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DECOMPENSATED HEART FAILURE (JE HO, SECTION EDITOR)

Cardiohepatic Syndrome: Liver Injury in Decompensated Heart Failure

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Abstract Heart failure (HF) is a major healthcare concern. Acute HF carries a high mortality and a high rehospitalisation rate. HF has a variety of detrimental effects on other organs. In recent years, the interactions between heart failure and the kidney have been the subject of significant investigations; this interaction, defined as "cardiorenal syndrome", is relatively well characterized. We describe here another interaction between the heart and the liver, the "cardiohepatic syndrome", in acute HF patients. Recent publications have shown that liver function test (LFT) abnormalities were associated with AHF severity. Clinical signs of systemic congestion were found to be associated with cholestasis, when signs of hypoperfusion were associated with liver cytolysis. Defining the LFT profile in AHF may play an important role in the future management of AHF patients.

Keywords Cardiohepatic syndrome · Acute heart failure · Liver function tests · Congestion

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Introduction

Heart failure (HF) is a major healthcare concern [1, 2]. Indeed, 2 % of the population in Western countries are affected by HF, and this prevalence increases from 1 % at 40 years of age to 10 % among the population over 70 years [3]. The burden of prevalent HF will increase due to an aging society, with improved survival of patients incurring acute and chronic coronary disease or with severe hypertension, plus the growing prevalence of obesity and diabetes. The pathophysiology of acute HF (AHF) is complex; patients can present with signs of congestion (pulmonary edema, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral edema, hepatomegaly) and/or signs of low cardiac output (e.g., peripheral hypoperfusion, low blood pressure). Systolic left ventricle (LV) failure presents reduced cardiac contractility, whereas diastolic LV failure exhibits impaired cardiac relaxation with abnormal ventricular filling. AHF carries a high mortality and a high rehospitalisation rate [4••]. Mean survival 5 years after an AHF episode is around 50 % [5].

It has been proposed to classify AHF patients in different clinical scenarios based on systolic blood pressure (SBP) on presentation. In clinical scenario 1 (CS1), SBP is over 140 mm Hg and symptoms often appear in few hours. In this clinical scenario, diffuse pulmonary edema is frequently observed and is the primary cause of dyspnea. This clinical scenario is characterized by a relatively preserved left ventricle ejection fraction, and patients are often euvolemic. In clinical scenario 2 (CS2), patients frequently present with signs of congestion. SBP is normal (100 – 140 mmHg). Symptoms in these patients usually appear over days or weeks prior to hospital admission. Patients usually report an increase in their body weight. Renal impairment, hypoalbuminemia, and anemia may also be observed in this clinical scenario. In clinical scenario 3 (CS3), SBP is less than 100 mmHg. Patients may present with signs of hypoperfusion or cardiogenic shock. [6].

We will see in this review that abnormal liver function tests (LFTs) have been found to be associated with congestion and/or hypoperfusion that, as seen above, are more frequently encountered in CS2 and 3.

HF has a variety of detrimental effects on other organs. In recent years, the interactions between heart failure and the kidney have been the subject of significant interest and investigation; this interaction, defined as "cardiorenal syndrome" (CRS), is relatively well characterized [7••]. We describe here another interaction between the heart and the liver, the "cardiohepatic syndrome" in AHF patients, and possible pathophysiological mechanisms involved. We will see that similarly to what is observed in CRS, congestion and hypoperfusion play a key role in the "cardiohepatic syndrome".

Cardiorenal Syndrome

Renal dysfunction is highly prevalent in HF patients and is one of the most important independent risk factors for prolonged hospitalization, rehospitalization, and short- and long-term mortality [8–10]. CRS has been recently classified into five distinct entities (Table 1) [11–15]. Mullens et al. reported in 2009 a study of 145 patients with acute decompensated heart failure [16]. They analyzed predictors of worsening renal function (WRF) and showed that patients with and without WRF had comparable levels of heart rate, systolic arterial blood pressure, and pulmonary capillary wedge pressure (PCWP) at admission. These clinical parameters were not found to be associated with WRF. In contrast, central venous pressure (CVP) was found by the authors to be associated with WRF. Risk of WRF has been found to increase with the level of baseline CVP. Mean CVP was lower in subjects that didn't develop WRF. In addition, the authors found a significant correlation between admission CVP and severity of WRF. Mullens et al.'s conclusion was that venous congestion is the most important hemodynamic factor driving WRF in decompensated patients with advanced heart failure. While there is a rapidly growing literature on the spectrum of pathophysiologic mechanisms involved in CRS [7••], interaction between the heart and the liver has been poorly described.

