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# Fontan-Associated Liver Disease: Evidence for Early Surveillance of Liver Health in Pediatric Fontan Patients

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## ABSTRACT

The growing awareness of Fontan-associated liver disease (FALD) in adults with Fontan physiology has provided the impetus to better understand the natural history of FALD and develop a reliable noninvasive method to diagnose and monitor liver health in this population. Biochemical and imaging tests have been investigated to determine their association with liver pathology. The congestive hepatopathy that develops after the Fontan procedure has made interpreting these tests challenging. We have reviewed and summarized the current understanding and ongoing challenges with respect noninvasive measures of liver health in Fontan patients including biochemical tests, elastography, hepatic ultrasound, cross-sectional imaging, and hemodynamics and how they relate to liver pathology. It has been demonstrated from biopsy data that liver disease is universal and progressive in Fontan patients. Traditional biochemical tests, elastography, and imaging methods are often abnormal in Fontan patients but do not reliably indicate significant liver pathology. Although a reliable means for surveillance of FALD remains elusive, this continues to be an active area of investigation, with promising recent developments. Therapeutic options for FALD are limited, with cardiac transplant as

## RÉSUMÉ

La sensibilisation grandissante à la maladie du foie associée à l'intervention de Fontan (FALD) chez les adultes ayant subi une telle intervention a donné l'impulsion nécessaire pour tenter de mieux comprendre l'histoire naturelle de la FALD et d'élaborer une méthode non invasive fiable de diagnostic et de surveillance de la santé hépatique dans cette population. Les tests biochimiques et les méthodes d'imagerie dont on dispose ont été analysés afin d'évaluer l'association entre leurs résultats et la pathologie hépatique. L'hépatopathie congestive qui apparaît après l'intervention de Fontan rend plus difficile l'interprétation des résultats de ces tests. Nous avons effectué une recension et une synthèse des connaissances actuelles et des difficultés persistantes relatives aux méthodes non invasives d'évaluation de la santé du foie chez les patients ayant subi une intervention de Fontan, y compris les épreuves biochimiques, l'élastographie, l'échographie du foie, l'imagerie transversale et l'hémodynamique, et à leur association avec la pathologie hépatique. Les données issues de biopsies ont démontré que chez les patients ayant subi une intervention de Fontan, la maladie du foie est universelle et progressive. Les épreuves biochimiques classiques,

The Fontan procedure is the final stage in the univentricular pathway that is applied to a range of congenital heart conditions. Patients who have had Fontan procedures have improved survival in the current era, with many surviving well into adulthood. Despite this, hemodynamic alteration following the Fontan procedure is associated with complications including thrombosis; protein losing enteropathy; and plastic bronchitis, culminating in Fontan failure. There is growing awareness of clinically significant liver disease in adult Fontan patients, making early recognition of liver disease in the pediatric cohort a priority. Despite growing awareness, the

natural history of Fontan-associated liver disease (FALD) remains unclear. This is especially the case with respect to the timing, onset, and rate of progression with pediatric patients. Since the publication of a comprehensive review by Rychik et al. in 2012,<sup>1</sup> wherein an emphasis was placed on instituting systematic liver surveillance in Fontan patients, FALD has become an active area of research. In particular, the development and validation of noninvasive methods to assess FALD reliably is at the forefront of these efforts. To date, there is no consensus on a reliable noninvasive measure to identify or monitor FALD. This review serves to summarize recent developments in the ongoing effort to better understand FALD, with an emphasis on investigative methods.

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## Pathology

The liver pathology in FALD is thought to be initiated with distension of hepatic sinusoids, causing chronic congestion, inflammation, and sinusoidal fibrosis. This can progress to include centrilobular fibrosis, bridging fibrosis, and portal

the only option that can stabilize FALD pathology and improve symptomatology. Given the limited therapeutic options and the prevalence of liver disease in Fontan patients, there is a compelling case for early routine surveillance of liver health and promotion of global liver health.

fibrosis due to portal hypertension. This continues to progress to cirrhosis, at which point liver dysfunction becomes more clinically apparent. The complications of liver failure and risk of hepatocellular carcinoma are significant morbidities at this final stage of the disease.

