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STATE-OF-THE-ART PAPER

Cardiohepatic Interactions in Heart Failure

An Overview and Clinical Implications

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Heart failure (HF) is a major public health problem leading to frequent hospitalizations, impaired quality of life, and shortened life expectancy. Heart failure leads to a chronic inability to meet metabolic requirements of end organs or skeletal muscle. Current literature lacks comprehensive descriptions of HF effects on hepatic function. In this review paper, we summarize the literature that is available in hopes of highlighting the key differences in clinical presentation, histological findings, and biochemical profiles of patients who present with both acute and chronic liver injury secondary to HF. We further discuss the use of liver function tests as prognostic markers in patients with HF, as well as the implications of liver injury on drug metabolism in this patient population. Finally, we provide recommendations regarding the management of both types of liver injury in HF patients. (J Am Coll Cardiol 2013;61:2397–405) © 2013 by the American College of Cardiology Foundation

Heart failure (HF) is a major public health problem, with frequent hospitalizations, impaired quality of life, and shortened life expectancy (1). As HF advances, it is often characterized by an increasing inability to meet the metabolic requirements of end organs or skeletal muscle. While much attention has been directed toward the intersection of HF and renal function, the impact of HF on hepatic function has been poorly described.

Similar to the now widely described "cardiorenal" syndromes, more attention is needed in describing "cardiohepatic" interactions. Over the last several years, a number of studies have described poor outcomes associated with the development of cardiorenal syndromes, as well as potential solutions to mitigate further renal injury while treating HF (2). In contrast, much less is known about impaired liver function in patients with HF. Furthermore, HF patients may present with liver-related symptoms including abdominal distention, intermittent right upper quadrant discomfort, nausea, early satiety, or anorexia. The presence of these symptoms may direct a primary gastrointestinal evaluation rather than consideration of primary cardiac pathology, thereby creating a delay in the initiation of life-prolonging interventions.

Abnormalities in liver function tests (LFTs) are not an uncommon finding in patients with HF. These abnormalities are a result of impaired perfusion or elevated right-sided cardiac pressures, or are secondary to drug toxicity. Attempts at describing the features of chronic liver damage secondary to HF have been ongoing since the early 20th century (3,4). Nevertheless, neither the pathophysiologic basis underlying these findings nor the clinical impact of impaired liver function on HF outcomes have been clearly delineated. In this paper, we review the contemporary data characterizing histopathological findings and biochemical profiles of various types of hepatic dysfunction occurring in acute and chronic HF. We explore the prognostic significance of liver injury markers in the various stages of HF. Finally, we discuss potential strategies to effectively investigate, manage, and treat liver dysfunction in HF patients, as well as future research efforts that may further improve our understanding of cardiohepatic interactions in HF.

Liver Dysfunction in HF Patients: Presentation, Histology, and Biochemical Profiling in Acute HF

Acute cardiogenic liver injury. PRESENTATION AND PATHOPHYSIOLOGY. Acute cardiogenic liver injury (ACLI), historically called "ischemic hepatitis," is often described in patients with HF who have progressed to critical cardiogenic

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Abbreviations and Acronyms

ACLI = acute cardiogenic liver injury
ALT = alanine aminotransferase
GGT = gamma-glutamyl transpeptidase
HF = heart failure
LDH = lactate dehydrogenase
LFT = liver function test
LVAD = left ventricular assist device
MELD = model for end-stage liver disease
modMELD = modified model for end-stage liver disease
NYHA = New York Heart Association
TR = tricuspid regurgitation

shock, in which cardiac output is no longer sufficient to meet the metabolic demands of hepatic cells (5). However, review of the literature suggests that an acute change in hepatic blood flow is not the sole incident responsible for the development of ACLI (6). In a retrospective analysis of patients with clinical and biochemical evidence of ACLI, Seeto et al. (7) found that hypotension alone did not induce acute liver injury. Patients with ACLI were compared with a control group comprising trauma victims who had evidence of prolonged hypotension (7). No patients in the control group had findings consistent with ACLI. Conversely, nearly all patients with a clinical diagnosis of ACLI had evidence of cardiac disease, with 29 of these 31 subjects demonstrating evidence of elevated right-sided or venous filling pressures (7). Similarly, Henrion et al. (8) examined ACLI in patients admitted to the coronary intensive care unit with evidence of low cardiac output. Patients with biochemical evidence of cardiogenic injury had significantly higher central venous pressures compared to patients who had low cardiac output but no ACLI (8).

