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Chapter

Cardiac Hepatopathy

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Abstract

Liver disease resulting from heart disease has generally been referred as "cardiac hepatopathy." The two main forms of cardiac hepatopathy are acute cardiogenic liver injury (ACLI) and congestive hepatopathy (CH). ACLI most commonly occurs in the setting of acute cardiocirculatory failure, whereas CH results from passive venous congestion in the setting of chronic right-sided heart failure (HF). Both conditions often coexist and potentiate the deleterious effects of each other on the liver. In CH, the chronic passive congestion leads to sinusoidal hypertension, centrilobular fibrosis, and ultimately, cirrhosis ("cardiac cirrhosis") and hepatocellular carcinoma. The differentiation between congestion and fibrosis currently represents an unmet need and a growing research area. Although cardiac cirrhosis may only arise after several decades of ongoing injury, the long-term survival of cardiac patients due to advances in medical and surgical treatments is responsible for the increased number of liver complications in this setting. Eventually, the liver disease could become as clinically relevant as the cardiac disease and further complicate its management.

Keywords: cirrhosis, portal hypertension, heart failure, heart transplantation, hepatitis

1. Introduction

Heart failure (HF) is a systemic clinical syndrome with typical symptoms and signs (e.g., dyspnea, paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in reduced cardiac output and/or elevated intracardiac pressures. It is a major public health problem with an estimated prevalence of 1–2% of the adult population in the developed countries, rising to ≥10% among people >70 years of age [1]. Although much of the research on its systemic interactions has focused on the so-called cardio-renal syndrome, cardio-hepatic interactions are arousing great interest in recent years [2]. These cardio-hepatic interactions have been classified into three groups according to the role of each organ as culprit or victim of the other [3, 4]: (1) liver disease resulting from heart disease; (2) heart disease resulting from liver disease (e.g., cirrhotic cardiomyopathy); and (3) systemic diseases that affect both the heart and the liver (e.g., systemic amyloidosis).

This chapter seeks to make a comprehensive review of the first group: liver disease resulting from heart disease. This type of liver disease has generally been referred as "cardiac hepatopathy," although there is still no consensus on terminology [5, 6]. The two main forms of cardiac hepatopathy are acute cardiogenic liver

injury (ACLI) and congestive hepatopathy (CH). ACLI most commonly occurs in the setting of acute cardiocirculatory failure, whereas CH results from passive venous congestion in the setting of chronic right-sided HF. Both conditions often coexist and potentiate the deleterious effects of each other on the liver [5–7]. In the following pages, we aim to describe their pathophysiology, clinical features, diagnosis, and treatment.

2. Hepatic circulation

The liver receives a dual blood supply from the hepatic artery and portal vein. The former delivers well-oxygenated blood and comprises approximately 25% of total hepatic blood flow, whereas the remaining 75% is deoxygenated blood supplied by the portal vein. The total hepatic blood flow ranges from 800 to 1200 ml/min, representing up to 25% of the total cardiac output [7]. As a highly vascular organ, it is sensitive to hemodynamic changes but resilient to ischemic damage through its robust vascular mechanisms of defense [3]. The hepatic artery buffer response is one of such mechanisms whereby decreased portal flow instigates compensatory up-regulation of hepatic arterial flow. It is estimated that it may be capable of compensating for up to a 60% decrease in portal flow [3, 7, 8]. The signaling pathway for this response is local, with the reduction of portal flow resulting in an increase in concentration of the vasodilator adenosine [9]. Unlike the hepatic artery, the portal vein does not have the ability to autoregulate its flow and is dependent on cardiac output and the gradient between portal and hepatic venous pressures [7, 8]. The high permeability of sinusoids represents a second mechanism of defense against hypoxia. It favors oxygen diffusion to the hepatocytes, increasing oxygen extraction to levels near 90%. It prevents any change in liver oxygen consumption despite decreases in liver blood flow up to half of its normal. It must be highlighted that this remarkable ability is exclusive to the liver [7, 10, 11].

By contrast, the protective mechanisms against congestion are less developed and mainly rely on the highly connected sinusoidal network to relieve the increase in pressure. This elevated pressure hits the sinusoidal bed without attenuation since the hepatic veins lack valves [6]. As will be explained in greater detail below, the pre-existing hepatic congestion predisposes the liver to hypoxic injury under any acute event resulting in reduced hepatic blood flow [7, 12].

3. Acute cardiogenic liver injury (ACLI)

ACLI has also been referred to as ischemic hepatitis, shock liver, or hypoxic hepatitis in medical literature. These terms reflect the long-standing debate regarding its pathogenesis [7]. In 1901, F.B. Mallory (of Mallory-Denk body fame) first described the typical pattern of centrilobular liver necrosis (CLN) characteristic of this entity based on a series of autopsies in Boston. He proposed a toxic theory whereby liver damage was secondary to toxins released by bacteria into the circulation [13]. This theory was soon challenged by Lambert and Allison who found no proof of bacterial infection in a series of 112 patients deceased from congestive HF, 30% of whom had CLN [14]. They then proposed passive congestion as its prime etiological factor, and this "congestion theory" prevailed for more than 50 years. The emergence of transaminases measurement in the early 1950s revealed the massive increase of these enzymes that come in parallel with CLN. The association between shock, CLN, and significant rise in transaminases found by different studies led some investigators to propose liver ischemia as the sole factor responsible for liver cell necrosis [15–18]. It was then that

the terms "shock liver" and "ischemic hepatitis" were introduced by Birgens et al. [19] and Bynum et al. [20], respectively. Hence, by the late 1970s, the "ischemic" theory had replaced the "congestion" theory and remained unquestioned until 1990. In this year, Henrion et al. reported the first prospective series with hemodynamic data of 45 episodes of ischemic hepatitis. They observed that a shock state was only present in 47% of the episodes and proposed renaming this liver injury "hypoxic hepatitis" as hypoxia from a variety of etiologies (e.g., sepsis and respiratory failure) was present in all cases [21]. These findings were later confirmed by the final report from the same authors including 142 episodes [22] and by the series of 322 cases of ischemic hepatitis published later by Birrer et al. [23]. Thus, the term hypoxic hepatitis together with ACLI is currently used to name this entity. Some authors believe that ACLI provides more details about the underlying pathophysiological process as an acute cardiac event in a patient with an underlying congestive liver represents the most common clinical scenario [2, 5, 24, 25].

3.1 Epidemiology

The prevalence of ACLI among patients admitted to hospital varies greatly depending on the severity of illness. Indeed, in a recent meta-analysis of 1782 cases, ACLI was present in two every 1000 patients for all levels of hospital care but increased to 2.5 out of every 100 patients in intensive care units (ICUs) [26]. Studies including very critically ill patients have described maximum figures ranging from 11.9 to 21.9% [27–29]. Although previously debated [7], recent series indicate that the presence of a primary liver disease also increases the risk of ACLI. In a nationwide study including patients with hemodynamic instability, Waseem et al. observed a prevalence of acute liver injury of 22% in patients with underlying liver disease compared to only 3% in those without baseline hepatopathy [30].

These variations in frequency of ACLI not only respond to the severity of illness or the presence of a primary liver disease, as sometimes the diagnosis is overlooked clinically and variable cutoffs of transaminases are an important determinant of prevalence. Thus, in the previous meta-analysis, different liver enzyme cutoffs were used among studies as inclusion criteria, and the highest frequency of ACLI was among patients with increased serum aminotransferases above 1000 IU/L, where the prevalence reached 57% [26]. Therefore, current prevalence rates of ACLI might be underestimated [7, 12].

