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MANAGEMENT OF CIRRHOTIC PATIENT (A CARDENAS AND P TANDON, SECTION EDITORS)

Liver Involvement after a Fontan Procedure for Congenital Heart Disease

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Abstract

Purpose of Review Patients with congenital heart disease are living longer into adulthood. As these patients age, we see extracardiac complications of Fontan circulation. Liver dysfunction is almost universal in patients who have had a Fontan surgery. This paper seeks to describe the current understanding of the pathophysiology, diagnosis, and management of Fontan-associated liver dysfunction (FALD).

Recent Findings In this era of noninvasive markers for liver diseases, unfortunately, these markers have been found to be less sensitive in patients with FALD. There have been small, mostly single center, reports about the need for combined heart and liver transplant in these patients.

Summary Clinical expertise is needed to determine optimal treatment for patients with FALD and it requires a multidisciplinary team of liver and congenital heart disease experts to manage this population.

Keywords Fontan associated liver disease · Congenital heart disease

Introduction

The incidence of congenital heart disease (CHD) is relatively low, affecting approximately 1% of births per year in the USA [1]. Single ventricle–type congenital heart defects, a severe form of congenital heart disease, make up less than 10% of the CHD population. Though severe CHD is rare, the natural course of single ventricle heart disease necessitates complex surgical and medical management from the time of diagnosis throughout palliative treatment.

Children affected by severe CHD are living longer and into adulthood [2•]; it is estimated that severe CHD has a prevalence of 0.62 per 1000 adults [3]. This is related to earlier diagnosis of congenital heart disease and advancements in surgical interventions. One effective surgical approach is the Fontan operation, which has evolved since its initial application for the surgical repair of tricuspid atresia as described by Francis Fontan in 1971, in which a "ventriclized" right atrium was used for the creation of a cavopulmonary anastomosis [4] (Fig. 1). The Fontan circuit has undergone many modifications since it was first described and includes several operation types that ultimately act to divert caval blood flow to pulmonary circulation, bypassing the cardiac malformation and correcting long-term arterial hypoxia.

The Fontan operation is often accomplished in stages with a series of operations after the postnatal time period [5]. Surgical intervention at birth is usually not feasible due to elevated pulmonary vascular resistance and the size of the great vessels is too small at that time to create a viable shunt. A stepwise approach often occurs between months and years after initial diagnosis [5].

With the evolution of the Fontan operation, the postoperative mortality has decreased over the last decades [6]. In an analysis of outcomes of patients who underwent modified Fontan operations between 1973 and 2012, early mortality decreased from 13% prior to 1991 to less than 7% after the year 2000 [7•]. In addition, the survival estimate post-Fontan operation has been shown to vary by operative era. Between 1973 and 1990, the 10-year survival was 69%, and in comparison, since 2001, the 10-year survival has risen to 95% [7•]. While the overall 30-year survival estimate between 1973 and

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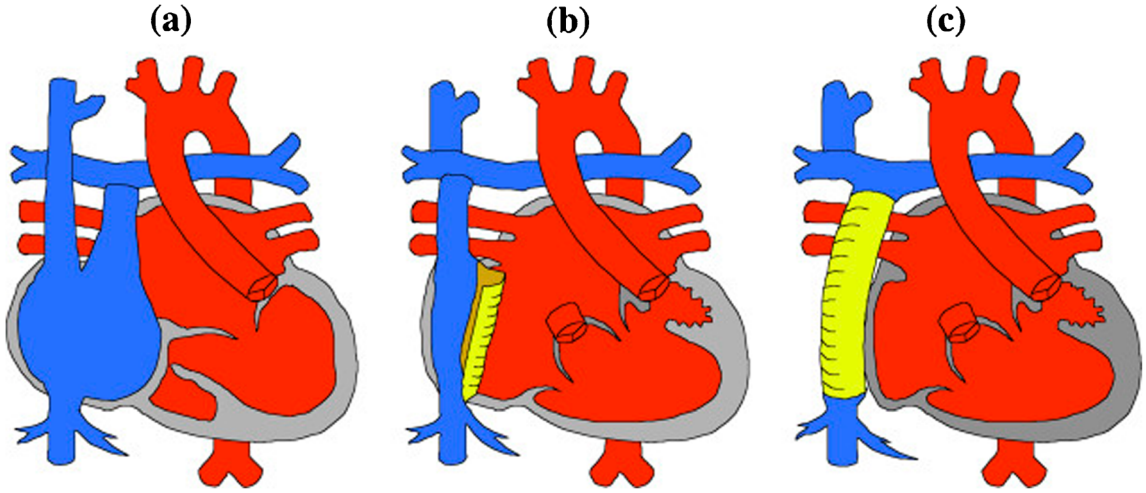

