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EDITORIAL

Fontan Associated Liver Disease: Canary in the Coal Mine or Silent Killer?

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Liver fibrosis in patients with a Fontan circulation was first described only a decade after Fontan and Baudet introduced the world to their groundbreaking palliative surgery for children with functionally univentricular heart disease.[1–3] Despite these early reports, Fontan associated liver disease (FALD) did not gain widespread awareness within the field of congenital heart disease until relatively recently.[4–6] Even with the growing knowledge of this disease, diagnosing and determining the severity of FALD remains challenging.

See Article by Guerrero-Chalela et al.

The mechanism of FALD is felt to be multifactorial. A Fontan circulation is largely dependent on pressure gradients between the central venous system and the pulmonary venous system to drive blood flow across the pulmonary bed. Creation of this circuit leads to chronically elevated systemic venous pressures. The combination of high central venous pressure, low cardiac output from the single ventricle Fontan system, chronic vascular congestion of the liver, and relatively low oxygen delivery to centrilobular hepatocytes is thought to create progressive liver disease.[6,7] While various mechanisms have been proposed that may accelerate the fibrotic process, the largest contributor to FALD appears to be the duration of time the patient has lived with a Fontan circulation,[6] which is typically performed between 2 and 5 years of age. As patients age, the shear stress on the hepatic vasculature caused by chronic congestion results in fibrogenesis caused by centrilobular hepatocyte atrophy, eventually leading to bridging fibrosis, cirrhosis, and increased risk for hepatocellular carcinoma.[6]

At its inception, FALD is often subclinical and is only detected through screening and surveillance. In one study, liver biopsy and cardiac catheterization were offered to all patients with Fontan, starting 10 years after completion of the Fontan.[8] All patients, regardless of clinical status, had evidence of fibrosis on biopsy. In another study of 106 adolescents with a Fontan circulation, bridging (grade 3) fibrosis was noted in over a third of the cohort.[9] Current recommendations urge practitioners to start screening for FALD beginning 10 years after completion of the Fontan circulation. However, the optimal method(s) and frequency of surveillance are still undetermined. At this point, the only treatment for advanced FALD is combined heart-liver transplant.[10]

Despite the high prevalence of liver disease in patients with a Fontan circulation, there is no agreement on what defines severe FALD. A recent European Society of Cardiology consensus statement defined FALD as “The broad spectrum of liver disease and its consequences, attributable to Fontan hemodynamics. FALD includes varying degrees of hepatic fibrosis, compensated and decompensated cirrhosis, focal nodular hyperplasia, laboratory evidence of hepatic injury or impaired synthetic function, and hepatocellular neoplastic lesions”.[11] Biopsy remains the gold standard to detect fibrosis in the liver. However, the fibrosis is often patchy in distribution, which can lead to sampling error and underestimation of disease. There is also no universally

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accepted scoring system to determine severity by biopsy.[6,8,9] Advanced imaging modalities such as computed tomography, magnetic resonance imaging, and ultrasound are frequently used for surveillance and are effective for identifying markers of advanced liver disease, including ascites, splenomegaly, varices, and portosystemic collaterals, but these methods are limited in their ability to detect early fibrosis or distinguish between fibrosis and congestion.[6] Serum markers are frequently normal in patients with FALD, even at advanced stages. As disease severity worsens, the only marker that reliably correlates with the degree of fibrosis is the international normalized ratio.[12] Several studies found that MELD or MELD-XI scores were inadequate to detect severe disease and did not provide a reliable score threshold with adequate sensitivity or specificity.[6,13]

In this issue of *Journal of the American Heart Association* (*JAHA*), Guerrero-Chalela et al[14] analyzed data from the Quebec Congenital Heart Disease Database, a population-wide administrative data set including patients treated in the province from 1983 to 2017, to evaluate liver disease and mortality in Fontan patients. Severe FALD was defined as hospitalization in a Fontan patient with an associated liver disease *International Classification of Diseases, Ninth Revision or Tenth Revision* (*ICD-9* or *ICD-10)* code. The Fontan cohort was compared against a propensity-matched cohort of patients with a simple ventricular septal defect diagnosis code to determine the prevalence of liver disease in patients with a Fontan compared with the congenital heart disease population at large. Predictably, the Fontan patient cohort had a 20-fold higher risk of liver disease compared with the ventricular septal defect cohort.

