Review

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

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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-

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tum, double-inlet right ventricle and complete atrioventricular septal defects [11]. Therefore "*Fontan-associated liver disease*" (FALD) is the most well-known type of hepatic disease secondary to cardiac malformations [12].

Liver biopsy is the gold standard method for diagnosing liver disease secondary to cardiac malformations. Despite the many advances in the field of non-invasive methods in evaluating the liver damage, such as 2D-shear wave elastography or transient elastography, the techniques are less applied to congestive hepatopathy because of the paucity of studies performed in this population [13].

The aim of this review is to summarize the information on the pathogenesis and diagnosis of congestive liver disease secondary to complex cardiac malformations, focusing on non-invasive diagnostic modalities.

Methods

We performed an electronic database search (Pubmed, Web of Science) with the data range from 2001 to 2020. The search terms 'noninvasive' + 'hepatopathy' + 'cardiac malformations'; 'noninvasive' +'congestive' + 'liver' + 'fibrosis'; 'noninvasive' + 'Fontan' + 'liver' were used. Firstly, we selected the studies that addressed the pathogenesis of congestive liver disease secondary to cardiac malformations. Secondly, articles regarding noninvasive methods of determining liver fibrosis in this group of patients were included. Papers in other language than English and articles without an available full text were excluded.

Results and discussions

Following the database search, 53 papers were selected: 8 on the physiopathology of congestive liver disease, 6 on serological markers of fibrosis, 3 on conventional imaging tools, 9 on transient elastography, 9 on shear wave elastography and 18 papers with matter-related information.

Physiopathology of congestive liver disease and FALD

The liver of patients with long-term increased hepatic pressure secondary to the Fontan procedure serves as a model for congestive hepatopathy [12]. The Fontan operation allows passive systemic venous return directly into the pulmonary circulation by connecting the superior and inferior vena cava to the pulmonary artery, resulting in the normalization of systemic oxygen saturation and ventricular volume load. Despite the improvement in survival and quality of life of patients with functional single ventricles after the Fontan palliation, long-term survivors 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]. Baek et al

[21] found that the risk of hepatic complications was 4.4 times greater in patients with a postoperative duration of 11 to 15 years compared to patients with a postoperative duration of 5 years or less. A study by Kiesewetter et al [20] on patients at a mean duration of the Fontan circuit of 14.1 years reported that 58.3% of patients had developed liver cirrhosis. In a different report 12/14 of patients with a postoperative duration of 20 years or more developed liver cirrhosis [22]. Although the median age of Fontan patients with carcinoma is 30 years, there have been reports of the tumor developing in adolescents as well [23]. A Japanese nation-wide survey on 2700 patients who had undergone the Fontan palliation was published in 2008 showing that 1.15 % of patients were diagnosed with liver cirrhosis or hepatocellular carcinoma [24].

Diagnosis of liver damage secondary to cardiac malformations

Invasive tool – liver biopsy

Although liver biopsy has been the gold-standard for staging LF, it has several limitations: invasiveness, the need for anesthesia, hemorrhagic complications, variability of the sampled area, intra- and inter-observer variability [25,26]. Coagulopathy due to liver disease or anticoagulants may increase the risk of complications. In addition, Fontan anatomy may complicate the biopsy technique. There is no histological score validated for the quantification of liver damage secondary to cardiac disease. The scoring systems devised to assess liver damage in chronic hepatitis reflect inflammation-induced necrosis derived from the portal area, whereas the damage in cardiac liver appears to be mostly central and sinusoidal. Interestingly, a recent study has shown previously unrecognized portal-based fibrosis in the majority of patients who died soon after the Fontan procedure, similar to fibrosis secondary to inflammatory causes (hepatitis, non-alcoholic fatty liver disease - NAFLD) [16].

The value of the liver biopsy for risk stratification prior to heart transplantation is also unclear: a study documenting 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 transplantation. Given the limitations of the liver biopsy, non-invasive 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 inflammatory and viral liver diseases. Laboratory tests, imagistic 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 congestive hepatopathy 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 patients 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, apolipoprotein A_1, total bilirubin, gamaglutamyl-transpeptidase) in order to evaluate the degree of fibrosis and necro-inflammatory 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 values measured by elastography [40]. On the contrary, other studies found elevated scores of the FibroTest but no correlation with the duration of the Fontan circulation [41]. Smaller studies have sought to determine the predictive value of FibroTest in adult Fontan patients, by comparison 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 Disease (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

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

Authors	**No.**	**Years 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 [20]	12	14.1	–	–	1.4 (1.2–4.6)	–	9.7±4.7	–	–	–
Friedrich-Rust 2008 [35]	39	5.6±3	–	57.8±34.3	0.98±0.6	–	–	–	–	–
Baek 2010 [21]	139	11.5±7	–	–	1.5±1.5	0,6±2	–	–	–	1.1±3.8
Yoo 2014 [31]	46	13.5	–	–	1.1±0.6	0,4±0.2	–	–	–	
Poterucha 2016 [45]	50	22	3.3±1.9	96±54	1.3±1	0,4±0.2	15±9	9±6	–	–
Wu 2016 [39]	27	20.4	–	84 (38–502)	0.9 (0.4-4.7)	0.39 (0.2–0.6)	–	–	0.44 (0.1–0.8)	–
Fidai 2017 [41]	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 [36]	64	12.1	2.97±2.47	59.2± 39.9	0.97± 0.55					
Evans 2017 [44]	30	15	–	–	–	0.39 (0.2-0.9)	–	10.6 (9.4–16)	–	–
Song 2018 [34]	26	10.5	2.5±1.3	69.7±33.9	0.9±0.7	–	–	–	–	–
Ackerman 2018 [46]	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 [47]	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 [40]	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].

Baek 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 values determined by TE were significantly higher in the Fontan group. The authors stated that a high 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

paring TE to fibrosis stage by biopsy in Fontan patients found that liver stiffness values overestimated 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 analyse. 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]. Smaś-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]. Mellero-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 cut-off 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

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