Noninvasive diagnosis of liver fibrosis in the complex cardiac malformation survivors – a review of the literature

Roxana-Cristina Mareș, Cristina Oana Mărginean

Department of Pediatrics, “George Emil Palade” University of Medicine, Pharmacy, Sciences and Technology Târgu Mureș, Romania

Abstract

The aim of this review is to summarize the information on the pathogenesis and diagnosis of congestive liver disease secondary to the Fontan and Glenn surgery for complex cardiac malformations, focusing on non-invasive diagnostic modalities. We performed an electronic database search (Pubmed, Web of Science) with the data range from 2001 to 2020. We selected the studies that addressed the pathogenesis of congestive liver disease secondary to cardiac malformations and articles regarding noninvasive methods of determining liver fibrosis in this group. We found that conventional imaging methods do not allow the detection of the initial stages of liver fibrosis. Elastography results are altered by congestion and cut-off values are not yet validated. More studies are required in order to provide evidence-based guidelines regarding the non-invasive diagnosis of hepatic fibrosis secondary to congenital heart disease. Patients with congenital cardiac malformations require close monitoring and early diagnosis of liver complications to allow prompt therapeutic intervention.

Keywords: congenital heart defects; Fontan correction; Glenn correction; liver fibrosis; elastography

Introduction

The prevalence of congenital heart disease has followed an increasing trend over the past 50 years [1] due to the growing detection of milder lesions such as atrial and ventricular septal defects or patent ductus arteriosus. Children born with congenital heart defects (CHD) represent 8 per 1000 births in Europe and North America and 1 of 4 infants which required surgery correction for critical congenital heart defects in the first year of life in the United States [2].

Over the last decades the survival and quality of life of children with complex cardiac malformations have increased due to the progress in cardiac surgery, pediatric cardiology and intensive care. It is known that children with CHD may have a congestive hepatopathy as an effect of chronically elevated hepatic venous pressures due to right-sided heart failure. Chronic hepatic congestion leads during time to bridging fibrosis, cirrhosis or hepatocellular carcinoma [3–7]. These children are also at risk of developing hepatic complications, before or after corrective surgery. Liver necrosis and fibrosis were documented in 43% of infants with hypoplastic left heart syndrome and in 30% of infants with coarctation of the aorta [8]. A recent study has shown that after the Mustard and Senning correction for transposition of the great arteries, 71% of patients showed signs of liver fibrosis (46%) or cirrhosis (25%) [9]. Patients with Eisenmenger syndrome may also develop liver complications due to congestion, hypoxemia and reduced cardiac output. Mebus et al have found that 6/10 Eisenmenger patients had a form of hepatic pathology and 5/10 hepatic fibrosis [10].

The Fontan operation, described in 1971, is a frequently used palliation for patients with functional single ventricle heart disease [11]. The procedure is the final part of a three-staged palliation, following the systemic-pulmonary shunt and the superior cavo-pulmonary connection (the Glenn shunt). It has been used in patients with tricuspid atresia, pulmonary atresia with intact ventricular sep-
Noninvasive diagnosis of liver fibrosis in the complex cardiac malformation survivors

Roxana-Cristina Mareş et al

Abstract

The incidence of hepatic complications is correlated to the time since the Fontan palliation [20,21]. Baek et al have developed a large number of complications such as liver disease, arrhythmias, protein-losing enteropathy, renal insufficiency and plastic bronchitis [14]. In the past four decades numerous studies have shown the deleterious effects of the circulation on the liver, ranging from liver fibrosis (LF) to cirrhosis and hepatocellular carcinoma. Liver damage is the most common organ complication secondary to the Fontan operation. A very important research was published by Golberg et al documenting the histopathological changes in FALD. They found that all 67 patients included in the study showed evidence of LF, while most of the patients had no overt symptoms of liver disease [15].

The importance of pre-Fontan hepatic injury in patients with single ventricles has recently been brought to light in an autopsy study. The authors found that a significant percentage of patients who died within 1 month after undergoing the Fontan operation had important LF, suggesting that fibrosis in those patients resulted from pre-Fontan insults [16]. Single ventricles often suffer from systolic and diastolic dysfunction, they may be overloaded from regurgitant valves and pressure loaded from distal stenosis. Cardiac output may be therefore impaired and compensatory changes in preload may occur [17]. After birth, the infant with a single ventricle may suffer from cardiovascular collapse, congestive heart failure and marked hypoxemia, factors well recognized of inducing acute liver injury. Perioperative ischemic insults at the time of systemic-pulmonary shunts, Glenn shunts, or completion of the Fontan circulation, as well as the medications used during and after the procedure are known to cause liver insults [18].

The Fontan palliation leads to increased central venous pressure and a decrease in cardiac output, which leads to hepatic hypoxia. Secondly, high central venous pressure leads to elevated hepatic vein pressure, which in turn decreases portal flow. As a response, the autoregulation of the arterial hepatic circulation leads to increased flow in the hepatic artery. If this autoregulation is insufficient the hepatic tissue will suffer ischemic lesions. Furthermore, the increase in central venous pressure determines sinusoid dilatation which stimulates satellite cells via compression and elongation, initiating a fibrotic reaction [19]. This mechanism is common to other causes of congestive hepatopathy which lead to elevated hepatic vein pressure secondary to right sided heart failure.

