Quantitative Evaluation of the Hepatic Parenchymal Change in Patients with Chronic Liver Disease Using Gd-EOB-DTPA-enhanced MRI: Comparison with Normal Liver[1]

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Purpose: We wanted to evaluate the capability of Gd-EOB-DTPA-enhanced MRI for diagnosing chronic liver disease by comparing the signal intensity change (SIC) of the hepatic parenchyma of patients with chronic liver disease with that of patients with a normal liver.

Materials and Methods: This retrospective study included 50 patients who were pathologically confirmed as having liver cirrhosis ($n=41$) or chronic hepatitis ($n=9$) by surgery ($n=9$) or biopsy ($n=41$), and they all underwent Gd-EOB-DTPA-enhanced MRI between June 2008 and May 2010 (i.e., the patient group). We also analyzed 30 patients with normal livers as the control group. Quantitative image analysis was performed by measuring the signal-to-noise ratios for the pre-contrast images and the post-contrast 2-, 3-, 10-, 20-min delay images and then calculating the SIC of the pre-contrast and post-contrast images. We performed a detailed analysis of the collected data, which was transformed into a logarithmic form. The SICs of the two groups were compared by Greenhouse-Geisser sphericity correction.

Results: Comparison of the SIC between the two groups showed a significant difference on the hepatocyte-phase 20-min image ($p<0.0001$). The mean SICs with log transformation for the patient and normal groups were 1.90 ± 0.10 and 2.23 ± 0.13, respectively, and the optimal cut-off value of the SIC with log transformation on the 20-min delay hepatocyte-phase image was 2.17 (sensitivity: 66.7%, specificity: 84.0%, positive predictive value: 71.4%, negative predictive value: 80.8%).

Conclusion: Quantitative measurement of the SIC on the hepatocyte-phase image by Gd-EOB-DTPA-enhanced MRI could provide a convenient method to noninvasively diagnose chronic liver disease.

Chronic liver diseases such as chronic hepatitis and liver cirrhosis are important causes of morbidity, mortality and increased health care costs for patients with chronic viral hepatitis. Therefore, the early detection of liver fibrosis and cirrhosis has important clinical implications for determining the antiviral treatment options and a patient's prognosis. Liver biopsy is the current reference standard for making the diagnosis of chronic liver disease; however, this is an invasive procedure, and 40% and 0.5% of the patients who undergo liver biopsy experience associated pain and major complications, respectively (1, 2).

The morphologic criteria used to diagnose early and advanced cirrhosis by conventional MRI have been described in several reports, and most of these reports were written by the same investigative group. These criteria have a sensitivity of 68–93% and a specificity of 77.4–98%, depending on the criterion used (3, 4). However, there is limited data on the quantitative analysis of advanced liver fibrosis and cirrhosis. Moreover, although some quantitative analyses of chronic liver disease or focal liver lesions based on MRI and using various contrast materials have been reported, there are few studies about quantitative evaluation for the detection of chronic liver disease using hepatocyte-specific contrast media.

Gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid (Gd-EOB-DTPA) (Primovist; Bayer Schering Parma AG, Berlin, Germany) has been recently approved as a hepatocyte-specific MR contrast agent. Gd-EOB-DTPA allows for both dynamic imaging and liver-specific static MRI of hepatocytes, along with the accurate delineation, classification and characterization of liver tumors (5, 6). Approximately half of the injected Gd-EOB-DTPA is taken-up by hepatocytes and this reaches a plateau after approximately 20 min and it last for approximately 2 hour. A few preclinical studies have reported that the MRI obtained using a hepatocyte-specific contrast agent such as Gd-EOB-DTPA allows monitoring of the excretory function of hepatocytes on the hepatocyte-phase image with a 20-min delay and this represents the liver function (5, 7). The purpose of our study was to evaluate the capability of Gd-EOB-DTPA-enhanced MRI to diagnose chronic liver disease by comparing the signal intensity changes (SICs) of the hepatic parenchyma of patients with chronic liver disease with that of patients with a normal liver, and particularly by analyzing the cut-off values of the SIC on the hepatocyte-phase images for making the diagnosis of chronic liver disease.

