REVUE SYSTÉMATIQUE

Cirrhotic cardiomyopathy

La cardiomyopathie du cirrhotique

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RÉSUMÉ

La présence de dysfonction cardiocirculatoire dans la cirrhose du foie a été décrite depuis 1960 et elle a été attribuée exclusivement à la cardiomyopathie alcoolique. Ce n'est que dans les deux dernières décennies que le terme de « cardiomyopathie du cirrhotique » (CCM) a été introduit pour décrire la dysfonction cardiaque chez les patients atteints de cirrhose. La prévalence de la CCM est sous estimée, parce que la mala¬die est généralement latente et ne se manifeste que lorsque le patient est soumis à un stress. En fait, une defaillance cardiaque a été décrite après une transplantation hépatique et notamment après la mise en place d'un TIPS. Le diagnostic de CCM est encore difficile à déterminer en raison de l'absence de tests spécifiques. Cette pathologie est l'expression d'une atteinte cardiaque variée associant une dysfonction systolique, une dysfonction diastolique et des anomalies électrophysiologiques. À l'heure actuelle, il n'existe pas de traitement spécifique en dehors de la transplantation hépatique, mais avec une une mortalité élevée dans le décours post-opératoire immédiat. Dans cette revue, nous présentons les caractéristiques épidémiologiques, cliniques, thérapeutiques de la CCM ainsi que son impact pronostique en se basant sur une revue récente de la littérature.

Mots clés : cirrhose, cardiomyopatie.

SUMMARY

The presence of cardiocirculatory dysfunction in liver cirrhosis has been described since 1960 and it was exclusively attributed to alcoholic cardiomyopathie. Only in the last two decades, the term of cirrhotic cardiomyopathy (CCM) was introduced to describe cardiac dysfunction in patients with cirrhosis. This entity is currently underdiagnosed because the disease is usually latent and manifests when the patient is under stress. However, overt cardiac failure has been described after transjugular intrahepatic portosystemic shun and liver transplantation. The diagnosis of CCM is still difficult to determine because of the lack of specific diagnosis tools. CCM is characterized by systolic dysfunction, diastolic dysfunction and electrophysiological abnormalities. At present, there is no specific treatment outside liver transplantation in the light of increased mortality and postoperative complications.Our review provides an overview of CCM, its definition, prevalence, pathogenic mechanisms, clinical presentation, various explorations and management in light of the most recent published literature.

Key words: Liver cirrhosis, cardiomyopathy

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INTRODUCTION

The presence of cardiocirculatory dysfunction in liver cirrhosis has been described since 1960 and it was exclusively attributed to alcoholic cardiomyopathy [1]. However, subsequent studies revealed that cirrhosis is associated with hyperdynamic circulation, witch corresponds to a high outpout heart failure under resting conditions [2]. This clinical entity, formally named cirrhotic cardiomyopathy (CCM) is unrelated to the etiology of cirrhosis and is different from alcoholic disease [3]. Thus, only in the last two decades, the term of CCM was introduced to describe cardiac dysfunction in patients with cirrhosis. Controversy exists regarding the relation between the CCM and the severity of the disease [3,4,5]. Our review provides an overview of CCM, its definition, prevalence, pathogenic mechanisms, clinical presentation, various explorations and management in light of the most recent published literature

DEFINITION

In 2005, a group of experts' cardiologists and hépatologists proposed several criteria to characterize this entity. In fact, CCM is defined as a chronic cardiac dysfunction characterized by impaired contractile responsiveness to stress stimuli and/ or impaired diastolic relaxation and electrophysiological abnormalities in the absence of other known cardiac disease [6]. The diagnosis of CCM is difficult to determine. Indeed, Universal consensus is still lacking and it is often necessary to perform a stress test to unmask CCM. At present, there is no pathognomonic diagnostic test and diagnosis is based on a set of clinical, biological, electrocardiographic and ultrasonographic elements [7]. The criteria for the diagnosis of CCM are shown in Table 1. These criteria were established In 2005 by a group of experts' cardiologists and hepatologists. However, with the remarkable developments in cardiac imaging, a critical revision of the criteria that define cirrhotic cardiomyopathy may be warranted. A multidisciplinary approach between cardiac imaging specialists, anesthesiologists, and hepatologists is needed to better describe unique cardiac imaging features in patients with cirrhosis compared to the general population, based on the recent advancements in echocardiography [8].

PREVALENCE

The prevalence of CCM is unknown. But, it is currently underdiagnosed even after a comprehensive evaluation at rest because the disease is usually latent and manifests when the patient is under stress. It is estimated that half of patients with cirrhosis undergoing liver transplantation (LT) show signs of heart dysfunction [9]. The prevalence of diastolic dysfunction (DD) is relatively high in patients with cirrhosis (43%-70%) despite a normal EF [9-10]. The prevalence ofprolonged QT interval exceeds 60% in patients with an advanced disease, and has been related to the severity of liver disease [4].

PHYSIOPATHOLOGY

The hyperdynamic circulation, associated concomitantly with intrinsic cardiac dysfunction is the basis of the physiopathology of CCM.

