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Update on cirrhotic cardiomyopathy: from etiopathogenesis to treatment

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Abstract

Cirrhotic cardiomyopathy represents a syndrome of cardiac dysfunction associated with advanced liver disease. It is the result of complex pathophysiological processes that complicate the course of the disease, and is generally associated with a poor prognosis. Pathophysiologically, portal hypertension is the key factor leading to hyperdynamic circulation, via over-activation of the neurohumoral axis. Intestinal obstruction, subclinical inflammation and hepatocellular insufficiency, with defective synthesis or metabolism of several vasoactive mediators, are essential components of this process. Since it is usually unapparent at rest and only unmasked by an inadequate cardiac response to hemodynamic stress, the diagnosis of cirrhotic cardiomyopathy is challenging and demands a multimodal approach. There is currently no specific therapy, but there are prognostically effective drugs available to treat heart failure. Therefore, it is crucial to identify patients with chronic liver disease and heart failure in order to ameliorate their outcome. This article attempts to highlight the most important aspects of cirrhotic cardiomyopathy and draws attention to this condition.

Keywords Cirrhosis, cardiomyopathy, liver, heart, portal hypertension

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Introduction

Chronic liver disease (CLD) and cirrhosis are responsible for two million deaths worldwide each year. The main causes of CLD and cirrhosis are alcohol-related liver disease (ALD), metabolically-associated fatty liver disease (MAFLD, previously also known as nonalcoholic fatty liver disease [NAFLD]) and chronic hepatitis B virus and hepatitis C virus, despite advances in the treatment of viral hepatitis [1,2]. The incidence of cirrhosis in Europe is rising and may become a growing public health problem. In particular, MAFLD is an emerging problem for CLD, not only in Europe but also worldwide, with an estimated global prevalence of 25% [3]. In 2020, MAFLD was introduced to replace the term NAFLD, since it better reflects the disease's association with metabolic dysfunction. The latter is characterized by fat accumulation in the liver, associated with low-grade smoldering inflammation, oxidative stress, mitochondrial dysfunction and gut microbiota dysbiosis, leading to long-term cardiovascular and hepatic complications [4,5]. Importantly, metabolically-associated steatohepatitis, a subtype of MAFLD associated with inflammation and hepatocyte injury, is the fastest growing cause of chronic liver failure requiring liver transplantation [6].

CLD can eventually lead to liver cirrhosis, and the course of the disease is mainly determined by the complications. The underlying mechanism that gives birth to complications in patients with cirrhosis is portal hypertension, which eventually leads to intestinal congestion, resulting in translocation of bacteria/endotoxins into the systemic circulation, thus causing a subclinical "smoldering" inflammatory state [7]. This state, together with hepatic insufficiency and impaired synthesis or metabolism of various substances (proteins and lipids/lipoproteins), is pathophysiologically associated with cardiac dysfunction in patients with cirrhosis. Patients with end-stage liver disease exhibit a 5-fold higher risk of developing heart failure, especially heart failure with preserved ejection fraction (HFpEF), which is a topic of interest among cardiologists [8]. A condition commonly seen in patients with end-stage liver

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disease is called cirrhotic cardiomyopathy (CCM). It is defined as a subclinical cardiac dysfunction, characterized by impaired cardiac contractility during exercise and/or altered diastolic relaxation with electrophysiological abnormalities, in patients without pre-existing heart disease [9,10]. CCM attracts attention because of its association with cardiovascular disease post liver transplantation, and because 7-24% of early deaths after liver transplantation are attributed to heart failure [11,12]. Furthermore, it has been revealed that the main cause of death in patients with cirrhosis treated with a transjugular intrahepatic portosystemic shunt (TIPS) was cardiac decompensation, and that 20% of these patients developed acute heart failure within 1 year of TIPS insertion, highlighting the paramount significance of cardiac diagnostics to assess cardiac function in patients with liver cirrhosis [13-16]. Within this review, we aim to focus on the hemodynamic and cardiac changes in advanced stages of liver cirrhosis, with an emphasis on CCM, including its pathophysiology, current diagnosis and treatment.

Epidemiology and definition

CCM is an underdiagnosed condition/complication of patients with liver cirrhosis. It is a subclinical cardiac dysfunction characterized by a blunted contractile response to exercise and/or altered diastolic relaxation with electrophysiological abnormalities, in the absence of a known history of cardiac disease [9,10]. In most cases, CCM is recognized when clinical decompensation occurs, with patients often presenting with features of high-output heart failure or HFpEF. As CCM defines a subclinical cardiac dysfunction, the disease becomes particularly relevant when a stressor, such as fluid overload, alters hemodynamics [10,16,17]. This has mostly been observed in the decompensated state of cirrhosis and/or advanced stages of cirrhosis, when the inflammatory state becomes the predominant pathophysiology [17,18]. Since CCM is clinically silent, and the number of unreported cases is thought to be high, the prevalence and incidence of CCM are rather underdiagnosed. Furthermore, the literature on the prevalence of CCM is conflicting (depending on the diagnostic criteria used) [10,19]. Studies have estimated the prevalence of CCM to be in the range 50-70%, using the 2005 criteria of the Cirrhotic Cardiomyopathy Consortium (CCC), and 29-55.7% using the 2019 criteria [19,20].

