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REVIEW

Pediatric MR elastography of hepatic fibrosis: principles, technique and early clinical experience

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Abstract Numerous pediatric conditions result in hepatic fibrosis. As treatments develop for the underlying disorders, a non-invasive assessment of liver fibrosis would be beneficial as an adjunct or possible replacement for the traditional gold standard, liver biopsy. Magnetic resonance elastography is a noninvasive imaging technique that has been used successfully in adults for identification and assessment of liver fibrosis. This review describes the basic principles of MR elastography as well as the technical aspects specific to children. Clinical pediatric applications, limitations and areas for future research are described.

Keywords MR elastography · Pediatric · Liver · MRE

Introduction

Children suffer from a variety of liver diseases that include congenital, infectious and inflammatory conditions that, when severe, can result in end-stage liver disease and hepatic fibrosis. Traditionally, liver biopsy has been the only accurate method to assess for the presence and severity of fibrosis. With the advent of effective treatments for many of these conditions that can arrest or delay hepatic fibrogenesis [1], non-invasive techniques for the identification and grading of hepatic fibrosis have become increasingly sought after. MR elastography is one of several novel, non-invasive techniques that assess liver stiffness for the presence and severity of liver fibrosis [2, 3]. It has recently been shown to accurately identify and stage hepatic fibrosis in adults [4]. This review discusses the physical principles and technical issues related to its performance in children. Additionally, future clinical applications are presented with case examples. Last, current limitations and potential areas for future research are addressed.

Principles and techniques of MR elastography

Diffuse infiltrative processes or tumors can alter the mechanical properties of soft tissues, typically resulting in increased firmness. These changes can be qualitatively assessed by physicians with palpation and percussion. In mechanical engineering terms, the force applied during palpation or percussion is termed *stress* and the resulting tissue movement is termed *strain*. Stresses and strains are related through a number of tissue-specific mechanical parameters (e.g., the shear and Young moduli) that characterize the mechanical properties and deformation behavior of the tissue, including its stiffness. In particular, tissues with high shear/Young moduli (e.g., cirrhotic liver tissue) are stiff and tissues with low moduli (e.g., normal liver) are soft. Given the same amount of applied force (stress) such as that applied during palpation, stiff tissues experience less deformation (strain) than soft tissues. With vibrational stresses, such as percussion, stiffer tissues will

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transmit the vibrational energy in the form of a shear wave deeper into the tissue whereas softer tissues will dissipate the energy and not transmit the shear wave effectively.

MR elastography assesses tissue stiffness by measuring the speed of shear waves propagating within it. As with other stiffness imaging techniques [5], this assessment involves three basic steps. First, an external source of tissue stress is applied. In the case of liver MR elastography this can be performed with an audio sub-woofer. The speaker's magnet must be located away from the MR imaging magnet, thus a connecting tube is used to transmit the vibrational energy to a passive driver. This driver is placed on the right anterior lower chest/upper abdominal wall and delivers the vibrations transcostally/transabdominally into the liver (Fig. 1). The frequency of the vibration is typically 60 Hz. Second, the response of the tissue to the mechanical stress introduced by this vibration is measured using standard MR phase-contrast imaging sequences with the addition of motion-encoding gradients (MEG) synchronized with the vibrational input (Fig. 2). These sequences allow for visualization of the propagating shear waves within the target tissue in what are often called wave images. The peaks and troughs of the waves can be identified as concentric rings similar to the effect of a pebble thrown into a pond (Fig. 3). Regions of interest (ROI) are selected avoiding large blood vessels and areas of low wave amplitude to provide an overall estimate of parenchymal stiffness with units of kiloPascals (kPa). The acquired wave images are used to generate quantitative maps of tissue stiffness referred to as elastograms (Fig. 3). Because motion, cardiac or respiratory, can degrade the elastography data, sampling of the liver is generally done in the right lobe. Additionally, these sequences are performed during breath-hold in cooperative patients. Infants and