3.2 Pathophysiology

Liver damage in ACLI is the result of several mechanisms: passive congestion reduced hepatic blood flow, total body hypoxemia, inability to utilize oxygen, and ischemia/reperfusion injury. Necrosis, rather than apoptosis, is the main mode of death due to these mechanisms [31]. Although frequently multifactorial, the predominating mechanism of damage can be different depending on the underlying condition [7, 12]. In this regard, the most frequent diseases leading to ACLI are HF, respiratory failure, and septic shock, accounting for more than 90% of cases [7]. These diseases often coexist and lead to ACLI. Hence, Fuhrmann et al. identified more than one disease contributing to ACLI in 74% of their study population [27].

As mentioned previously, HF represents the main underlying condition in ACLI. The proportion of ACLI cases due to HF published in the literature ranges from 39 to 78% [7, 12, 22, 23, 26–28]. In this condition, the main mechanisms involved in the development of ACLI are passive congestion and ischemia of the liver. Indeed, in this scenario, ACLI is believed to reflect the extreme of a spectrum of liver injury that begins with passive hepatic congestion since the vast majority of patients have

markedly elevated cardiac filling pressures [17, 22, 26, 32, 33]. Thus, several studies have shown how, despite similar hemodynamic derangements, only those with a pre-existing congestive liver developed ACLI [23, 29, 33]. This crucial role of passive congestion of the liver justifies the rare occurrence of ACLI in hemorrhagic or hypovolemic shock [7]. Most importantly, Seeto et al. showed that 15–20 minutes of hypotension is sufficient to provoke ACLI [33]. This explains why hemodynamic instability is not systematically observed, since such a brief period can easily be unrecognized.

Respiratory failure accounts for approximately 15% of ACLI cases [7]. Severe hypoxemia resulting from an exacerbation of chronic respiratory disease is the main mechanism leading to ACLI. Very low levels of arterial pressure in oxygen (i.e., under 40 mmHg) are commonly observed, as well as the coexistence of hepatic venous congestion. In this setting, cardiac output and hepatic blood flow are normal or even increased [22, 23].

Septic shock is the cause of ACLI in 15–30% of cases. The prime factor leading to hypoxia is both the increased demands of oxygen and the decreased ability of hepatocytes to utilize oxygen [7]. It has been postulated that inflammatory mediators and endotoxins may be behind this abnormal oxygen utilization [7, 34, 35]. Although at the initial phases of septic shock hepatic blood flow is increased, the progression from high to low cardiac output may occur rapidly and aggravate the hypoxic damage [12].

While the previously described mechanisms induced ACLI by causing liver hypoxia, it has been postulated that re-oxygenation is also required [7, 12]. Several observations support this role of ischemia/reperfusion injury in ACLI: (1) it has been described that liver cell necrosis occurs at the time of reperfusion not ischemia [7]; (2) the incidence and severity of CLN correlate with the duration of shock. In fulminant and refractory cardiogenic shock (median duration of shock was 3 hours), CLN was only observed in a minority of patients and was mild [21, 29], whereas earlier studies showed how the longer the period of shock the greater the severity and frequency of CLN [36, 37]. One explanation of these findings is that long-lasting shocks probably harbor transient periods of hemodynamic stability and re-oxygenation that can cause ischemia/reperfusion injury and subsequently induce ACLI. (3) In a minority of ACLI cases, liver necrosis is limited to the mediolobular zone and spares the centrilobular zone [38–40]. Henrion et al. postulated that this atypical histological pattern could be due to an incomplete liver reperfusion prior to death that only reached periportal and mediolobular liver cells. Hence, periportal and centrilobular cells would have survived, the former because of oxygen delivery remained sufficient, and the latter because of the absence of reperfusion injury. Mediolobular hepatocytes, on the other hand, would have been destroyed due to ischemia/reperfusion injury [7].

3.3 Clinical presentation and diagnosis

The majority of ACLI cases occur in elderly men (i.e., 65–70 years) with congestive HF that has deteriorated over the past few days. It must be highlighted that a shock state is far from being a constant feature as is observed in around half of the cases. Moreover, the cardiac component may not be apparent at first evaluation as usual signs of HF, such as painful hepatomegaly, ankle edema, or hepatojugular reflux, are frequently lacking. Therefore, the diagnosis of ACLI cannot be rejected because of the absence of shock and of signs of HF, and in case of uncertainty, a cardiac evaluation is warranted [6, 7]. Symptoms due to ACLI are often absent or resemble those from acute viral hepatitis [24], and more commonly, the clinical picture is dominated by symptoms of the underlying conditions. Overt jaundice is absent at admission, and encephalopathy can develop but is usually the result of hemodynamic instability and hypoxia, rather than liver failure [7, 12].

Laboratory tests show a substantial and rapid increase in aminotransferases and lactate dehydrogenase (LDH) levels to 10–20 times the upper limit of normal, usually 1–3 days after hemodynamic deterioration. These elevations generally return to normal within 7–10 days if hemodynamic stability is restored [3, 41]. A progressive increase in bilirubin is usually seen but is seldom severe [3, 7, 12]. The higher values reported by recent series may be explained by the inclusion of more patients with septic shock. Nonetheless, the mean bilirubin value in these studies was lower than 6 mg/dL [27, 28]. Higher values may suggest progression to acute liver failure [6]. Unlike in children where hypoglycemia has been regarded as a distinct feature of ACLI, in adults both hypoglycemia and hyperglycemia have been reported [7, 12]. Although no analytical alteration is pathognomonic of ACLI, there are some findings that suggest its diagnosis [7]: (1) an alanine aminotransferase (ALT)-to-LDH ratio <1.5 is of great help in the differential diagnosis as it is rarely seen in other etiologies of hepatitis [42]; (2) the aspartate aminotransferase (AST) generally peaks earlier and higher than ALT [41]. The rational behind this finding lays on the concentration of aminotransferases throughout the hepatic acinus. ALT reaches the highest concentration at the level of periportal hepatocytes (Rappaport liver zone 1) and the lowest concentration at the level of pericentral hepatocytes (Rappaport liver zone 3), while AST maintains a stable concentration throughout the entire acinus. Hence, after the hypoxic insult, the initial concentrations of AST are higher than those of ALT, since the lower oxygen concentration of pericentral hepatocytes makes them more susceptible to hypoxic damage [43]. Once the cause of liver damage is resolved, the concentration of ALT exceeds that of AST in subsequent days, due to its longer half-life (47 ± 10 hours versus 17 ± 5 hours, respectively) [44]. Aboelsoud et al. [41] universally observed this pattern, but it was only described in 75% of the cases in Henrion's study [22]. The rapid decline and reversal of the AST-ALT ratio may explain these differences, and therefore, an ALT higher than AST should not discard ACLI; (3) an early and sharp deterioration in prothrombin activity and renal function also supports ACLI. Such abnormalities are unusual at presentation in patients with viral or drug-induced hepatitis, unless ALF is already established [7]. **Figure 1** shows a typical biochemical profile of ACLI in a patient treated in our hospital.

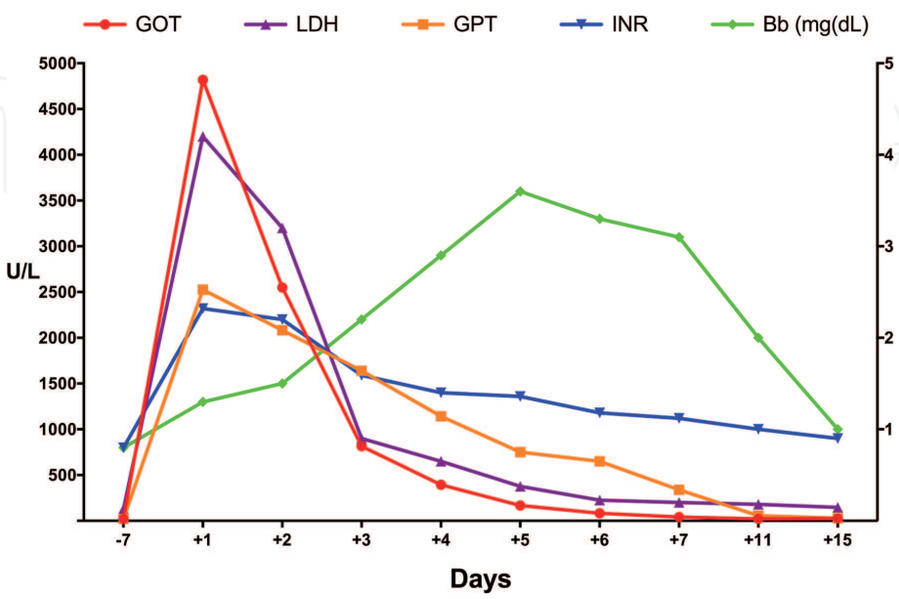


Figure 1.
Laboratory parameters during the course of ACLI in a patient with respiratory failure due to drug overdose. Abbreviations: AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; Bb; bilirubin; INR: International normalized ratio.