Thus, hepatic disease secondary to the Fontan operation is multifactorial and may be secondary to an increase in central venous pressure, a decrease in cardiac output and pre-Fontan injury.

The incidence of hepatic complications is correlated to the time since the Fontan palliation [20,21].
istic investigations and elastographic assessments have
matory and viral liver diseases. Laboratory tests, imag-
tation. Given the limitations of the liver biopsy, non-in-
revision, heart transplantation, and heart-liver transplan-
hepatitis, non-
inflammatory causes (hepatitis, non-
congenital hepatic disease - NAFLD) [16].

The value of the liver biopsy for risk stratification
prior to heart transplantation is also unclear: a study
documented fibrosis in liver biopsy samples obtained
before heart transplantation has shown no correlation to
the clinical status and the post-operative liver function
[27]. Hepatic insufficiency in patients with congenital
heart disease influences surgical options, such as Fontan
revision, heart transplantation, and heart-liver transplan-
tation. Given the limitations of the liver biopsy, non-in-
vasive means for evaluating the liver damage secondary
to CHD are of great interest.

Non-invasive diagnostic tools

Non-invasive methods of determining liver damage
are well studied and validated in a number of inflam-
atory and viral liver diseases. Laboratory tests, imag-
istic investigations and elastographic assessments have
excellent predictive value for advanced fibrosis when
compared to liver biopsy, especially in hepatitis C and
NAFLD [28-30].

However, fewer studies address the matter of non-
invasive markers of liver disease secondary to congest-
hepatic erythema or lack the comparison with the liver
biopsy. The studies that do address the issue mainly focus
on FALD as the extreme of congestive hepatopathy and
less on liver damage secondary to other CHD.

Laboratory tests

The average values of non-invasive biomarkers in
Fontan patients are presented in Table I. Standard blood
tests are often normal or only mildly abnormal even in
Fontan patients with advanced liver fibrosis [31]. The
most frequently modified laboratory test in patients
with Fontan circulation is a moderate increase in gamma-glutamyl transpeptidase (GGT) [32–36]. In patients
with congestive hepatopathy, standard laboratory tests
such as transaminases, alkaline phosphatase, bilirubin,
prothrombin index were not correlated with the fibrosis
detected by liver biopsy [37]. Also, other studies showed
no difference in GGT level or platelet count between pa-
ients with low and high stage fibrosis on biopsy [14,24].

More complex scores based on laboratory tests
such as FibroTest (also called FibroSure), Forns index,
MELD-XI (Model for end-stage liver disease excluding
INR) were understudied in congestive hepatopathy in
comparison to other etiologies of liver disease and lack
validation with biopsy.

The FibroTest investigation is based on an algorithm
that combines the results of several serum biochemical
markers (alpha 2 macroglobulin, haptoglobin, apolipo-
protein A1, total bilirubin, gamaglutamyl-transpeptidase) in
order to evaluate the degree of fibrosis and necro-in-
flamatory activity [38,39].

A recent study of 145 patients with Fontan palliation
found that the liver fibrosis score calculated by FibroTest
had a strong correlation with the duration of the Fontan
circulation and a mild correlation with liver stiffness val-
ues measured by elastography [40]. On the contrary, other
studies found elevated scores of the FibroTest but no cor-
relation with the duration of the Fontan circulation [41].

Smaller studies have sought to determine the predictive
value of FibroTest in adult Fontan patients, by compari-
son with liver biopsy. In a small cohort of 14 adult Fontan
patients FibroTest was shown to correctly stage fibrosis
only in 5/14 subjects (35.7%), in 2 cases the fibrosis
was overestimated and in 7 cases underestimated [42].

In many studies, the Model for End-Stage Liver Dis-
ease (MELD) score demonstrated to be a good predictor
for clinical outcome in patients suffering from various
liver diseases [43]. It was calculated using a logarithmic


diagnoses...
Table I. Average values of non-invasive biomarkers of fibrosis in Fontan patients

