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Review article

Fontan-associated Liver Disease

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ABSTRACT

Fontan-associated liver disease refers to the disturbance in the liver secondary to hemodynamic changes and systemic venous congestion following Fontan surgery. Although the natural history of this disease has not yet been established, patients with more advanced liver injury develop the complications of portal hypertension, such as ascites, variceal haemorrhage, or encephalopathy. Moreover, patients with Fontan surgery may have an increased risk of hepatocellular carcinoma. Periodic liver monitoring is essential to prevent this disease and provide early treatment of liver complications.

Enfermedad hepática crónica asociada con cirugía de Fontan

Palabras clave:
Cirugía de Fontan
Enfermedad hepática
Hepatocarcinoma
Fracaso del Fontan

RESUMEN

La enfermedad hepática relacionada con la cirugía de Fontan hace referencia a los cambios hepáticos secundarios a las alteraciones hemodinámicas y la congestión venosa sistémica que se producen tras ese procedimiento. Aunque su historia natural aún no está establecida, los pacientes con daño hepático más avanzado pueden presentar complicaciones de la hipertensión portal, como la ascitis, la hemorragia por rotura de varices o encefalopatía. En los últimos años se ha demostrado que el riesgo de hepatocarcinoma está incrementado. El seguimiento hepático periódico es fundamental para prevenir y tratar precozmente las complicaciones hepáticas.

Abbreviations

FALD: Fontan-associated liver disease
FS: Fontan surgery
HVPG: hepatic vein pressure gradient
MELD: Model for End-stage Liver Disease
TIPS: transjugular intrahepatic porto-systemic shunt

INTRODUCTION

Fontan-associated liver disease (FALD) refers to a wide range of structural and functional alterations of the liver caused by hemodynamic changes associated with the Fontan circulation (FC). As in all chronic liver diseases, the individual passes through various stages before reaching the final phase, which is when most of the complications appear, such as hepatocellular carcinoma, variceal bleeding, ascites, and hepatic encephalopathy. Although hepatic impairment eventually develops in all patients with FC, its adequate characterization is essential to allow us to determine the degree of liver damage and thereby establish screening and follow-up programs to prevent and/or treat at an early stage any liver complications that may arise. This review summarizes the current evidence on the pathophysiology of FALD, as well as the methods available for its diagnosis and management. Finally, we propose a follow-up strategy tailored to the peculiarities of these patients.

FONTAN SURGERY: DEFINITION, TYPES, AND CONSEQUENCES

The FC is used to treat several complex congenital heart diseases with a common characteristic: the presence of a functional single ventricle. The surgical objective is to ensure that the systemic venous return is directed into the pulmonary artery, bypassing the right ventricle. Simply put, the Fontan technique surgically creates an anastomosis between the systemic venous return from both vena cavae and the pulmonary artery that passively carries the blood to the single ventricular chamber. Therefore, the FC is a curative surgery whose main objective is to mitigate the hypoxemia and prolong survival.[1]

There are 2 main variations of the technique: the atriopulmonary (classic) procedure and the total cavopulmonary

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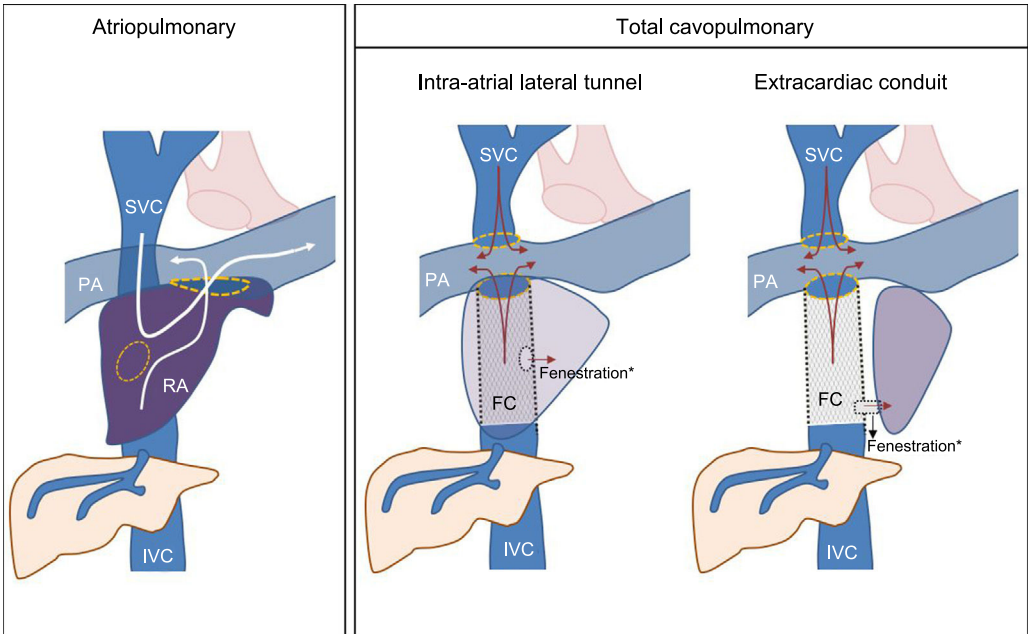


Figure 1. Variants of the Fontan procedure. FC, Fontan circuit; IVC, inferior vena cava; PA, pulmonary artery; RA, right atrium; SVC, superior vena cava. * The creation of a fenestration joining the Fontan circuit and the right atrium is a variant used in only some patients.

(Figure 1). The classic FC involves transformation of the atrium into a channel connecting both vena cavae to the pulmonary artery. For this, an anastomosis is created between the atrium and the pulmonary artery, and the tricuspid valve and atrial septal defect are closed. Although it was initially thought that maintenance of the participation of the atrium in the circuit would facilitate the propulsion of the blood to the lungs, this approach was later found to increase the risk of atrial tachyarrhythmias and thromboses.[2,3] The total cavopulmonary variant, the technique of choice in recent years, is carried out in 2 stages: in the first, the venous return of the superior vena cava is connected to the pulmonary arterial circulation (Glenn procedure), with completion of the procedure at the same time or later with an anastomosis from the inferior vena cava to the pulmonary artery using an artificial conduit (Fontan conduit).

Although the technique was first described in 1968, its use was quite limited until the 1980s.[4] Accordingly, its long-term results are unknown. Nonetheless, the FC represents one of the greatest advances in pediatric cardiology, ensuring survival rates of about 80% at 20 years, which must be considered a huge success given the severity of the cardiac anatomic defects addressed.[5,6] However, the long-term hemodynamic changes caused by the surgery are now associated with a considerable number of complications that can affect virtually all organs.[7,8]

The concept of "Fontan failure" refers to the syndromic set of systemic conditions that develop in the long term in most patients who undergo the procedure. Whatever the cause, the result is always the same: increased systemic venous pressure. Fontan failure can be precipitated by different events, such as heart arrhythmia, stenosis, or obstruction of the Fontan conduit, or, in its

Table 1
Systemic Implications of "Failure" of the Fontan Circulation

Organ/system	Complication	Mechanism	Clinical manifestation
Lungs	Atrial/venovenous shunts	Passive gradient-dependent circulation	Cyanosis, dyspnea, hypoxia, exercise intolerance
	Plastic bronchitis	↓ lymphatic return	
	Chylothorax	↓ lymphatic return	
	Thromboembolism	Hypercoagulability	
	Pulmonary hypertension	Vascular hyperreactivity	
Kidneys	Proteinuria	Hyperfiltration via venous hyperpressure	Edema, ascites
	Renal failure (acute/chronic)	Ischemia due to ↓ CO	Dyspnea, oliguria
Intestine	Protein-losing enteropathy	↓ lymphatic return Splanchnic venous congestion Systemic inflammation Hormonal activation	Malnutrition, edema, ascites, diarrhea
Liver	Chronic liver disease	Hepatic congestion Ischemia due to ↓ CO	Ascites, varices, encephalopathy, hepatocellular carcinoma
Brain	Cerebrovascular disease	Cardioembolic ischemia due to ↓ CO	Diminished executive functions
Heart	Bradyarrhythmias and tachyarrhythmias	Atrial and ventricular remodeling	Hemodynamic instability
	Ventricular dysfunction	Activation of neurohormonal systems	Dyspnea, exercise intolerance
Vascular system	Varices	Venous hyperpressure ↓ venous return	Edema, varicose veins in the extremities

