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ULTRASOUND

Effect of Fontan operation on liver stiffness in children with single ventricle physiology

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Abstract

Objectives Assess liver stiffness using ultrasound point shear wave elastography (US P-SWE) in children before and after the Fontan operation.

Methods Eighteen children undergoing the Fontan operation were prospectively enrolled. Eight US P-SWE measurements were obtained from the right hepatic lobe before surgery, and at multiple postoperative time points. Temporally related inferior vena cava pressure (IVC) data was collected from medical records, when available. Changes in mean liver shear wave speed (SWS) were assessed using a mixed-effect model with post hoc Tukey correction. Changes in IVC pressure were evaluated using the Wilcoxon signed-rank test. A p value less than 0.05 was considered significant.

Results Mean age at enrolment was 33.5 ± 10.5 months. Baseline mean liver SWS was normal at 1.18 ± 0.29 m/s, increased to 2.28 ± 0.31 m/s at 2.5 ± 1.2 days ($p < 0.0001$) and to 2.22 ± 0.38 m/s at 7.5 ± 1.4 days ($p < 0.0001$). Five subjects returned at a mean of 185 ± 28 days, and mean liver SWS remained elevated at 2.08 ± 0.24 m/s ($p < 0.0001$). Mean IVC pressure increased from 7.2 ± 2.6 mmHg at baseline to 16.44 ± 3.3 mmHg at 2.2 ± 0.8 days post-surgery ($p = 0.004$).

Conclusion The Fontan operation immediately and chronically increases liver stiffness and IVC pressure. Our study provides further evidence that congestion is a key driver of Fontan-associated liver disease.

Key points

- *The Fontan operation triggers immediate hepatic congestion and marked liver stiffening.*
- *Congestion, not fibrosis, drives early increased liver stiffness in Fontan patients.*
- *Hepatic congestion persists chronically for months after the Fontan operation.*
- *Congestion confounds shear wave elastography as a post-Fontan liver fibrosis biomarker.*

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Keywords Hepatopathy · Congestion · Congenital heart disease · Ultrasound · Shear wave elastography

Abbreviations

FALD	Fontan-associated liver disease
IVC	Inferior vena cava
MR	Magnetic resonance
P-SWE	Point shear wave elastography
SWE	Shear wave elastography
SWS	Shear wave speed
US	Ultrasound

Introduction

Children born with cardiac lesions in which there is only one functional ventricle suffer from cyanosis. Cardiac surgeons have developed a series of three palliative operations ("stages") that allow for adequate cardiac output and systemic oxygen saturation [1]. The final (third) stage, the Fontan operation, results in systemic venous return from the upper and lower parts of the body bypassing the heart and flowing passively to the lungs. Patients typically complete the Fontan operation in early childhood and now routinely survive into adulthood [2, 3].

Liver injury is a well-known complication of the Fontan operation and is commonly termed Fontan-associated liver disease (FALD) [4, 5]. The pathophysiology of FALD is not well understood but likely involves chronic hepatic congestion. In support of this theory, sinusoidal dilatation and sinusoidal fibrosis are common histopathologic findings when liver biopsy is performed years after the Fontan operation [6–10]. Liver fibrosis due to FALD is progressive, and advanced liver fibrosis can lead to serious complications, including decompensated portal hypertension and intrahepatic mass lesion development such as hepatocellular carcinoma [8, 11–14].

Prevention and treatment strategies for FALD are currently lacking, in part because of a lack of sensitive diagnostic tests. Blood laboratory tests are often normal or only mildly abnormal even in Fontan patients with advanced liver fibrosis [9, 15–18]. Conventional imaging tools can be insensitive to early liver fibrosis, and liver biopsy is not an ideal method because it can fail to detect histopathology that is not uniformly distributed within the liver and because it is invasive.

A technique that shows promise in the noninvasive assessment of liver fibrosis after the Fontan operation is ultrasound (US) shear wave elastography (SWE). In this technique, a standard US system is used to generate a focused acoustic radiation force impulse (so-called push pulse) within the liver. This push pulse gives rise to shear waves in the liver, and the speed of the waves is measured using the same transducer that generates the push pulse.

Recent, small cross-sectional studies demonstrate that both US SWE and magnetic resonance (MR) elastography may be useful in the detection of FALD [10, 19, 20]. The studies show that these modalities, when applied several years to decades after the Fontan operation, detect significantly increased liver stiffness in patients as compared to healthy controls. The severity of liver stiffness was proportional to time elapsed from operation, suggesting that fibrosis due to FALD is progressive. However, liver stiffness also directly correlated with indices of central venous pressure, implying that hepatic congestion also potentially increases stiffness estimates in these children.

The aim of our study was to use US SWE to describe the early natural history of liver stiffness in children undergoing the Fontan operation. We hypothesized that, on average, (1) children have normal preoperative liver stiffness, (2) liver stiffness increases immediately after the operation as a result of hepatic congestion and (3) liver stiffness remains increased at the time of hospital discharge.

Methods

This prospective cohort study was approved by the Institutional Review Board at the University of Michigan and is Health Insurance Portability and Accountability Act (HIPAA, United States) compliant. Parent/guardian written informed consent was obtained for all participants.

