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EDITORIAL

Assessment of diastolic function in the management of patients with cirrhosis

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For many years, it has been known that impaired liver function and portal hypertension are associated with a pronounced splanchnic vasodilatation. This leads to important circulatory changes with displacement of the circulating blood volume resulting in central hypovolemia [1]. The combination of effective hypovolemia, arterial hypotension, and baroreceptor-activation of potent vasoconstricting systems such as the sympathetic nervous system leads to a hyperdynamic circulation and a multi-organ failure including impaired function of the heart [2]. In a patient with a full-blown decompensated state of cirrhosis, the heart rate and cardiac output are typically increased [1]. Both experimental and clinical studies have shown that the dimensions of the cirrhotic heart are augmented and the contractility and electromechanical function are impaired [3, 4]. This condition has been termed *cirrhotic cardiomyopathy*, which designates a cardiac dysfunction that includes impaired cardiac contractility with systolic and diastolic dysfunction and electromechanical abnormalities in the absence of other known causes of cardiac disease [4]. Cirrhotic cardiomyopathy can be demasked by physical or pharmacological stress, which may reveal in particular a systolic dysfunction, which seems to contribute to several cirrhotic complications such as the formation of ascites [5, 6] and the development of hepatic nephropathy [7, 8]. Additionally, cirrhotic cardiomyopathy seems associated with the development of heart failure in relation to invasive procedures such as shunt insertion and liver transplantation [9, 10].

Abnormal left ventricular diastolic function, caused by decreased left ventricular compliance and relaxation, implies an abnormal filling pattern of the ventricles. The transmitral blood flow is changed, with an increased atrial contribution to the late ventricular filling [4]. The pathophysiological background of the diastolic dysfunction in cirrhosis is an increased stiffness of the myocardial wall, most likely because of a combination of mild myocardial hypertrophy, fibrosis, and subendothelial edema [2, 3]. The increase in myocardial stiffness is also reflected by other parameters of diastolic dysfunction, such as a prolonged time for the ventricles to relax after diastolic filling at a specific end-diastolic volume, which reflects an increased resistance to the ventricular inflow [4].

Natriuretic peptides are regarded as markers of volume overload and impaired contractility, and are released by stretch of the atrial fibers such as in patients with ascites where the right atrium has been reported increased partly because of volume overload with expanded blood volume [1, 4]. However, the interpretation of increased natriuretic peptides in patients who from a functional point of view suffer from effective hypovolemia is complex. Activation of the renin–angiotensin–aldosterone system (RAAS) is associated with cardiac disease such as hypertrophy and heart failure, and seems to be related to diastolic dysfunction in both cirrhotic and non-cirrhotic patients with portal hypertension [11]. Furthermore, RAAS may induce fibrosis, and there is evidence of relationships between plasma aldosterone and *E*/*A* ratio; thus, RAAS may be both directly and indirectly involved in diastolic dysfunction [4].

Echocardiography is the method more frequently utilised for the detection of left ventricular diastolic dysfunction. Diastolic dysfunction is expressed as a decreased

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E/*A* ratio, prolonged deceleration and isovolumetric contraction times [4]. The *E*/*A* ratio is measured from velocities of the left ventricle inflow during early, rapid passive filling (*E* wave) and during atrial contraction (*A* wave), and in the presence of diastolic dysfunction, the *E*/*A* ratio is less than 1. Measurement of the mitral annular E wave (E') has been suggested as a more accurate marker for evaluation of diastolic dysfunction due to the independency of loading conditions. Hence, as diastolic function worsens, the E' decreases reflects the increased stiffness of the ventricle. Moreover, the E/E' ratio has been found to reflect left ventricular filling pressure, and this ratio increases as diastolic function worsens [12]. An enlarged left atrium also reflects diastolic dysfunction whereas Doppler velocities reflect filling pressure at the time of the measurement. Left atrial volume reflects the cumulative effect of filling pressures over time, thereby being a marker of chronic diastolic dysfunction [4, 12].

In the study by Karagiannakis et al. [13] published in this issue of *Hepatology International*, the authors evaluated the relationship between diastolic dysfunction and severity of the liver disease. They studied 45 patients by conventional tissue Doppler imaging, and the cohort was followed up for 2 years. Of the 45 patients, 17 (38 %) had diastolic dysfunction as assessed according to international guidelines. After end of the follow-up period, more patients with diastolic dysfunction had died and, together with serum albumin, the presence of diastolic dysfunction came out as a significant predictor of mortality.

The results of the present study adhere to the results of the increasing number of studies on diastolic dysfunction in cirrhosis. The prevalence of diastolic dysfunction among patients with cirrhosis varies according to the type of population and the severity of the disease, but there seems to be no relationship to etiology of cirrhosis. Different prevalences have been published ranging from 15 % to as high as 67 % [5, 6, 8, 14–16]. A considerable number of studies have reported a direct relationship between the severity of diastolic dysfunction and severity of the liver disease, as reflected by the MELD-score, presence of ascites, and Child–Turcotte score, whereas some studies have been unable to detect a relationship with the degree of liver dysfunction [6, 8]. As in the present study by Karagiannakis et al., several studies have reported a direct relation to prognosis, whereas other studies have failed to do so [6, 8, 14]. In a recent study by Ruiz-del-Arbol et al. [8], the authors reported a direct relationship between variables obtained from tissue Doppler imaging (E/e') ratio and prognosis. In patients undergoing invasive procedures such as insertion of a transjugular intrahepatic porto systemic shunt (TIPS), the presence of diastolic dysfunction has been shown to predict survival [9]. The increase in diastolic volumes after TIPS seems to normalise after months but with persistence of a mild left ventricular hypertrophy [17]. Moreover, reduced diastolic function seems to be associated with slower mobilisation of ascites [18]. In candidates for liver transplantation, assessment of cardiac function including diastolic dysfunction has been associated with the outcome after liver transplantation. In a new retrospective study by Mittal et al. [19], a relative low frequency of diastolic dysfunction was reported, but with significant relationships to the development of acute cellular rejection and graft-failure after liver transplantation. Moreover, the presence of diastolic dysfunction has been associated with the development of circulatory and renal disturbances relating to central hypovolemia and hyperdynamic circulation including presence of autonomic dysfunction [10, 20].

In conclusion, the present study by Karagiannakis et al. supports and emphasizes the importance of diastolic dysfunction as playing a role in the development of complications of cirrhosis including hepatic nephropathy. In particular, patients undergoing invasive procedures such as surgery, TIPS-insertion, and liver transplantation should undergo a careful cardiac evaluation. Currently, an international multicentre study has been conducted on the prevalence of diastolic dysfunction in cirrhosis and its clinical significance [5]. In this large study now including more than 355 patients, the prevalence of diastolic dysfunction was reported in 56 % and patients with diastolic dysfunction had a high prevalence of ascites. The final results of this impressive study are awaited with great interest. Future larger prospective studies are warranted in order to finally determine the impact of diastolic dysfunction on the circulatory and renal complications of cirrhosis and on the risk assessment in patients undergoing invasive procedures.

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