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Review

Fontan-associated liver disease: A review

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ABSTRACT

The Fontan procedure has led to increased long-term survival of patients with single ventricle congenital heart disease. Hemodynamic changes associated with the Fontan circulation, including elevated central venous pressure and diminished cardiac output are responsible for the development of Fontan-associated liver disease (FALD). Liver fibrosis is a universal feature following the Fontan operation. The incidence of both liver cirrhosis and hepatocellular carcinoma (HCC) increases with the duration of the Fontan circulation. The staging of liver fibrosis in FALD requires a multi-modality approach involving clinical assessment, biochemical/hematological parameters, non-invasive fibrosis scores, radiological imaging, elastography, and liver histology. Patients with a failing Fontan circulation who have evidence of significant hepatic congestion require careful hemodynamic assessment to optimize the Fontan pathway and physiology. This may necessitate percutaneous or surgical intervention, or heart transplantation. Combined heart-liver transplantation may be required in patients with clinical, imaging, or biopsy evidence of advanced liver cirrhosis, particularly if there is evidence of hepatic decompensation or localized HCC. Patients with suspected liver cirrhosis should be enrolled into HCC surveillance and require endoscopic variceal assessment. There is a clear need to establish local/national registries for Fontan patients with standardized guidelines for the management of FALD, bringing together the expertise of professional bodies representing both cardiologists and hepatologists.

Contents

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Introduction

The Fontan procedure: a historical perspective

The Fontan procedure is a palliative operation for patients with single ventricle congenital heart disease (CHD). The operation directs the systemic venous return into the pulmonary circulation, achieving passive filling of the pulmonary circulation without ventricular propulsion (Fig. 1). This arrangement abolishes intra-cardiac mixing and raises arterial saturations while reducing volume overload on the single ventricle. The procedure results in obligatorily elevated central venous pressure (CVP). There is a reduction in cardiac output due to limited pre-load filling of the systemic ventricle in the absence of a pulmonary pump.

Patients receiving Fontan palliation represent a growing population that now survives deep into adulthood. In 2010, in the USA, it was estimated that 300,000 people had severe CHD [1]. Their median age increased from 17 years in 2000 to 25 years in 2010 [2,3]. This reflects better survival after the Fontan procedure with 15- and 20-year transplant-free survival in early survivors of 87% and 83%, respectively [4,5]. This longer survival has heralded not only late cardiac, but also, importantly long-term extra-cardiac complications. Between 2001 and 2011, there were an estimated 8330 hospital admissions in the USA for individuals with single-ventricle physiology [6]. Long-term complications include cardiac arrhythmias, valvular insufficiency, heart failure particularly diastolic heart failure, plastic bronchitis, and pulmonary thromboembolic disease. Chronic elevation of CVP has an impact on a range of organ systems resulting in peripheral venous insufficiency, protein-losing enteropathy, and Fontan-associated liver disease (FALD).

Fontan-associated liver disease: pathophysiology

The effect of Fontan physiology on the dual blood supply of the liver is responsible for at least part of the injury pattern seen in FALD. In the Fontan circulation, the hepatic veins discharge directly into the Fontan circuit and the liver is therefore particularly susceptible to the effects of central venous hypertension. High CVP is transmitted into the hepatic sinusoids, which may further reduce portal vein in-flow. The hepatic artery demonstrates autoregulation and can in normal circumstances compensate for a significant reduction (30–60%) in portal venous flow. In contrast, there is no mechanism for autoregulation of portal blood flow, which depends on mesenteric blood flow and the pressure gradient between the portal and hepatic veins. It is unable to compensate for diminished hepatic blood flow due to impaired cardiac output. Although hemodynamic data are limited, it is expected that in the Fontan circulation portal vein flow and portal vein oxygen saturations are reduced, with the liver increasingly reliant on the diminished buffering capacity of the hepatic arterial supply. As a result, the liver will be increasingly vulnerable to hemodynamic insults consequent on impaired cardiac output. Although not a universal finding, cardiac output is usually reduced following the Fontan procedure. In addition, exercise is associated with further increases in CVP and reduced oxygen delivery [7]. There is evidence that central venous hypertension renders the liver more vulnerable to ischemic injury [8,9]. Ischemic hepatitis occurs when a patient with chronic passive congestion of the liver develops systemic hypotension resulting in hepatic infarction. This is characterized histologically by centrilobular necrosis around branches of the hepatic veins.

Liver fibrosis/cirrhosis develops in response to either chronic or repeated liver injury. In FALD, the liver is exposed to chronic and repeated hepatic insults from the time of birth. Liver damage may occur prior to the formation of the Fontan circulation [10,11]. The effect of an abnormal fetal circulation, and of cyanosis on the liver remains unclear. Staged cardiac interventions may provide additional hemodynamic insults. Immediately following the Fontan procedure, the liver is exposed to elevated CVP and diminished cardiac output. Post-mortem studies show that histological abnormalities, including sinusoidal (65–91%) and portal (30–57%) fibrosis are present in the majority of patients dying early post-operatively (20–35 days) [11,12]. In the post-operative period, chronic venous hypertension may promote liver fibrosis. Possible mechanisms include vascular shear stress and increased parenchymal stiffness, which may directly promote hepatic myofibroblast activation (Fig. 2) [13–15].

