MINIREVIEWS

Cirrhotic cardiomyopathy: Implications for the perioperative management of liver transplant patients

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Abstract

Cirrhotic cardiomyopathy is a disease that has only recently been recognised as a definitive clinical entity. In the setting of liver cirrhosis, it is characterized by a blunted inotropic and chronotropic response to stress, impaired diastolic relaxation of the myocardium and prolongation of the QT interval in the absence of other known cardiac disease. A key pathological feature is the persistent over-activation of the sympathetic nervous system in cirrhosis, which leads to down-regulation and dysfunction of the β-adrenergic receptor. Diagnosis can be made using a combination of echocardiography (resting and stress), tissue Doppler imaging, cardiac magnetic resonance imaging, 12-lead electrocardiogram and measurement of biomarkers. There are significant implications of cirrhotic cardiomyopathy in a number of clinical situations in which there is an increased physiological demand, which can lead to acute cardiac decompensation and heart failure. Prior to transplantation there is an increased risk of hepatorenal syndrome, cardiac failure following transjugular intrahepatic portosystemic shunt insertion and increased risk of arrhythmias during acute gastrointestinal bleeding. Liver transplantation presents the greatest physiological challenge with a further risk of acute cardiac decompensation. Peri-operative management should involve appropriate choice of graft and minimization of large fluctuations in preload and afterload. The avoidance of cardiac failure during this period has important prognostic implications, as there is evidence to suggest a long-term resolution of the abnormalities in cirrhotic cardiomyopathy.

Key words: Cirrhotic cardiomyopathy; Liver transplantation; Diastolic dysfunction; Electrophysiological abnormalities; Perioperative care

Core tip: Cirrhotic cardiomyopathy is characterised by a blunted inotropic and chronotropic response to stress, impaired diastolic relaxation and prolongation of the QT interval. It is only recently that it has been recognised as a definitive clinical entity, and yet it has significant implications in a number of clinical situations in which there is increased physiological demand, which can lead to acute cardiac decompensation and heart failure. Liver transplantation is one such situation, and in this review we discuss criteria for diagnosis, possible methods to limit further deterioration and the perioperative management of these patients.

INTRODUCTION

Cirrhotic cardiomyopathy (CCM) in a patient with chronic liver disease is a clinical entity characterised by a blunted inotropic and chronotropic response to stress, impaired diastolic relaxation and prolongation of the QT interval. These abnormalities occur in the absence of other known cardiac disease, are independent of liver aetiology, and occur to a variable degree in up to 40%-50% of patients with cirrhosis.

Currently, CCM is often undetected, as it is not widely recognised and is largely asymptomatic at rest, with overt heart failure being rare in cirrhosis. This latent cardiomyopathy classically only manifests itself during periods of physiological or pharmacological stress, but it assumes clinical importance in the setting of events that challenge the cardiovascular system. It is associated with an increased risk of hepatorenal syndrome, particularly following sepsis, and insertion of transjugular intrahepatic portosystemic shunts (TIPS) can precipitate acute cardiac failure following the sudden delivery of an increased volume load to the heart. Liver transplantation presents the greatest physiological challenge, with the significant fluctuations in preload and afterload during the peroperative period. Cardiac decompensation at this stage can lead to graft failure, multi-organ failure and death.

Long term however, there is a reversal of the abnormalities evident in cirrhotic cardiomyopathy, with both structural and functional improvements seen by six to twelve months post-transplantation. It is important therefore to recognise and diagnose this condition of impaired cardiac reserve function to minimise the incidence of decompensation during periods of increased demand. Careful patient selection and additional monitoring for invasive procedures pre-transplantation, followed by appropriate graft allocation and tailoring of both anaesthetic and surgical techniques at the time of transplant may improve postoperative outcomes with improved longer-term survival. The key points are summarised in Table 1.

CLINICAL FEATURES

Cirrhotic cardiomyopathy is characterised by an impaired contractile response to stress, diastolic dysfunction and electrophysiological abnormalities. It is a spectrum of cardiological impairment that has its origin in the haemodynamic changes that accompany end stage liver disease (ESLD). The definition and diagnostic criteria were defined by an international expert consensus committee at the World Congress of Gastroenterology in 2005[1] (Table 2).

Hyperdynamic circulation of cirrhosis

Kowalski *et al*[2] were the first to report the existence of an altered circulation in 1953, describing an increased cardiac output at rest, with an inverse relationship to systemic vascular resistance. In addition, they noted that the increase in cardiac output was not accompanied by a parallel increase in oxygen consumption and that in one third of their study population, the QT interval was prolonged. Their findings were consistently reproduced in subsequent studies[3-7] and the concept of the "hyperdynamic circulation of cirrhosis" was established.

An altered vascular resistance and redistribution of plasma volume has been implicated as the cause of this hyperdynamic circulation[8]. The increase in intrahepatic resistance due to fibrosis causes hypertension in the portal circulation, which stimulates the release of circulating and endothelial vasodilators (both due to a compensatory release and an impaired hepatic degradation). The resulting peripheral arterial vasodilatation and subsequent volume expansion leads to an initially appropriate response of hyperkinesis in the circulatory system.

Over time, with worsening hepatic dysfunction, the increased volume is redistributed to the splanchnic bed. There is a resultant relative reduction in central blood volume (despite an increase in absolute volume), triggering an activation of the SNS and the renin-angiotensin-aldosterone system in an effort to counteract the low arterial blood pressure and volume reduction. Thus patients with cirrhosis exhibit enhanced activity of the SNS with increased circulating catecholamines in direct relation to the severity of the disease[9,10].

These findings of an increased cardiac output at rest and reduced systemic vascular resistance are not present in all patients with ESLD, with the degree of hyperkinesis correlating with worsening hepatocellular insufficiency and portal hypertension[11].