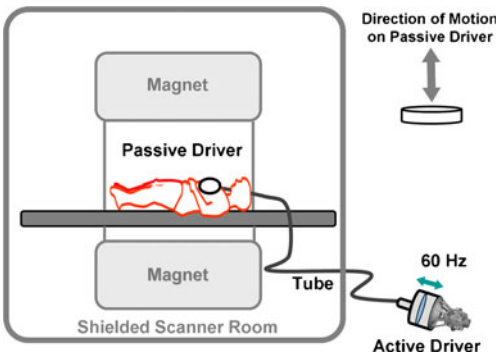

Fig. 1 Schematic drawing of an acoustic speaker source with connecting tubing and a driver for MR elastography. The active driver is shielded from the imaging magnet and delivers vibrational energy to the passive driver at 60 Hz through the connecting tube. The passive driver is placed across the right anterior chest wall to deliver vibrations transcostally into the liver

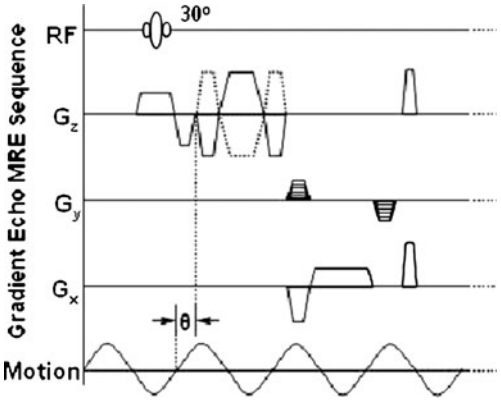

Fig. 2 MR elastography pulse sequence diagram illustrates the timing of the imaging and motion-encoding gradients in relation to the applied vibration. Theta indicates an adjustable phase delay between the motion and the motion-encoding gradients to capture the tissue motion at different time points during the wave propagation

young children are typically sedated for the MR liver or MR enterography that accompanies the MR elastography examination and breathing can be controlled in these patients. Work to develop respiratory-gated MR elastography techniques is underway. For more details of the technique of MR elastography, the reader is referred to a recent technical review [6].

In our practice MR elastography is typically incorporated with a diagnostic MR liver or MR enterography exam, depending on the clinical indication, and can be performed at 1.5 T or 3 T with equivalent results. The MR elastography study requires approximately 5–10 min of additional setup and table time. The acquisition parameters have been reported [4]: axial FOV=30–44 cm, acquisition matrix=256×64, TR/TE=50/20 ms, flip angle=25°, slice thickness=10 mm, ±32 kHz receiver bandwidth, 1 pair of 1st moment nulled MEG with motion sensitivity of 6.2 μm/radians, mechanical frequency=60 Hz, 4 slices, parallel imaging acceleration factor of 2, and 4 time points evenly sampled over 1 period of the motion. The acquisition is typically performed in four 15-s breath-holds at end expiration. This protocol is performed using software developed at the Mayo Clinic (Rochester, MN) and is equivalent to the commercially available MR Touch (GE Healthcare, Waukesha, WI, USA).

Technical issues unique to pediatric MR elastography

In very young children (<1 year old), the standard driver power level is reduced by 50% from what is used in adult patients. A folded towel is placed between the driver and the child to (1) improve the mechanical coupling between the chest and abdomen wall and the comparatively large