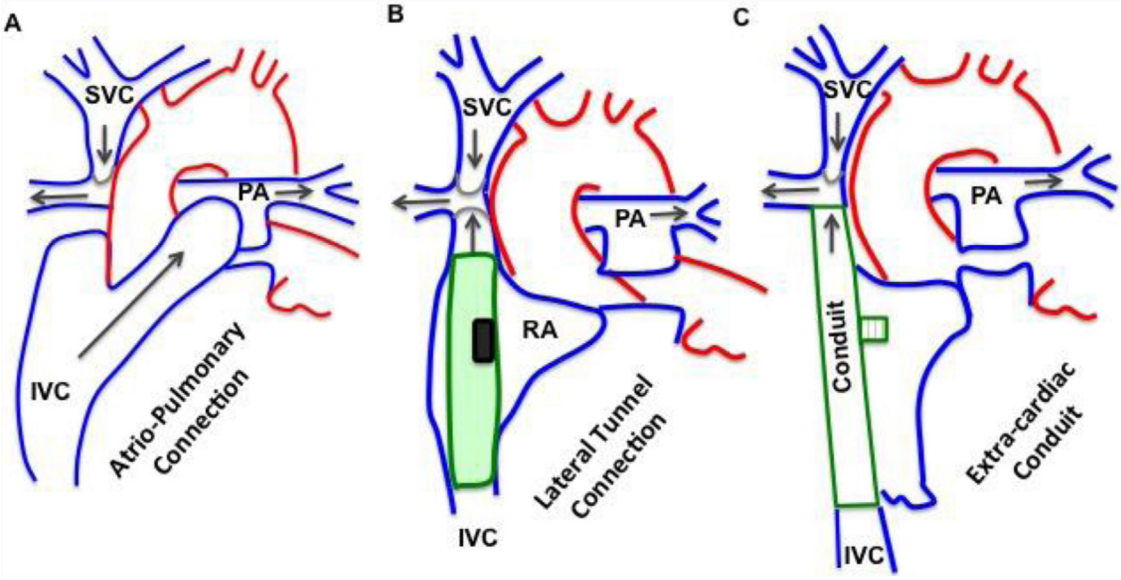

Fig. 1. Diagram illustrating the Fontan circulation. (A) Atrio-pulmonary connection: the superior vena cava (SVC) is connected to the right pulmonary artery (PA). The right atrium (RA) is connected to the left PA, diverting blood from the inferior vena cava (IVC). (B) Lateral tunnel correction: the SVC is attached to the right PA. The IVC is attached to the SVC by a tunnel (baffle) inside the RA. (C) Extra-cardiac conduit repair: the SVC is attached directly to the PA and the IVC is connected to the PA via a Gore-tex™ conduit. In both the lateral tunnel and extra-cardiac tunnel operations a fenestration allows blood flow between the lateral tunnel/conduit and the RA.

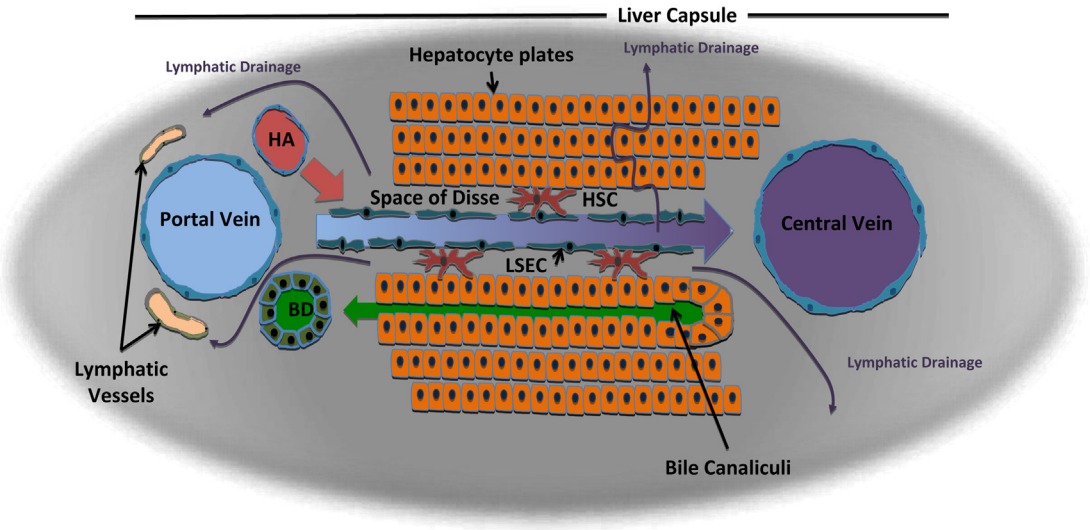

Fig. 2. Putative pathophysiological mechanisms promoting liver injury and fibrosis in Fontan-associated liver disease. The diagram illustrates the microanatomy of the liver. Formation of the Fontan circulation results in obligatory high central venous pressure leading to chronic passive congestion centered on branches of the portal vein and impaired lymphatic drainage. Resulting sinusoidal dilatation with increased vascular shear stress and matrix stiffness may promote liver fibrogenesis through effects on liver sinusoidal endothelial cells (LSECs) and hepatic stellate cells (HSCs). Reduced cardiac output with intermittent hypoxic and hypotensive insults results in centrilobular ischemia that may further promote hepatic fibrosis.
BD, bile duct; HA, hepatic artery.

Liver histology is abnormal in the majority of patients following the Fontan procedure [16–21]. Kendall et al. demonstrated that the histological features in the livers from Fontan patients were similar to those encountered in congestive cardiac failure (Fig. 3) [18]. Elevated CVP and impaired venous drainage results in sinusoidal dilatation. Liver fibrosis was centered on the peri-venular regions with fibrous spurs extending into the parenchyma. Peri-sinusoidal fibrosis was common. Portal fibrosis is another common feature and in one cohort was present in 87% of Fontan patients (median Fontan duration 18.1 years) [22]. When fibrosis progresses, central–central vein and central–portal vein bridging occurs, culminating in liver cirrhosis. Biopsy studies have shown that liver fibrosis is a universal feature following the Fontan operation and the severity of fibrosis is correlated with both Fontan duration and CVP [19].

Abnormal lymphatic anatomy/physiology are increasingly demonstrated in the liver and elsewhere in Fontan patients. Previous work has demonstrated increased hepatic lymphangiogenesis, lymphatic drainage, and pressure in the presence of cirrhosis [23,24]. Elevated lymphatic pressure is believed to be a key mechanism causing protein-losing enteropathy following the Fontan procedure [25]. Interestingly when the thoracic duct is tied off there is evidence of sinusoidal dilation similar to that seen in congestive cardiac failure [26]. The role of lymphatic dysregulation in the genesis of hepatic fibrosis needs further exploration.