The American Heart Association and American College of Cardiology guidelines define heart failure as a clinical syndrome (applicable to the full spectrum of heart failure) divided into 4 distinct categories (Table 1). Stage A is characterized by risk factors such as arterial hypertension and type 2 diabetes mellitus, which we often see in patients with metabolic syndrome. Stage B is characterized by demonstrable structural changes in the heart without clinical manifestations, and stage C is defined by additional clinical manifestations. The final stage, D, is described by refractory symptoms [21].

From a theoretical perspective, this classification seems reasonable and enables us to better comprehend the progression of heart failure. However, in real-world clinical practice, CCM is difficult to distinguish and diagnose. For instance, CCM at rest corresponds to stage B heart failure, with no clinical manifestations of the disease. In addition, in advanced liver cirrhosis, the symptoms of increased total body water can mask the presence of heart failure. The unique pathophysiology of CCM demands a specific clarification in which various findings, such as clinical, echocardiographic, electrocardiographic and biomarkers, are considered for the diagnosis. The definition of CCM, was first described in 2005 at the World Congress of Gastroenterology (WCG) in Montreal, and was updated in 2020 to take account of further developments in ultrasound diagnostics. The latter were based particularly on the development of tissue Doppler imaging and speckle-tracking echocardiography [22].

Pathophysiology

Portal hypertension and hemodynamic changes

The main pathophysiological cause of cardiac dysfunction is the maximally activated neurohumoral axis and associated cardiac changes [9,23,24]. This pathophysiological response is well known in cardiology, and therapeutic approaches aim to interrupt this vicious circle ("Fantastic Four" for the treatment of heart failure with reduced ejection fraction, HFrEF) [25]. The pathophysiological cause of CCM in patients with liver cirrhosis is portal hypertension (Fig. 1) leading to hyperdynamic circulation, intestinal obstruction and a subclinical inflammatory state, as well as hepatocellular insufficiency with defective synthesis or metabolism of several vasoactive mediators [9,16,18]. Two main mechanisms contribute to portal hypertension: first, increased resistance to portal blood flow, and second, raised portal blood flow as a counter-reaction to maintain metabolic hemostasis. The progressive fibrotic transformation of liver parenchyma leads to changes in hepatic and vascular architecture that ultimately increase resistance to portal blood flow and represent the initial mechanism of portal hypertension [7,26-28]. The elevation of resistance occurs dynamically at the intrahepatic vascular level. Both activated stellate cells in the hepatic sinusoids, which acquire more contractile properties, and an imbalance between vasoconstrictive and vasodilating mediators, result in a net intrahepatic vasoconstriction leading to an increase in vascular resistance, and can induce rapid changes in portal pressure [7,28,29]. The best studied vasoactive mediator in this context is nitric oxide (NO). Impaired NO production in sinusoidal endothelial cells due to increased caveolin expression is thought to be the main cause of intrahepatic vascular resistance [30]. The elevation of portal pressure leads subsequently to changes in the peripheral circulation, particularly in the splanchnic bed. In contrast to the intrahepatic circulation, the splanchnic circulation is characterized by raised endothelial NO production [29,31]. In addition to NO, other mediators have also been associated with splanchnic arterial vasodilation, including carbon monoxide (CO) and endogenous cannabinoids (ECs) [32]. Insufficient

Table 1 Classification of CCM

	Early stage		Late stage	
	Stage A	Stage B	Stage C	Stage D
ACCF/AHA HF Stage	High risk for HF, without structural heart disease or symptoms of HF	Structural heart disease but without signs or symptoms of HF	Structural heart disease with prior or current symptoms of HF	Refractory HF requiring specialized interventions
CCM Correlate	Cirrhosis or metabolic syndrome with risk for HF without structural heart disease or symptoms of HF	Structural heart disease e.g., systolic and/or diastolic dysfunction without signs or symptoms of HF	Structural heart disease e.g., systolic and/or diastolic dysfunction with prior or current signs or symptoms of HF	Refractory HF requiring specialized interventions

ACCF, American College of Cardiology Foundation; AHA, American Heart Association; CCM, cirrhotic cardiomyopathy; HF, heart failure