Hyperdynamic circulation

Cirrhosis is associated with a hyperdynamic circulatory syndrome, characterized by an increase in cardiac output and a decrease in peripheral vascular resistance [4]. In deed, portal Hypertension leads to a significant release of vasodilators mediators activating the release of Nitric oxide (NO) by the splanchnic arterial endothelium. The relative hypovolemia thus constituted generate a stimulation of Sympathetic system, renin -angiotensin-aldosterone (RAAS) and arginine vasopressin (AVS) systems leading respectively to an acceleration of the heart rate and an increase of preload by fluid retention. NO has been recognized as the most important vasodilator molecule in the splanchnic and systemic circulation of patients with cirrhosis. The relative hypovolemia and low blood pressure that often accompanies, it generate a stimulation of the sympathetic system, renin -angiotensin-aldosterone (RAAS) and arginine vasopressin (AVS) systems leading respectively to an acceleration of the heart rate and an increase of preload by fluid retention. Therefore, the cardiac output increases progressively while the peripheral vascular resistance remains low, constituting hyperdynamic circulation **[7].**

Intrinsic cardiac dysfunction:

Diastolic dysfunction (DD) may be a consequence of cardiac hypertrophy, patchy fibrosis and subendothelial edema [11]. In addition, salt retention may play a part in the

development of DD. Indeed, animal models have shown that high salt intake can lead to fibrosis and concentric left ventricular hypertrophy through the activation of cardiac aldosterone production [10]. Also, it has been demonstrated that plasma membranes from the cardiac myocyte in cirrhotic patients becomes more rigid and less permeable with increase in membrane cholesterol content [12]. Such alterations in membrane properties are likely to play an important role in inducing ECG abnormalitie in cirrhosis. The mechanisms underlying prolonged QTc interval are not clear. Bernardi and al found that the prolonged QT interval correlated with circulating plasma noradrenaline which suggests that enhanced sympatho-adrenergic abnormalities are implicated in its pathophysiology [13].

CLINICAL PRESENTATION

CCM is a subclinical entity. Cardiovascular complications are not clinically evident in patients with CCM during the follow up, probably because of the peripheral vasodilatation. However, overt cardiac failure has been described after transjugular intrahepatic portosystemic shunt (TIPS) and LT [5].

Systolic dysfunction

The left ventricular ejection (LVEF), evaluated by the two or three- dimensional Echocardiography, is widely used in systolic function assessment. Two- dimensional echocardiography was the most commonly used modality for assessing fraction ejection. But, three-dimensional echocardiography is becoming more available and increasingly used in clinical practice. The LVEF has several limitations and is insufficient to evaluate cardiac function in patients with cirrhosis. In fact, LVEF is not an index of contractility and depends on loading conditions, heart rate and valvular function. Besides, the inter-observer agreement in different measurements can be modest and LVEF can be found normal at rest in cirrhotic patients. Conversely, an attenuated LVEF has been shown after several stimuli such as exercise, sodium load or erect posture. Consequently, a stress test, particularly, dobutamine stress echography, should always be considered in the diagnostic approach of CCM [14,15]. Currently, new echocardiographic techniques may identify patients with subclinical ventricular dysfunction more accurately than conventional methods [9,13]. The most reported is Tissue Doppler imaging (TDI) or speckle tracking echocardiography. These methods have the advantage of being able to quantify all the components of myocardial mechanics (longitudinal, circumferential and radial motion/deformation as well as rotation and torsion) within the image plane. [10,14].

Diastolic dysfunction

Abnormalities of diastolic function are an early marker of CCM and may precede systolic dysfunction in cirrhotic patients. Diagnostic evidence of DD can be obtained invasively by left ventricular end-diastolic pressure or noninvasively by Doppler echocardiography by showing decreased ratio of early to late atrial phases of ventricular filling less than 1 (E/A ratio)(early diastolic/atrial filling ratio) E/A ratio (less than 1), which is the ratio of early to late atrial phases of ventricular filling (early diastolic/atrial filling ratio). However, conventional Doppler echocardiographic indices (E/A ratio) have some limitations such as age and load conditions. In addition to that, using this ration, differentiation between normal and pseudonormal left ventricular diastolic pattern is difficult. TDI measures the slow velocity high amplitude annular tissue motion (denoted by E') that is less affected by preload. An increase in the E/E' ratio has been used as a more sensitive measure of diastolic dysfunction [16]. Indeed, TDI velocities have demonstrated a significant correlation with invasive indices of left ventriculr relaxation.

Electrophysiological abnormalities

Several electrophysiological abnormalities are found in cirrhotic patients. These include QT interval prolongation, electromechanical dyssynchrony and chronotropic incompetence.

QT-Interval prolongation :

The QT interval represents the depolarization and repolarization of the ventricles. QT interval is affected by heart rate and therefore must be expressed as a rate-corrected (QTc) interval. Prolonged QT interval (≥ 500 ms) on the electrocardiogram is present in 60% of cirrhotic patients with an advance disease [4]. In addition, a prolonged QTc interval is frequently observed throughout the procedure of LT, and even after TIPS insertion [**16,17**]. Patients with cirrhosis and prolonged QTc interval are at risk of developing ventricular arrhythmias such as torsades de pointes. This risk is unknown but is thought to be rare [**9**].

