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Fontan-associated liver disease: Implications for heart transplantation

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Chronic liver diseases are associated with multiple complications, including cirrhosis, portal hypertension, ascites, synthetic dysfunction and hepatocellular carcinoma, and these processes are increasingly recognized in post-Fontan patients. Fontan-associated liver disease (FALD) can be defined as abnormalities in liver structure and function that result from the Fontan circulation and are not related to another disease process. FALD arises due to chronic congestion of the liver created by the elevated venous pressure and low cardiac output of the Fontan circulation, which may be superimposed on previous liver injury. Pathology studies have generally shown that FALD worsens as time post-Fontan increases, but the prevalence of FALD is not well defined because the majority of Fontan patients, even those with significant hepatic fibrosis, appear to be asymptomatic and biochemical or functional hepatic abnormalities are usually subtle or absent. Alternate non-invasive investigations, derived from the study of other chronic liver diseases, have been tested in small series of pediatric and adult Fontan patients, but they have been confounded by congestion and do not correlate well with liver biopsy findings. Liver disease can complicate Fontan circulatory failure and may even be significant enough to be considered a contraindication to heart transplantation or require combined heart–liver transplantation. The search for the optimal management strategy continues in the setting of increasing numbers of Fontan patients surviving to adulthood and being referred for heart transplantation. Thus, in this review we attempt to define the scope and significance of FALD and address transplant-related assessment and management of this challenging disorder.

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The Fontan operation has, without doubt, extended the lifespan of individuals born with only a single functional ventricle.[1] This procedure has evolved through multiple refinements (Figure 1) and patient outcomes have continued to improve.[2–4] Currently performed as the culmination of a series of palliative surgeries, the Fontan operation separates venous return from the heart, which allows volume unloading of the single ventricle and permits arterial saturations within normal limits (Figure 1C). However, this is achieved at the expense of elevated central venous pressure (CVP) and decreased cardiac output.[5] The

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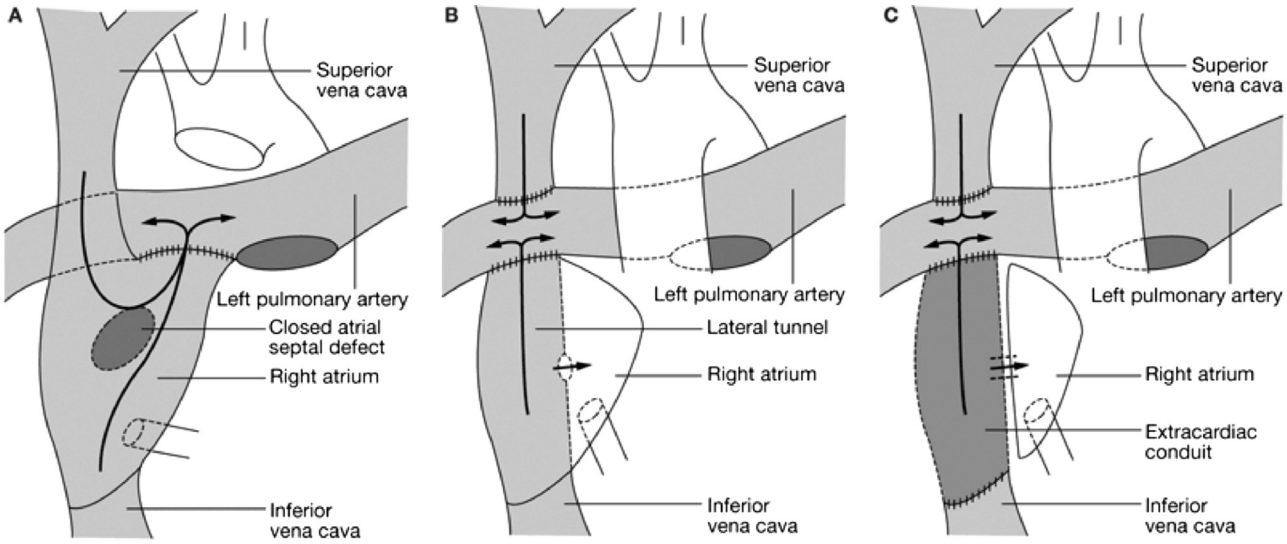

