Fontan-associated liver disease

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INTRODUCTION

Fontan-associated liver disease (FALD) is a form of congestive hepatopathy, which is universal among patients who have undergone Fontan palliation for functional single ventricle congenital heart disease (CHD). Due to improvements in surgical techniques and the management of pediatric CHD, the adult CHD population grows by ~5% each year.[1] This growth of the adult CHD population is consequential for health care utilization, with a particular impact on access to organ transplantation given ongoing shortages in organ supply.

FALD encompasses a spectrum of liver pathology, which includes fibrosis, cirrhosis, and portal hypertension (PHTN). Fontan patients are additionally at increased risk of HCC. This article summarizes a review in Hepatology[2] of the pathophysiology, clinical manifestations, and management of FALD.

PATHOPHYSIOLOGY OF FALD

Fontan physiology is characterized by a chronic, sustained elevation in central venous pressure, which predisposes to a range of physiologic consequences, including liver dysfunction. The Fontan surgery creates a total cavopulmonary anastomosis, which induces non-pulsatile flow and increased pressure in the IVC and hepatic veins. Elevation in the hepatic venous pressure minimizes the pressure gradient between the hepatic veins and portal veins (PVs) and compromises PV inflow. Decreased cardiac output may further compromise PV inflow. The liver in the Fontan physiology is, therefore, more reliant on hepatic arterial inflow and is susceptible to changes in the arterial circulation. Relative hypoxia impairs oxygenation of zone 3 hepatocytes and exacerbates fibrogenesis.[3]

CLINICAL MANIFESTATIONS OF FALD

FALD is often clinically indolent. Common laboratory manifestations include predominantly indirect hyperbilirubinemia and prolongation of the prothrombin time out of proportion to other coagulation indices. Patients often have moderate elevations in alkaline phosphatase and gamma-glutamyl transpeptidase, while mild elevations in aminotransferases are less commonly encountered.[4] Patients with compensated cirrhosis may be asymptomatic or may present with nonspecific symptoms, such as anorexia, fatigue, or weight loss. Clinical signs and symptoms of cirrhosis may be observed in late, advanced FALD.

Complications of PHTN are important to note, given their association with adverse outcomes in the post-Fontan population.[5] If ascites develops, measurement of the serum albumin ascite gradient, ascites total protein, and serum brain natriuretic peptide may help to differentiate ascites of cardiac or hepatic origin. Patients with Fontan physiology are additionally at increased risk of chylous ascites due to lymphatic congestion.[6] The reported incidence of varices in patients who have

Abbreviations: APRI, AST to platelet ratio index; CHD, congenital heart disease; CHLT, combined heart and liver transplantation; FALD; Fontan associated liver disease; FIB-4, fibrosis-4; FNH, focal nodular hyperplasia; HT, heart transplantation; HVPG, hepatic venous pressure gradient; IHT, isolated heart transplantation; LT, liver transplantation; LI-RADS, Liver imaging reporting and data system; MELD-XI, model for end-stage liver disease without internal normalized ratio; PV, portal vein; PHTN, portal hypertension.
undergone the Fontan procedure ranges from 9.3% to 38%, although variceal bleeding is uncommon.[7]

DIAGNOSIS OF FALD

The accurate diagnosis and staging of FALD remain a clinical challenge. Liver biopsy has several limitations in FALD, particularly an increased risk of sampling error given the heterogenous nature of FALD.[6] Laboratory scoring systems, such as the Fibrosis-4 (FIB-4) and AST to platelet ratio index (APRI) scores, have not been validated in the Fontan population but can supplement radiologic studies and clinical assessment in determining the severity of FALD. The role of elastography in the staging of FALD remains unclear, as congestion may confound stiffness measurements. In the setting of FALD, studies additionally reveal a poor correlation of the hepatic venous pressure gradient (HVPG) with disease stage, likely due to the unique hemodynamics of the Fontan circulation and the presence of intrahepatic veno-venous collaterals.[9]

LIVER LESIONS IN FALD

Hypervascular liver nodules are common in FALD, the vast majority of which represent benign focal nodular hyperplasia (FNH). Fontan patients are at increased risk of developing HCC, which may resemble FNH.[10] Given the increased risk of HCC among Fontan patients, screening to detect hepatic nodules is advocated, although formal recommendations are lacking to date.