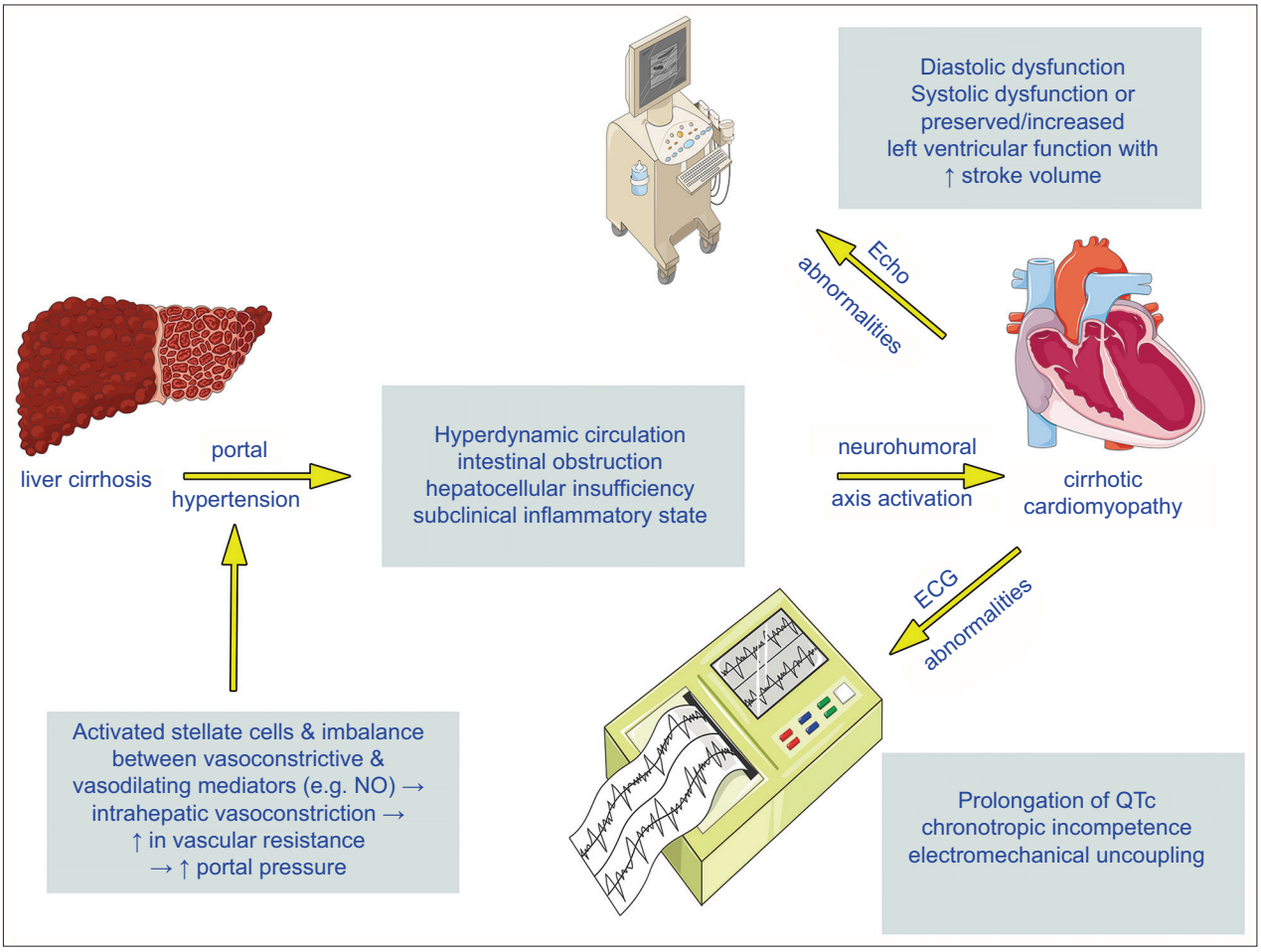

Figure 1 Pathophysiology of cirrhotic cardiomyopathy
ECG, electrocardiography; NO, nitric oxide; QTc, corrected QT

hepatic degradation or escape of vasodilators through portosystemic shunts as the disease progresses maintains the vasodilatory state. The vasodilation in the splanchnic capillaries and arterioles increases portal flow, which, in combination with increased intrahepatic vascular resistance, eventually leads to portal hypertension (forward and backward portal hypertension) [26]. As the splanchnic area accounts for approximately 25% of peripheral resistance, vasodilation leads to a reduction in effective circulating blood volume, which subsequently activates several neurohumoral mechanisms for circulatory regulation (i.e., sympathetic nervous system (SNS), renin–angiotensin–aldosterone system (RAAS) and non-osmotic release of vasopressin) [7]. To maintain circulatory function, plasma volume is increased and the SNS is activated. As liver cirrhosis progresses, these compensatory mechanisms are unable to counteract the vasodilatory state

and systemic blood pressure progressively decreases. The maximum activation of these compensatory mechanisms leads to an increase in cardiac output, resulting in a hyperdynamic circulatory state. These changes occur at rest to maintain organ perfusion, and cardiac decompensation may occur during exercise. In summary, the maximal activation of neurohumoral mechanisms over time is responsible for the systolic, diastolic and electromechanical changes in the cirrhotic heart, known as CCM [9,16,31,33].

Inflammatory state in liver cirrhosis

The hyperdynamic circulatory state has long been regarded as the core causality for the development of extrahepatic organ dysfunction in patients with advanced liver cirrhosis (e.g., CCM, hepatorenal syndrome, hepatopulmonary syndrome). However, in recent years it has become more evident that the complex effects on other organs cannot be explained by hemodynamic changes alone. For instance, it was previously not clear how to interpret the strong production of vasodilating mediators (NO, CO, ECs, prostacyclin). It has been demonstrated nowadays that patients with advanced liver cirrhosis often have subclinical inflammation due to a plethora of different circulating cytokines [34,35]. Mesenteric congestion due to portal hypertension leads to translocation of intestinal bacteria and endotoxemia. The disruption of the intestinal mucosal barrier and changes in the microbiome allow bacteria and bacterial components (pathogen-associated molecular patterns) to enter the bloodstream from the gut via the mesenteric lymph nodes. Loosening of cell–cell connections (tight junctions) and increased venous congestion with subsequent edema of the intestinal wall are regarded as the cause of increased bacterial translocation [36]. Although the intestinal mucosal immune system eliminates translocated bacteria to prevent an infection, a chronic inflammatory response nevertheless occurs [37]. This inflammation advances as liver cirrhosis also progresses. The cytokines released eventually affect various organs, including the heart [35].