In accordance with the above, diagnosis of ACLI is usually made when the following criteria are met [12, 22, 26]: (1) an appropriate clinical setting of cardiac, respiratory, or circulatory failure; (2) a severe increase in aminotransferase levels; and (3) exclusion of other causes of acute liver damage. The differential diagnosis for severe elevations of transaminases is relatively limited and includes ACLI, acute viral hepatitis, toxin- or drug-induced liver injury, autoimmune hepatitis, Wilson's disease, acute bile duct obstruction, and acute Budd-Chiari syndrome [44]. Imaging techniques are essential to rule out some of these etiologies and can also support the diagnosis by finding a dilation of inferior vena cava and suprahepatic veins due to passive congestion [7]. Liver biopsy is rarely necessary and only when the underlying cause remains unclear. It will show features of coagulative necrosis of centrilobular hepatocytes without significant inflammation (**Figure 2A–C**). In biopsies delayed several days, however, there may be neutrophils infiltrating the affected regions [25]. As already stated, necrosis rarely occurs predominantly in the middle zone [38–40].

3.4 Prognosis and treatment

The prognosis of ACLI is poor with an overall hospital mortality of 51% [26] and 1-year survival rate of approximately 25% [7]. The cause of death is usually the underlying condition, as it is an uncommon cause of ALF. In a study from the Acute Liver Failure Study Group, only 4.4% of the ALF cases had ACLI as their final diagnosis [45]. Nevertheless, there is some indirect evidence that suggests that ACLI influences outcome in this setting. Hence, prolonged international normalized ratio (INR) and jaundice have been identified as independent risk factors for ACLI mortality [27, 28, 41, 46]. Other factors that have been associated with increased risk of in-hospital mortality include a baseline liver disease [30], higher elevations of transaminases [27, 45], LDH [27, 41], serum phosphate [45], concomitant renal failure [28, 41], septic shock [27, 28], and more advanced encephalopathy [45].

The management of the underlying diseases remains the only established treatment for ACLI. Although data are limited, some experts recommend using N-acetylcysteine, avoiding excessive vascular filling to minimize passive congestion of the liver, and favoring the use of dobutamine in patients with low cardiac index given its inotropic and vasodilating effects [2, 3, 7, 12].

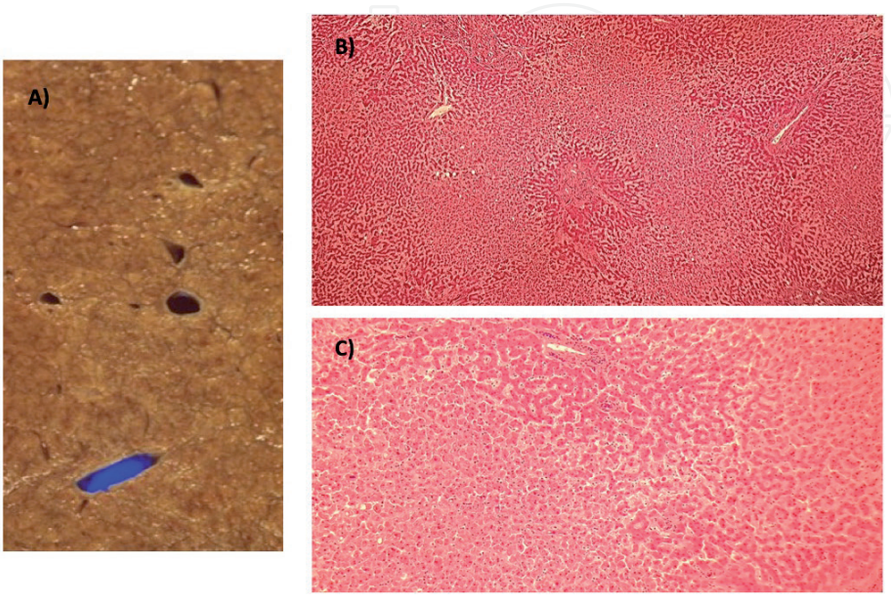


Figure 2.
(A) Postmortem example of a liver with ischemic zones around centrilobular veins. (B) Centrilobular regions show congestion and coagulative necrosis (hematoxylin-eosin). (C) Same findings than 2.B with greater magnification.

4. Congestive hepatopathy (CH)

Liver disease as a consequence of HF has been known for a long time. The histological description of the "nutmeg," congestive liver is attributed to Kiernan in 1833 [25, 47]. Earlier studies from the beginning of the twentieth century started providing data on the structural and functional changes that develop in the liver in the setting of HF [47, 48]. The classic work from Sheila Sherlock, published in 1951, stood for decades as the standard reference on this entity. In this article, the renowned author correlated liver tests, systemic hemodynamic parameters, and histology [47]. Progress has been made since then, but there are still important gaps concerning its pathophysiology, assessment of liver fibrosis, and clinical impact on overall HF prognosis [2, 6].

4.1 Epidemiology

CH occurs in the setting of any cause of right ventricular failure such as constrictive pericarditis, mitral stenosis, severe tricuspid regurgitation, cor pulmonale, or end-stage cardiomyopathies [8, 49]. The current spectrum of CH differs from earlier reports due to several reasons [3, 4, 6, 50]: (1) the etiology of HF has changed over the years with ischemic cardiomyopathy surpassing rheumatic valvular disease; (2) after major advances in medical treatment and the widespread use of heart transplantation, the prognosis of HF has greatly improved, and as a result, cardiac cirrhosis is declining; (3) these same medical advances are responsible for the improved survival of patients with a variety of congenital heart diseases that lead to right HF. The most illustrative example is the Fontan procedure to palliate single-ventricle physiology. Unlike patients with acquired heart disease, these patients may develop "cardiac cirrhosis" in early adulthood.

This heterogeneous cause of CH together with the limited validated techniques available to diagnose and, specially, stage the disease may explain that the burden of CH has not yet been adequately described [51]. Non-congenital HF studies using liver blood tests to determine the prevalence of CH have described figures ranging from 15 to 80%, depending on the severity of heart disease [24, 52–57]. However, liver blood tests neither accurately diagnose CH nor reflect the stage of liver disease [51]. Future studies should use a more comprehensive approach to overcome these biases and to provide solid data on this issue.