Fig. 1 Type of Fontan procedures. **a** Atriopulmonary connection; **b** intra-atrial rerouting (IAR); **c** extracardiac rerouting (ECR). The total cavopulmonary connection includes IAR and ECR. (Reprinted from Ohuchi, H., Adult patients with Fontan circulation: What we know and how to manage adults with Fontan circulation?, Journal of Cardiology. 2016; 68: 181–189; with permission from Elsevier)

2012 is 43%, it is reasonable to expect the percentage survival estimate at the 30-year mark will increase as data reported from later operative eras are gathered [7•].

While both early and late complications may follow a Fontan operation, late complications are likely to be encountered by primary care providers and adult medicine subspecialists, especially as this population transitions from adolescence to adulthood. Some of the most common complications include limited exercise tolerance, ventricular dysfunction and heart failure, arrhythmia, lymphatic disruptions such as protein-losing enteropathy, thrombosis, liver dysfunction, and plastic bronchitis. This article will address the complexities in diagnosis and management of Fontan-associated liver disease (FALD).

Liver Dysfunction after Fontan Surgery

Liver disease after Fontan palliation is an increasingly recognized extracardiac complication in both the adolescent and adult CHD population. The adverse effects inherent to Fontan physiology exert chronic injury to the liver, causing Fontan-associated liver disease. These changes, though varying in severity, are considered to be ubiquitous [8].

FALD is likely a cumulative outcome of multiple stressors to the liver, from the earliest effects of restricted systemic perfusion in utero to longstanding biochemical and physiologic changes, as well as the chronic alterations of normal hemodynamics [9]. Elevated central venous pressure and continuous non-pulsatile passive venous congestion is a feature of Fontan circulation. However, it leads to sinusoidal dilation and congestive hepatopathy [10]. Also, in states of Fontan failure, poor cardiac output puts the liver at risk for acute ischemic injury. Cardiac output, which is traditionally regulated by heart rate, venous return, and contractility, critically hinges on low-pulmonary vascular resistance in the Fontan circuit [8]. The differences in the circuit cause difficulty in attempts to correct failing physiology.

Fontan palliated patients also are subject to acquired liver diseases including viral hepatitis, autoimmune hepatitis, alcoholic liver disease, and non-alcoholic fatty liver disease (NAFLD), which would be expected to promote further fibrogenic alterations in the hepatic architecture when superimposed on underlying FALD. It is important to screen all patients with CHD for hepatitis C as many infants with CHD who received blood transfusions prior to 1992 could have been infected with hepatitis C; in 1992, there were standardized screening protocols by the blood bank to screen for hepatitis C.

Liver Fibrosis after Fontan Surgery

FALD can be thought of as a class of clinical and histologic pathologies ranging from abnormal liver-related laboratory findings to fibrosis, as well as cirrhosis and hepatocellular carcinoma (HCC). After Fontan repair, abnormal liver histology is the expectation and is present in virtually all patients [11]. The progression of abnormal histologic changes occurs unlike the evolution of fibrosis seen after viral hepatitis or steatohepatitis [12•]. Elevated central venous pressure and compromised hepatic venous drainage lead to sinusoidal dilation first around the central veins which progresses to perisinusoidal and pericentral fibrosis; notably, there is minimal or even complete absence of inflammation [12•]. The progression of fibrosis along the central veins leads to bridging fibrosis between central veins, as well as central-portal fibrosis [12•].

