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ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Acoustic radiation force impulse of the liver after Fontan operation: Correlation with cardiopulmonary exercise test

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Abstract

Background: The current management paradigm for children with single ventricle heart disease involves a series of palliative surgeries, culminating in the Fontan operation. This physiology results in a high central venous pressure, and in the setting of single ventricle heart disease, results in hepatic injury and fibrosis over time. Fontan-associated liver disease (FALD) is universally present in this cohort, and the current gold standard for diagnosis remains biopsy. Noninvasive assessments of liver fibrosis, such as ultrasound with elastography or acoustic radiation force impulse (ARFI), has been utilized in this cohort. The effect of poor cardiovascular efficiency, as measured by cardiopulmonary exercise test (CPET), on assessments of liver fibrosis remains poorly understood.

Methods: Retrospective, cross-sectional study. Subjects were evaluated in a multidisciplinary clinic setting for patients who have undergone Fontan operation. CPETs, liver ultrasound with elastography (ARFI), and standard laboratory tests were performed as part of routine clinical care pathway. Statistical analysis included linear correlation.

Results: There was a poor correlation between mean ARFI velocity and peak oxygen consumption (VO_{2max}) in this cohort ($r = .20$, $P =$ NS). Similarly, there was poor correlation between ARFI and biomarkers of liver injury, time since Fontan operation and Fontan pressure.

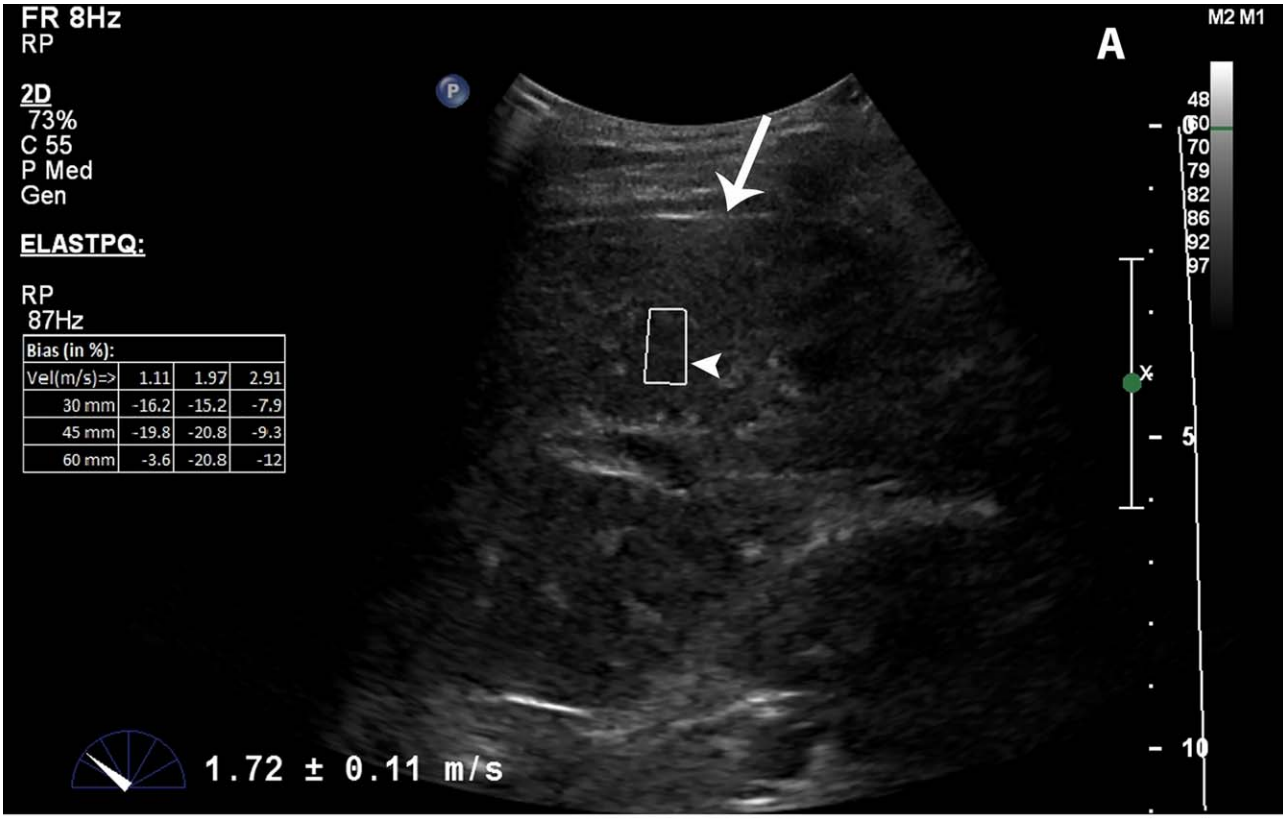
Discussion: ARFI had poor correlation with functional capacity after Fontan, as measured by VO_{2max} obtained during CPET. While a single measurement of liver elastography was not associated with cardiopulmonary efficiency, longitudinal data may reveal an association.