FNH in FALD demonstrates imaging findings similar to those found in other patient populations. However, in FALD, FNH may show washout in the delayed phase,[10] which is highly associated with HCC in patients with noncardiac etiologies of cirrhosis. While delayed washout is not specific for HCC in this patient population, washout in the PV phase may be more closely associated with HCC and should raise suspicion for malignancy.[11] Liver imaging reporting and data system (LI-RADS) criteria specify that a noninvasive diagnosis of HCC cannot be made in the setting of congestive hepatopathy due to an increased risk of false positive results. When using hepatocyte-specific contrast agents with MRI, the majority of HCC either does not retain contrast or retains it in a heterogenous pattern.

Evaluation of focal lesions in FALD

If a liver lesion is noted on imaging in the setting of FALD, further evaluation with hepatobiliary contrast-enhanced MRI or triple-phase CT scan is warranted (Figure 1). Features that are atypical for FNH, such as restricted diffusion, a heterogenous pattern of enhancement, or lack of uptake of hepatobiliary phase contrast, warrant follow-up with a liver biopsy or short-term imaging within 3–6 months. Elevation of alpha fetoprotein, especially at a rising level, favors malignancy in any situation. Lesions that have typical FNH-like characteristics and homogenous uptake of hepatobiliary phase contrast are less concerning and may be monitored with CT or MRI in 6 months.

HCC IN FALD

HCC has a prevalence of 0.18 to 1.3% among patients with FALD.[12] In 2 retrospective, multicenter studies of HCC among Fontan patients,[12,13] the mean age at the time of HCC diagnosis was 30 years. The median duration from Fontan operation to HCC diagnosis was 22 years, and cumulative survival was 50% at 12 months. Interestingly, cirrhosis is only present in ~50% of Fontan patients with HCC, suggesting that cirrhosis is not prerequisite for the development of HCC in the setting of Fontan physiology. This highlights the need for further studies to stratify risk and to define surveillance protocols for Fontan patients to diagnose HCC in its early stages.

TRANSPLANTATION

With the growth of the adult CHD population, the rate of combined heart and liver transplantation (CHLT) for adults with CHD is increasing. While PHTN and HCC are considered indications for CHLT, which preclude isolated heart transplantation (IHT), the patient selection remains a significant challenge in determining the need for IHT versus CHLT for other indications. Without defined guidelines, the decision to proceed with IHT versus CHLT is often done on a case-by-case basis, and criteria vary between transplant centers. Liver transplantation (LT) alone is not recommended in adults with Fontan physiology due to difficulty managing right-sided cardiac pressures during the surgery. In addition, the elevated central venous pressures that characterize Fontan physiology may harm the liver allograft. Higher MELD-XI scores have been correlated with inferior survival after heart transplantation (HT). Therefore, the evaluation of liver function is a vital component of the HT evaluation for Fontan patients.

Single center series of CHLT for FALD report limited but good posttransplant outcomes. A multi-institutional retrospective review of the OPTN/United Network for Organ Sharing (UNOS) database revealed that patients with CHD who underwent IHT had a higher incidence of acute rejection at one year and inferior survival up to 10 years after transplant when compared with CHD patients who underwent CHLT.[14] The authors attributed this to the higher incidence of rejection among patients...
undergoing IHT. Other studies have confirmed a decreased incidence of rejection after CHLT, leading to a hypothesis that the liver confers immunotolerance after multiorgan transplantation. This is particularly important in the setting of HT, as high levels of calculated panels of reactive antibodies constitute a risk factor for inferior outcomes in HT recipients. In such situations, at the time of CHLT, the liver is grafted before the heart.

The decision to proceed with CHLT versus IHT ultimately relies on many factors, including center-specific experience, particularly in the complex anesthetic perioperative management of Fontan patients. Given reports of good outcomes following IHT in select cases, it may be reasonable to pursue IHT in patients with adequate liver synthetic function and no evidence of PHTN or HCC. While the immunologic benefit of CHLT is attractive, organ shortages necessitate a more refined approach to the selection of patients with adequate synthetic function and without PHTN for IHT.

CONFLICTS OF INTEREST
The authors have no conflicts to report.

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REFERENCES

How to cite this article: Hilscher MB, Kamath PS. Fontan-associated liver disease. Clin Liver Dis. 2023;22:130–133. https://doi.org/10.1097/CLD.0000000000000061