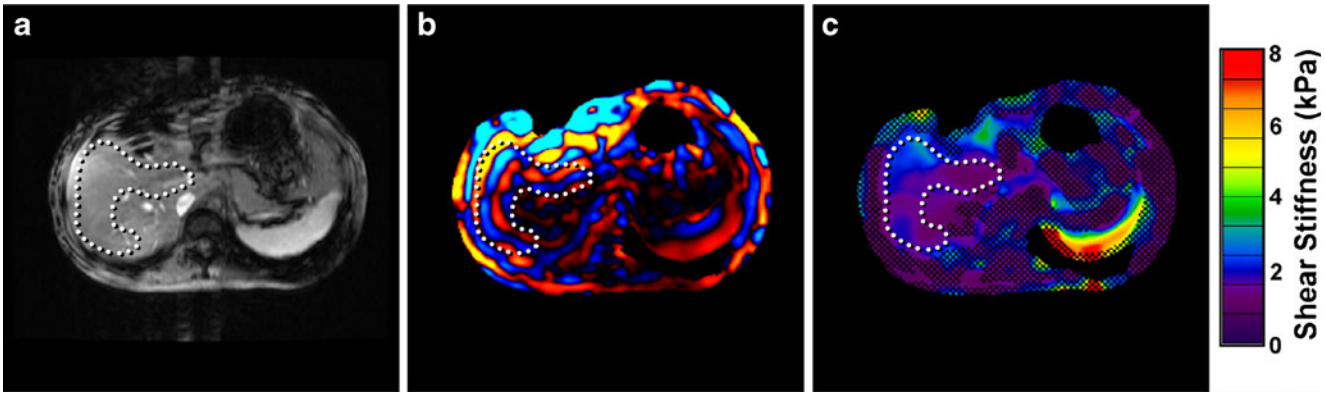

Fig. 3 Wave propagation and elasticity. **a** MR magnitude image. The C-shape ROI (*dotted line*) within the hepatic parenchyma is defined to avoid the central portal vessels. **b** Wave image shows the propagation of the shear waves through the hepatic parenchyma. The wave pattern within the liver can be visualized by the alternating colored bands. **c** Color-coded elastogram. Post-processing of the MR elastography wave data identifies poor wave propagation in the hatched areas. These areas are not included in the elasticity assessment. The ROI shows blue and purple areas corresponding to normal elasticity values <2.9 kPa

passive driver, (2) maintain image quality as less driver power is required in a small child to achieve the same displacement amplitude obtained in adults, and (3) to minimize any risk of mechanical or thermal injury to the child. As with other pediatric body MRI examinations, the specific absorption rate is maintained within acceptable limits based upon patient weight, with automated adjustments incorporated by the MRI manufacturer into the imaging protocol. The relatively small surface in infants and children has not been a technical limitation for MR elastography, as the driver can be placed over the lower chest and upper abdomen and still be effective in generating hepatic vibrations. ROI selection in small children, as in adult MR elastography, must be done with care to stay within the liver but avoid large blood vessels and extraparenchymal structures such as the gall bladder. Because the increased portal venous flow present after eating can result in transiently increased hepatic stiffness (average increase 18%, range 5–48%) in patients with liver disease (but not in normal subjects), children should fast for at least 4 h prior to MR elastography [7].

Clinical applications

In infants the liver response to injury includes parenchymal cellular injury as well as cholestasis injury, as the metabolism of bile formation and excretion are immature. The resulting insult can lead to rapidly progressive liver fibrosis brought about by chronic inflammation. For example, early cirrhosis is common in patients with extrahepatic biliary atresia. Likewise, several metabolic liver diseases occur at an early age leading to progressive fibrosis, such as familial intrahepatic cholestasis syndromes and α-1-antitrypsin deficiency. Liver fibrosis leading to portal hypertension might be the presenting feature in a variety of conditions such as autoimmune hepatitis, sclerosing cholangitis and congenital hepatic fibrosis. At present specific therapeutic tools to treat and reverse fibrosis are lacking but many conditions are amenable to palliative or curative treatment. Examples include the use of replacement bile salt therapy for cholestasis and immune suppression for autoimmune liver disease. With early interventions, hepatic fibrosis can be minimized. Traditionally, percutaneous liver biopsy has been required to monitor the fibrotic changes associated with these conditions.

The need for a noninvasive assessment of hepatic parenchymal inflammation and fibrosis arises in several patient groups: patients with elevated liver function tests of unknown cause; patients with hepatitis; patients with a known diagnosis that is associated with liver fibrosis such as cystic fibrosis, polycystic kidney disease or biliary atresia; and in those being assessed for treatment response. Disadvantages of percutaneous liver biopsy, including expense, need for sedation, potential complications and insufficient sampling, have become more relevant in clinical decision-making as potential alternatives to biopsy have been developed. Liver biopsy is an invasive procedure, often requiring deep sedation or general anesthesia in pediatric patients. Though image-guided percutaneous liver biopsy is an extremely safe procedure when performed by an experienced physician [8], the risks of hemorrhage, infection, injury to the liver or adjacent structures, and death are not inconsequential. Additionally, the costs of the biopsy procedure and pathological analysis of the liver sample exceed those of MR elastography. Last, because of the heterogeneity of liver fibrosis, the accuracy of liver biopsy, the traditional gold standard for parenchymal

assessment, is subject to sampling error. Percutaneous liver biopsy obtains a small parenchymal sample, approximately 1/50,000th of the liver mass, and this may not reflect the overall degree of liver damage. MR elastography samples a large fraction of the liver, as much as 20% based on the number of slices of liver imaged and average liver size. Thus the results of biopsy and MR elastography might be discrepant, with both upgrading and downgrading possible. In sampling a larger volume of liver tissue, MR elastography likely provides a more global assessment of liver fibrosis and a more robust evaluation of overall liver fibrosis than biopsy.

