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Review

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From congestive hepatopathy to hepatocellular carcinoma, how can we improve patient management?

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Summary

Heart failure and liver disease often coexist because of systemic disorders and diseases that affect both organs as well as complex cardio-hepatic interactions. Heart failure can cause acute or chronic liver injury due to ischaemia and passive venous congestion, respectively. Congestive hepatopathy is frequently observed in patients with congenital heart disease and after the Fontan procedure, but also in older patients with chronic heart failure. As congestive hepatopathy can evolve into cirrhosis and hepatocellular carcinoma, screening for liver injury should be performed in patients with chronic cardiac diseases and after Fontan surgery. Fibrosis starts in the centro-lobular zone and will extend progressively to the portal area. Chronic liver injury can be reversible if heart function improves. However, in the case of terminal heart failure, uncontrolled by medical resources or by assistive device support, the combination of heart and liver transplants must be discussed in patients with chronic advanced liver fibrosis. In this review of the literature, we will focus on congestive hepatopathy and its complications, such as liver fibrosis and hepatocellular carcinoma, with the aim of improving the management and surveillance of patients experiencing these complications.

Keywords: Congestive hepatopathy; Fontan-associated liver disease; Combined heart and liver transplant

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Introduction

A close association between the liver and heart has been known for many years. As it receives up to 25% of total cardiac output, the liver is very sensitive to haemodynamic modulation and heart dysfunction. Moreover, heart failure and liver disease often coexist because of systemic disorders that affect both organs (metabolic syndrome, alcohol abuse, drugs, inflammation, autoimmunity, infections) and complex cardio-hepatic interactions.[1] For instance, cirrhosis alters the haemodynamic system and leads to cardiac dysfunction independently of the cause of the underlying liver disease, so called cirrhotic cardiomyopathy. In such cases, the arterial vasodilatation related to portal hypertension may evolve into hyperdynamic circulation characterised by increased cardiac output associated with reduced cardiac contractility, low arterial blood pressure and decreased systemic vascular resistance, resulting in central hypovolemia. Cirrhotic cardiomyopathy occurs in about 50% of patients with cirrhosis and significantly contributes to morbi-mortality.[2,3]

Conversely, heart failure can cause acute or chronic liver injuries due to ischaemia and passive venous congestion, respectively.[4] Passive venous congestion can evolve into congestive hepatopathy, which encompasses the spectrum from fibrosis to cardiac cirrhosis. Such liver damage was initially described by Dame Sheila Sherlock in 1951 in liver necropsy specimens and is frequently observed after congenital heart diseases and a Fontan procedure but also in older patients with chronic heart failure.[5] The risk factors of liver diseases such as viral hepatitis, alcohol-related liver disease and non-alcoholic fatty liver disease (NAFLD) potentiate the liver injury induced by congestive hepatopathy and its progression toward cirrhosis and its complications, such as hepatocellular carcinoma (HCC). The occurrence of HCC in such a population of patients clearly affects outcomes, as the diagnosis is made at advanced stages. Interestingly, chronic liver injury can be reversible after an improvement in heart function. However, in cases of terminal heart failure, uncontrolled by medical resources or by assistive device support, the combination of heart and liver transplants must be discussed in patients with chronic advanced liver fibrosis.

In this review of the literature, we will focus on congestive hepatopathy and its complications, such as HCC, in order to improve the management and surveillance of patients experiencing these complications.

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Definition of congestive hepatopathy

The starting point of congestive hepatopathy is an increase in the central venous pressure secondary to right heart failure with a high level of filling pressure. This high pressure is transmitted to the central veins of the liver, resulting in sinusoidal dilatation and decreased hepatic blood flow with a decreased arterial oxygen saturation leading to progressive bridging fibrosis, cirrhosis then HCC. The congestive hepatopathy is related to a chronic cardiopathy in about 90% of cases.[6–8] The spectrum of cardiac diseases which can lead to such liver injury is large and summarised in Table 1. The Fontan operation performed for congenital heart diseases has also been known to cause congestive hepatopathy due to chronic liver congestion and suboptimal liver oxygenation. During the last decades, the incidence of congestive hepatopathy has decreased owing to a reduced frequency of rheumatic heart diseases or constrictive pericarditis. This decrease was also associated with a change in the most common cause of congestive hepatopathy. For instance, in a series from 1961, 34.8% of congestive hepatopathies were related to ischaemic cardiomyopathies, 33.3% to rheumatic heart diseases, 13% to hypertensive cardiomyopathies, 8.7% to constrictive pericarditis, 7.2% to cor pulmonale and 2.9% to congenital diseases.[9] In a recent series, valvular cardiomyopathy only accounted for 18% of cases, and ischaemic cardiomyopathies were the cause of congestive hepatopathy in 50 to 72% of cases.[6,7,10] The incidence of congestive hepatopathy is estimated to be between 15% to 65% according to the series and is probably higher with candidates for left ventricular assistance device implantation.[6–8,10,11] However, such epidemiological data must be analysed cautiously because of the heterogeneous causes and symptoms of chronic heart failure as well as the limited validated techniques available to diagnose congestive hepatopathies. For instance, biopsies are not performed in all studies, and the diagnosis of congestive hepatopathy is made on non-invasive tests for some of them. Nowadays, we must also consider that patients with ischaemic and hypertensive cardiomyopathies may show associated risk factors for liver diseases, such as metabolic syndromes and chronic alcohol intake, and these risk factors may have an impact on the epidemiological data.