4.2 Pathophysiology

Congestion produces liver damage through several pathogenic mechanisms: (1) increased sinusoidal pressure leads to hepatic stellate cell activation and decreases nitric oxide production by endothelial cells through shear stress, all of which induce sinusoidal ischemia and promote fibrogenesis [51, 58]; (2) decreased hepatic blood flow further aggravates liver ischemia. Portal venous inflow is reduced as a result of the transmission of the elevated central venous pressure to the sinusoidal network, while arterial flow can also be compromised in patients who also harbor a left-sided HF [8, 51]; (3) Accumulation of exudate into the space of Disse due to the existing congestion impairs diffusion of oxygen and nutrients to hepatocytes and accelerates fibrosis pathways [8]; (4) Sinusoidal stasis and congestion promote sinusoidal thrombosis, which in turn contributes to liver fibrosis by causing parenchymal extinction and by activating hepatic stellate cells via protease-activated receptors [59, 60]. The former refers to a hypothesis based on retrospective observations of ex-vivo human liver specimens of patients with CH. In this autopsy study, Wanless et al. demonstrated sinusoidal thrombi confined to areas of fibrosis, thereby suggesting that intrahepatic thrombosis is involved in liver fibrosis progression [61]. A recent experimental study provided evidence of the

mechanistic link between CH and liver fibrosis through this mechanism [58]. These findings settle the rational basis for testing anticoagulant drugs in patients with CH, but so far, no clinical trial has addressed this issue. In comparison, research in this area in primary liver cirrhosis is more advanced. Hence, several experimental studies have shown that anticoagulant therapy improves liver fibrosis and reduces portal hypertension [62–73], and a clinical trial demonstrated that anticoagulation led to a reduction in portal thrombosis and other complications of liver disease and to increase in survival [74]. New clinical trials are needed in order to confirm these preliminary results and to establish whether the stage of liver disease may influence its efficacy [75].

It must be highlighted that contrary to primary liver diseases, in CH inflammation seems to play no role in the progression of liver fibrosis. Indeed, several studies of patients with Fontan circulation demonstrated minimal inflammatory changes in liver biopsy specimens, despite accentuated hepatic fibrosis [76–78].

4.3 Clinical presentation and diagnosis

CH may be asymptomatic for a long time, and frequently, its presence is suspected through abnormalities in liver tests [8]. Symptoms attributed to CH may include dull right upper quadrant pain, nausea, vomiting, anorexia, early satiety, malaise, and mild jaundice [3]. The abdominal symptoms respond to the stretching of the liver capsule due to hepatic congestion and may occur in the absence of overt ascites or lower extremity edema. These symptoms, however, are usually masked by those related to right-sided HF [2].

Physical examination may often show hepatomegaly and signs of HF, including hepatojugular reflux and peripheral edema. A pulsatile liver may also be seen, and its loss suggests progression to cardiac cirrhosis [49]. Overt ascites is also a frequent finding, although it is rarely refractory. In a series of 83 patients with CH of whom only one had established cardiac cirrhosis, up to 57% had ascites. Moreover, ascites and edema had no relation to the extent of liver fibrosis, and therefore, they are due to elevated right-sided cardiac pressure hitting the sinusoidal network [50]. The differentiation of cardiac ascites from cirrhotic ascites can be cumbersome. In these conditions, the serum-ascites albumin gradient is ≥1.1 g/dL since they both respond to hepatic sinusoidal hypertension [79]. There are, however, some ascites findings that are useful to make a differential diagnosis. Cardiac ascites has higher protein levels (>2.5 g/dL). This is due to preserved liver synthetic function and absence of capillarization of the liver sinusoidal endothelial cells [3, 8, 80]. The latter refers to the lost of fenestrae and development of a basement membrane by these cells as a consequence of liver fibrosis. In cirrhosis, these features make hepatic sinusoids less leaky and prevent the passage of proteins to the space of Disse and from here to the peritoneal fluid [81]. Other less reliable findings in cardiac ascites are higher LDH levels and higher red blood cell counts due to leaking of red blood cells into the ascites via lymph tissue, with resulting lysis [80]. Despite these differences, a significant number of cases are still misclassified. Measurement of serum B-type natriuretic peptide (BNP) or of its inactive pro-hormone (N-terminal-proBNP) in serum and ascites has been recently suggested as an aid tool in uncertain cases. Thus, Sheer et al. reported that both serum and ascites NT-proBNP levels had high sensitivity and specificity in predicting HF as the cause of ascites [82]. More recently, Farias et al. found serum BNP to be superior to the total ascitic fluid protein concentration with regard to discriminating cardiac ascites from cirrhotic ascites. A serum BNP cutoff of >364 pg/mL had 98% sensitivity, 99% specificity, 99% diagnostic accuracy, and a positive likelihood ratio of 168.1 for the diagnosis of cardiac ascites. Conversely, a serum BNP cutoff of ≤182 pg/mL was excellent for ruling out ascites due to heart failure [79].

The differentiation of cardiac cirrhotic ascites from cardiac ascites without cirrhosis is especially challenging and of great clinical importance. On the one hand, the diagnosis of cardiac cirrhosis warrants further evaluations such as bi-annual surveillance ultrasonography or endoscopic screening for esophageal varices. On the other hand, its presence may preclude a heart transplant or require a combined heart-liver transplant. Apart from some diagnostic tools such as liver biopsy and hepatic venous pressure gradient (HVPG) that will be later discussed, there are some clinical clues that help in the differential diagnosis. In patients with cardiac ascites without cirrhosis, splenomegaly and spider angiomata are absent, and varices are rarely identified on upper endoscopy [3, 49]. This can be explained by the fact that varices represent collateral vessels from the high-pressure portal system to the low-pressure systemic circulation, and in CH without cirrhosis, no pressure gradient exists because pressure remains high along the entire path of venous return to the right atrium [50]. Complications of cirrhosis may occur in the late stages of cardiac cirrhosis. Although in the past the traditional patient with cardiac cirrhosis died from his cardiac disease before progressing to decompensated cirrhosis, advances in medical and surgical treatments are responsible for the increased number of liver complications in this setting [3]. The risk of hepatocarcinoma after the Fontan procedure is probably the best example. The success of this surgery to palliate right-sided congenital heart lesions permits long-term survival in the setting of elevated right-sided heart pressures. Eventually, the liver disease could become as clinically important as the cardiac disease and further complicate its management [51].

Besides the presence of right-sided HF (or other cause of high central pressures) and the aforementioned clinical findings, the diagnosis of CH should be further supported on compatible results of diagnostic tools and exclusion of other possible causes of liver disease [49, 50].

4.3.1 Biochemical profile

Elevation of serum cholestasis markers (alkaline phosphatase, GGT, and bilirubin) is characteristic of CH. Total bilirubin levels rarely exceed 3 mg/dL, and indirect bilirubin usually predominates over direct bilirubin [3]. The degree of cholestasis is related to the severity of both the elevation of right atrial pressure and tricuspid regurgitation [55, 83]. These data suggest that elevated right-sided filling pressures may contribute more to LFT elevation than reduced cardiac output [2]. The mechanism of cholestasis in this setting is thought to be due to the compression of the bile canaliculi and small ductules by centrally congested sinusoids [25]. Other laboratory findings include mild elevations of serum aminotransferases to two to three times the upper limit of normal and mild hypoalbuminemia. The latter may also be secondary to malnutrition or protein-losing enteropathy [8]. As liver disease progresses, liver function tests (i.e., bilirubin, INR, and albumin) may continue to worsen. Importantly, liver enzymes are often normal, and in the presence of other findings suggestive of CH, this diagnosis cannot be ruled out based on these normal values [3]. As already discussed, CH predisposes the liver to ACLI in the face of hemodynamic instability, instigating the aforementioned marked elevation of liver enzymes [8].

4.3.2 Imaging tests

Imaging tests help both to support the diagnosis of CH and to identify complications. Characteristic conventional imaging findings include dilation of inferior vena cava and hepatic veins, loss of normal triphasic hepatic venous wave-form, and abnormal kinetics of intravenous contrast enhancement (e.g., delayed bolus arrival to the liver suggesting slow systemic circulation, diffusion of extracellular

contrast media into the periportal lymphatic space in the delayed phase, retrograde hepatic venous opacification during the early phase of intravenous contrast material injection into the upper extremities, and a predominantly peripheral heterogeneous pattern of hepatic enhancement due to stagnant blood flow) [84] (**Figure 3A**, **B**). Importantly, the appearance of a nodular or heterogeneous liver on standard imaging is not sufficient to diagnosis cirrhosis in CH [51].

