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ORIGINAL ARTICLE

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Serial cardiac MRIs in adult Fontan patients detect progressive hepatic enlargement and congestion

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Abstract

Background: The progression of hepatic disease in adult Fontan patients is not well understood. They reviewed the experience with serial cardiac MRIs (CMR) in adult Fontan patients to determine if hepatic anatomic markers of prolonged Fontan exposure were present and if clinical predictors of progressive hepatic congestion could be identified.

Methods and Results: A retrospective cohort study of all adult Fontan patients who had undergone at least two CMRs was performed. Hepatic dimensions, inferior vena cava (IVC) size, right hepatic vein (RHV) size and spleen diameter were determined from images acquired at the time of clinically guided CMR. Two radiologists with expertise in hepatic imaging graded congestion and liver size independently using post–gadolinium contrast sequences. Twenty-seven patients met inclusion criteria. Over a mean time of 5.1 years between CMRs, there was a significant increase in mean lateral-medial hepatic dimension ($P = .005$), mean RHV diameter ($P = .004$), and mean splenic diameter ($P = .001$). Serial post–gadolinium imaging was available in 25/27 (93%) patients of which 15/27 (55%) showed evidence of progressive hepatic congestion across serial studies. Progressive hepatic congestion was associated with single ventricle ejection fraction (SVEF) less than 50% ($P = .008$), and larger indexed end-diastolic (EDVI) and end-systolic volume (ESVI). RHV diameter was the only anatomic variable significantly correlated with time from Fontan completion ($P = .004$).

Conclusions: Serial CMRs detected progressive liver and hepatic vein enlargement in our cohort of adult Fontan patients over a mean time of 5.2 years. Progressive hepatic congestion occurs in a significant number of adult Fontan patients and may be associated with ventricular enlargement and decreased ventricular function by CMR.

KEYWORDS
adult Fontan, cardiac MRI, hepatic disease

1 | INTRODUCTION

First described in 1971, the Fontan procedure remains the treatment of choice for palliation of single ventricle physiology.[1] While its application has improved the survival of patients with complex congenital heart disease,[2,3] morbidity is common. In particular, progressive hepatic dysfunction has been increasingly identified and may be associated with adverse outcomes.[4–7] However, determining which patients are at greatest risk for severe hepatic disease remains challenging and is complicated by the lack of established risk factors and the poorly defined timeframe of hepatic disease progression.[8–12]

Magnetic resonance imaging (MRI) provides detailed information about hepatic morphology and can detect subclinical disease prior to the development of abnormal liver function tests.[8,13] MRI also provides valuable information about hepatic venous morphology, an early marker for cirrhosis, and, with post–gadolinium contrast imaging, can identify hepatic congestion and fibrosis.[14] Because widespread recognition of hepatic disease in the Fontan population occurred only

recently, serial MR imaging of adult Fontan patients is limited. Consequently, predictors and the course of progression of remain undefined.[15] However, because the liver abuts the heart and is within the imaging field of view at the time of cardiac MRI (CMR), retrospective evaluation of hepatic imaging markers of disease is possible in most patients who had previously undergone CMR. We reviewed our experience with serial CMRs in adult Fontan patients to determine if anatomic markers of hepatic disease progression were evident and to assess for predictors of progressive hepatic congestion.

2 | METHODS

2.1 | Study design and patient population

We conducted a retrospective, observational cohort study evaluating all patients age 18 years or older with a Fontan who underwent a CMR at the Schneeweiss Adult Congenital Heart Center at Columbia University between 8/2000 and 1/2015. Details regarding the patient's diagnosis and associated cardiac abnormalities were recorded. A predetermined set of clinical variables and imaging characteristics were defined prior to data acquisition. The Columbia University Medical Center Institutional Review Board reviewed and approved this study prior to data collection.