CO, cardiac output.

most advanced form, ventricular dysfunction. This pressure elevation triggers 2 key phenomena: *a)* congestion in the splanchnic venous circulation (which is unable to self-regulate flow), and *b)* decreased lymphatic return via the thoracic duct. Finally, when Fontan failure is accompanied by a deterioration in single ventricular systolic function, cardiac output decreases, which promotes ischemia in target organs. These and the other mechanisms discussed below determine the damage to the different organs and systems, as summarized in Table 1.[9–12]

PATHOPHYSIOLOGY OF FONTAN-ASSOCIATED LIVER DISEASE

The liver is an organ with a complex dual vascularization architecture that receives two-thirds of its blood through the portal venous system and approximately one-third through the hepatic artery. However, venous drainage only occurs through the hepatic veins, which drain the blood to the inferior vena cava and from there to the heart. This peculiar vascularization explains the microscopic polyhedral lobule architecture of the liver, which is fundamental to the understanding of the pathophysiology of FALD[13] (Figure 2).

In most liver diseases, the damage is caused through inflammatory mechanisms by the arrival to the liver of toxic products such as alcohol or drugs, viral infections, and other agents. Because the inflammation requires a large amount of oxygen, the damage initially appears in the most oxygenated regions, namely, the periportal zones.[14] However, in patients with FC, the pathophysiology is quite distinct because there are no inflammatory phenomena, and the injury model is primarily due to the persistent hepatic congestion.[15]

Because of the location of the liver, an elevated central venous pressure is easily transmitted to the liver. If this pressure is maintained, it causes congestion and increased intrahepatic pressure. The result of these phenomena at the microscopic level is sinusoidal dilatation, which is more evident in the centrilobular area. The sinusoidal hyperpressure transmitted from the systemic circulation promotes hyperfiltration of the blood and causes edema to develop in the space between the sinusoidal endothelial cells and the hepatocytes (space of Disse). This edema, coupled with the low cardiac output, limits the arrival of oxygen and facilitates hepatocyte necrosis phenomena and the emergence of profibrogenic mediators such as tumor growth factor beta.[16] In addition, exposure of the sinusoidal endothelial cells to the vascular tension and stress induces a phenotypic change that converts them into fenestrated cells that release various mediators. These agents permit activation of the hepatic stellate cells located in the space of Disse that have a large fibrogenic capacity (Figure 3). Although the changes are initially perisinusoidal and in zone 3, they can eventually affect the entire liver lobule via the formation of bridging fibrosis and regenerative areas, which are indicative of cirrhosis (Figure 4).

Patients with FC show important hemostatic alterations affecting all of the disease stages and mirror those found in patients with advanced liver disease, which confers them with a latent state of hypercoagulability.[17] If this state is coupled with intrahepatic endothelial damage and considerable venous stasis, Virchow's triad is perfectly fulfilled, meaning that intrahepatic microthrombotic phenomena that aggravate and perpetuate the liver damage are very likely.[18] This hypothesis, although requiring further study, opens the door to alternative therapies, such as anticoagulation, which can reduce the liver damage.

Finally, the liver disease in patients with FC can occur for reasons other than the cardiac surgery itself, such as hepatotoxicity due to amiodarone,[19] an antiarrhythmic agent commonly used in this population, or hepatitis C.[20]

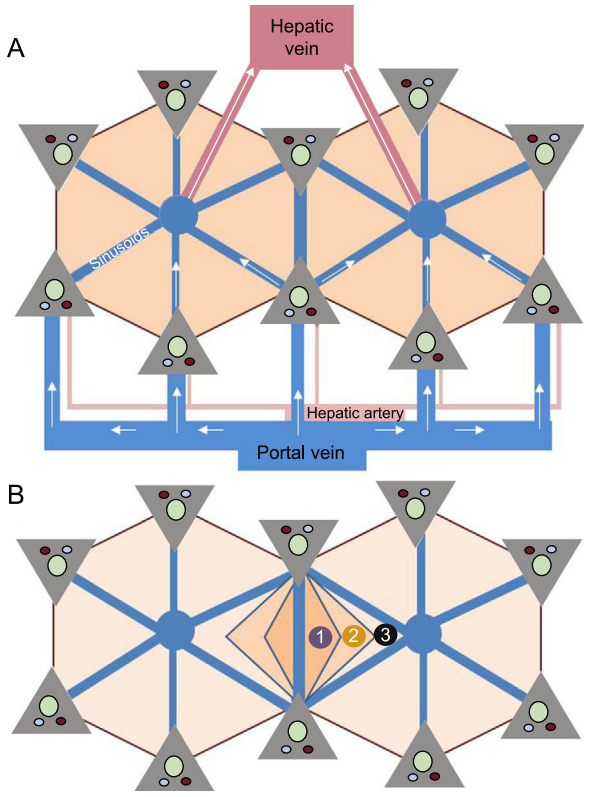


Figure 2. Microscopic architecture of the liver. A: The main afferent vessels of the liver (portal vein and hepatic artery) are divided into venules and arterioles, which in turn give rise to small vessels that converge in the hepatic sinusoids; the sinusoids are small vascular spaces formed by endothelial cells and surrounded by hepatocytes that enable the distribution of the blood flow and return the blood through the centrilobular veins to the systemic circulation. B: The liver lobule shows a polyhedral architecture whose ends contain the "portal spaces", formed by small arterial and portal vessels and bile ducts; the centrilobular vein is located in the center of the lobule and is connected to the portal spaces through the sinusoids. Because the portal spaces and the centrilobular vein are anatomically separated, there is an oxygen and nutrient concentration gradient in the blood that is higher in areas close to the portal spaces and lower in those near the centrilobular vein. This gradient allows the lobule to be divided into 3 zones: zone 1 is the periportal region and zone 3 is the pericentral region.

NATURAL HISTORY AND CLINICAL FORMS OF FONTAN-ASSOCIATED LIVER DISEASE

FALD is one of the main and often the first manifestation of Fontan failure. Although its natural history remains to be established, it can be generally divided into 3 main stages (Figure 5):

1. *Liver congestion and sinusoidal dilatation.* This stage begins even before the FC and continues during the first years after the procedure.[21,22] About 53% of these patients have painful hepatomegaly and/or hepatojugular reflux, although many are asymptomatic. On blood analysis, this stage is characterized by mild indirect hyperbilirubinemia and a gamma-glutamyl transpeptidase increase that is related to the canalicular congestion secondary to perisinusoidal edema. On biopsy, sinusoidal dilatation and hepatocellular necrosis are evident in zone 3 of the lobule.[23]
2. *Fibrosis without portal hypertension.* After between 5 and 10 years, there are signs of perisinusoidal fibrosis, regenerative nodules, and hepatocellular necrosis. At this stage, necrotic phenomena may be accentuated if there is low cardiac output,

