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HEPATOBILIARY

Assessment of liver T1 mapping in fontan patients and its correlation with magnetic resonance elastography-derived liver stiffness

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Abstract

Objectives To explore the utility of liver T1 mapping in Fontan patients and its correlation to magnetic resonance elastography (MRE)-derived liver stiffness.

Background and aims Liver disease is a major long-term extra cardiac complication in the Fontan population. MRE is frequently used to quantify liver stiffness in Fontan patients; however, it has certain limitations. Native T1 mapping by cardiac magnetic resonance (CMR) is useful in assessment of cardiac fibrosis, but its potential in evaluating liver fibrosis and its correlation to MRE-derived liver stiffness in Fontan patients have not been reported.

Methods Fontan patients who underwent CMR and MRE were included. Liver Native T1, extracellular volume (ECV) and delta coefficients were measured and correlated with MRE-derived liver stiffness in all Fontan patients. Native liver T1 in Fontan patients were compared to normal controls with biventricular circulation and no known liver disease.

Results A total of 17 Fontan patients and 7 normal controls were included in this study. Fontan patients had significantly higher liver native T1 (690 ± 41 ms vs 620 ± 35 ms; $p < 0.001$) as compared to controls. There was strong positive correlation between MRE derived liver stiffness and liver native T1 ($r = 0.81$, $p < 0.001$).

Conclusions Liver native T1 was significantly elevated in Fontan patients compared to controls and strongly correlated with MRE-derived liver stiffness. This technique may prove to be a useful noninvasive imaging biomarker for assessing liver fibrosis in the Fontan population.

Keywords Single ventricle · Congenital heart disease · Liver fibrosis · Fontan · Parametric mapping

Introduction

Fontan associated liver disease (FALD) is a major extra-cardiac complications in patients with single ventricle anatomy who have been palliated by total cavo-pulmonary anastomosis [1–6]. FALD can range from benign nodular hyperplasia to liver cirrhosis and failure. Exact prevalence of FALD is not known; however, one case series has reported incidence of liver cirrhosis to be as high as 43% with a mean age of follow up 30 years after Fontan surgery [1]. Due to limited understanding of timeline and progression of liver disease in these patients, frequent surveillance for management becomes necessary [7].

The cause of liver dysfunction is multifactorial in FALD. Creation of a passive systemic venous return circuit, elevated central venous pressure, chronic passive venous congestion and lymphatic obstruction have been implicated. Decreased portal venous flow and impaired hepatic venous drainage

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cause hepatic arterialization [3, 5, 8, 9]. Over time sinusoidal dilation, parenchymal atrophy and progressive collagen deposition in a perivenular distribution occur, which can progress to bridging fibrosis. This diffuse parenchymal disease predisposes to development of liver nodules, generally of the regenerative/hyperplastic type but occasionally premalignant and malignant nodules [2, 8].

Clinical implications of FALD are serious since its presence tends to be associated with greater morbidity and mortality in Fontan patients [4, 10–12]. Therefore, recognition and screening for FALD are critical [3, 13]. Abnormalities in routine liver labs are typically mild and do not correlate well with clinical and histologic findings. Liver biopsy is the traditional gold standard for the detection of fibrosis; however, it is invasive and can be limited by the heterogeneity of the biopsy sites, which can result in qualitative and variable interpretation [3, 13]. Noninvasive liver stiffness measurements by magnetic resonance elastography (MRE) methods are now being increasingly used when available [14, 15]. Cardiac magnetic resonance (CMR) measurement of myocardial T1 relaxation times has been used to quantify diffuse myocardial fibrosis [16, 17]. Native T1 mapping of the liver has been reported by multiple studies for fibrosis assessment, especially in patients with fatty liver diseases and in patients with auto-immune hepatitis [16, 18–20]. Native T1 of the liver for FALD evaluation has not been studied. In this study, we investigated the utility of T1 mapping of the liver in Fontan patients and correlated with MRE-derived liver stiffness measures.