| Authors             | No. from surgery | α-FP (n<0.6 ng/ml) | GGT (n = 10-30 U/L) | TB (n = 0.2-1.4 mg/dl) | APRI (n<0.3) | MELD (n<6) | MELD-XI (n<11) | Fibro-Test (n<0.21) | Forns Index (n<4.2) |
|---------------------|------------------|--------------------|---------------------|------------------------|--------------|------------|----------------|-------------------|-------------------|
| Kiesewetter 2007    | 12 14.1          | –                  | –                   | 1.4 (1.2–4.6)          | –            | 9.7±4.7    | –              | –                 | –                 |
| Friedrich-Rust 2008 | 39 5.6±3         | –                  | 57.8±34.3           | 0.98±0.6               | –            | –          | –              | –                 | –                 |
| Baek 2010           | 139 11.5±7       | –                  | 1.5±1.5             | 0.6±2                  | –            | –          | –              | –                 | 1.1±3.8            |
| Yoo 2014            | 46 13.5          | –                  | 1.1±0.6             | 0.4±0.2                | –            | –          | –              | –                 | –                 |
| Potenucha 2016      | 50 22            | 3.3±1.9            | 96±54               | 1.3±1                  | 0.4±0.2      | 15±9       | 9±6            | –                 | –                 |
| Wu 2016             | 27 20.4          | –                  | 84 (38–502)         | 0.9 (0.4-4.7)          | 0.39±0.2     | –          | –              | 0.44 (0.1–0.8)     | –                 |
| Fidai 2017          | 19 3.7           | 1.2 (0.5-3.6)      | 42 (24–89)          | 0.4 (0.2-1.2)          | –            | –          | –              | 0.45 (0.2-0.6)     | –                 |
| Kim 2017            | 64 12.1          | 2.97±2.47          | 59.2±39.9           | 0.97±0.55              | –            | –          | –              | –                 | –                 |
| Evans 2017          | 30 15            | –                  | –                   | –                      | 0.39 (0.2-0.9) | 10.6 (9.4–16) | –              | –                 | –                 |
| Song 2018           | 26 10.5          | 2.5±1.3            | 69.7±33.9           | 0.9±0.7                | –            | –          | –              | –                 | –                 |
| Ackerman 2018       | 28 19.7          | 3.15±1.21          | 68.2±39.1           | 1.16±0.98              | 0.4 (0.2–0.5) | –          | –              | –                 | 3.03 (1.8-4.2)    |
| Smaś-Suska 2019     | 59 18            | 2.5 (0.8–18.6)     | 78 (25–255)         | 20.5 (3.5–135)         | 0.4 (0.2–1.5) | 9.7 (1–19) | –              | 4.5±1.9            | –                 |
| Schleiger 2020      | 101 10.3         | 71.1 (28-114)      | 1 (0.4-1.6)         | –                      | –            | –          | –              | 0.5                | –                 |

Data are expressed as number, mean±standard deviation or as median (interquartile range). α-FP: alpha-fetoprotein, ALT: alanin-aminotransferase, APRI: AST-to platelet ratio index, AST: aspartate-aminotransferase, GGT: Gamma-glutamyl transpeptidase, MELD: Model for end-stage liver disease, MELD-XI: Model for end-stage liver disease excluding INR, n: normal values, No.: number of patients, TB: total bilirubin.
function from serum creatinine, total serum bilirubin and the International Normalized Ratio (INR) [20]. However, most patients following the Fontan operation are treated with anticoagulants, for whom the MELD-XI score, which uses serum bilirubin and serum creatinine while excluding the INR was developed. In a retrospective study of 70 post-Fontan patients MELD-XI values were correlated with fibrosis scores determined from transvenous hepatic biopsy samples [44]. However, receiver-operated curves analysis did not identify a specific cut-off score of sufficient sensitivity or specificity. In other studies MELD-XI values were correlated with the time since the Fontan operation and to liver stiffness values [45].

Back et al investigated non-invasive fibrosis markers in 138 patients post-Fontan [21] and found that non-invasive scores showed significant abnormalities in patients with hepatic complications. The Forns index, combining age, platelet count, GGT and cholesterol concentrations was the best predictor for the presence of Fontan hepatopathy. A different study [46] found that the Forns index could identify moderate fibrosis in 29% of patients, although it lacked comparison with biopsy-proven fibrosis. Forns index also correlated significantly with time post-Fontan; however, it did not correlate with liver stiffness and aberrant liver morphology on ultrasonography. Contrariwise, Smas-Suska et al demonstrated that patients with an increased Forns index had significantly higher liver stiffness values [47].

Conventional imaging tools

Table II emphasizes the frequency of imagistic changes in patients with FALD in different studies, using conventional imaging tools.

Abdominal ultrasound, computed tomography and magnetic resonance imaging are insensitive to early stages of LF [40,46]. Advanced LF may determine surface irregularity, a coarsening of the liver parenchyma, nodular appearance, hypervascular regenerative nodules and left lobe hypertrophy [39,41,48]. Another study found a significant correlation between the presence of splenomegaly and elevated liver stiffness results determined by transient elastography in patients with FALD, suggesting it may be a marker for evolving portal hypertension [49]. Approximately 30% of patients who underwent the Fontan palliation had hypervascular lesions with nodular regenerative hyperplasia due to the “arterialization” of the hepatic circulation [34,45,50]. These lesions may indicate a more severe disease or patients at a greater risk of developing hepatocellular carcinoma [20,51].

Elastography

Elastography is a much more sensitive method for assessing LF compared to previously employed imaging techniques. To date, the methods for determining liver elasticity are: Transient Elastography (FibroScan), Sono-Elastography (Real-Time Tissue Elastography), Acoustic Radiation Force Impulse Elastography (ARFI), Supersonic Shear-Wave Elastography (2D-SWE) [52] and Magnetic Resonance Elastography (MRE). The techniques were also validated in the pediatric population and cut-off values have recently been published [53,54].