Clinical cases (Table 1)

Potential clinical applications of MR elastography include noninvasive assessment of the liver in patients with elevated liver function tests of unknown etiology, screening for liver fibrosis in patients with inflammatory bowel disease and at risk for primary sclerosing cholangitis (Fig. 4), patients with known congenital fibrogenic liver diseases such as primary familial intrahepatic cholestasis or α-1-antitrypsin deficiency (Fig. 5), patients with autoimmune or infectious conditions associated with liver fibrosis (Fig. 6), and patients with cystic fibrosis or surgically treated biliary atresia. Additionally, if pediatric MR elastography proves to accurately and reliably grade hepatic fibrosis, it could replace liver biopsy in the assessment of treatment response (Fig 6.). Preliminary work suggests children with cirrhosis might be distinguished from those without cirrhosis based on MR elastography (M. Siegel, personal communication).

Discussion

MR elastography has been applied to a variety of diseases that alter soft-tissue physical properties including breast, brain, heart and lung. To date, its most extensive clinical use has been for the assessment of liver disease. MR elastography has been shown to be accurate in the staging of liver fibrosis in adults when compared to liver biopsy and pathological grading [4, 9]. The presence or absence of liver fibrosis is demonstrated with MR elastography with a sensitivity of 98% and specificity of 99% when using a shear stiffness normal cutoff value of <2.93 kPa. MR elastography-derived shear stiffness values increased with increasing liver fibrosis grade. Specifically, low-grade fibrosis was found in livers with elasticity measurements of >2.93 and <5.5 whereas high-grade fibrosis was found in livers with values >5.5 [4]. It is important to note that shear stiffness values were found to be independent of fatty changes in the liver and could be accurately assessed in the presence of ascites [4]. When compared to other non-invasive assessments of liver fibrosis, MR elastography was found to be superior to US-based transient elastography (UTE), with higher technical success (94% vs. 84%) and to be more highly correlated with hepatic fibrosis [10]. This is thought to result from several advantages of MR elastography over UTE. MR elastography assesses liver strain in two or more dimensions and has a much larger sample volume than UTE, reducing the potential of sampling error. The use of continuous vibratory compression waves with MR elastography allows for deeper penetration into the liver [11]. MR elastography is not degraded by iron deposition in the liver except when extensive, as in

Table 1 Summary of clinical cases

Figure	Age/gender	Diagnosis	Duration	MRE[a] kPa	Fibrosis grade	Laboratory values
4a	16 y/M	Ulcerative colitis Primary sclerosing cholangitis	2 months	3.2 kPa	1–2 of 4	Elevated LFTs and bilirubin Esophageal varices
4b	14 y/F	Crohn colitis	3 months	2.3	normal	Elevated LFTs Normal bilirubin
5a	10 mo/F	Primary familial cholestasis, type 3	congenital	3.9	3 of 4	Elevated LFTs and bilirubin
5b	10 y/F	ά-1 antitrypsin, MZ type, Joubert variant, nephronophthisis	congenital	4.1	3 of 4	Elevated LFTs Normal bilirubin
6a	16 y/M	Hepatitis B	>12 years	2.4	1–2 of 4	+ HBs antigen, − antibody Elevated HBV DNA
6b	17 y/F	Autoimmune hepatitis, type 2	2 years	2.5	3 of 4	−ANA, ASMA Elevated IgG1 and 3
7	15 y/F	Hepatoportal sclerosis with idiopathic portal hypertension	Unknown	5.0	3 of 4	Esophageal varices

[a] The abbreviation for MR elastography, MRE, has been used for many years and predates the development of MR enterography. However, because MR enterography has achieved wider application than MR elastography, we chose not to abbreviate MR enterography as MRE in the paper to avoid confusion for the reader