CH may lead to the generation of benign regenerative nodules or focal nodular hyperplasia (FNH)-like lesions and hepatocarcinoma. The former is referred to as "FNH-like" despite having characteristic pathological findings of FNH due to the presence of abnormal background liver parenchyma. Although they most commonly demonstrate typical imaging findings (i.e., well-circumscribed, homogeneous nodule with late arterial hyperenhancement that fades to isointensity/isoattenuation on delayed phase imaging), they sometimes have a washout appearance that could be mistaken for hepatocarcinoma due to abnormally increased background parenchymal enhancement in the delayed phase [84] (**Figure 4**). Indeed, distinguishing hepatocarcinoma from these atypical imaging represents an unmet need, and biopsy is frequently required for accurate diagnosis. Radiological findings that support the diagnosis of hepatocarcinoma include the following: significant change in appearance of a nodule, venous invasion, a heterogeneous-appearing mass, and elevated alpha-fetoprotein [51, 84]. There are currently no screening guidelines for hepatocarcinoma in CH. In post-Fontan patients, some experts recommend to begin screening at 15–20 years after the operation [51], while the newly released guidelines from the American Heart Association recommend a much more comprehensive surveillance (**Table 1**) [85]. In patients with CH due to other conditions, it seems reasonable to perform bi-annual screening once cardiac cirrhosis is established.

4.3.3 Histology

The congestive liver explant has been characterized as a "nutmeg liver" due to the presence of dark centrilobular zones that reflect sinusoidal congestion alternating with pale periportal zones with normal or fatty liver tissue [84] (**Figure 5A**). Characteristic histological findings include sinusoidal dilatation and congestion, hepatocyte atrophy most prominent in zone 3, extravasation of red blood cells into the space of Disse, regenerative hyperplasia emerging from periportal regions, and

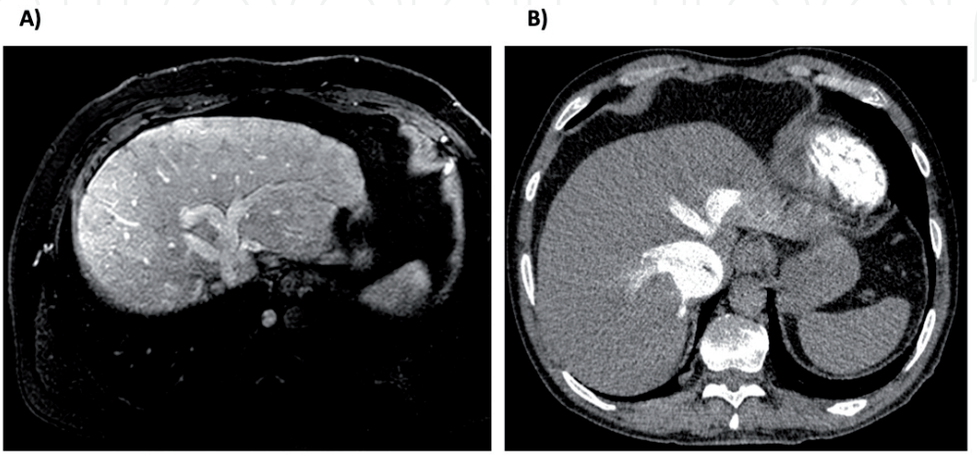


Figure 3.
(A) Idiopathic membranous inferior vena cava obstruction in a 44-year-old man. MRI shows a mildly nodular liver with altered parenchymal perfusion and dilatation of hepatic veins. (B) Severe tricuspid regurgitation in a 49-year-old man. CT scan shows dilatation of hepatic veins and reflux of contrast into the inferior vena cava and hepatic veins.

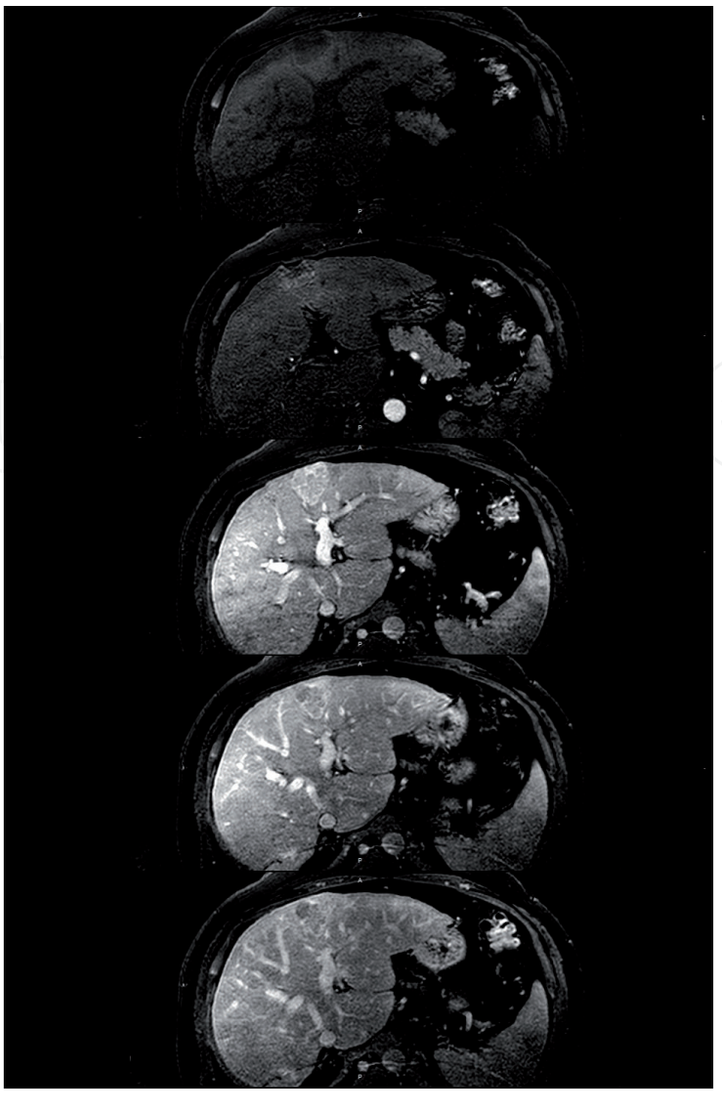


Figure 4.
Idiopathic membranous inferior vena cava obstruction in a 44-year-old man. The image shows the dynamic phase of MRI. Besides the significant hypertrophy of segment I, MRI shows a mass (3.8 cm × 4.2 cm) that after administration of intravenous contrast presents a heterogeneous enhancement in the arterial phase with washout in the portal phase. Liver biopsy showed histological changes compatible with focal nodular hyperplasia.

centrilobular fibrosis (**Figure 5B**, **C**) [25]. The degree of sinusoidal dilatation is positively correlated with the degree of elevation of right atrial pressure. As liver disease progresses, bridging fibrosis typically extends between central veins to produce a pattern that has been name "reversed lobulation" since it contrasts to the typical fibrosis pattern found in most primary liver diseases where bridging fibrosis occurs between portal triads (i.e., zone 1) [3]. As far as the correlation between fibrosis extension and systemic hemodynamic parameters is concerned, there are discordant results with most studies finding no correlation [50, 54, 86–89].