MRE is a novel technique which showed promising results in predicting fibrosis in congestive hepatopathy. Poterucha et al demonstrated a positive correlation between MRE values and histological liver fibrosis score on a group of Fontan patients [45].

Liver stiffness values in congestive hepatopathy, determined through the various elastographic modalities are summarized in Table III.

Transient elastography (TE)

TE uses a special device, FibroScan (EchoSens, Paris, France), which incorporates a transducer mounted on the shaft of a vibrator. It generates a painless vibration that causes “shear waves” that propagate through the superficial tissues to the liver. The speed of these waves is directly proportional to the stiffness of the tissues, being then calculated by the device and expressed in kilopascals [55]. TE has been proven to be a reliable method to assess the degree of LF in adult and pediatric patients with chronic hepatic pathologies and it has high inter- and intra-observer agreement [56]. The strong point of TE is its wide availability, whereas its weaknesses are the lack of imagistic guidance, the inability to use in cases of ascites and a decreased applicability in patients with obesity [57].

A study using TE found that 87% of the Fontan patients had liver stiffness suggestive for significant liver cirrhosis. Liver stiffness values were positively correlated with time interval since the Fontan operation and FibroTest scores [35]. Rathgeber and al. reported the same correlation of liver stiffness values determined by TE and time post-Fontan in a cohort of 76 patients [49]. Similar results were reported in other studies, in which most patients had elevated FibroScan results, suggesting the presence of fibrosis, and liver stiffness increased with the time post-Fontan [21,40,41]. A study comparing patients with Fontan circulation to patients with right sided heart failure and hepatic congestion found that the liver stiffness value early after the Fontan procedure might indicate inappropriate Fontan circulation and may identify patients at a high risk of developing congestive hepatopathy. Changes in liver stiffness values in patients with chronic stable Fontan circulation might give information regarding the progression of liver LF [31]. A study com-
Table II. The imagistic findings in Fontan patients

| Authors                     | Method    | No. | Abnormal echo-structure (%) | Caudate lobe hypertrophy (%) | Splenomegaly (%) | Hepatomegaly (%) | Nodules (%) | Ascites (%) |
|-----------------------------|-----------|-----|------------------------------|------------------------------|------------------|-----------------|-------------|-------------|
| Kiesewetter 2007 [20]       | CT        | 11  | NA                          | NA                           | 72               | 90              | 18          | 18          |
| Poterucha 2016 [45]         | MRE/MRI   | 50  | NA                          | 52                           | NA               | 60              | 68          | 46          |
| Buendia-Fuentes 2017 [50]   | MRI       | 37  | NA                          | 27                           | 8                | 32              | 18          | 8           |
| Fidai 2017 [41]             | Echo      | 16  | 35.7                        | NA                           | 20               | NA              | 50          | NA          |
| Wu 2017 [39]                | Echo      | 54  | NA                          | 54                           | 40               | 79              | NA          | 30          |
| Ackerman 2018 [46]          | Echo      | 24  | 8                           | NA                           | 41               | NA              | 29          | 3           |
| Schleiger 2020 [40]         | Echo      | 117 | 70.9                        | NA                           | 32.5             | 14.5            | 11          |             |
| Rathgeber 2020 [49]         | Echo      | 51  | 52                          | NA                           | 29               | 31              | 15          | 11          |

CT: computed tomography, Echo: echography, MRE: magnetic resonance elastography, MRI: magnetic resonance imaging, NA: not addressed, No.: number of patients

Table III. Liver Stiffness Values in Congestive Hepatopathy

| Authors                     | Method    | No. | Population Studied | Years from surgery | Liver stiffness (KPa) | Normal values stiffness (KPa) | Liver velocity (m/s) | Normal value of velocity (m/s) | p values |
|-----------------------------|-----------|-----|---------------------|--------------------|-----------------------|------------------------------|----------------------|--------------------------------|----------|
| Yoo 2014 [31]               | TE        | 46  | Fontan              | 13.5               | 21.1±8                | 7                            | –                    | –                              | –        |
| Chen 2016 [66]              | TE        | 22  | Fontan              | 9.6                | 18.6                  | 4.7                          | –                    | –                              | p=0<0.001 |
| Fidai 2017 [41]             | TE        | 19  | Fontan              | 3.7                | 14.6                  | 7                            | –                    | –                              | p=0.0024 |
| Song 2018 [34]              | TE        | 26  | Fontan              | 10.5               | 18.2±3.3              | 7                            | –                    | –                              | –        |
| Rathgeber 2020 [49]         | TE        | 76  | Fontan              | 8.4                | 16.8                  | 7                            | –                    | –                              | –        |
| Schleiger 2020 [40]         | TE        | 61  | Fontan              | 10.3               | 27.7                  | 7                            | –                    | –                              | –        |
| Kutty 2016 [18]             | 2D-SWE    | 20  | Glenn               | –                  | 7.2                   | 5.7                          | –                    | –                              | p<0.001  |
| Evans 2018 [63]             | 2D-SWE    | 30  | Fontan              | 15                 | 7-21                  | 5.5                          | –                    | –                              | p=0.002  |
| Smaś-Suska 2019 [47]        | 2D-SWE    | 59  | Fontan              | 18                 | 9.1                   | 5.5                          | –                    | –                              | –        |
| Poterucha 2016 [45]         | MRE       | 50  | Fontan              | 22                 | 5.5±1.4               | 2.3                          | –                    | –                              | –        |
| Melero-Ferrer 2014 [64]     | ARFI      | 21  | Fontan              | 16.8 ± 6.5         | –                     | 1.86±0.5                    | 1.09±0.05            | p <0.001                        |          |
| Buendia-Fuentes 2017 [50]   | ARFI      | 37  | Fontan              | 15.8 ± 6.9         | –                     | 1.8 (1.4-2.1)               | <1.19                | –                              | –        |
| Kim 2017 [36]               | ARFI      | 64  | Fontan              | 12.1               | –                     | 1.95                         | <1.3                 | –                              | –        |