2.2 | Clinical variables

Information regarding the patient's clinical status was defined via review of electronic and written medical records. Patient diagnosis, prior surgical procedures and type of Fontan were extracted from chart review. Patient specific data including symptoms, medications, and functional status were ascertained from the patient's clinical visit closest to the time of CMR. Functional status was categorized using the New York Heart Association classification. Liver function tests were recorded. Elevated liver markers were defined according to conventional standards and reviewed with a hepatologist prior to data coding. MELD-XI was calculated as $5.11 \times \ln(\text{total bilirubin}) + 11.76 \times \ln(\text{creatinine}) + 9.44$, where total bilirubin (mg/dL) and creatinine (mg/dL) are equal to 1 if the raw lab values are less than 1.[16] Indexed ventricular end diastolic (EDVI) and end systolic (ESVI) volumes were recorded and used to calculate singe ventricular ejection fraction (SVEF).

2.3 | CMR image acquisition

CMR studies were performed with breath holding and ECG gating at 1.5 Tesla (Signa, General Electric, Milwaukee, WI) using an 8-channel phased array cardiac coil for signal reception. A dedicated cardiac protocol included pre, during, and post intravenous injection of a gadolinium chelate agent (Gadoteridol, 0.2 mmol/kg at 2 mL/s) with coronal 3D spoiled gradient echo imaging including the entire thoracic aorta, pulmonary arteries, and most of the liver.

2.4 | Delineation of hepatic anatomic dimensions and hepatic congestion

Two abdominal radiologists with expertise in MR imaging blinded to clinical results read all CMRs. Mean values from each separate read were utilized for analysis. Maximum lateral to medial linear liver dimension, maximum spleen diameter, maximum inferior vena cava, and maximum right hepatic vein diameter were determined for each study based on all available imaging and included: the upper abdomen, the multiplanar localizer nongated 2D steady state free precession, multiplanar ECG-gated 2D steady state free precession and single shot fast spin echo sequences and dynamic coronal 3D spoiled gradient echo MR angiography sequences. Anatomic landmarks were utilized to identify the same location for measurements in follow-up studies and to assess the change in each variable of interest.

Hepatic congestion was assessed on post-gadolinium images and scored on a qualitative scale from 0 (no congestion) to 4 (severe congestion) by two radiologists with expertise in hepatic MR imaging. A methodology similar to prior studies was utilized.[8] The degree of heterogeneous enhancement and, when possible, the presence of a reticular enhancement pattern was considered in conjunction with specific aspects of hepatic morphology including ascites, hepatic nodularity, significant hepatic edema, and the presence of arterial enhancing hepatic lesions. Given the lack of pathological correlates, livers were not designated as cirrhotic based on imaging.

2.5 | Statistics

Univariate analyses comparing discrete clinical variables were performed using a χ^2 test or Fisher's exact as required. Continuous variables were analyzed using standard *t*-tests and paired *t*-tests when appropriate. The Wilcoxon signed-rank sum test was used for ordinal data and the Pearson's correlation coefficient was utilized to assess for correlation between continuous variables. Statistical analysis was performed using STATA statistical software (Version 13.1, Stata Corp, College Station, TX, USA).

3 | RESULTS

Twenty-seven patients (48% male) met inclusion criteria. There was no significant difference in congestion scores or hepatic measurements between the two readers. Table 1 delineates patient characteristics. Diagnoses included ten (37%) patients with tricuspid atresia, eight (30%) patients with double inlet left ventricle, six (22%) patients with unbalanced AV canal, and three patients (11%) with other diagnoses. Two patients with heterotaxy syndrome were asplenic. Baseline clinical data were available on all patients and baseline laboratory data were available on 25 (93%) patients. Cardiac catheterization data was available on 15 patients (55%) during the study period. Mean time between the final CMR and cardiac catheterization was 1.9 years. During the study period, one patient underwent ultrasound elastography and one patient underwent a liver biopsy. At the time of the first CMR, 8