FALD: the timescale of events

Histological studies suggest that 43% of Fontan patients have evidence of advanced liver fibrosis 30 years after the Fontan operation [27]. Cardiac cirrhosis has been described in patients as young as 10 years (4 years post-Fontan) [16]. In a study of asymptomatic patients who underwent hepatic biopsies at the time of elective cardiac catheterization, sinusoidal or portal fibrosis was present in 20/21 of biopsies [20]. The etiological basis of portal fibrosis in this context is uncertain but may be related to impaired lymphatic drainage. Liver fibrosis appears to be an inevitable feature of patients with Fontan physiology, with the degree of fibrosis on biopsy increasing with the time from Fontan [19]. Similar findings have been confirmed by imaging studies. In a retrospective study of Fontan patients receiving surveillance imaging for FALD, 90/145 patients (62%) had evidence of chronic liver disease on initial imaging (median age 27 years) [28]. Abnormalities included liver heterogeneity, portal hypertension, and cirrhosis. Similarly, a large retrospective study of Fontan patients with liver function and imaging data identified 40/195 patients who were diagnosed with cirrhosis during long-term follow-up [27]. The mean duration of Fontan operation to a diagnosis of cirrhosis was 23.4 years.

Diagnosing cirrhosis in FALD

The approach to investigating patients at risk of FALD should be the same as that used in other forms of liver disease, while recognizing the limitations of the toolbox we have available to us. Liver biopsy remains the gold standard for the quantification of liver fibrosis and diagnosis of liver cirrhosis. Percutaneous sampling provides liver cores of better quality for histological evaluation. Trans-venous biopsies provide more slender cores but are useful in coagulopathic patients and can be combined with hemodynamic measurements. Fibrotic changes may be patchy and liver biopsy frequently reveals less severe fibrosis than suggested by imaging. The routine sampling of multiple cores from different sites within the liver might improve the sensitivity of biopsy, reducing false negative rates.

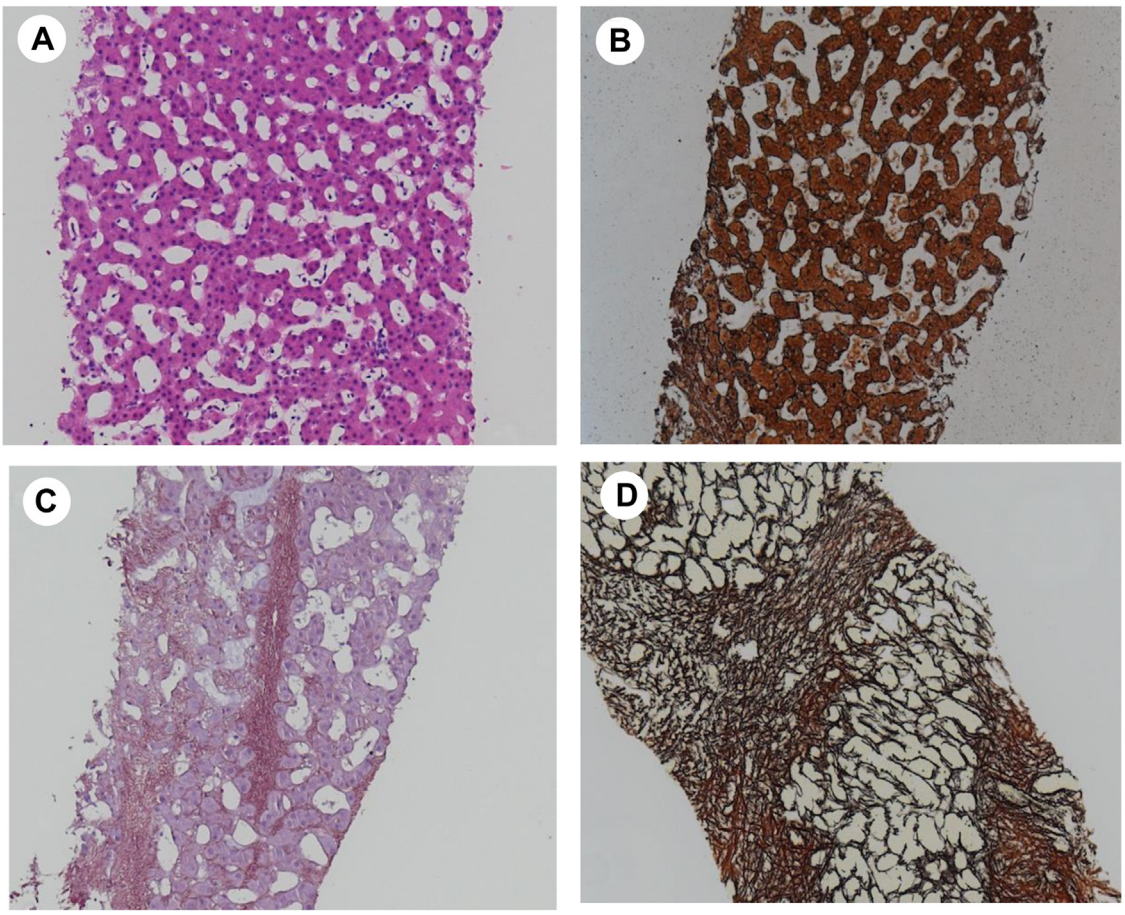

Fig. 3. Histological features of Fontan-associated liver disease. The liver parenchyma in patients with a Fontan circulation is characterized by marked sinusoidal dilatation, extending from pericentral areas toward portal tracts (A; hematoxylin and eosin, 10× objective) in the absence of lobular inflammation. The extent of scarring is variable, some patients may have minimal fibrosis despite the presence of sinusoidal dilatation (B; reticulin stain, 10× objective). With disease progression, sinusoidal dilatation is accompanied by sinusoidal fibrosis and broad scars (C; reticulin stain 10× objective and D; Shikata's orcein stain, 10× objective).
Images kindly provided by Dr. Timothy Kendall, Senior Clinical Fellow in Pathology, Division of Pathology, University of Edinburgh, Edinburgh, UK.