KEYWORDS
cardiopulmonary exercise test, elastography, Fontan, Fontan-associated liver disease

1 | INTRODUCTION

Single ventricle heart disease is a life-threatening condition defined by the presence of one functional pumping chamber. The current management paradigm includes a series of palliative surgeries culminating in the Fontan operation, a total cavopulmonary connection. In this physiology, systemic venous return from the inferior vena cava is routed via conduit or baffle directly into the pulmonary arteries. The resultant elevation in central venous pressure has now been associated with adverse changes in multiple organs, including the liver.[1,2]

Abnormalities in the liver parenchyma have been shown to precede the Fontan operation in children with single ventricle heart disease.[3] Fontan-associated liver disease (FALD) has near universal penetrance, with time since Fontan operation emerging as a primary risk factor.[4] The combination of decreased antegrade perfusion and elevated central venous pressure appear to contribute to liver injury.[5] Patients who have undergone Fontan operation are, therefore, at risk for the development of portal hypertension, liver failure and hepatocellular carcinoma.[6,7] The current gold standard for the assessment of FALD is liver biopsy. There is risk associated with percutaneous or



B

EQI Liver Stiffness Calculations

Liver EQI Avg Vel	1.62 m/s
Liver EQI Std Vel	0.12 m/s
Liver EQI Med Vel	1.61 m/s
Liver EQI IQR Vel	0.17 m/s
Liver EQI IQR/Med Vel	11 %

EQI Liver Stiffness Measurements Velocity

	EQI Avg Vel	EQI Std Vel	EQI Med Vel	EQI IQR Vel	EQI IQR/Med Vel	Circ	Conf. Threshold
Liver EQI 1	1.59 m/s	0.286 m/s	1.57 m/s	0.432 m/s	28 %	3.15 cm	60 %
Liver EQI 2	1.52 m/s	0.263 m/s	1.48 m/s	0.341 m/s	23 %	3.15 cm	60 %
Liver EQI 3	1.62 m/s	0.355 m/s	1.55 m/s	0.528 m/s	34 %	3.15 cm	60 %
Liver EQI 4	1.50 m/s	0.247 m/s	1.46 m/s	0.374 m/s	26 %	3.15 cm	60 %
Liver EQI 5	1.70 m/s	0.245 m/s	1.66 m/s	0.380 m/s	23 %	3.15 cm	60 %
Liver EQI 6	1.59 m/s	0.362 m/s	1.61 m/s	0.665 m/s	41 %	3.15 cm	60 %
Liver EQI 7	1.69 m/s	0.365 m/s	1.70 m/s	0.635 m/s	37 %	3.15 cm	60 %
Liver EQI 8	1.90 m/s	0.235 m/s	1.94 m/s	0.278 m/s	14 %	3.15 cm	60 %

FIGURE 1 (A) Grayscale ultrasound image with elastography showing the sample box (white arrow) from which the elastography velocities will be calculated. Velocities for that sample are depicted on the table to the left of the image. (B) Report page showing the elastography software calculation of the interquartile ration, average, standard, and median velocities based on the 10 sample measurements obtained

transjugular liver biopsy in these patients, including the need for anesthesia, pain,[8] bleeding, and infection. The optimal biopsy technique (percutaneous vs transjugular) has not been determined, as fibrosis is typically not uniformly distributed; therefore, the likelihood of false negative biopsy results is high.[9] In addition, liver biopsy is not appropriate for frequent, longitudinal follow-up. Acoustic radiation force impulse (ARFI) is a type of ultrasound with elastography able to evaluate tissue stiffness and relies on the propagation of acoustic waves in the interrogated attenuating tissue (Figure 1A & B). ARFI produces an invisible displacement, or movement of the tissue, which is detected by the ultrasound machine and offers additional information about the tissue than the traditional two-dimensional (2D) or Doppler ultrasound. One of its main applications is in the liver to evaluate for fibrosis. Prior studies have shown that ARFI correlates well with the severity of liver fibrosis in viral hepatitis,[10,11] but has not been adequately studied in patients who have undergone Fontan operation. Liver stiffness can be affected by fibrosis and congestion, and so ARFI may serve as a surrogate marker for both cardiac and hepatic dysfunction.