Systolic dysfunction under stress

Left ventricular ejection fraction (LVEF) at rest in the context of chronic liver disease has been reported to be normal[12,13] and often higher than controls[14]. In patients without ascites, the increased pre-load can compensate for cardiac dysfunction, whereas in patients with ascites, the reduced afterload secondary to the systemic arterial vasodilatation compensates for both a decreased preload and contractile dysfunction[15]. Thus, the majority of patients are asymptomatic for heart failure at rest.

When subjected to physiological[5,6,12-14,16] or pharmacological[17,18] stress however, the increase in contractility and cardiac output is significantly blunted in comparison to matched controls. There is an abnormal ventricular response to an increased

Table 1 Cirrhotic cardiomyopathy and liver transplantation

Key points

CCM is a latent cardiac dysfunction that is independent of aetiology and may be unmasked during periods of increased cardiovascular demand
It is characterised by systolic incompetence to stress, diastolic dysfunction and electrophysiological abnormalities
The persistent over-activation of the SNS in cirrhosis leads to down-regulation and dysfunction of the β-adrenergic receptor, a key pathological feature in CCM
Clinical implications include an increased risk of hepatorenal syndrome, cardiac failure following TIPS insertion and increased risk of arrhythmias during acute gastrointestinal bleeding
Diagnosis can be made using a combination of echocardiography (resting and stress), tissue Doppler imaging, cardiac MRI, 12 lead ECG and measurement of biomarkers
Cardiac status should be re-evaluated regularly until liver transplant
Peri-operative management at transplantation should involve careful choice of graft and minimisation of large fluctuations in preload and afterload
Long term there is a resolution of the abnormalities in CCM

CCM: Cirrhotic cardiomyopathy; SNS: Sympathetic nervous system; TIPS: Transjugular intrahepatic portosystemic shunts; ECG: Electrocardiogram.

Table 2 2005 World Congress of Gastroenterology diagnostic and supportive criteria for cirrhotic cardiomyopathy[1]

A working definition of cirrhotic cardiomyopathy
  A cardiac dysfunction in patients with cirrhosis characterised by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease
Diagnostic criteria
  Systolic dysfunction
    Blunted increase in cardiac output on exercise, volume challenge or pharmacological stimuli
    Resting LVEF < 55%
  Diastolic dysfunction
    E/A ratio < 1 (age-corrected)
    Prolonged deceleration time (> 200 ms)
    Prolonged isovolumetric relaxation time (> 80 ms)
Supportive criteria
  Electrophysiological abnormalities
  Abnormal chronotropic response
  Electromechanical uncoupling
  Prolonged QTc interval
  Enlarged left atrium
  Increased myocardial mass
  Increased BNP (brain natriuretic peptide) and pro-BNP
  Increased troponin I

BNP: B-type natriuretic peptide; LVEF: Left ventricular ejection fraction.

ventricular filling pressure, which correlates with the severity of liver disease. During certain treatment interventions therefore, such as liver transplantation and TIPS, the volume and pressure load stresses may be significant enough to overcome the "auto-protection" provided by the low systemic vascular resistance and acutely unveil previously asymptomatic latent cardiac disease.

Diastolic dysfunction

Left ventricular diastolic dysfunction (LVDD) is the most prominent characteristic of cirrhotic cardiomyopathy and is thought to precede systolic dysfunction. Its prevalence has been found to be over 50% in cirrhotic patients[19-21] and can be detected at rest using trans-thoracic echocardiography (TTE).

In the early stages of cirrhosis, the expanded blood volume and subsequent increased cardiac preload causes overloading of the left ventricle (LV) and can lead to impaired contractility. There is a resultant increase in LV mass[21] with decreased compliance and relaxation, resulting in abnormal filling of the ventricle. The presence of LVDD has not been found to correlate with the aetiology of liver disease[22], however, the severity of LVDD correlates with worsening liver disease[22,23]. Its prevalence is higher in patients with ascites[19,21,23] and there is evidence to suggest that paracentesis induces an improvement (Figure 1)[24].

The presence and severity of LVDD prior to transplantation has been found to be associated with an increased mortality[22,23,25]. Karagiannakis *et al*[22] evaluated the 2-year probability of patients' survival classified by the presence of diastolic dysfunction and reported survival rates of patients with and without LVDD to be 88.2% *vs* 96.4% at 6 mo; 70.6% *vs* 89.3% at 12 mo; 53% *vs* 85.7% at 18 mo and 47% *vs* 82.1% at 24 mo (Figure 2).

The difference in survival becomes more significant after the first year of follow-up, which is presumably why some shorter studies cannot elucidate a trend. In addition, survival is also related to the severity of LVDD. Ruíz-del-Árbol *et al*[23] reported that after a twelve month follow up period from baseline investigations, survival was 95% in those without LVDD, 79% in those with grade 1 LVDD and 39% in those with grade 2 LVDD.

Electrophysiological abnormalities

Three main electrophysiological abnormalities exist in cirrhotic cardiomyopathy: (1) Prolongation of the QT interval; (2) electromechanical dyssynchrony; and (3) chronotropic incompetence.

A prolonged QTc interval (> 440 ms) is reported to be present in up to 50% of patients with cirrhosis. It is not related to aetiology of liver disease, worsens in parallel with the severity of disease (Figure 3) and may be associated with a reduced survival[26,27]. This abnormality is also frequently prolonged in non-cirrhotic patients with portal hypertension[28].