TABLE 1 Patient characteristics

	All patients ($n = 27$)
Male	13 (48%)
Age at Fontan, mean (years)	
Age at 1st CMR (years)	29 (9)
Time between Fontan and MR, mean (years)	19 (4)
Time between CMRs, mean (years)	5.2 (2)
Fontan Type	
Classic	10 (37%)
Lateral tunnel or extracardiac	17 (63%)
Fontan pressure, mean (mm Hg)	14.4 (1)
Ventricular morphology:	
Right	4 (15%)
Left	23 (85%)
Clinical symptoms	
History of supraventricular tachycardia	12 (44%)
Palpitations	10 (37%)
Decreased exercise tolerance	16 (59%)
Baseline laboratory values	
Alanine aminotransferase, mean (U/L)	31 (3)
Aspartate aminotransferase, mean (U/L)	28 (2)
Total bilirubin, mean (mg/dL)	1.4 (0.2)
Total protein, mean	7.2 (0.13)
Creatinine (mg/dL), mean	0.8 (0.2)
Platelet count, mean	217 (11)
CMR parameters	
Indexed end diastolic volume, mean (mm/m^2)	96 (29)
Indexed end systolic volume (mm/m^2)	48 (19)
Ejection fraction, mean (%)	51 (9)

patients (30%) were on diuretics and 16 patients (59%) were NYHA class two or greater.

Post–gadolinium imaging was available for 25 (93%) patients using the most recent CMR, and serial post–gadolinium imaging was available in 23 patients (85%). There was a significant increase in hepatic congestion over serial imaging studies ($P = .02$) with 15 patients (65%) exhibiting progressive hepatic congestion. Table 2 displays the relationship between progressive hepatic congestion and select clinical variables. Single ventricle ejection fraction (SVEF) less than 50% was associated with progressive hepatic congestion ($P = .008$). A sensitivity analysis was performed such that all patients with a morphological systemic right ventricle were removed from the analysis without change in the significance of this association. Patients with progressive hepatic congestion had significantly larger mean EDVI (106 mL/m^2 vs. 83 mL/m^2 $P = .048$), mean ESVI (55 mL/m^2 vs. 39 mL/m^2 $P = .032$), and a significantly higher MELD-XI score (9.3 vs. 6.1, $P = .045$). Patients with progressive hepatic congestions also had a significantly longer time between scans (6.1 vs. 4.1 years, $P = .018$). Patient age, gender, diagnosis, Fontan type, morphologic right or left systemic ventricle, and functional class were not significantly associated with progressive hepatic congestion.

Table 3 displays the mean values for the hepatic indices measured at the time of the first and second CMR. Notably, there was a significant increase in the lateral to medial linear liver dimension, the splenic diameter and the diameter of the right hepatic vein over the study period. Specifically, serial lateral-medial liver dimensions were assessed in 26 patients (96%) and 25 (96%) had an increase in size over the study period. Serial right hepatic vein diameter increased in 21 (81%) of the 26 patients and 20 of 25 patients (80%) had an increase in splenic diameter. There was no significant increase in mean IVC diameter over the study period. Figure 1 displays scatter plot matrices of time from Fontan completion with each hepatic parameter. Notably, RHV diameter was significantly correlated with time from Fontan completion. In contrast, there was no significant association between increase in liver span, spleen size, or IVC diameter and time from Fontan completion. There was also no significant association between serial changes in any anatomic variable and elevated liver function tests, low albumin, low platelets, ventricular morphology, diagnosis, EDVI, ESVI, or SVEF.

4 | DISCUSSION

There is increasing evidence that hepatic disease may be a risk factor for adverse outcomes in the adult Fontan patient.[7] Despite this recognition, the course of hepatic dysfunction remains poorly defined. To our knowledge, this is the first study to retrospectively utilize CMR data to evaluate hepatic disease in this population. In so doing, we

TABLE 2 Univariate associations between select variables and progressive hepatic congestion

Variable	*P*
Age, mean (years)	.20
Male gender	.054
Tricuspid atresia	.45
Double inlet left ventricle	.41
Unbalanced AV-canal	.11
Classic Fontan	.71
Palpitations	.25
Decreased exercise tolerance	1.0
New York Heart Association class < 2	1.0
Systemic right ventricle	1.0
MELD-XI score*	.045
Total bilirubin	.35
Creatinine	.30
Platelets	.52
Ejection fraction < 50%*	.008
Indexed end-diastolic volume*	.048
Indexed end-systolic volume*	.03

*Significant at alpha = 0.05.