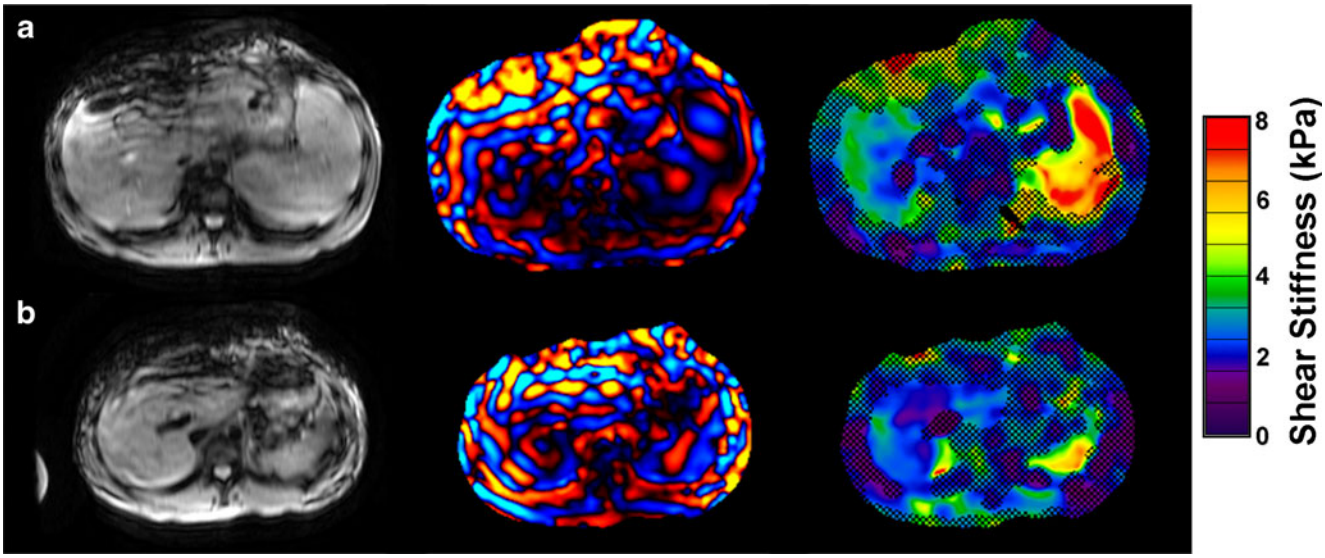

Fig. 4 MR elastography of two children with inflammatory bowel disease. **a** MR elastography in a 16-year-old with chronic ulcerative colitis and primary sclerosing cholangitis demonstrates mildly increased liver elasticity: mean=3.2 kPa, range=3.0–3.4 kPa, normal <2.9 kPa, consistent with mild hepatic fibrosis. Liver biopsy on the same day demonstrated low-grade bridging fibrosis (grade 1–2 of 4). **b** MR elastography in a 14-year-old with Crohn colitis and PSC is normal, mean=2.3 kPa (normal <2.9 kPa). Biopsy from the same day showed no hepatic fibrosis

hemochromatosis [12]. In our practice, the presence of hepatic iron overload has caused the liver signal to be so low that waves cannot be visualized and stiffness cannot be measured. This has happened in approximately 5% of 1,377 adults but in none of our pediatric MR elastography exams that we recently reviewed. Sequences less sensitive to local iron concentrations, such as spin-echo and short-TE gradient-echo sequences, can reduce this potential source of technical failure. Additionally, MR elastography can be performed in the presence of ascites and obesity, both of

