Relation of Magnetic Resonance Elastography to Fontan Failure and Portal Hypertension

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Fontan associated liver disease is associated with morbidity and mortality in palliated single-ventricle congenital heart disease patients. Magnetic resonance elastography (MRE) provides a quantitative assessment of liver stiffness in Fontan patients. We hypothesized that MRE liver stiffness correlates with liver enzymes, hemodynamics, portal hypertension, and Fontan failure (FF). All adult Fontan patients who had MRE between 2011 and 2018 were included. Radiologic portal hypertension was defined as splenomegaly, ascites, and/or varices. FF was defined as death, transplantation, or heart failure symptoms requiring escalation of diuretics. Seventy patients with a median age of 24.7 years and a median follow-up from MRE of 3.9 years were included. The median liver stiffness was 4.3 kPa (interquartile range [IQR]: 3.8 to 5.0 kPa). There was a weak, positive correlation between liver stiffness and Fontan pathway pressure ($r = 0.34$, $p = 0.03$). There was a moderate negative correlation of liver stiffness with ventricular ejection fraction ($r = -0.52$, $p = 0.03$). Liver stiffness was weakly positively correlated with liver transaminases and gamma glutamyl transferase. Patients with portal hypertension had higher liver stiffness compared to patients without (5.2 ± 1.3 vs 4.2 ± 0.8 kPa, $p = 0.03$). At MRE or during follow-up, 13 patients (19%) met definition of FF and had significantly higher liver stiffness compared to patients without FF (5.1 [IQR: 4.3 to 6.3] vs 4.2 [IQR: 3.7 to 4.7] kPa, $p = 0.01$). Liver stiffness above 4.5 kPa differentiated FF with a sensitivity of 77% and specificity of 77%. In conclusion, elevated MRE-derived liver stiffness is associated with worse hemodynamics, liver enzymes and clinical outcomes in Fontan patients. This measure may serve as a global imaging biomarker of Fontan health. **(Am J Cardiol 2019;124:1454−1459)**

Fontan-associated liver disease (FALD) is recognized as a major noncardiac complication of the Fontan circulation and may lead to substantial morbidity and early mortality.[1,2] FALD is also associated with the development of Fontan failure (FF).[3,4] The etiology of FALD is likely multifactorial with chronically elevated central venous pressure, low cardiac output, and possibly abnormal liver lymphatic drainage as contributing mechanisms.[5−7] However the correlation between liver fibrosis detected on liver biopsy and noninvasive assessment of liver stiffness including liver magnetic resonance elastography (MRE) has shown mixed results in the literature with some studies showing strong correlation while others showing only weak correlation.[8−10] This could be related to the inherent limitations of the liver biopsy which samples only a small piece of the liver or to the etiology of the liver disease which includes congestion and fibrosis, both of which increase measured liver stiffness.[11-13] Abdominal ultrasound and MRI, including MRE, are accepted noninvasive screening tools for FALD and are recommended every 1 to 2 years in adolescents and adults.[1,5,14,15] This study evaluates the relationships between liver stiffness measured by MRE and hemodynamics, liver enzymes, portal hypertension, and FF.

Methods

This retrospective study was approved by our institutional review board and is in compliance with the Health Insurance Portability and Accountability Act. The requirement for informed consent/assent was waived due to the retrospective nature of the study. Institutional electronic medical records were searched (using Insight; Softek Illuminate, Overland Park, KS) to identify all adult patients with Fontan circulation (≥18 years of age) who had undergone MRE of the liver between January 2012 and December 2018. Patients were excluded if they already had a heart transplantation or Fontan take down before MRE. MRE of the liver is used as a routine clinical surveillance test for all Fontan patients at our institution.