Figure 1 The Fontan circulation. (A) Atriopulmonary connection. (B) Lateral tunnel. (C) Extracardiac total cavopulmonary connection. Permission obtained from the Nature Publishing Group © de Leval MR. *Nat Clin Pract Cardiovasc Med* 2005;2:202–208.

surgically created Fontan circulation is profoundly abnormal and intolerance of this physiology can arise early or, more commonly, during adulthood.[6]

Liver disease, including cirrhosis, ascites, synthetic dysfunction, hepatocellular carcinoma (HCC) and portal hypertension, is increasingly recognized as a potentially serious morbidity post-Fontan.[7–12] Its cause is multifactorial; the liver has usually been exposed to hypoxemia and ischemia–reperfusion injury during the surgeries and may also have undergone intrahepatic venous thrombosis, viral or bacterial infections or exposure to hepatotoxic drugs.[13–15] The Fontan circulation compounds these factors by exposing the liver to higher hepatic venous pressure, which creates chronic congestion, decreases portal blood flow and compromises liver perfusion. Fontan-associated liver disease (FALD) is defined as abnormalities in liver structure and function resulting from the abnormal circulation of the Fontan state and not related to another process (e.g., viral hepatitis, medications or alcohol toxicity).[14]

The prevalence of FALD is not well defined. Liver histology post-Fontan has been reviewed in multiple small case series, including autopsy reviews[16–18] and liver biopsies.[19–22] At autopsy, varying degrees of liver congestion and fibrosis were identified in all patients studied with generally more severe disease identified in patients further out from Fontan completion. However, very early fibrotic changes were identified, suggesting that hepatic pathology can arise even pre-Fontan and be confused with FALD. Liver biopsies from clinically well Fontan patients are rare but may provide a more accurate estimate of FALD prevalence. Transvenous hepatic biopsies performed at the time of surveillance cardiac catheterization showed sinusoidal and/or portal fibrosis in 20 of 21 patients with a positive correlation ($R = 0.60$) between fibrosis score and time since Fontan surgery.[23] In another group of 10 Fontan patients, liver biopsy identified cirrhosis in 2 patients (20%) and fibrosis in 7 patients (70%).[24] These studies suggest that liver fibrosis is common in Fontan patients. Given the large and increasing population of adults with congenital heart disease (CHD), this has major implications for these patients and the health systems that care for them.[25]

Heart failure causing chronic hepatic congestion is profibrotic,[26] but the hepatic abnormalities seen in Fontan patients are characterized as being more severe in comparison, which may be related to chronicity and the absence of a sub-pulmonary pump.[11,14] In FALD, the histologic process usually begins with sinusoidal dilation, parenchymal atrophy and progressive collagen deposition in a perivenular distribution, followed by bridging of vascular structures with fibrotic septa (bridging fibrosis) (Figure 2).[13] This pattern is quite different from viral hepatitis[27] and may partly explain why tests and scoring systems used in inflammatory chronic liver diseases may be inappropriate for FALD.[11] Liver nodules are a common finding post-Fontan and are usually caused by focal nodular hyperplasia, a benign condition created by a hyperplastic response of the liver parenchyma to relative ischemia. Some younger patients have been described with hepatic adenoma, another usually benign condition.[16,28] Occasionally, a subgroup of adenomas will have malignant potential and there are reports of HCC developing in post-Fontan patients.[15,16,28,29] Fontan patients may also develop complications of portal hypertension, including gastroesophageal varices, driven by the gradient between portal and systemic venous pressures.[13]