The longstanding vascular stress and ischemic insults that occur with Fontan physiology worsen in Fontan failure and further instigate fibrogenic pathways that cause varying degrees of fibrosis and can ultimately culminate in the development of cirrhosis [13].

Clinical Manifestations of Liver Disease after Fontan Surgery

The manifestation of clinical liver disease is variable, with some patients being completely asymptomatic while others present with signs and symptoms usually attributed to severe decompensated hepatic disease. Biochemical markers can demonstrate underlying abnormalities of hepatic pathology, but patients can have liver disease without any remarkable derangements in serum labs. Conversely, many patterns of abnormalities can be seen in FALD. In a retrospective study of 12 patients with failing Fontan circulation, seven had abnormal liver function tests, two with elevated ALT, five with elevated alkaline phosphatase, and seven had elevated total bilirubin levels. However, histology revealed parenchymal atrophy and sinusoidal dilation with mature sinusoidal collagen deposition in all of the patients. In addition, of the 12 patients, seven had histologic changes characteristic of cardiac cirrhosis [11]. With regard to serum biomarkers, liver enzymes and bilirubin are normal or mildly elevated in FALD, and histologic fibrosis does not necessarily correlate with degree of serum biomarker abnormalities [14].

Many patterns of laboratory derangements can be seen and elevated indirect bilirubin, prolonged INR, and mildly elevated aminotransferases can be characteristics of passive venous congestion, a feature inherent to normal Fontan physiology. A cholestatic pattern of liver enzymes is often suggestive of a state of chronic low cardiac output. In one study, the GGT was mildly elevated in the majority of evaluated patients [8].

Noninvasive markers to assess liver dysfunction have been studied in all liver diseases, including the FALD population. Hypoalbuminemia, an APRI (AST/platelet ratio) score that is greater than 2, and a FIB-4 score (age multiplied by AST and ALT divided by platelets) greater than 3.25 can be suggestive of cardiac cirrhosis [15]. The FibroSURE blood test, a measure of liver fibrosis and inflammation in the hepatitis C population, was found to be a poor predictor of the severity of hepatic fibrosis when compared to liver biopsy in FALD [16•]. As for clinical findings, ascites, hepatomegaly, and jaundice are clinical findings that can be seen with the development of cirrhosis. The presence of portal hypertension, including the development of esophageal varices is a poor prognostic indicator in this population [17].

Hematologic abnormalities after Fontan procedure are also frequently encountered, with an elevated thrombosis risk in up to 30% of patients often require chronic anticoagulation [17]. The increased risk of thrombosis is seemingly paradoxical as these patients often have a chronic mild thrombocytopenia. However, due to a complex interplay of hemostasis, there is an overall reduction in coagulation factor production, but with reduced protein S, endothelial dysfunction, and increased platelet activation, there is an overall tendency towards thrombosis despite chronic thrombocytopenia [17]. Although thrombocytopenia may be a marker of hepatic fibrosis in most liver diseases, one should view this marker with caution in patients with CHD as this thrombocytopenia may be secondary to splenomegaly that is a result of venous congestion and not necessarily cirrhosis [18].

Liver Cancer and Fontan-Associated Liver Disease

An increasingly recognized consequence of FALD is the development of HCC. Children who underwent the Fontan procedure are at risk for developing cirrhosis as early as one decade following the operation [19]. A report of four patients who had Fontan repair for complex cyanotic congenital heart disease and diagnosed with HCC has been described. They had varying corresponding levels of alpha-fetoprotein ranging between 106 and 5000 ng/ml [19]. This raises the question regarding surveillance strategies for HCC in this newly recognized high-risk population.