Between November 2014 and September 2015, we prospectively and consecutively enrolled children with single ventricle congenital heart disease presenting for the Fontan operation. Exclusion criteria were defined as (1) any pre-existing laboratory evidence of chronic liver disease as defined by chronic elevation (greater than 4 weeks) of alanine aminotransferase, aspartate aminotransferase or direct bilirubin up to greater than two times the upper limit of normal, (2) evidence of cirrhosis by conventional greyscale US imaging or (3) any portal vein or hepatic vein thrombosis or other hepatic vascular anomaly as assessed by a combination of greyscale and colour Doppler US imaging. In order to establish the presence or absence of exclusion criteria, blood was collected for laboratory testing, including alanine aminotransferase, aspartate aminotransferase and total and direct bilirubin, and conventional greyscale and Doppler US imaging of the liver was performed after the acquisition of informed consent. Inclusion US examinations were reviewed by a single fellowship-trained paediatric radiologist.

Thirty-three consecutive children and their parents/guardians were approached to participate in our study (Fig. 1). A total of 21 families agreed to participate, and all 21 children met study criteria and were enrolled. Three patients were withdrawn just after enrollment at the request of their parents/guardians because the patients were unable to keep still enough to allow accurate baseline US SWE data acquisition. Therefore, 18 children including 6 (33 %) girls and 12 (67 %) boys completed the study. The mean age at enrollment for girls was 33 months (range 24–47 months) and for boys was 34 months (range 18–52 months), and for all 18 subjects combined was 33.5 (range 18–52 months).

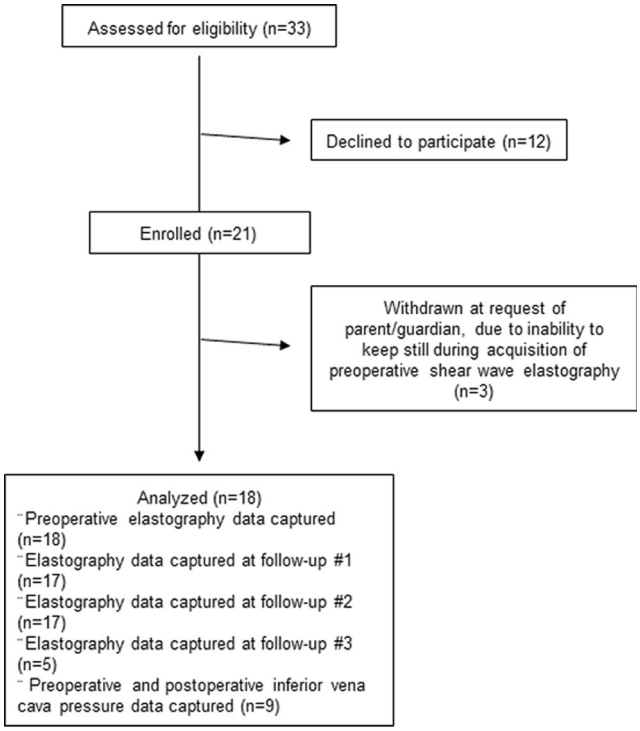

Fig. 1 Study subject flow diagram. A total of 33 subjects and their parent/guardians were approached consecutively, and 21 subjects were officially enrolled while 12 families declined to participate. Of the 21 enrolled subjects, three were withdrawn just after enrollment at the request of their parent/guardian due to inability to cooperate with the initial elastography exam. Therefore, a total of 18 subjects were analysed. The final box shows the total number of subjects for which data was captured at each of the study time points

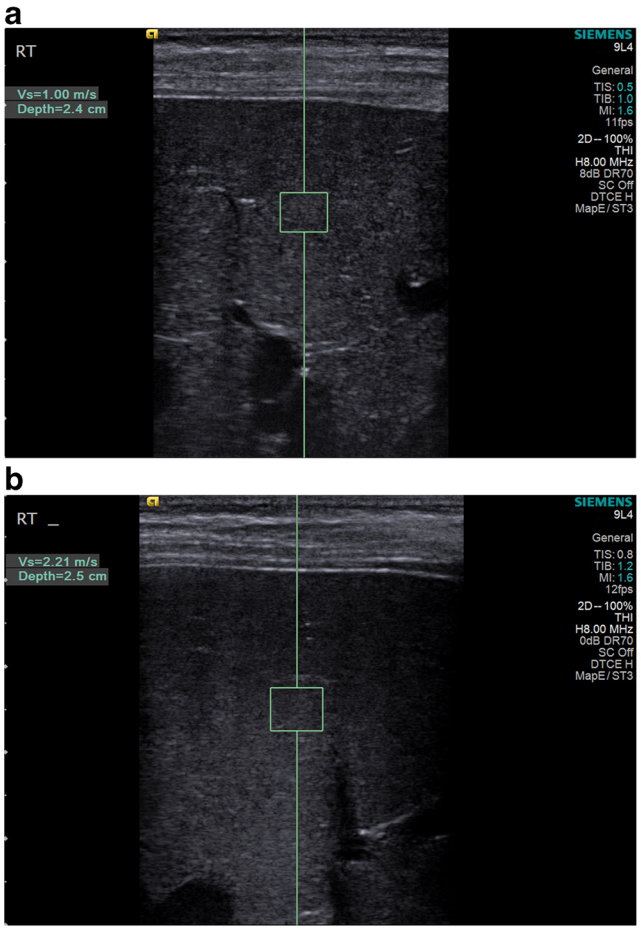

Fig. 2 Ultrasound hepatic point shear wave elastography images from a 34-month-old female patient with single ventricle congenital heart disease. **a** Point shear wave elastography (p-SWE) image obtained prior to stage 3 of the Fontan operation shows normal liver stiffness (shear wave speed measurement = 1.00 m/s). **b** p-SWE image obtained 24 h after surgery shows marked interval liver stiffening due to hepatic congestion (shear wave speed measurement = 2.21 m/s)

Baseline data were recorded, including age, gender, details of original cardiac lesion and dates of the stage 1 and stage 2 operations. As standard of care, all patients underwent preoperative assessment of ventricular function and intracardiac pressures, including right atrial pressure, by cardiac catheterization. Pressure data were obtained by chart review and documented.