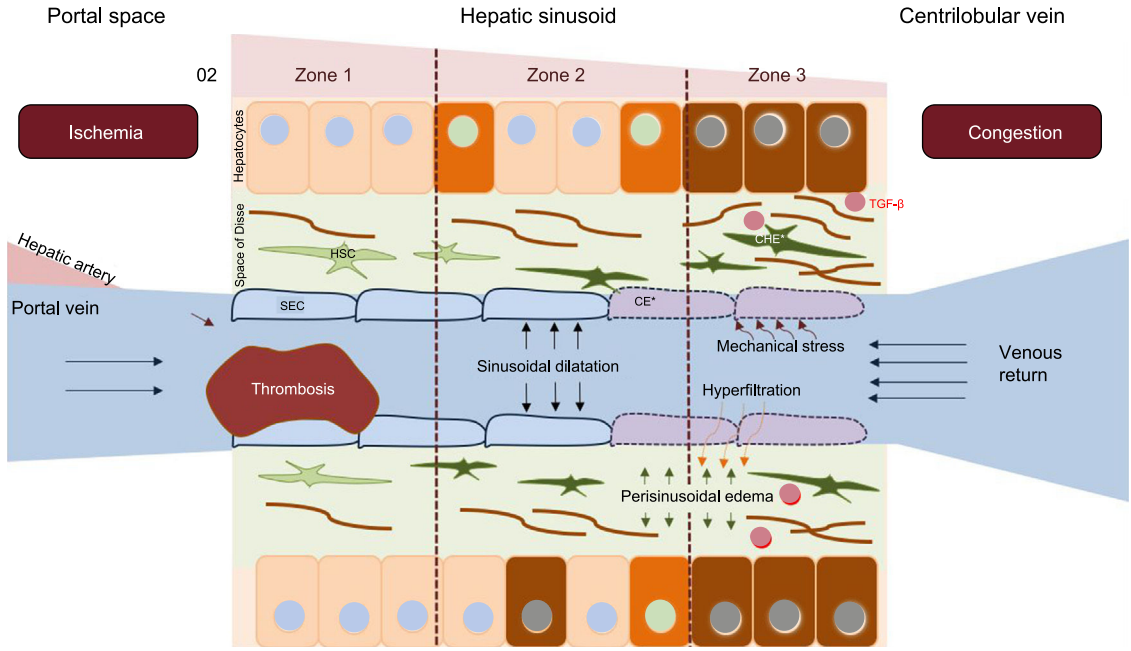


Figure 3. Pathophysiology of Fontan-associated liver disease. Systemic venous hypertension secondary to the FC decreases venous return, which increases the pressure and dilates the sinusoid in a retrograde manner. Hyperfiltration phenomena occur toward the space of Disse, and mechanical stress induces a phenotypic change in sinusoidal endothelial cells. The release of certain molecules by these cells activates in an autocrine manner hepatic stellate cells, which facilitate fibrogenesis phenomena. Over time, the hypoxia and perisinusoidal fibrosis produce parenchymal hepatocyte necrosis that is more evident in zone 3 (close to the centrilobular vein). HSC, hepatic stellate cell; SEC, sinusoidal endothelial cell.

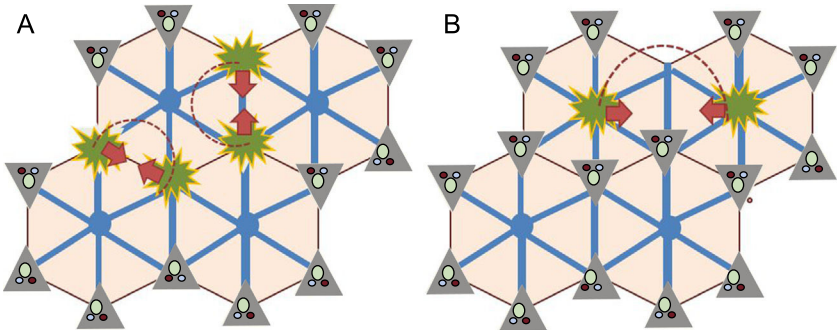


Figure 4. Fibrogenesis in Fontan-associated liver disease. Whereas in the conventional models of cirrhosis (A), the bridging fibrosis appear between the portal spaces, in the model of Fontan-associated liver damage, the bridges are formed between the centrilobular areas (B), which gives rise to the concept of "inverted cirrhosis", a characteristic of these patients.

so there are often slight increases in aspartate aminotransferase, alanine transaminase, and lactate dehydrogenase. The fibrosis is potentially reversible if the patient undergoes heart transplantation.[24]

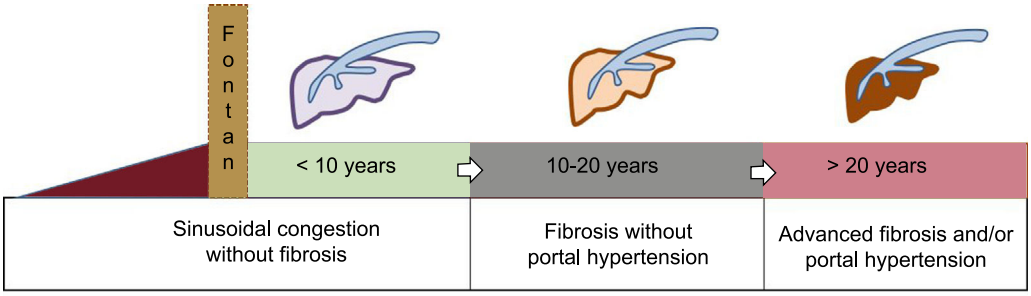
3. *Advanced fibrosis with portal hypertension.* This is the final stage of all liver diseases. It shows hypoalbuminemia, prolonged coagulation times, and decreased platelet counts. At this stage, the risk of hepatocellular carcinoma is increased, as well as portal hypertension complications, such as ascites or bleeding due to rupture of gastroesophageal varices.[25]

A distinct clinical entity can be encountered in any of the stages described: ischemic hepatitis, which is characterized by a marked elevation in aspartate aminotransferase, alanine transaminase, and lactate dehydrogenase and takes place in the acute context of low cardiac output. It is usually reversible after resolution of the event underlying the precarious hemodynamic situation.

The time course of FALD is difficult to establish because, given that it is not a primary disease of the liver, its clinical course depends on the cardiac situation. The variables associated with increased risk of liver damage are listed in Table 2.[26–28] However, the main determinant of liver complications is time, with a risk of decompensation 4 and 9 times higher 15 and 20 years after FC than after 5 years, respectively.[29]

DIAGNOSIS OF ADVANCED CHRONIC FONTAN-ASSOCIATED LIVER DISEASE

The liver damage in patients with FC is universal. However, because not all patients manifest the complications, methods are required to permit the identification of at-risk individuals who would benefit from close and directed follow-up.[30] For compensated patients, the only diagnostic method currently allowing an adequate staging of liver disease is biopsy. However, recent advances in hepatology have attempted to develop noninvasive diagnosis methods, which have also been evaluated in patients with FC.



Clinical	Asymptomatic Painful hepatomegaly (53%) Hepatojugular reflux	Asymptomatic Painful hepatomegaly Hepatojugular reflux	Ascites Gastroesophageal varices Hepatocellular carcinoma Hepatic encephalopathy
Analytics	Indirect hyperbilirubinemia ↑↑↑ GGT	Indirect hyperbilirubinemia ↑↑↑ GGT ↑ AST – ALT (x3 – 5) (30%)	Hyperbilirubinemia Thrombocytopenia ↑↑↑ INR
Histology	Sinusoidal dilatation in zone 3 Hemorrhagic necrosis in zone 3	Necrosis in zone 3 Perisinusoidal fibrosis Regenerative nodules	Central-central bridging fibrosis Regenerative nodules

Figure 5. Natural history of Fontan-associated liver disease. The temporal sequence is illustrative because the timeline depends on the course of the heart disease. Arrhythmias or ventricular dysfunction can accelerate the clinical course. ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase.