Table.1. Causes of congestive hepatopathy.

Constrictive pericarditis	Idiopathic Infectious Neoplastic Post-trauma Connective tissue disease Radiotherapy Chronic kidney failure
Tricuspid regurgitation	Severe pulmonary arterial hypertension Hepatic metastasis of carcinoid tumour
Right ventricular failure	Decompensated cor pulmonale Mitral stenosis Ischemic cardiomyopathy
Left heart failure	Ischemic cardiomyopathy Hypertensive cardiomyopathy Valvular cardiomyopathy
Cardiac tumour	Myxoma Atrial right metastasis
Congenital heart disease	Postoperative consequences of surgical repair in congenital heart disease including the Fontan procedure*

* Fontan procedure is performed for pulmonary atresia and hypoplastic left heart syndrome.

Key points

- A congestive hepatopathy is frequently observed after a congenital heart disease and a Fontan procedure but also in older patients with chronic heart failure.
- The evaluation of fibrosis remains difficult in cases of congestive hepatopathy.
- Hepatocellular carcinoma has an impact on the outcome of patients with congestive hepatopathy and HCC surveillance must be performed in case of proven cirrhosis and after Fontan surgery.
- Chronic liver injury can be reversible after an improvement in heart function.
- A combination of heart and liver transplants must be discussed in patients with chronic advanced liver fibrosis and terminal heart failure.

Pathophysiology and consequences

The passive congestion of the liver is directly linked to increased central venous pressure secondary to right heart failure, with a high level of filling pressure transmitted by the hepatic vein to the sinusoids. Increased sinusoidal pressure leads to sinusoidal distension and increased sinusoidal filtration. Sinusoidal distension is positively correlated with the degree of elevation of right atrial pressure and explains the hepatomegaly frequently observed in patients with congestive hepatopathies. Due to the Glisson capsule, the increase in liver volume is limited and the resulting tension can lead to liver pain. In cases of chronic heart failure, increased central venous pressure can be associated with reduced cardiac output and a proportional reduction in hepatic blood flow. In these cases, the diffusion of oxygen and nutrients will be redistributed to the periportal hepatocytes rather than to those located near the central lobular vein, explaining centrolobular hepatocyte death and atrophy with respect to the periportal region.[5,12] Congestive hepatopathy is associated with minimal inflammation as hepatocyte death seems to occur through atrophy and apoptosis.[13] In addition, increased pressure within the hepatic sinusoid leads to bile duct damage by disrupting endothelial cells and the inter-hepatocytic tight junctions that separate the extravascular space from the bile canaliculus. Finally, a stagnant flow favours thromboses within sinusoids, hepatic venules, and portal tracts. Microthromboses and hypoxia mainly contribute to the occurrence of liver fibrosis which will start from the centro-lobular zone and will extend progressively to the portal area. The degree of fibrosis differs from one region of the liver to another. This variability may be explained by the fibrogenic effects of the focal thrombi within the sinusoids, hepatic venules and portal veins as a result of chronic vascular stasis; these elements make the evaluation of fibrosis difficult[5] (Fig. 1). Partial inferior vena cava ligation in mice models has improved our pathophysiological understanding. Interestingly, the disruption of the coagulation cascade, through pharmacological and molecular approaches, reduced congestion-related fibrosis within mice models following partial inferior vena cava ligation.[14] The enlargement of the sinusoidal fenestrae also results in the exudation of a protein rich fluid that is drained through the lymphatic system. When fluid production exceeds the elimination rate corresponding to the lymphatic draining capacity, exudative ascites can occur. The extravasation of red blood cells from the centrilobular sinusoids also lead to reddened areas within the hepatic parenchyma. It is frequent to observe some diffuse regenerative nodules and a nodular contour of the liver in congestive hepatopathies which may mimic end-stage fibrosis. Untreated and longstanding congestion can