Systolic dysfunction

Systolic dysfunction is one of the criteria for CCM and is usually the result of a contractility disorder. According to the 2005 WCG, systolic dysfunction is defined as a left ventricular ejection fraction (LVEF) <55% at rest and/or blunted contractile response to exercise [9,11,16]. However, the majority of patients with CCM have preserved or increased left ventricular function, with an increased stroke volume due to the hyperdynamic state, and this is associated with an increased preload, a higher heart rate and a low afterload, which may mask the resting contractile dysfunction of the heart. Because of this phenomenon, the systolic dysfunction appears mainly under physical stress. It is assumed that patients with CCM exhibit a contractility disorder under "stress", i.e., exercise, circulatory changes or vasoactive drug infusions, and are not able to increase LVEF and cardiac output as expected [9,10,16,31,33]. This was postulated in 1969 in a study of patients with alcoholic cirrhosis, and has been further demonstrated in other studies [38]. In 2001, Wong *et al* similarly reported that patients with liver cirrhosis, regardless of the cause, were unable to increase LVEF or cardiac output during exercise [39]. The systolic dysfunction is explained by the fact that the heart is already pumping at the limit of its capacity at rest, so further increases in output and contractility cannot be achieved on demand. Studies reporting a decrease in LVEF after liver transplantation, due to a sudden increase in afterload and reversal of the hyperdynamic circulation, suggest that a contractile defect must be present from the outset in these patients [40]. Furthermore, Shin *et al* demonstrated the differences in cardiac mechanics in CCM compared to the normal population, exhibiting a rightward shift of the cardiac pressure–volume curve. In the shifted curve, end-systolic elastance and arterial elastance were reduced; therefore, they demonstrated reduced intrinsic ventricular contractility and integrated arterial load in CCM [41]. The underlying molecular mechanisms that play a central role in the pathogenesis of the contractile dysfunction are an increased level of cardiac depressant and vasoactive molecules and an altered β-adrenergic signaling pathway [16-18,31]. Pressure and volume receptors are important components of circulatory regulation and serve to maintain proper peripheral perfusion by activating the SNS. The activated SNS ultimately acts on the heart and circulation in response to the central hypovolemia seen in cirrhotic patients due to splanchnic and systemic vasodilation. In the long term, repetitive activation of the SNS contributes to the hyperdynamic syndrome and leads to elevated catecholamine levels. The elevated levels of catecholamines and the overactive SNS cause damage to cardiomyocytes, downregulation of β-adrenergic receptors, and desensitization of β-adrenergic receptors by uncoupling of G-protein from the β-adrenergic receptor, with decreased formation of cyclic adenosine monophosphate (cAMP) [42,43]. The subclinical inflammatory state caused by endotoxemia and elevated cytokine levels further enhances the production of vasoactive mediators (e.g., NO, CO, EC) and is postulated to depress cardiac function. These cardiodepressant mediators may cause dysfunction of myocardial membrane-bound calcium channels (e.g., L-type calcium channels, sodium–calcium exchanger), leading to an imbalance in intracellular calcium homeostasis, resulting in myocardial contraction–relaxation dysfunction and impaired electromechanical coupling [17,18,31]. In addition, studies with animal models suggest that NO and CO may increase the production of guanosine monophosphate, which leads to the depletion of cAMP and has negative inotropic effects [44,45]. Preclinical studies have also revealed that proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-6 and IL-1β are significantly elevated in cirrhotic rat hearts, and that inhibition of these cytokines alleviates myocardial inflammation, cardiac remodeling and contractile dysfunction [18].

Diastolic dysfunction

Retrospective data suggest that diastolic dysfunction has a prevalence of 10.5-33.3% in patients with cirrhosis [20,46]. Diastolic dysfunction is characterized by a stiff ventricle with impaired relaxation and filling. The most common histomorphological changes of the ventricles are myocardial hypertrophy, increased subendothelial edema formation and fibrosis [9,47]. These changes are mainly induced by an over-activated neurohumoral axis (SNS, RAAS), mechanical overload and the inflammatory state usually seen in advanced stages of cirrhosis with hyperdynamic circulation [31]. Inflammatory cytokines, such as IL-8, IL-6, IL-1β, TNF-α and transforming growth factor (TGF)-β, activate stress signaling pathways in the heart, promoting cardiomyocyte apoptosis and cell death [17]. The RAAS is thought to induce diastolic dysfunction via angiotensin II (AT II), by increasing salt and volume overload and inducing myocardial remodeling. Studies in rats show that AT II leads to increased expression of extracellular matrix proteins and increased TGF-β expression via the AT II type 1 (AT 1) receptor [31]. Cardiac fibrosis constitutes an important feature of pathological hypertrophy and heart failure, and is characterized by an increase in collagen and various other extracellular matrix components in the myocardium. In a relevant study using magnetic resonance imaging (MRI), Wiese *et al* demonstrated an increase in extracellular volume in the liver and heart in patients with liver cirrhosis, compared to non-cirrhotic controls, and associated elevated extracellular volume values in cirrhosis as a sign of diffuse myocardial fibrosis, a key morphological change in CCM [48]. Isaak *et al*, in a similar study using advanced contrast MRI, reported an association of myocardial fibrosis and subclinical myocardial inflammation in CCM with systolic and diastolic dysfunction [49]. Mechanistically impaired distensibility and relaxation impede adequate blood flow to the ventricles, resulting in a longer isovolumetric relaxation time and worsening passive early diastolic filling of the ventricles; the atria begin to contribute more to ventricular filling and left ventricular end-diastolic pressure rises. Thus, in 2005, the WCG characterized diastolic dysfunction in CCM according to one of the following criteria: prolonged deceleration time of early left ventricular filling velocity (DT >200 msec), prolonged isovolumetric relaxation time (IVRT >80 msec), or ratio of early (E) to late (A) left ventricular filling velocity <1 (E/A ratio <1) [9,22].