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Clinical and demographic data, including underlying anatomic diagnoses and type of single ventricle congenital heart disease, were abstracted from the medical record (Epic Medical Systems Corporation, Verona, WI). The type of Fontan was classified as lateral tunnel (LT), extracardiac conduit, or atriopulmonary (AP) connection. Additional parameters included date of birth, sex, age at Fontan operation, and history of arrhythmia requiring intervention, antiarrhythmic medications or resulting in admission. Other variables included New York Heart Association functional class, protein losing enteropathy, and thromboembolism. FF was defined as death, listing for heart transplantation, or heart failure symptoms requiring escalation of diuretic therapy.[16] Laboratory data included complete blood count, liver function tests, factor V and VIII levels, protein C and S, and antithrombin 3 levels. The clotting factor tests were obtained as part of the comprehensive hematologic assessment of the Fontan circulation and were included in our study as protein C, S, and factor V are produced in the liver and may reflect altered hepatic synthetic function.[17,18] These tests were not obtained in any patient on warfarin treatment. Due to the retrospective nature of the study, not all the patients had all the laboratory, catheterization, or imaging studies.

Liver MRE examinations had been performed on 1.5-T MRI scanners (Ingenia; Philips Healthcare, Best, the Netherlands; and Signa HDx or Optima MR450w; GE Healthcare, Waukesha, WI). Both 2-D gradient recalled echo and spin-echo planar imaging techniques had been used during the study period which have previously been shown to yield comparable results.[19,20] In brief, 4 axial images had been obtained through the mid liver, avoiding the most superior and inferior portions of the liver. Regions of interest (ROI) were drawn on each image to measure shear stiffness. ROIs included the right hepatic lobe as well as segment 4 of the left lobe, while excluding visible blood vessels, avoiding areas of artifact, and staying at least 1 cm from the liver capsule.[21] Mean liver stiffness was abstracted from the electronic medical record by a single investigator. The upper limit for normal liver stiffness in our institution is 2.9 kPa. Figure 1 shows examples from 2 patients with relatively soft and a stiff liver. Patients were kept nil per os (NPO) for 6 hours before the MRE.

Cardiac MRI (CMR) studies had been performed with 1.5 Tesla scanners (Philips Healthcare, Best, the Netherlands). Ventricular assessment was performed by an electrocardiographically gated, balanced steady-state free precession cine CMR in vertical and horizontal ventricular long-axis planes, and a stack of slices in a ventricular short-axis plane or axial plane. All analyses were performed using commercially available software (QMass, Medis Medical Imaging Systems, Leiden, the Netherlands and cmr42, Circle Cardiovascular Imaging Inc., Calgary, Canada). Cardiac catheterization had been performed according to the standard institutional clinical protocol. Fontan pressure and ventricular end diastolic pressures were recorded.

The Student's *t* test or Mann-Whitney *U* test was used to compare 2 groups of continuous parametric or nonparametric variables, respectively. Fisher exact test was used for categorical variables. Univariate association between normally distributed variables was estimated using the Pearson correlation coefficient, while Spearman correlation was used for non-normally distributed data. Correlation coefficients were interpreted as follows: 0 to 0.19 = very weak; 0.2 to 0.39 = weak; 0.40 to 0.59 = moderate, 0.60 to 0.79 = strong, and 0.80 to 1.0 = very strong. To evaluate the

