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Review

# Congestive hepatopathy and hypoxic hepatitis in heart failure: A cardiologist's point of view

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ABSTRACT

In the setting of long-standing severe chronic heart failure, other organ systems are also involved. The liver is one of the organs that are very sensitive to haemodynamic changes. Differential diagnosis of the liver injury is extremely important in the cardiologist's clinical practice and calls for cardiologist's and hepatologist's collaboration because there are many other diseases that can affect the liver and mimic haemodynamic injury. In this article, liver injuries depending on cardiocirculatory dysfunction such as hypoxic hepatitis and congestive hepatopathy are analysed.

The material in the article is presented in two aspects: the evaluation and treatment of heart failure in order to prevent pathologic processes in the liver, and the recognition of the liver injury, including diagnostic tests which are essential for differential diagnosis of different liver pathologies.



## 1. Introduction

The liver is very sensitive to haemodynamic changes because of its complex vascular system and high metabolic activity. It is a highly vascular organ which receives up to 25% of the total cardiac output [1]. There is a number of hepatic vascular injury forms. The most recognised include the Budd–Chiari syndrome, hepatic veno-occlusive disease, congestive hepatopathy (CH), hepatic infarction, and hypoxic hepatitis (HH). Differential diagnosis of the liver injury is extremely important in cardiologist's clinical practice and calls for cardiologist's and hepatologist's collaboration. However, the straight diagnosis of the hepatic injury still remains a frequently overlooked diagnosis in severe heart failure (HF) patients and vice versa [2].

## 2. Background of definition

### 2.1. Hypoxic hepatitis in acute cardiocirculatory failure

In cases of acute cardiocirculatory failure, the systemic arterial pressure suddenly becomes reduced and leads to subsequent hepatocellular hypoxia which results in diffuse liver injury morphologically defined as centrilobular liver necrosis. HH is also known as "ischaemic hepatitis", "hypoxic hepatopathy" or "shock liver". Although these terms are still frequently observed in medical literature, they are misleading as it is considered that several pathogenic mechanisms overlap [3]. In cases of acute cardiocirculatory failure, the pathogenesis comprises not only hepatic ischaemia, but also systemic blood flow reduction and passive congestion of the liver, which may predispose hepatocytes to greater hypoxic injury resulting from hypotension [4,5].

The diagnosis of HH can be defined by three criteria: 1. Appropriate criteria of cardiac, circulatory or pulmonary failure; 2. Severe and transient increase in aminotransferase levels; and 3. Exclusion of other possible causes of liver damage [6].

### 2.2. Congestive hepatopathy in chronic cardiocirculatory failure

The aetiology of CH comprises a number of disorders severely impairing right heart function such as constrictive pericarditis, mitral stenosis, severe tricuspid regurgitation, decompensated cor pulmonale, or advanced HF in the presence of end-stage cardiomyopathies [7]. In the setting of chronic heart and cardiocirculatory failure, hepatic dysfunction occurs as a result of passive venous congestion. Morphologically, hepatic injury ranges from the mild deposition of sinusoidal collagen to formation of broad fibrous septa and so called "cardiac cirrhosis" [8]. However, the term "cardiac liver fibrosis" is more accurate, reflecting the difference between liver morphology in cases of congestive HF and pathological pattern of true (portal) liver cirrhosis [7].

The diagnosis of CH can be defined by these criteria: 1. Structural heart disease impairing right heart function; 2. Signs and symptoms of right HF (jugular venous distension, hepatomegaly, hepatojugular reflux, pitting oedema, ascites); 3. Elevation of serum cholestasis markers: alkaline phosphatase (AP), total and direct bilirubin, gamma-glutamyl transferase (GGT); 4. Exclusion of other possible causes of liver damage [6,7,9–12].

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## 3. Pathophysiology

### 3.1. Hypoxic hepatitis

It was thought that hypotension is the key pathogenic mechanism of HH. However, current research shows that such factors as venous congestion, reduced capability of hepatocytes to extract oxygen and reperfusion injury are of greatest importance [7]. It is already known that congestive HF predisposes the liver to a greater hypoxic injury. Seeto et al. concluded that 94% of patients with HH previously have had chronic HF [5]. In Henrion et al. study, patients with chronic HF comprised 70% of all HH cases [13]. In the setting of chronic blood congestion, hepatocytes compensate disrupted blood flow by increasing oxygen extraction. In cases of prolonged cardiocirculatory stress, when decreased heart function does not ensure normal liver perfusion and metabolic demands, the compensatory mechanism of hepatocytes to extract more oxygen is exceeded, and it leads to hepatocellular hypoxia and necrosis, especially in zone 3 of the hepatic acini [7] (Fig. 1; [[]]). According to the Rappaport et al. classification, zone 1 is often referred to as periportal region and is closest to the portal vascular inflow, receiving blood with the highest levels of oxygen and nutrients. In contrast, pericentral or zone 3 hepatocytes are closest to the central venous outflow, receiving relatively hypoxic blood that has passed through zones 1 and 2, which makes them the most vulnerable to oxygen deprivation [15] (Fig. 2; [[]]).

