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Can MR elastography be used to measure liver stiffness in patients with iron overload?

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Abstract

Untreated hepatic iron overload causes hepatic fibrosis and cirrhosis and can predispose to hepatocellular carcinoma. MR elastography (MRE) provides a non-invasive means to measure liver stiffness, which correlates with liver fibrosis but standard gradient recalled echo (GRE)-based MRE techniques fail in patients with high iron due to very low hepatic signal. Short echo time (TE) 2D spin echo echoplanar imaging (SE-EPI)-based MRE may allow measurement of stiffness in the iron loaded liver. The purpose of this study was to describe the use of such an MRE sequence in patients undergoing liver iron quantification by MRI. In our preliminary study of 43 patients with mean LIC of 9.3 mg/g (range 1.8–21.5 mg/g), liver stiffness measurements could be made in 77% (33/43) of patients with a short TE, SE-EPI based MRE sequence. On average, mean LIC in patients with failed MRE was higher than in those with successful MRE (15.9 mg/g dry weight vs. 7.3 mg/g), but a cut-off value for successful MRE could not be established. Seven patients (21% of those with successful MRE) had liver stiffness values suggestive of the presence of significant fibrosis (> 2.49 kPa). A short TE, SE-EPI based MR elastography sequence allows successful measurement of liver stiffness in a majority of patients with liver iron loading, potentially allowing non-invasive screening for fibrosis.

Key words: Liver elastography—Iron overload—MR elastography—Liver fibrosis

There are multiple causes for accumulation of excess iron in the body, the most common of which is transfusional iron overload. This occurs in the context of diseases that result in ongoing destruction of red blood cells such as β-thalassemia major, Diamond Blackfan anemia, and sickle cell anemia [1, 2]. Iron from repeated transfusions and red blood cell destruction accumulates in multiple tissues in the body but particularly in the liver and spleen. Iron that accumulates within tissues has deleterious effects related to free radical formation. In the liver, accumulated iron has the potential to induce hepatic fibrosis, various degrees of which have been reported, especially in patients with β-thalassemia [3, 4]. Hepatic fibrosis, in turn, can progress to cirrhosis and predisposes to hepatocellular carcinoma.

Historically, liver biopsy was performed to quantify liver iron which is considered a marker for total body iron stores. More recently, magnetic resonance imaging (MRI) utilizing relaxometry (R2 or R2*) has become the mainstay of non-invasive monitoring of liver iron stores, allowing serial assessment as a means to titrate therapy and obviating the majority of biopsies [5]. With the advent of MR elastography (MRE), which allows the non-invasive assessment of liver stiffness, it is now theoretically possible to both quantify liver iron stores, utilizing relaxometry, and to assess for liver fibrosis, using elastography, in a single imaging exam [6, 7]. Such an exam may provide a more comprehensive assessment of liver health and might bring clinical benefit to the population of patients with iron overload.

Gradient recalled echo (GRE)-based MRE is clinically available on at least three MR vendor platforms. However, in patients with liver iron overload, GRE-based MRE techniques are likely to fail due to very low signal from the liver related to the sequence echo time (TE) and the paramagnetic effect of the tissue iron. Alternative MRE sequences are available that theoretically provide more signal, including spin echo–echo planar imaging (SE-EPI)-based sequences. SE-EPI sequences, which are utilized on some vendor platforms at 3T, have higher wave signal-to-noise because of a higher number of wave cycles encoded per trigger. Further, short TE, SE-EPI-based sequences exist for research

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purposes. These sequences provide improved signal-to-noise, should be less susceptible to susceptibility related signal loss, and provide increased scan efficiency [8–10].

The purpose of this study was to review clinical application of a modified short TE, SE-EPI-based MRE sequence in patients with liver iron, assessing for frequency of exam failure and iron level at which the sequence failed.

Methods

In this retrospective, IRB approved study, imaging and clinical records for patients referred for MRI for evaluation of hepatic iron overload were reviewed. All study activities were conducted in a Health Insurance Portability and Accountability Act (HIPAA)-compliant manner. As part of our routine clinical MRI for hepatic iron quantification, a modified, short TE, SE-EPI-based MRE was included as an optional sequence (when time allowed) between July 2015 and August 2017 to assess sequence performance.

MR examination

Per our routine practice, all patients had been instructed to fast for a minimum of 4 hours prior to their examination. MRI scans had been obtained on a GE Signa HDxt 1.5T magnet with software version HD 23 (GE Healthcare, Waukesha, WI, USA). This magnet is equipped with a gradient system with a maximum amplitude of 33 mT/m and a 150 mT/m/msec slew rate. Patients were positioned supine with an 8-channel torso phased array coil centered over the abdomen.