Clinical assessment

Clinical signs and symptoms attributable to liver cirrhosis are generally late features in FALD. Patients with compensated cirrhosis are generally asymptomatic or present with non-specific symptoms such as lethargy, anorexia, or weight loss. Decompensated liver disease is characterized by the development of complications, including jaundice, encephalopathy, ascites, and variceal hemorrhage. Physical examination may reveal features of chronic liver disease, including palmar erythema, spider naevi, dilated abdominal veins, and abdominal distension.

Laboratory findings and non-invasive markers of liver fibrosis

Standard laboratory investigations are of limited value in the staging of liver fibrosis. Chronic hepatic congestion in FALD may be associated with variable but limited elevation of liver enzymes. However, liver enzymes and clotting parameters are frequently normal, even in advanced disease. Hyperbilirubinemia will typically occur as a late feature in patients with decompensated liver cirrhosis. Thrombocytopenia is a useful surrogate marker of portal hypertension/hypersplenism and is correlated to increased portal fibrosis in FALD [20].

Composite scoring systems have been developed that demonstrate clinical utility in the diagnosis of cirrhosis across a range of chronic liver diseases. These include serum aspartate aminotransferase to alanine aminotransferase ratio (AST/ALT ratio), Fibrosis-4 score (FIB4), aspartate aminotransferase to platelet index (APRI), Forns index, and Model for End-stage Liver Disease (MELD) score. Most of these scores have not been validated in FALD and diagnostic "cut-offs" predictive of cirrhosis in FALD have not been determined. Baek et al. investigated non-invasive fibrosis scores in a population of 138 patients Fontan patients [29]. The mean age of participants was 19 ± 6.3 years and mean time since the initial Fontan operation was 11.5 ± 4.7 years. Subjects were divided into those with or without hepatic complications. Hepatic complications were present in 41% of patients, including nodular liver surface (35.8%), hepatic nodules (2.9%), hyperbilirubinemia (20.9%), and thrombocytopenia (7.2%). Non-invasive scores showed significant abnormalities in patients with hepatic complications. In this study Forns index was the best predictor of cardiac hepatopathy, with receiver-operator-curves (ROC) value of 0.781.

MELD-XI is a composite score related to Model for End-stage Liver disease (MELD) that excludes coagulation parameters [30]. Evans et al. undertook a study of 70 stable Fontan patients who underwent trans-venous hepatic biopsy at the time of cardiac catheterization [31]. There was a statistically significant correlation between fibrosis score and MELD-XI score (correlation coefficient 0.4, $p = 0.003$). However, ROC analysis did not identify a specific cut-off score of sufficient sensitivity or specificity. The VAST (Varices, Ascites, Splenomegaly, and Ascites) score in which 1 point is bestowed for each of the aforementioned features of portal hypertension has been applied to FALD [32]. In a cohort of

73 adult and pediatric Fontan patients, a VAST score ≥2 was associated with a significantly increased incidence of major adverse events, including death (12), cardiac transplantation (6), and hepatocellular cancer (1).

Radiological imaging

Early radiological features of FALD include hepatic congestion with hepatic vein enlargement and sinusoidal dilatation. Progressive liver fibrosis is associated with coarsening of the liver parenchyma, surface irregularity, hypervascular regenerative nodules, left lobe hypertrophy, and gross cirrhosis [33]. Features such as splenomegaly, abdominal varices, and ascites are suggestive of portal hypertension. Ultrasound (US) is a valuable screening tool in identifying features of FALD and may be useful in identifying progression of FALD before biochemical hepatic dysfunction (Fig. 4). In one cohort (mean age 13.3 years) US findings such as heterogeneous echo-texture and nodular surface irregularity were present in two-thirds of patients [34]. In contrast to other chronic liver diseases where surface irregularity is highly specific for advanced liver fibrosis/cirrhosis a nodular liver surface is a common/non-specific feature in FALD [35].

Both computed tomography (CT) and magnetic resonance imaging (MRI) are helpful in delineating liver injury/scarring in FALD (Fig. 4) and are better able to detect liver masses and detailed liver architecture than US. Heterogeneous hepatic enhancement, with mosaic or reticular patterns on contrast-enhanced imaging is a frequent finding in FALD [36,37]. It arises due to relatively slow enhancement around congested hepatic veins and is associated with increased liver fibrosis [17,38]. In contrast, zonal enhancement (differential enhancement of the liver peripheries and central hilar zone) is associated with a lower incidence of cirrhosis [17]. Arterially-enhancing nodules, if present, may represent either areas of focal nodular hyperplasia (FNH) or hepatocellular carcinoma (HCC). On MRI, there are areas of increased T2-weighted and diffusion-weighted signal with reduced T1-weighted signal intensity in the periphery of the liver, corresponding to areas of abnormal contrast enhancement [37]. MRI with diffusion-weighted imaging may be helpful in evaluating liver fibrosis, with low apparent diffusion co-efficients suggestive of progressive liver damage due to hepatic congestion [39].

Elastography is widely used in chronic liver disease to measure liver stiffness, a surrogate of liver fibrosis. The clinical utility of single elastography measurements in FALD is limited due to difficulties in determining the relative contributions of hepatic congestion and fibrosis. Serial changes in liver stiffness may be more helpful. Using magnetic resonance elastography (MRE) it has been shown that liver stiffness is significantly increased post-Fontan [40–43]. CVP is an independent predictor of liver stiffness while liver stiffness is inversely correlated to cardiac index [40–42,44]. Using ultrasound elastography (FibroScan™, Echo-Sens, Paris, France) it has been shown that liver stiffness increases rapidly in the 5-year period after Fontan before stabilizing [43]. In patients with Fontan duration >10 years there was a linear correlation between liver stiffness and MELD-XI score. In a separate study, liver stiffness values measured with FibroScan were positively correlated with age and FibroTest™ (Biopredictive S.A.S, Paris, France) scores (serum fibrosis marker) [45]. Poterucha et al. reported a small study of Fontan patients in which they demonstrated a positive correlation between MRE values and histological liver fibrosis score [42].