Preoperative US SWE was performed using an Acuson S3000 US system and 9L4 transducer (Siemens Medical Solutions USA, Inc.; Mountain View, CA). Using Virtual Touch Quantification (VTQ), eight consecutive point SWE (P-SWE) shear wave speed (SWS) measurements were acquired from the central right hepatic lobe (segment 6 or 7) at least 1 cm deep to the liver capsule (Fig. 2). Subjects were imaged free-breathing in the supine position with the right arm in abduction. The US transducer was positioned either subcostal or in a lateral intercostal space adjacent to the right lobe of the liver.

US P-SWE was repeated postoperatively at multiple time points, including (1) within 24–72 h of the Fontan operation ("follow-up #1"), (2) just prior to hospital discharge ("follow-up #2") and (3) at approximately 6 months after the operation if the subject returned to our institution for follow-up clinical evaluation ("follow-up #3"). When available, pressure data was collected from centrally positioned vascular catheters (placed according to operative/postoperative standard of care) at the same time as follow-up US P-SWE.

Statistical analyses

Continuous data were summarized as means and standard deviations, while categorical data were summarized as counts. Tukey box plots and spaghetti plots were used to visually assess change in individual mean liver SWS measurements versus time as well as inferior vena cava (IVC) pressures versus time. Comparison of mean SWS from different time points was performed using a mixed effect model with post hoc Tukey correction to adjust for multiple comparisons. Mean IVC pressures from different time points were compared using the Wilcoxon signed-rank test.

A p value less than 0.05 was considered significant for all inference testing. Statistical analyses were performed using SAS, version 9.4 (SAS Institute; Cary, NC).

Results

Demographics and baseline data

The demographic, preoperative cardiac anatomic, baseline laboratory and US characteristics of the study subjects, and whether or not a fenestration (surgical window which allows systemic venous return to bypass the pulmonary circulation) was performed during Fontan operation are summarized in Table 1. Baseline serum aspartate aminotransferase, alanine aminotransferase, total bilirubin, and direct bilirubin were available for 16 of 18 patients and were within normal limits. Baseline labs were not drawn by the clinical team for two patients despite our request; neither of the two patients had any documented history of chronic liver disease. There was no US evidence of liver cirrhosis and Doppler examination of the portal and hepatic veins was normal for all 18 patients.

Liver SWS measurements over time

Follow-up #1 ($n = 17$) was 2.5 ± 1.2 days post-surgery, follow-up #2 ($n = 17$) was 7.5 ± 1.4 days post-surgery and follow-up #3 ($n = 5$) was 185 ± 28 days post-surgery. US P-SWE pairwise comparison results between various time points are summarized in Table 2. Tukey box plots and spaghetti (individual trend) plots showing subject mean liver SWS measurements over time are presented in Figs. 3 and 4.

Mean preoperative liver SWS was 1.18 ± 0.29 m/s. Mean liver SWS was 2.28 ± 0.31 m/s at follow-up #1, 2.22 ± 0.38 m/s at follow-up #2 and 2.08 ± 0.24 m/s at follow-up #3. There were significant differences in mean liver SWS between baseline and all three follow-up time points (p values <0.0001 for baseline vs. all follow-up time points). There was no difference in mean liver SWS between follow-up #1 and #2 ($p = 0.93$), between follow-up #1 and follow-up #3 ($p = 0.53$) or between follow-up #2 and #3 ($p = 0.75$).

IVC pressure measurements over time

Postoperative IVC pressure data was available at follow-up #1 for 9 out of 18 patients (patients 1, 2, 3, 4, 6, 9, 13, 15 and 18). For this subset of patients, follow-up #1 was 2.2 ± 0.8 days post-surgery. This data was unavailable in the other patients at follow-up #1 because of prior discontinuation of the central line at the discretion of the clinical team. The central line was discontinued in every enrolled patient in the study prior to follow-up #2. Tukey box plots and spaghetti plots showing subject mean IVC measurements over time are presented in Figs. 5 and 6.

Table 1 Demographics and baseline clinical information for the study subjects

Subject	Sex	Original cardiac lesion	Functional ventricle	Age (days) at stage 1	Age (months) at stage 2	Age (months) at Fontan operation	AST/ALT (IU/mL)	Total bilirubin (mg/dl)	Nodularity by gray-scale US?	PV/HV patent?	Did Fontan operation include fenestration?
1	F	Tricuspid atresia	L	*	4	47	42/22	0.7	No	Yes	No
2	M	HLHS	R	4	5	22	52/21	0.5	No	Yes	Yes
3	F	HLHS	R	3	5	36	50/26	0.8	No	Yes	Yes
4	M	HLHS	R	7	4	38	39/11	0.2	No	Yes	Yes
5	F	HLHS	R	14	6	26	46/23	0.5	No	Yes	Yes
6	M	Truncus arteriosus, mitral valve atresia	R	6	6	23	46/29	0.2	No	Yes	Yes
7	F	Tricuspid stenosis, pulmonary stenosis	L	6	6	24	42/15	0.7	No	Yes	Yes
8	M	HLHS	R	3	3	22	39/18	0.7	No	Yes	Yes
9	F	PA/IVS	L	5	5	34	Not drawn	Not drawn	No	Yes	No
10	M	HLHS	R	6	3	46	47/20	0.7	No	Yes	No
11	M	DORV/PS	R	5	6	46	34/19	0.3	No	Yes	No
12	M	HLHS	R	8	5	46	Not drawn	Not drawn	No	Yes	Yes
13	M	PA/IVS	L	205	18	35	36/17	0.5	No	Yes	No
14	M	HLHS	R	8	4	52	43/21	1.0	No	Yes	Yes
15	M	DILV	L	18	4	24	37/19	0.5	No	Yes	Yes
16	F	Tricuspid atresia	L	6	5	31	32/17	0.6	No	Yes	Yes
17	M	HLHS	R	2	8	18	36/20	0.5	No	Yes	Yes
18	M	HLHS	R	2	5	34	55/63	0.8	No	Yes	Yes