The QT interval represents length of ventricular electric systole and a prolongation can lead to severe ventricular arrhythmias, syncope and sudden death. The coupling of electrical depolarisation to ventricular
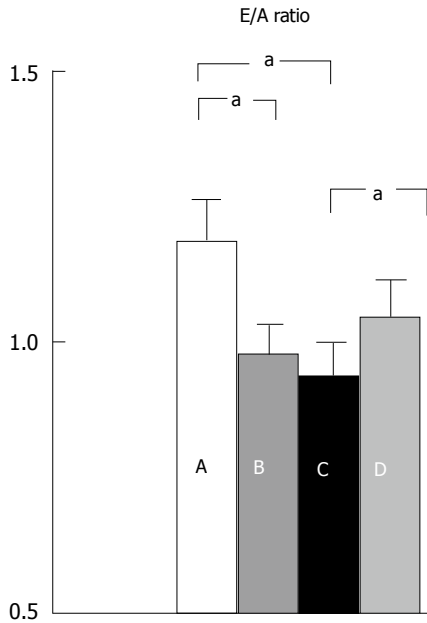
Figure 1 Left ventricular diastolic function in normal subjects (A); cirrhosis (B); cirrhosis with tense ascites (C); cirrhosis with ascites after paracentesis (D). [a]$P < 0.05$, E/A ratio: (early peak: late peak filling velocities). Ratio declines with worsening LVDD. Pozzi *et al*[24].
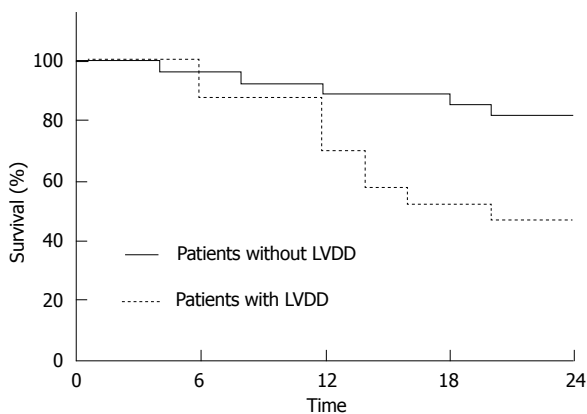

Figure 2 Differences in survival of patients according to the presence of left ventricular diastolic dysfunction. LVDD: Left ventricular diastolic dysfunction. Karagiannakis *et al*[22].

contraction is also abnormal in cirrhosis. Henriksen and colleagues[27] found this electromechanical dyssynchrony to be greater in patients with a prolonged QTc interval, which in turn was related to systemic circulatory dysfunction. The resultant effect of this abnormality is a further impairment of cardiac contractility.

Finally, in CCM there is an impaired ability to increase heart rate in response to activation of the sympathetic nervous system and an increased demand in cardiac output[13,16,29,30]. The decrease in heart rate variability has been found to be associated with increasing severity of cirrhosis and additionally to poor prognosis and increased mortality[31]. It represents an impaired ability to maintain cardiac output at a level that matches cellular demands.
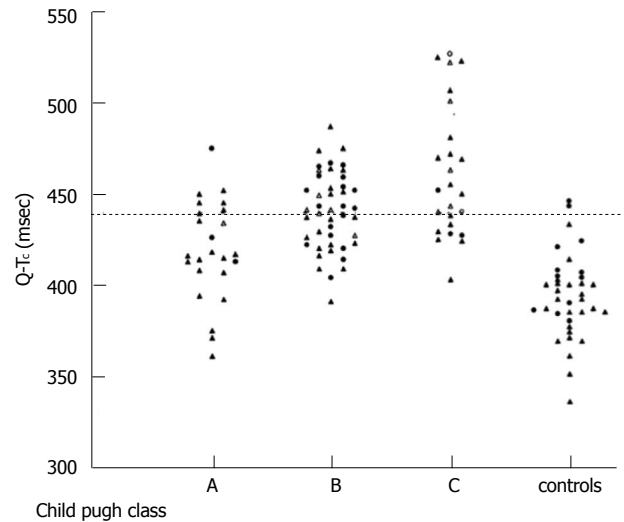

Figure 3 Individual values of QTc interval in patients with cirrhosis (divided according to Child-Pugh classes) and controls. Bernardi *et al*[26].

Cardiac autonomic dysfunction

Autonomic dysfunction is common in cirrhosis and is characterised by an increase in baseline sympathetic nervous system (SNS) activity[10] and decreased baroreflex sensitivity[32]. The baroreceptor and volume receptor stimulation caused by the low arterial blood pressure and blood volume drives this over-activity, causing an increased cellular exposure to noradrenaline and an eventual impairment in β-adrenergic function[9]. These changes play an important role in the development of the hyperdynamic circulation and its adverse effects.

PATHOPHYSIOLOGY

Multiple pathogenic mechanisms have been implicated in the development of cirrhotic cardiomyopathy[33,34]. The diminished inotropic and chronotropic responses to sympathetic stimulation are mainly secondary to a significant down-regulation (reduced density and function) of the β-adrenergic receptors[35] following long-term exposure to persistently high levels of catecholamines[36].

In addition, there is a decrease in the fluidity of the cardiomyocyte plasma membrane caused by an accumulation of cholesterol and bile acid. This adversely affects the receptor-agonist interaction of not only the β-adrenergic receptors[37], but also the other protein receptors embedded in the plasma membrane, ultimately having the effect of compromising cardiomyocyte activation.

There is also increased activity of the cardiac inhibitory systems in cirrhosis, involving substances such as nitric oxide (NO)[38], carbon monoxide (CO)[39] and endogenous cannabinoids (endocannabinoids)[40,41]. The resultant effect is negative inotropy, which further exacerbates the cardiac dysfunction in cirrhotic

cardiomyopathy.

DIAGNOSIS

There is no single diagnostic test that can identify patients with cirrhotic cardiomyopathy and predict who will develop postoperative complications[42,43]. Furthermore, there is no comprehensive data that exists to guide the preoperative cardiac assessment of patients undergoing consideration for liver transplantation.

Diastolic dysfunction

Two-dimensional transthoracic echocardiography: A number of studies to date have used the E/A ratio to determine the presence of diastolic dysfunction, with a ratio < 1 being considered as a positive finding[15,24,44,45]. It represents the pattern of blood flow through the mitral valve. Under normal conditions, early rapid passive filling causes a peak in the transmitral flow profile, known as the E wave, and late rapid filling due to atrial contraction results in a second smaller peak known as the A wave. In the presence of diastolic dysfunction, early passive filling (E wave) is reduced due to an increasingly non-compliant left ventricle, with a greater contribution to filling from atrial contraction during the late phase of diastole (represented by an abnormally large A wave). The overall effect is a reduction in the E wave to A wave ratio.