Within the Fontan group, the median age at diagnosis of severe FALD was 15 years. Among patients meeting the study's criteria for severe FALD, mortality was 12.6% at 5 years after the first hospitalization with a liver disease code, 3-fold higher than the 3.7% risk in patients with a Fontan without severe FALD. This relationship is not surprising, and, indeed, the association between advanced FALD and mortality was identified in a recent multicenter study of patients who underwent heart or combined heart-liver transplant.[10] Nonetheless, while the presence of FALD in a hospitalized patient with a Fontan may portend a worse prognosis, it is unclear if FALD was a direct cause of the increased mortality, or if this group simply represents a sicker cohort overall. For example, the separation between Kaplan–Meier curves in patients with and without FALD in this study was apparently related primarily to mortality events within the first few months after diagnosis of severe FALD, indicating that those patients were diagnosed with severe FALD (and possibly with FALD altogether) only at the time of hospitalization shortly preceding their death. Further insight into this question was limited by the lack of data on cause of death, which precluded assessment of relationships between mortality and other important risk exposures, such as surgical or interventional procedures. It is also noteworthy that, while the authors reported prior supraventricular tachyarrhythmia and congestive heart failure to be risk factors for severe FALD in this cohort, these too are adverse outcomes of a Fontan circulation, and coding for these complications at an earlier date than the diagnosis of severe FALD does not necessarily indicate that they preceded the development of liver disease. This clustering of hospitalization, FALD diagnosis, other adverse Fontan outcomes, and death is confounding. There is no way to determine if liver disease was a contributing factor in the patient's demise, or if FALD was simply present and diagnosed as part of the sentinel hospitalization that preceded the patient's death.

This points to one of the major methodologic limitations of this study. Namely, it is difficult to analyze complex or clustered outcomes in patients with congenital heart disease followed over time, particularly when potentially important variables are not represented in the data set. Associations between outcomes may or may not be causal in nature, and even when they are, the causal nexus can be difficult to sort out, particularly when diagnosis of a purported risk factor is conditional on testing that may be performed at different points in disease progression or not at all. Given that FALD is known to be ubiquitous within 10 to 15 years after Fontan completion, most if not all the patients in this study with a Fontan a likely had some degree of liver fibrosis, including those not hospitalized. In that regard, the diagnosis of FALD may have been more a function of how a patient was evaluated than whether liver disease was present. Moreover, because the diagnosis of severe FALD in this study was based on clinical factors (ie, hospitalization) and diagnosis codes, there is no accounting for its relationship to the actual degree of liver disease. Causation is challenging to study, particularly when information is derived from an administrative data set,[15] not to mention one that was accumulated over a period of time when awareness of FALD and approaches to its evaluation evolved dramatically. Despite the authors' sophisticated and careful analysis, it is difficult to account for potential ascertainment bias, whether over time, between institutions, or for other reasons. Liver disease is clearly a significant issue in patients with a Fontan circulation, and this large population-based study provides a welcome addition to the rapidly growing literature on this topic, confirming the association between hospitalization with a diagnosis of liver disease and subsequent mortality. However, the role of liver disease in this association remains unclear, despite the authors' rigorous efforts. To some extent, uncertainty about causal connections is intrinsic to retrospective outcome analysis, and while that uncertainly

does not lessen the importance of the finding, it is important to foreground the limitations intrinsic to the data source and analytic methodology.

Multiple studies have looked at the correlation between FALD and hemodynamics of the Fontan circuit.[9,16,17] While favorable Fontan hemodynamics do not preclude the diagnosis of FALD, some studies have suggested that higher central venous pressure is associated with more severe fibrosis.[18,19] Based on this, the sentinel hospitalization event characterized in this study may represent the initial presentation of a sicker cohort with an overall higher mortality risk, a profile that also includes the presence of FALD.

The study by Guerrero-Chalela et al[14] highlights one of the dilemmas of caring for a patient with a Fontan circulation—how does one assess mortality risk and what role does advanced liver disease play in that risk? Devising a standard approach to diagnosis and characterization of the severity of FALD remains a challenge. While it should be assumed that all patients with a Fontan begin to accumulate liver fibrosis within the first decade after the Fontan procedure, identifying FALD and deciding how its presence should affect the evaluation of the patient and the timing of advanced therapies such as transplant needs further study. The analysis by Guerrero-Chalela et al[14] suggests that a hospitalization event in a patient with Fontan with known FALD, particularly one that involves heart failure or supraventricular tachycardia, should prompt a more expedited evaluation by the heart failure/transplant group for advanced therapy, given the associated mortality risk following that sentinel presentation to the hospital. With the growing number of patients with a Fontan and FALD advancing into their adult years, distinguishing which of our patients have a higher risk of decline or mortality becomes paramount to improving outcomes. By highlighting these considerations, the paper by Guerrero-Chalela et al[14] represents a valuable addition to the literature on this complex and growing problem.

ARTICLE INFORMATION

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Disclosures

None.

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