Laboratory testing for FALD

Multiple studies have demonstrated evidence of liver dysfunction in the Fontan population with a pattern of mild cholestasis and elevations in serum gamma-glutamyltransferase (GGT), bilirubin, alkaline phosphatase and aminotransferase levels.[14,19,30–36] Although synthetic function is usually preserved, low-grade inflammation, thrombocytopenia, mild elevation of the international normalized ratio (INR) and

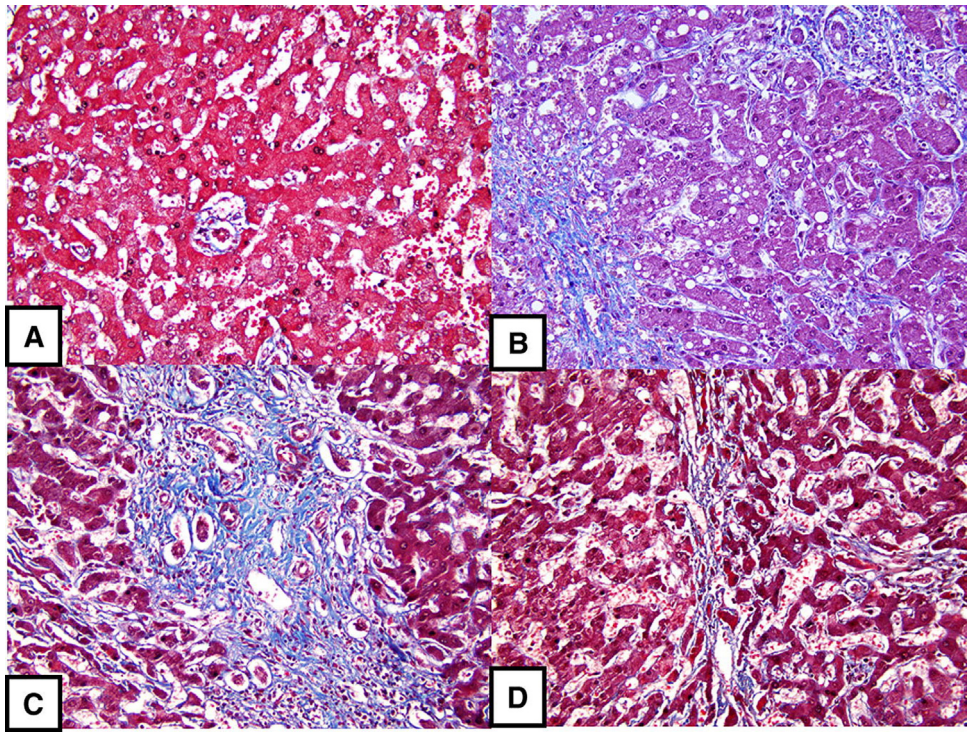

Figure 2 Fontan liver histology (Masson trichrome stain). (A) Liver without portal or sinusoidal fibrosis. (B) Severe sinusoidal fibrosis. (C) Marked portal fibrosis with bile duct proliferation. (D) Severe sinusoidal fibrosis. Permission obtained from Elsevier, Ltd. © Johnson JA, et al. *J Thorac Cardiovasc Surg* 2013;146(1):140–145.

clotting factor abnormalities (e.g., low Factor V levels, elevated Factor VIII levels) are frequent findings.[19,35,37,38]