Table 2
Risk Factors for Liver Damage in Patients With the Fontan Circulation

Related to the hemodynamic situation
Reduced cardiac output
Elevated pulmonary capillary wedge pressure
Elevated central venous pressure
Related to the surgery
Pulmonary atresia as a cause of the procedure
Classic technique (atriopulmonary variant)
Stenosis/thrombosis of the Fontan circuit
Time from surgery
Related to cardiac events
Cardiac arrhythmias
Ventricular systolic dysfunction
Others
Infection by hepatotropic viruses
Exposure to hepatotoxic drugs (amiodarone)

Serological Methods

A complete blood count may be sufficient as a diagnostic strategy for liver disease in patients with FC. A platelet count less than 150 000/μL is the main indicator of hypersplenism, one of the clearest analytical findings of portal hypertension. Multiple simple methods have been developed in recent years that correlate various analytical parameters with each other and with certain radiological findings. Although these methods were developed to diagnose liver cirrhosis with other indications besides FC, many have been used for this indication (Table 3). The main drawback is that they have not yet been validated against the reference standard, liver biopsy, which is why no validated cutoff points are available. Nonetheless, several methods were comparatively evaluated in a cohort of 204 patients[29]; 26% had signs of hepatic decompensation. The Forns index was determined to be the best predictor of the presence of advanced liver damage, with an area under the curve of 0.786. In patients with advanced liver damage of any cause, the MELD (Model for End-stage Liver Disease) scale is a very useful prognostic tool, so much so that it is used in most

Table 3
Serological Diagnostic Methods for Patients With the Fontan Circulation

Marker	Parameters included	Evidence
APRI	AST, platelets	Demonstrated correlation with radiological findings
AST/ALT	AST, ALT	Demonstrated correlation with radiological findings
FIB-4	Age, AST, ALT, platelets	Demonstrated correlation with radiological findings
Forns index	Age, AST, cholesterol, platelets	Demonstrated correlation with radiological findings
ELF score	TIMP-1, PIIINP, and hyaluronic acid	Has not been shown to be useful
Platelets	Total platelet count	Demonstrated correlation with radiological findings
MELD-XI	Bilirubin, creatinine	Demonstrated correlation with radiological findings. Without cutoff points with adequate sensitivity and specificity
FibroSure	ALT, A2-macroglobulin, apolipoprotein A-1, bilirubin, GGT, haptoglobin, AST, glucose, total cholesterol, and triglycerides	Correlation with histologic findings not shown

ALT, alanine transaminase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4; GGT, gamma-glutamyl transpeptidase; MELD-XI, Model for End-stage Liver Disease-XI; PIIINP, N-terminal polypeptide of collagen type III; TIMP-1, tissue inhibitors of metalloproteinases-1.

centers to establish the indication and priority for liver transplantation. Its main disadvantage is that it relies on the INR, which is artificially elevated by some anticoagulants commonly used in patients with FC. However, the MELD-XI scale does not include the INR and has been created for patients treated with oral anticoagulants.[31] Although the MELD-XI has been correlated with the degree of fibrosis, it has not been possible to define an appropriate cutoff point to categorize the FALD.[32]

Abdominal Doppler Ultrasound

This is the method of choice in the initial evaluation of all patients with suspected chronic liver disease and typically enables its diagnosis thanks to the signs listed in Table 4. An irregular outline of the parenchyma on a high-frequency transducer is the most specific ultrasound finding for the diagnosis of advanced liver disease.[33–35] Additionally, portal flow inversion is 100% specific for the diagnosis of portal hypertension.[36] A combination of analytical and radiological methods, such as the platelet count/spleen diameter ratio, can facilitate the diagnosis of portal hypertension and select patients at risk of the development of gastroesophageal varices.[37] In patients with FALD, the most frequent echographic findings are heterogeneous echogenicity, a nodular surface, and small hyperechoic nodules.[35,38] Kutty et al.,[39] via a controlled Doppler study of 106 individuals, showed higher resistance and pulsatility indexes in the celiac artery and superior mesenteric artery, with a significant reduction in portal velocity in patients with FC. The loss of the triphasic Doppler pattern of the hepatic veins is universal in the total cavopulmonary variant (due to absence of atrial beat transmission), but the presence of a monophasic pattern indicates advanced liver damage.[26]

Liver Elastography

This simple noninvasive diagnostic method permits the measurement of liver stiffness. A transducer emits a mechanical vibration in the form of a low-frequency and high-amplitude sound waves that reach the liver tissue and generate a longitudinal wave that is registered by the transducer. The more rigid the tissue, that is, the more fibrosis it has, the higher the transmission speed of the wave. The speed is converted by mathematical algorithms into stiffness, measured in kilopascals.[40] There are 2 main elastographic methods: transient elastography (FibroScan), which is simpler and more widely used in Europe, and sonoelastography, which requires an experienced operator and is more popular in North America. Elastography allows classification of patients in the 4 classic stages of fibrosis and has been validated for practically all etiologies, eliminating the need for many of the previously performed biopsies.[30] One of its main drawbacks is the false positives that can occur in a number of situations, such as liver congestion.[41] This means that elastography values can be overstated in patients with FC. In fact, the procedure induces an almost immediate elevation in elastography values that is solely due to the liver congestion.[42] Nonetheless, as the years pass and signs of Fontan failure and liver damage appear, the transient elastography values eventually exceed 15 kPa, probably due to the fibrosis.[43,44] A proof-of-concept study performed using sonoelastography with the shear-wave technique showed a positive correlation between histological liver damage and rigidity.[39] Therefore, although the appropriate cutoff points for the diagnosis of advanced liver disease are unknown, elastography can be a useful tool.

Table 4
Ultrasound Findings Indicating Advanced Liver Damage and Portal Hypertension in Fontan-associated Liver Disease

B-mode
Dull or nodular liver edges
Heterogeneity of the hepatic parenchyma
Intrahepatic venovenous shunts
Portal vein diameter > 12 mm
Splenomegaly (area > 50 cm^2)
Doppler
Decreased portal velocity (< 16 cm/s)
Portal flow inversion
Hepatic arterial resistive index > 0.71 and pulsatility index > 1.3 in the hepatic artery
Monophasic or biphasic flow in the suprahepatic veins

Magnetic Resonance Imaging

Magnetic resonance imaging can be very useful in FALD.[45] Its main advantage in this scenario is its ability to diagnose and characterize hepatic nodules. In addition, because cardiac magnetic resonance is currently one of the main tools used during follow-up in this population, it can be combined with dynamic hepatic magnetic resonance to minimize patient discomfort and optimize resources. Although its use is not yet widespread due to its high cost, magnetic resonance elastography can also evaluate fibrosis; indeed, there is a positive correlation between the stiffness values obtained with this method and the APRI index, MELD score, Fontan circuit pressure, and even histological damage.[46]

Hepatic Hemodynamics

Measurement of the hepatic venous pressure gradient (HVPG) may help to better grade the FALD and can even be a tool to aid in the differential diagnosis of ascites. The procedure is quick, simple, and minimally invasive and does not require sedation.[47] The HVPG is defined as the difference between the wedge and free pressures in one of the hepatic veins, preferably the right. Measurement of the HVPG permits the differential diagnosis of portal hypertension symptoms, with some elevated pressures with normal HVPG indicating a posthepatic origin, which is the most common post-FC finding.[27] In the presence of advanced parenchymal damage, the HVPG can exceed 6 mm Hg, even 10 mmHg, a threshold that is considered to indicate risk of decompensation in most liver diseases.[48] However, various circumstances can lead to underestimation of the HVPG, such as the presence of vascular fistulas between the hepatic veins themselves or between these veins and the portal branches. In our experience, such fistulas are very frequent in patients with FC, which complicates the interpretation of the HVPG result and means that experienced staff is required to perform the measurement.