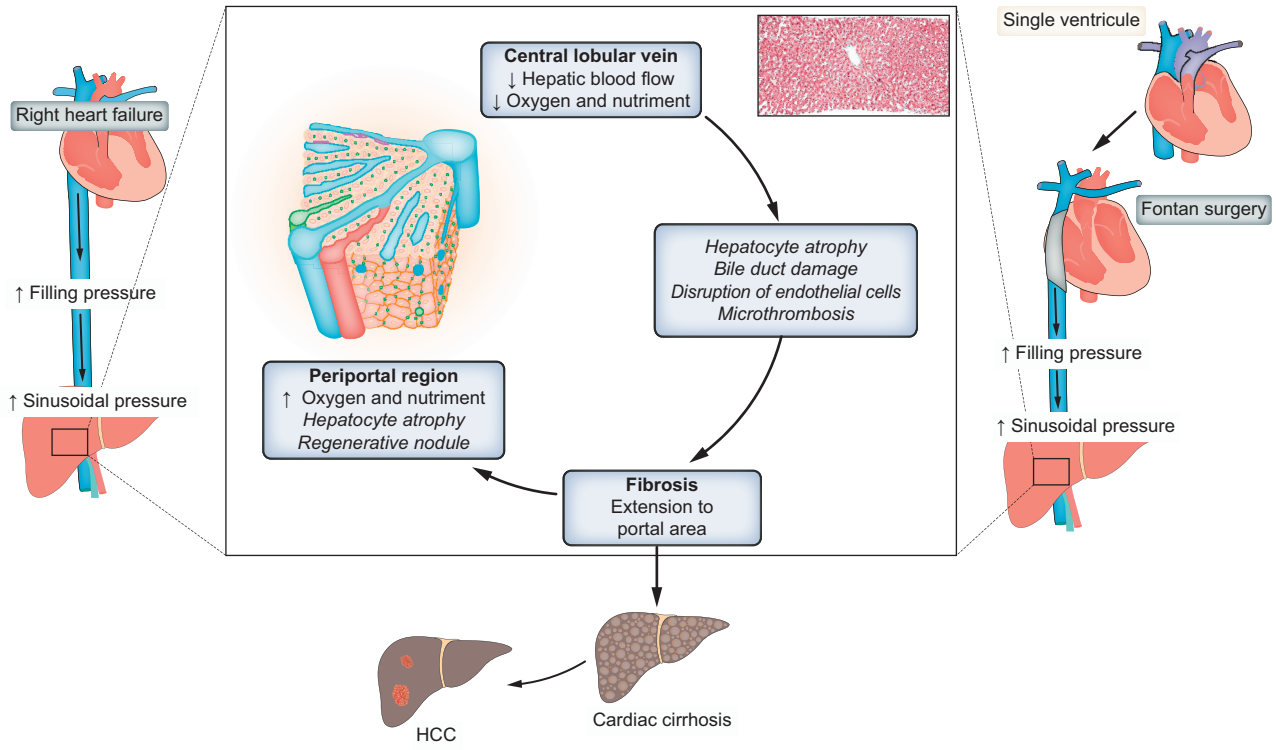

Fig. 1. Pathophysiology of congestive hepatopathies in case of chronic right heart failure and after a Fontan surgery.

lead to fibrosis and, ultimately, to cardiac cirrhosis after years of evolution. However, the term cardiac cirrhosis is frequently used improperly as the degree of fibrosis differs according to region of the liver, which prevents a clear classification of fibrosis stage. Nevertheless, cardiac cirrhosis continues to be a rare condition and patients tend to die of their cardiac conditions before the evolution of cirrhosis.[15]

Specificity of the Fontan-associated liver disease

The Fontan procedure, first described in 1971, refers to any operation that results in diverting the venous blood flow from the right atrium to the pulmonary arteries, which leads to central venous hypertension and a decrease in cardiac output, followed by late ventricular dysfunction.[16] The Fontan procedure is the final step in the surgical palliation of congenital cardiac patients with a single functional ventricle.[17] An estimated 70,000 patients had Fontan circulation in 2018, with 40% of patients older than 18 years old.[18] The current estimation of 30-year survival after surgery reaches 85%[19,20] and some variations can be observed due to physiological features in different forms of a single ventricle and surgical techniques.[21] This surgery improves oxygen saturation but it is associated with long-term complications

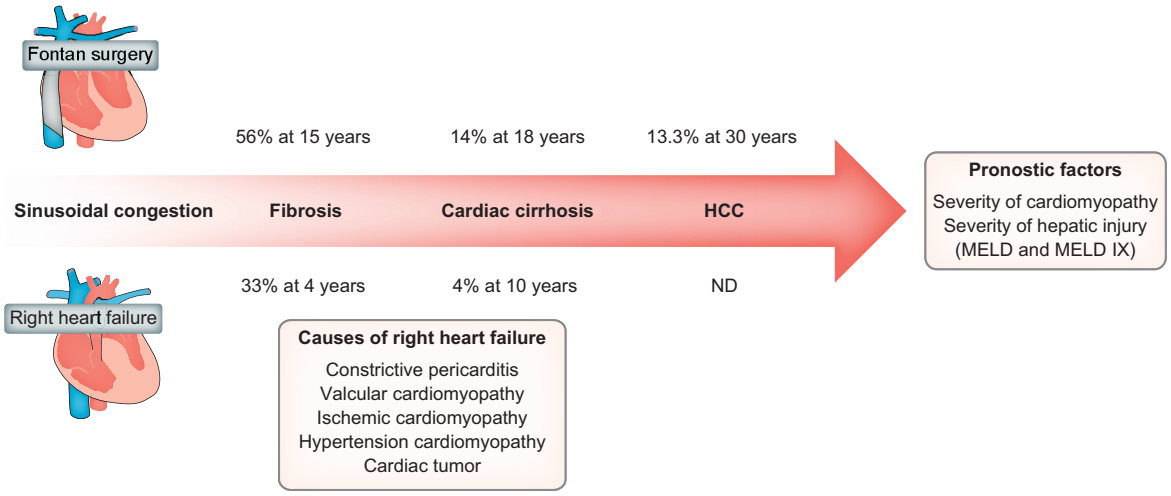

Fig. 2. Natural history of congestive hepatopathies related to chronic right heart failure and to Fontan surgery.