Electromechanical dyssynchrony :
A functional electromechanical uncoupling has been confirmed in patients with cirrhosis and prolonged QTc interval who showed that the electrical systole was longer than the mechanical systole [**19**]. The clinical significance of these findings remains unclear.

Chronotropic incompetence :
Chronotropic incompetence (CI) is defined as the heart inability to proportionally increase heart rate in response to metabolic demand. CI is common in patients with cirrhosis regardless of its cause and there is more evidence of contractile dysfunction in patients with ascites despite a decrease in afterload [**19**].

PROGNOSIS IMPACT

Given its clinical and pronosis implication, CCM should be screened. Indeed, heart failure linked to this pathology is the third cause of mortality post LT, after the rejection and infection [15].

TIPS
TIPS insertion leads to significant hemodynamic changes, with a sudden increase in the preload, that may rapidly worsen the hyperdynamic circulatory state of cirrhotic patients. Multiple cardiovascular complications such as arrhythmias, heart failure, myocardial ischemia, and acute pulmonary edema have been reported following TIPS insertion [21]. This may be the consequence of diastolic dysfunction in these patients. Indeed, previous studies have demonstrated that E/A ratio < 1 was an independent predictor of mortality in patients with cirrhosis who are treated with TIPS. Also, survival was significantly lower in patients with E/e' ratios >10 in the subsequent year independently of the severity of liver dysfunction estimated by MELD [10].

Liver transplantation (LT):
The clinical consequences of CCM are evident during and after LT, because the hemodynamic system is further compromised by the effect of anesthesia, mechanical ventilation, and surgical clamping, with a significant reduction in the cardiac output [22]. The presence of pre-operative CCM could be a risk factor for complications after LT [10]. These most common complications are pulmonary edema. Other complications includE overt heart failure, arrhythmia, pulmonary hypertension, pericardial effusion, and cardiac thrombus formation [22]. The presence of preoperative cardiac dysfunction is not a contraindication for intervention, but an indication for more careful monitoring particularly the maintenance of a β-blocker therapy in the postoperative.

TREATMENT

Medical treatment
At present, there is no specific medical treatment. In the acute phase of decompensation, general measures are indicated: bed rest, oxygen therapy, diuretics and other medications reducing preload such as nitrates [24].Theoretically, pharmacological agents that facilitate myocardial relaxation and improve left ventricular compliance would be ideal for the treatment of CCM. But, unlike other patients, cirrhotic patients have a peripheral vasodilatation and will be vulnerable to drugs that reduce afterload such as inhibitors of the renin-angiotensin system. These inhibitors are contraindicated because may precipitate profound hypotension and aggravate the systemic vasodilatory state of patients with advanced cirrhosis. In addition to that, by inhibiting the vasoconstrictor effect of angiotensin II on the efferent arteriole of the glomerulus, a functional renal failure can be triggered [25]. The β-blockers, widely used in cirrhosis to reduce portal hypertension and prevent the variceal bleeding appear to present a risk / benefit more favorable. Indeed, the improvement in cardiac function is obtained, on the one hand, by shortening corrected QT interval and, secondly, by an opposition effect to depression of β receptors [8]. But, β-blockers may be harmful due to reduction in cardiac output in accordance with a decrease in the portal hypertension. In fact, the administration of β-blockers is associated with poor longterm survival in patients with cirrhosis and refractory ascites. These results suggest that β-blockers should be avoided in these patients. The aldosterone antagonists appear promising on cardiac remodeling and diastolic function. Pozzi et al have demonstrated that aldosterone blockade in Child A cirrhotic patients can lead to decreases in the left ventricular wall thickness [25]. The effect of aldosterone antagonists on Child B-C patients is unknown.

LT :
LT remains the curative option of structural and functional alterations of CCM in the light of increased mortality and immediate postoperative complications [24]. Post-

reperfusion syndrome, characterized by a decrease in mean arterial pressure with bradycardia after unclamping of the portal vein and liver reperfusion, affects 8%-30% of patients. Heart failure, myocardial infarction, and arrhythmias in the perioperative and postoperative periods after LT have been reported in 25%-70% of patients [10]. Because overt heart failure in cirrhotic cardiomyopathyoccurs when the heart is challenged, future research could examine possible preoperative preparation to improve cardiac function, such as albumin infusion [26].

CONCLUSION

CCM has a major importance in the management of the cirrhotic patient as it contributes to the high cardiovascular morbidity and mortality related to TIPS insertion and liver transplantation. Hepatologists should be aware of this silent entity and actively search to better define CCM diagnostic criteria and to suggest specific protocols. The transthoracic echocardiography at rest is the routine examination to detect some structural and dynamic abnormalities directing the diagnosis. Surely diastolic dysfunction is virtually present in all patients. So, systematic evaluation of diastolic function in patients with cirrhosis especially in decompensated patients seems necessary.The management of these patients must be done in collaboration between hepatologists and cardiologists to optimize their medical care.

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