The relationship between cavopulmonary hemodynamics (pressure, flow, and resistance in the Fontan circuit) and liver injury is poorly understood. In adult Fontan survivors, decline in peak oxygen consumption (VO_{2max}) has been linked to increased odds of FALD,[12] as determined by various liver imaging studies (including ultrasound and/or computed tomography). We hypothesized that poor cardiovascular status, manifesting as lower VO_{2max}, would be related to elevated elastography and markers of hepatic fibrosis. Our aim was to assess the correlation between cardiovascular status after Fontan operation and FALD, quantified by both liver ultrasound elastography and biomarkers of liver injury. More specifically, we sought to characterize the relationship between contemporaneous peak oxygen consumption (VO_{2max}) by cardiopulmonary exercise test (CPET) and hepatic stiffness determined by ARFI.

2 | METHODS

2.1 | Study design and subject characteristics

This is a retrospective, cross-sectional study. Study subjects were seen at the Children's Hospital Colorado Single Ventricle Care Program Multidisciplinary clinic (MDC) between January 2015 and June 2017. Patients who have undergone Fontan operation are referred to our MDC on a biennial basis. All patients who attend the clinic undergo liver ultrasound with elastography by ARFI; subjects who had undergone Fontan operation and liver ultrasound with ARFI were included in the study. Demographic and anthropometric data were reviewed, as well as cardiac diagnosis and time since Fontan operation. The internal review board (COMIRB) approved this study.

2.2 | Cardiovascular testing

A review of medical records included formal CPET. Variables included in the analysis were respiratory exchange ratio (RER), peak oxygen consumption (VO_{2max}), watts, and anaerobic threshold (AT). A 6-minute walk test was also available for most subjects and the distance walked was included in the analysis (6MWD). The subject's most recent echocardiogram and cardiac catheterization reports were also reviewed. The presence of a fenestration was noted, as well as the severity of atrioventricular valve regurgitation (AVVR) and a qualitative assessment of ventricular function on echocardiogram. Fontan conduit pressures, as well as a hepatic vein wedge pressure (HVWP) and gradient, were recorded from the catheterization report.

2.3 | Hepatic testing

Transaminases, total bilirubin, serum albumin, and international normalized ratio (INR) were abstracted from the medical record. The AST to platelet ratio index (APRI)[13,14] and the fibrosis-4 (FIB-4) index[15] were calculated from the above data. Liver ultrasounds, including the ARFI evaluation, were reviewed and results were recorded. All the ultrasounds were performed using two Philips (Philips Healthcare, Andover, Massachusetts) machines: Epiq and iU22. The curvilinear probes used were C5-2 (operating frequency range 2–5 MHz) and C5-1 (frequency range 1–5 MHz) for each machine respectively. With the patient lying in supine position the liver was approached via intercostal or subcostal space and the liver was imaged. Ten measurements within the right lobe were taken in an area free of blood vessels and at least 2 cm deep to the liver capsule while the patient suspended his/her respiration. The elastography software then calculated the median value, average value, and the interquartile ratio using the ten measurements.

Liver biopsies were performed on an as needed bases, on the recommendation of the multidisciplinary team. Biopsies were reviewed and scored according the system described by Wu et al.[16] Biopsies were scored for the presence or absence of sinusoidal fibrosis and dilatation, and if present, the percentage of sinusoids affected. In addition, portal fibrosis was also staged using the Ishak staging system. Evidence of liver injury was assessed by the presence of piecemeal necrosis, focal lobular necrosis, bile ductular reaction, and lipofuscin. Finally, other markers included steatosis and iron deposition.

2.4 | Statistical analysis

Data are presented as mean (standard deviation) or count (percent). Testing included Pearson correlation for continuous, normally distributed variables. A *P* value of $<.05$ was deemed statistically significant. STATA, version 12, was used for statistical analysis (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, Texas).

3 | RESULTS

Eighty-four subjects were included in the analysis, with CPET available in 48 and ARFI in 32 subjects. Subject characteristics are shown in Table 1. Mean age of study subjects was 10.7 (4.2) years, with no gender predominance.