such as heart failure, pleural effusion, hypercoagulability and atrial fibrillation, as well as with congestive hepatopathy, known as Fontan-associated liver disease (FALD).[21–23] Although the survival rate of this population has improved, up to 50% of the patients will present major adverse events before reaching adulthood.[24] Liver dysfunction among Fontan patients is frequent and may be a significant cause of late morbidity and mortality in adults with congenital heart diseases.[25–28] Fibrogenesis in FALD is a multifactorial process that is related to both chronic congestive venous overflow and systemic hypoxia secondary to left ventricular dysfunction and diffuse pulmonary veno-venous shunts.[29] In the largest series to date, cirrhosis is estimated to occur in 14% of patients 18 years following the Fontan procedure (Fig. 2). Cirrhosis is undoubtedly more frequent in patients following the Fontan procedure than in patients who develop chronic heart failure at an older age who have a shorter duration of chronic liver congestion.[30] In addition, features of portal hypertension (varices, ascites, splenomegaly or thrombocytopenia) are associated with major adverse events in Fontan patients (deaths, need for transplant, or HCC).[31]

New concepts

Recently, a link between the heart failure and the microbiome has been suggested. Heart failure induces intestinal ischaemia, leading to disruption of the mucosal epithelial barrier and leakage of gut-derived toxic metabolites into the systemic circulation, exposing the liver to these toxic substances.[32] As the intestinal microbiota and bacterial products contribute to the development of liver diseases,[33] bacterial translocation induced by chronic heart failure may promote the occurrence of chronic liver diseases.

Some epigenetic-sensitive modifications such as DNA methylation, histone modifications, and noncoding RNAs, which are already known to play a role in heart failure and liver disease pathophysiology separately, could also appear as an interesting area of research to better understand the cardio hepatic interactions and to identify patients who may develop liver damage.[34]

Features of congestive hepatopathy

The presence of congestive hepatopathy should be discussed in cases of:

1. Structural heart diseases impairing right heart function;
2. Signs and symptoms of right heart failure (jugular venous distensions, hepatomegaly, hepatojugular refluxes, pitting oedema, ascites);
3. An elevation of the serum cholestasis markers (alkaline phosphatase [ALP], total and direct bilirubin, gamma-glutamyltransferase [GGT]);
4. The exclusion of other possible causes of liver damage.[8]

Clinical point of view

Congestive hepatopathy may be asymptomatic for a long time and patients are frequently diagnosed at a histologically advanced stage because of the absence of specific clinical or laboratory signs. In fact, in a cohort of terminal cardiac failures awaiting heart transplantation (n = 392), ascites was reported in just 16% of patients, while cardiac cirrhosis was reported in only 1 patient.[35] The diagnosis of congestive hepatopathy is not easy because symptoms are not specific and are frequently associated with concomitant right heart failures. A number of published series have studied the clinical signs of congestive hepatopathies, revealing that the most frequent clinical signs are discomfort, a mild right upper quadrant pain (caused by the tension of the Glisson capsule), an early feeling of satiety or anorexia, hepatomegaly and peripheral oedema. A presystolic pulsation of the liver, attributable to an enlarged right atrial, can occur in tricuspid stenoses, constrictive pericarditis, restrictive cardiomyopathy involving the right ventricle, and pulmonary hypertension.[36] Ascites is present in up to 25% of these patients and splenomegaly is usually absent except in the cases of an association with end-stage fibroses. Ascites is characterised by an increased serum ascites-albumin gradient (>1.1 g/dl) and a high protein concentration (>2.5 g/dl).[7,37] This high protein content is an indication of the preserved synthetic function of the liver and may be attributed to the sinusoidal hypertension that leads to the disruption of fenestrae and the exudation of a protein rich fluid.[37,38] In fact, it must be noted that the ascites is a result of a high level of pressure in the centrolobular area resulting from right heart failure with no evident liver dysfunction, as is the case in other causes of cirrhosis. Higher lactate dehydrogenase and red cell counts in ascites have also been noticed in cases of congestive hepatopathies.[37,39] Recently, the measurement of serum B-type natriuretic peptide (BNP) and its inactive prohormone (N-terminal-pro BNP) in serum and ascites has been suggested as an aid in uncertain cases.[40] A serum BNP cut-off of >364 pg/ml has 98% sensitivity and 99% specificity for the diagnosis of cardiac ascites. Conversely, a serum BNP cut-off inferior or equal to 182 pg/ml was excellent for ruling out ascites due to heart failure.[41]

Oesophageal and gastric varices, as well as splenomegaly and collateral vessels resulting from the shunting of blood from the high-pressure portal system to the low-pressure systemic circulation, are rarely identified because of the lack of portals to the systemic venous pressure gradient.[7] Finally, some pruritus, probably connected to cholestasis, is present in terminal heart failure and appears as an infrequent sign of congestive hepatopathy (personal data, unpublished).

