Published in final edited form as:

Magn Reson Imaging. 2012 January ; 30(1): 128–132. doi:10.1016/j.mri.2011.08.005.

Effects of gadoxetic acid on liver elasticity measurement by using magnetic resonance elastography

Utaroh Motosugi, MD¹, Tomoaki Ichikawa, MD¹, Katsuhiko Sano, MD¹, Hironobu Sou, MD¹, Ali Muhi, MD¹, Richard L Ehman, MD², and Tsutomu Araki, MD¹

¹Department of Radiology, University of Yamanashi, Yamanashi, Japan

²Department of Radiology, Mayo Clinic, Rochester, MN, USA

Abstract

The purpose of this study was to evaluate the effect of gadoxetic acid (Gd-EOB-DTPA) on measurements of liver stiffness by using magnetic resonance elastography (MRE). In this study, 104 consecutive patients (mean age, 67.7 ± 9.4 years) underwent MRE using a 1.5-T MR scanner equipped with a cylindrical passive driver that was placed across the right chest wall for delivering vibrations. Axial gradient-echo images, which were automatically converted to elastograms that represented stiffness (kPa), were acquired using a continuous sinusoidal vibration of 60 Hz. Two raters independently placed a region of interest on the right lobe of the liver on the elastograms obtained before and after Gd-EOB-DTPA was administered. Liver stiffness was measured using these 2 elastograms and compared using a paired *t*-test and correlation analysis. No significant difference was observed in liver stiffness before and after Gd-EOB-DTPA was administered (rater 1, $P = 0.1200$; rater 2, $P = 0.3585$). The correlation coefficients were 0.986 (rater 1) and 0.984 (rater 2), indicating excellent correlation between the stiffness values before and after Gd-EOB-DTPA was administered. Liver stiffness measured by MRE did not differ before and after Gd-EOB-DTPA was administered.

Keywords

MR Elastography; gadoxetic acid (Gd-EOB-DTPA); liver cirrhosis

1. Introduction

In the management of patients with chronic liver disease, determining of the degree and rate of progression of fibrosis is important to predict prognosis or cancer development [1–3]. Liver fibrosis is currently diagnosed by analyzing liver biopsy specimens with a semiquantitative pathologic scoring system. However, liver biopsy is an invasive procedure and involves the risk of complications such as hemorrhage and infection. Noninvasive methods such as blood tests or liver stiffness measurements with transient ultrasound elastography have been proposed for estimating liver fibrosis. Magnetic resonance elastography (MRE) has recently been developed for measuring liver stiffness by analysis of images of propagating shear waves in the liver [4–6]. Several researchers have previously reported that MRE is a novel noninvasive method for estimating liver fibrosis [5–11].

Gadoxetic acid (gadoxetate disodium or Gd-EOB-DTPA) has been widely used as a hepatobiliary MR contrast agent because of its great contrast ability [12–13]. For achieving

adequate liver parenchymal enhancement, an MR examination using Gd-EOB-DTPA necessitates a waiting period of 10–20 min before the contrast agent is taken up by the hepatocytes [14–15]. This 20-min duration is the recommended delay time, according to the package insert, and has been widely accepted as an adequate delay time for the hepatocyte phase in previous studies [14, 16]. However, a 20-min wait is very long, considering that other MR sequences such as precontrast T1-weighted, T2-weighted, balanced steady-state free precession sequence, and diffusion-weighted images that require about 15 min. The total examination time should be reduced without compromising the quality of the examination, not only to increase patient comfort but also to reduce medical costs. Several researchers have proposed the use of T2-weighted and diffusion-weighted images after administering of Gd-EOB-DTPA to shorten the examination time, because images obtained after Gd-EOB-DTPA is administered can be used as substitutes for precontrast images [17–20]. The presence of the contrast agent in the liver may affect the phase changes of the protons in the liver owing to the paramagnetic effect of the agent [21]. To acquire an accurate stiffness map by MRE, it is critical to obtain optimal-phase images, which are controlled only by external vibration and bipolar gradient synthesized by the vibration [22]. Although both paramagnetic effect and bipolar gradient used in MRE generate phase shifts, it can easily be hypothesized that the phase shift used for the measurements of the stiffness map is macroscopic voxel-based so that the phase shift from the contrast agent does not affect the stiffness measurement by MRE. However, the influence of the gadolinium-based contrast agent on the stiffness measurement needs to be confirmed before MRE obtained in the post-contrast phase can be applied in clinical practice.