Methods

This was a single center retrospective study that was approved by our institutional review board (IRB) to study Fontan patients who underwent CMR study and MRE of the liver on the same scanner and in the same MR scan session between January 2015 and December 2017. Demographic and clinical data, including cardiac diagnosis, surgical details and imaging studies, were collected. Hematocrit was collected if performed with a month of the CMR scan. Cardiac index was recorded if hemodynamic data were available. Hemodynamic data were excluded, if acquired greater than ± 6 months from the date of the MRE and CMR studies or if they had undergone an interventional catheterization or surgical procedure in the interim. Control patients without liver disease and with biventricular circulation were prospectively recruited as part of separate study approved by the IRB. These patients underwent liver MRE along with native T1 estimation using MOLLI sequence as described under CMR protocol section on the same magnet and in the same scan session; however, they did not undergo a dedicated CMR study at the same time.

CMR protocol

Cardiac MRI was performed on a 1.5T magnet (Philips Healthcare, Eindhoven, Netherlands). CMR imaging was performed using a retrospective electrocardiogram (ECG) gated, segmented k-space, steady state free precession (SSFP) sequence. Standard imaging included a SSFP cine short axis stack from cardiac base to apex. Breath held modified look locker inversion recovery (MOLLI) sequences were performed pre-contrast and 15 min post-contrast administration. Total of 0.1 mmol/kg of Gadoterate Meglumine (Dotarem) was administered in Fontan patients. Post-MOLLI images were not performed in controls since no contrast was administered. Total of 3 short axis slices at the base, mid ventricular and ventricular apex level were acquired. MOLLI sequences were ECG triggered, motion corrected and obtained in end diastole. The MOLLI sequence used was the 5(3)3 protocol which comprised of acquiring 5 images after the first inversion with a 3 s pause followed by 3 images after the second inversion [21, 22]. Post-processing for native T1, ventricular volumes and ejection fraction was performed using CVI[42] (Circle cardiovascular imaging Inc., Calgary, Canada).

MRE protocol

MRE was performed using standard technique on the same 1.5T MRI scanner using the 16 channel cardiac/torso coil. Limited MRE protocol using gradient recalled echo (GRE) acquisition sequence was performed in axial plane with matrix of 256 × 64, slice thickness of 10 mm and minimum TR/TE. Four axial slices were obtained as per protocol outlined in a previous study by Serai et al. [23]. Elastograms and confidence maps were generated on the scanner console. Liver stiffness was measured by placement of regions of interests (ROI), defined by confidence maps and avoiding large vascular structures. A single PhD level investigator with 10+ years of experience in analyzing elastography data drew ROIs. Liver stiffness was calculated as a mean of the liver stiffness values obtained from each of the four images.

Liver T1 mapping

Short axis MOLLI slices acquired at the time of cardiac T1 mapping were reviewed to assess the slice where the greatest amount of liver parenchyma was visible. Three ROIs (approximately 30-40 mm^2) were carefully drawn including liver parenchyma and excluding biliary and vascular tree structures (Fig. 1), and a mean value was recorded. Liver Native T1 was measured in patients and controls. Additionally, liver post-contrast T1, ECV and delta coefficient values were calculated