Hyperenchancing nodules can be prevalent in failing Fontan circulation and are typically benign vascularized lesions due to abnormalities of hepatic blood flow with less portal venous blood flow due to elevated CVP [20]. However, on the differential of hyperenhancing lesions is HCC.

CT and MRI can be used to differentiate liver nodules, a common finding in FALD. These radiologic tests can help distinguish nodules attributable to cirrhosis, focal nodular hyperplasia, or HCC. Four phase CT scan and MRI with gadodexate disodium can be used to distinguish hyperenhancing nodules including vascularized nodules and HCC. Even with these techniques, this can sometimes be a difficult distinction to make and for someone, a biopsy is needed to confirm this diagnosis.

Evaluation of Liver Fibrosis in Fontan-Associated Liver Disease

The Model for End-Stage Liver Disease (MELD) score has been used to evaluate patients for liver transplant and is generally predictive of prognosis in chronic liver disease. The MELD score is determined based on the serum sodium, total bilirubin, serum creatinine, and INR. However, the MELD score is not as useful for patients on chronic anticoagulation due to elevations of INR, which is one of the components of

the MELD score. Many FALD patients are chronically anticoagulated, and so the applicability of INR and subsequently, the MELD score may be restricted in this population.

Because of this, the MELD-XI score, which excludes the INR, has been proposed to assess patients with FALD. In a retrospective review of 70 post-Fontan patients undergoing elective cardiac catheterization, MELD-XI scores were found to correlate with total fibrosis scores (a sum of portal and sinusoidal fibrosis scores) [21•]. Of available noninvasive testing, the MELD-XI score is a practical and convenient predictor of hepatic fibrosis in patients with FALD.

Abnormal imaging is commonly seen in FALD. Multiple imaging modalities are used in the evaluation of FALD including CT, MRI, and ultrasound. Each technique has limitations including repeated radiation exposure, expense, and though ultrasound is often used to detect chronic liver disease, it has not been studied specifically for FALD [18]. MR elastography, a technique by which the stiffness or elasticity of tissue is assessed by the generation of mechanical waves, has been used for predicting the degree of fibrosis in chronic liver disease. However, in patients with congestive hepatopathy, as seen in FALD, it is difficult to isolate whether increased liver stiffness is secondary to fibrosis or underlying venous congestion [22].

The gold standard for evaluation of the presence and severity of hepatic fibrosis is still a percutaneous or transjugular biopsy. This may be a technically difficult endeavor, due to the inherent differences in Fontan anatomy. It also may be a risky procedure if the patient is on chronic anticoagulation. However, a liver biopsy provides the most accurate information regarding underlying liver pathology. The timing of initial liver biopsy and the role of biopsies in surveillance of patients with strong clinical suspicion of advancing liver disease is unknown. At present, no scheme exists for the development of fibrosis in the specific context of heart disease [12•]. Standardization of histological grading of fibrosis has not been established and multiple scoring systems have been used including the total fibrosis score, sinusoidal fibrosis score, and METAVIR. Ultimately, there is a need for standardization of fibrosis scoring in FALD for greater conveyance of information between involved specialists.

We propose the algorithm in Fig. 2 to follow patients for FALD.

Liver Transplantation After Fontan Operation

In patients with a failing Fontan circuit, consideration is given to transplantation, either isolated heart transplant or combined heart-liver transplantation (CHLT). Patients with advanced fibrosis, cirrhosis, or HCC could be considered for CHLT. This is an uncommon and complex surgical intervention and between the years of 1987 and 2005, less than 100 CHLTs were performed according to reporting to the United Network of Organ Sharing (UNOS) database [22]. In addition, only a very limited number of transplant centers offer this intervention and many centers have performed less than ten procedures [22].