Electrophysiological abnormalities

The most commonly reported electrophysiological changes in patients with CCM are prolongation of the corrected QT interval (QTc), chronotropic incompetence and electromechanical uncoupling [16,31]. QTc prolongation is the most common electrophysiological abnormality in patients with CCM. Up to 50% of patients with liver cirrhosis are thought to have a prolonged QTc, regardless of the cause of the cirrhosis [9]. The QTc is also believed to correlate with the severity of cirrhosis, and should normalize after transplantation in 50% of cases [33,50,51]. However, *torsade de pointes* tachycardias, which can be associated with QTc prolongation, are much less common in CCM [10,52]. Nevertheless, it is essential to avoid drugs that may be associated with QTc prolongation [53]. The cause of QTc prolongation in CCM is regarded to be multifactorial, including shunting of cardioactive substances into the systemic circulation, ion channel remodeling and autonomic dysfunction [17,31].

Chronotropic incompetence is the inability of the heart to increase its rate in response to stress, such as physical exercise or pharmacological stimulation, to meet the metabolic demands of the peripheral circulation. Heart rate is an essential component in any further increase of cardiac output; thus, chronotropic incompetence has been associated with increased perioperative risk in patients undergoing liver transplantation [54]. Altered β-adrenergic signaling and/or autonomic dysfunction are thought to be responsible for chronotropic incompetence in CCM [55]. Another observation in patients with CCM is an increase in the time between electrical stimulation of the heart and immediate mechanical systole, known as electromechanical dyssynchrony [56]. This phenomenon is associated with a reduced cardiovascular response to exercise and, according to Bernardi *et al*, may contribute to systolic dysfunction [57].

Diagnosis

The absence of underlying chronic heart disease is a prerequisite for the diagnosis of CCM. The diagnostic criteria for CCM were published for the first time in 2005 at the WCG in Montreal. These diagnostic criteria were divided into 3 main categories, the first 2 of which assessed systolic and diastolic function. The last category included supporting criteria, such as the presence of electrophysiological or structural cardiac changes and laboratory findings, e.g., elevated levels of brain natriuretic peptide or n-terminal pro b-type natriuretic peptide [9,10].

In view of the significant advances in transthoracic echocardiography in recent years, particularly in tissue Doppler imaging (TDI) and myocardial strain analysis, new echocardiographic parameters have emerged to assess systolic or diastolic function. In 2015, the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) recommended myocardial strain analysis, more specifically longitudinal strain (GLS), in addition to LVEF, for the assessment of left ventricular contractility [58]. In addition, the ASE and EACVI updated their guidelines on the diagnosis and classification of left ventricular diastolic dysfunction in 2016 [59]. Based on these advances, the CCC, a group of multidisciplinary international experts, proposed new criteria for CCM in 2019 [22]. Taking into account the particular pathophysiology of CCM, characterized by a hyperdynamic circulation with low peripheral resistance and increased venous return, the new criteria, including the parameters of GLS and tissue Doppler velocity, appear to be more accurate in assessing systolic and diastolic dysfunction.

LVEF is a parameter of global left ventricular function, so in 2005 systolic dysfunction was defined as an LVEF <55% at rest, or as an inadequate increase in cardiac function (LVEF increase <5%) in response to extra metabolic demand, for instance physical exercise, volume loading or drug stimulation. However, the lower systemic vascular resistance and reduced afterload in CCM resulted in falsely high LVEF measurements and misinterpretation of systolic function [9]. Changes in contractility are not the only aspect affecting ejection fraction: preload, afterload and heart rate are also important, so knowledge of these conditions is required to interpret ejection fraction as a measure of contractility [60]. Therefore, the CCC recommended in 2019 that echocardiographic strain imaging should be performed to assess ventricular contractile function, updating the 2005 criteria for systolic dysfunction by further defining systolic dysfunction with a GLS <18% [22].

Echocardiographic deformation analysis or strain analysis examines the deformation of the myocardium in different dimensions (longitudinal, circumferential and radial) during systole, and quantifies regional myocardial contractile function by measuring myocardial shortening as a percentage [58]. As LVEF mainly represents the radial strain on the heart, and longitudinal strain is often impaired before radial function, the GLS is suitable for detecting subclinical systolic dysfunction before LVEF declines [22]. A GLS below 18% is indicative of early contractile dysfunction of the myocardium, and reveals a contractile dysfunction with preserved LVEF [61]. However, GLS is also a parameter that can be influenced by age, sex and left ventricular load. In addition, data on GLS in cirrhosis are sparse and several results are contradictory. While some studies have claimed that GLS is lower in cirrhotic patients compared with controls, other studies have reported higher or similar GLS in these patients.