Liver Biopsy

This is the diagnostic reference standard and, because the noninvasive diagnosis methods remain to be adequately validated, is still necessary to irrefutably determine the liver damage. The biopsy can be performed via a transjugular approach, together with the HVPG measurement, or via percutaneous access. The characteristic histologic findings are reported in Table 5. Sinusoidal dilatation is present in 90% to 97% of patients with FC and is the earliest finding. Characteristically, the sinusoidal dilatation is more pronounced than for other causes of cardiogenic cirrhosis. The

Table 5
Characteristic Histological Findings of Fontan-associated Liver Disease

Sinusoidal dilatation
Centrilobular hemorrhagic necrosis
Perisinusoidal fibrosis
Ductular reaction
Perivenular or septal fibrosis
Central-central bridging fibrosis
Nodular regenerative hyperplasia

fibrosis distribution in early stages is typically perisinusoidal (in the space of Disse), an indicator that is absent from other liver diseases of cardiac origin. The most severe and delayed finding is that of extensive centrilobular bridging fibrosis with regenerative nodules, which are usually indicative of an irreversible disease state. Periportal inflammation is generally absent, allowing its differential diagnosis with other liver disease etiologies.[49] Some authors recommend a biopsy in all patients 10 years after the FC.[25] In a cohort of 67 patients, this strategy revealed that 100% of them had developed liver fibrosis and that its degree increased with time. However, because it has not been possible to correlate the degree of fibrosis with clinically relevant events or hemodynamic or analytical parameters,[50] its usefulness as a prognostic marker that facilitates decision-making is still unclear. Currently, a liver biopsy is recommended in patients with liver disease of unknown etiology and in heart and/or liver transplantation candidates.[39,40]

LIVER COMPLICATIONS OF THE FONTAN SURGERY

Advanced stages of FALD, similar to other forms of liver cirrhosis, may show gastroesophageal varices, ascites, hepatic encephalopathy, hepatocellular carcinoma, and splenomegaly with thrombocytopenia. No study has evaluated in detail the characteristics or natural history of these complications in FALD.

Hepatic Nodules and Hepatocellular Carcinoma

Large regenerative nodules are frequently found in the liver parenchyma in FALD, as in other congestive liver diseases.[15,51] These nodules are usually multiple, hypervascular in the arterial phase and hyperechoic in the ultrasound, and less than 3 cm in size, located in the liver periphery, and show a prevalence that is directly proportional to the time since the surgery. In the histological study, these nodules are typically regenerative, adenomas, or of focal nodular hyperplasia.[28,38,52,53] Although the pathophysiology of benign liver nodules in patients with FALD is unknown, their peripheral location and radiological behavior indicate a vascular origin (Figure 6).[54]

In recent years, isolated cases or small series have been published on hepatocellular carcinoma in patients with FALD.[54–67] These patients usually have advanced liver disease and a time from surgery greater than 5 to 10 years. Malignant nodules tend to be hypervascular in the arterial phase, with clearance in the portal phase, and show increased alpha-fetoprotein (Figure 7). However, these characteristics are not pathognomonic and may be absent in some patients. In addition, their diagnostic accuracy in FALD remains to be evaluated. Thus, the differential diagnosis of nodules in FALD remains to be defined. Additionally, the criteria of hepatocellular carcinoma used in cirrhosis have not been validated in other liver diseases such as FALD. Thus, the diagnosis of hepatocellular carcinoma in patients with FALD always requires histological confirmation.[46]

Screening every 4 to 12 months using imaging techniques is cost-effective and improves the survival of patients with cirrhosis because it allows early detection of hepatocellular carcinoma and offers curative treatments.[68] Nandwana et al.[69] retrospectively analyzed a cohort of 145 patients with FC who periodically underwent a liver imaging test; the authors found 1 case of hepatocellular carcinoma in the first imaging test and 4 incident cases after a median follow-up of 3.05 years. Most experts recommend periodic screening, although the optimal interval and imaging tests are unknown.[25,52] Hepatocellular carcinoma management should adhere to the clinical practice guidelines for other forms of cirrhosis.[68]

Gastroesophageal Varices

The prevalence of gastroesophageal varices is estimated to range between 2% and 43% after a FC.[25,30,70] In a retrospective study of 73 patients, the concomitance of varices with other manifestations of portal hypertension was associated with an increased risk of death, heart transplantation, and hepatocellular carcinoma.[70] Because cases have been published of gastroesophageal variceal bleeding, some with a fatal outcome, screening and proper prevention should be systematic.[25] The prophylactic mainstay of variceal bleeding in other forms of cirrhosis is the use of noncardioselective beta-blockers; however, their effects have not been analyzed in this patient group.[71] Because the portal hypertension model in patients with FALD is characteristically hypodynamic, in contrast to the other forms of cirrhosis, the efficacy of these drugs is questionable. In addition to the possible deleterious effects of beta-blockers on the FC itself, elastic band ligation is proposed as a method of primary and secondary prophylaxis. An acute episode of gastrointestinal bleeding due to variceal rupture should be treated with vasoactive drugs (somatostatin, terlipressin, or octreotide) and endoscopic therapy (band ligation). In cases of bleeding refractory to standard treatment, the creation of an intrahepatic portosystemic shunt (IPSS) improves survival in other types of liver disease[71]; however, the excessive flow of blood to the FC from the splanchnic territory can precipitate a clinical profile of pulmonary hypertension and heart failure. The bibliography contains only 1 case in which IPSS placement controlled variceal bleeding; however, IPSS use should be restricted to highly selected nonresponders to conventional treatment that maintain good heart function.[72]

Ascites

Ascites is a late manifestation of liver cirrhosis that is associated with worse survival and quality of life.[73] It is the most frequent clinical liver decompensation, with a prevalence ranging between 2% and 17% in patients with FC.[52] In chronic liver disease with intrahepatic portal hypertension, ascites appear when the HVPG is $\geq$ 10 mmHg, a level that also has prognostic value.[48] However, in FALD, the HVPG is usually normal and ascites can occur in the absence of liver cirrhosis, which is why its value as a prognostic marker and its physiopathological mechanisms do not overlap those of other liver diseases.[28,74] Because there are several causes of ascites in patients with FC (Table 6), appropriate differential diagnosis is essential.[74] Regardless, to a greater or lesser extent, it is always accompanied by liver damage and is its most evident clinical marker.

Ascites is usually treatable by optimizing cardiac function and nutrition and by using loop diuretics and aldosterone antagonists

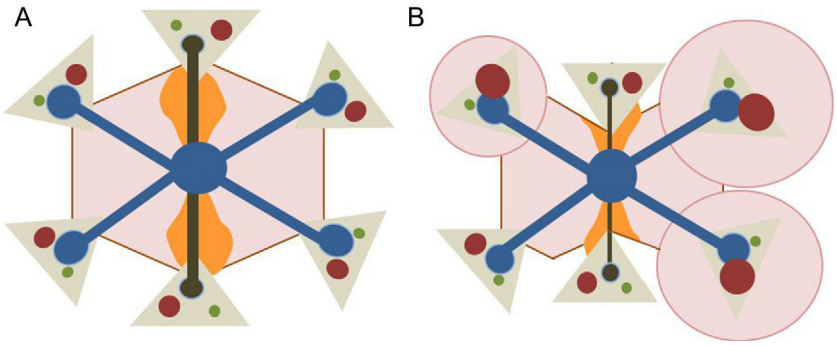


Figure 6. Nodular regenerative hyperplasia in Fontan-associated liver disease. A: Liver congestion and decreased cardiac output decrease the portal blood flow in the more peripheral regions of the liver and cause focal ischemia. B: Extinction of the parenchyma secondary to ischemia triggers an arterial vasodilatory response that stimulates the proliferation of healthy hepatocytes in the form of nodular regenerative hyperplasia.