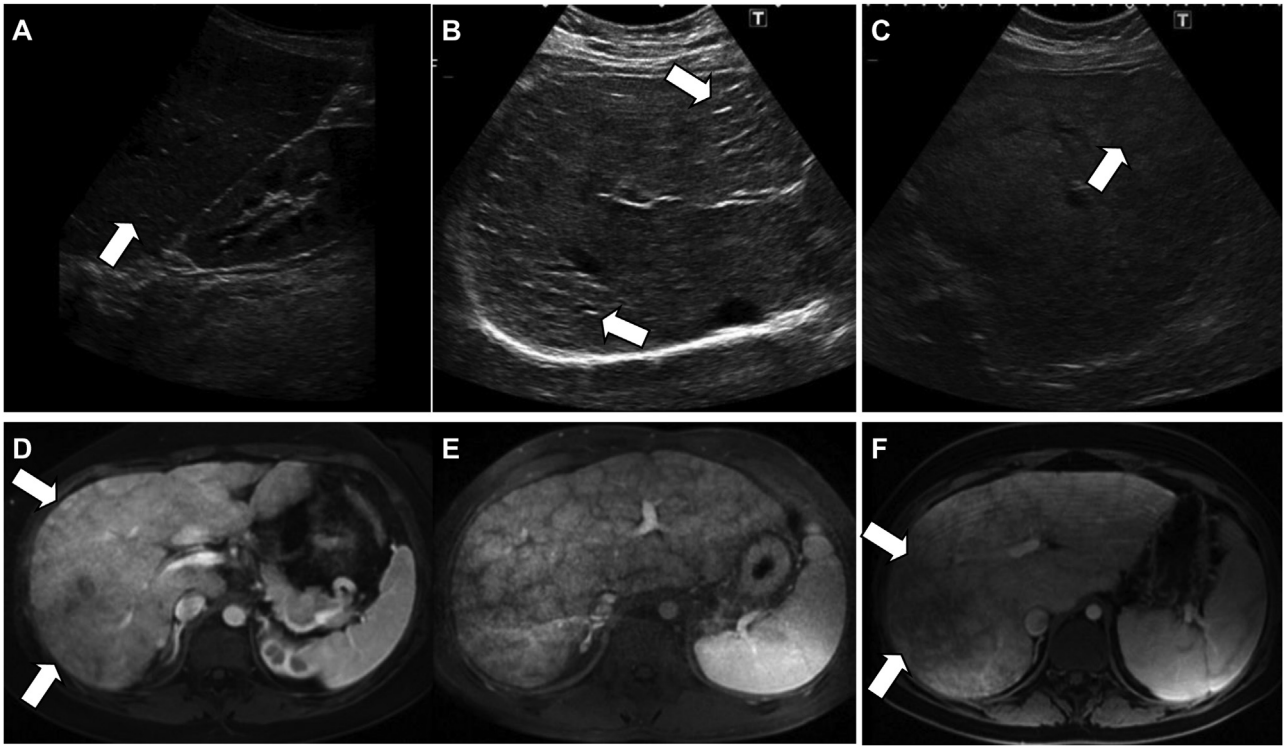

Fig. 4. Radiological imaging tracks the progression of liver fibrosis in Fontan-associated liver disease (FALD). Ultrasound shows variable echo-texture in Fontan patients. (A) Ultrasound image of a 5-year-old female with extra-cardiac Fontan showing normal echo-texture. (B) Image of liver from a 16-year-old male, 14 years following an extra-cardiac Fontan with very coarse echo-texture and patchy areas of focally increased echogenicity. (C) Ultrasound image from a 28-year-old female, 24 years after lateral tunnel Fontan with diffusely increased liver echo-texture with nodularity and irregular liver contour, suggestive of liver cirrhosis. Abnormal liver enhancement in FALD. (D) Portal venous phase contrast magnetic resonance image shows relatively mild peripheral reticular enhancement (arrows). (E) Diffuse peripheral and central reticular enhancement pattern is seen in more advanced congestive hepatopathy. (E) Increased congestion with fibrosis is suggested by severe enhancement abnormalities with larger areas of focally diminished enhancement in the right lobe (arrows).

Portal hypertension

In FALD, the development of features of portal hypertension is associated with major adverse events [32]. Hemodynamic studies can be used to assess portal hypertension, although their utility in routine clinical practice is questionable. Hepatic venous pressure gradient (HVPG) is the difference between wedged hepatic vein pressure (portal vein pressure) and free hepatic vein pressure. It reflects the intrahepatic contribution to portal hypertension [46,47]. In patients with Fontan physiology, it can be difficult to assess true hepatic vein wedge pressures because of the existence of intra-hepatic macro or micro veno-venous collateralization. Therefore rarely are transhepatic gradients of >2–3 mmHg demonstrated. The delineation and characterization of varices also needs careful scrutiny because of the frequent occurrence of veno-venous collateralization from the systemic veins to the pulmonary venous circuit, without truly being driven by a significant transhepatic pressure gradient. Similarly the presence of ascites may indicate lymphatic overflow and decompressing collaterals to the peritoneal cavity. The assessment of portal hypertension needs to be done with a meticulous integration of resting and exercise hemodynamics and an awareness of particular lymphatic circulation characteristics of the patient. Typically, without cirrhosis, both the free and wedged hepatic venous pressures are increased but HVPG should be ≤5 mmHg. Elevated HVPG (>5 mmHg) is suggestive of parenchymal liver disease. Complications of portal hypertension including ascites and variceal hemorrhage are more likely once HVPG is >10 mmHg [48]. There is a general consensus that severe portal hypertension is uncommon in FALD, but in the absence of direct puncture of the portal vein, there is a paucity of data to support this assumption. In a single case report Velpula et al. demonstrated a pressure gradient of 10 mmHg in a post-operative Fontan revision patient who bled from an esophageal varix [49]. A study of patients with chronic decompensated cardiac failure reported that while free and wedged hepatic vein pressure were frequently elevated, HVPG was typically normal [50]. However, extrapolation of these data to FALD (a protracted form of congestive hepatopathy) is flawed. Clinical features of portal hypertension are well described in FALD and confer poor outcome [32].