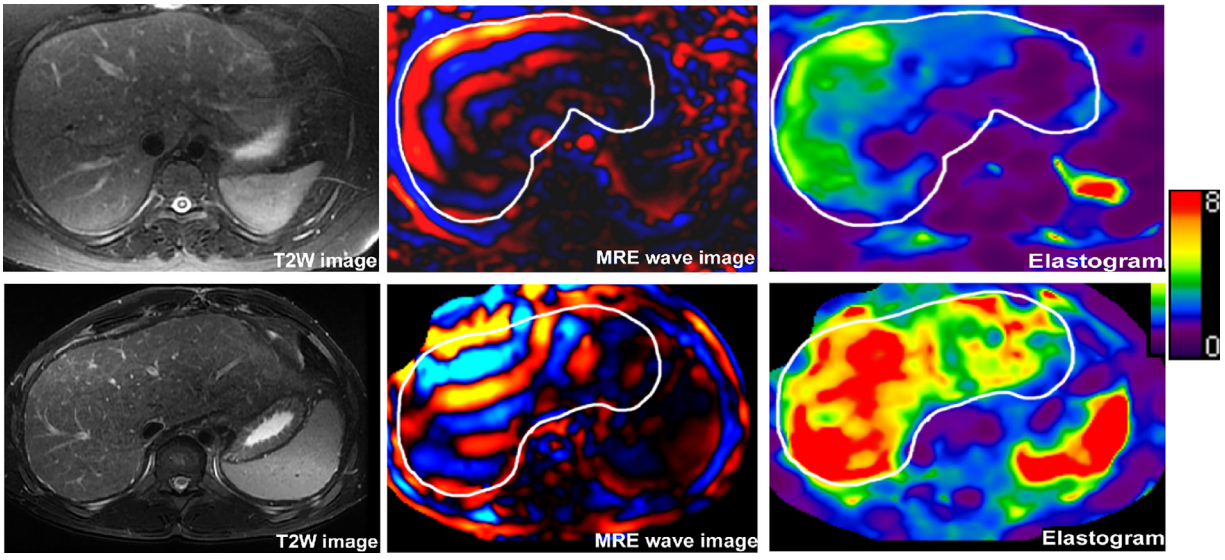

Figure 1. Magnetic resonance images from 2 patients with history of Fontan palliation of congenital heart disease. Left column: T2-weighted images. Middle column: MR elastography (MRE) wave images. Right column: MR elastograms showing tissue stiffness. Outlines on the wave and elastogram images show the margins of the liver for localization purposes but do not define the area of stiffness measurement. First row of images are from a 31-year-old female patient with liver stiffness of 3.0 kPa. Anatomic images show an enlarged, mildly T2-weighted hyperintense liver compatible with congestion. There are no morphologic findings of fibrosis. Shear wave images show waves with relatively (versus the second patient) short wave length reflective of a less stiff liver. The elastogram shows mildly elevated liver stiffness (green and yellow on the color map) with the color scale provided for reference. Second row of images are from a 27-year-old male patient with liver stiffness of 7.1kPa. Anatomic images show an enlarged liver with subtle surface nodularity and reticular increased T2-weighted signal in the anterior section of the right hepatic lobe suggestive of fibrosis. The spleen is also enlarged. Shear wave images show waves with relatively longer wave length reflective of a stiffer liver. The elastogram shows diffuse liver stiffness (red).

Table 1
Demographic and clinical characteristics of the study cohort

Variable	All patients (n = 70)	Fontan failure		p Value
		Yes (n = 13)	No (n = 57)	
Age at MRE (years)	26.7 ± 7.3	33.6 ± 11.2	25.5 ± 11.2	0.03
BMI (kg/m^2)	24.5 ± 4.9	27.2 ± 4.4	24.0 ± 4.8	0.03
Cardiac diagnosis				0.65
Tricuspid atresia	23 (32%)	3 (24%)	20 (35%)	
Double-inlet left ventricle	11 (16%)	3 (24%)	8 (14%)	
HLHS	17 (24%)	3 (24%)	14 (24%)	
Unbalanced AV canal	3 (4%)	0	3 (5%)	
Double-outlet right ventricle	4 (6%)	2 (16%)	2 (4%)	
Complex two ventricles	6 (9%)	1 (10%)	5 (8%)	
Hypoplastic TV/RV	1(2%)	0	1 (2%)	
Pulmonary atresia/IVS	2 (3%)	1 (2%)	1 (2%)	
Mitral atresia	1 (2%)	0	1 (2%)	
Ebstein anomaly	2 (3%)	0	2 (4%)	
Type of Fontan circulation				0.04
Atriopulmonary Fontan	13 (16%)	6 (46%)	7 (11%)	
Lateral tunnel	37 (54%)	5 (39%)	32 (56%)	
Extracardiac conduit	20 (30%)	2 (15%)	19 (33%)	
Dominant ventricular morphology				0.2
Left ventricle	42 (60%)	7 (58%)	35 (60%)	
Right ventricle	28 (40%)	5 (42%)	23 (40%)	
Arrhythmia	22 (31%)	9 (69%)	13 (22%)	0.002
Protein losing enteropathy	3 (4%)	1 (8 %)	2 (4%)	0.7
Thromboembolism	11 (15%)	4 (31%)	9 (69%)	0.1
NYHA class				<0.001
I	41 (59%)	3 (23%)	38 (66%)	
II	25 (35%)	6 (46%)	19 (33%)	
III	4 (6%)	4 (31%)	0	