Liver function tests

Moderate elevations in serum cholestasis markers (GGT and ALP) are the most common abnormalities observed in congestive hepatopathies. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations of more than 2–3 times the upper normal reference level have also been observed, with AST elevations observed in two thirds of cases. Hyperbilirubinemia, which is rarely greater than 3 mg/dl but is associated with an increase in both direct and indirect bilirubin, is also common (55–70% of patients).[9,42] Hyperbilirubinemia is multifactorial and results from a combination of hepatocellular dysfunction, with an obstruction following a passive congestion and less frequently a biliary stricture due to past severe ischaemic insults, concomitant inflammatory or infectious diseases, haemolysis, and medications. Despite the hyperbilirubinemia, the presence of clinical jaundice is not common.[5] Interestingly, the levels of liver function abnormalities increase with a decreasing cardiac index (particularly AST, ALT, bilirubin) and increasing central venous pressure (particularly ALP, GGT). The elevation of ALP, GGT, ALT, AST and bilirubin is associated with all-cause mortality in patients with heart failure.[8] In patients with long-standing heart failure, albumin synthesis is also impaired in 30–50% of cases,

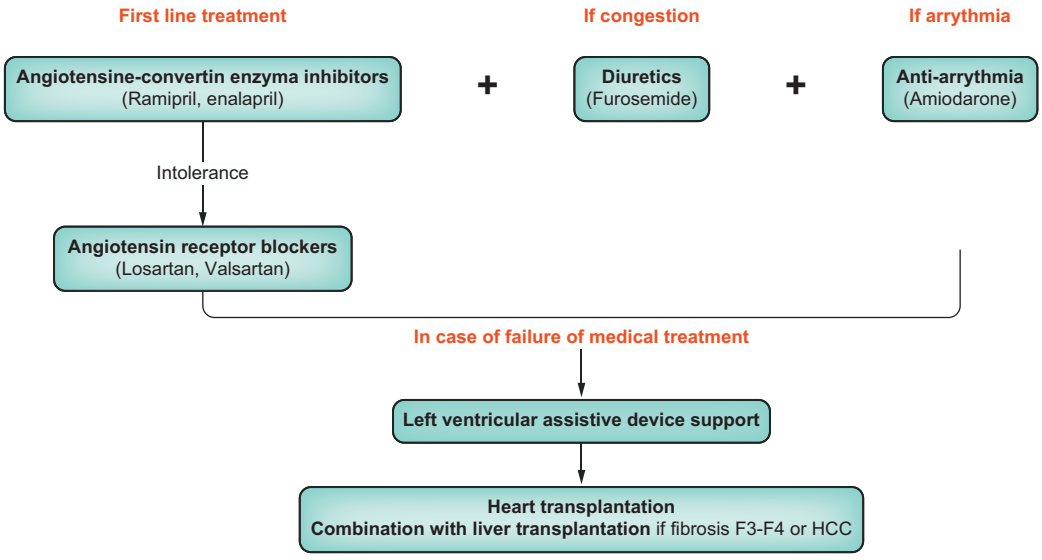

Fig. 3. Algorithm for the management of congestive hepatopathies.

leading to hypoalbuminemia and contributing to the presence of ascites.[43] It is frequently not possible to evaluate liver function using the international normalised ratio (INR) as a large cohort of patients receive long-term anticoagulative treatment.[13] That is why the MELD-XI (MELD without INR), a composite score derived from the prognostic MELD score, has been developed. It eliminates the anticoagulation variable in patients with combined cardiac and hepatic dysfunction and can predict short-term mortality in patients with heart failure and after cardiac interventions.[44–49]

Evaluation of fibrosis

One of the major concerns in cases of congestive hepatopathy is the evaluation of fibrosis stage. Non-invasive diagnostic tests of liver fibrosis have an excellent predictive value for advanced fibrosis in patients with other hepatic aetiologies. Nevertheless, their performance in assessing the severity of the fibrosis in cases of congestive hepatopathy is poor.

Data regarding non-invasive tests are limited. The FibroTest® score is a non-contributory test in about 50% of cases because of the frequent increase of GGT and bilirubin and the reduction of apolipoprotein A1 in chronic cardiac failures without any relation to liver fibrosis. The Fibrometre® score has not been studied yet. Interesting results were observed with the Fibrosis-4 index (FIB-4) and non-alcoholic fatty liver disease fibrosis score (NFS), but further studies are needed to confirm these results. The FIB-4 test (age (years) × AST (IU/L)/platelet count (109/L) × square root of ALT (IU/L)) is connected with markers of liver fibrosis, a larger right and left heart volume overload and was associated with higher all-cause mortality rates in patients with heart failure in a cohort of 1,058 patients.[50] Another biological test to assess fibrosis in NAFLD, which is called the NFS is based on the AST to ALT ratio, platelet count, and albumin. The NFS is also correlated with a central venous pressure (right atrial pressure, inferior vena cava diameter, right atrial area, left atrial volume, and BNP) and some circulating markers of systemic fibrosis (collagen peptide and hyaluronic acid) and is associated with a higher mortality rate in cases of heart failure with preserved ejection fraction.[51]