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *DILV* double inlet left ventricle, *DORV/PS* double outlet right ventricle and pulmonary stenosis, *F* female, *HLHS* hypoplastic left heart syndrome, *HV* hepatic vein, *L* left, *M* male, *R* right, *PA/IVS* pulmonary atresia with intact ventricular septum, *PV* portal vein, *US* ultrasound

* This patient underwent the bidirectional Glenn operation (typically a second stage in the palliative series) as the first operation

Table 2 Comparison of mean shear wave speed between time points

Pairwise comparisons	Mean (standard deviation) shear wave speed (m/s)	*P* value
Baseline vs. follow-up #1 ($n = 17$)	1.18 (0.29) vs. 2.28 (0.31)	<0.0001
Baseline vs. follow-up #2 ($n = 17$)	1.18 (0.29) vs. 2.22 (0.38)	<0.0001
Baseline vs. follow-up #3 ($n = 5$)	1.18 (0.29) vs. 2.08 (0.24)	<0.0001
Follow-up #1 vs. #2 ($n = 17$)	2.28 (0.31) vs. 2.22 (0.38)	0.93
Follow-up #1 vs. #3 ($n = 5$)	2.28 (0.31) vs. 2.08 (0.24)	0.53
Follow-up #2 vs. #3 ($n = 5$)	2.22 (0.38) vs. 2.08 (0.24)	0.75

Among patients with available data, measured IVC pressure (i.e. right atrial pressure preoperatively and Fontan pressure postoperatively) was significantly increased from baseline to follow-up #1 (7.17 ± 2.6 mmHg vs. 16.44 ± 3.3 mmHg, $p = 0.004$). Of the nine patients with central line data at follow-up #1, six patients had a fenestration and three patients did not have a fenestration, and there was no significant difference in mean IVC pressure at follow-up #1 between the two groups (17.2 ± 3.8 mmHg in the fenestration group versus 15 ± 2.0 mmHg in the non-fenestration group, $p = 0.54$).

Discussion

Our data confirm that the Fontan operation causes a marked immediate increase in liver stiffness from an average baseline of normal stiffness, and that the increase in liver stiffness coincides with a significant increase in IVC pressure. Taken together, our data implicate hepatic congestion, and not liver fibrosis, as the singular driver of increased liver stiffness in the early postoperative period in this patient population. These results are in agreement with a recently published study ($n = 9$) using transient elastography that demonstrated an increase in liver stiffness from normal at 4 months following the Fontan operation [21]. We are the first to demonstrate that the increase occurs immediately (within the first 48 h) and is sustained chronically.

US SWE is an accurate means of assessing liver stiffness in children and adults [22–24]. A recent two-centre investigation showed that US SWE is also highly reproducible, with low coefficients of variation (0.5–3.8 %) and near-perfect interoperator agreement when evaluating soft and hard US elasticity phantoms [25]. Similar data has been obtained in healthy human subjects and in patients with chronic liver disease, showing low variability between measurements of liver stiffness obtained by the same examiner and excellent