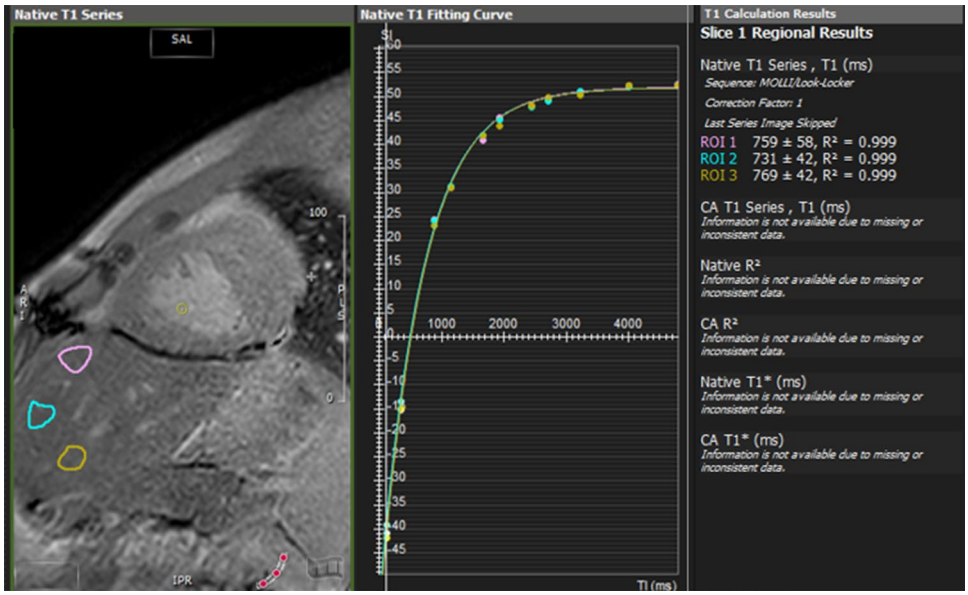

Fig. 1 Native T1 mapping with three regions of interests placed in the liver, avoiding visible blood vessels (left panel). The middle panel shows the liver recovery curve, which is used to measure native T1 and the right panel, shows the native T1 values

for the patients. Liver delta reduction rate ($\Delta R1_{liver}$) was calculated as per the following formula

$$\Delta R1_{liver} = \frac{1}{\text{Liver post contrast T1 (ms)}} - \frac{1}{\text{Liver native T1 (ms)}}$$

Delta R1 of blood ($\Delta R1_{Blood}$) was calculated as

$$\Delta R1_{blood} = \frac{1}{\text{Blood post contrast T1 (ms)}} - \frac{1}{\text{Blood native T1 (ms)}}$$

Liver extracellular volume (ECV) was calculated as following

$$\text{Liver ECV} = \left(\Delta R1_{liver}/\Delta R1_{blood}\right) \times (1 - \text{Hematocrit}).$$

ECV and Hematocrit were expressed as percentage.

Statistical analysis

Continuous variables were expressed as means and standard deviations after testing for normality. Categorical variables were expressed as frequencies and percentages. Correlation analysis was performed using Pearson correlation test. Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM, Armonk, New York) and JMP® (Version 12 from SAS Institute Inc., Cary, North Carolina).

Results

Demographic description of cases and controls

A total of 17 Fontan patients and 7 normal controls were included in the study. Patients included in the Fontan group were patients referred for routine cardiac imaging study. Demographic details of the Fontan group and the control group are provided in Tables 1 and 2. 14 of the 17 Fontan patients had a single left ventricle and the remaining were single right ventricles. Eight patients had extra-conduit type repair, 10 had lateral tunnel type reconstruction and 1 patient had an atriopulmonary Fontan repair.

Table 1 Demographics details of Fontan patients

Fontan[a]	$N = 17$
Age (years)	23 ± 6.5
Sex (females)	35%
Time since Fontan (years)	19 ± 5.8
Hematocrit around time of study (%)	46 ± 5
Fontan type	
Extra-cardiac conduit	7
Lateral tunnel	9
Atrio-pulmonary	1
Single ventricle dominance	
Right ventricle	5
Left ventricle	12
CMR Parameters	
Median SV EDV (ml/m^2)	98 ± 38
Median SV EF (%) (range)	46 ± 8.5
AV valve regurgitation grade	
None	3
Trivial	7
Mild	5
Moderate	1
Not reported	1

[a]Data is reported as mean ± standard deviation

Table 2 Demographic details of controls

Control[a]	$N=7$
Age (yrs.)	15 ± 3.7
Sex (female)	57%

[a]Data is reported as Mean ± standard deviation

Table 3 Comparison of Fontan patients and controls MRE and native T1 data

Parameter[a]	Fontan ($N=17$)	Control ($N=7$)	p value
MRE liver stiffness (kPa)	4.7 ± 1.2	2.3 ± 0.5	< 0.001
Liver native T1 (ms)	690 ± 68	620 ± 35	< 0.05
Post-contrast liver T1 (ms)	307 ± 55	–	–
Extracellular volume	42 ± 10	–	–