Elastography enables the non-invasive measurement of tissue mechanical properties through the observation of shear-wave propagation in the liver. Quantitative ultrasonography elastography methods include transient elastography and acoustic radiation force impulse techniques. Magnetic resonance elastography provides a stiffness measurement over a large area of the liver and may be associated with a better diagnostic accuracy, but it requires wider validation. Moreover, the higher cost of this technique and its limited availability may limit its worldwide implementation.[52] Data on elastography in congestive hepatopathy are sparse and its performance is limited by the presence of ascites. Liver stiffness was correlated with the grade of fibrosis but it also reflected increased central venous pressure in 42 patients with congestive liver diseases. A liver stiffness measurement superior to 8.8 kPa seems to be an optimal cut-off value for the detection of central venous pressure superior to 10 mmHg (sensitivity = 91.67%, specificity = 96.25%).[53] However, the use of the liver stiffness tool may be hampered by the fact that liver congestion increases liver stiffness values, which can be reversible upon correction of cardiovascular dysfunction.[54–56] The development of magnetic resonance elastography or diffusion-weighted magnetic resonance imaging may potentially differentiate fibrosis from congestion but this requires validation.[57]

In abdominal imaging, dilation of the inferior vena cava and hepatic veins associated with hepatomegaly is typical of congestive hepatopathy. During a contrast material-bolus injection, a congested hepatic parenchyma results in patchy irregular regions of poor enhancement typically located in the periphery due to a slow enhancement near the hepatic veins. The evaluation of extrahepatic structures also provides information for the diagnosis of a congestive hepatopathy and this information corresponds to right atrial and/or right ventricular enlargement, pericardial thickening and calcification for constrictive pericarditis and pericardial effusion for cardiac tamponade. It is important to note that portosystemic shunts are uncommon in

cases of congestive hepatopathy.[58] In magnetic resonance imaging enhanced with a hepatobiliary contrast agent, the hypoenhancing scars are frequent. A nodular contour of the liver does not necessarily account for cirrhosis, but it can be associated with diffuse nodular regenerative hyperplasia. Thus, abdominal imaging is not an appropriate method to evaluate the stage of fibrosis.

Even if non-invasive tests can be useful to guide the suspicion of liver fibrosis, the reference standard for staging liver fibrosis remains the liver biopsy, usually performed via the transjugular route. Transjugular liver biopsy is a well-established technique for obtaining adequate liver tissue and it is preferred in cases of congestive hepatopathy because of its safety (minor risk of bleeding especially with coagulation disorders) and because it enables ancillary procedures, such as the measurement of the hepatic venous pressure gradient.[59] Liver biopsy can confirm the role of heart failure in liver diseases, due to the particular distribution of fibrosis. In fact, centrilobular fibrosis often implies a cardiac origin and when associated with centrilobular necrosis implies possible ischaemic involvement. In cases of periportal fibrosis, another cause of liver disease such as NAFLD or viral hepatitis must be investigated, as well as alcohol-induced liver disease in cases of perisinusoidal fibrosis. Moreover, liver biopsies allow us to identify other structural changes that may influence clinical management and prognosis. According to the METAVIR score, fibrosis is scored from F0, where F0 indicates no fibrosis to F4 corresponding to cirrhosis. To date, no specific classification for congestive hepatopathy is available. A congestive hepatic fibrosis score, with a 5-stage staining process based on autopsy studies, has been proposed and recently validated for 38 liver biopsies.[60–62] Another staging system has been proposed in patients awaiting heart transplantation (stage 0: no fibrosis; stage 1: pericellular fibrosis; stage 2: bridging fibrosis; and stage 3: regenerative nodules).

The presence of a bridging fibrosis was not significantly associated with post-operative survival and these patients may still be considered viable candidates for isolated heart transplantation.[13]

Thus, despite its numerous assets, liver biopsy has several drawbacks as it enables the analysis of only a small portion of the liver, introducing sampling variability, especially in the case of congestive hepatopathy. Confirming the presence of hepatic fibrosis is not necessary relevant for the management of these patients as fibrosis is not associated with an increased mortality rate.[13,63] However, decompensated cirrhosis (Child-Pugh B and C) should be identified as it is related to higher mortality rates after cardiac surgeries or the placement of heart support devices.[64]

Treatment of congestive hepatopathy

The treatment of congestive hepatopathy consists of managing the underlying cardiac condition to optimise cardiac output. Liver diseases related to congestive hepatopathy are rarely responsible for a significant morbidity or mortality and some reversibility of liver fibrosis has been observed after optimisation of cardiac function. The underlying cardiac disease generally determines the clinical outcome. The main lines of medical treatment for congestive hepatopathy are angiotensin-converting enzyme (ACE) inhibitors and beta blockers (Fig. 3).