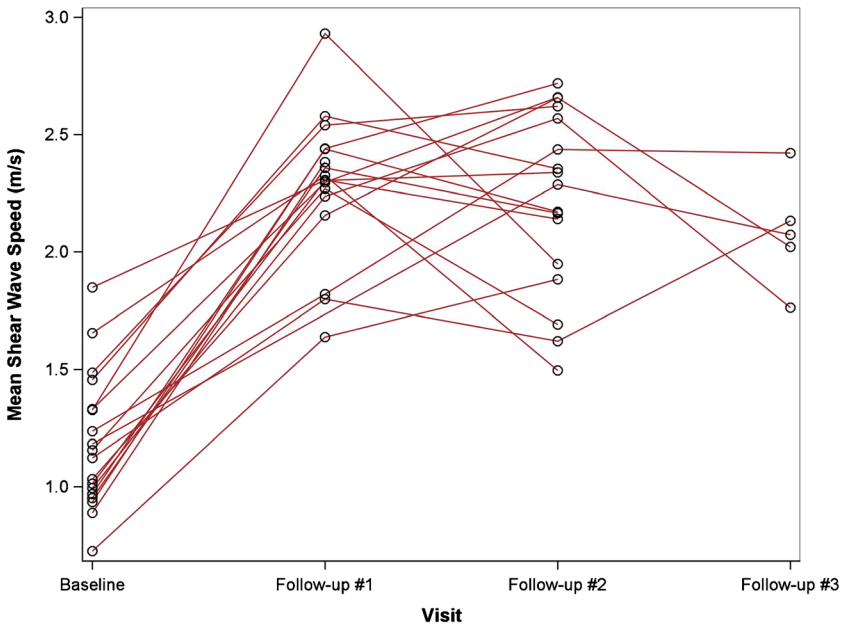

Fig. 3 Spaghetti plot showing individual changes in mean liver shear wave speeds from baseline to time points following the Fontan operation. All subjects demonstrated a marked increase in mean liver stiffness (shear wave speed) from baseline (preoperative) to immediately after surgery. Mean times elapsed from surgery were 2.5 ± 1.2 days at follow-up #1, 7.5 ± 1.4 days at follow-up #2 and 185 ± 28 days at follow-up #3. Some subjects showed a decrease in mean liver stiffness between follow-up time points, while other subjects showed an increase; on average, there was no significant difference between the three follow-up time points. *Circles* at each time point represent the mean liver stiffness values for each individual study subject

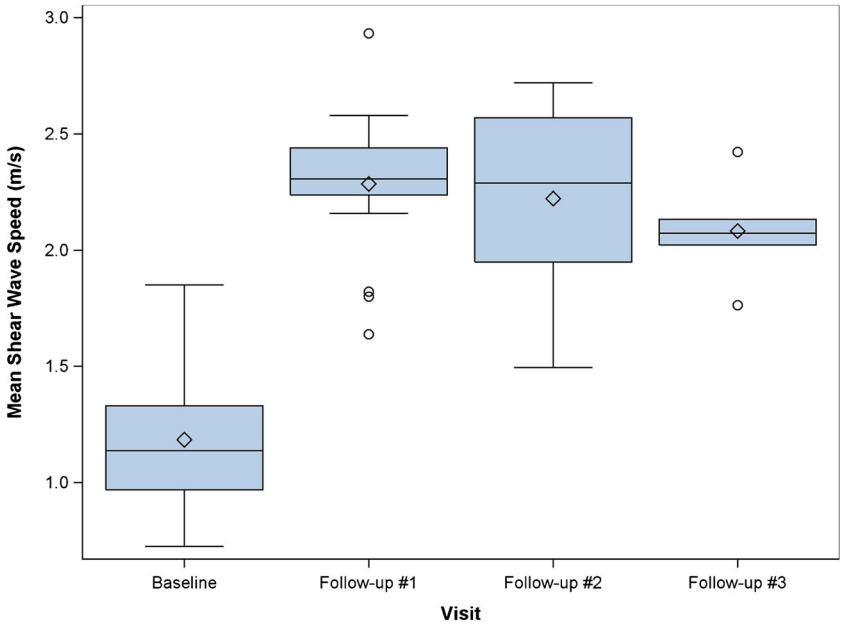

Fig. 4 Tukey box plot showing change in liver shear wave speed from baseline to time points following the Fontan operation. There was a significant increase in mean liver stiffness (shear wave speed) between baseline (preoperative) and all three follow-up time points ($p < 0.0001$ for baseline versus all follow-up time points). Mean times elapsed from surgery were 2.5 ± 1.2 days at follow-up #1, 7.5 ± 1.4 days at follow-up #2 and 185 ± 28 days at follow-up #3. There were no significant differences in mean liver stiffness between any of the follow-up time points. *Diamonds* represent the mean of all subjects combined for each time point; *circles* represent statistical outliers; the *bottom* and *top* of each box represent the first and third quartiles respectively; the *band* within each box represents the median; the *whiskers* of each box represent the range

agreement between multiple examiners [26–28]. Our study adds to the body of literature demonstrating that US SWE is an important tool in the assessment of children after the Fontan operation.

MR elastography is also an excellent means of assessing liver stiffness, although there is a paucity of published literature describing the use of this technique in young children. In this technique, a pneumatic passive driver is placed over the

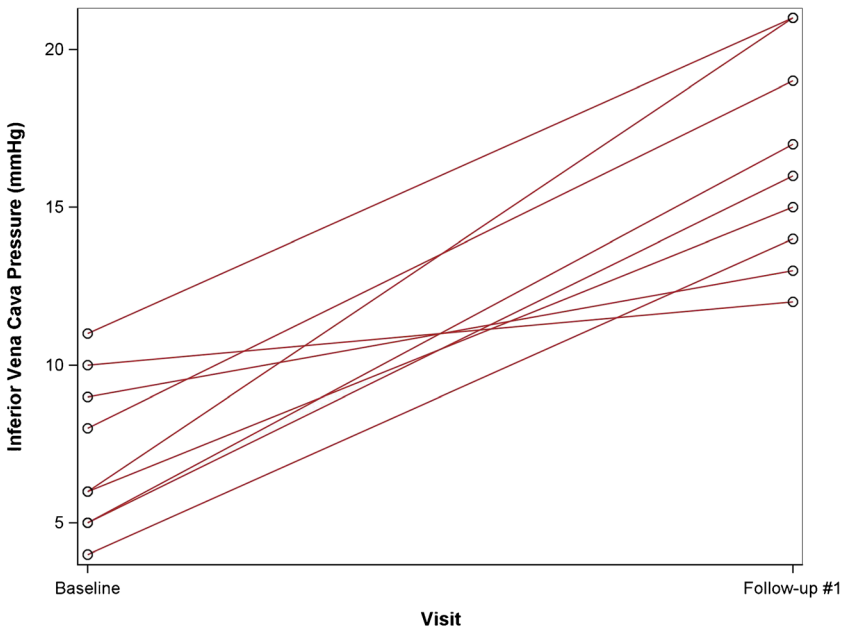

Fig. 5 Spaghetti plot showing individual changes in inferior vena cava pressure from baseline to immediately following the Fontan operation ($n = 9$). Inferior vena pressures increased from baseline (preoperative) to immediately after surgery (follow-up #1) in each subject. Mean time elapsed from surgery at follow-up #1 in this subgroup of patients was 2.2 ± 0.8 days. *Circles* at each time point represent the mean liver stiffness values for each individual study subject. Data points upon which two lines converge represent two patients with the same inferior vena cava pressure