Further studies have also investigated the relationship between GLS and the severity of cirrhosis according to the model for end-stage liver disease (MELD) and the Child-Pugh scores, and whether GLS is related to prognosis [62]. Mechelink *et al* showed that patients with advanced cirrhosis, including significant portal hypertension or decompensated cirrhosis, had a higher resting GLS. However, other studies report contradictory findings: for instance, more advanced cirrhosis, as defined by Child-Pugh or MELD, was not necessarily associated with a significantly higher GLS [62]. In the study by Mechelink *et al*, patients with a higher GLS were characterized by a lower contractile reserve, as shown by a dobutamine stress test, than patients with an initially lower GLS. Both low and high levels of GLS were associated with a greater risk of death. Since GLS is a parameter influenced by both contractility and preload, a high GLS at baseline highlighted the high output state and hemodynamic stress associated with advanced cirrhosis. Given that patients with advanced cirrhosis are already likely to have a higher mortality rate, a low GLS was considered an independent predictor of mortality [62,63]. On the other hand, in a study by Skouloudi *et al*, there was no difference in mortality in cirrhotic patients with a GLS lower or higher than the absolute mean of 22.7% [46]. These conflicting results suggest that several issues related to GLS remain unresolved, including its association with cirrhosis severity and prognosis, and that further research is warranted.

Another change in the definition of systolic dysfunction relates to LVEF, which has often been estimated to be higher as a result of the unique pathophysiology of CCM. Therefore, systolic dysfunction has been defined as LVEF ≤50% according to the 2019 diagnostic criteria [22]. Assessment of cardiac contractility under stress, one of the main criteria from 2005, was removed from the revised 2019 criteria, on the grounds that most patients with advanced cirrhosis are treated with β-blockers to lower portal pressure, and therefore diagnostic stress tests are not a valid way of assessing cardiac response [11]. The fact that the stress test has lost significance according to the new criteria seems unfortunate, as an insufficient increase in cardiac output is ultimately a key feature of CCM. Nevertheless, stress echocardiography is an important tool, not essential for diagnosis, but for the further assessment, preprocedural evaluation and risk stratification of patients with CCM [62].

In 2005, the presence of any of the aforementioned parameters (DT >200 msec, IVRT >80 msec, E/A ratio <1) was associated with diastolic dysfunction and defined the diastolic component of CCM. However, these echocardiographic parameters are dynamic, volume-dependent, and therefore not sufficiently specific to detect reduced compliance and hence diastolic ventricular dysfunction [22]. Given the improvements in transthoracic echocardiography for the assessment of diastolic dysfunction in heart failure secondary to chronic heart disease, and based on the recommendations of the ASE, the CCC recommended new criteria for the assessment of diastolic function in 2019 [22,59]. According to these criteria, diastolic dysfunction was defined by the presence of at least 3 of the following parameters. Early diastolic transmitral flow (E) to early diastolic mitral annular tissue velocity (e') ratio (E/e') ≥15, septal e' <7 cm/sec, left atrial volume index >34 mL/m^2 or peak velocity of tricuspid regurgitation >2.8 m/sec in the absence of pulmonary hypertension. The E/A ratio is recommended to assess the severity of diastolic dysfunction. Patients with 2 of the above criteria were recommended to undergo further diagnostics to assess diastolic dysfunction. In 2020, the CCC published the revised diagnostic criteria for CCM [11,22] (Table 2).

Table 2 Revised diagnostic criteria for cirrhotic cardiomyopathy

2005 Criteria	2020 Criteria
Systolic dysfunction (any of the following)	
LVEF <55% Blunted response to stress	LVEF ≤50% GLS with absolute value <18%
Diastolic dysfunction (any of the following)	Diastolic dysfunction (≥3 of the following)
E/A <1 DT >200 msec IVRT >80 msec	Septal e velocity <7 cm/sec E/e' ≥15 LAVI >34 mL/m^2 TR peak velocity >2.8 m/sec

LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; E/A, ratio of early to late left ventricular filling velocity; DT, deceleration time; IVRT, isovolumetric relaxation time; E/e', ratio of early diastolic transmitral flow to early diastolic mitral annular tissue velocity; LAVI, left atrial volume index; TR, tricuspid regurgitation