AV = atrioventricular; BMI = body mass index; HLHS = hypoplastic left heart syndrome; IVS = intact ventricular septum; RV = right ventricle, TV = tricuspid valve. Results are presented as mean ± standard deviation or frequency (%).

utility of the liver stiffness to differentiate FF and portal hypertension, receiver operating characteristic (ROC) curve analyses were performed and the area under the curve (AUC) was reported. P values were reported using a bootstrap method. All p-values were 2-tailed, and differences and associations were considered significant when $p < 0.05$. Statistical analyses were performed using IBM SPSS Statistics for Windows (version 24.0, Armonk, NY) and JMP (version 12, SAS Institute Inc., Cary, NC).

Results

A total of 70 unique patients underwent liver MRE examinations in the period between 2011 and 2018. The median age was 24.7 years (interquartile range [IQR]: 21.6 to 32.1 years), and 36 patients (52%) were males (Table 1). The median time since Fontan was 17.9 years (IQR: 15.1 to 23.4 years). When more than one MRE was performed, only the first MRE was included in this study. The median follow-up from the time of MRE was 3.9 years (IQR: 1.7 to 5.4 years). The median liver stiffness was 4.3 kPa (IQR: 3.8 to 5.0 kPa, range: 3.0-7.3 kPa). There was no significant correlation between MRE liver stiffness and patient age ($r = 0.01$, $p = 0.44$) or time since Fontan ($r = 0.02$, $p = 0.32$). There was one case of hepatocellular carcinoma identified with MRE screening.

All patients had an echocardiogram evaluation with a median time difference between MRE and echocardiogram of 11 months. 46 patients had a cardiac catheterization with a median time difference between cardiac catheterization and MRE of 1.1 (IQR: 0.2 to 3.3) years. Forty-nine patients had a cardiac MRI with a median time difference between cardiac MRI and MRE of 0.2 (IQR: 0 to 14) months. There was a weak positive correlation between liver stiffness and Fontan pressure ($r = 0.34$, $p = 0.03$) (Figure 2). Using CMR measures, there was a moderate negative correlation of liver stiffness with ventricular ejection fraction ($r = -0.52$, $p = 0.03$) and ventricular end-diastolic volume ($r = -0.54$, $p = 0.02$) (Figure 3). Patients with moderate-to-severe atrioventricular valve

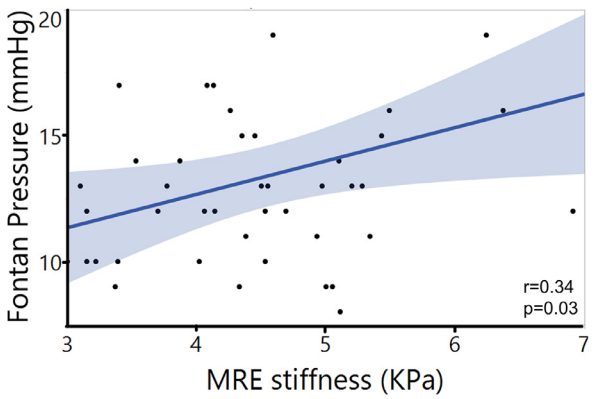

Figure 2. Positive linear relationship between MRE liver stiffness and Fontan pressure.

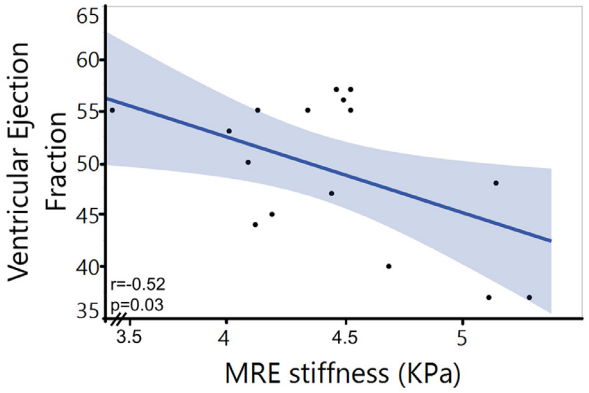

Figure 3. Negative linear relationship between MRE liver stiffness and ventricular ejection fraction.