The E/A ratio may be insufficient as a single parameter to characterise LVDD as it can normalise despite increasing severity of dysfunction. As LV stiffness increases and impairs passive filling, left atrial pressure rises (along with increasing LA dilatation) and eventually drives the filling of the ventricle in early diastole, thereby increasing the E wave. This initially restores the E/A ratio to the normal range, with eventual elevation to supra-normal values. Other features of the TTE are subsequently used to supplement the evaluation of LV relaxation, such as the deceleration time (DT) and isovolumetric relaxation time (IVRT), both of which are initially prolonged, then shortened with increasing severity of dysfunction. Interventricular septal and posterior wall thickness have also been found to be increased in LVDD[14,15,24,46].

In the general population left ventricular stiffness and hence diastolic dysfunction increase with age, so interpretation of TTE findings should be made in context of this variable[47].

Tissue Doppler imaging: The parameters that are measured on conventional two-dimensional (2D) ECHO are dependent on cardiac loading conditions and describe fluid movements rather than tissue dynamics. Tissue Doppler echocardiography has now been suggested as a more accurate modality to assess for diastolic dysfunction[8,47].

Cardiac MRI: Cardiovascular magnetic resonance (CMR) has become the gold standard method for assessing function and morphology in diseases of the myocardium[48], and is of particular use in obese patients where TTE may be suboptimal. It allows repeated evaluation of disease course and detection of subclinical changes prior to dysfunction. The addition of gadolinium contrast (late gadolinium enhancement) has allowed analysis of the intercellular matrix in post-infarct scars, non-ischaemic cardiomyopathies and amyloidosis[48,49]. This ability to analyse myocardial infiltration and fibrosis has diagnostic potential in the early recognition of cirrhotic cardiomyopathy.

Systolic incompetence

Dobutamine and exercise stress echocardiography: In addition to assessing for inducible ischaemia secondary to coronary artery disease, stress echocardiography can be used to detect underlying chronotropic and inotropic incompetence under conditions of increased cardiovascular demand. They are useful screening tools prior to transplantation, but the criteria for undertaking these tests remains varied between institutions.

In a review of 157 pre-transplant dobutamine stress echocardiographys (DSEs), Umphrey *et al*[50] found 37% to be inconclusive due to failure to reach 85% of their maximum predicted heart rate.

Furthermore, the inability to achieve > 82% of this target correlated with an increased risk of having an adverse cardiovascular event up to 4 mo post-OLT. Another group found the incidence of chronotropic incompetence on DSE in cirrhosis to be over 85%[51], when defined by a heart rate reserve of less than 80%. No patient had taken medication that had an effect on haemodynamics until the study was completed. In contrast to this, out of the 58 patients with an inconclusive test in the previous study, 50% had taken a beta-blocker within 12 h of the investigation.

Since beta blockade is responsible for moderation of the heart rate, it raises the question as to whether or not patients undergoing DSE, in part to assess for chronotropic incompetence, should have this drug withheld for 24 h prior to this investigation to enable a more accurate and comparable evaluation of their underlying cardiac reserve function.

STRAIN AND STRAIN RATE IMAGING BY ECHOCARDIOGRAPHY

Strain imaging using either tissue doppler or myocardial speckle tracking and strain rate imaging are becoming increasingly recognised as valuable non-invasive tools for a more comprehensive and reliable assessment of myocardial function[52]. These modalities can detect early changes in systolic function at rest. The long axis sub-endocardial fibres are thought to be more susceptible to damage than the radial-
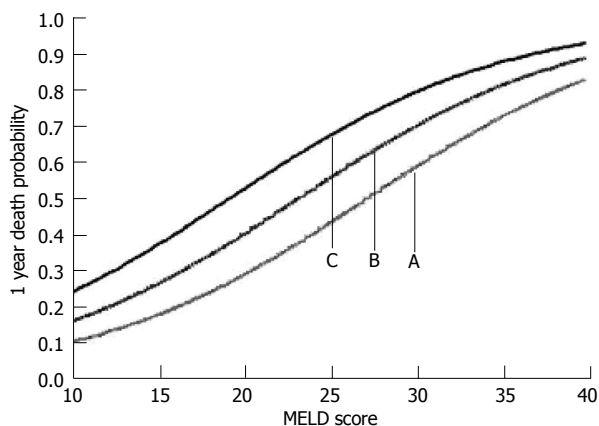
Figure 4 Estimated 1 year probability of dying as a function of: (A) MELD score alone; (B) MELD score and hs-TnT of 4-8 ng/L; and (C) MELD score and hs-TnT of > 8 ng/L. Taken from Wiese *et al*[64].

orientated ones in the midwall[20] so may convey the first manifestation of cardiac impairment. In addition, peak systolic strain rate has been found to be more closely related to contractility than ejection fraction determined by TTE[52].

Electrophysiological abnormalities
Twelve lead Electrocardiogram: Prolongation of the QT interval, when corrected for heart rate (QTc) is commonly quoted to be > 440 ms. In normal subjects, QT interval is also affected by age and gender, with the length being longer in older subjects and females. However, in cirrhosis this gender difference is abolished[53].

Biomarkers
Atrial natriuretic peptide (ANP) is secreted in response to atrial stretch, with the resultant effect of lowering blood pressure and cardiac preload. It is stored as pro-ANP, which is cleaved to ANP and NT-proANP, the latter of which is thought to be a better marker of LV dysfunction[54,55]. ANP levels reflect volume overload and are increased in patients with ascites[46].