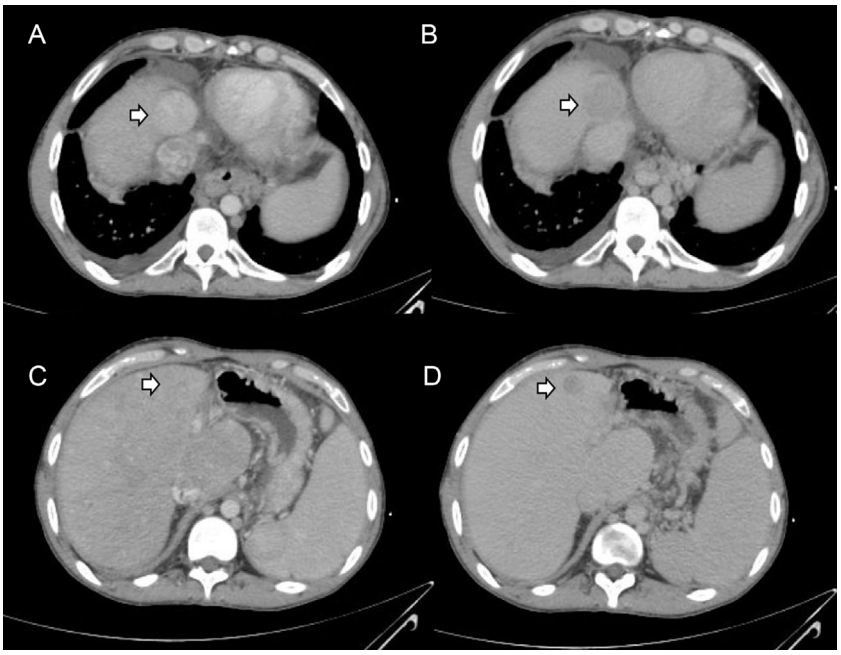


Figure 7. Radiological diagnosis of hepatocellular carcinoma. These 4 images are from the same patient with Fontan surgery who had 2 focal lesions; biopsies were taken. A: Hepatocellular carcinoma showing hyperdensity in the arterial phase. B: Hepatocellular carcinoma showing hypodensity in the delayed phase. C: Benign peripheral nodule without arterial hyperdensity. D: Benign peripheral nodule with clearance in the venous phase.

because the renin-angiotensin-aldosterone system is increased in patients with portal hypertension and heart failure.[48,75] Repeated paracentesis is a rescue option, although no FALD series have shown it to be necessary.

Hepatic Encephalopathy

Hepatic encephalopathy is defined as a brain dysfunction secondary to liver failure and/or portosystemic shunts. It manifests as a broad spectrum of neurological and psychiatric disorders ranging from subclinical changes to coma. An estimated 30% to 40% of patients with cirrhosis will show this clinical profile at some point in clinical course,[76] although it is a poorly documented event in FALD. Only 3 cases have been published[25,30,77]; nonetheless, its incidence and prevalence are probably underestimated by the retrospective nature of the work and by the low possibility that hepatic encephalopathy is considered in the differential diagnosis.

Liver Transplantation

Liver transplantation is the treatment of choice for decompensated cirrhosis with a MELD score > 15 and in certain patients with hepatocellular carcinoma. In the 20th century, cirrhosis was considered an irreversible illness; however, numerous studies of viral and alcoholic cirrhosis show that the fibrosis can be partially or even completely reversed by elimination of the toxic agent causing the liver damage.[78,79] Regarding cirrhosis of cardiac origin,

Table 6
Causes of Ascites in Patients With the Fontan Circulation

Systemic venous hypertension due to Fontan circulation failure (arrhythmias, conduit thrombosis/stenosis, ventricular dysfunction, pulmonary hypertension)
Portal hypertension of posthepatic origin
Sinusoidal portal hypertension (advanced liver fibrosis)
Hypoalbuminemia/hypoproteinemia secondary to protein-losing enteropathy

Table 7
Liver Follow-up Recommendations After Fontan Surgery From the *Hospital Universitario Ramón y Cajal*

Diagnosis of FALD		
0-10 years after surgery	HAV serology (IgG) and HBV and HCV ELISA[a] and screening for metabolic and autoimmune liver diseases	Baseline
	Liver function parameters	Annual
	Abdominal Doppler ultrasound	Every 5 years
	Transient elastography	Every 5 years
≥ 10 years after surgery or "Fontan failure" data	Liver function parameters	Every 6 months
	Alpha-fetoprotein	Every 6 months
	Abdominal Doppler ultrasound	Every 6 months
	Transient elastography	Baseline and annual
	MRI/CT	Baseline
Liver biopsy	In patients with an unclear diagnosis and in candidates for liver and/or heart transplantation	
Hepatocellular carcinoma screening and diagnosis		
Abdominal ultrasound	Every 6 months after the 10th year[b]	
Abdominal MRI/CT	≥ 10 years after surgery (baseline)	
	If there is evidence of benign nodules in the baseline test (multiple and peripheral nodules, increased uptake in the arterial phase, without clearance in the venous phase or late, normal AFP), repeat scan in 3 months. If there are no data suggesting hepatocellular carcinoma, continue with 6-monthly ultrasound screenings	
	In the presence of 1 or more new nodules on ultrasound	
	Liver MRI is recommended each time cardiac MRI is performed	
Biopsy/nodule puncture	All nodules suggestive of hepatocellular carcinoma (clearance in the venous phase, nodule growth, or elevated AFP) requires histological confirmation	
Screening of esophageal varices		
Analytical, clinical, radiological, or elastographic data of FALD	Baseline upper gastrointestinal endoscopy	
	If there are no varices or they are small, monitor every 1 to 3 years	

AFP, alpha-fetoprotein; CT, computed tomography; FALD, Fontan-associated liver disease; HAV, hepatitis A virus; HBcAb, hepatitis B virus core antibody; HBsAb, hepatitis B virus surface antibody; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; MRI, magnetic resonance imaging.
[a] Perform HAV serology (IgG) and HCV and HBV ELISA (HBsAg, HBsAb, and HBcAb) in all patients with Fontan surgery. If this patient is not immunized, vaccinate against HAV and HBV and evaluate vaccine effectiveness with new serological tests. After 10 years of effective vaccination against HBV, HBsAb levels must be determined and the vaccination repeated if they are < 100 IU/L.
[b] Perform sooner in patients with "Fontan failure", thrombosis of the Fontan conduit, or transient elastography ≥ 15 kPa.

experimental models and small case series indicate that the liver disease can also improve and even return to normal if heart function is restored.[74,80,81] Because the severity of the heart disease is directly related to the amount of liver damage and that this is universal to a greater or lesser degree, the main unknown is which subgroups of patients require a heart transplantation alone or a double transplantation.

The 2 most significant studies to analyze this issue were retrospective, had a small sample size, and suffered from methodological limitations.[82,83] They stressed the good prognosis of heart transplantation in compensated cirrhosis and of double transplantation but did not include patients with decompensated liver disease. Regardless, the results of both studies open an interesting debate on whether double transplantation should be considered for patients with suspected advanced liver disease before the decompensation or whether it should be reserved for those with complications. From our perspective, double transplantation in patients with compensated liver disease is too aggressive, because the severity of the liver damage in these patients is probably insufficient to justify the liver transplantation, particularly given the current shortage of organs, the surgical morbidity involved, and the potential improvement in liver function after heart transplantation alone. In addition, no study has shown that compensated liver disease is a perioperative risk factor or an indicator of poor long-term prognosis after heart transplantation. There is currently no consensus on when to perform a double transplantation. The most experienced institutions in this field recommend an individual analysis of each patient in a multidisciplinary committee.

CONCLUSIONS

All patients with FC develop chronic liver disease. Although its natural history is poorly understood and depends on the course of the heart disease, the presence of liver disease should be systematically investigated 10 years after the surgery. In recent years, due to the reported cases of hepatocellular carcinoma, interest has grown in FALD. Its peculiar pathophysiology and clinical behavior make FALD a unique type of liver disease requiring a specific approach that must involve a hepatologist. In our experience, these patients must undergo a periodic liver follow-up (Table 7). Because many questions remain to be answered about the pathophysiology and management of FALD, the creation is required of multicenter research groups that can accumulate sufficient scientific evidence to establish the optimal follow-up of these patients.