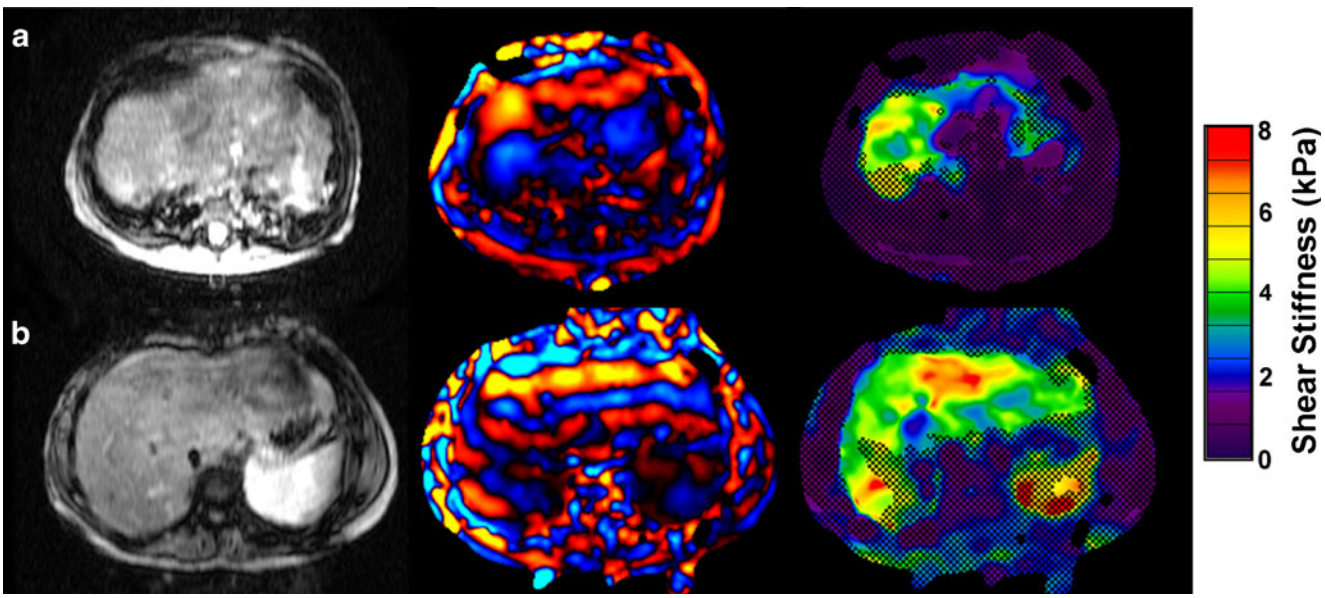

Fig. 5 MR elastography of two patients with congenital fibrogenic liver disease and marked liver fibrosis on biopsy (grade 3 of 4). Yellow, green and red areas indicate elevated liver stiffness. **a** MR elastography in a 10-month-old with familial cholestasis type 3 demonstrates markedly elevated liver stiffness, (mean=3.9 kPa, range=3.2–6.1 kPa, normal <2.9 kPa). **b** MR elastography in a 10-year-old with α-1-antitrypsin deficiency demonstrates elevated liver stiffness (mean=4.1 kPa, range=3.9–4.3 kPa, normal <2.9 kPa)