ACE inhibitors are the first-line therapy. They increase cardiac output and decrease left ventricular filling pressure thanks to their vasodilatory effect. The choice of ACE inhibitor must consider liver function as some inhibitors are prodrugs and require transformation by the liver into active metabolites.[65] A reduced efficacy in cases of liver dysfunction has been observed with enalapril, ramipril, fosinopril, trandolapril, quinapril, benazepril and moexipril; frequent monitoring is recommended for these compounds.[66] No adjustments are needed with the use of lisinopril and captopril.[65]

For patients who cannot tolerate ACE inhibitors due to coughing symptoms, angiotensin receptor blockers such as losartan, valsartan and irbesartan are recommended. However, losartan is also metabolised by the liver and in patients with hepatic impairment, the bioavailability is doubled and the total plasma clearance is halved. Therefore, lower initial doses are recommended. Valsartan and irbesartan do not require liver metabolism, so a dosage adjustment for these drugs is not needed.[67–69]

The use of β-blockers is associated with a 30% reduction in total mortality in patients with heart failure. Propranolol should be administered cautiously in patients with hepatic impairment due to their extensive first-pass metabolism. No dose adjustments are needed for carvedilol, bisoprolol, nebivolol and meteprolol.[70–72]

Diuretics are recommended in patients with heart failure and clinical signs or symptoms of congestion. Jaundice, hepatic congestion, and ascites usually respond to diuretics. However, they should be used with caution to avoid dehydration, hypotension, and even secondary hepatic ischaemia[12] Moreover, loop diuretics, such as furosemide, bumetanide, and torsemide, should be used because of their superior natriuretic effects compared with other classes of diuretics. For unknown reasons, the pharmacologic response in patients with liver dysfunction and heart failure is diminished, and there is a significant decrease in sodium excretion when compared with healthy individuals taking the same dose. No adjustments are necessary if renal function is normal.[73]

Amiodarone has proven to be effective for suppressing ventricular arrhythmias, reducing sudden death and cardiac mortality, and improving exercise tolerance and ejection fraction. This drug can accumulate in the liver, but no dosage reduction is indicated in cases of hepatic impairment. However, amiodarone can cause apparent liver diseases especially when high or long-term doses are provided. In addition, amiodarone can remain in liver tissues even after cessation of therapy. The liver injury induced by amiodarone resembles alcohol-related liver disease clinically and histologically (micro- and macro-vesicular fat, ballooning degeneration, mild inflammation and variable amounts of fibrosis). The cause of amiodarone hepatotoxicity appears to be direct damage to the lipid bilayers and lysosomal and/or mitochondrial dysfunction.[74]

For patients who are refractory to medical therapy and who may be candidates for cardiac surgery, congestive hepatopathy resulting from chronic heart failure can improve and decline after the use of left ventricular assistive device support, as well as after cardiac transplantation.[35,75]

When considering cardiac transplantation, the liver function rather than the liver pathology must be considered, as patients with higher MELD and MELD-XI have worse outcomes 30 days after surgery, as well as reduced 10-year survival rates.[76] Interestingly, bridging fibrosis was not significantly associated with post-operative liver failure or survival, probably because of the high rate of heterogenous fibrosis within the liver for these

Table 2. Surveillance strategy after Fontan surgery.

Tests	No FALD			FALD or cirrhosis
	<12 years old	12-18 years old	>18 years old	all ages
Laboratory liver tests	every 3 to 4 years	every 2 years	every 1 to 2 years	every 6 months
α-fetoprotein	every 3 to 4 years	every 2 years	every 1 to 2 years	every 6 months
Serum FibroSure biomarkers	every 3 to 4 years	every 2 years	every 1 to 2 years	no
Liver elastography (ultrasound or MRI)	every 3 to 4 years	every 2 years	every 1 to 2 years	no
Abdominal ultrasound	every 3 to 4 years	every 2 years	every 1 to 2 years	every 6 months
Complete blood cell count	every 3 to 4 years	every 2 years	every 1 to 2 years	every 6 months
PT/INR*	every 3 to 4 years	every 2 years	every 1 to 2 years	every 6 months

* INR, international normalized ratio; PT, prothrombin time.

patients.[13,63] The presence of ascites and renal dysfunction at listing were also independently associated with primary graft dysfunction and post-operative 90-day mortality.[77]

In selecting patients with established cirrhosis, combined heart and liver transplantation is a potential option but no official guidelines are available and the decision is often taken on a case-by-case basis.[78] Some centres use an HVPG value inferior to 12 mmHg as a cut-off for offering isolated heart transplantation instead of combined heart-liver transplantations.[79] In the United States, indications for combined heart-liver transplants are restrictive and associated with congenital heart diseases, whereas heart-liver transplants are associated with dilated and ischaemic cardiomyopathies in France. The transplantation of both the heart and liver is usually performed at the same time, starting with the heart transplantation in order to limit the cold ischaemia time of the cardiac graft and to avoid any risk of heart failure during the reperfusion of the hepatic graft. The survival rates after combined heart-liver transplantations are close to those observed in single-organ heart transplants with estimated 3-year survival rates of 75% *vs.* 79%, respectively.[7] The 10-year survival rate after combined transplants is even better for congenital heart diseases compared to single heart transplants (83% *vs.* 39%, $p = 0.03$).[80] The treatment decision for combined heart-liver transplantations must consider the model of liver damage, the level of liver fibrosis, the degree of liver impairment and the number of organ failures. In cases of pure congestive hepatopathy or associated liver diseases with a fibrosis stage between F0 and F2 and the absence of HCC, a heart transplantation alone should be proposed. However, in the presence of fibrosis stage F3 to F4 or HCC, a combined transplantation should be discussed collegially. A MELD score >14 must lead to consideration of first-line ventricular assistance in order to improve hepatic or renal dysfunction related to heart failure. The persistence of multi-organ failure contraindicates organ transplants.[81]