B-type natriuretic peptide (BNP) is similarly cleaved from its pro-peptide and released from ventricular myocytes in response to ventricular wall stretch or myocardial ischaemia[56], with the primary purpose of reducing cardiac hypertrophy and fibrosis[57]. Increased concentrations have been detected in cirrhosis, with levels correlating with the severity of liver dise-ase, presence of diastolic dysfunction, myocardial hypertrophy and survival[46,49,58,59]. Preoperative levels of BNPs (BNP and NT-proBNP) are powerful independent predictors of cardiovascular events and mortality in patients undergoing non-cardiac surgery[60,61], with further enhancement of this risk stratification seen with the additional measurement of postoperative levels[62,63].

High sensitivity Troponin T (hs-TnT) is also incr-eased in decompensated cirrhosis with evidence

emerging for it to be a strong independent prognostic marker for survival. Wiese *et al*[64] found that the risk of dying within 1 year predicted by the MELD score is increased by a factor of 1.6 if the hsTnT is 4-8 ng/L and by a factor of 2.7 if hsTnT is more than 8 ng/L (Figure 4).

Proinflammatory markers: Inflammatory activation has been shown to aggravate the circulatory failure and worsen the prognosis in cirrhosis. There is evidence to show that levels of soluble urokinase-type plasminogen activator receptor (suPAR) and high-sensitive C-reactive protein (hsCRP) are potential markers of this interaction. Levels have been found to correlate significantly with Child class and haemodynamic derangement[64].

Currently, the commonly used scoring systems for assessment of severity of liver disease such as MELD and Child Pugh do not incorporate the circulatory or inflammatory state. Therefore, these markers may in the future enable a more comprehensive assessment of the liver transplant candidate.

CLINICAL IMPLICATIONS

Pre-transplant
TIPS: Prior to liver transplantation, additional events that take place in the clinical course of a patient with end stage liver disease may be impacted on by the presence of cirrhotic cardiomyopathy. In particular, diastolic dysfunction may become clinically problematic following procedures that involve a sudden volume load to a stiff, non-compliant ventricle.

One such procedure is the insertion of a TIPS, in which a high splanchnic blood flow is rapidly delivered to the systemic circulation, resulting in an almost two fold increase in central pressures and pulmonary capillary wedge pressure[65,66]. This not only aggravates the hyperdynamic circulation, with a sustained rise in cardiac output for up to 1 year post procedure[49], but also several cases of heart failure following TIPS have been reported[67-69]. In addition, there is evidence to suggest that those patients with diastolic dysfunction defined by an E/A ratio $\leq$ 1 have a lower post-TIPS ascites clearance and probability of survival at one year than those without[44,45] (Figures 5 and 6).

The non-compliant left ventricle renders the patient less able to adequately increase their cardiac output in response to the sudden volume load which, in addition to the worsening of the vasodilation following the procedure, results in a relative under-filling of the central blood volume and poor clearance of the ascites. The dumping of cardioactive substances from the splanchnic to systemic circulation post-TIPS also causes a further prolongation of the QT interval, which worsens post procedure at 1-3 mo and stays elevated above the baseline value[28].

The above findings suggest that careful patient selection for TIPS is needed and a consideration of
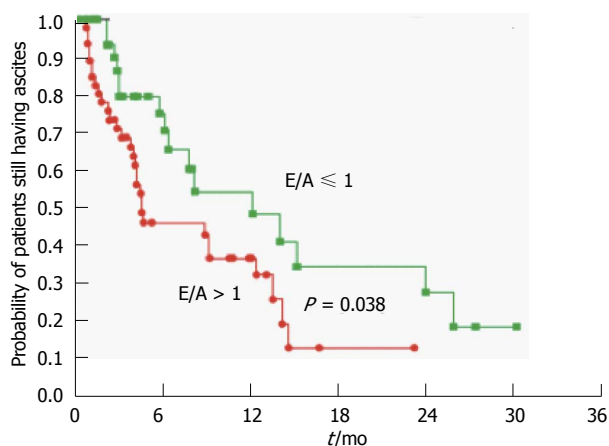
Figure 5 Probability of patients still having ascites after transjugular intrahepatic portosystemic shunts insertion in the group with diastolic dysfunction (E/A ≤ 1) and the group without (E/A > 1). Rabie *et al*[45].

Figure 6 Probability of survival in patients with (E/A ≤ 1) or without (E/A > 1) diastolic dysfunction. Rabie *et al*[45].

referral directly to transplantation may be warranted in those with diastolic dysfunction. If TIPS is undertaken, increased cardiac monitoring post-procedure may be beneficial in those patients with suspected cirrhotic cardiomyopathy, for early recognition and treatment of potential cardiovascular complications.

Hepatorenal syndrome
This is a functional renal failure that occurs in the presence of liver dysfunction, splanchnic vasodilatation and intense activation of the endogenous vasoconstrictor systems, with important prognostic implications in a patient with decompensated cirrhosis. There is increasing evidence to suggest that inotropic and chronotropic insufficiency in CCM may have a role in the progression to hepatorenal syndrome (HRS). Krag *et al*[70] demonstrated that the number of cirrhotic patients with ascites who developed HRS type 1 within three months of initial assessment was higher in the group with a low cardiac index (< 1.5 L/min per square meter) than in the high cardiac index group (43% *vs* 5% respectively). Furthermore, patients with the lowest cardiac index at baseline had significantly poorer survival at 3, 9 and 12 mo.

Likewise a cardiac output < 6.0 L/min was found to be an independent predictor of HRS in a group of patients with cirrhosis and tense ascites who, at baseline had normal creatinine levels (Figure 7)[71]. The implication is that the patients who are unable to maintain cardiac output in the presence of systemic arterial vasodilatation at a level that maintains a sufficient renal perfusion pressure are predisposed to the development of renal dysfunction and HRS.