Old vs. new diagnostic criteria

Studies comparing the CCC criteria with the WCG criteria for the diagnosis of CCM have revealed that there is a discrepancy in the prevalence of CCM (Table 3), particularly with regard to diastolic dysfunction. This discrepancy between the old and new criteria can largely be explained by the fact that the CCC criteria are less influenced by changes in intravascular volume status and preload. Thus, the parameters for TDI appear to be more specific in the diagnosis of diastolic dysfunction, although the CCC criteria make the assessment of diastolic function more complex. It should be stressed that the CCC criteria practically exclude patients with grade I diastolic dysfunction, and that in one group of patients, diastolic function is defined as indeterminate, which complicates the classification of these patients [62]. However, studies have shown that abnormalities in TDI parameters of diastolic dysfunction in CCM are associated with disease progression after transplantation. For instance, an abnormal septal e′ (<7 cm/sec) was the most predictive marker of cardiac events after transplantation, or an E/e' >9.2 correlated with the occurrence of arrhythmias and atrial fibrillation in patients with decompensated liver cirrhosis after transplantation [64,65]. In a recently published study, evaluation of TDI parameters (septal e′ and E/e) in patients with acute-on-chronic liver failure (ACLF) and sepsis-induced hypotension was able to predict circulatory failure and mortality. Furthermore, the study indicated that the integration of these variables into traditional risk prediction models, such as MELD-Sodium and the Chronic Liver Failure Consortium ACLF, improved the predictive performance of these scores [66]. On the other hand, there is also established evidence that a normal E/e' does not rule out diastolic dysfunction. The study by Karagiannakis *et al* had an interesting approach and assessed diastolic dysfunction under stress. It was striking that some parameters exhibited significant deterioration under stress, so that the authors recommended evaluating diastolic function under stress, especially in more advanced liver disease [67]. There are only a few studies in the literature that have compared and analyzed the mortality and prognosis of CCM according to the CCC and WCG criteria. Skouloudi *et al* and Singh *et al* evaluated mortality in CCM according to the CCC criteria and found no association. In a retrospective study by Spann *et al*, the occurrence of major adverse cardiac events and death after liver transplantation was associated with CCM according to the CCC criteria, but not according to the WCG criteria. In this study, 30% of patients who underwent echocardiography before liver transplantation were diagnosed with CCM according to the CCC criteria. All cases of CCM diagnosed according to the CCC criteria were due to diastolic dysfunction. The authors concluded that the CCC criteria are superior to the WCG criteria in predicting adverse cardiac events and death after liver transplantation [46,68,69].

HFpEF and CCM

Diastolic dysfunction in CCM actually implies HFpEF, but it cannot be deduced with certainty that patients with CCM who are diagnosed with diastolic dysfunction, according to the CCC criteria, also satisfy the HFpEF diagnosis, according to the criteria of the European Society of Cardiology (ESC). HFpEF is not a simple clinical diagnosis, so in 2019 the ESC's Heart Failure Association proposed the HFA-PEFF diagnostic algorithm. This is a step-by-step diagnostic procedure that combines parameters from clinical, laboratory and imaging tests to determine the likelihood of a diagnosis. According to the algorithm, a HFA-PEFF score of more than 5 points indicates definite HFpEF, whereas a score of 1 point renders HFpEF unlikely (Table 3) [70]. In a study by Shin *et al*, 6.6% of patients with end-stage liver disease (ESLD) had a high probability of HFpEF according to the HFA-PEFF score, and HFpEF was associated with poorer long-term survival after liver transplantation, especially in patients with advanced liver disease. They concluded that identification of HFpEF using the HFA-PEFF score and management of modifiable risk factors may improve post-liver transplantation survival [71]. Dimitroglou *et al*, who conducted a prospective cohort study of patients with liver cirrhosis, reported that 1- and 2-year cumulative mortality rates were higher in those with high HFA-PEFF scores compared to those with intermediate/low scores [72].

Table 3 Prevalence of cirrhotic cardiomyopathy (CCM) according to the Cirrhotic Cardiomyopathy Consortium (CCC) criteria

Authors [ref.]	2019 CCC	Study objective
Izzy *et al* [64]	34.8%	Prevalence of CCM according to the new criteria and its impact on post-transplant cardiovascular disease
Razpotnik *et al* [20]	19%	Prevalence of CCM using the CCC criteria in cirrhotic patients
Köckritz *et al* [90]	27.5%	Assessment of left ventricular function and atrial myocardial deformation in ESLD
Singh *et al* [68]	85.6%	Assessment of frequency of CCM, association of CCM with pre- and post-transplant outcomes according to CCC criteria
Spann *et al* [69]	30%	Prediction of post-transplant cardiac outcomes in CCM according to CCC criteria
Arman *et al* [91]	17.6%	CCM in patients who have undergone liver transplantation
Cesari *et al* [92]	29%	Prevalence and prognostic association of CCM according to CCC criteria
Skouloudi *et al* [46]	8.1%	To evaluate LV-GLS and left atrial strain in relation to the severity of liver disease and to assess the characteristics of CCM

ESLD, end-stage liver disease; LV-GLS, left ventricular global longitudinal strain

Current and novel treatments

There has been significant progress in the treatment of heart failure in recent years. The prognosis for individuals with heart failure has ameliorated considerably. Angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor/neprilysin inhibitors (sacubitril/valsartan), β-blockers, mineralocorticoid receptor antagonists (MRAs) and sodium-glucose co-transporter 2 inhibitors (SGLT2i), also known as the "Fantastic Four", are the standard of care for patients with HFrEF (LVEF <40%) [25]. They have also been shown to be beneficial in heart failure patients with mildly reduced ejection fraction (HFmEF, LVEF 40-50%) [73]. The SGLT2i EMPEROR-Preserved and DELIVER studies, 2 large positive-endpoint trials, also reported further positive prognostic effects in patients with preserved ejection fraction (HFpEF, LVEF >50%), who primarily have diastolic dysfunction [74,75].