Table 2 summarizes CPET and 6MW results. Average time elapsed since Fontan at the time of CPET was 8.7 (2.5) years. Mean VO_{2max} for

TABLE 1 Sample characteristics

	Mean (SD) or N (%)
Age at CPET (y)	10.7 (4.2)
Male gender	39 (50.6%)
Height at CPET (cm)	135.4 (22.4)
Height for age *Z*-score	−0.13 (5.8)
Weight at CPET (kg)	35.4 (16.9)
Weight for age *Z*-score	−0.37 (1.3)
Body surface area (m^2)	1.1 (0.3)
Body mass index	18.3 (4.1)
Body mass index *Z*-score	0.04 (1.3)

TABLE 2 Cardiopulmonary exercise test and 6-minute walk (6MW) metrics

	Mean (SD)
Time from Fontan at CPET (y)	8.7 (2.5)
Respiratory exchange ratio	1.08 (0.1)
Peak oxygen consumption (mL/kg/min)	28.8 (5.9)
Watts	91.3 (31.7)
Anaerobic threshold (mL/kg/min)	18.0 (5.1)
6MW distance (m)	434.3 (110.5)

the cohort was 28.8 (5.9) mL/kg/min, with a mean AT of 18.0 (5.1) mL/kg/min. The average watts generated was 91.3 (31.7), and the average 6MWD was 434.3 (110.5) m.

Table 3 shows ARFI, hepatic injury biomarker and liver biopsy results. Mean liver ultrasound shear wave elastography values were 1.81 (0.44) m/s. Mean transaminase concentrations were slightly above the normal range, typical for children who have undergone Fontan operation. Total bilirubin, serum albumin, INR and platelet count were within normal limits. The mean APRI and FIB-4 indices of liver injury were 0.56 (0.23) and 0.41 (0.23), respectively. Twelve subjects had an APRI >0.7 and none had a FIB-4 value of greater than 1.4. Liver biopsy was performed in a subset of 11 subjects, with scores for sinusoidal and portal fibrosis shown.

TABLE 3 Liver ultrasound elastography, hepatic injury biomarkers, and liver biopsy results

	Mean (SD)
Time from Fontan at liver ultrasound (y)	7.1 (3.4)
Elastography mean (m/s)	1.81 (0.44)
Aspartate aminotransferase (AST) (U/L)	47.4 (16.1)
Alanine aminotransferase (ALT) (U/L)	37.8 (12.9)
Total bilirubin (mg/dL)	0.9 (0.6)
Albumin (g/dL)	4.2 (0.7)
Platelet count ($\times 10^3/\mu L$)	227 (65)
International normalized ratio (INR)	1.25 (0.28)
AST to platelet ratio index (APRI)	0.56 (0.23)
Fibrosis-4 (FIB-4)	0.41 (0.23)
Liver biopsy performed	11
Sinusoidal fibrosis	
Grade 1	4 (36%)
Grade 2	2 (18%)
Grade 3	5 (45%)
Portal fibrosis	
Grade 1	0 (0%)
Grade 2	4 (36%)
Grade 3	2 (18%)
Grade 4	4 (36%)
Grade 5	1 (9%)

TABLE 4 Cardiac catheterization and echocardiography

Cardiac catheterization	
Time from Fontan at catheterization (y)	5.1 (4.0)
Fontan pressure (mm Hg)	13.1 (2.9)
Hepatic vein wedge pressure (mm Hg)	13.6 (2.0)
Hepatic vein gradient (mm Hg)	1.0 (0.7)
Echocardiography	
Atrioventricular valve insufficiency	
Trivial or none	59 (84%)
Mild	10 (14%)
Moderate	1 (1%)
Severe	0 (0%)
Ventricular function	
Normal	69 (97%)
Mildly depressed	1 (1.5%)
Moderately depressed	0 (0%)
Severely depressed	1 (1.5%)
Fontan fenestration present	34 (51%)

Table 4 shows cardiac catheterization and echocardiographic data. Mean Fontan baffle pressures (ie, central venous pressures) for the cohort were 13.1 (range 8–24) mm Hg. Mean hepatic venous wedge pressure was 13.6 (range 10–19) mm Hg, with a hepatic vein gradient of 1.0 (range 0–3) mm Hg. The majority of patients had no or mild AVVR (98%) and normal systolic function (97%). Half of the study subjects had a patent Fontan fenestration.