Fibrosis is characterized by an increase in extracellular matrix production and the proliferation of hepatic stellate cells, which transform into myofibroblasts.[39] Many of the biomarkers used to assess fibrosis in viral hepatitis have been extrapolated to FALD.[30,37,40–44] The best characterized is the FibroTest (FibroSURE in the USA), which utilizes α_2-macroglobulin, haptoglobin, GGT, bilirubin, apolipoprotein A1 and a proprietary algorithm to calculate a score predictive of fibrosis stage.[45–47] Most Fontan patients have significantly elevated FibroTest scores (range 0.33 to 0.82, normal ≤ 0.21), but there is poor correlation with time post-Fontan, other investigations or biopsy.[30,32,48] The Model for End-stage Liver Disease (MELD) score has been validated as a predictor for mortality in adults awaiting liver transplantation, but it may not correlate with post-transplant outcomes[49] and was not found to be a predictor of mortality after heart transplantation in a small cohort of 19 adult CHD patients.[50] In one single-center retrospective study, a MELD eXcluding INR (MELD-XI) score of >18 was associated with a hazard ratio (HR) of 7.76 (95% confidence interval 2.05 to 29.33, $p = 0.008$) for reaching the end-point of sudden death, death from CHF or cardiac transplantation.[51] A recent retrospective study combined MELD-XI and liver biopsy in a heterogeneous pre-transplant population to calculate a novel liver risk score that was associated with increased risk of death at 1 year, but the findings need to be validated prospectively.[52]

Non-invasive imaging for detection of FALD

Liver ultrasound (US) can identify changes in liver parenchyma (e.g., increased echogenicity, parenchymal heterogeneity or liver surface nodularity) and complications related to liver cirrhosis (e.g., hepatomegaly, splenomegaly, varices and hypervascular nodules).[33,35] The frequency of abnormal US findings has been shown to increase with time post-Fontan, but no correlation has been found between abnormal liver structure and biochemical parameters, hemodynamic data, age at surgery, underlying diagnosis or ventricular morphology.[35] Changes in portal vein flow velocity and waveform have been observed, but their clinical relevance remains to be determined.[35] Liver abnormalities identified by computed tomography (CT) and magnetic resonance imaging (MRI) include hepatic vein congestion, inferior vena cava (IVC) engorgement, liver surface irregularity, ascites, mesenteric edema and hypervascular masses.[29,32,37,53,54] A reticular enhancement pattern on CT was positively associated with the extent of broad scars and degree of fibrosis on histologic examination.[19] All imaging modalities have demonstrated that liver changes secondary to FALD are not uniformly distributed and therefore liver biopsy may underestimate the presence or nature of disease as a result of sampling error.[55] Imaging of the entire liver is an essential component of pre-transplant evaluation and, although CT may be more reproducible than US and more convenient than MRI, it does involve exposure to ionizing radiation.[37]

Liver elastography

Several US-based methods have been developed to measure liver stiffness (i.e., fibrosis) non-invasively. FibroScan or transient elastography (TE) was the first test introduced into routine clinical practice and has found widespread use in multiple chronic liver diseases.[56–58] The transducer, placed in a right-sided intercostal space, transmits low-frequency vibrations that induce an elastic shear wave that propagates through the liver with faster wave progression occurring through stiffer, more fibrotic material.[55] TE is rapid, painless and easy to perform but cannot assess the left lobe of the liver and variability arises from the intercostal space used, position of the patient, presence of ascites or obesity and other factors.[55] Several studies have applied TE to Fontan patients, but, similar to the FibroTest, results have not consistently correlated with evidence of liver disease, time post-Fontan or biopsy results.[48,51] Furthermore, TE was found to overestimate fibrosis by at least 1 stage for 70% of Fontan subjects and by 2 stages for 50% of subjects, likely due to liver congestion.[30]

The influence of CVP on liver stiffness, as measured by TE, has been demonstrated in a pig model with a linear and reversible increase in TE-measured liver stiffness with occlusion of the suprahepatic IVC.[59] Liver stiffness was also demonstrated to be elevated to levels suggestive of liver cirrhosis in patients with decompensated congestive heart failure, but it improved dramatically after diuresis and weight loss.[60] The hepatic venous congestion present in all Fontan patients makes it impossible for TE to determine the true stage of fibrosis, because the liver stiffness measurement is reflective of both parenchymal fibrosis and CVP elevation and the relative contribution of each cannot be known on the basis of a single examination.[30]