The purpose of this study was to evaluate the effect of Gd-EOB-DTPA on measurements of liver stiffness by using MRE.

2. Methods

2.1 Subjects

The study was performed in accordance with the principles of the Declaration of Helsinki. The study was approved by the institutional review board and included all patients who underwent abdominal MR examination between January 2010 and March 2010, except 2 patients who did not agree to undergo MRE. In all, 104 patients were enrolled (mean age, 67.7 ± 9.4 years; range, 46–82 years; 70 men and 34 women). Written informed consent was obtained from all the patients. The study population consisted of patients with chronic liver disease due to hepatitis C ($n = 58$), hepatitis B ($n = 13$), alcoholism ($n = 4$), other ($n = 8$), and those without chronic liver disease ($n = 21$). MR examinations were performed to screen for cancer or monitor the effect of therapy.

2.2 Magnetic Resonance Elastography

MRE was performed using a 1.5-T MR scanner (Signa; GE Healthcare, Milwaukee, WI). Images were obtained while the patients were in a supine position by using a cylindrical passive driver placed across the right chest wall to deliver vibrations via a transcostal approach [5]. The generator placed outside of the MR examination room produced a pneumatic vibration that was delivered to the passive driver via a plastic cylinder. The passive driver was attached using an elastic (rubber) belt to deliver the vibration to the patients' chest wall and the liver. The generator of the vibration and passive driver was developed in Mayo clinic (Rochester, MN) and provided to our institute with service agreement.

A 2D gradient-echo MRE sequence was used to acquire axial wave images. The scanning position was set above the gallbladder and below the subphrenic region of the liver. For

acquiring images of the liver at consistent positions at each phase offset, the patients were asked to hold their breath after expiration [11]. The imaging parameters for MRE were as follows: repetition time/echo time (TR/TE), 100/27 ms; continuous sinusoidal vibration, 60 Hz; field of view, 30–34 × 40–45 cm; matrix size, 256 × 64; flip angle, 30°; slice thickness, 10 mm; number of slices obtained, 2; evenly spaced phase offsets, 4; and a single cycle of a 60-Hz trapezoidal motion-encoding gradient with zeroth- and first-moment nulling along the through-plane direction. A parallel imaging technique was not used. Two spatial presaturation bands were applied to each side of the selected slice to reduce motion artifacts due to blood flow. The total acquisition time was 64 s (four 16-s breath holds).

For all the patients, MRE was performed twice, that is, before and 20 min after Gd-EOB-DTPA was administered. The patients remained on the scanning table between the 2 MRE acquisitions.

2.3 Analysis of Liver Elasticity

The MR scanner automatically generates elastograms by processing the acquired propagating shear wave images by using a previously described inversion algorithm [22]. The shear stiffness of the tissue is determined as a pixel value (kPa) [10, 23]. Two raters independently selected the region of interest (ROI) in the right lobe of the liver on the basis of the elastograms. They chose 1 slice near the center of the driver for the ROI measurement, because the traveling direction of the penetrating wave was considered parallel to the imaging plane around the center of the driver, and because it is necessary to ensure that the wave travels along the imaging plane, else the wavelength could be overestimated. ROIs were obtained for each patient, and the average value was recorded. As a rule, the ROI was at least 1.5 cm² and excluded blood vessels and the liver edge. To determine the ROI, 1 rater (a radiologist with 12 years of experience in abdominal diagnostic radiology) used the MR scanner and another (a radiation technologist with 7 years of experience in abdominal MR examination) used a workstation (Advantage Workstation; GE Healthcare).

The difference between the stiffness values before and after Gd-EOB-DTPA was administered, was defined as follows:

$$D \text{ (kPa)} = (\text{stiffness measured on precontrast MRE by 1 rater}) - (\text{stiffness measured on postcontrast MRE by the same rater}).$$

2.4 Statistical analysis

The stiffness values determined by MRE before and after the contrast agent was administered were compared using a paired *t*-test, and the correlation between these values was determined by calculating the correlation coefficient. An inter-rater correlation coefficient was also calculated for the stiffness values before and after Gd-EOB-DTPA was administered. An inter-rater difference was also calculated for the stiffness values before and after Gd-EOB-DTPA administration and compared using paired *t* test.

3. Results

All 208 MRE examinations were successfully performed for all the patients. The mean (standard deviation) of the stiffness measurement by rater 1 and 2 were 4.3 (2.2) kPa (rater 1) and 4.3 (2.1) kPa for MRE before Gd-EOB-DTPA and 4.4 (2.3) and 4.3 (2.2) kPa for MRE after Gd-EOB-DTPA.