[a]Data reported as Mean ± standard deviation

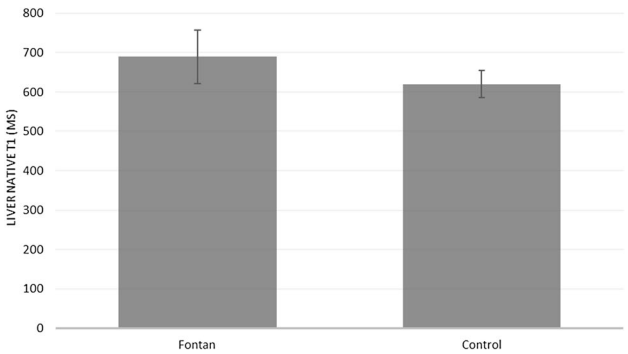

Fig. 2 Comparison of native liver T1 in Fontan patients and controls

MRE findings

MRE liver elasticity < 2.9 kPa was considered normal based on previously reported findings [15]. Fontan patients had mean MRE-derived liver stiffness values of 4.7 ± 1.2 kPa (Table 3). Normal controls had mean MRE values of 2.3 ± 0.5 kPa. MRE Liver stiffness was significantly higher in Fontan patients compared to controls ($p < 0.001$).

Liver T1 findings

Mean liver native T1 values in Fontan patients were 690 ms ± 68 ms and in controls were 620 ± 35 ms (Table 3). Patients with Fontan circulation were found to have significantly higher liver native T1 values compared to controls ($p < 0.05$) (Fig. 2). Mean post-contrast liver T1 was 307 ms ± 55 ms and liver ECV was 40 ± 10% in Fontan patients. Post-contrast T1 and ECV values could not be estimated in controls since contrast was not administered due to ethical considerations.

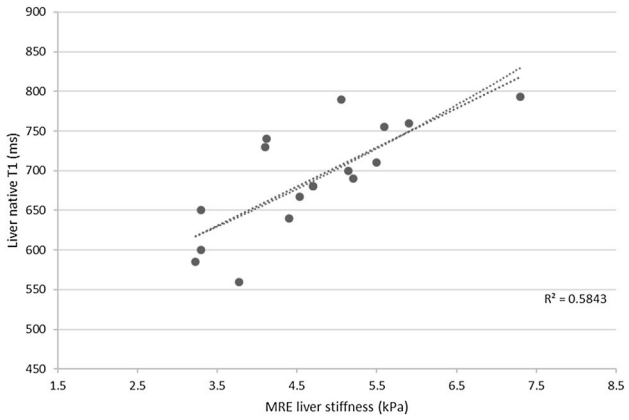

Fig. 3 Correlation between Liver Native T1 and MRE-derived Liver Stiffness in Fontan patients

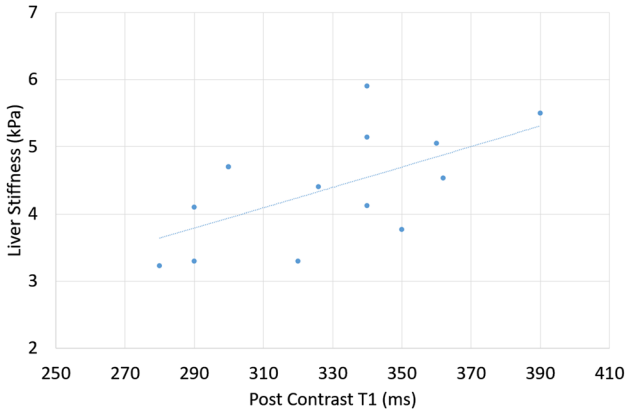

Fig. 4 Correlation of post-contrast T1 with MRE-derived liver stiffness

Correlation between MRE and liver T1

There was a strong, positive correlation between native T1 and MRE-derived liver stiffness in Fontan patients ($r = 0.81$, $p < 0.001$) (Fig. 3). There was also strong positive correlation between post-contrast T1 and MRE liver stiffness ($r = 0.7$; $p < 0.001$) (Fig. 4). No significant correlation was found between ECV ($r = 0.06$, $p = 0.7$) or $\Delta R1_{liver}$ ($r = 0.26$, $p = 0.3$) with MRE-derived liver stiffness.