Hepatocellular carcinoma

Cirrhosis is the single most important risk factor for the development of HCC [51]. All etiological forms of cirrhosis are associated with an increased HCC incidence. HCC is now recognized as an uncommon complication of FALD. Evidence has come from an increasing number of case series/reports of HCC complicating cirrhosis in FALD [16,52–57]. HCC complicating FALD-associated cirrhosis has been described in patients as young as 16 years [55]. Without large-scale longitudinal studies, the natural history and risk factors for HCC development in FALD remain poorly characterized. Longitudinal studies in cirrhotic patients of diverse etiology suggest an annual risk of HCC development of 1–8% [58]. On this basis the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) guidelines recommend that cirrhotic patients should be enrolled into HCC surveillance with 6-monthly abdominal US [51,59]. Radiological surveillance may be supplemented with measurement of alfa-feto protein (AFP). There is evidence that the annual risk of HCC in FALD-associated cirrhosis is comparable to that in cirrhosis of other etiology. On the basis of previous studies it has been estimated that the annual risk of HCC in cirrhotic FALD patients is 1.5–5% [52]. In a retrospective study of 145 patients receiving surveillance liver imaging following a Fontan procedure (median follow-up 3 years), HCC was identified in 5 patients (3.4%). In this cohort HCC developed at a median of 22 years post-Fontan (IQR 10–29) [28]. In our own series (unpublished data), we estimated the prevalence to be around 1.5%. This is likely to be an underestimate as only histologically proven cases were included.

There are significant caveats associated with extension of standard adult HCC surveillance protocols to FALD. The diagnosis of HCC is predominantly based on imaging criteria of arterially-enhancing lesions that demonstrate washout on portal venous and delayed-phase images [51]. Biopsy is reserved for diagnosis of indeterminate lesions. Patients with CHD have an increased incidence of vascular anomalies and hyperenhancing nodules that may mimic HCC (Fig. 5). As a result standard triple-phase cross-sectional imaging will be associated with increased false-positive rates. The reverse is also true, as the arterial enhancement of HCC may be obscured in the presence of cardiac failure and intrahepatic vascular shunts [52]. There are other practical difficulties. The high frequency of pacemakers in this group limits the utility of MRI. There is an increased risk of bleeding following liver biopsy due to elevated CVP and the increased use of oral anticoagulants in this population. There is also a small but appreciable risk of biopsy tract seeding in association with biopsy of tumor nodules (2.7%) [60].

There is limited evidence as to the optimum treatment strategy for HCC complicating FALD. Surgical resection will be limited by underlying cirrhosis and cardiac failure, although has been described [61]. Liver transplantation might theoretically be considered in patients with early stage HCC but in reality, will be constrained by the associated circulatory characteristics of the Fontan and SV physiology. Therefore, in reality heart-liver transplantation may be the only realistic option. There is however only limited experience of combined heart-liver transplantation in FALD [62–64]. The early mortality is greater than with heart or liver transplantation alone but in the longer term cardiac graft rejection appears significantly lower than with heart transplant only [65]. Loco-regional treatment with radiofrequency ablation (RFA) may potentially be curative in patients with early stage disease. Both RFA and transarterial chemo-embolization (TACE) may be effective in palliation but may be limited by the presence of pacemakers (RFA) and abnormal vasculature (TACE).

Identifying FALD: recommended surveillance

It is important that Fontan patients are screened for FALD. Although consensus guidelines for FALD surveillance do not currently exist, the American College of Cardiology has published a report that seeks to provide a platform for future guideline development [2]. The aim of surveillance should be to diagnose FALD at a sufficiently early stage that interventions can be considered to optimize the Fontan circulation and so prevent/slow progression to advanced cirrhosis (Table 1). Patients that develop cirrhosis should be identified promptly and enrolled into HCC surveillance/variceal assessment. Given the wide spectrum of disease severity, to some extent screening for FALD should be individualized. The severity of liver fibrosis is related both to the elevation of CVP and duration post-Fontan [2]. Older patients and those with higher CVP are most at risk of liver complications. Most clinical reviews would recommend that Fontan patients should be assessed clinically on an annual basis [2,66]. Liver function should be assessed at baseline and then on a 2–3 yearly basis or more frequently if there is clinical suspicion of liver disease. US may be performed every 5 years until 10-years post-Fontan or if there evidence of liver dysfunction.

There is general agreement that the intensity of FALD surveillance should increase at 10 years following Fontan completion. This represents the time-point at which the clinically significant endpoints of cirrhosis and HCC have been consistently