It must be highlighted that the distribution of fibrosis throughout the liver is extremely heterogeneous in patients with CH [86, 90], and it may be explained by the fibrogenic effects of intrahepatic thrombosis caused by static blood flow [61]. This variability raises concern about sampling error and about the role of liver biopsy as the gold standard tool for fibrosis assessment. Moreover, liver biopsies may not predict post-heart transplant outcomes. In a retrospective study, Louie et al. found that the presence of bridging fibrosis was not significantly associated with post-operative survival or post-operative liver failure, based on which they concluded that patients with bridging fibrosis may still be considered viable

	Basic*	In-Depth*	Investigational*
Childhood (every 3–4 years)	• CMP • Platelet count • Serum GGT	• PT/INR • Serum FibroSure biomarkers • Serum α-fetoprotein • Abdominal ultrasound • Total serum cholesterol	• Liver imaging via CT or MRI • Liver elastography (ultrasound or MRI) • Liver biopsy
Adolescence (every 1–3 years)	• CMP • Platelet count • Serum GGT • PT/INR	• Serum FibroSure biomarkers • Serum α-fetoprotein • Abdominal ultrasound • Total serum cholesterol • Liver imaging via CT or MRI • Liver elastography (ultrasound or MRI)	• Liver biopsy
Adulthood (every 1–2 years)	• CMP • Platelet count • Serum GGT • PT/INR • Total serum cholesterol • Abdominal ultrasound	• Serum FibroSure biomarkers • Serum α-fetoprotein • Liver imaging via CT or MRI • Liver elastography (ultrasound or MRI)	• Liver biopsy

**Tests are stratified as basic (fundamental and rudimentary level of assessment), in-depth (more detailed level of characterization), and investigational (possible or likely of value; however, greater experience and study may be necessary before widespread use can be suggested).*
Abbreviations: CMP: comprehensive metabolic panel; CT: computed tomography; GGT: γ-glutamyl transferase; INR: international normalized ratio; MRI: magnetic resonance imaging; PT: prothrombin time.

Table 1.
Tests recommended by the American Heart Association for surveillance of liver disease in post-Fontan patients.

candidates for isolated heart transplantation [90]. Similar results were described by Dhall et al. [86]. Regardless of these limitations, liver biopsy still plays an important role in the assessment of the stage of liver disease, in ruling out hepatocarcinoma and alternative etiologies of liver disease and in determining candidacy for isolated heart transplantation or combined heart-liver transplantation. Its findings, however, should be correlated with the clinical presentation and results of other diagnostic tools [51, 86].

4.3.4 Non-invasive assessment of liver fibrosis

Non-invasive diagnostic tests of liver fibrosis have been extensively studied and have excellent predictive value for advanced fibrosis in patients with viral hepatitis and non-alcoholic fatty liver disease [91]. Nevertheless, the performance of these tests in assessing the severity of fibrosis in CH is poor. A detail description of each of these tests in this setting is beyond the scope of this chapter and can be found elsewhere [51, 92, 93].

Briefly, among serological markers, the Model for End-Stage Liver Disease (MELD)-XI score has been suggested to be potentially useful as some studies have

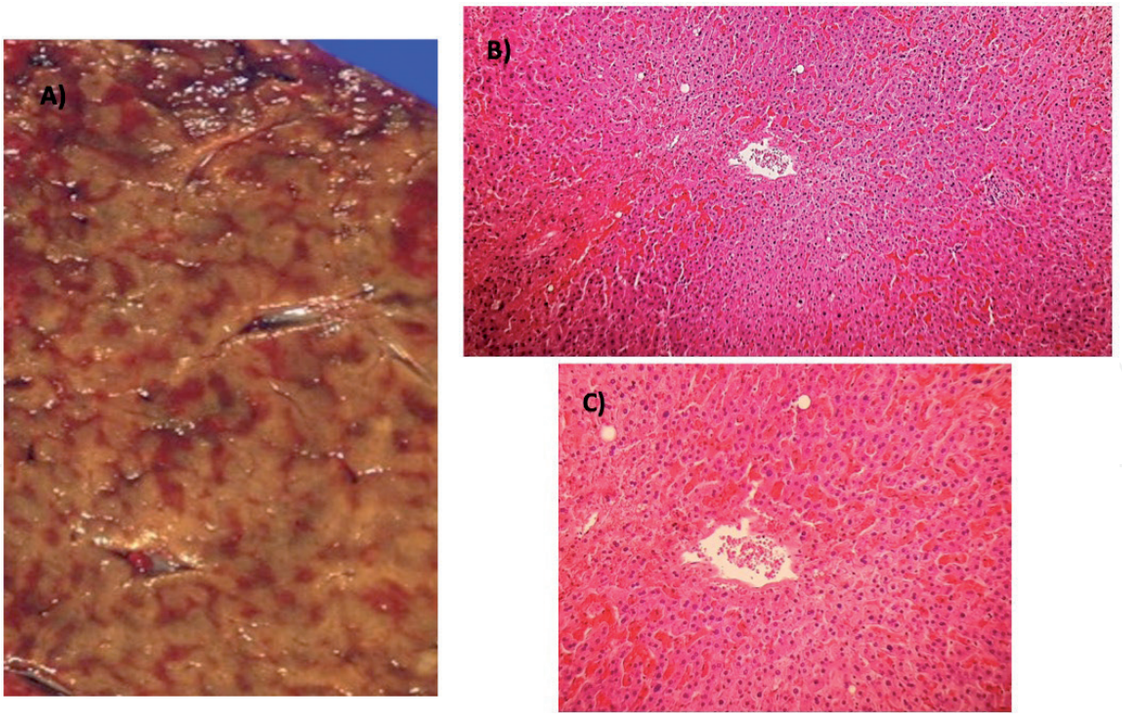


Figure 5.
(A) Postmortem example of the classical "nutmeg" liver with centrilobular congestion in CH. (B) Centrilobular regions show congestion and extravasation of red blood cells. (C) Same findings than 5.B with greater magnification.

shown a moderate correlation with the stage of fibrosis in post-Fontan patients [94, 95]. This score excludes INR given the high prevalence of anticoagulation use in CH. Despite these results, further studies are needed as other studies have described opposite results [78, 90]. The remaining tests (i.e., standard serum markers, FibroSure testing, hyaluronic acid levels, and most clinical risk calculators) are inaccurate at staging liver fibrosis [51]. The use of liver stiffness tools is hampered by the fact that congestion increases liver stiffness values [91]. Hence, in CH, it provides unreliable information regarding the grade of fibrosis, although some evidence suggests that liver and spleen stiffness calculated by magnetic resonance elastography may be more accurate. Finally, new advances in imaging techniques, such as magnetic resonance imaging with diffusion-weighted imaging, may potentially differentiate fibrosis from congestion but require validation [51].

4.3.5 Hepatic hemodynamic study

Hepatic vein catheterization with measurement of the HVPG is currently the gold standard technique for determining portal pressure. It represents the difference between the wedged hepatic venous pressure (WHVP) and the free hepatic venous pressure (FHVP). The WHVP is usually measured by occluding the right hepatic vein through the inflation of a balloon, whereas the FHVP is measured without occluding it. The occlusion of the vein forms a continuous static column of blood between the catheter and the hepatic sinusoids. Thus, WHVP measures sinusoidal pressure. Due to the scarce connections between sinusoids existing in cirrhosis, pressure cannot be decompressed through the sinusoidal network, and therefore, WHVP reflects portal pressure in this setting. FHVP, on the other hand, is a surrogate for inferior vena cava pressure. Normal values of HVPG are <5 mmHg. The HVPG is a strong and independent predictor of outcomes in compensated and decompensated cirrhosis due to primary liver diseases [96–98].

The diagnostic and prognostic value of HVPG measurement in CH has not been adequately assessed. In this context, both FHVP and WHPV are elevated, and the HVPG is within the normal range (**Figure 6**). Once cardiac cirrhosis is established, the HVPG is expected to increase beyond 6 mmHg (**Figure 7**) [51]. Hence, HVPG could theoretically provide relevant information about the stage of CH. The few clinical studies that have provided hemodynamic data in this regard have described inconsistent results. For instance, in the study of Myers et al., esophageal varices were seen in some patients despite having a HVPG below 6 mmHg. As previously explained, the high pressures along the entire path of venous return to the right atrium prevent the formation of varices unless the establishment of cirrhosis creates a pressure gradient between the portal and systemic circulation. In order to explain these discordant results, the same authors argued that it was possible that the varices observed in a few patients represented either false-positive endoscopies or undetected concomitant disease such as portal vein thrombosis [50]. Moreover, it has not yet been demonstrated that the HVPG correlates with the stage of fibrosis in CH [50, 86]. These findings probably respond to several confounders: the inclusion of few patients with advanced fibrosis, the variable distribution of fibrosis throughout the liver, and the absence of a full and reliable characterization of the liver disease. As far as its prognostic utility is concerned, no study has evaluated the HVPG for predicting hepatic decompensation events and survival after isolated heart transplantation [51]. Despite this, many academic centers, including our own, measure the HVPG to assist in the transplant decision-making process. Finally, it must be reminded that the hepatic vein catheterization also allows performing a transjugular liver biopsy. This technique is safer than the percutaneous biopsy and can be performed even under anticoagulation or ascites [99].