Correlation of liver native T1 with other clinical parameters

No significant correlation of native liver T1 with age of patient ($r = -0.4$, $p = 0.08$) (Fig. 5). There was no significant

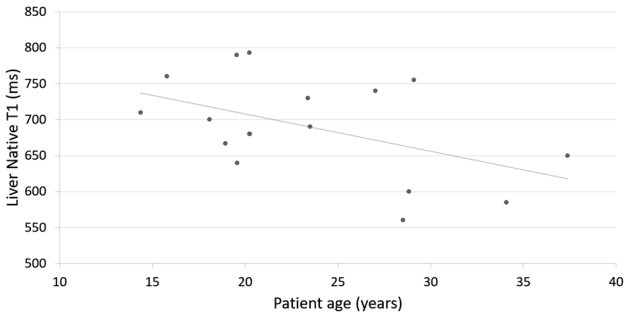

Fig. 5 Correlation of liver native T1 with age of Fontan patient

correlation between Fontan liver native T1 values and cardiac index calculated at time of recent cardiac catheterization in these patients ($r=0.4$, $p=0.12$). There was no significant correlation between cardiac index and liver stiffness ($r=0.46$, $p=0.06$).

Discussion

Early identification of FALD is critical in the Fontan population to initiate intervention. FALD assessment is challenging due to the inability to predict disease by laboratory investigations [3]. Therefore, clinicians are reliant on noninvasive imaging for surveillance [24, 25]. MRE is frequently used in addition to liver ultrasound [26]. MRE generates shear waves in the liver tissue, and the shear wave propagation is used to calculate liver elasticity [27]. Patients with longer duration of Fontan circulation show greater liver stiffness and therefore potentially increased fibrosis; however, utility of MRE is limited by the ability of additional hardware and its inability to distinguish between contribution of liver fibrosis and congestion, both of which can increase liver stiffness [14, 23].

Native T1 mapping has been extensively studied in cardiac diseases such as cardiomyopathy and storage disease such as amyloidosis [28, 29]. It has been shown to have the ability to detect subclinical diffuse myocardial fibrosis at a time when manifestation of fibrosis by late gadolinium enhancement or echocardiography has not occurred. Multiple studies using cardiac animal model biopsies have shown that native T1 strongly correlated with diffuse fibrosis [17, 18, 30]. Similar to MRE, it is currently unknown if T1 mapping can differentiate congestion from fibrosis. Our work shows that T1 mapping can add value in a clinical setting when MRE hardware is unavailable or is limited as in obese patients and patients with ascites. Unlike acoustic based methods, T1 mapping is unaffected by degree of adiposity or presence of ascites.

Our study shows significantly elevated liver native T1 values in Fontan patients compared to normal controls with strong correlation with MRE-derived liver stiffness. These findings lead us to believe that measuring native T1 of the liver could be used as an alternative noninvasive modality to estimate liver stiffness in Fontan patients. Elevated native T1 may represent tissue edema or fibrosis. Prospective studies need to be designed to begin understanding the progression of native liver T1 over time in these patients. This may not just help us gain more understanding the natural history of FALD but also monitor the response to treatment. Additionally in our study, Fontan patients had elevated liver native T1 irrespective of their age when compared to controls. This is concurrent with studies which have shown liver fibrosis has been detected as early as the time of the bidirectional Glenn procedure [31].

Liver T1 mapping also offers the logistic benefit of not needing a separate scan since T1 maps of the liver can relatively easily be acquired and generated in-line on the same scanner and at the same time as the cardiac MR scan. In our study, extracellular volume and delta coefficients did not correlate with MRE. We suspect this is related to small sample size and timing of hematocrit. Alternatively, we could also debate if this finding is because liver ECV and delta coefficiency are measuring liver fibrosis and MRE is measuring both fibrosis plus edema? Larger prospective studies with control data may help better answer this question.

Limitations of our study include the retrospective nature of this study that resulted in collecting liver native T1 from cardiac T1 mapping. Although best attempts were made to match the slices and include as much of the liver parenchyma as available on the slices, however, due to the retrospective nature of this study, it is possible that liver T1 and MRE regions were from separate areas of the liver. Our control data were limited by lack of ECV information. Larger prospective studies with dedicated T1 mapping of the liver with long-term follow-up data may further delineate the role of liver T1 mapping in FALD.

Conclusions

CMR-derived native T1 values of the liver were significantly higher in Fontan patients compared to healthy controls. We report a strong positive correlation of liver native T1 with MRE-derived liver stiffness, thereby justifying the potential use of liver T1 mapping as a noninvasive biomarker for diffuse liver fibrosis in the Fontan population.

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