The mean *D* value and standard error was 0.060 (0.038) and 0.036 (0.039) according to raters 1 and 2, respectively. No significant difference was observed between the stiffness

values before and after Gd-EOB-DTPA was administered (rater 1, $P=0.1200$; rater 2, $P=0.3585$). The absolute value of D was <0.6 kPa in 92% of the cases, and <0.2 kPa in 77% (rater 1) and 70% (rater 2) of the cases (Figure 1).

The correlation coefficients (95% confidence interval) were 0.986 (0.979–0.990) (rater 1) and 0.984 (0.976–0.989) (rater 2); this result indicates an excellent correlation between the stiffness values before and after Gd-EOB-DTPA was administered (Figures 2, 3a, and 3b).

The inter-rater correlation coefficients (95% confidence interval) for before and after Gd-EOB-DTPA was administered were 0.983 (0.976–0.989) and 0.985 (0.978–0.990), respectively. The mean (standard deviation) of inter-rater difference (0.1 (0.4) kPa) for stiffness measurement before Gd-EOB-DTPA was identical to that after Gd-EOB-DTPA (0.1 (0.4) kPa).

4. Discussion

Chronic liver diseases can lead to hepatic fibrosis, cirrhosis, portal hypertension, and hepatocellular carcinomas (HCCs), and are an important cause of morbidity and mortality. Liver fibrosis is usually diagnosed by analyzing liver biopsy specimens by using semiquantitative methods such as the METAVIR scoring system [24]. The fibrosis stage determined by analysis of liver biopsy specimens is believed to be one of the most reliable prognostic factors and biomarkers for HCC [1–3]. Many researchers have attempted to assess liver fibrosis by using noninvasive methods, including the analysis of serological markers, sonographic elastography, and MRI [25–27]. MRE is a recently developed noninvasive method for estimating liver fibrosis and is reported to have a high validity and reproducibility [8, 28].

Gd-EOB-DTPA has been widely accepted as one of the most reliable diagnostic tools for chronic liver diseases. A review of published articles showed that a delay of 20 min is adequate for the hepatocyte phase. Previous studies have shown that T2-weighted and diffusion-weighted imaging can be performed after Gd-EOB-DTPA is administered, because the signal intensities are not affected by the distribution of the contrast agent in the liver parenchyma [29–31]. Our findings indicate that MRE can also be conducted after Gd-EOB-DTPA is administered; this observation suggests that liver stiffness can be measured without increasing the examination time.

A limitation of this study was that we were unable to pathologically confirm liver disease, that is, this study only proved the reproducibility of the stiffness measurement after Gd-EOB-DTPA was administered rather than validating the technique. Further study with pathological examination of the liver is required to validate the results of MRE. Another limitation of this study was that a contrast agent-induced phase shift was not directly confirmed. Our results suggest that the contrast agent does not induce a significant net phase shift throughout the liver, that is, the calculated stiffness is not altered by the contrast agent. Basic examinations such as a phantom study rather than a clinical study are required for a further investigation of this physiological phenomenon. In conclusion, MRE after administering Gd-EOB-DTPA can be used as a substitute for precontrast MRE without compromising measurements of liver stiffness.

Acknowledgments

This work was supported in part by NIH grant EB001981.