ARFI: acoustic radiation force impulse elastography, MRE: magnetic resonance elastography, No.: number of patients, p: statistical value, SWE: shear-wave elastography, TE: transient elastography
Comparing TE to fibrosis stage by biopsy in Fontan patients found that liver stiffness values underestimated the level of fibrosis by at least one stage in seven out of ten patients, and in nine out of ten subjects overestimated the fibrosis level by two stages [39]. Deorsola et al. performed a study on patients undergoing the Fontan operation and used TE to evaluate the degree of liver stiffness before and after the surgery [58]. Patients with the Glenn shunt exhibited liver stiffness values close to normal before the conversion to total cavo-pulmonary connection (the Fontan surgery), the values ranging between 3.4-8 kPa. Four months after surgery the liver stiffness values significantly increased to a mean value of 11.2±4 kPa. The authors attributed the change in liver stiffness to congestion determined by the increase in pressures in the inferior vena cava secondary to the Fontan hemodynamics [58].

2D-SWE

The 2D-SWE technique generates shear waves inside the hepatic parenchyma by using radiation force from a focused ultrasound beam. The software evaluates shear wave propagation and provides a quantitative estimate of stiffness in the region of interest. To aid in assessment, color coding is used to display the stiffness values [59]. Unlike TE, SWE is integrated into an ultrasound system. Therefore, a conventional echography can be performed at the same time in order to select a hepatic parenchymal region without blood vessels or focal lesions to analyze. Several papers have reported higher accuracy of 2D-SWE than TE [60].

Using 2D-SWE, Kutty et al. found significantly higher hepatic stiffness values compared to controls (15.6 vs 5.5 kPa), in a study on adult and pediatric Fontan patients [61]. In research documenting liver disease in patients who had undergone the Glenn procedure, the same team found that patients have mildly elevated hepatic stiffness determined by 2D-SWE compared with healthy subjects (7.2 vs 5.7 kPa) [18]. A small study on 14 Fontan patients compared the results of 2D-SWE with biopsy samples and found that 2D-SWE overestimated the liver fibrosis in 10 cases and underestimated it in 4 cases [40]. Smaš-Suska et al. conducted a study on the liver health of patients with Fontan palliation using 2D-SWE and other noninvasive diagnostic tools and they observed that all patients had elevated liver stiffness (65% of patients had higher liver stiffness corresponding to F3 or F4 fibrosis stage) [47]. DiPaola et al. evaluating children before and after undergoing the Fontan procedure using 2D-SWE observed that liver stiffness in children with Glenn palliation was normal at 1.18 ± 0.29 m/s but markedly increased immediately after the Fontan procedure and with chronic evolution. The authors concluded that hepatic congestion is a key contributor to early FALD [62].

In 2017 a study on 30 post-Fontan patients validated a non-invasive index using the results from 2D-SWE, MELD-XI and time from Fontan surgery, which significantly correlated with total fibrosis scores (consisting of a sum between sinusoidal and portal fibrosis scores). 2D-SWE results were significantly correlated with individual sinusoidal and portal fibrosis scores and also to the sum of the fibrosis scores, the total fibrosis score being significantly correlated to the Fontan duration. The authors found no significant correlations between total fibrosis scores or elastography measurements and APRI scores (AST/thrombocyte ratio), alanine-aminotransferase (ALT) values or aspartate-aminotransferase (AST)/ALT ratios [63].

ARFI elastography is based on a similar principle as 2D-SWE, with the difference of examining a smaller region of interest (point quantification SWE) [29]. Melero-Ferrer et al. evaluated patients with Fontan circulation using ARFI elastography and found that 76% of the patients had shear wave propagation velocities over the cirrhosis threshold, while 90% of patients had evidence of liver fibrosis. When comparing the Fontan group to the control group and to a group of patients with cirrhosis, the authors found statistically significant differences in shear wave velocities [64]. ARFI elastography was used by a different team in evaluating patients post-Fontan, with similar results: 17/37 patients had shear wave velocity values compatible with advanced fibrosis, velocities in the Fontan population being much higher than normal values (1.8 m/sec vs 1.19 m/sec) [50]. Similarly, Kim et al. also reported higher values of velocity on a cohort of 64 patients with a Fontan circulation [36].