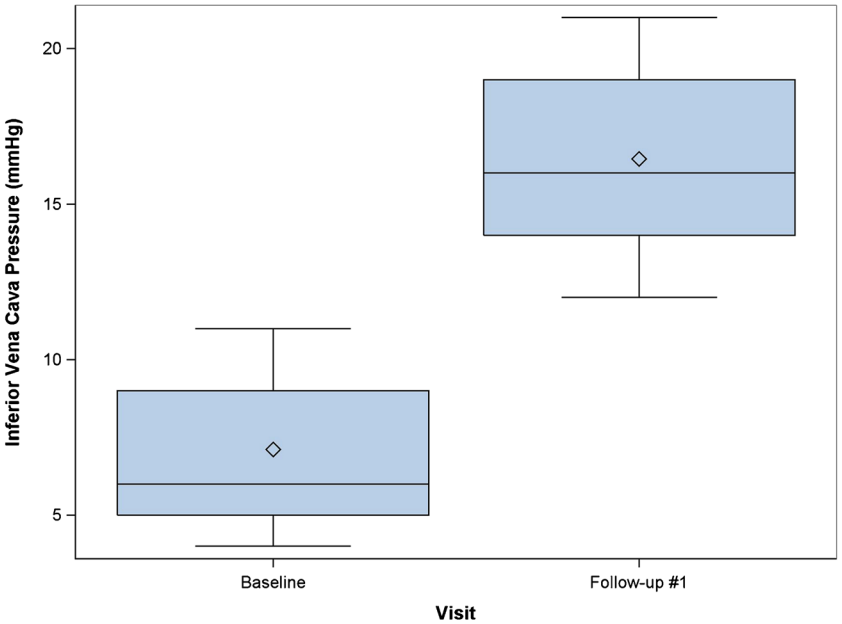

Fig. 6 Tukey box plot showing change in inferior vena cava pressure from baseline to immediately following the Fontan operation ($n = 9$). Mean inferior vena cava pressure increased significantly from baseline (preoperative) to immediately after surgery (follow-up #1), from 7.17 ± 2.6 mmHg to 16.44 ± 3.3 mmHg ($p = 0.004$). Mean time elapsed from the operation at follow-up #1 was 2.2 ± 0.8 days. *Diamonds* represent the mean of all subjects combined for each time point; the *bottom* and *top* of each box represent the first and third quartiles respectively; the *band* within each box represents the median; the *whiskers* of each box represent the range

right upper quadrant abdominal wall, and modified phase contrast pulse sequences are used to track mechanically induced shear waves within the liver. The technique has been shown to provide reproducible results between manufacturers of scanners (e.g. Philips Healthcare versus GE Healthcare) and across different field strengths and different pulse sequences [29].

We chose US SWE over MR elastography for our study because it is portable and very practical for bedside use, and because of the other relative disadvantages of MR elastography including higher cost, more limited availability, the potential need for sedation in children and possible contraindications (e.g. presence of non-MR-compatible devices or surgical materials).

We did not include a cohort of healthy children for sake of establishing normal mean liver stiffness in our hands, because normal values for healthy young children as measured using Siemens Acuson SWE technology are well established in the literature. Four recent, independent studies including a combined 164 healthy children ranging in age from 1 to 5 years reported mean liver SWS in this age group ranging from 1.11 to 1.26 m/s with reported standard deviations ranging from 0.05 to 0.19 m/s [30–33]. The mean preoperative SWS in our cohort (1.18 m/s) falls within this range of normal, suggesting that children in our study had normal (on average) liver stiffness prior to the Fontan operation, followed by a marked and sustained increase in stiffness.

A recent study suggests that liver fibrosis might begin even before the Fontan operation [34]. However, this study reviewed autopsy tissue from relatively sick patients, many of whom may have had other early forms of liver injury such as ischemic injury. While a small number of subjects (2 of 18) in our study had mildly elevated baseline mean liver stiffness measurements (defined as mean liver SWS greater than 1.5 m/s), which in theory could be due to mild fibrosis, mean preoperative liver stiffness was normal (on the basis of published literature documenting normal liver SWS values in the paediatric population using VTQ). Furthermore, it is not plausible that hepatic fibrosis could progress rapidly enough following the Fontan operation to explain the change in liver stiffness observed in the early postoperative period. Thus, our results suggest that liver fibrosis is negligible at the time of the Fontan operation in most single ventricle congenital heart disease patients.

The noted increase in IVC pressure in the immediate postoperative period (follow-up #1) substantiates that the physiology of the newly completed Fontan circuit (IVC to pulmonary artery anastomosis) drives hepatic congestion (see Supplementary Figs. 1 and 2 for illustrations of pre- and postoperative cardiac anatomy and associated IVC pressures). While we were not able to analyse for correlation between change in mean liver stiffness and change in IVC pressure because of the small sample size, it is mechanistically likely. We hypothesize that there is a direct positive linear correlation between the increases in IVC pressure which occur following the Fontan operation and increases in liver SWS. Study of a larger number of patients would allow this correlation to be more precisely defined.