Acoustic radiation force impulse (ARFI) and shear wave elastography (SWE) also use US-created shear waves to assess elasticity and have some practical advantages over TE,[55] but studies post-Fontan are limited.[24,27] SWE identified hepatic stiffness to be markedly increased in Fontan patients compared with controls, but no significant relationship was seen between hepatic stiffness and patient age, time post-Fontan or ventricular morphology. SWE-measured hepatic stiffness was 13.4 ± 1.3 kPa in patients with a fibrosis score <2 ($n = 4$) and 19.8 ± 2.6 kPa in patients with a fibrosis score ≥ 2 ($n = 6$, presence of periportal fibrosis, bridging fibrosis or cirrhosis). Furthermore, of the 16 patients with catheterization data, there was a significant correlation for SWE with ventricular end-diastolic pressure and pulmonary artery wedge pressure.[24] These preliminary data suggest that SWE may be the most promising US-based method to assess FALD-related liver stiffness.

Magnetic resonance elastography (MRE), unlike US-based elastography, provides 3D mapping of the entire organ, has better reproducibility, and is unaffected by obesity.[29,61–63] In one small retrospective study, all Fontan patients had elevated liver stiffness according to MRE, along with a significant association ($p = 0.02$) between higher liver stiffness and longer duration of Fontan circulation.[29] Another recent study included biopsy and MRE data for 8 patients and identified a reasonable correlation ($R = 0.74$, $p = 0.02$) between liver stiffness by MRE and biopsy fibrosis score but an excellent correlation between biopsy fibrosis score and spleen stiffness ($R = 0.97$, $p = 0.002$).[64]

Screening for FALD

Non-invasive tests for FALD remain limited or have not been adequately validated. The lack of correlation between biomarkers and clinical parameters and the overestimation of fibrosis by TE suggest that current non-invasive tests do not reliably reflect hepatic pathology. Further complicating test interpretation is the dynamic nature of liver stiffness that is affected by CVP, food intake, respiration, inflammation, fibrosis and steatosis.[55] Therefore, although patients with FALD may benefit from increased surveillance, the best way to identify these patients remains unclear and it remains unclear whether these patients all require liver biopsy.

We believe that all Fontan patients should undergo screening for liver disease on an annual basis. From the available evidence, GGT, albumin, INR, α-fetoprotein and US imaging appear to be the most helpful. Additional liver imaging with MRI or CT would be reasonable if abnormalities are identified through screening. Liver biopsy may be useful if it can be performed safely with quality and yield of transvenous samples equivalent to those obtained percutaneously and with additional information obtained regarding the hepatic vein pressure gradient.[44] However, given the often patchy nature of fibrosis and the risks of the procedure, we suggest that biopsy be reserved for when there is genuine concern for the possibility of HCC or for exclusion of other causes of liver disease when suspicion is high. Furthermore, although it is suggested that there may be a role for liver biopsy in distinguishing whether or not cirrhosis is reversible, the information gained from biopsy does not appear sufficiently discriminatory to determine whether the patient will survive heart-only transplantation or aid in the decision with regard to timing of transplant.[22] Finally, if biopsy is employed in cases of suspected HCC, due to the theoretical risk of causing metastases along the biopsy tract, the biopsy tract is burnt on withdrawal. An alternative is to screen for the consequences of liver cirrhosis directly (e.g., endoscopy or CT to identify the presence of esophageal varices). Measurement of the hepatic vein pressure gradient may be helpful in predicting the risk of variceal bleeding[44]; however, because the hepatic venous wedge pressure can be low and falsely reassuring in the presence of a low output state and significant venous collateral vessels, we and others are reluctant to use this measurement as a truly reliable marker for portal hypertension.[11] We are more interested in the portal venous anatomy (e.g., presence of varices, abnormalities of the splenic vein) than the pressure itself. We seek evaluation by a hepatologist when there is evidence of worsening liver dysfunction, severe liver disease or portal hypertension.