The utility of single elastography measurements in congestive hepatopathies seems to be limited due to difficulties in determining the relative contributions of hepatic congestion and fibrosis [65]. Hepatic congestion starting in the early post-operative period has been shown to overestimate the degree of fibrosis [62]. Consequently, serial measurements of liver stiffness might be more valuable in detecting true fibrotic changes and future studies should try to correlate liver stiffness values with liver biopsy in order to validate the method and establish cutoff values in the context of congestive hepatopathy. Until then, liver elastography may be useful in monitoring liver disease progression after the Fontan procedure and in the stratification of patients with high-risk congestive hepatopathy [34,62,66].

Conclusions

Liver pathology in the complex cardiac malformation survivors is extensive but understudied. In Fontan-palli-
ated patients particularly, the FALD is the most common second-organ dysfunction. The dreaded complications of this dysfunction are liver cirrhosis and hepatocellular carcinoma.

Elastography is a fascinating non-invasive method that could be used to assess liver fibrosis in children with cardiac diseases. There are conflicting data regarding the non-invasive methods of determining liver damage secondary to congestive heart disease. More evidence is required from larger studies correlating the results of elastography and serologic fibrosis markers to liver biopsy. Patients with congenital cardiac malformations require close monitoring and early diagnosis of liver complications to allow prompt therapeutic intervention.