Despite these advances in the treatment of heart failure, there is currently no specific treatment for CCM and the prognosis for CCM is poor. If symptomatic heart failure is present, diuretics should be used initially [76]. In fact, most patients with (decompensated) liver cirrhosis and ascites are usually treated with high doses of MRAs, which are the standard of care, along with loop diuretics and sodium restriction in the presence of volume overload. From a pathophysiological point of view, MRAs represent an important aspect of therapy because of the secondary hyperaldosteronism associated with the hyperdynamic state [77-79]. Studies have also shown that MRAs inhibit myocardial fibrosis and left ventricular remodeling, thereby improving diastolic function [80,81]. Similarly, ACEi inhibit the neurohumoral axis, but ACEi can decrease systemic vascular resistance and thereby reduce systemic perfusion, and are therefore contraindicated in liver cirrhosis [7,55].

Patients with liver cirrhosis usually receive non-selective β-blockers, such as carvedilol, for primary and secondary prophylaxis in the presence of portal hypertension and evidence of varices. By reducing portal pressure, they reduce intestinal congestion and bacterial translocation from the gut [82]. They also have a beneficial effect on the hyperdynamic circulation, reducing cardiac workload and improving the QTc interval [9]. However, it is unclear to what extent this shortening of the QTc interval has a beneficial effect on the prognosis of CCM [9,10]. Despite the benefits of β-blockers mentioned above, there is evidence that they can shorten survival time in advanced stages of cirrhosis with CCM and hyperdynamic syndrome, where a maximally activated sympathetic nervous system maintains peripheral organ perfusion. Ultimately, the patient with CCM is dependent on the increased cardiac output. The negative inotropic and chronotropic effect can impair perfusion. β-Blockers are therefore contraindicated in decompensated liver cirrhosis, as they can cause end-organ damage, for instance hepatorenal syndrome [83]. The so-called "window theory" has been proposed to describe the time when the negative effects of β-blocker therapy become predominant. According to this theory, patients benefit most from the beneficial effects of β-blockers in the phase between mild and decompensated cirrhosis. However, the exact timing of the opening and closing of this window is unclear [84].

Sacubitril/valsartan has not been studied in patients with CCM. However, data have proposed that significant arterial hypotension can occur with sacubitril/valsartan therapy, so this option appears to be more limited in CCM [85]. SGLT2i have not been studied in CCM, but SGLT2i have demonstrated beneficial effects in MAFLD by reducing intrahepatic triacylglycerol levels and improving hepatic steatosis and fibrosis. They reduce insulin concentrations and enhance insulin sensitivity, leading to reduced inhibition of lipolysis. They have also been shown to improve liver function by reducing inflammation and oxidative stress [4]. A meta-analysis has reported that the SGLT2i dapagliflozin improves liver function parameters and metabolic outcomes in patients with MAFLD [86]. Studies with SGLT2i in patients with cirrhosis and ascites are ongoing. In this context, it might be interesting to investigate what effect they might have on CCM. Based on current observations, liver transplantation appears to be the only option to reverse the hyperdynamic state and treat CCM. Liver transplantation is a hemodynamically demanding procedure, both perioperatively and in the early postoperative period, which increases the risk of acute heart failure in CCM. Nevertheless, data have shown that, after correction of the metabolic and/or inflammatory state and subsequent reversal of the hyperdynamic circulation, there is an improvement in systolic and diastolic cardiac function over the course of the disease. As CCM may require up to 6 months to resolve, close postoperative monitoring with follow-up echocardiography 3-6 months after transplantation is essential and recommended [6,11,19].

Artificial extracorporeal liver support is used to replace failing liver function as a bridge to recovery and/or a bridge to transplantation in acute liver failure and acute-on-chronic liver failure. The molecular adsorbent recirculation system and therapeutic plasma exchange, 2 modalities used for liver support, have revealed beneficial effects on systemic hemodynamics by reducing endogenous vasodilators and proinflammatory cytokines; therefore, these modalities may have a beneficial effect on CCM. However, there are no data or observations regarding their effect in CCM [87].

Concluding remarks

CCM is a clinically relevant condition that complicates the course of advanced liver disease. There is no specific treatment for CCM, although liver transplantation appears to resolve the cardiac dysfunction [19]. However, CCM has also been associated with an increased risk of cardiovascular disease after liver transplantation. In this respect, identification of these jeopardized patients and more precise guidelines, with a focus on clinical trials evaluating different cardiac imaging modalities, may improve outcomes for these patients in the future.

In addition, accurate and early assessment of patients with CLD and risk factors for CCM before the disease advances, might improve patient outcomes [6]. Furthermore, relevant

studies have reported an association between MAFLD and HFpEF, and HFpEF is the most common cardiac dysfunction in ESLD [8,88]. Since CCM appears to be independent of the etiology of liver disease, and to our knowledge there are no studies evaluating MAFLD and CCM [89], it would be an attractive field of research, as SGLT2i have demonstrated beneficial effects in MAFLD [4].

Taken together, CCM is an underdiagnosed and relevant pathology with a generally bad prognosis, and the only effective treatment might be liver transplantation. There is a clear necessity for further disease-modifying therapies and studies targeting inflammation, as the inflammatory state is the dominant phenotype in patients with ESLD and CCM.

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