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CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Gewillig M, Brown SC. The Fontan circulation after 45 years: update in physiology. *Heart.* 2016;102:1081–1086.
2. Quinton E, Nightingale P, Hudsmith L, et al. Prevalence of atrial tachyarrhythmia in adults after Fontan operation. *Heart.* 2015;101:1672–1677.
3. Balaji S, Gewillig M, Bull C, De Leval MR, Deanfield JE. Arrhythmias after the Fontan procedure. Comparison of total cavopulmonary connection and atriopulmonary connection. *Circulation.* 1991;84:III162–III167.
4. Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax.* 1971;26:240–248.
5. Downing TE, Allen KY, Glatz AC, et al. Long-term survival after the Fontan operation: Twenty years of experience at a single center. *J Thorac Cardiovasc Surg.* 2017;154:243–25300.
6. Pundi KN, Johnson JN, Dearani JA, et al. 40-year follow-up after the Fontan operation: long-term outcomes of 1,052 patients. *J Am Coll Cardiol.* 2015;66:1700–1710.
7. Ohuchi H. Adult patients with Fontan circulation: What we know and how to manage adults with Fontan circulation? *J Cardiol.* 2016;68:181–189.
8. Menon S, Chennapragada M, Ugaki S, Sholler GF, Ayer J, Winlaw DS. The lymphatic circulation in adaptations to the Fontan circulation. *Pediatr Cardiol.* 2017;38:886–892.
9. Ostrow AM, Freeze H, Rychik J. Protein-losing enteropathy after Fontan operation: investigations into possible pathophysiologic mechanisms. *Ann Thorac Surg.* 2006;82:695–700.
10. Heinemann M, Breuer J, Steger V, Steil E, Sieverding L, Ziemer G. Incidence and impact of systemic venous collateral development after Glenn and Fontan procedures. *Thorac Cardiovasc Surg.* 2001;49:172–178.
11. Anne P, Du W, Mattoo TK, Zilberman MV. Nephropathy in patients after Fontan palliation. *Int J Cardiol.* 2009;132:244–247.
12. Egbe AC, Connolly HM, Khan AR, et al. Outcomes in adult Fontan patients with atrial tachyarrhythmias. *Am Heart J.* 2017;186:12–20.
13. Fernández-Iglesias A, Gracia-Sancho J. How to face chronic liver disease: the sinusoidal perspective. *Front Med.* 2017;4:7.
14. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet.* 2014;383:1749–1761.
15. Asrani SK, Asrani NS, Freese DK, et al. Congenital heart disease and the liver. *Hepatology.* 2012;56:1160–1169.
16. Greuter T, Shah VH. Hepatic sinusoids in liver injury, inflammation, and fibrosis: new pathophysiological insights. *J Gastroenterol.* 2016;51:511–519.
17. Tomkiewicz-Pajak L, Hoffman P, Trojnarska O, Lipczyńska M, Podolec P, Undas A. Abnormalities in blood coagulation, fibrinolysis, and platelet activation in adult patients after the Fontan procedure. *J Thorac Cardiovasc Surg.* 2014;147:1284–1290.
18. Simonetto DA, Yang H, Yin M, et al. Chronic passive venous congestion drives hepatic fibrogenesis via sinusoidal thrombosis and mechanical forces. *Hepatology.* 2015;61:648–659.
19. Sung PS, Yoon SK. Amiodarone hepatotoxicity. *Hepatology.* 2012;55:325–326.
20. Wang A, Book WM, McConnell M, Lyle T, Rodby K, Mahle WT. Prevalence of hepatitis C infection in adult patients who underwent congenital heart surgery prior to screening in 1992. *Am J Cardiol.* 2007;100:1307–1309.
21. Schwartz MC, Sullivan L, Cohen MS, et al. Hepatic pathology may develop before the Fontan operation in children with functional single ventricle: an autopsy study. *J Thorac Cardiovasc Surg.* 2012;143:904–909.
22. Johnson JA, Cetta F, Graham RP, et al. Identifying predictors of hepatic disease in patients after the Fontan operation: a postmortem analysis. *J Thorac Cardiovasc Surg.* 2013;146:140–145.
23. Wu FM, Jonas MM, Opotowsky AR, et al. Portal and centrilobular hepatic fibrosis in Fontan circulation and clinical outcomes. *J Heart Lung Transplant.* 2015;34:883–891.
24. Dichtl W, Vogel W, Dunst KM, et al. Cardiac hepatopathy before and after heart transplantation. *Transpl Int.* 2005;18:697–702.
25. Rychik J, Veldtman G, Rand E, et al. The precarious state of the liver after a Fontan operation: summary of a multidisciplinary symposium. *Pediatr Cardiol.* 2012;33:1001–1012.
26. Camposilvan S, Milanesi O, Stellin G, Pettenazzo A, Zancan L, D'Antiga L. Liver and cardiac function in the long term after Fontan operation. *Ann Thorac Surg.* 2008;86:177–182.
27. Mori M, Hebson C, Shioda K, et al. Catheter-measured hemodynamics of adult Fontan circulation: associations with adverse event and end-organ dysfunctions. *Congenit Heart Dis.* 2016;11:589–597.
28. Kiesewetter CH, Sheron N, Vettukattill JJ, et al. Hepatic changes in the failing Fontan circulation. *Heart.* 2007;93:579–584.
29. Baek JS, Bae EJ, Ko JS, et al. Late hepatic complications after Fontan operation; non-invasive markers of hepatic fibrosis and risk factors. *Heart.* 2010;96:1750–1755.
30. Pundi K, Pundi KN, Kamath PS, et al. Liver disease in patients after the Fontan operation. *Am J Cardiol.* 2016;117:456–460.
31. Heuman DM, Mihas AA, Habib A, et al. MELD-XI: a rational approach to "sickest first" liver transplantation in cirrhotic patients requiring anticoagulant therapy. *Liver Transpl.* 2007;13:30–37.
32. Evans WN, Acherman RJ, Ciccolo ML, et al. MELD-XI scores correlate with post-Fontan hepatic biopsy fibrosis scores. *Pediatr Cardiol.* 2016;37:1274–1277.
33. Colli A, Fraquelli M, Andreoletti M, Marino B, Zuccoli E, Conte D. Severe liver fibrosis or cirrhosis: accuracy of US for detection—analysis of 300 cases. *Radiology.* 2003;227:89–94.
34. Martin-Garre S. Liver and cardiovascular disease: what cardiologists need to know about ultrasound findings. *Rev Esp Cardiol.* 2017;70:399–401.
35. Martínez-Quintana E, Rodríguez-González F. Liver imaging in patients with Fontan circulation. *Rev Esp Cardiol.* 2017;70:517–518.
36. Berzigotti A, Ashkenazi E, Reverter E, Abraldes JG, Bosch J. Non-invasive diagnostic and prognostic evaluation of liver cirrhosis and portal hypertension. *Dis Markers.* 2011;31:129–138.
37. Giannini E, Botta F, Borro P, et al. Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis. *Gut.* 2003;52:1200–1205.
38. Bae JM, Jeon TY, Kim JS, et al. Fontan-associated liver disease: Spectrum of US findings. *Eur J Radiol.* 2016;85:850–856.
39. Kutty SS, Peng Q, Danford DA, et al. Increased hepatic stiffness as consequence of high hepatic afterload in the Fontan circulation: a vascular Doppler and elastography study. *Hepatology.* 2014;59:251–260.
40. Sandrin L, Fourquet B, Hasquenoph JM, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol.* 2003;29:1705–1713.
41. Castéra L, Foucher J, Bernard PH, et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. *Hepatology.* 2010;51:828–835.
42. Deorsola L, Aidala E, Cascarano MT, Valori A, Agnoletti G, Pace Napoleone C. Liver stiffness modifications shortly after total cavopulmonary connection. *Interact Cardiovasc Thorac Surg.* 2016;23:513–518.
43. Agnoletti G, Ferraro G, Bordese R, et al. Fontan circulation causes early, severe liver damage. Should we offer patients a tailored strategy? *Int J Cardiol.* 2016;209:60–65.
44. Chen B, Schreiber RA, Human DG, Potts JE, Guttman OR. Assessment of liver stiffness in pediatric Fontan patients using transient elastography. *Can J Gastroenterol Hepatol.* 2016;7125193. 2016.
45. Bulut OP, Romero R, Mahle WT, et al. Magnetic resonance imaging identifies unsuspected liver abnormalities in patients after the Fontan procedure. *J Pediatr.* 2013;163:201–206.
46. Poterucha JT, Johnson JN, Qureshi MY, et al. Magnetic resonance elastography: a novel technique for the detection of hepatic fibrosis and hepatocellular carcinoma after the Fontan operation. *Mayo Clin Proc.* 2015;90:882–894.
47. Bosch J, Abraldes JG, Berzigotti A, García-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. *Nat Rev Gastroenterol Hepatol.* 2009;6:573–582.
48. Bosch J, Abraldes JG, Albillos A, et al. Hipertensión portal: recomendaciones para su evaluación y tratamiento. *Gastroenterol Hepatol.* 2012;35:421–450.
49. Kendall TJ, Stedman B, Hacking N, et al. Hepatic fibrosis and cirrhosis in the Fontan circulation: a detailed morphological study. *J Clin Pathol.* 2008;61:504–508.
50. Goldberg DJ, Surrey LF, Glatz AC, et al. Hepatic fibrosis is universal following Fontan operation, and severity is associated with time from surgery: a liver biopsy and hemodynamic study. *J Am Heart Assoc.* 2017. https://doi.org/10.1161/JAHA.116.004809.
51. Ford RM, Book W, Spivey JR. Liver disease related to the heart. *Transpl Rev (Orlando).* 2015;29:33–37.
52. Wu FM, Kogon B, Earing MG, et al. Liver health in adults with Fontan circulation: A multicenter cross-sectional study. *J Thorac Cardiovasc Surg.* 2017;153:656–664.
53. Wallihan DB, Podberesky DJ. Hepatic pathology after Fontan palliation: spectrum of imaging findings. *Pediatr Radiol.* 2013;43:330–338.
54. Shimamatsu K, Wanless IR. Role of ischemia in causing apoptosis, atrophy, and nodular hyperplasia in human liver. *Hepatology.* 1997;26:343–350.
55. Ghaferi AA, Hutchins GM. Progression of liver pathology in patients undergoing the Fontan procedure: Chronic passive congestion, cardiac cirrhosis, hepatic adenoma, and hepatocellular carcinoma. *J Thorac Cardiovasc Surg.* 2005;129:1348–1352.
56. Saliba T, Dorkhom S, O'Reilly EM, Ludwig E, Gansukh B, Abou-Alfa GK. Hepatocellular carcinoma in two patients with cardiac cirrhosis. *Eur J Gastroenterol Hepatol.* 2010;22:889–891.
57. Asrani SK, Warnes CA, Kamath PS. Hepatocellular carcinoma after the Fontan procedure. *N Engl J Med.* 2013;368:1756–1757.
58. Elder RW, Parekh S, Book WM. More on hepatocellular carcinoma after the Fontan procedure. *N Engl J Med.* 2013;369:490.
59. Takuma Y, Fukada Y, Iwadou S, et al. Surgical resection for hepatocellular carcinoma with cardiac cirrhosis after the Fontan procedure. *Intern Med.* 2016;55:3265–3272.
60. Rajoriya N, Clift P, Thorne S, Hirschfield GM, Ferguson JW. A liver mass post-Fontan operation. *QJM.* 2014;107:571–572.
61. Weyker PD, Allen-John Webb C, Emond JC, Brentjens TE, Johnston TA. Anesthetic implications of extended right hepatectomy in a patient with fontan physiology. *A A Case Rep.* 2014;2:99–101.
62. Kwon S, Scovel L, Yeh M, et al. Surgical management of hepatocellular carcinoma after Fontan procedure. *J Gastrointest Oncol.* 2015;6:E55–E60.
63. Yamada K, Shinmoto H, Kawamura Y, et al. Transarterial embolization for pediatric hepatocellular carcinoma with cardiac cirrhosis. *Pediatr Int.* 2015;57:766–770.
64. Oh C, Youn JK, Han JW, Kim GB, Kim HY, Jung SE. Hepatocellular carcinoma after the Fontan procedure in a 16-year-old girl: A case report. *Medicine (Baltimore).* 2016;95:e4823.
65. Conroy MR, Moe TG. Hepatocellular carcinoma in the adult Fontan patient. *Cardiol Young.* 2017;27:407–409.
66. Josephus Jitta D, Wagenaar LJ, Mulder BJM, Guichelaar M, Bouman D, Van Melle JP. Three cases of hepatocellular carcinoma in Fontan patients: Review of the literature and suggestions for hepatic screening. *Int J Cardiol.* 2016;206:21–26.
67. Martínez-Quintana E, Monescillo A, Rodríguez-González F. Hepatocellular carcinoma in a non-failing Fontan circulation. *Rev Esp Enferm Dig.* 2017;109:375.
68. Forner A, Reig M, Varela M, et al. Diagnosis and treatment of hepatocellular carcinoma. Update consensus document from the AEEH, SEOM, SERAM, SERVEI and SETH. *Med Clin (Barc).* 2016;146:511.e1–511.e22.