Table 1 Cardiorenal syndrome (CRS) classification

CRS type 1 occurs mostly in the setting of AHF where approximately 25 % of patients develop a rise in serum creatinine and a reduction of urine output following the use of intravenous diuretics. Altered hemodynamics in the heart and in the kidney are believed to be the determinants of CRS type 1.
CRS type 2 is chronic kidney disease (CKD) evolution in the setting of chronic HF. Accelerated renal cell apoptosis and fibrosis is considered to be the principal mechanism.
CRS type 3 is an AHF episode following acute kidney injury. This syndrome is precipitated by salt and water overload, acute myocyte dysfunction, and neurohormonal dysregulation.
CRS type 4 is the acceleration of the progression of chronic heart failure in the setting of CKD. Cardiac myocyte dysfunction and fibrosis is believed to be the predominant pathophysiologic mechanism.
CRS type 5 is simultaneous acute cardiac and renal injury in the setting of a systemic disease such as sepsis. In this scenario, the predominant pathophysiological disturbance is microcirculatory and enzymatic activation which result in simultaneous organ injury.

Liver Dysfunction in Chronic Heart Failure

Liver function abnormalities have been well characterized in patients with chronic heart failure [17–20]. The primary pathophysiologic mechanism described that is involved in liver dysfunction is transmission of elevated CVP to the hepatic venous system leading to passive hepatic congestion. Another mechanism involved in liver injury is the decrease in cardiac output leading to impaired liver perfusion associated with acute hepatocellular necrosis [21]. Additionally, several reports have linked abnormal LFTs with poor outcome in chronic HF [22–24]. The impact of chronic HF on LFTs was described in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trial [25•]. In this trial, total bilirubin was found to be significantly elevated in patients with signs of hypervolemia compared with euvolemic patients. Poelzl et al. analyzed a cohort of stable HF patients and showed that disease severity was positively correlated with cholestasis. Total bilirubin and alkaline phosphatase were, for example, correlated with jugular venous distension and tricuspid regurgitation [26]. These data suggest that abnormal LFTs in stable HF patients are more likely related to congestion rather than reduced cardiac output.

Liver Dysfunction in Acute Heart Failure

Unlike chronic HF, there are only few reports comprehensively assessing liver function in AHF patients [27, 28]. A recent post hoc analysis of the SURVIVE trial improved our knowledge on LFT abnormalities in patients admitted with AHF [29, 30•]. LFTs at admission were abnormal in 46 % of the study population. LFTs were found in this analysis to be one to two times the upper normal limit in more than 50 % of AHF patients with abnormal LFTs. The authors showed that patients with abnormal alkaline phosphatase had more frequently signs of congestion like peripheral edema. These patients had also a higher 180-day mortality. Thirty-one- and 180-day mortality were also found to be more elevated in patients with abnormal transaminases as compared to patients with normal AST and ALT. Patients with abnormal AST and/or ALT featured more frequently signs of hypoperfusion.. This analysis showed that LFT abnormalities can be possible surrogates