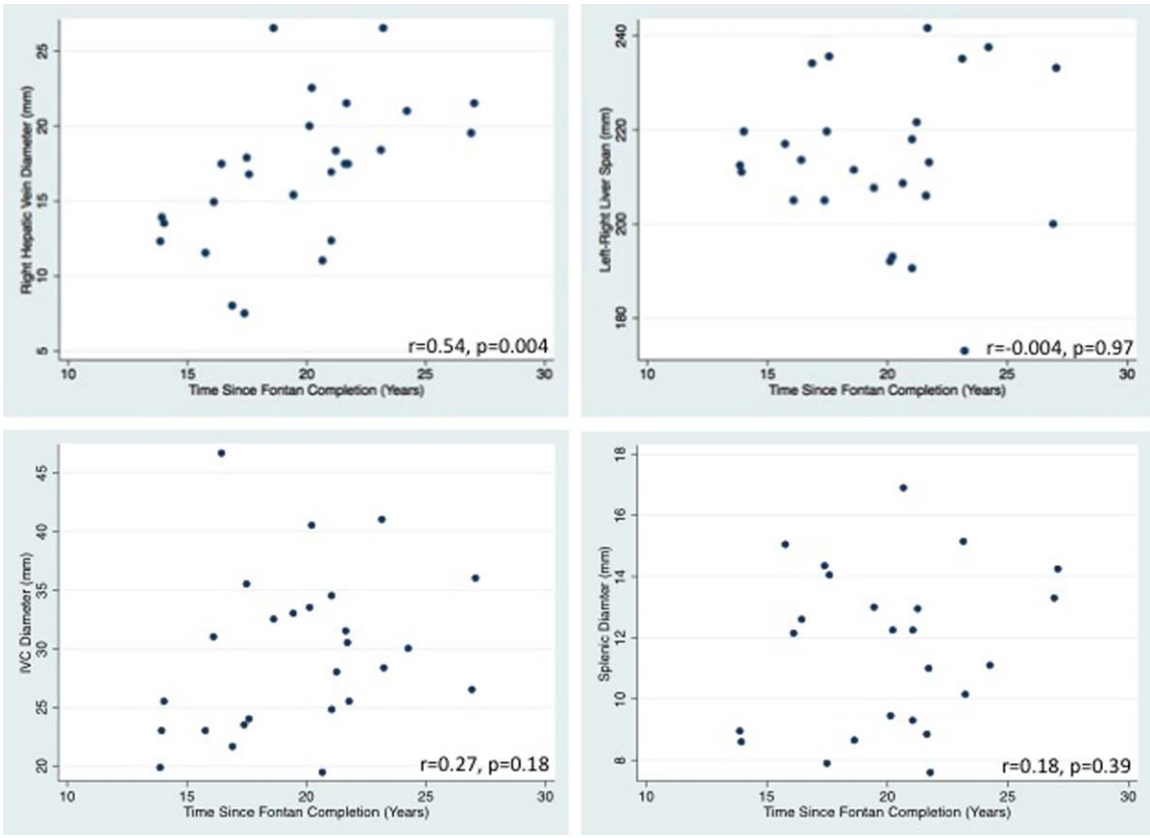

FIGURE 1 Scatter plots of select hepatic parameters and time from fontan completion. Pearson's correlation coefficient and the associated *P* value is presented with each plot

found a progressive increase in hepatic congestion over serial studies with a concordant increase in the size of select hepatic parameters. In addition, we found an association between progressive hepatic congestion and lower SVEF by CMR.

The etiology of hepatic dysfunction in this population remains incompletely defined. Chronic liver injury has been hypothesized to result from both elevated central venous pressure and impaired tissue oxygenation;[17] however, the precise relationship between Fontan hemodynamics and progression of liver injury remains unclear. Similarly, the optimal modality to assess liver damage in the adult Fontan patient remains undefined. Although liver biopsy has been considered the gold standard for assessment of liver disease, sampling variability and rare, but serious complications have limited its clinical application. Furthermore, liver biopsy results may not reliably correlate with disease burden.[18] Transient elastography, increasingly used to assess hepatic stiffness in adult Fontan patients, may be limited by its lack of specificity and inability to distinguish hepatic congestion from fibrosis. [19] As a result of these limitations, MRI is frequently utilized as a noninvasive alternative for hepatic assessment in adult Fontan patients.[20] However, the relationship between markers of hepatic disease on MRI and clinical characteristics is not well established.