Liver R2* imaging had been performed by acquiring gradient echo multi-echo MR images collected at increasing echo times based on methodology reported by Wood et al. [11]. Per our standard clinical protocol, eight echo times were collected with the first TE set as close to 1 ms as possible (Table 1). We acquired 4–8 axial slices through the liver, depending on the chosen field of view. The acquisition was performed in a single breath-hold of approximately 10–15 s.

MRE had been performed using MR Touch® hardware (GE Healthcare, Waukesha, WI, USA) and a modified short TE SE-EPI sequence (Table 2). Four slices were obtained through the mid-liver in two breath-holds. Elastograms and confidence maps were generated on the scanner console using a multiscale direct inversion (MSDI) algorithm and were transferred offline for further analysis and measurements.

Table 1. Protocol parameters for R2* imaging of the liver

Sequence	R2* liver MRI
Scan mode	2D
TR (msec)	7.1
No. of echoes	8
first TE (msec)	1
delta TE (msec)	0.8
Flip Angle	25
Matrix size	140 × 140
Slice thickness (mm)	6
Acceleration factor	2
No. of slices	4–8
Scan time (s)	0:12

TE, echo time; TR, repetition time; msec, time in milliseconds

Image analysis

T2* analysis was performed on a pixel-by-pixel basis utilizing MEDIS (Medis Medical Imaging Systems, Leiden, the Netherlands). A single trained observer with 8+ years of MRE post-processing experience (SDS) drew four irregular polygon regions of interest (ROIs) on four consecutive images of the liver. ROIs were drawn to be as large as possible while excluding large vessels and the central biliary tree. Curve fitting utilizing a mono-exponential fit with a noise floor was then performed based on the signal decay curves generated from each ROI [12, 13]. Overall liver T2* was calculated as a mean of the four T2* values and was converted to R2* (R2* = 1000/T2*) and estimated liver iron content (LIC).

Liver stiffness was measured by placing four irregular polygon ROIs in the right hepatic lobe; one on each of the four elastograms in conjunction with the magnitude and wave images. ROIs were drawn by a same single trained observer (SDS) to be as large as possible while remaining within the margins of the confidence map, avoiding major blood vessels, regions close the paddle and remaining ~ 1 cm inside the liver boundary of the liver. Overall liver stiffness was calculated as a mean of the mean liver stiffness values obtained from each of the

Table 2. MRE protocol parameters

Parameter	2D GRE MRE	2D SE-EPI MRE
Pulse sequence type	GRE	EPI
Matrix size	256 × 64	80 × 80
No. of signals acquired	1	0.75
No. of EPI shots		8
TR (mS)	50	1000
TE (ms)	20	10
Bandwidth (kHz)	32	250
No. of slices	4	4
Slice thickness (mm)	10	10
Gap (mm)	5	5
No. of phases	4	4
MEG frequency (Hz)	60	250
Axis of MEG	z	z
Wave frequency	60	60
Wave cycles per trigger	3	60
No. of breath holds	4	2
Acceleration factor	2	2
Scan time (min:s)	1:00	0:30

four liver slices, weighted by ROI area [7, 15]. For the purpose of this study, successful MRE was defined as visible varying phase (waves) in the liver on the phase images that produced measureable data within the bounds of the elastogram confidence maps [6, 14]. Failed MRE was defined as no visible waves, or disordered, fragmented waves in the liver on the phase images with no measurable area of liver within the bounds of the elastogram confidence maps.

Clinical data collection

Electronic medical records were reviewed for each patient to collect indication for liver iron quantification, height, weight, body mass index (BMI), and liver biopsy data (if available).

Data analysis

Continuous variables were summarized with descriptive statistics including means and medians as appropriate. Student t test was used for comparison of means and Pearson correlation was used for correlation analyses. A p value < 0.05 was considered statistically significant for all analyses. Analyses were performed using MedCalc version 18.2 (MedCalc Software, Ostend, Belgium). Per Garbowski et al., LIC was calculated based on the equation: LIC = $31.94(T2^*)^{-1.014}$ [16]. A mean liver stiffness value $>$ 2.49 kPa was considered suggestive of the presence of significant (≥ stage F2) fibrosis [15, 17–19].