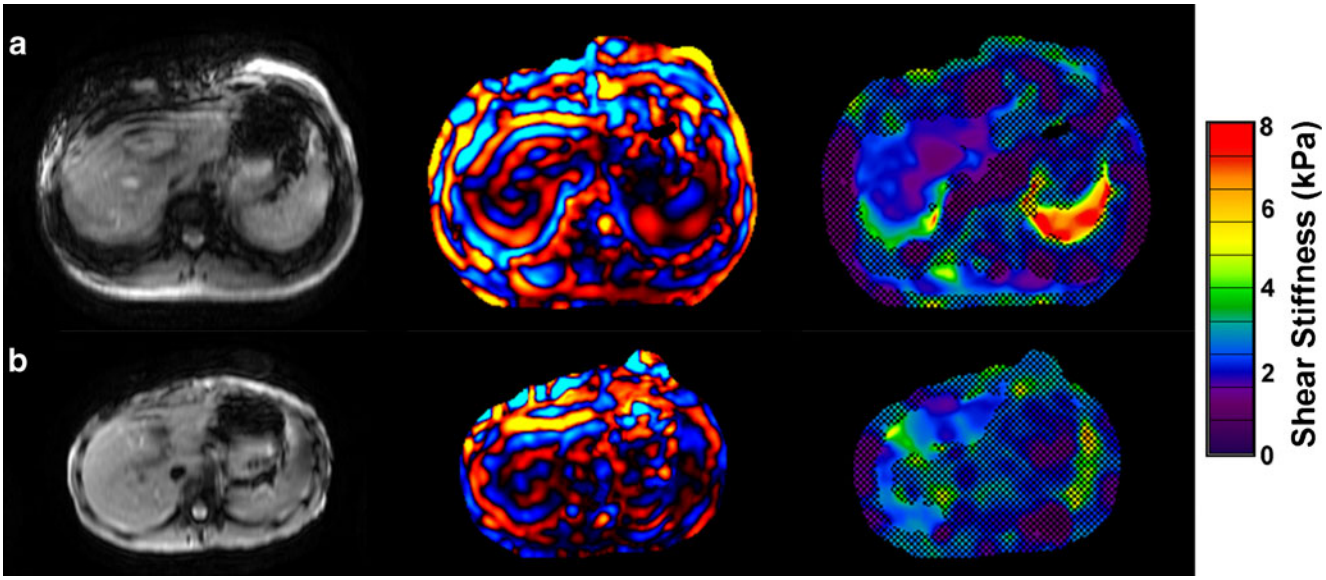

Fig. 6 MR elastography in assessments. **a** A 16-year-old with chronic hepatitis B. Elastogram was normal (mean=2.4 kPa, normal <2.9 kPa) though biopsy showed areas of both grade 1 and grade 2 fibrosis. **b** A 17-year-old with autoimmune hepatitis. Pre-treatment liver biopsy showed marked hepatic fibrosis (grade 3 of 4). Following 1 month of treatment with the resolution of the clinical and laboratory findings of hepatitis, MR elastography demonstrated normal elastogram (mean= 2.5 kPa, range=2.3–2.9 kPa, normal <2.9 kPa). Follow-up liver biopsy was not performed after the MR elastography

which are limitations of standard UTE, which samples tissues at a set depth from the skin surface, typically 6 cm. This preset depth can be too shallow in the presence of obesity or ascites. However, recent developments in UTE will likely permit sampling of deeper tissues, overcoming this limitation [13].

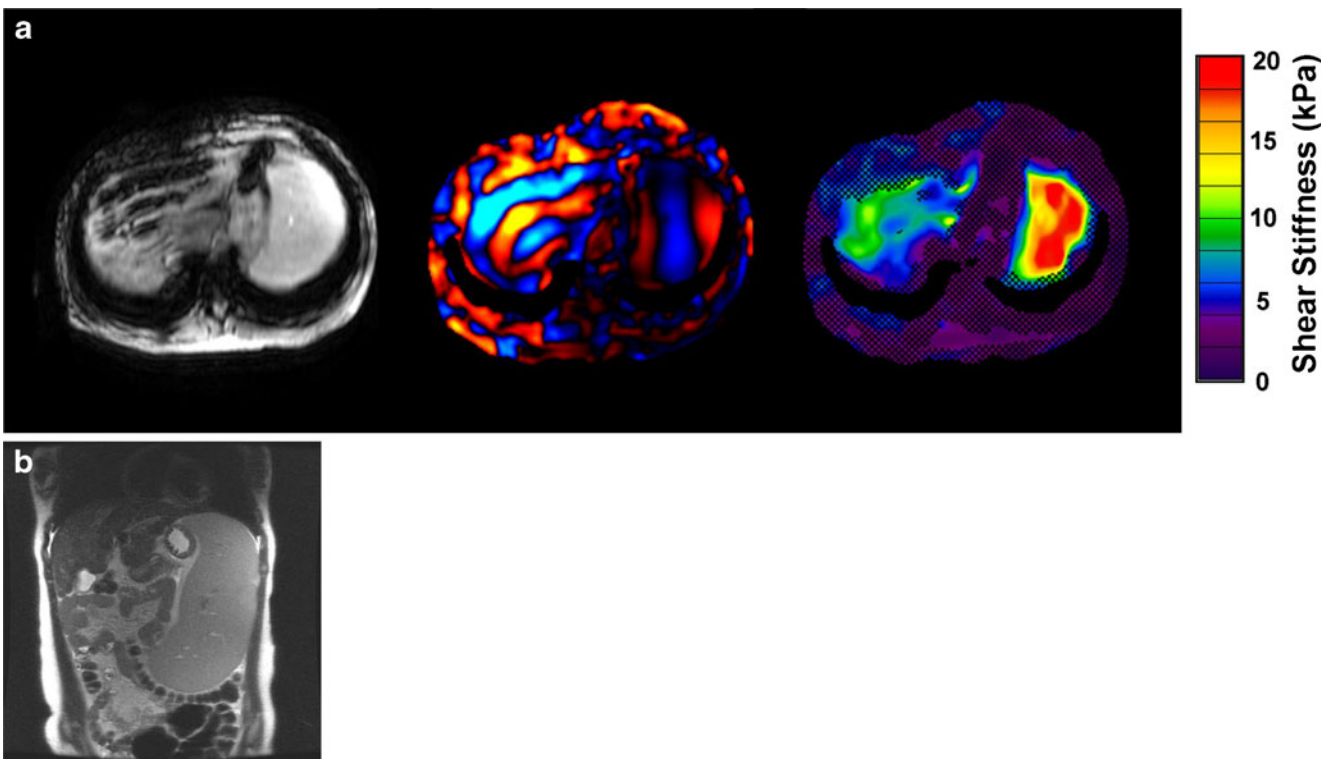

Fig. 7 MR elastography in a 15-year-old with EBV-related liver disease resulting in cirrhosis, marked portal hypertension with varices and severe splenomegaly. **a** Elastogram demonstrates elevated mean liver stiffness of 5 kPa (normal <2.9 kPa). Note elevated splenic stiffness up to 20 kPa (*red*). **b** Coronal MRI shows severe splenomegaly