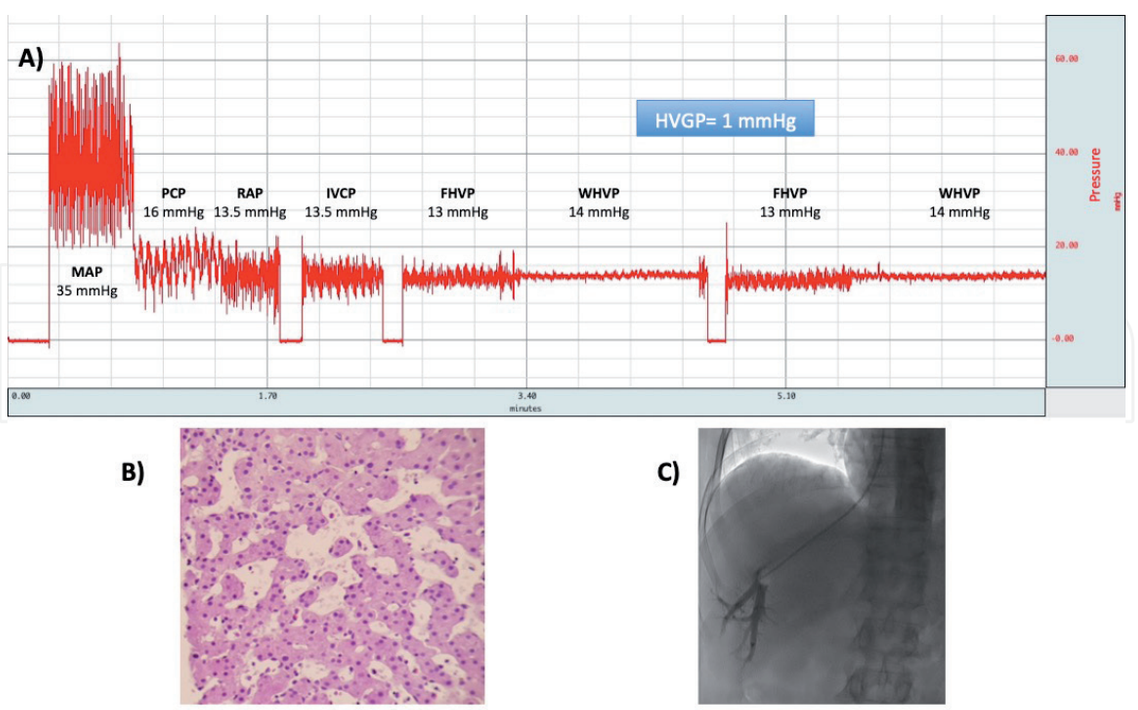


Figure 6.
(A) A typical hemodynamic tracing of a patient with congestive hepatopathy due to cor pulmonale. The HVPG is calculated as the difference between WHVP and FHVP. Both of them are elevated, but the HVPG is within the normal range. (B) Transjugular liver biopsy was performed and showed sinusoidal dilatation without significant fibrosis (hematoxylin-eosin stain; the image of Masson stain is not shown). (C) Occlusion of the hepatic vein with the balloon catheter. Abbreviations: MAP: Mean pulmonary arterial pressure; PCP: Pulmonary capillary pressure; RAP: Right atrial pressure; IVCP: Inferior vena cava pressure; FHVP: Free hepatic venous pressure; WHVP: Wedged hepatic venous pressure; HVPG: Hepatic venous pressure gradient.

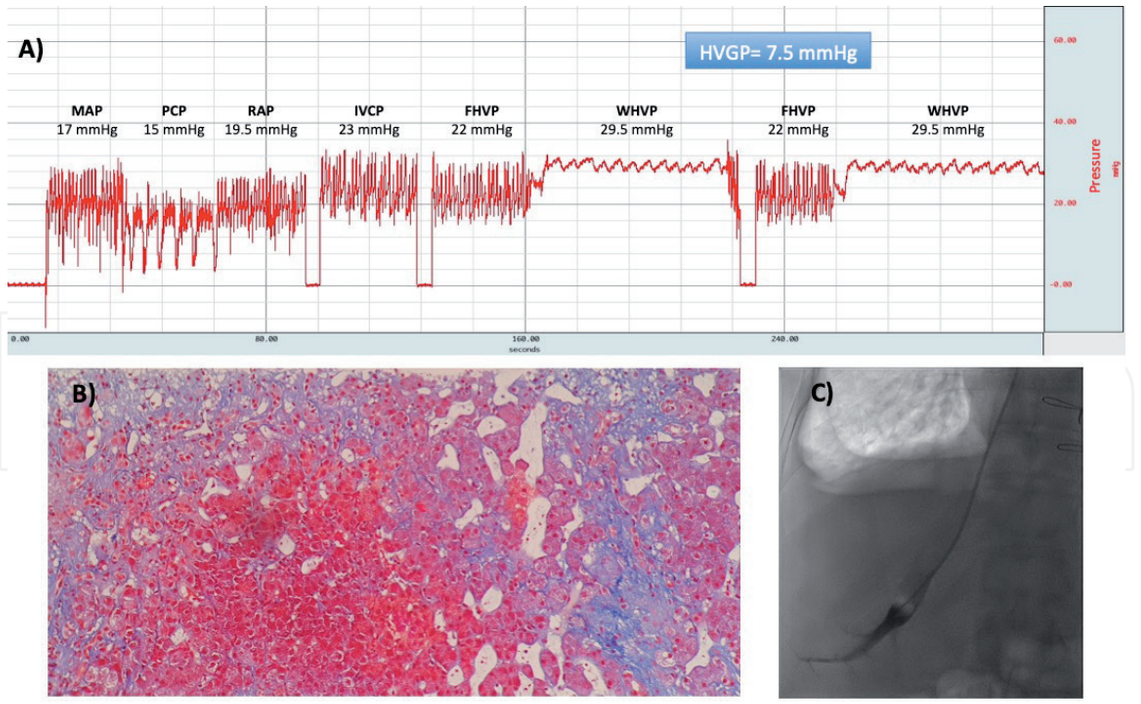


Figure 7.
(A) A typical hemodynamic tracing of a patient with severe tricuspid regurgitation and concomitant hepatitis C. The HVPG is calculated as the difference between WHVP and FHVP. Both of them are elevated, and the HVPG is slightly elevated. (B) Transjugular liver biopsy was performed and showed significant fibrosis forming nodules (Masson stain). (C) Occlusion of the hepatic vein with the balloon catheter. Abbreviations: MAP: Mean pulmonary arterial pressure; PCP: Pulmonary capillary pressure; RAP: Right atrial pressure; IVCP: Inferior vena cava pressure; FHVP: Free hepatic venous pressure; WHVP: Wedged hepatic venous pressure; HVPG: Hepatic venous pressure gradient.