**Conflict of interest:** none

**References**

1. Liu Y, Chen S, Zühlke L, et al. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. Int J Epidemiol 2019;48:455–463.
2. Oster ME, Lee KA, Honein MA, Riehle-Colarusso T, Shin M, Correa A. Temporal trends in survival among infants with critical congenital heart defects. Pediatrics 2013;131:e1502-e1508.
3. Wells ML, Fenstad ER, Poterucha JT, et al. Imaging Findings of Congestive Hepatopathy. Radiographics 2016;36:1024–1037.
4. Hilscher M, Sanchez W. Congestive hepatopathy. Clin Liver Dis (Hoboken) 2016;8:68–71.
5. Izumi Y, Hiramatsu N, Itose I, et al. Juvenile hepatocellular carcinoma with congestive liver cirrhosis. J Gastroenterol 2005;40:204–208.
6. Augustyn A, Peng L, Singal AG, Yopp AC. Surveillance for hepatocellular carcinoma secondary to cardiogenic cirrhosis in patients with congenital heart disease. Clin Res Cardiol 2015;104:446–449.
7. Yoshihara T, Sakamori R, Furuta K, et al. Hepatocellular carcinoma due to a baffle obstruction after the mustard operation: A case report. Hepatology 2018;67:2471–2473.
8. Weinberg AG, Bolande RP. The liver in congenital heart disease. Effects of infantile coarctation of the aorta and the hypoplastic left heart syndrome in infancy. Am J Dis Child 1970;119:390–394.
9. Nagdyman N, Mebus S, Kügel J, et al. Non-invasive assessment of liver alterations in Senning and Mustard patients. Cardiovasc Diagn Ther 2019;9:S198–S208.
10. Mebus S, Nagdyman N, Kügel J, et al. Non-invasive assessment of liver changes in Eisenmenger patients. Int J Cardiol 2017;249:140–144.
11. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax 1971;26:240–248.
12. Lemmer A, VanWagner LB, Ganger D. Assessment of Advanced Liver Fibrosis and the Risk for Hepatic Decompensation in Patients With Congestive Hepatopathy. Hepatology 2018;68:1633–1641.
13. Daniels CJ, Bradley EA, Landzberg MJ, et al. Fontan-Associated Liver Disease: Proceedings from the American College of Cardiology Stakeholders Meeting, October 1 to 2, 2015, Washington DC. J Am Coll Cardiol 2017;70:3173–3194.
14. Khairy P, Fernandes SM, Mayer JE Jr, et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. Circulation 2008;117:85–92.
15. Goldberg DJ, Surrey LF, Glatz AC, et al. Hepatic Fibrosis Is Universal Following Fontan Operation, and Severity is Associated With Time From Surgery: A Liver Biopsy and Hemodynamic Study. J Am Heart Assoc 2017;6:e004809.
16. Schwartz MC, Glatz AC, Daniels K, et al. Hepatic Abnormalities Are Present Before and Early After the Fontan Operation. Ann Thorac Surg 2015;100:2298–2304.
17. Ghaferi AA, Hutchins GM. Progression of liver pathology in patients undergoing the Fontan procedure: Chronic passive congestion, cardiac cirrhosis, hepatic adenoma, and hepatocellular carcinoma. J Thorac Cardiovasc Surg 2005;129:1348–1352.
18. Kutty SS, Zhang M, Danford DA, et al. Hepatic stiffness in the bidirectional cavopulmonary circulation: The Liver Adult-Pediatric-Congenital-Heart-Disease Dysfunction Study group. J Thorac Cardiovasc Surg 2016;151:678–684.
19. Komatsu H, Inui A, Kishiki K, et al. Liver disease secondary to congenital heart disease in children. Expert Rev Gastroenterol Hepatol 2019;13:651–666.
20. Kiesewetter CH, Sheron N, Vettukattill JJ, et al. Hepatic changes in the failing Fontan circulation. Heart 2007;93:579–584.
21. Baek JS, Bae EJ, Ko JS, et al. Late hepatic complications after Fontan operation; non-invasive markers of hepatic fibrosis and risk factors. Heart 2010;96:1750–1755.
22. Shimizu M, Miyamoto K, Nishihara Y, et al. Risk factors and serological markers of liver cirrhosis after Fontan procedure. Heart Vessels 2016;31:1514–1521.
23. Oh C, Youn JK, Han JW, Kim GB, Kim HY, Jung SE. Hepatocellular carcinoma after the Fontan procedure in a 16-year-old girl: A case report. Medicine (Baltimore) 2016;95:e4823.
24. Kuwabara M, Niwa K, Toyoda T, et al. Liver Cirrhosis and/or Hepatocellular Carcinoma Occurring Late After the Fontan Procedure - A Nationwide Survey in Japan. Circ J 2018;82:1155–1160.
25. Bedossa P, Dargère D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology 2003;38:1449–1457.
26. Bravo AA, Sheth SG, Chopra S. Liver biopsy. N Engl J Med 2001;344:495–500.
27. Louie CY, Pham MX, Daugherty TJ, Kambham N, Higgins JPT. The liver in heart failure: a biopsy and explant series of the histopathologic and laboratory findings with a particular focus on pre-cardiac transplant evaluation. Mod Pathol 2015;28:932–943.
28. Castera L. Noninvasive methods to assess liver dis- ease in patients with hepatitis B or C. Gastroenterology 2012;142:1293-1302.e4.
29. Lurie Y, Webb M, Cyttor-Kuinit R, Shteingart S, Lederkre- mer GZ. Non-invasive diagnosis of liver fibrosis and cir- rhosis. World J Gastroenterol 2015;21:11567–11583.
30. Crossan C, Tschochatzis EA, Longworth L, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. Health Technol Assess 2015;19:1–409.
31. Yoo BW, Choi JY, Eun LY, Park HK, Park YH, Kim SU. Congestive hepatopathy after Fontan operation and related factors assessed by transient elastography. J Thorac Cardiovasc Surg 2014;148:1498–1505.
32. Kaulitz R, Haber P, Sturm E, Schäfer J, Hofbeck M. Serial evaluation of hepatic function profile after Fontan operation. Herz 2014;39:98–104.
33. Lindsay I, Johnson J, Everitt MD, Hoffman J, Yetman AT. Impact of liver disease after the fontan operation. Am J Cardiol 2015;115:249–252.
34. Song J, Kim K, Huh J, et al. Imaging Assessment of Hepatic Changes after Fontan Surgery. Int Heart J 2018;59:1008–1114.
35. Friedrich-Rust M, Koch C, Rentzsch A, et al. Noninvasive assessment of liver fibrosis in patients with Fontan circulation using transient elastography and biochemical fibrosis markers. J Thorac Cardiovasc Surg 2008;135:560–567.
36. Kim S-O, Lee SY, Jang SI, et al. Hepatic Stiffness Using Shear Wave Elastography and the Related Factors for a Fontan Circulation. Pediatr Cardiol 2018;39:57–65.
37. Wu FM, Kogon B, Earing MG, et al. Liver health in adults with Fontan circulation: A multicenter cross-sectional study. J Thorac Cardiovasc Surg 2017;153:656–664.
38. Griroescu M, Rusu M, Neculoiu D, et al. The FibroTest value in discriminating between insignificant and significant fibrosis in chronic hepatitis C patients. The Romanian experience. J Gastrointestin Liver Dis 2007;16:31–37.
39. Wu FM, Opopowski AR, Raza R, et al. Transient elastography may identify Fontan patients with unfavorable hemodynamics and advanced hepatic fibrosis. Congenit Heart Dis 2014;9:438–447.
40. Schleiger A, Salzmann M, Kramer P, et al. Severity of Fontan-Associated Liver Disease Correlates with Fontan Hemodynamics. Pediatr Cardiol 2020;41:736–746.
41. Fidai A, Dallaire F, Alvarez N, et al. Non-invasive Investigations for the Diagnosis of Fontan-Associated Liver Disease in Pediatric and Adult Fontan Patients. Front Cardiovasc Med 2017;4:15.
42. Schachter JL, Patel M, Horton SR, Mike Devane A, Ewing A, Abrams GA. FibroSURE and elastography poorly predict the severity of liver fibrosis in Fontan-associated liver disease. Congenit Heart Dis 2018;13:764–770.
43. Kamath PS, Kim WR, Advanced Liver Disease Study Group. The model for end-stage liver disease (MELD). Hepatology 2007;45:797–805.
44. Evans WN, Acherman RJ, Ciccolo ML, et al. MELD-XI Scores Correlate with Post-Fontan Hepatic Biopsy Fibrosis Scores. Pediatr Cardiol 2016;37:1274–1277.
45. Poterucha JT, Johnson JN, Qureshi MY, et al. Magnetic Resonance Elastography: A Novel Technique for the Detection of Hepatic Fibrosis and Hepatocellular Carcinoma After the Fontan Operation. Mayo Clin Proc 2015;90:882–894.
46. Ackerman T, Geerts A, Van Vlierberghje H, De Backer J, François K. Hepatic Changes in the Fontan Circulation: Identification of Liver Dysfunction and an Attempt to Streamline Follow-up Screening. Pediatr Cardiol 2018;39:1604–1613.
47. Smaś-Suska M, Skubera M, Wilkosz T, et al. Noninvasive assessment of liver status in adult patients after the Fontan procedure. Pol Arch Intern Med 2019;129:181–188.
48. Kim TH, Yang HK, Jang HJ, Yoo SJ, Khalili K, Kim TK. Abdominal imaging findings in adult patients with Fontan circulation. Insights Imaging 2018;9:357–367.
49. Rathgeber SL, Guttmann OR, Lee AF, et al. Fontan-Associated Liver Disease: Spectrum of Disease in Children and Adolescents. J Am Heart Assoc 2020;9:e012529.
50. Buendia-Fuentes F, Melero-Ferrer JL, Plaza-López D, et al. Noninvasive Liver Assessment in Adult Patients With Fontan Circulation Using Acoustic Radiation Force Impulse Elastography and Hepatic Magnetic Resonance Imaging. World J Pediatr Congenit Heart Surg 2018;9:22–30.
51. Romero R. Liver in congenital heart disease: Implications of the fontan procedure for pediatric and adult liver specialists. Clin Liver Dis (Hoboken) 2013;2:210–214.
52. Jeong JH, Kim TY, Sohn PJ, et al. Real-time shear wave elastography in chronic liver diseases: accuracy for predicting liver fibrosis, in comparison with serum markers. World J Gastroenterol 2014;20:13920–13929.
53. Mărginean CO, Meliţ LE, Ghiga DV, Săsăran MO. The assessment of liver fibrosis in children with obesity on two methods: transient and two dimensional shear wave elastography. Sci Rep 2019;9:19800.
54. Mărginean CO, Meliţ LE, Ghiga DV, Săsăran MO. Reference values of normal liver stiffness in healthy children by two methods: 2D shear wave and transient elastography. Sci Rep 2020;10:7213.
55. Bamber J, Cosgrove D, Dietrich CF, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. Ultraschall Med 2013;34:169–184.
56. Fraquelli M, Rigamonti C, Casazza G, et al. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. Gut 2007;56:968–973.
57. Ferrarioli G, Wong VWS, Castera L, et al. Liver Ultrasound Elastography: An Update to the World Federation for Ultrasound in Medicine and Biology Guidelines and Recommendations. Ultrasound Med Biol 2018;44:2419–2440.
58. Deorsola L, Aidala E, Cascarano MT, Valori A, Agnoletti G, Pace Napoleone C. Liver stiffness modifications shortly
after total cavopulmonary connection. Interact Cardiovasc Thorac Surg 2016;23:513–518.