Results

Of the 43 subjects included in this study, 13 (30%) were male and 30 (70%) were female and the mean age was 11.7 years (range 2.7–21.0 years). Sickle cell anemia (20/43, 47%) and β-thalassemia (11/43, 26%) were the most common indications for hepatic iron quantification. Mean R2* for the population was 232 Hz (range 45–678 Hz). This equates to a mean liver iron content of 9.3 mg/g (range 1.8–21.5 mg/g).

MRE was successful in 33 patients (77%) and failed in ten patients (23%). Representative images from successful and failed MRE exams are shown in Figs. 1 and 2 respectively. In the subgroup of patients with successful MRE, there were 13 patients with sickle cell anemia and nine patients with β-thalassemia, three patients were status-post chemotherapy, three patients were status-post bone marrow transplant with multiple transfusions, two patients had Diamond Blackfan anemia, two patients had a history of Neuroblastoma status-post chemotherapy requiring transfusion support, and one patient was status-post multi-visceral transplant. In the subgroup of patients with failed MRE, there were eight patients with sickle cell anemia (80% of 10) and two patients with β-thalassemia (20% of 10).

Mean R2* was significantly different between patients with successful (mean 232 Hz ± 168) vs. failed MRE (mean 504 Hz ± 140) ($p < 0.0001$) (Fig. 3A). This equates to a mean LIC in patients with successful MRE of 7.3 mg/g dry weight (± 5.4 mg/g) vs. 15.9 mg/g in patients with failed MRE (± 4.5 mg/g) (Fig. 3B). There were no significant differences in height, weight or BMI between patients with failed MRE vs patients with successful MRE (Failed MRE: Mean height = 131.4 cm; mean weight = 33.3 kg and mean BMI = 18.7 kg/m^2 vs. Successful MRE: Mean height = 137 cm; mean weight = 37.7 kg and mean BMI = 18.5 kg/m^2).

Among the 33 patients with successful MRE, mean liver stiffness was 2.15 kPa (range 1.35–4.47 kPa; median = 2.11 kPa). There was no significant correlation between liver R2* and liver stiffness values ($r = 0.05$; $p = 0.79$). Seven patients (21.2% of 33) had liver stiffness values suggestive of the presence of significant fibrosis. Only two patients had a liver biopsy performed, both of whom had liver stiffness values below the cut-off suggestive the presence of significant fibrosis. One patient had incomplete bridging fibrosis (F2) and the other had no fibrosis.

Discussion

Iron deposition in the liver can be the result of multiple disease processes. Tissue injury associated with iron deposition can lead to liver fibrosis and, if progressive, to cirrhosis and its complications. Chelation therapy, which is typically guided by estimates of body iron stores, provides a therapeutic method to control tissue iron deposition and adequate chelation therapy has been shown to control progression of liver fibrosis in transfusion dependent thalassemia patients [20].

MRI has become the dominant surveillance method for hepatic iron deposition and can provide guidance for chelation therapy in patients with iron overload [21, 22]. Although liver biopsy remains a gold standard for evaluating hepatic fibrosis, MRE now provides a means to non-invasively assess liver stiffness which correlates with liver fibrosis [23–25]. New short TE SE-EPI MRE sequences have made it possible to measure liver stiffness in patients with hepatic iron overload [8]. In combination, it is now possible to perform a single non-invasive imaging exam to both quantify liver iron and screen for developing fibrosis. In this study, we have explored utilization of such an exam, and have shown that liver stiffness can successfully be measured in a majority (77%) of patients with liver iron deposition, demonstrating clinical feasibility of this technique.

While we have shown that it is possible to measure liver stiffness with MRE in individual patients with liver iron content as high as 21.5 mg/gm, SE-EPI MRE failed to produce usable liver stiffness data in 10 of 43 patients in our study (23%). On average, R2*and hence LIC was