4.4 Prognosis and treatment

The underlying cardiac disease generally determines prognosis in CH. Liver enzymes (i.e., bilirubin, alkaline phosphatase, GGT, and albumin) and scores such as the MELD and MELD-XI have been associated with prognosis in HF patients [53, 56, 100–103]. Based on these findings, both the American College of Cardiology and the European Society of Cardiology Heart Failure Guidelines recommend the inclusion of liver function tests in the diagnostic workup of all patients presenting with HF [1, 104]. However, it must be pointed out that they predict cardiac or overall mortality, not liver-related mortality. Therefore, they seem to act as indirect markers of the severity of cardiac disease rather than reflecting the effect of liver disease on outcomes. Indeed, the effect of cardiac cirrhosis on overall prognosis has not been clearly established [6].

Management of the underlying cardiac disease is the mainstay of treatment. There is no specific therapy of CH [8]. Concerns about modification of drug dosage have been raised, although there are no solid rules in this regard. This is partially explained by the lack of correlation of available diagnostic tools with the hepatic function [5]. Theoretically more relevant are the detrimental effects that some of the medical therapies used to treat HF may have on the physiopathology of cirrhosis. For instance, vasodilators such as angiotensin-converting-enzyme inhibitors are contraindicated in decompensated cirrhosis, and doses of diuretics in HF are often higher than in cirrhosis and may precipitate hepatorenal syndrome [3]. Again, no solid recommendations are available, and treatment modifications should be patient-specific. Eventually, some patients will require a heart transplant, and this poses the question of whether the liver is "in shape" to tolerate a heart transplant.

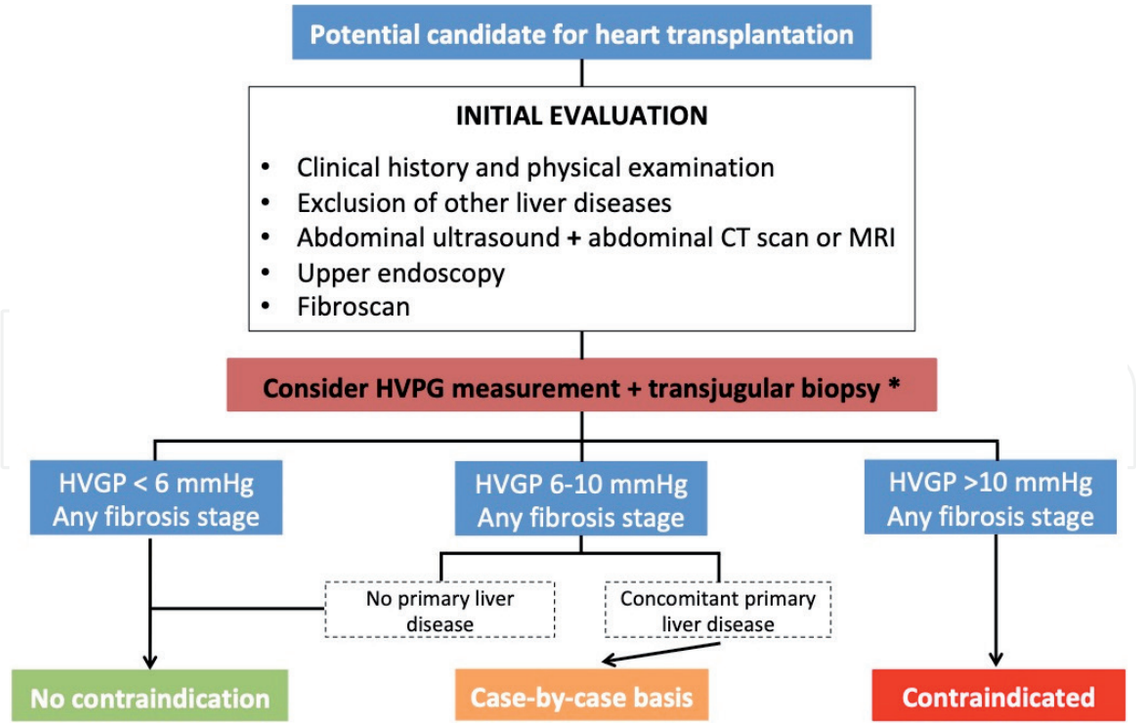


Figure 8.
Protocol to determine the recommendation regarding liver disease in a potential candidate for a heart transplant when CH is suspected. We proceed to HVPG measurement and transjugular biopsy in those patients in whom advanced liver disease cannot be ruled out after the initial evaluation (e.g., nodular appearance of the liver). Our recommendation is hemodynamic-dependent, regardless of the fibrosis stage. In cases with a HVPG below 5 mmHg, there is no contraindication to perform an isolated heart transplant, whereas a HVPG >10 mmHg discards it (no combined heart-liver transplantation has been performed so far in our hospital). In patients with a concomitant primary liver disease and a HVPG between 6 and 10 mmHg, the decision is patient-specific and relies mainly on the type of disease. If it is treatable (e.g., hepatitis C or B), we recommend proceeding with the heart transplant. Same recommendation is given in the absence of a primary liver disease and a HVPG between 6 and 10 mmHg. Abbreviations: CT: Computed tomography; MRI: Magnetic resonance imaging; HVPG: Hepatic venous pressure gradient.

4.5 Determining candidacy for heart transplantation

Given the aforementioned limitations of available invasive and non-invasive tests to assess hepatic fibrosis and function, determining whether a patient with CH is a candidate for isolated heart transplantation or may require a combined heart-liver transplantation is especially challenging. Not surprisingly, there are no official guidelines, evaluation is institution dependent, and the decision is often taken on a case-by-case basis. It must be highlighted that cardiac cirrhosis may be reversed after heart transplantation. Based on this premise, some centers use an HVPG value of <12 mmHg as a cutoff for offering isolated heart transplantation instead of combined heart-liver transplantation. Nevertheless, this protocol requires validation before its widespread use in clinical practice. **Figure 8** shows our protocol for determining our recommendation regarding liver disease in a potential candidate for a heart transplant when CH is suspected.

5. Take-home messages and pitfalls facing management

- The diagnosis of ACLI cannot be rejected because of the absence of shock and of signs of HF, and in case of uncertainty, a cardiac evaluation is warranted.

- CH is frequently observed in patients suffering ACLI since it predisposes the liver to hypoxic damage.

- Diagnosis of ACLI can be suspected based on the following analytical alterations: ALT-to-LDH ratio <1.5, AST higher than ALT at initial phase, and an early and sharp deterioration in prothrombin activity and renal function.

- The current spectrum of CH differs from earlier reports with HF due to ischemic cardiomyopathy and congenital heart disease having surpassed rheumatic valvular disease.

- Contrary to primary liver diseases, inflammation seems to play no role in the progression of liver fibrosis in CH.

- The clinical picture of CH is usually masked by symptoms and signs related to right-sided HF.

- There are some ascites findings that help differentiate cardiac ascites from cirrhotic ascites: higher protein (>2.5 g/dL) and LDH levels, and higher red blood cell counts. Serum BNP also seems to be a useful tool in this regard.

- The diagnosis of cardiac cirrhosis warrants further evaluations such as bi-annual surveillance ultrasonography or endoscopic screening for esophageal varices.

- CH may lead to the generation of benign regenerative nodules and hepatocarcinoma. Distinguishing one from the other frequently requires a liver biopsy due to the abnormal background liver parenchyma.

- In contrast to most primary liver diseases where bridging fibrosis occurs between portal triads, in CH it typically extends between central veins to produce a "reversed lobulation" pattern.

- The distribution of fibrosis throughout the liver is extremely heterogeneous in CH leading to sampling error. Moreover, fibrosis stage determined by liver biopsies does not seem to predict post-heart transplant outcomes.

- The performance of non-invasive diagnostic tests of liver fibrosis in CH is poor.

- HVPG measurement might be a useful tool for assessing the stage of CH and helps in the decision-making process of transplant candidacy. However, no evidence in this regard has been published so far.

- In both ACLI and CH, the prognosis is dependent on the underlying condition, and treatment is focused on the latter.

Conflict of interest

The authors declare no conflict of interest.

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