References

1. Perrillo RP. The role of liver biopsy in hepatitis C. *Hepatology*. 1997; 26(3 Suppl 1):57S–61S. [PubMed: 9305665]
2. Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, Inoue O, Yano M, Tanaka M, Fujiyama S, Nishiguchi S, Kuroki T, Imazeki F, Yokosuka O, Kinoyama S, Yamada G, Omata M. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. *Ann Intern Med*. 1999; 131(3):174–181. [PubMed: 10428733]
3. Tsukuma H, Hiyama T, Tanaka S, Nakao M, Yabuuchi T, Kitamura T, Nakanishi K, Fujimoto I, Inoue A, Yamazaki H, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. *N Engl J Med*. 1993; 328(25):1797–1801. [PubMed: 7684822]
4. Glaser KJ, Felmlee JP, Manduca A, Ehman RL. Shear stiffness estimation using intravoxel phase dispersion in magnetic resonance elastography. *Magn Reson Med*. 2003; 50(6):1256–1265. [PubMed: 14648574]
5. Rouviere O, Yin M, Dresner MA, Rossman PJ, Burgart LJ, Fidler JL, Ehman RL. MR elastography of the liver: preliminary results. *Radiology*. 2006; 240(2):440–448. [PubMed: 16864671]
6. Talwalkar JA, Yin M, Fidler JL, Sanderson SO, Kamath PS, Ehman RL. Magnetic resonance imaging of hepatic fibrosis: emerging clinical applications. *Hepatology*. 2008; 47(1):332–342. [PubMed: 18161879]
7. Ehman RL. Science to practice: can MR elastography be used to detect early steatohepatitis in fatty liver disease? *Radiology*. 2009; 253(1):1–3. [PubMed: 19789246]
8. Huwart L, Sempoux C, Salameh N, Jamart J, Annet L, Sinkus R, Peeters F, ter Beek LC, Horsmans Y, Van Beers BE. Liver fibrosis: noninvasive assessment with MR elastography versus aspartate aminotransferase-to-platelet ratio index. *Radiology*. 2007; 245(2):458–466. [PubMed: 17940304]
9. Faria SC, Ganesan K, Mwangi I, Shiehorteza M, Viamonte B, Mazhar S, Peterson M, Kono Y, Santillan C, Casola G, Sirlin CB. MR imaging of liver fibrosis: current state of the art. *Radiographics*. 2009; 29(6):1615–1635. [PubMed: 19959511]
10. Venkatesh SK, Yin M, Glockner JF, Takahashi N, Araoz PA, Talwalkar JA, Ehman RL. MR elastography of liver tumors: preliminary results. *AJR Am J Roentgenol*. 2008; 190(6):1534–1540. [PubMed: 18492904]
11. Yin M, Talwalkar JA, Glaser KJ, Manduca A, Grimm RC, Rossman PJ, Fidler JL, Ehman RL. Assessment of hepatic fibrosis with magnetic resonance elastography. *Clin Gastroenterol Hepatol*. 2007; 5(10):1207–1213. e1202. [PubMed: 17916548]
12. Ba-Ssalamah A, Uffmann M, Saini S, Bastati N, Herold C, Schima W. Clinical value of MRI liver-specific contrast agents: a tailored examination for a confident non-invasive diagnosis of focal liver lesions. *Eur Radiol*. 2009; 19(2):342–357. [PubMed: 18810454]
13. Ichikawa T, Saito K, Yoshioka N, Tanimoto A, Gokan T, Takehara Y, Kamura T, Gabata T, Murakami T, Ito K, Hirohashi S, Nishie A, Saito Y, Onaya H, Kuwatsuru R, Morimoto A, Ueda K, Kurauchi M, Breuer J. Detection and characterization of focal liver lesions: a Japanese phase III, multicenter comparison between gadoxetic acid disodium-enhanced magnetic resonance imaging and contrast-enhanced computed tomography predominantly in patients with hepatocellular carcinoma and chronic liver disease. *Invest Radiol*. 2010; 45(3):133–141. [PubMed: 20098330]
14. Hamm B, Staks T, Muhler A, Bollow M, Taupitz M, Frenzel T, Wolf KJ, Weinmann HJ, Lange L. Phase I clinical evaluation of Gd-EOB-DTPA as a hepatobiliary MR contrast agent: safety, pharmacokinetics, and MR imaging. *Radiology*. 1995; 195(3):785–792. [PubMed: 7754011]
15. Motosugi U, Ichikawa T, Tominaga L, Sou H, Sano K, Ichikawa S, Araki T. Delay before the hepatocyte phase of Gd-EOB-DTPA-enhanced MR imaging: is it possible to shorten the examination time? *Eur Radiol*. 2009; 19(11):2623–2629. [PubMed: 19471935]
16. Reimer P, Rummeny EJ, Shamsi K, Balzer T, Daldrup HE, Tombach B, Hesse T, Berns T, Peters PE. Phase II clinical evaluation of Gd-EOB-DTPA: dose, safety aspects, and pulse sequence. *Radiology*. 1996; 199(1):177–183. [PubMed: 8633143]