Management of FALD

The diagnosis of FALD should lead to an assessment of cardiac systolic function by echocardiography and/or MRI.

Cardiac catheterization should also be undertaken to measure PVR and intracardiac and transhepatic pressures and to identify anatomic obstruction or diastolic dysfunction. Initial treatment could include therapies treating the hemodynamic abnormalities that result in FALD, including pulmonary vasodilators,[65] endothelin-1 receptor antagonists,[66] fenestration and after-load reduction.[67] However, there are few data showing that any of these therapies have an impact on the development of FALD. Although surgery to revise an atriopulmonary Fontan and improve circulatory efficiency is suggested, there are no data demonstrating the effectiveness of this surgery or for delaying or improving FALD.[68] Management of the specific complications (i.e., bleeding varices, abnormal coagulation and nutritional deficiencies) that may accompany Fontan failure and/or FALD follows standard practice. Unfortunately, none of these treatments fully address the primary problem and the only truly long-term strategy is complete restoration of normal hepatic venous pressure, cardiac output and hepatic blood flow. Although ventricular assist devices (including the total artificial heart) have revolutionized biventricular heart failure management, their use in single-ventricle or Fontan patients remains experimental or anecdotal,[69–71] and the definitive treatment remains cardiac transplantation.

Implications of FALD for cardiac transplantation

Two key and related questions are: (1) When does FALD become a contraindication to heart-only transplantation in a symptomatic Fontan patient? (2) When does FALD constitute an indication for cardiac transplantation in an otherwise stable Fontan patient? The most common situation involves a symptomatic patient with a failing Fontan and FALD for whom the only option is transplantation. As we have described, assessing the functional status of the Fontan liver is difficult as is differentiating acute from chronic hepatic injury. Candidacy for transplantation is based on the likelihood of acute improvement in hepatic function and whether long-term changes are reversible with restoration of normal hemodynamics. However, the lack of reliable prognostic markers makes this assessment difficult. Improvement in the elevated aminotransferases after treatment (e.g., reduction in the Fontan pressure with diuretics or dialysis, improvement in cardiac output with inotropes) is a reassuring sign that some of the liver injury will reverse post-transplant. Evidence from human and animal studies suggests that hepatic fibrosis and even cirrhosis may be reversible once the insult is removed.[44,72]

Perhaps the most important point to assess is whether the liver will be able to cope with the stress of the often long and complex surgery. A pragmatic approach is to consider each patient on a case-by-case basis with no absolute criteria to allow or preclude heart-alone transplantation. In general, patients who have less advanced liver disease (Child–Pugh Class A [score <7] or MELD score <12) may be considered for isolated cardiac transplant. However, these prognostic scores do not address the full potential for an adverse outcome in these patients, who generally have increased post-operative mortality.[11,73] At the Institute of Transplantation at Freeman Hospital, with one of the largest experiences to date with transplantation from Fontan in adulthood, all potential candidates have a triple-phase CT scan of the abdomen to assess liver size and degree of intra-abdominal portal hypertension and also to exclude any focal lesions (e.g., HCC). Patients with any degree of FALD also undergo endoscopy to screen for varices. Patients with more advanced liver disease or significant abnormalities of hepatic venous return are assessed for combined heart–liver transplantation.

Implications of current listing criteria for patients with FALD

A less common scenario involves a stable Fontan patient who presents with worsening liver dysfunction secondary to FALD. Theoretically, a patient could develop FALD to such a degree that they may cease to become a heart-alone transplant candidate. It seems reasonable that a patient with progressive symptoms for whom cardiac transplantation is recognized as inevitable, and who is also developing increasing hepatic dysfunction, should be considered for cardiac transplantation before there is a deterioration in hepatic function to the point at which candidacy for heart-alone transplantation is lost. However, patients in this situation will not meet urgent listing criteria and therefore they are very unlikely to receive a new heart.

