

Cross-talk between the Liver, Heart and Kidney – another Piece in the Puzzle

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We have known about the hemodynamic changes and renal failure in cirrhosis since the 1950s [1]. In 1956, Hecker and Sherlock described the clinical course of nine patients with severe liver disease and renal failure with an increase in urea, oliguria and hyponatremia combined with a decrease in the systolic blood pressure [2]. The condition is now classed as hepatorenal syndrome (HRS) - a term that was originally used to describe renal failure after biliary surgery [3]. Almost 50 years later, we still do not completely understand the underlying mechanism.

In 1969, Koppel and colleagues reported successful transplantation of cadaveric kidneys from six patients with cirrhosis and renal failure to patients with end-stage kidney disease [4]. The paper pointed towards HRS as a potentially reversible, functional condition. The following year, Epstein and colleagues published their landmark paper, which coupled vasoconstriction with renal failure in cirrhosis [5].

The first consensus conference to define HRS and propose diagnostic criteria was held in Sassari, Italy in 1978. The Sassari major diagnostic criteria for HRS included evidence of renal insufficiency (plasma creatinine >1.5 mg/dL) that progresses over days or weeks in the presence of severe liver disease plus absence of

nephrotoxic agents, lack of response to volume expansion and an intact tubular function. In 1996, the International Ascites Club proposed a revised set of diagnostic criteria, which were revised again in 2007 [6, 7]. Based on the current diagnostic criteria HRS includes cirrhosis with ascites and elevated creatinine, absence of shock, structural kidney disease and use of nephrotoxic agents combined with a lack of response to volume expansion. The importance of evaluating the effect of volume expansion was rooted in both clinical and basic research. The evidence suggested that vasodilation followed by renal sodium and water retention precedes ascites formation [8].

Pathogenetic aspects of cirrhotic cardiomyopathy

Cirrhosis is often associated with cardiovascular abnormalities. In more advanced disease stages with severe splanchnic and arterial vasodilation the circulation becomes vulnerable with impaired response to hemodynamic challenges as sepsis or bleeding. Thus an intact cardiac output and cardiac compensatory reserve becomes increasingly important, in order to protect the circulation and secure sufficient organ perfusion and oxygenation, especially in the kidneys [9]. Activation of the sympathetic nervous system, decreased arterial pressure and peripheral resistance, a reduced cardiac stress response, changes in the cardiac electromechanical function and enlarged cardiac chambers are all features associated with "cirrhotic cardiomyopathy" [10]. Cirrhotic cardiomyopathy is associated with an impaired beta-adrenergic receptor signaling, cardiomyocyte plasma membrane properties and changes in the intracellular calcium concentration [11]. Humoral factors including nitric oxide and carbon monoxide are also important. Cirrhotic cardiomyopathy contributes to the pathogenesis of the HRS. Clinical studies show that patients with spontaneous bacterial peritonitis have an increased risk of developing HRS if their baseline cardiac output is low and if it does not increase after the resolution of their infection [12]. Ruiz-del-Arbol and colleagues conducted a cohort study on patients with cirrhosis and found that a reduced cardiac output and increased plasma renin were the only predictors of HRS in a cohort of patients with cirrhosis [13]. The evidence suggests that the pathogenesis of HRS includes inadequate cardiac contractility combined with marked peripheral vasodilatation [9, 14].

The value of natriuretic peptides in cirrhotic cardiomyopathy

Natriuretic peptide hormones affect the excretion of sodium and the systemic vascular and central venous pressure. Measurements of the natriuretic peptide B-type natriuretic peptide (BNP) and its pro-hormone N-terminal proBNP (NT-pro-BP) are recommended in the guidelines for the management of patients with heart failure [15]. BNP and NT-pro-BNP are secreted from the ventricles in response to increased cardiac filling pressure. Increased levels of BNP and NT-pro-BNP predict mortality and cardiac outcomes in coronary artery disease and heart failure. Elevated levels of both hormones are seen even before symptoms of heart disease occur. Increased hormone levels are also associated with other edematous disorders with sodium and fluid overload and increased atrial or ventricular wall tension. In clinical practice, the interpretation of increased hormone levels may be difficult if patients have kidney disease. Accordingly, patients with cirrhosis and ascites also have increased BNP and NT-pro-BNP [16].

Cardiac electrophysiological changes in cirrhotic cardiomyopathy

Cirrhotic cardiomyopathy is a condition that consists of systolic impairment during stress, diastolic dysfunction with altered relaxation and electrophysiological abnormalities combined with the absence of other cardiac diseases. The electrical changes include an impaired repolarization, QT prolongation and dyssynchronous electromechanical coupling [17-20]. The ratio between the pre-ejection period and the left ventricular ejection time is an important parameter for the assessment of the left ventricular contractile function. An inadequate response to a physiological or pharmacological challenge may detect the condition. Increased levels of natriuretic peptides are also seen and have been associated with ventricular dysfunction due to prolonged cardiac repolarization [16]. The prolonged repolarization results in prolonged QT intervals on the electrocardiogram. The exact underlying mechanism that leads to the changes is not known, but there are clinical studies showing an association between prolonged QT intervals and the severity of liver disease [21]. The prevalence of QT interval prolongation among cirrhotic patients is about 45% compared with 5% in the general population. The changes are potentially reversible and often disappear after liver transplantation.

In the most recent issue of the *J Gastrointest Liver Dis*, Cavaşi and colleagues [22] report a cross-sectional study including 88 patients with cirrhosis. The study provides new information about NT-pro-BNP levels investigated in 88 cirrhotic patients divided into three groups including patients i) without ascites, ii) with ascites and a normal renal function and iii) with HRS. NT-pro-BNP and QTc interval were evaluated as markers of cardiac function. The renal function was estimated based on glomerular filtration rates using creatinine and serum cystatin C. The results showed that patients with HRS had the highest NT-pro-BNP levels. The proportion of patients with prolonged QTc intervals was similar in the two groups

of patients with ascites (patients with HRS and patients with ascites and a normal renal function). The group of patients without ascites had a lower proportion with prolonged QTc interval compared with the other groups. This study adds to the knowledge obtained through the last 50 years in the search for better understanding and therapies in HRS. It comprises another piece in the puzzle of current and emerging data on cardiorenal interdependence in advanced cirrhosis.

A number of studies have confirmed cardiorenal interdependence in patients with cirrhosis [9, 12, 13]. Interventions that affect the cardiac output are often used in the treatment of patients with cirrhosis and portal hypertension including volume expansion with human albumin and non-selective beta-blockers. In patients with cirrhosis, albumin infusion improves survival in patients with spontaneous bacterial peritonitis, HRS and large volume paracentesis [23-25]. The specific mechanism of action is not known, but key factors are likely to include an improved cardiac output and mean arterial pressure. In contrast, drugs that decrease the cardiac output seem to worsen outcomes with an increased risk of HRS and decreased survival. Observational studies suggest that non-selective beta-blockers have a negative impact on survival in patients with refractory ascites and after the first episode of spontaneous bacterial peritonitis [26-28]. Non-selective beta-blockers are titrated to decrease heart rate by 25%, which reduces cardiac output by 25%. In high doses this will occupy most beta-1-receptors in the heart and impair the cardiac compensatory reserve. A recent study by Mandorfer et al suggests that after the first episode of spontaneous bacterial peritonitis patients on non-selective beta-blockers have a doubled risk of acute kidney injury and HRS [28]. Again this reinforces the cardiorenal connection. Thus, at a certain point in the disease non-selective beta-blockers may not be beneficial and should be discontinued or titrated very carefully [29, 30].

Conflicts of interest: None.

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