Figure 2 is a scatter plot depicting VO_{2max} vs mean ARFI, showing no correlation ($r = -.09$, P = NS); if this analysis is limited to the 32 subjects with an RER of $\geq$1.05 (N = 32, $r = -.03$, P = NS), or $\geq$1.1 (N = 11, $r = -.20$, P = NS), the correlation remained non-significant. Because liver fibrosis determined by histology appears to correlate with time since Fontan, we also assessed this relationship. Figure 3 is a scatter plot of time since Fontan vs mean ARFI, also showing no correlation ($r = -.09$, P = NS). If the cohort is divided into groups by 5-year age intervals as shown in Figure 4, the older teenagers do not

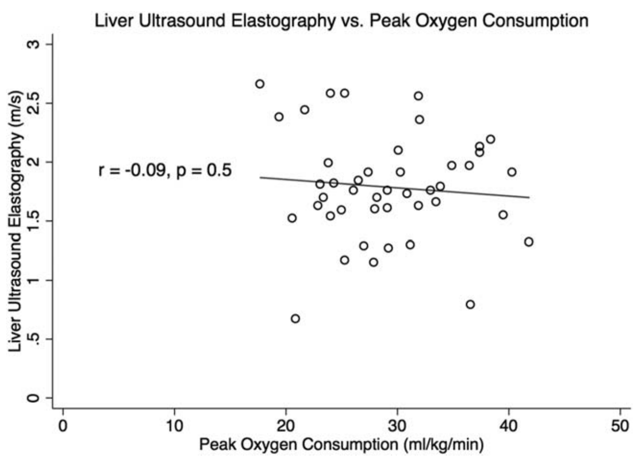


FIGURE 2 This is a scatter plot, showing peak oxygen consumption (mL/kg/min) vs average liver ultrasound elastography velocity (m/s). No correlation was found ($r = -.09$, P = NS)

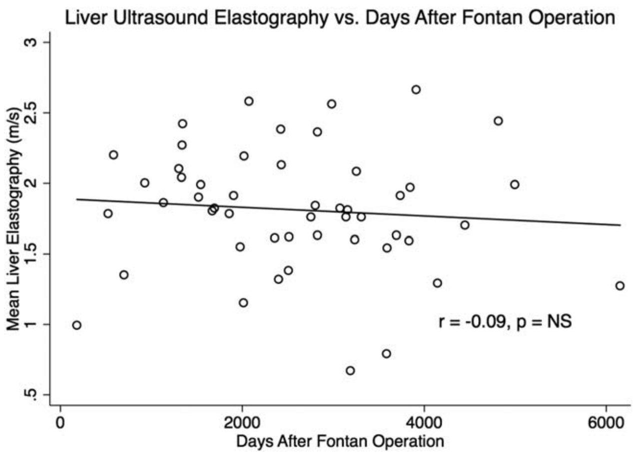


FIGURE 3 In this is a scatter plot of days after Fontan vs average liver ultrasound elastography velocity (m/s). No correlation was found ($r = -.09$, P = NS)

have a statistically significant difference in mean elastography when compared with their younger counterparts.

Table 5 shows correlation coefficients of ARFI vs biomarkers of hepatic injury. There was no correlation between any of the included biomarkers and ARFI, with the exception of INR ($r = .33$, $P = 0.009$).

4 | DISCUSSION

We showed that cardiovascular status after Fontan, as defined by peak oxygen consumption on CPET, did not correlate with liver stiffness as measured by liver ultrasound elastography or biomarkers of liver injury. Invasive hemodynamic data with concurrent liver imaging and CPET assessment are limited in this population, and the lack of an association provides clinically relevant information, especially as it pertains to designing approaches for the diagnosis and monitoring of FALD. In the search for non-invasive measures for the monitoring of progression in FALD, our results suggest that an alternative modality may be needed. The primary confounding factor in this cohort, congestion of the liver

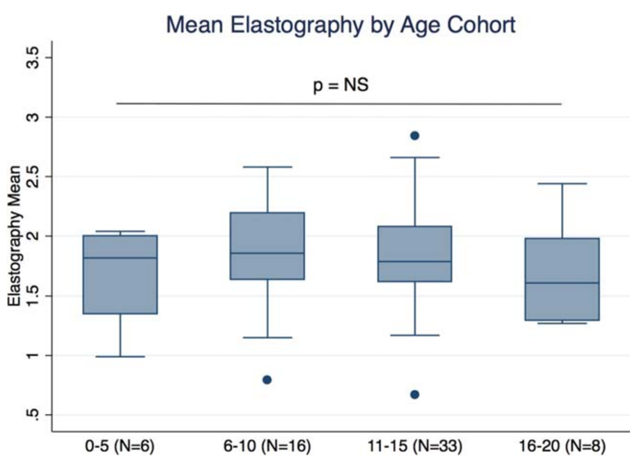


FIGURE 4 This is a box plot, showing mean liver ultrasound elastography by age quartile. There was no significant difference in elastography assessments between groups