regurgitation (AVVR) had significantly higher liver stiffness compared to patients with no or mild AVVR (5.2 ± 0.08 vs 4.3 ± 0.08 kPa, p = 0.01) (Figure 3). Patients with a history of thromboembolism had higher liver stiffness compared to patients without prior thromboembolism (5.1 [IQR: 3.7 to 4.8] vs 4.2 [IQR: 3.7 to 4.8] kPa, p = 0.03).

Liver stiffness was weakly positively correlated with AST (r = 0.35, p = 0.02), ALT (r = 0.37, p = 0.02), and GGT (r = 0.37, p = 0.03). For other labs that may reflect liver synthetic function, liver stiffness was moderately negatively correlated with factor V (r = −0.45, p = 0.008), and weakly negatively correlated with protein C (r = −0.37, p = 0.04). There was no significant correlation with factor VIII. There was no difference in any of the laboratory levels between patients with and without FF (Table 2).

Patients with radiologic signs of portal hypertension (splenomegaly, varices, and/or ascites) had higher liver stiffness compared to patients without (5.2 ± 1.3 vs 4.2 ± 0.8 KPa, p = 0.03) (Figure 2). Liver stiffness also had a weak negative correlation with platelet count (r = −0.3, p = 0.04). Using ROC analysis, liver stiffness had an AUC of 0.69 (confidence interval: 0.53 to 0.83, p = 0.004) to differentiate portal hypertension. A liver stiffness above 4.5 kPa differentiated portal hypertension with a sensitivity of 69% and specificity of 65%.

Thirteen patients (19%) met the definition of FF at the time of MRE or during follow up (4 deaths, 1 cardiac transplant, and 8 developed heart failure symptoms requiring escalation of diuretics one of them received ventricular assist device and is currently awaiting transplantation). Patients with FF had significantly higher liver stiffness compared to patients without FF (5.1 [IQR: 4.3 to 6.3] vs 4.2 [IQR: 3.7 to 4.7] kPa, p = 0.01) (Table 3). Using ROC