The Hospital of the University of Pennsylvania has published their data on CHLT in patients with CHD [23•]. From 2000 to 2013, there were 17 patients referred for a heart transplant with Fontan surgery. On these 17, ten were ineligible for transplantation and seven received CHLT. These patients did

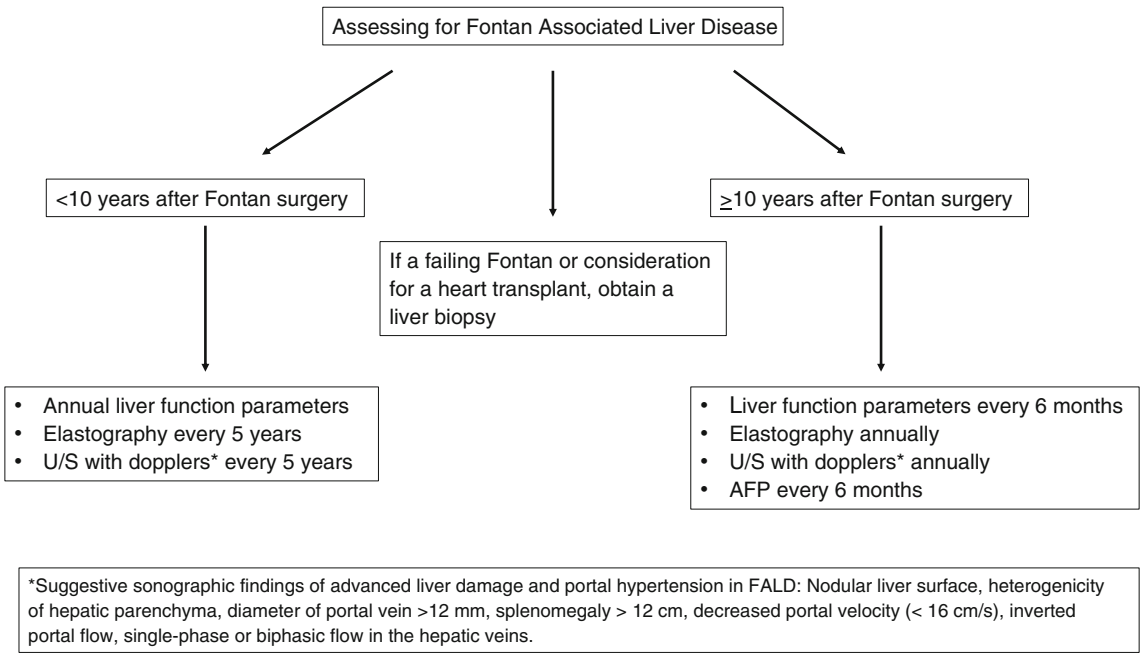

Fig. 2 Algorithm for assessment of liver disease in patients after Fontan surgery

very well with the biggest postoperative complication being acute renal failure. It should be noted that only one of these patients had abnormal liver enzymes, and yet many had evidence of cirrhosis, ascites, and varices seen on imaging, shedding more proof that enzymes alone are not enough to rule in or out liver fibrosis.

With regard to isolated heart transplantation, ultimately, candidacy for transplantation depends on the potential for improvement in hepatic function when the hemodynamics of a failing Fontan circuit is corrected. Patients require individual review by a multidisciplinary team when consideration for either heart transplant or CHLT is being decided.

Conclusions

Liver disease is often found incidentally in the post-Fontan population. Evaluating the degree of pathology starts with recognizing a need for a multimodal approach that begins with a history and physical exam and incorporates noninvasive testing including imaging and laboratory studies along with the careful use of invasive measures, such as biopsy. Patients with advanced liver disease may present in a compensated state without the identifying stigmata of liver disease such as jaundice and ascites. Routinely evaluating for evidence of liver disease is crucial as hepatic fibrosis and cirrhosis causes significant challenges to the care of Fontan patients and can affect clinical outcomes as well as shorten life expectancy [24].

FALD continues to be a subject of ongoing research interest. Greater understanding of the disease process aids in evaluating clinical symptoms to identify risk factors that may affect a patient's clinical outcomes. Guidelines for the evaluation of FALD are not protocolled but movement has been made to create multimodal tools for surveillance in order to make clinically relevant assessments that may impact patient outcomes.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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