69. Nandwana SB, Olaiya B, Cox K, Sahu A, Mittal P. Abdominal imaging surveillance in adult patients after Fontan procedure: risk of chronic liver disease and hepatocellular carcinoma. *Curr Probl Diagn Radiol.* 2017. http://dx.doi.org/10.1067/j.cpradiol.2017.04.002.
70. Elder RW, McCabe NM, Hebson C, et al. Features of portal hypertension are associated with major adverse events in Fontan patients: the VAST study. *Int J Cardiol.* 2013;168:3764–3769.
71. De Franchis R, Baveno VI, Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol.* 2015;63:743–752.
72. Velpula M, Sheron N, Guha N, Salmon T, Hacking N, Veldtman GR. Direct measurement of porto-systemic gradient in a failing Fontan circulation. *Congenit Heart Dis.* 2011;6:175–178.
73. Pericleous M, Sarnowski A, Moore A, Fijten R, Zaman M. The clinical management of abdominal ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: a review of current guidelines and recommendations. *Eur J Gastroenterol Hepatol.* 2016;28:e10–e18.
74. Myers RP, Cerini R, Sayegh R, et al. Cardiac hepatopathy: Clinical, hemodynamic, and histologic characteristics and correlations. *Hepatology.* 2003;37:393–400.
75. Hilscher MB, Johnson JN, Cetta F, et al. Surveillance for liver complications after the Fontan procedure. *Congenit Heart Dis.* 2017;12:124–132.
76. American Association for the Study of Liver Diseases, European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. *J Hepatol.* 2014;61:642–659.
77. Koteda Y, Suda K, Kishimoto S, Iemura M. Portal-systemic encephalopathy after Fontan-type operation in patient with polysplenia syndrome. *Eur J Cardiothorac Surg.* 2009;35:1083–1085.
78. Zoubek ME, Trautwein C, Strnad P. Reversal of liver fibrosis: From fiction to reality. *Best Pract Res Clin Gastroenterol.* 2017;31:129–141.
79. Ellis EL, Mann DA. Clinical evidence for the regression of liver fibrosis. *J Hepatol.* 2012;56:1171–1180.
80. Dichtl W, Vogel W, Dunst KM, et al. Cardiac hepatopathy before and after heart transplantation. *Transpl Int.* 2005;18:697–702.
81. Crespo-Leiro MG, Robles O, Paniagua MJ, et al. Reversal of cardiac cirrhosis following orthotopic heart transplantation. *Am J Transplant.* 2008;8:1336–1339.
82. D'Souza BA, Fuller S, Gleason LP, et al. Single-center outcomes of combined heart and liver transplantation in the failing Fontan. *Clin Transplant.* 2017. http://dx.doi.org/10.1111/ctr.12892.
83. Simpson KE, Esmaeeli A, Khanna G, et al. Liver cirrhosis in Fontan patients does not affect 1-year post-heart transplant mortality or markers of liver function. *J Heart Lung Transplant.* 2014;33:170–177.