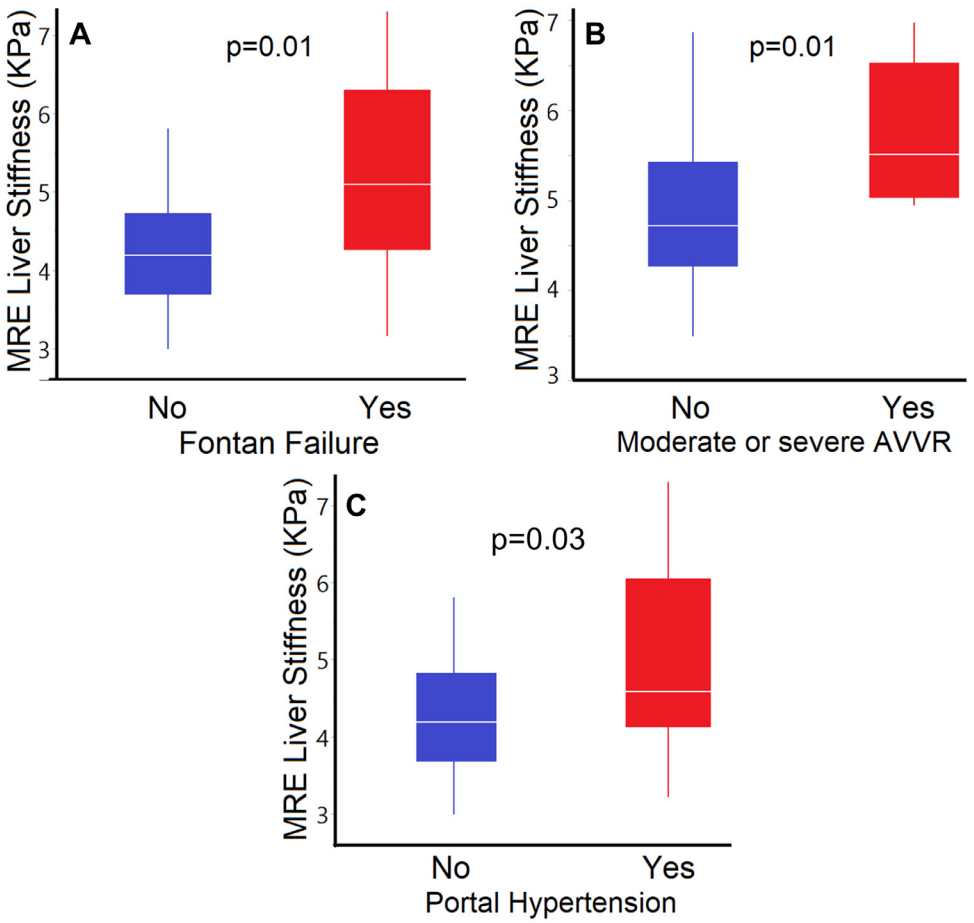

Figure 4. (*A*) Patients with Fontan failure have significantly higher MRE liver stiffness. (*B*) Patients with moderate or severe atrioventricular valve regurgitation (AVVR) have higher MRE liver stiffness. (*C*) Patients with radiologic portal hypertension have significantly higher liver stiffness. All the plots are Tukey outlier box plots.

Table 2
Laboratory and liver imaging results in patients with and without Fontan failure

Variables	Number of patients with each test	All patients (n = 70)	Fontan failure		p Value
			Yes (n = 13)	No (n = 57)	
Alanine aminotransferase (unit/L)	65	37 ± 18	45 ± 25	36 ± 18	0.35
Aspartate aminotransferase (unit/L)	65	25 ± 9	72 ± 111	28 ± 16	0.33
Total bilirubin (mg/dL)	65	0.96 ± 0.69	1.14 ± 0.83	0.84 ± 0.39	0.39
Gamma glutamyl transferase (Unit/L)	65	100 ± 9	159 ± 140	96 ± 70	0.34
Total protein (gm/dL)	66	7.8 ± 0.7	7.8 ± 0.7	7.9 ± 0.7	0.60
Albumin (gm/dL)	66	4.3 ± 0.5	4.0 ± 0.4	4.2 ± 0.4	0.25
Hemoglobin (gm/dL)	68	16.2 ± 1.6	15.9 ± 1.7	16.3 ± 1.5	0.43
Hematocrit (%)	68	47.7 ± 4.7	47.8 ± 4.8	47.1 ± 4.4	0.61
Platelet count (K/mcL)	67	187 ± 67	158 ± 66	180 ± 60	0.42
Protein S (%)	34	84 ± 27	83 ± 26	84 ± 28	0.89
Protein C (%)	34	86 ± 35	79 ± 23	87 ± 25	0.41
Factor VIII (%)	36	163 ± 43	133 ± 49	168 ± 41	0.19
Factor V (%)	34	75.9 ± 18.9	69.7 ± 33.1	76.9 ± 15.8	0.65
Antithrombin III (%)	33	115 ± 70	104 ± 14	118 ± 77	0.38

Table 3
Hemodynamic and imaging results

Variables	Number of patients with each test	All patients (n = 70)	Fontan failure		p Value
			Yes (n = 13)	No (n = 57)	
Liver stiffness (kPa, MRE)	70	4.3 (3.8-5.0)	5.1 (4.2-6.3)	4.2 (3.7-4.7)	0.03
Liver volume (ml, MRE)	70	1999 ± 432	2084 (1741-2529)	1865 (1670-2218)	0.28
Findings of portal hypertension (ascites, varices and/or splenomegaly)	70	17 (26%)	6 (46%)	11 (20%)	0.04
Ejection fraction (%, CMR)	49	51 (45-55)	45 (36-51)	53 (45-56)	0.08
End diastolic volume (ml/m^2, CMR)	49	92 (78-113)	97 (82-146)	92 (76-112)	0.45
End systolic volume (ml/m^2, CMR)	49	44 (39-60)	54 (50-94)	41 (36-60)	0.04
At least moderate atrioventricular v alve regurgitation (CMR/Echo)	70	8 (11%)	3 (23%)	5 (9%)	0.16
Fontan pressure (mm Hg)	46	13.0 (10.8-15.3)	15.5 (12.8-19.0)	12.0(10.0-14.0)	0.01
Ventricular end diastolic pressure (mm Hg)	46	10.6 ± 3.9	13.8 ± 5.2	9.6 ± 2.9	0.02
Pulmonary vascular resistance (iWu)	46	1.2 (1.0-2.1)	1.8 (1.2-2.8)	1.2 (0.9-2.0)	0.02
Aortic saturation (%)	46	91 ± 5	92 ± 4	89 ± 5	0.13