Spontaneous bacterial peritonitis
The susceptibility of a patient with a decreased cardiac reserve to further organ impairment becomes more pronounced in the face of systemic infection. In a study of patients with a diagnosis of spontaneous
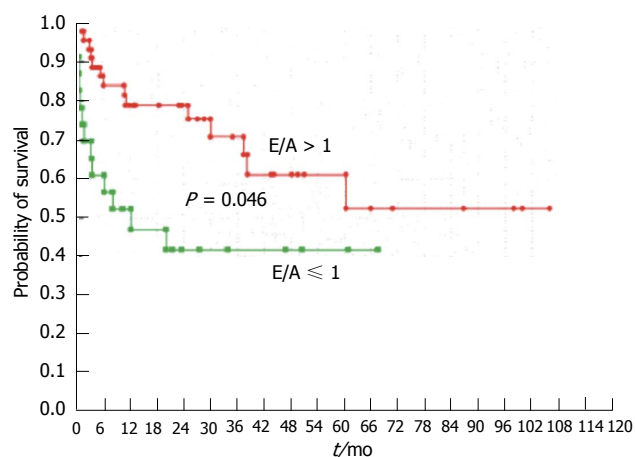
bacterial peritonitis (SBP), those that subsequently developed renal failure had a reduced cardiac output both at the time of infection diagnosis and at infection resolution[72]. If the additional physiological demands caused by the inflammatory mediated vasodilatation and negative inotropy could not be met, a rapidly progressive impairment of systemic haemodynamics followed, with severe renal and hepatic failure, aggravation of portal hypertension, encephalopathy and death.

Gastrointestinal bleeding
QT prolongation in cirrhosis is common and one of the postulated causes is the baseline sympathetic nervous system hyperactivity. Therefore, a sudden increase in this activity caused by acute gastrointestinal bleeding further lengthens this time interval with potential adverse outcomes. Trevisani *et al*[73] showed that in a group of cirrhotic patients with this complication, the QT interval lengthened at the time of bleeding and all those that died had a longer QTc than survivors. In addition, QTc was able to independently predict survival, with a best cut-off value of ≥ 460 ms.

IMPLICATIONS OF DIAGNOSIS AND MANAGEMENT

When a patient displays features of CCM, this is an indication to perform more frequent cardiovascular reassessment, with regular TTE studies perhaps every three months prior to transplantation. Deterioration can then be detected earlier, enabling prompt management of symptomatic heart failure, appropriate cardiovascular monitoring at the time of TIPs or acute gastrointestinal bleeding and appropriate fluid therapy and circulatory support on diagnosis of SBP.

Positive diagnosis may also affect the decision to proceed with TIPS, as underlying CCM has been associated with not only suboptimal ascites clearance and LV dysfunction, but also increased mortality. In
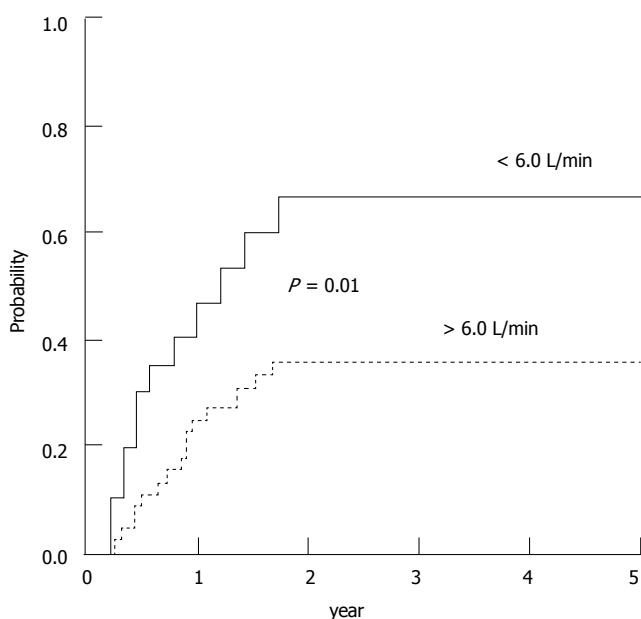
Figure 7 Probability of developing hepatorenal syndrome during follow-up in patients with baseline cardiac output higher and lower than 6 L/min. Ruiz-del-Arbol *et al*[71].

this situation the decision may be to refer straight to transplantation.

At the time of transplantation, the presence of an underlying latent cardiac failure may also affect the choice of graft. Mittal *et al*[74] followed up 970 liver transplant recipients over an average of 5.3 years, and found that those with pre-transplant diastolic dysfunction were significantly more likely than those without to develop acute cellular rejection (58.6% *vs* 31% respectively), graft failure and all-cause mortality, making the initial quality of graft ever more important (Figures 8 and 9).

Management
There is currently no specific treatment for cirrhotic cardiomyopathy. Patients are managed as for heart failure due to other aetiologies, with sodium restriction, diuretics and careful management of their preload and afterload. Vasodilators such as ACE inhibitors are avoided as they exacerbate the reduced systemic vascular resistance.

Many patients with cirrhosis are beta-blocked for the management of portal hypertension. It is still unclear what impact this has on CCM, but the additional negative inotropic and chronotropic effects may have an important role in the development of and outcome from adverse cardiac sequelae during periods of increased physiological demand. On the other hand, both the acute and chronic administration of beta-blockers have been shown to shorten the QT interval in cirrhotic patients who have elevated baseline values[75,76]. Although the improved QT interval potentially has preventative benefits in the context of life-threatening arrhythmias, the deleterious effect of beta blockade on cardiac output and hence clinical outcome remains to be studied.

Long-term aldosterone blockade may also have potential therapeutic benefits. In preliminary studies it has been shown to reduce left ventricular wall

thickness and may potentially improve diastolic dysfunction[77].

INTRAOPERATIVE

Maintaining preload and fluid management
During liver transplantation there are significant haemodynamic fluctuations and immense physiological demands on the recipient. The third space losses over the long procedure can be copious with the added effect of substantial blood loss and on-going ascites production[43]. If a patient has cirrhotic cardiomyopathy, an important intraoperative aim should be to minimise excessive fluctuations in preload and afterload, to avoid acute cardiac decompensation.