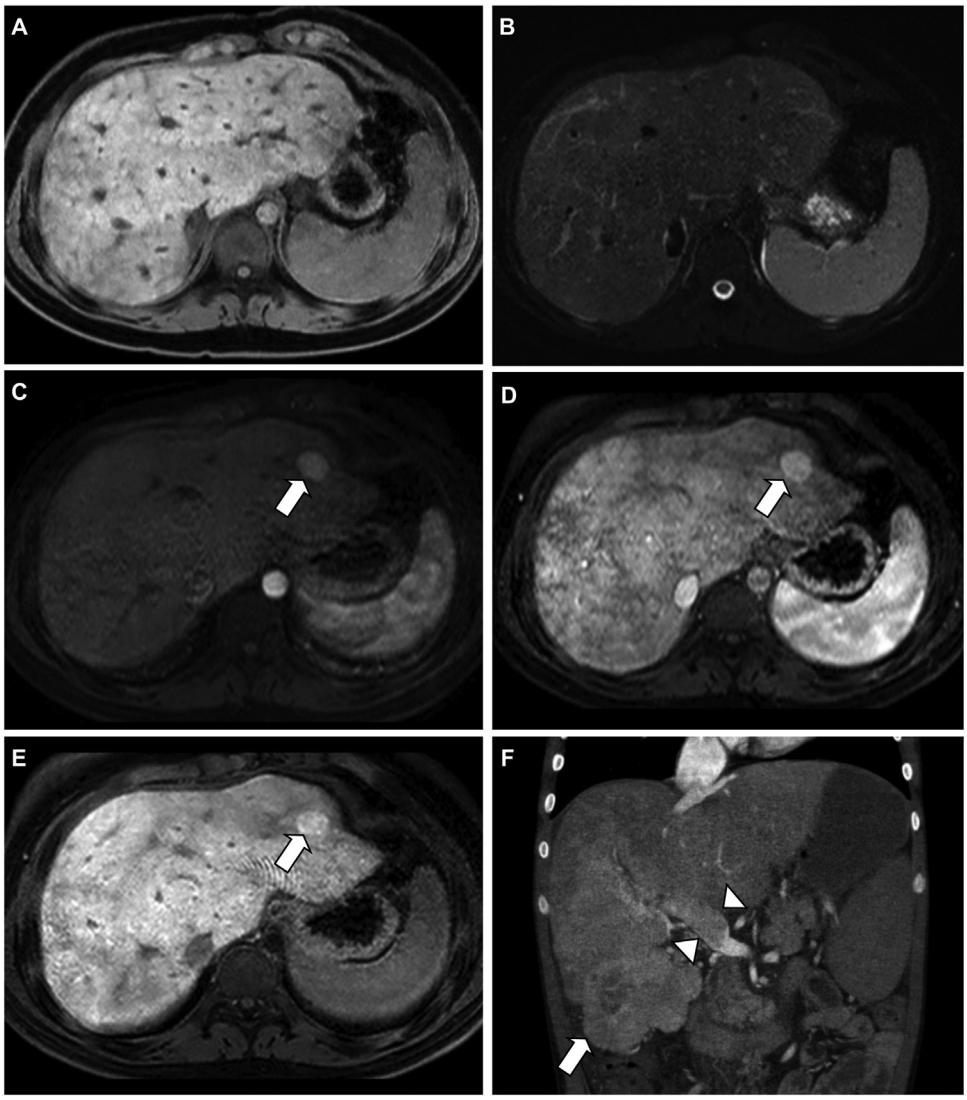

Fig. 5. Example of hepatic nodules in Fontan-associated liver disease. Benign liver nodule (A–E). Pre-contrast T1-weighted magnetic resonance imaging (MRI) (A) and T2-weighted image (B) showing that the nodule is isointense to the surrounding parenchyma. Post-contrast (gadoxetate disodium) image shows that the nodule hyperenhances in the arterial phase (C) and remains hyperintense in the portal (D) and delayed hepatocyte (E) phases. These are the characteristics of a benign arterialized nodule. (E) Coronal view of T2-weighted MRI showing a hypervascular exophytic mass arising in the right lobe of liver (arrows). There is associated portal vein thrombus (arrow heads).

Table 1
General approach to the management of Fontan-associated liver disease.

Optimize Fontan circulation	
Optimize anatomy	Optimize physiology
• Identify/treat anatomical abnormalities that adversely affect physiology, e.g. pulmonary artery stenosis, Fontan baffle stenosis, or arch obstruction	• Consider invasive and "stress" hemodynamic studies in symptomatic patients and those with apparently advanced liver disease, tailoring medical therapy accordingly
• Consider invasive hemodynamic studies +/− intervention if imaging studies are inconclusive	• Treat systolic heart failure [diuretics, spironolactone, angiotensin converting enzyme inhibitors, digoxin, beta-blockade]
	• Pacemaker insertion if appropriate
	• Compression hosiery for venous insufficiency
	• Manage other conditions that may affect pulmonary vascular resistance, e.g. obesity, obstructive sleep apnea, and chest wall deformity
Prevent liver injury	
Pre-Fontan	Post-Fontan
• Pre-natal diagnosis of cardiac abnormalities and managed delivery to avoid low output/shock presentation	• Screen and treat co-existing liver disease, e.g. viral hepatitis • Avoid alcohol and hepatotoxic medication
• Specialist anesthetic/intensive care input to avoid low output/hypotensive insults during cardiac surgery	• Advise against and treat obesity as could promote non-alcoholic fatty liver disease
• Hepatitis A/Hepatitis B immunization	• Hepatocellular carcinoma surveillance in patients with suspected cirrhosis

described, although isolated cases of cirrhosis have been described as early as 4–5 years post-Fontan [16,67]. Patients should be reviewed annually with clinical examination, blood tests (including liver biochemistry, full blood count), and US. At the time of writing there are insufficient data to recommend the routine use of any single non-invasive score for assessment of liver fibrosis. It is essential that longitudinal data from large cohorts of patients be collected to allow validation of these scoring systems in Fontan populations. Repeated liver stiffness measurements using either MR or US elastography on a 2-yearly basis will provide additional information regarding the progression of liver fibrosis. Some centers advocate the routine use of cross-sectional imaging. However, given the increased frequency of indeterminate hypervascular lesions in this population, the cost-effectiveness of this approach has not been established. Liver biopsy should be reserved for patients in whom a diagnosis of cirrhosis remains in doubt and for the assessment of some focal liver lesions [2,68], or when dual pathology is suspected. An algorithm for the routine surveillance of FALD patients is presented (Fig. 6).

One of the key questions to address during liver screening/surveillance is whether the liver disease is proportional to the perceived cardiac hemodynamics. An unexpectedly stiff liver, or the presence of radiological evidence of portal hypertension, or indeed worrisome features in the liver parenchyma, in our opinion should prompt invasive hemodynamic study with hemodynamic stress. This should include a fluid challenge during cardiac catheterization and/or exercise cardiac catheterization to unmask unfavorable hemodynamics due to occult diastolic single ventricular disease. Other Fontan pathway lesions may also be unmasked during such assessments such as mechanical obstruction, increased pulmonary vascular disease, pulmonary venous hypertension, and/or pulmonary venous atrial hypertension.

Recommended treatment strategies

Although there are no established medical therapies for the treatment of FALD, a few emerging therapies are worthy of further investigation. Prevention of FALD should focus on optimization of the Fontan circulation with surgical/medical interventions that increase cardiac output/reduce CVP (Table 1). Efforts should be made to avoid ischemic liver injury prior to formation of the Fontan circulation and during cardiac intervention. Pre-natal diagnosis may avoid hypotensive crises in newborns. Fontan patients should be screened for other chronic liver disease and receive Hepatitis A and B immunization. They should be counseled to avoid alcohol and obesity. Recently a potential role for nitrates has been suggested to increase venous compliance, reduce ventricular afterload, and reduce venous pressure response during exertional stress [69].