CMR = cardiac MRI; iWu = indexed Woods unit; MRE = magnetic resonance elastography.
Results are presented as mean ± standard deviation, median (interquartile range), or frequency (%).

analysis, liver stiffness had an AUC of 0.72 (confidence interval: 0.53 to 0.86, p = 0.004) to differentiate FF. A liver stiffness above 4.5 kPa differentiated FF with a sensitivity of 77% and specificity of 77%.

Discussion

Liver stiffness by MRE was universally increased in our population and correlated with increased Fontan pressure, lower ventricular ejection fraction, and the severity of AVV regurgitation. Increased liver stiffness was also associated with FF, with radiologic signs of portal hypertension and with elevated liver enzymes.

Liver imaging is routinely employed in the surveillance of Fontan patients because of the inherent limitations of liver laboratory testing and liver biopsy.[22,23] Imaging findings of FALD include hepatomegaly (due to congestion), heterogeneous parenchymal ultrasound texture, surface macronodularity, or abnormal parenchymal enhancement on CT and MRI.[22,24] Abdominal imaging also identifies findings of portal hypertension (splenomegaly, varices and/or ascites) in these patients.[4,5] Noninvasive MRE measures of liver stiffness correlate very well with liver fibrosis in other chronic liver diseases, including viral hepatitis.[25] However, the value of MRE- and ultrasound-derived liver stiffness has recently been debated in FALD as one study showed weak correlation with the severity of fibrosis on liver biopsy although another recent study showed strong correlation.[9,26] These findings might be explained by the fact liver stiffness in FALD is a reflection of both congestion and fibrosis.[11,26,27] Our study found that liver stiffness measured by MRE correlated with radiologic findings of portal hypertension and with laboratory findings of hepatic injury including liver transaminases. Furthermore, liver stiffness by MRE measures correlated with higher Fontan pressure, worse ejection fraction, and significant AVV regurgitation. Our study also showed that MRE-derived liver stiffness correlated with FF. These findings suggest that MRE is a reflection of cardiac and liver "health" and might be used as a global assessment of the Fontan circulation that correlates reasonably well with the development of clinical symptoms and outcomes.[22,23] Recent evidence suggested an added value of repeated monitoring of

elastography as a marker of progression of FALD.[22] Our findings suggest that a stiffness value of 4.5 kPa in Fontan patients is associated with the presence of portal hypertension and FF and thus should prompt careful attention to the patient's hemodynamics and liver disease.[28] Of note, unlike previous studies, we found no association of MRE liver stiffness with age or time since Fontan as out-population consisted of adults only.[23]

The limitations of this study include a single center retrospective study design and further studies are needed to validate our findings in other Fontan cohorts. Also, our study did not evaluate the dynamic changes of liver disease over time and the value of serial assessments of liver stiffness. This will be the target of future research. Furthermore, we did not evaluate how medications and interventions may result in a change in liver stiffness. Finally, many patients did not have catheterization or CMR data and very few patients had a liver biopsy. Thus we have incomplete data for many of the clinical testing variables which were obtained as clinically indicated. This limited our ability to perform multivariable analysis.

In conclusion, MRE-derived liver stiffness is associated with hemodynamics, liver function, and clinical outcomes in Fontan circulation. Thus, MRE-derived liver stiffness may be a biomarker reflecting the "health" of the heart and liver in Fontan patients. A stiffness cut-off of 4.5 kPa correlated with portal hypertension and FF.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.07.052.

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