17. Choi JS, Kim MJ, Choi JY, Park MS, Lim JS, Kim KW. Diffusion-weighted MR imaging of liver on 3.0-Tesla system: effect of intravenous administration of gadoxetic acid disodium. *Eur Radiol.* 2010; 20(5):1052–1060. [PubMed: 19915849]
18. Saito K, Araki Y, Park J, Metoki R, Katsuyama H, Nishio R, Kakizaki D, Moriyasu F, Tokuyue K. Effect of Gd-EOB-DTPA on T2-weighted and diffusion-weighted images for the diagnosis of hepatocellular carcinoma. *J Magn Reson Imaging.* 2010; 32(1):229–234. [PubMed: 20578029]
19. Tamada T, Ito K, Yoshida K, Sone T, Murakami K, Kanki A, Watanabe S, Higashi H, Yamashita T. T2-weighted magnetic resonance imaging of the liver: evaluation of the effect in signal intensity after Gd-EOB-DTPA enhancement. *J Comput Assist Tomogr.* 2010; 34(2):182–186. [PubMed: 20351500]
20. Tanimoto A, Lee JM, Murakami T, Huppertz A, Kudo M, Grazioli L. Consensus report of the 2nd international forum for liver MRI. *Eur Radiol.* 2009; 19 (Suppl 5):S975–989. [PubMed: 19851766]
21. Brown, MA.; Semelka, RC. *MRI Basic Principles and Applications.* 3. Hoboken: Wiley-Liss; 2003.
22. Manduca A, Oliphant TE, Dresner MA, Mahowald JL, Kruse SA, Amromin E, Felmlee JP, Greenleaf JF, Ehman RL. Magnetic resonance elastography: non-invasive mapping of tissue elasticity. *Med Image Anal.* 2001; 5(4):237–254. [PubMed: 11731304]
23. Talwalkar JA, Yin M, Venkatesh S, Rossman PJ, Grimm RC, Manduca A, Romano A, Kamath PS, Ehman RL. Feasibility of in vivo MR elastographic splenic stiffness measurements in the assessment of portal hypertension. *AJR Am J Roentgenol.* 2009; 193(1):122–127. [PubMed: 19542403]
24. The French METAVIR Cooperative Study Group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. *Hepatology.* 1994; 20(1 Pt 1):15–20. [PubMed: 8020885]
25. Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, Darriet M, Couzigou P, De Ledinghen V. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology.* 2005; 128(2):343–350. [PubMed: 15685546]
26. Luciani A, Vignaud A, Cavet M, Nhieu JT, Mallat A, Ruel L, Laurent A, Deux JF, Brugieres P, Rahmouni A. Liver cirrhosis: intravoxel incoherent motion MR imaging--pilot study. *Radiology.* 2008; 249(3):891–899. [PubMed: 19011186]
27. Patel J, Sigmund EE, Rusinek H, Oei M, Babb JS, Taouli B. Diagnosis of cirrhosis with intravoxel incoherent motion diffusion MRI and dynamic contrast-enhanced MRI alone and in combination: preliminary experience. *J Magn Reson Imaging.* 2010; 31(3):589–600. [PubMed: 20187201]
28. Motosugi U, Ichikawa T, Sou H, Sano K, Muhi A, Koshiishi T, Ehman RL, Araki T. Magnetic resonance elastography of the liver: preliminary results and estimation of interrater reliability. *Jpn J Radiol.* 2010; 28:623–627. [PubMed: 20972864]
29. Tamada T, Ito K, Yoshida K, Sone T, Murakami K, Kanki A, Watanabe S, Higashi H, Yamashita T. T2-weighted magnetic resonance imaging of the liver: evaluation of the effect in signal intensity after Gd-EOB-DTPA enhancement. *J Comput Assist Tomogr.* 2010; 34(2):182–186. [PubMed: 20351500]
30. Nakamura Y, Ohmoto T, Saito T, Kajima T, Nishimaru E, Ito K. Effects of gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid on T2-weighted MRCP. *Magn Reson Med Sci.* 2009; 8(4):143–148. [PubMed: 20035122]
31. Choi JS, Kim MJ, Choi JY, Park MS, Lim JS, Kim KW. Diffusion-weighted MR imaging of liver on 3.0-Tesla system: effect of intravenous administration of gadoxetic acid disodium. *Eur Radiol.* 2010; 20(5):1052–1060. [PubMed: 19915849]

Figure 1.

Histogram showing differences (D) in elasticities measured on elastograms obtained before and after gadoxetic acid (Gd-EOB-DTPA) was administered. The absolute value of D was <0.6 kPa in 92% of the cases, and <0.2 kPa in 77% (rater 1) and 70% (rater 2) of the cases.

Figure 2. Scatterplots of the intensities measured on elastograms obtained before and after Gd-EOB-DTPA was administered.

Figure 3.

A patient with liver cirrhosis and type C hepatitis. An elastogram obtained before (a) and after (b) Gd-EOB-DTPA was administered. Stiffness as measured by raters 1 and 2 was 5.8 and 5.9 kPa for (a) and 6.0 and 5.8 kPa for (b), respectively. (c) T1-weighted image corresponding to the elastograms.