The consensus from investigations of autopsy and biopsy data from adult and pediatric Fontan patients is that fibrosis is universally present and progressive. Although hepatic congestion following the Fontan procedure is likely the most significant component of the pathophysiologic process, biopsy data from early post Fontan patients suggests that liver disease may predate the Fontan procedure in some patients. Autopsy specimens collected within months after the Fontan procedure have significant liver pathology.<sup>2</sup> Furthermore, abnormal ultrasound imaging has been identified in pre-Fontan patients. This suggests that acute insults, or a chronic congestive physiology prior to the Fontan procedure, may also contribute to FALD.

### Elastography

Liver biopsy is the gold standard for the diagnosis of liver fibrosis and cirrhosis. To minimize the need for this invasive procedure, liver elastography has been validated as a noninvasive technique for the assessment of liver fibrosis and cirrhosis in primary hepatic disease. This technology has been applied in the Fontan population with the intention to use it for diagnosis and surveillance of FALD. Three modalities of elastography have been studied in FALD. Transient elastography (TE) and acoustic radiation force impulse (ARFI) are ultrasound-based methods that calculate the liver stiffness based on tissue deformation following an induced shear wave or vibration. Magnetic resonance elastography is another method that assesses tissue stiffness of the entire liver by quantifying a propagating waveform from mechanical excitation.

Liver stiffness is significantly higher in Fontan patients compared with age-matched controls. Unfortunately, interpreting elastography values in the context of FALD is problematic owing to the inherent increase in central venous pressure (CVP) following the Fontan palliation, leading to hepatic congestion. Investigations into liver stiffness measurements before and immediately after Fontan have shown a significantly elevated stiffness that is attributed to the increase in CVP, as opposed to fibrosis. This is supported by a positive correlation between liver stiffness and hemodynamic

l'élastographie et les méthodes d'imagerie produisent souvent des résultats anormaux dans cette population de patients, mais ne donnent aucune indication fiable d'une pathologie hépatique importante. Même s'il reste toujours à trouver un moyen de surveillance fiable de la FALD, ce domaine de recherche n'en demeure pas moins actif et a connu récemment des développements prometteurs. Les options de traitement de la FALD sont rares, et la transplantation cardiaque est le seul moyen de stabiliser cette pathologie et d'en atténuer les symptômes. L'éventail restreint d'options thérapeutiques et la prévalence de la maladie hépatique chez les patients ayant subi une intervention de Fontan mettent en relief l'importance de la surveillance précoce et systématique et de la promotion globale de la santé hépatique.

parameters that include CVP, ventricular end diastolic pressure, and pulmonary vascular resistance. This has led many to question the utility of elastography to detect fibrosis in the context of hepatic congestion. Despite many investigations using different modalities of elastography, the results are divergent with respect to the change in liver stiffness over time. Given that it is well understood that liver pathology progresses over time in Fontan patients, the inability to demonstrate a time-dependent change in liver stiffness makes it difficult to postulate that elastography on its own will be a reliable indicator of FALD. Multiple investigations comparing histopathological results directly with liver stiffness have not provided any further clarity, as liver stiffness is not universally associated with fibrosis on biopsy.<sup>3</sup>

### Biochemical Tests

Most biochemical tests of liver health in Fontan patients have not been demonstrated to be reliable indicators of pathology. Although often abnormal in Fontan patients, transaminitis and impaired synthetic function have not demonstrated a reliable association with other measures of liver health that include elastography, hemodynamic measurements, or liver fibrosis. Alpha-fetoprotein (AFP) is used as a specific marker for hepatocellular carcinoma (HCC) and would complement ultrasound imaging for early identification of HCC in Fontan patients, but the age when HCC screening should be started is unclear. More specialized tests of liver function include biomarkers of extracellular matrix metabolism, such as hyaluronic acid (HA) and type IV collagen 7s, have shown potential as indicators of liver pathology. Composite scores are also promising markers of evolving FALD. The model for end-stage liver disease (MELD) score and the aspartate-to-platelet ratio index (APRI) have both been validated as serum markers of fibrosis and cirrhosis in common hepatic diseases. The APRI has not shown consistent results; however, the MELD score has been shown to correlate with time from Fontan, liver stiffness, and liver fibrosis. To further elaborate on the MELD score, Evans et al. combined results from elastography, MELD score, and time from Fontan as parameters in a model of best fit for the evolution of liver fibrosis over time in Fontan patients. This model was named the Fontan hepatic index (FHI) and has been shown to correlate strongly with fibrosis in a single small cohort of Fontan patients.<sup>3</sup> Although there have been promising results from biomarkers of extracellular matrix metabolism and

composite scores, further investigation is required to validate their use in the Fontan population.