Surgical technique can greatly influence physiological status, with cross clamping of the inferior vena cava causing the greatest cardiovascular instability. In a patient with cirrhotic cardiomyopathy the use of caval preservation techniques (piggyback), or the addition of veno-venous bypass if caval cross clamp is employed, will minimise the large variations in preload with the maintenance of caval flow during explantation[78,79]. This would decrease the reliance on positive chronotropy to maintain cardiac output in the face of reduced venous return, a compensation mechanism that may be impaired in CCM. It could also attenuate the sudden change in preload on reperfusion of the new liver, which can precipitate acute left ventricular failure and pulmonary oedema if diastolic dysfunction is present.

Reperfusion also involves the release of cold, ischaemic metabolites and vasoactive mediators from the graft that can further exacerbate systemic vasodilatation and cause myocardial depression. An impaired contractile response to stress may render the patient unable to overcome these effects and result in an inadequate cardiac output for tissue perfusion, including the newly implanted liver. Techniques to
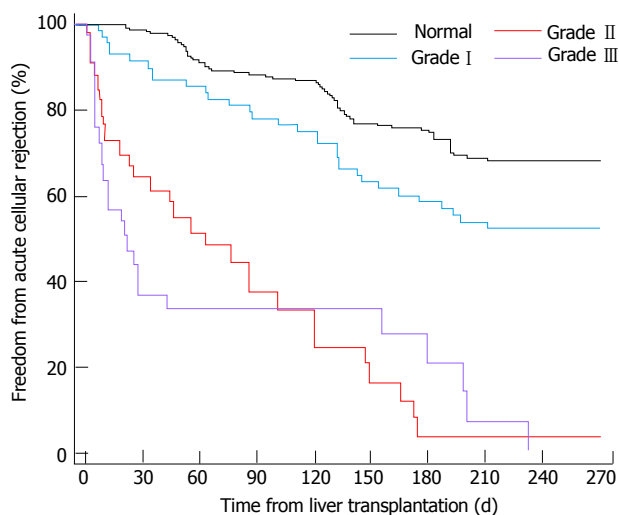
Figure 8 Time to acute rejection for various grades of left ventricular diastolic dysfunction. Mittal *et al*[74].

Figure 9 Survival analysis for patients with left ventricular diastolic dysfunction *vs* patients without. Mittal *et al*[74].

minimise reperfusion "hit" are especially important in the context of CCM, including normalising acid base and electrolyte status prior to reperfusion, and the use of as good quality grafts as possible.

Haemodynamic monitoring

In light of the special considerations in CCM during OLT, additional haemodynamic monitoring may be warranted for the early detection of cardiac decompensation and to guide therapy. Both aggressive fluid administration and excessive vasoconstriction can precipitate acute cardiac failure in this group, so careful titration of inotropic support and the avoidance of excess intravenous fluids are necessary.

The use of pulmonary artery flotation catheters (PAFC) enables measurement of continuous cardiac output and the derivation of systemic vascular resistance and hence afterload. In addition many PAFCs allow measurement of right ventricular end diastolic pressures and volume. Other methods of continuous non-invasive cardiac output (CO) monitoring are less accurate, unless recalibrated at times when there are significant changes in CO, *i.e.*, after caval cross clamping and following reperfusion.

Transesophageal echocardiography (TOE) is an imaging modality that is becoming increasingly popular in evaluating intraoperative haemodynamic status during liver transplantation[80]. It provides the added benefit of real time assessment of the response to fluid, direct visualisation of global and regional myocardial performance and detection of air and thromboembolism[81]. In addition, it can allow an earlier visual detection of right ventricular failure, as the substantial compliance of the right ventricle allows significant dilation before any pressure changes that would be detected with a PAFC[82]. It also permits re-evaluation of the recipient's cardiac function at the start of surgery, which would highlight deterioration since previous assessment. A limiting factor over its
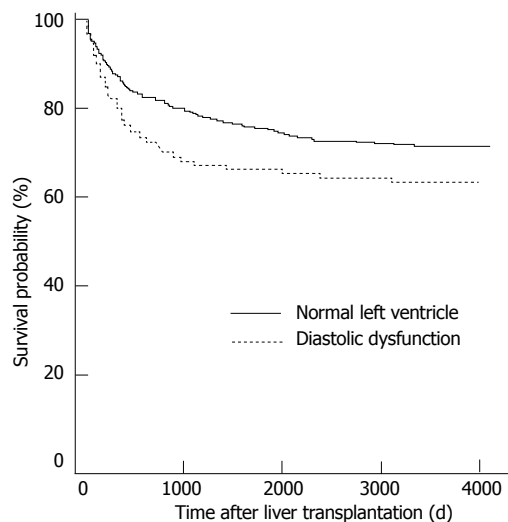
use however, is the training required for competent scanning and interpretation of images[83]. There is also the small risk of bleeding from oesophageal varices.

Both PAFC and TOE have important advantages in the guidance of therapy for the CCM patient. The choice between the two remains operator dependent and reliant on skill base and experience.

Electrolytes/arrhythmias

During liver transplantation, there can be further prolongation of the QT interval with the associated increased risk of ventricular arrhythmias. One study reported that 54% of recipients showed a marked prolongation of QTc ($\geqslant$ 500 msec) during the anhepatic phase, with values remaining prolonged at each stage compared to baseline[84]. 77% of the patients with a pre-operative increased QTc and 36% of the group with a normal starting value showed this abnormality.

Electrolyte imbalance is common during this procedure and can further precipitate cardiac instability. Ionised hypocalcaemia can occur as a result of citrate toxicity following the transfusion of large amounts of citrated blood products causing further depression of myocardial contractility. Reperfusion of the donor liver can acutely raise serum potassium to levels that can potentially result in fatal arrhythmias. Additionally, hypomagnesaemia has been shown to precipitate cardiac arrhythmias that are refractory to conventional treatment and can also lead to hypokalaemia and hypocalcaemia[85]. Careful monitoring of these electrolytes and judicious replacement should be employed to minimise further cardiac instability in a condition with pre-existing limited cardiac reserve.