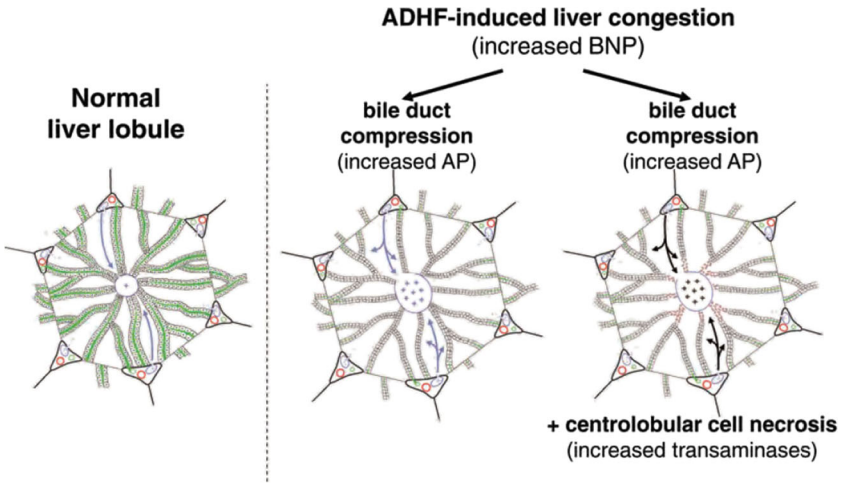

Fig. 1 Suggested mechanism of liver injury in acute decompensated heart failure. ADHF, acute decompensated heart failure; AP, alkaline phosphatase; BNP, B-type natriuretic peptide. From Nikolaou M, et al., "Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure." *Eur Heart J*. 2013 Mar; 34(10):742-9, with permission from Oxford University Press

of haemodynamics. LFT abnormalities were associated with increased mortality in this cohort of AHF patients. The authors suggest as a possible mechanism for liver injury in AHF that increased hydrostatic pressure related to congestive liver sinusoids would possibly be responsible for bile canaliculi and ductules compression. In contrast, hypooxygenation and/or hypoperfusion of the centrilobular region of the liver could lead to hepatic cytolysis (Fig. 1) [30•]. Another recent publication from Vyskocilova and colleagues analyzed 1,473 AHF patients from the AHEAD registry. Seventy-six percent of patients in this registry featured abnormal LFTs. Total bilirubin was present in 34 % of patients, γ-glutamyltransferase in 44 %, alkaline phosphatase in 20 %, aspartate aminotransferase in 42 %, and alanine aminotransferase in 35 %. The authors showed that LFT abnormalities were strongly associated with AHF severity (left ventricular ejection fraction and NYHA functional class). They also showed that, whereas elevation of cholestatic enzymes occurs mainly in right-sided heart failure related to systemic congestion, elevation of transaminases is mainly related to clinical signs of hypoperfusion (systemic hypotension) [31].

Elevated Intra-Abdominal Pressure as Potential Contributor to Liver Dysfunction

Mullens et al. showed a few years ago that elevated intra-abdominal pressure (IAP) in AHF patients could be a potential contributor to worsening renal function. They analyzed data from 40 patients admitted with severe AHF and showed that patients with elevated IAP (≥8 mmHg) had higher serum creatinine levels at baseline and at follow-up compared with those who had a normal IAP at baseline. The authors also showed that improvement in renal function after medical therapy is associated with a reduction of IAP [32]. A similar impact of elevated IAP on liver function could be another possible pathophysiological mechanism in the "cardiohepatic syndrome" in conjunction with congestion.

Potential Clinical Implications

The main implication is that LFTs should be measured at admission for AHF. It is likely that this will be added to future HF guidelines. Measuring LFTs at admission will provide an additional biomarker to clinical signs of congestion and/or hypoperfusion. Though it needs to be demonstrated, one may suggest that dose and length of diuretics may be adjusted depending on the time course of LFTs. Furthermore, impairment of LFTs is also a sign of liver dysfunction. This prompts physicians to adapt the dosages of all cardiovascular therapies and of adjunct therapies, such as anti-vitamin K or antibiotics, in the initial phase of AHF management. Indeed, many patients (around 30 %) have an atrial fibrillation at admission and may be on treatment with anti-vitamin K, and so the dose should probably be adjusted.

Conclusions

Incidence of abnormal LFTs have been shown to range from 46 % to 76 % in AHF patients, when worsening renal function is observed in 25 % of AHF patients (CRS type 1). Even though LFT abnormalities related to HF have been studied for many years, the exact mechanisms of liver injury in HF patients are still unclear. Liver dysfunction has been shown to be mainly related to liver congestion. In recent years, there have been growing data on the "cardiohepatic syndrome" in severe AHF patients. Future investigations are needed in less severe AHF patients and in the emergency department setting. Defining the LFT profile in AHF plays an important role in management of AHF patients, and early recognition of hepatic impairment may warrant more intensive treatment of AHF

and therapy optimisation. This will possibly lead to decreased morbidity and mortality in patients with "cardiohepatic syndrome".

Compliance with Ethics Guidelines

Conflict of Interest Said Laribi declares that he has no conflict of interest.

Alexandre Mebazaa has received speaker's honoraria from Alere, BRAHMS, Edwards, Orion, and Bayer.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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