Fontan patients requiring cardiac transplant who do not have evidence of cirrhosis, do not require liver transplant. A single-center study of 44 patients undergoing cardiac transplantation on a background of Fontan physiology, reported 5- and 10-year survival of 72% and 69%, respectively [70]. Fontan patients with

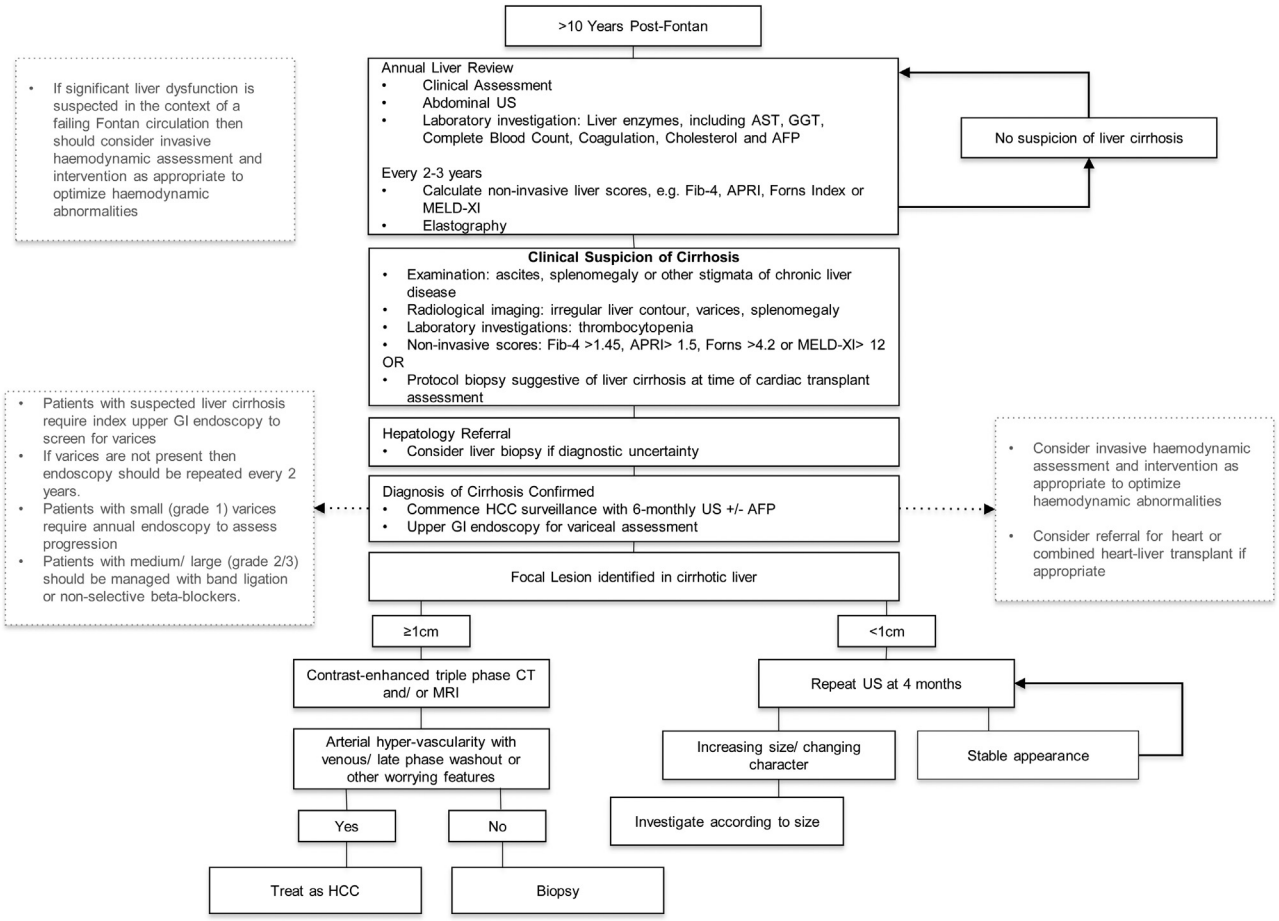

Fig. 6. Diagnostic algorithm for liver disease surveillance in Fontan patients. *Abbreviations*: alfa-feto protein (AFP), aspartate aminotransferase (AST), gamma glutamyl-transferase (GGT), aspartate aminotransferase to platelet index (APRI), Fibrosis-4 score (Fib-4), Model of End-stage Liver Disease excluding international normalized ratio (MELD-XI), gastrointestinal (GI), computerized tomography (CT), magnetic resonance imaging (MRI), ultrasound (US) and hepatocellular carcinoma (HCC).

well-compensated cirrhosis that undergo isolated cardiac transplant will continue to be at risk for HCC development and will require ongoing screening. In many cases FALD may be severe enough to contraindicate isolated cardiac transplant [71]. There are limited data to recommend isolated liver transplantation in patients with severe CHD [72]. Severe cardiorespiratory disease is a relative contraindication to liver transplant in adult patients and exposure of the graft to chronically elevated CVP would be expected to promote graft cirrhosis.

Combined heart-liver transplant (CHLD) should be considered in Fontan patients with clinical, imaging, or biopsy evidence of cirrhosis and certainly if there is evidence of decompensation. It is clear that combined heart-liver transplant (CHLT) is both feasible and can provide excellent results in selected patients [63]. According to UNOS data, between 1987 and 1991 there were a total of 190 CHLDs [64]. Of these 41 were performed in patients with CHD. In 26 of these patients the indication for CHLT was liver cirrhosis of cardiac origin. Ten-year survival for CHLT with CHD was 83%.

Future directions

There is a clear need to establish local/national registries of Fontan/FALD patients. This approach could be used to facilitate enrollment of these patients into large-scale multicenter longitudinal studies to address important questions regarding pathophysiology, optimal staging of liver disease, and preventative strategies. Standardized guidelines bringing together professional organization from cardiology and hepatology would simplify/harmonize the management of FALD. There is also a need to establish clear pathways for transplant assessment and organ listing.

Conflicts of interest

Dr. Timothy Gordon-Walker: No financial disclosures.
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