Our data also suggest that hepatic congestion persists chronically after the Fontan operation. With respect to chronic FALD, since the stiffness of the liver is eventually almost certainly influenced by both congestion and fibrosis, any study of one of these factors by US SWE is potentially confounded by the other. Thus, we believe that further prospective studies are necessary to complete a "roadmap" of the natural history of liver stiffness following the Fontan operation at later time points (e.g. yearly throughout childhood and adolescence), which may reveal a pattern of liver stiffness over time that permits the detection of the typical timing of onset of liver fibrosis. Such knowledge might further elucidate the pathophysiology of both liver congestion and fibrosis in these children.

We note that our data also suggests that US SWE is sensitive in the detection of acute changes in IVC pressure that happen early on and which appear to drive hepatic congestion. If congestion is the primary or sole trigger of liver fibrosis, US SWE may eventually become a useful noninvasive, low-cost proxy assessment of Fontan haemodynamics and a clinical means of determining which patients are at highest risk of fibrosis development.

Finally, it is conceivable that changes in liver stiffness over time may predict a variety of important Fontan-related complications, such as eventual need for heart transplantation or the development of protein-losing enteropathy. Careful assessment of Fig. 3 shows that some subjects experience increases in liver stiffness between the follow-up time points, while other subjects show decreases. It is such changes, especially in the long run, that we believe may have predictive abilities.

The primary limitations of this study are the small sample size and the limited capture of follow-up US SWE data at 6 months, since most subjects undergoing the Fontan operation at our hospital live far away and receive follow-up care closer to home. Therefore, our study does not definitively address the trend in liver stiffness beyond the near-immediate postoperative period. That said, we have clearly shown that all subjects undergoing the Fontan operation experience immediate and marked liver stiffening that is equal to that attributed in the literature to moderate to severe liver fibrosis [35, 36]. Second, missing postoperative IVC pressure data from multiple subjects, due to early discontinuation of the central venous line postoperatively at the discretion of the treating physician, hindered our ability to assess the exact relationship between liver SWS measurements and IVC pressure. Third, our study involved patients who were clinically stable at the time of presentation for the operation. Patients who suffer substantial cardiac morbidity prior to the Fontan operation may have earlier onset of liver injury and therefore may have a unique profile when assessed by US SWE. However, our study remains broadly generalizable since most children present semi-electively for the Fontan operation in good clinical condition. Finally, we point out that we performed eight P-SWE measurements per US elastography session rather than ten measurements per session as currently recommended according to a recently published consensus guideline, which was made available after initiation of our study [35]. However, we do not believe that this fact substantively impacted our results.

Conclusion

The Fontan operation immediately and chronically increases liver stiffness and IVC pressure, indicating that hepatic congestion is a key contributor to early FALD. Further longitudinal research is needed to definitively determine how liver stiffness changes over time beyond the immediate postoperative period and if different patterns exist. It is conceivable that baseline postoperative SWS measurements or change in SWS over time may predict important long-term clinical outcomes, such as FALD or Fontan failure with need for eventual cardiac transplantation. Finally, and of equal importance, our data convincingly show that US SWE is a confounded biomarker in the Fontan population (and likely in other populations with right-sided cardiac disease), as liver SWS measurements can be impacted significantly by passive congestion in addition to fibrosis.

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Aishwarya Parameswaran, MS, of the Michigan Institute for Clinical and Health Research (MICHR) and one of the authors, has significant statistical expertise and kindly provided statistical advice for this manuscript. Institutional review board approval was obtained. Written informed consent was obtained from all subjects (patients) in this study. Methodology: prospective, cohort study, performed at one institution.

References

1. de Leval MR, Deanfield JE (2010) Four decades of Fontan palliation. Nat Rev Cardiol 7:520–527
2. Khairy P, Fernandes SM, Mayer JE Jr et al (2008) Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. Circulation 117:85–92
3. d'Udekem Y, Iyengar AJ, Cochrane AD et al (2007) The Fontan procedure: contemporary techniques have improved long-term outcomes. Circulation 116:I157–I164
4. Rychik J, Veldtman G, Rand E et al (2012) The precarious state of the liver after a Fontan operation: summary of a multidisciplinary symposium. Pediatr Cardiol 33:1001–1012
5. Greenway SC, Crossland DS, Hudson M et al (2015) Fontan-associated liver disease: implications for heart transplantation. J Heart Lung Transplant. doi:10.1016/j.healun.2015.10.015