Several larger studies characterizing the etiology of ACLI have shown that the majority of cases of ACLI are related to acute HF, respiratory failure, and septic shock. However, these same studies have also shown that between 39% and 70% of patients with ACLI have the underlying diagnosis of chronic HF (6,9,10). These findings suggest that ACLI does not result from a single hemodynamic insult, but rather, ACLI is linked to the combination of hepatic congestion from elevated hepatic venous pressure coupled with impaired perfusion (Fig. 1) (8). Venous congestion may ultimately increase the susceptibility of the liver to injury caused by reduced perfusion. The notion that a "second hit" is required for acute liver injury is not captured in the nomenclature commonly used to describe this process, such as "ischemic hepatitis" or "shock liver." Therefore, we believe that "ACLI" is a more accurate diagnostic term (5), encapsulating the underlying pathophysiological process.

Although the pathophysiological process is not clearly defined, the injury pattern of ACLI represents the release of hepatic proteins in response to tissue hypoxia and cell death (6). After hemodynamic recovery, symptoms related to the liver injury can present after a latency period of 2 to 24 h (5). These symptoms may include weakness, apathy, and (in a minority of cases) persistent mental confusion, tremor, hepatic coma, and jaundice (11). A bleeding diathesis from acquired coagulopathy may also develop due to impaired production of coagulation factors (11). These abnormalities peak at 1 to 3 days after onset of symptoms and, in patients who survive, return to normal within 5 to 10 days after onset (5,12,13).

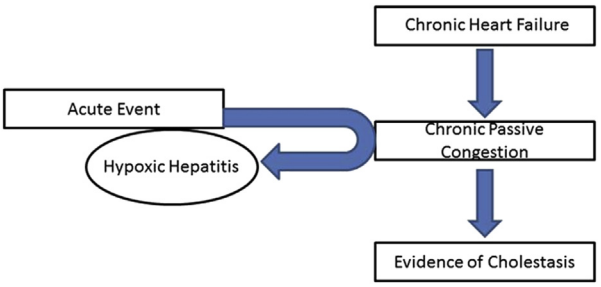

Figure 1 **Mechanisms Leading to 2 Types of Cardiogenic Liver Injury**

Chronic heart failure (HF) leading to chronic passive congestion of the liver leads to a liver function panel consistent with cholestasis. Patients with chronic HF who experience an acute decompensation show evidence of hypoxic hepatitis.

HISTOPATHOLOGY. The histologic hallmark of ACLI is necrosis surrounding the central vein where oxygenation is poor (zone 3) (4). Depending on the duration of ischemia, a variable degree of architectural collapse around the central veins can occur (4,14). Necrosis can extend to the mid-zonal hepatocytes with prolonged ischemia; however, necrosis rarely occurs predominantly in the middle zones (Fig. 2) (4,14). Although clinical and laboratory diagnostic data are usually sufficient for the diagnosis, a liver biopsy may be useful when it is necessary to clarify the underlying etiology of an acute rise in aminotransferase levels (15).

BIOCHEMICAL PROFILE. The typical pattern in laboratory studies consists of a substantial and rapid elevation in aminotransferase and lactate dehydrogenase (LDH) levels to 10 to 20 times normal, typically between 1 and 3 days after hemodynamic insult, and without evidence of another etiology such as cholecystitis or viral hepatitis (8,11). With correction of hemodynamics, these levels will return to normal within 7 to 10 days (5). Early and rapid increase in serum LDH is a distinguishing feature of ACLI, and a ratio of serum alanine aminotransferase (ALT) to LDH <1.5 early in the course of liver injury is characteristic of cardiogenic injury as opposed to other etiologies of hepatitis (16). Laboratory abnormalities may also include sharp increases in serum ALT and aspartate aminotransferase (AST; typically 10 times normal values), increased serum bilirubin, and prolongation of the prothrombin time (5). In fact, 2 studies have shown as much as a 50% decrease in prothrombin activity in 79.5% and 84% of ACLI patients, which is thought to be unusual in the case of viral hepatitis (6).

Although there are few data regarding LFT alterations among patients with acute HF, a recently published analysis