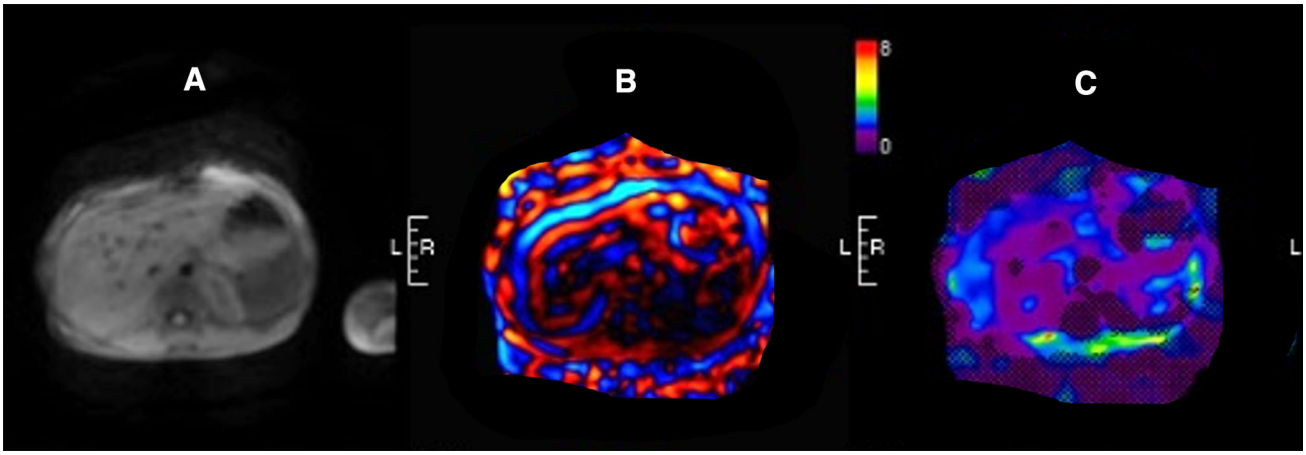

Fig. 1. Magnitude (**A**), and wave (**B**) images from a successful MRE showing excellent illumination of waves through the liver. Stiffness map (**C**) showing elevated liver stiffness suggestive of significant fibrosis.

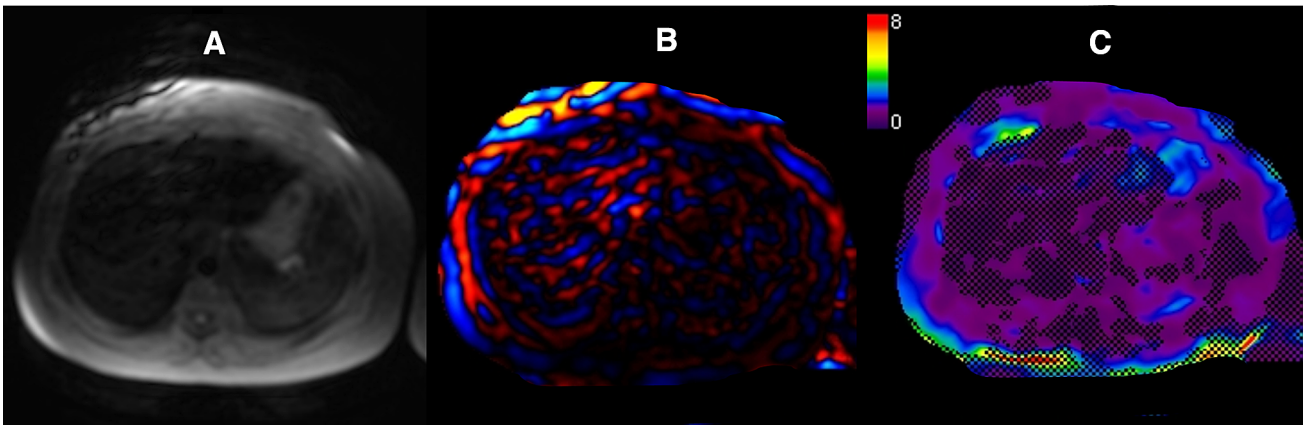

Fig. 2. Failed MRE—representative images of a MRE failed due to liver with severe iron overload. Magnitude image (**A**) shows the liver to be diffusely low in signal while the phase (**B**) image shows no organized waves traversing the liver. Stiffness map (**C**) is not valid.

significantly higher in patients in whom MRE failed (Fig. 3). That said, our data were insufficient to identify a threshold R2* value that could be used to predict whether MRE would be successful. Patients with successful stiffness measurements had R2* values as high as 667 Hz and those with failed measurements had R2* values as low as 235 Hz. Unfortunately our study population is too small to specifically define the causes of exam failure in individual patients.

