patients with heart failure. Thiazide diuretics may be useful in hypertensive patients with the symptoms of moderate fluid retention since their administration results in a more pronounced antihypertensive effect [81].

Aldosterone receptor antagonists

Hyperaldosteronism is present in nearly all patients with cirrhosis and heart failure. Aldosterone may have various harmful effects on the myocardium and the cardiovascular system [16]. Consequently, mineralocorticoid receptor antagonists may be among the first choices of therapy [84]. They can improve the hemodynamic properties of patients with cirrhosis and may decrease the severe symptoms of heart failure [85]. According to the data obtained from the RALES (Randomized Aldactone Evaluation Study) trial, a 30% reduction in all-cause mortality and a reduced risk of sudden cardiac death can be reached with the use of spironolactone in patients with chronic heart failure (left ventricular EF <35%) [86]. The selective aldosterone blocker, eplerenone has also been shown to reduce cardiovascular deaths and hospitalizations due to heart failure in a wider range of patients [87]. Therefore, aldosterone receptor antagonists are useful therapeutic tools in the management of patients with symptomatic heart failure and reduced left ventricular ejection fraction. Importantly, the careful monitoring of serum potassium and renal function can help to avoid the danger of hyperkalemia and renal insufficiency. A beneficial effect of the aldosterone antagonist, K-canrenoate has been shown to reverse myocardial fibrosis in patients with pre-ascitic cirrhosis [81, 88].

Beta-receptor blockers

The beta-adrenoceptor blockers, especially the non-selective ones (propranolol, nadolol) are effective in reducing portal hypertension and thus in the prevention of the gastroesophageal bleeding. More recently, carvedilol – a vasodilator, non-selective beta-blocker (NSBB) with intrinsic anti-alfa adrenergic activity – has been reported to have greater effect on decreasing portal hypertension than propranolol or nadolol. Additionally, beta-blockers can improve the cardiac contractile function [89, 90]. At the same time, no studies on beta-blockers for CCM are available so far. Beta-receptor blockers may be one of the choices of treatment since more trials showed their effectiveness in the reduction of mortality in patients with systolic heart failure [51, 91]. Bisoprolol, metoprolol succinate and carvedilol have been proven to be the most effective in this field. Due to the beneficial effect of carvedilol on portal hypertension, this agent could be the first consideration in CCM [81]. Furthermore, long-term treatment with beta-blockers can decrease the symptoms of heart failure, and improve the patient's clinical status. Management with beta-blockers should be initiated at low doses, and patients should be carefully monitored, since therapy may result in fluid retention and worsening heart failure, bradycardia, pulse conduction abnormalities and hypotension. Even if symptoms do not improve, long-term treatment should be maintained in order to reduce cardiovascular mortality [81, 92]. In addition, NSBBs have been proven to restore lengthened QT intervals towards normal in patients with cirrhosis [51]. Despite all these beneficial clinical data currently no definitive recommendation for the chronic administration of beta-blockers can be made in patients with cirrhosis.

Transjugular intrahepatic portosystemic shunt (TIPS)

Since TIPS can rapidly shift a significant amount of blood from the splanchnic area to the heart, it may result in a sudden worsening of the cardiac function in patients with cirrhosis, especially in individuals with impaired diastolic function [93].

Liver transplantation

Liver transplantation is known to be a solution for liver failure due to cirrhosis. Interestingly, it seems to cure the associated cardiomyopathy as well [20]. Previously, amelioration of left ventricular hypertrophy, diastolic (lusitropic) dysfunction and normalization of the contractile function after transplantation have been reported [7]. Prolonged QTc has also been shown to be reversible by liver transplantation, despite remaining lengthened right after the surgery [94]. On the contrary, orthotropic liver transplantation may cause severe hemodynamic consequences, since it can result in an abrupt decrease in cardiac output due to the clamping of the inferior vena cava. Moreover, a post reperfusion injury, secondary coagulopathy, and post-operative hydrostatic pulmonary edema may worsen the clinical outcome [95]. In addition, cirrhotic patients with concomitant severe cardiomyopathy may benefit from cardiac transplantation [96].

Farnesoid X receptor agonists

Novel therapeutic attempts are aiming to increase the intrahepatic concentration of vasodilators. Farnesoid X

receptor agonists are responsible for hydrogen sulfide production; moreover, NCX-1000 may release NO in the liver [97]. These agents are promising for future therapeutic regimens but their exact role is not yet elucidated in CCM.

CONCLUSIONS

Currently, there is no single diagnostic tool that can help to identify patients with CCM. Patients with symptoms of heart failure suffering from cirrhosis should undergo a cardiac screening to clarify the structural and functional properties of the heart. We emphasize that an early recognition of systolic or diastolic myocardial dysfunction by means of echocardiography may help to prevent the patient from further worsening of his/her clinical status. Furthermore, electrocardiography can help to recognize the increased risk for arrhythmias and sudden cardiac death. Natriuretic peptides may attract attention to the altered intracardiac pressure and volume conditions, while novel laboratory markers may reflect cardiac and hepatic fibrosis. Evidence for cardiomyopathy should be suspected in patients with worsening symptoms and clinical results, who may benefit from a proper treatment of the underlying pathology. At present the management of CCM should follow the recommendations for the treatment of patients with heart failure. Further investigations may help to improve our knowledge on cardiac consequences of liver diseases.

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Conflicts of interest: None to declare.

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