TABLE 5 ARFI vs hepatic injury biomarkers: Correlation coefficients

Biomarker of liver injury	Linear correlation coefficient (r) with mean ARFI	P value
Aspartate aminotransferase (AST) (U/L)	−0.10	.4
Alanine aminotransferase (ALT) (U/L)	−0.17	.1
Total bilirubin (mg/dL)	0.01	.9
Albumin (g/dL)	−0.09	.5
Platelet count ($\times 10^3/\mu L$)	−0.01	.9
International normalized ratio (INR)	0.33	**.009**
INR (subjects on warfarin removed)	0.22	.1
AST to platelet ratio index (APRI)	0.01	.9
Fibrosis-4 (FIB-4)	0.01	.9

related to the total cavopulmonary connection and elevated central venous pressure, may alter the velocity with which the shear wave propagates through the liver. The relationship between cavopulmonary hemodynamics and liver injury remains fairly opaque. Of note, a recent study of liver biopsy results after Fontan operation did not show an association between pressure in the inferior vena cava and collagen deposition in the liver ($r = .003$, $P = .98$). It may also be the case that our population of children who have undergone Fontan operation have yet to manifest the decline in exercise tolerance known to occur in late adolescence,[17] or significant liver fibrosis; however, as noted above, hepatic fibrosis has been shown to precede the Fontan operation in children with single ventricle heart disease.[3]

Our data also show that ARFI also did not correlate with time since Fontan. A recent publication evaluating liver biopsy results after Fontan operation showed that the severity of hepatic fibrosis was associated with time since Fontan.[4] The lack of an association between ARFI and the duration of Fontan physiology in our cohort is also unexpected, and may reflect the fact that confounders alter the relationship between shear wave propagation and fibrosis, as mentioned above. The age of the cohort presented by Goldberg et al is greater than 17 years, whereas our cohort has an average age of 10 years, and this difference in age may have an impact on the detection of liver fibrosis.

There was similarly a poor correlation between ARFI and biomarkers of liver injury, such as APRI or FIB-4, with the exception of INR. This weak correlation appears dominated by several outliers; more specifically, these were subjects who are taking warfarin for thromboprophylaxis and have an iatrogenic elevation in INR. When subjects on warfarin were removed from the sample, the relationship lost statistical significance. A clear pathophysiologic mechanism is not readily apparent to explain this association between INR for subjects on warfarin and AFRI, and it may reflect statistical noise.

Prior studies evaluating ARFI or shear wave ultrasound elastography have shown a significant association between liver stiffness as measured by transient elastography and time since Fontan operation,[18] though the association with functional capacity was not assessed.

Possible explanations for the differences between the findings in the two studies include the different methodologies employed, as the above study utilized FibroScan.[19] The combination of magnetic resonance imaging and elastography (MRE) has been postulated as an alternative to ultrasound-based assessments, with the advantage of a larger field of view and potentially less susceptibility to congestion-related confounding; however, data are lacking with regard to direct comparison of the two techniques.

4.1 | Limitations

The present study has several limitations, including the relatively small sample size and retrospective nature of the study. Ideally, in addition to testing our hypothesis that liver injury varies directly with decline in cardiovascular status, we would be able to compare ARFI to liver biopsy in all subjects, as liver biopsy remains the gold standard. Liver biopsy carries a quantifiable risk, and biopsies are often performed during cardiac catheterization at our center, and hence are not available in a large number of patients. ARFI is likely to be useful for longitudinal follow-up of individual patients, but such an analysis was not part of this cross-sectional study.

5 | CONCLUSIONS

Liver ultrasound with elastography, ARFI in this case, had poor correlation with functional capacity after Fontan, as measured by VO_{2max} obtained during CPET. In our study, there was also a poor correlation between time since Fontan and ARFI. The relationship between cavopulmonary hemodynamics and liver injury over time will require further study, ideally in a multicenter, prospective cohort in which longitudinal data can be obtained and related to liver histology.

AUTHOR CONTRIBUTIONS

Concept/Design, Data collection, Data analysis/interpretation, Drafting article, Critical revision of article: Michael V. Di Maria

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