POST OPERATIVE COURSE

Immediately after liver transplantation there is a significant increase in blood pressure and peripheral vascular resistance with restoration of normal liver
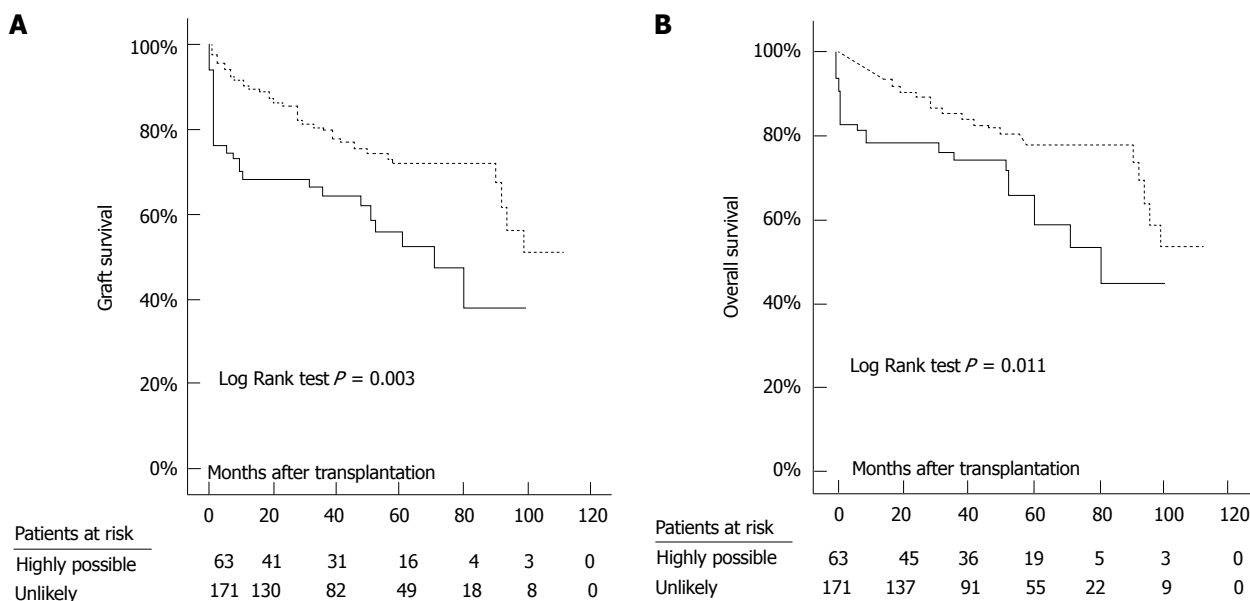
Figure 10 Graft (A) and overall (B) survival in patients with highly possible (continuous line) and those with unlikely (dashed line) peri-transplant heart failure. Josefsson *et al*[25].

function and portal pressure. This increase in preload and afterload can be another stage at which cardiac de-compensation in CCM occurs, typically in the first week after OLT. Various authors have reported cases of pulmonary oedema following this procedure, a complication that can impair gas exchange and stress critical oxygen delivery to the new organ[86,87], with incidences being reported at between 30% and 50%[88-90].

Peri-transplant heart failure and myocardial depression have been found to correlate with both a preoperative impaired cardiac reserve function and increased morbidity and mortality post-operatively[25,91]. Josefsson *et al*[25] found it to be associated with a longer ITU stay (14.5 d *vs* 4 d), a longer inpatient stay (33 d *vs* 21 d), a higher peri-transplant infection rate (42% *vs* 19.9%) and higher long term patient and graft mortalities (Figure 10).

In a search to identify predictors of heart failure after liver transplantation, Dowsley *et al*[92] found that markers of diastolic dysfunction on pre-operative TTE (E/e' > 10 and LA volume index $\geqslant$ 40 mL/m^2) were associated with a 3.4 fold and 2.9 fold increase in risk respectively. Furthermore, Kaplan-Meier analysis of LA volume index below and above 40 mL/m^2 revealed survival differences of 82% *vs* 54% at 1 year and 71% *vs* 50% at 5 years respectively. Therapondos *et al*[93] found elevated baseline BNP levels in those who went on to develop pulmonary oedema in the first 3 mo after transplant. These pre-transplant markers that are associated with an increased risk of heart failure may aid the prediction of post liver transplant outcomes.

LONG TERM POST OLT

After transplantation, there is a triphasic course of myocardial recovery in CCM. The first phase is the aforementioned perioperative cardiac failure. Over the next few weeks, the restoration of the portal circulation and the hypertensive side effects of the calcineurin inhibitors administered for immunosuppression, result in an additional increase in afterload, potentially leading to further decompensation. LV diastolic function (as measured by E/A and IVRT) has been shown to deteriorate for up to 3 mo post transplant[93].

In the final phase, there appears to be a recovery of functional, structural and electrophysiological abnormalities. Whereas the hyperdynamic syndrome normalizes in some patients over time[94], it persists in others[95]. There is a significant improvement in myocardial performance, with normalization of the systolic response to stress, improvement of diastolic dysfunction and regression of ventricular wall thickness between 6-12 mo after transplantation[30,49]. In addition, there is an improvement of QT prolongation in approximately 50% of patients from as early as three months[96-98].

CONCLUSION

Cirrhotic cardiomyopathy describes a condition of impaired cardiac reserve function. It is characterised by a systolic incompetence to stress, diastolic dysfunction and electrophysiological abnormalities. Although mostly asymptomatic at rest, it can be unveiled during periods of physiological or pharmacological stress and predisposes the patient to complications such as hepatorenal syndrome, acute cardiac failure and life-threatening arrhythmias. Regular re-evaluation of cardiac status should be undertaken to minimise the risk of decompensation. Management at the time of liver transplantation should involve careful selection of donor grafts and tailoring of the anaesthetic and

surgical techniques to avoid large fluctuations in preload and afterload. If cardiac failure in the peri-operative period can be avoided, there is potentially a good outcome with long term reversal of the cardiovascular abnormalities.

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