To our knowledge, this is the first study of the application of MRE in a clinical population of patients with hepatic iron loading. Prior studies exist utilizing other elastographic techniques in both children and adults [26]. In a study by Hamidieh et al. transient elastography was used to measure liver stiffness in pediatric patients with thalassemia major [27]. In that study, liver stiffness measurements were successfully obtained in 60% of patients at LIC values up to 15.7 mg/g. The authors reported a median stiffness score of 4.3 kPa, showed that stiffness measurements correlated with METAVIR scoring of liver fibrosis and showed that stiffness measurements correlated with LIC ($r = 0.42$, $p < 0.001$). This latter finding of a correlation between stiffness measured by transient elastography and LIC has been shown by other authors as well, including Pipaliya et al. who showed it in a population of children evaluated with transient elastography [28]. In that study the correlation between stiffness and LIC was sufficiently strong that the authors suggested that transient elastography might be used to estimate LIC. This suggests a confounding effect of liver iron loading on ultrasound-based liver stiffness measurements. Interestingly, in our population, there was no significant correlation between R2* and liver stiffness as measured by MRE suggesting presence of iron may not confound MRI-based liver stiffness measurements.

In our population, seven patients (21% of those with successful MRE exams, 16% of the total population) had elevated liver stiffness values suggestive of the presence of significant fibrosis based on prior studies of MRE in

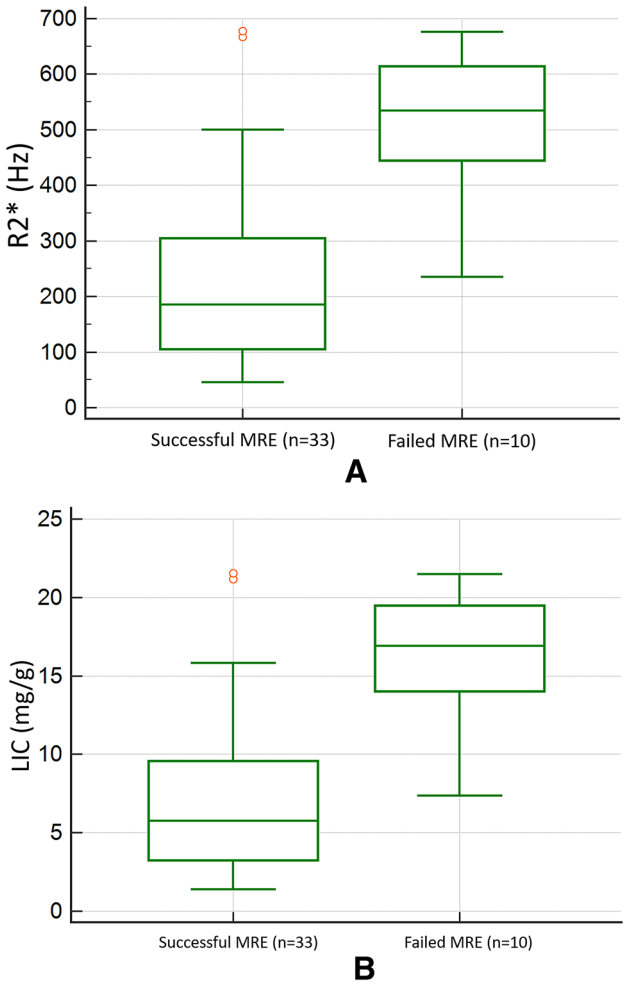

Fig. 3. Box and whisker plot of R2* (**A**) and its corresponding calculated LIC (**B**) for patients with successful vs failed MRE.

children [6, 15, 17, 29]. This is a slightly lower prevalence of possible fibrosis than previously reported by Elalfy et al. who performed liver stiffness measurements utilizing transient elastography [30]. In that study, the authors found evidence of cirrhosis in 23% and evidence of liver fibrosis in 35% of young (adolescent and young adult) Egyptian patients with thalassemia major. Unfortunately, patients with elevated liver stiffness in our population did not undergo biopsy for confirmation of liver fibrosis.

Our study had some limitations. First, this study was conducted at a single institution on a single MRI scanner, which may limit its generalizability. That said, our patient cohort was diverse in terms of disease resulting in iron loading and the severity of hepatic iron loading. Second, our patients did not have biopsy confirmation of the liver stiffness values obtained. Third, this is a preliminary, observational study that did not compare the commercially available GRE-based MRE techniques to the short TE SE-EP-based technique used in this study to demonstrate the added value of the short TE sequence in patients with iron overload [8].

Conclusion

A short TE, SE-EPI based MR elastography sequence allows successful measurement of liver stiffness in a majority of patients with liver iron loading, potentially allowing non-invasive screening for fibrosis.

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Conflicts of interest and source of funding There were no grants or other financial assistance for this research.

Compliance with ethical standards

Funding Not applicable.

Disclosure of potential conflict of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent This was a retrospective study and informed consent was waived by the IRB.

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