59. Ferraioli G, Parekh P, Levitov AB, Filice C. Shear wave elastography for evaluation of liver fibrosis. J Ultrasound Med 2014;33:197–203.

60. Barr RG. Shear wave liver elastography. Abdom Radiol (NY) 2018;43:800–807.

61. Kutty SS, Peng Q, Danford DA, et al. Increased hepatic stiffness as consequence of high hepatic afterload in the Fontan circulation: a vascular Doppler and elastography study. Hepatology 2014;59:251–260.

62. DiPaola FW, Schumacher KR, Goldberg CS, Friedland-Little J, Parameswaran A, Dillman JR. Effect of Fontan operation on liver stiffness in children with single ventricle physiology. Eur Radiol 2017;27:2434–2442.

63. Evans WN, Acherman RJ, Ciccolo ML, et al. A composite noninvasive index correlates with liver fibrosis scores in post-Fontan patients: Preliminary findings. Congenit Heart Dis 2018;13:38–45.

64. Melero-Ferrer JL, Osa-Sáez A, Buendia-Fuentes F, et al. Fontan Circulation in Adult Patients: Acoustic Radiation Force Impulse Elastography as a Useful Tool for Liver Assessment. World J Pediatr Congenit Heart Surg 2014;5:365–371.

65. Gordon-Walker TT, Bove K, Veldman G. Fontan-associated liver disease: A review. J Cardiol 2019;74:223–232.

66. Chen B, Schreiber RA, Human DG, Potts JE, Guttman OR. Assessment of Liver Stiffness in Pediatric Fontan Patients Using Transient Elastography. Can J Gastroenterol Hepatol 2016;2016:7125193.