### Imaging

The significance of most imaging abnormalities with respect to the severity of FALD remains unclear. Cross-sectional imaging with computed tomography (CT) and magnetic resonance imaging (MRI) often reveals abnormalities in Fontan patients. CT and MRI in Fontan patients often demonstrate abnormalities such as zonal enhancement and reticular changes that are typically associated with liver congestion and fibrosis in other disease processes. Less commonly, hypervascular nodules are found, which are concerning for more advanced liver disease and hepatocellular carcinoma. Although evidence of liver abnormalities by CT and MRI are well documented in Fontan patients, the evidence correlating these findings with documented liver pathology is not robust.

Ultrasound imaging also commonly finds abnormalities in Fontan patients that include hepatomegaly, splenomegaly, abnormal echotexture, abnormal hepatic artery flow, and surface nodularity. Surface nodularity is often an indication of advanced liver pathology, such as hepatocellular carcinoma, and is the only finding in Fontan patients that is associated with fibrosis on biopsy.<sup>4</sup> Splenomegaly is also important to monitor, as it is an indication of portal hypertension. Further investigations and consultation with a hepatologist would be prudent in these cases.

### Transplant

The growing knowledge of FALD has led to questions regarding the role of concurrent liver transplantation in those with a failing Fontan who are listed for cardiac transplant. Hepatic failure is typically cited as a reason for combined heart and liver transplant (CHLT) as opposed to an isolated heart transplant (IHT). This concept is being challenged with reports showing positive outcomes following IHT in Fontan patients with FALD. Investigations following IHT in patients with FALD have demonstrated improved sinusoidal dilation but persistent fibrotic changes on biopsy. Despite this, the 1-year survival of Fontan patients with and without cirrhosis after IHT is the same. It remains unknown if IHT will result in reversal of pre-existing FALD; however, the limited evidence that is available suggests that IHT may stabilize pre-existing liver pathology and cirrhosis does not increase postcardiac transplant mortality.<sup>5</sup>

### Conclusion

FALD is ubiquitous and progressive, but an evidence-based protocol for surveillance has not been established. Laboratory investigations are largely unhelpful in guiding management. Nearly all results of investigations of liver health—including biochemical markers, ultrasound, cross-sectional imaging, and elastography—will be abnormal in Fontan patients. The clinical significance and appropriate action to take upon discovery of mild abnormalities in individual tests is unclear. Patients with severe abnormalities or progressive worsening should be referred for hepatology consultation and undergo liver biopsy. Our current understanding of FALD should also

Every 2-3 years following Fontan completion
Physical examination <ul style="list-style-type: none"> <li>- Hepatomegaly</li> <li>- Splenomegaly</li> <li>- Liver span</li> <li>- Ascites</li> </ul>
Laboratory studies <ul style="list-style-type: none"> <li>- CBC</li> <li>- AST, ALT, GGT Bilirubin, Albumin, INR</li> <li>- Hepatitis serology</li> </ul>
Abdominal ultrasound with doppler <ul style="list-style-type: none"> <li>- Liver size</li> <li>- Spleen size</li> <li>- Portal vein flow</li> <li>- Presence of collateralization</li> </ul>
Transient elastography (Fibroscan®)
10 years post-Fontan [Earlier if clinically indicated]
Cardiac catheterization <ul style="list-style-type: none"> <li>- Fontan pressure</li> <li>- Ventricular end-diastolic pressure</li> </ul>
Transjugular liver biopsy

**Figure 1.** Fontan liver health surveillance pathway implemented at British Columbia Children’s Hospital.

encourage pediatric practitioners to counsel families about liver health and promote routine hepatitis vaccination and recommendations regarding diet, hepatotoxic medications, exercise, and consumption of alcohol. Although therapeutic options for FALD are limited, proactively monitoring these patients will allow for new developments to be initiated more efficiently and effectively. At British Columbia Children’s Hospital, we have implemented a routine liver health surveillance pathway for all Fontan patients that commences within the first year following Fontan surgery (Figure 1). We believe that implementation of a standardized pathway for liver health in centres managing Fontan patients will ensure regular examination and investigation for evidence of evolving liver disease and improve patient awareness of this important condition.

### Disclosures

The authors have no conflicts of interest to disclose.

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