Surveillance and hepatocellular carcinoma occurrence

All patients with Fontan circulation should undergo regular hepatic screening with assessments which may include serum screenings and imaging as proposed in Table 2, according to the American Heart Association statement.[21] In a series of 650 patients who underwent the Fontan procedure, 12 developed HCC. The incidence of HCC was of 0.8%, 2.9%, and 13.3% at 10, 20, and 30 years after the surgical procedure.[82] HCC seemed to occur late after the Fontan surgery (after 10 years) with a mean age around 30 years and, due to the absence of a screening strategy, patients are often diagnosed at an advanced stage.[82–85] In a recent study prospectively conducted on 152 Fontan patients, liver nodules were frequent. The nodules were mostly located in the liver periphery (75%), hyperenhanced in the arterial phase in 92% of cases, associated with a wash-out for some of them, and corresponding to non-neoplastic regenerative hepatocytes in most patients.[86] Thus, a non-invasive diagnosis of HCC in patients who underwent a Fontan procedure remains difficult due to the presence of benign nodules that mimic HCC. For instance, in 18 patients that presented with hyperenhanced nodules with washout in the portal venous phase, 7 were finally diagnosed with HCC. The appearance of washout, a long time elapsed since the initial Fontan operation, large nodule size and elevated serum α-fetoprotein (AFP) were associated with HCC.[87] On the contrary, hyperenhanced nodules without additional findings supportive of malignancy (portal venous phase washout, mosaic architecture, elevated AFP, presence of cirrhosis) were all benign nodules. Moreover, in this study, the stability of the size of the lesions (≥24 months) was an ancillary finding favouring benignity based on LI-RADS for atypical nodules. Thus, in patients with FALD, these atypical nodules should be approached with caution and follow-up seems to be necessary.

Even if the risk of HCC is low among this population of patients, HCC surveillance should be proposed. However, as arterial hyperenhancement and washout are not specific to HCC in this population of patients, non-invasive HCC diagnostic criteria do not seem to be applicable in FALD, and a confirmatory biopsy is always required.[86,88] Recently, the use of 18F-fluorocholine and 18F-fluorodeoxyglucose positron emission tomography/computed tomography enabled improved HCC diagnosis by discriminating doubtful lesions.[89] The use of such techniques could be useful in patients who have undergone a Fontan procedure.

However, the choice of HCC treatment remains difficult as some options are contraindicated. Open liver resections are associated with high risks of bleeding and post-operative liver-decompensation causing severe cardiac dysfunction.[90,91] A laparoscopic approach for the treatment of HCC has been proposed and was associated with low-risks of liver and cardiac decompensation, minimising the pneumoperitoneum insufflation to ensure low intra-abdominal/intra-thoracic pressures and providing accurate anaesthetic management to maintain proper cardiac preload and output.[92] Transarterial chemoembolisation has also been offered in cases of HCC not eligible for surgery. Despite some cases of heart failure, the tolerance was good and positive results were observed .[93] The best approach for HCC has not been defined yet and combined liver-heart transplantation still has to be discussed. Currently, the prognosis of HCC-related to Fontan procedure is poor (1-year survival around 50%) and the management and surveillance of patients has to be

improved.[85,94] Recently, the American Heart Association published new guidelines for the surveillance of the patients and a bi-annual screening for HCC should be proposed once the diagnosis of cardiac cirrhosis is established[21] (Table 2).

No guidelines have been proposed for surveillance in patients with non-Fontan congestive hepatopathy. Even if the data are sparse, the risk of fibrosis and HCC exists for these patients and can increase in cases of associated liver disease. Regular liver test screening could help to diagnose liver injury and systematic assessments for associated viral hepatitis, chronic alcohol intake, iron overload and metabolic syndrome should be performed. Bi-annual imaging surveillance must be proposed to detect HCC in case of cardiac cirrhosis.[95] However, as discussed, the diagnosis of HCC according to non-invasive criteria remains difficult as some nodules can present arterial hyperenhancement and wash out. Some guided biopsies for suspicious lesions (*i.e.* new or solitary atypical lesion >2 cm) should be performed.

Conclusions

Liver injury resulting from cardiac disease is relatively common but poorly diagnosed. As congestive hepatopathy can evolve into cirrhosis then HCC, screening for liver injury should be performed in patients with chronic cardiac disease and after Fontan surgery. Most of the time, liver injury will regress after adapted treatment for heart disease. However, in case of medical failure, a heart transplant can be proposed, while combined heart-liver transplantation should be discussed in case of significant liver fibrosis. Research on the microbiome could reveal a new treatment approach to prevent liver damage associated with heart diseases.

Abbreviations

ACE, angiotensin-converting enzyme; AFP, α-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate amino transferase; BNP, B-type natriuretic peptide; GGT, gamma-glutamyl-transferase; FALD, Fontan-associated liver disease; FIB-4, Fibrosis-4 index; HCC, hepatocellular carcinoma; INR, international normalised ratio; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

Study concept and design: Sessa, Allaire and Cadranel. Drafting of the manuscript: Sessa, Allaire, Lebray and Cadranel. Final approval of the version to be submitted: Sessa, Allaire, Lebray, Medmoun, Tiritill, Iaria and Cadranel.

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Supplementary data

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