Current limitations and future directions of pediatric liver MR elastography

Despite increasing acceptance of MR elastography for the assessment of liver fibrosis in adults, there are several important considerations to be addressed before it can become an established clinical tool for hepatic fibrosis assessment replacing liver biopsy in children. There is no normal pediatric liver MR elastography database to date nor have MR elastography cutoff values been established for mild, moderate or severe fibrosis specific for children. However, pediatric liver tissue, normal and diseased, appears to have similar mechanical properties to that of adults. UTE studies performed on normal children and in patients with a wide variety of liver diseases support the use of adult normative data and cutoff values for children. UTE values were found to be independent of age in normal children and in patients with cystic fibrosis [14]. Normal pediatric controls have been found to have UTE measurements similar to normal adult patients. Additionally, pediatric UTE appears to identify children with pathologically proven mild, moderate and severe fibrosis using adult cutoff values [15]. Though our experience is limited, our preliminary results have been encouraging with MR elastography results compared to liver biopsy pathological findings. Thus, it appears that MR elastography will prove to be an accurate and reliable non-invasive tool for assessment of pediatric liver disease. Prospective studies comparing liver MR elastography with percutaneous biopsy will be necessary to confirm this as well as to firmly establish the role of MR elastography in tracking progression of hepatic fibrosis in children.

Liver fibrogenesis can be a spatially heterogeneous process. MR elastography offers a unique opportunity to examine the spatial patterns of hepatic fibrosis in various diseases. Because MR elastography visually quantifies and localizes the extent of fibrosis throughout the liver, it provides the opportunity to create a visual map of the extent of fibrosis in the whole liver. This can provide unique diagnostic and prognostic information in various disease states. The range and distribution of elasticity within the liver might also give insights into the nature of fibrogenesis. For example, livers with mean stiffness of 3.0 kPa and range of 2.9–3.1 kPa might have different rates of fibrosis progression or treatment response from livers with the same mean stiffness but a broader range with areas of very high stiffness. This spatial information might also be used to guide biopsy site selection, targeting areas of higher stiffness, or explain discrepant MR elastography and biopsy results (Fig. 6). Additionally, increased liver stiffness in the absence of fibrosis might reflect changes caused by increased extracellular matrix in the early, pre-fibrotic stages of liver disease such as steatohepatitis [16], presumably reflecting changes in the mechanical properties of the extracellular matrix, which are now known to contribute to the activation of stellate cells and the eventual development of fibrosis. Identification of such livers might be achievable with paired MR elastography studies, pre- and post-prandial, and allow for earlier treatment. A discussion of the role of extra-cellular matrix in liver fibrogenesis is beyond the scope of this article but an excellent article has recently been published [5]. The effect of portal hypertension on splenic stiffness might permit MR elastography of the spleen to provide an opportunity for non-invasive assessment of portal venous hypertension [17] and follow interventions intended to reduce portal venous pressure (Fig. 7). Pediatric-specific applications might include distinguishing biliary atresia from neonatal hepatitis, identifying patients with cystic fibrosis or biliary atresia at risk for varices, early recognition of TPN-induced liver disease in short gut patients, and early recognition of hepatic transplant dysfunction.

Summary

MR elastography is a non-invasive technique that can accurately and reliably identify and stage liver fibrosis. It has been shown to more effectively stage liver fibrosis in adults than other non-invasive assessments and thus can be used to follow treatment response or disease progression. The mechanical properties of liver tissue appear to be the same for adults and children, suggesting MR elastography will be an accurate non-invasive test for identifying, staging and tracking liver fibrosis. In our experience it is technically feasible for pediatric patients, even young infants. MR elastography findings appear to correlate well with liver biopsy results in the small number of patients for whom we have pathological correlation but larger studies will be needed to confirm the reliability and accuracy of this technique to establish it as an alternative to pediatric liver biopsy.

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