TABLE 3 Change in select indices of liver size over serial MRIs

Variable	MRI-1	MRI-2	P
Mean left-right liver Span (mm)	192	214	.005*
Mean spleen diameter (mm)	10.6	11.6	.001*
Mean inferior vena cava Diameter (mm)	30	29	.42
Mean right hepatic vein Diameter (mm)	15.4	16.9	.004*

mm = millimeters.
*Significant at alpha = .05.

In our cohort, patients with progressive hepatic congestion had a longer time between scans and worse ventricular function. To our knowledge, this is the first study to illustrate an association between progressive congestion and cardiac function over time. While the relationship between hepatic congestion by MRI and outcomes remains unclear, there is some evidence to suggest that congestion may lead to worse hepatic specific outcomes. In our study worsening hepatic congestion on CMR was associated with a higher MELD-XI score. Elevated MELD-XI scores have been shown previously to predict mortality and need for heart transplantation in adult patients with a Fontan.[21,22] While adequately powered prospective studies are needed, this association suggests that patients with decreased cardiac function may be at increased risk for progressive liver injury and warrant more frequent hepatic imaging.

We assessed how hepatic parameters changed over the course of serial examinations in order to determine if select anatomic factors

could be identified that reflected duration of Fontan pressure exposure. Although some degree of reduction in liver size is expected in cirrhotic patients, we found that liver span actually increased in the majority of patients. Because liver span is constrained and may decrease once a patient becomes cirrhotic, progressive enlargement over the long-term is unlikely. As such, we found no correlation with liver span and time from Fontan completion. On the contrary, time from Fontan completion to hepatic imaging was most strongly correlated with RHV diameter. Given its anatomic location and early takeoff from the IVC, RHV diameter may be particularly sensitive to Fontan pressure, and may serve as proxy for protracted exposure to high Fontan pressures. Whether there is a relationship between hepatic vein morphology and outcomes has yet to be defined; however, these results suggest that future studies powered to discern associations with clinical outcomes should consider hepatic vein assessment in accord with assessment of hepatic parenchyma.

While we found progression of hepatic congestion in serial studies of adult Fontan patients, the relationship remains complex and challenging to define. Newly detected hepatic congestion was found in only four patients in the cohort, implying that the vast majority of patients have congestive disease by the time they reach adulthood. Liver function tests did not correlate well with the degree of hepatic congestion or the size of preselected hepatic parameters and there was no significant difference in hepatic congestion between "classic" Fontans and lateral tunnel/extracardiac Fontans. Given the time frame of the study, few patients had concomitant hepatic elastography or liver biopsy. Future studies may be able to determine if either correlate well with radiographic evidence of hepatic congestion. While our study suggests that accounting for ventricular function may facilitate the identification of patients at risk for more rapid progression of hepatic congestion, understanding the heterogeneity inherent in hepatic outcomes will likely require a concerted longitudinal approach starting soon after Fontan completion.

4.1 | Study limitations

As a retrospective study, we are limited in drawing definitive conclusions and may have overlooked unknown, but important, confounders. Our sample size was limited and we were underpowered to detect associations with outcomes; however, this is the largest series of serial liver studies in the adult Fontan patient using a single imaging modality. Given the limited sample size, we were constrained to aggregating across different diagnoses. However, removing patients with a morphologic right ventricle from the analysis did not impact the significance of the association between cardiac function and hepatic congestion. Cardiac catheterization data was not available for the entire cohort at the time of imaging, limiting our ability to detect a relationship between hemodynamics and variables of interest. Finally, assessment of hepatic congestion was qualitative and may have been affected by differences in contrast timing and enhancement between studies.

5 | CONCLUSIONS

In our cohort of adult Fontan patients, worsening hepatic congestion was associated with a longer time between imaging, a higher MELD-XI score and decreased ejection fraction. In addition, right hepatic vein diameter was significantly correlated with time from Fontan completion. These findings may impact frequency of hepatic screening in this population.

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