### 3.2. Congestive hepatopathy

As mentioned before, hepatic blood flow and perfusion are decreased in severe congestive HF. Elevated central venous pressure is transmitted to hepatic sinusoids through hepatic vessels, resulting in sinusoidal dilatation and oedema, as well as atrophy of zone 3 hepatocytes. Enlargement of sinusoidal fenestrae results in exudation of protein rich-fluid that is drained through the hepatic lymph system. When fluid production exceeds elimination rate, it is drained to the peritoneal cavity, leading to formation of ascites. Prolonged perivenular congestion results in collagen deposition, which later may form fibrous septa and bridges connecting two adjacent central veins [7]. The degree of fibrosis is variable from one region of the liver to another. This variability may be explained by the fibrogenic effects of focal thrombi within the sinusoids, hepatic venules, and portal veins as a result of chronic vascular stasis [16].

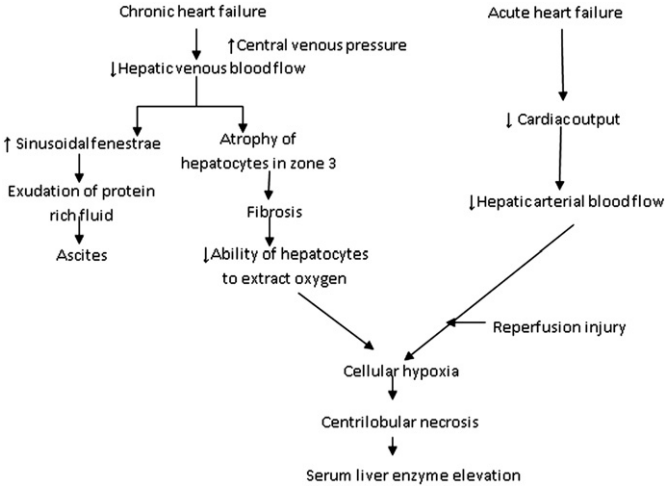


**Fig. 2.** Mechanism of liver injury in acute and chronic heart failure. Modified from Birrer et al. [[]].

## 4. Clinical and laboratory features of the liver injury in heart failure

### 4.1. Clinical presentation of hypoxic hepatitis

There are a few presumptions for HH to occur. Firstly, HH can be expected in patients with chronic HF, whose liver is more vulnerable from transient reductions in hepatic arterial perfusion [7]. Secondly, HH usually occurs in patients with clinical setting of circulatory failure [8].

No unique clinical symptoms and signs refer to HH, and usually its clinical course remains asymptomatic. However, some patients may have symptoms of acute symptomatic hepatitis such as nausea, vomiting, anorexia, malaise, right upper quadrant pain, and sometimes even mild jaundice. During physical examination, some patients have tenderness to palpation in the right upper quadrant [7].

Changes in the mental status, when present, more often represent cerebral hypoperfusion and hypoxia rather than hepatic encephalopathy [6]. However, a few cases of hepatic encephalopathy have also been described [17]. It is one of the most serious complications of HH. A complex of neuropsychiatric, cognitive and motor components

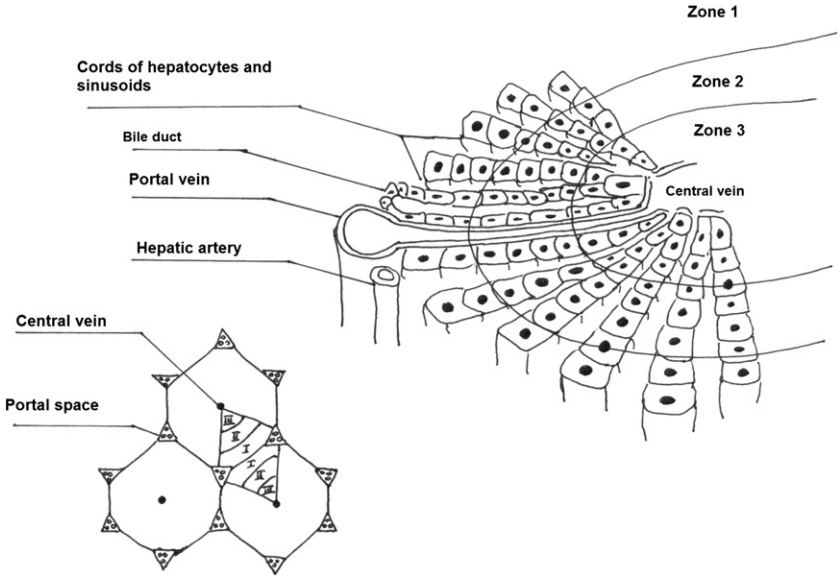


**Fig. 1.** Schematic presentation of a hepatic acinus. Modified from Brosnan and Brosnan.