6. Kendall TJ, Stedman B, Hacking N et al (2008) Hepatic fibrosis and cirrhosis in the Fontan circulation: a detailed morphological study. J Clin Pathol 61:504–508
7. Kiesewetter CH, Sheron N, Vettukattill JJ et al (2007) Hepatic changes in the failing Fontan circulation. Heart 93:579–584
8. Ghaferi AA, Hutchins GM (2005) Progression of liver pathology in patients undergoing the Fontan procedure: chronic passive congestion, cardiac cirrhosis, hepatic adenoma, and hepatocellular carcinoma. J Thorac Cardiovasc Surg 129:1348–1352
9. Schwartz MC, Sullivan LM, Glatz AC et al (2013) Portal and sinusoidal fibrosis are common on liver biopsy after Fontan surgery. Pediatr Cardiol 34:135–142
10. Kutty SS, Peng Q, Danford DA et al (2014) Increased hepatic stiffness as consequence of high hepatic afterload in the Fontan circulation: a vascular Doppler and elastography study. Hepatology 59:251–260
11. Wallihan DB, Podberesky DJ (2013) Hepatic pathology after Fontan palliation: spectrum of imaging findings. Pediatr Radiol 43:330–338
12. Asrani SK, Warnes CA, Kamath PS (2013) Hepatocellular carcinoma after the Fontan procedure. N Engl J Med 368:1756–1757
13. Saliba T, Dorkhom S, O'Reilly EM, Ludwig E, Gansukh B, Abou-Alfa GK (2010) Hepatocellular carcinoma in two patients with cardiac cirrhosis. Eur J Gastroenterol Hepatol 22:889–891
14. Elder RW, Parekh S, Book WM (2013) More on hepatocellular carcinoma after the Fontan procedure. N Engl J Med 369:490
15. Baek JS, Bae EJ, Ko JS et al (2010) Late hepatic complications after Fontan operation; non-invasive markers of hepatic fibrosis and risk factors. Heart 96:1750–1755
16. Ginde S, Hohenwalter MD, Foley WD et al (2012) Noninvasive assessment of liver fibrosis in adult patients following the Fontan procedure. Congenit Heart Dis 7:235–242
17. Shah H, Kuehl K, Sherker AH (2010) Liver disease after the Fontan procedure: what the hepatologist needs to know. J Clin Gastroenterol 44:428–431
18. Bulut OP, Romero R, Mahle WT et al (2013) Magnetic resonance imaging identifies unsuspected liver abnormalities in patients after the Fontan procedure. J Pediatr 163:201–206
19. Serai SD, Wallihan DB, Venkatesh SK et al (2014) Magnetic resonance elastography of the liver in patients status-post fontan procedure: feasibility and preliminary results. Congenit Heart Dis 9:7–14
20. Wallihan DB, Podberesky DJ, Marino BS, Sticka JS, Serai S (2014) Relationship of MR elastography determined liver stiffness with cardiac function after Fontan palliation. J Magn Reson Imaging 40:1328–1335
21. Deorsola L, Aidala E, Cascarano MT, Valori A, Agnoletti G, Napoleone CP (2016) Liver stiffness modifications shortly after total cavopulmonary connection. Interact Cardiovasc Thorac Surg. doi:10.1093/icvts/ivw186
22. Ferraioli G, Tinelli C, Dal Bello B et al (2012) Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology 56:2125–2133
23. Ferraioli G, Parekh P, Levitov AB, Filice C (2014) Shear wave elastography for evaluation of liver fibrosis. J Ultrasound Med 33:197–203
24. Castera L (2012) Noninvasive methods to assess liver disease in patients with hepatitis B or C. Gastroenterology 142:1293–1302 e1294
25. Dillman JR, Chen S, Davenport MS et al (2015) Superficial ultrasound shear wave speed measurements in soft and hard elasticity phantoms: repeatability and reproducibility using two ultrasound systems. Pediatr Radiol 45:376–385
26. Muller M, Gennisson JL, Deffieux T, Tanter M, Fink M (2009) Quantitative viscoelasticity mapping of human liver using supersonic shear imaging: preliminary in vivo feasibility study. Ultrasound Med Biol 35:219–229
27. Ferraioli G, Tinelli C, Zicchetti M et al (2012) Reproducibility of real-time shear wave elastography in the evaluation of liver elasticity. Eur J Radiol 81:3102–3106
28. Woo H, Lee JY, Yoon JH, Kim W, Cho B, Choi BI (2015) Comparison of the reliability of acoustic radiation force impulse imaging and supersonic shear imaging in measurement of liver stiffness. Radiology 277:881–886
29. Trout AT, Serai S, Mahley AD et al (2016) Liver stiffness measurements with MR elastography: agreement and repeatability across imaging systems, field strengths, and pulse sequences. Radiology. doi:10.1148/radiol.2016160209:160209
30. Eiler J, Kleinholdermann U, Albers D et al (2012) Standard value of ultrasound elastography using acoustic radiation force impulse imaging (ARFI) in healthy liver tissue of children and adolescents. Ultraschall Med 33:474–479
31. Hanquinet S, Courvoisier D, Kanavaki A, Dhouib A, Anooshiravani M (2013) Acoustic radiation force impulse imaging-normal values of liver stiffness in healthy children. Pediatr Radiol 43:539–544
32. Lee MJ, Kim MJ, Han KH, Yoon CS (2013) Age-related changes in liver, kidney, and spleen stiffness in healthy children measured with acoustic radiation force impulse imaging. Eur J Radiol 82:e290–e294
33. Matos H, Trindade A, Noruegas MJ (2014) Acoustic radiation force impulse imaging in paediatric patients: normal liver values. J Pediatr Gastroenterol Nutr 59:684–688
34. Schwartz MC, Sullivan L, Cohen MS et al (2012) Hepatic pathology may develop before the Fontan operation in children with functional single ventricle: an autopsy study. J Thorac Cardiovasc Surg 143:904–909
35. Barr RG, Ferraioli G, Palmeri ML et al (2015) Elastography assessment of liver fibrosis: Society of Radiologists in Ultrasound Consensus Conference Statement. Radiology 276:845–861
36. Dillman JR, Heider A, Bilhartz JL et al (2015) Ultrasound shear wave speed measurements correlate with liver fibrosis in children. Pediatr Radiol 45:1480–1488