Criteria for the listing of cardiac transplant candidates are primarily based on the risk profiles of patients with normal cardiac structure and impaired function, with higher listing status requiring use of short-term mechanical support, ventilation or inotropes—all of which are inappropriate for most Fontan patients. Waiting until Fontan patients meet conventional urgent listing criteria means waiting until the FALD is more advanced. This significantly increases the risks associated with the transplant and may preclude heart-alone transplantation.

Impact of FALD on post-transplant outcome

Transplanting Fontan patients involves longer bypass times, increased risk of bleeding and resultant increased use of blood products and increased risk of post-operative right ventricular failure, systemic vasodilation and low cardiac output. These factors increase the risk of acute hepatic failure compared with other transplant patients, particularly in the context of pre-existing liver damage, as has been seen in patients with cirrhosis related to other causes undergoing general surgery.[74–76] Furthermore, vasopressors can reduce blood flow to the bowel, which increases the risk of bowel ischemia compounded by pre-existing portal hypertension. Assessment of venous return to the heart and potential resistance to flow across the cirrhotic liver are key components to a successful outcome of isolated cardiac transplant in FALD. Patients with cirrhosis, even outside the setting of FALD, have decreased effective circulating

arterial volume, which may be reduced further by impaired venous return related to resistance to flow across the liver or the presence of ascites.

Combined heart and liver transplantation is a rare event (1% of multiple-organ transplants performed)[13] and the potential negative effect of FALD on heart transplant outcomes is only beginning to be examined.[77] A single-center study reported that, of 20 patients who underwent heart transplantation (7 with liver cirrhosis and 13 with either normal liver or non-cirrhotic findings), the 1-year post-transplant survival was 80% for all patients, with no significant difference between the cirrhotic and non-cirrhotic groups.[78] The study suggested that FALD may not be an absolute contraindication to heart transplantation, but careful pre-transplant assessment is necessary (as outlined earlier). Among those patients in whom there is concern for significant liver disease, successful en bloc single donor heart–liver transplant has been reported in a small case series of children with CHD (2 of the 3 patients were post-Fontan).[79] Our current practice is that suitability for heart-only transplantation is made on a case-by-case basis with close collaboration between the hepatology and congenital transplant teams. As a guide, patients with evidence of cirrhosis who have normal synthetic liver function, normal hepatic venous anatomy, a liver volume of >800 ml, and evidence of only mild portal hypertension and no HCC are considered suitable for heart-only transplantation. Those with more advanced liver disease are assessed for combined heart–liver transplantation.

Conclusions

FALD is increasingly being recognized as a complication of the Fontan circulation and is likely to be present to a certain degree in all Fontan patients referred for transplantation. That this disease appears to correlate with time post-Fontan makes it a particular concern for those caring for adults with CHD and may further complicate the risk of transplantation for these patients, especially when compared with ischemic cardiomyopathy patients. The methodology for screening and diagnosis remain unclear, although data seem consistent with respect to the need for tests that are not confounded by congestion. Although the implications of different degrees of FALD for cardiac transplantation remain uncertain, the exclusion of HCC, confirmation of adequate hepatic venous drainage, and absence of severe portal hypertension are likely to be important components in improving post-transplant survival. Current listing criteria may disadvantage patients who are developing FALD, and transplantation earlier in the disease process may mitigate many of the associated risks. Future work should include improving the prognostic value of non-invasive hepatic investigations and the development of ventricular assist devices able to resuscitate organs, especially the liver, as part of the bridge to cardiac transplantation. Studying FALD's natural history, the effects of medical therapy, developing listing priorities, and studying the timing and risks of transplantation, especially in the adult Fontan patient, will be necessary to guide decisions as to whether heart, heart–liver or no transplant is the most appropriate therapeutic option.

Disclosure statement

The authors have no conflicts of interest to disclose.

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