Materials and Methods

Patients

During a 23-month period (June 2008 to May 2010), 50 adult patients (36 men and 14 women, mean age: 53.9 years, range: 28–77 years) with chronic liver disease and who underwent Gd-EOB-DTPA-enhanced MRI were enrolled in this retrospective study (i.e., the patient group). Of these 50 patients, 41 (31 men and 10 women, mean age: 55.2 years) had a known diagnosis of liver cirrhosis and nine (five men and four women, mean age: 47.9 years) had chronic hepatitis. The underlying causes of the chronic liver disease were associated with hepatitis B (41 patients), hepatitis C (three patients), alcohol abuse (three patients) and idiopathic causes (three patients). All of these histological diagnoses were confirmed by surgery ($n = 9$) or biopsy ($n = 41$). The mean interval between MRI and the histological diagnosis was 17.5 days.

Another 30 adult patients (15 men and 15 women, mean age: 49.9 years, range: 27–73 years) with a normal liver underwent Gd-EOB-DTPA-enhanced MRI for various clinical reasons during the study period. They were included in the control group since they had no clinical history, clinical signs, imaging findings or laboratory parameters of liver dysfunction (i.e., normal serum values for the blood coagulation parameters, liver enzymes and total bilirubin).

Gd-EOB-DTPA-enhanced MRI Technique

The MR data was obtained on a 3.0-Tesla scanner (Achieva; Philips, Netherlands). All the individuals underwent MRI of the liver using the hepatocyte-specific contrast agent gadoxetic acid (Gd-EOB-DTPA; Primovist, Bayer-Schering Pharma AG, Berlin, Germany). The Gd-EOB-DTPA was administered intravenously as a bolus dose at a rate of 2~3 mL/sec through an intravenous cubital line at a dosage of 10.0 ml irrespective of the body weight. We obtained the pre-contrast and post-contrast 2-, 3-, 10- and 20-min delay images in the transverse plane using the fat-suppressed T1-weighted gradient-echo technique with a 4-mm section thickness and a 2-mm overlap (i.e., a 2-mm interval).

Quantitative analysis

The relative signal intensity of the hepatic parenchyma measured on the post-contrast 2-, 3-, 10-, and 20-min delay images was compared quantitatively with that of

the pre-contrast images as follows. Measurement of the signal intensity was performed using a circular region of interest (ROI) placed over four points of the liver parenchyma, and these included the right and left lobes of the liver. Each of the four ROIs was drawn on the same axial image at each phase with a size of 10–15 mm in diameter (Fig. 1). These ROIs were positioned to avoid signals from vessels, bile ducts, focal lesions and artifacts. We calculated the mean signal intensity of the four ROIs at each phase in each individual. The noise was measured using ROIs located just lateral to the abdominal wall. Areas with the most prominent ghost artifacts were not included. The signal intensity values were corrected to the standard deviation of the background noise and the values were expressed as the signal-to-noise ratio (SNR) according to the following formula (8, 9):

$$SNR = \text{Signal intensity}_{\text{liver}} / \text{Standard deviation}_{\text{noise}}$$

The signal intensity change (SIC) between the pre-contrast and post-contrast images was calculated as a percentage at each phase according to the following formula:

$$SIC\,(\%) = (SI_{\text{post}} - SI_{\text{pre}}) / SI_{\text{pre}} \times 100$$
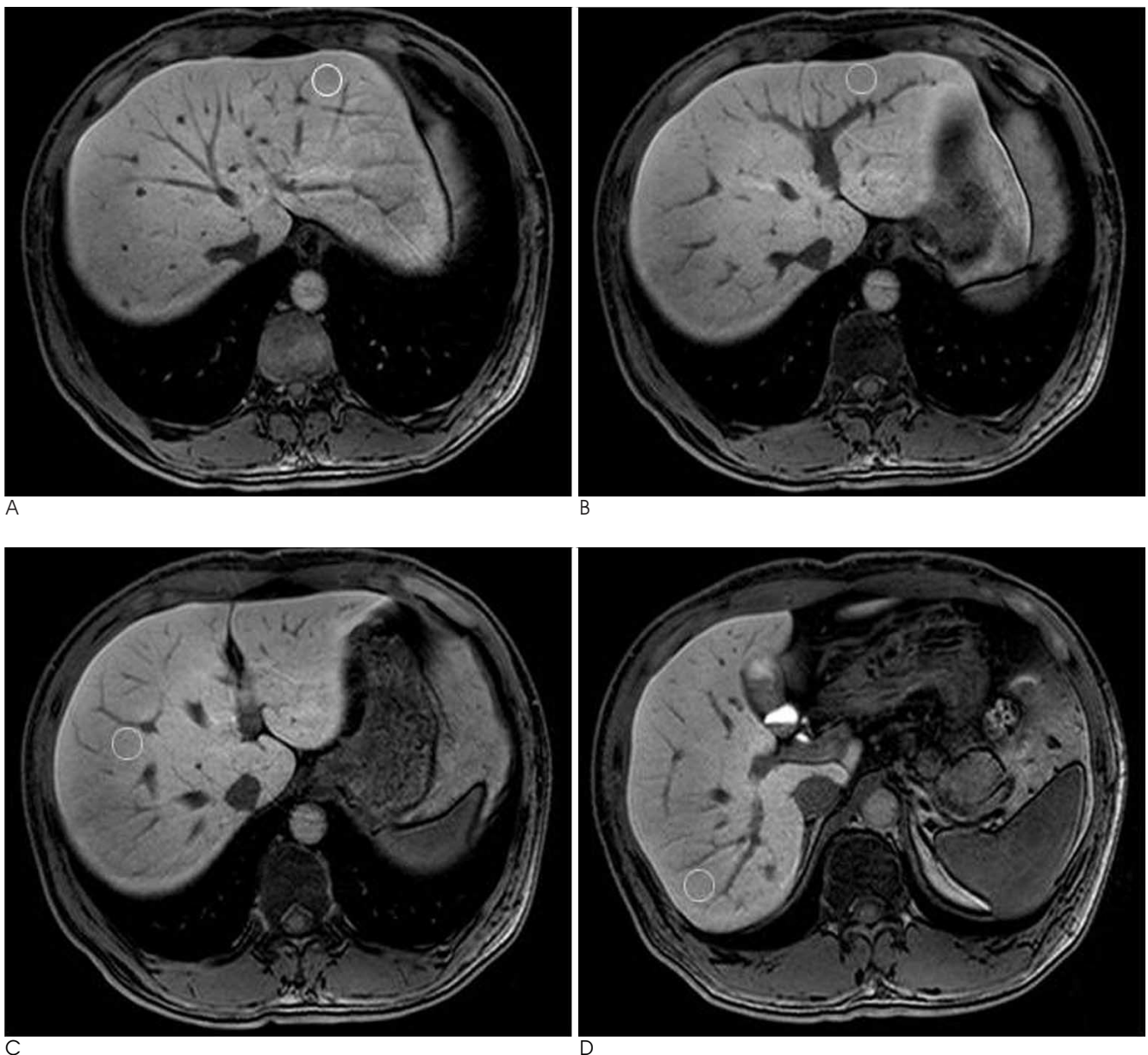

Fig. 1. A-D. The method for measuring the regions of interest at four points of the hepatic parenchyma in the right and left lobes of the liver.

SI_{pre} and SI_{post} are the corrected signal intensity using the SNR on the pre-contrast and post-contrast images at the corresponding location, respectively (9).

Statistical analysis

All the data was analyzed after logarithmic transformation because the initial data was not normally distributed and it was difficult to interpret statistically. Therefore, it was necessary to transform the data set to resemble a normal distribution (10). Statistical analysis was performed using SPSS 12.0.1 for Windows (SPSS, Chicago, IL, USA). Comparisons of the SICs between the patient group and control group were performed using the Greenhouse-Geisser sphericity correction with repeated measures of ANOVA, and comparison of the SICs at each phase between the two groups was performed using a least squares method after natural log transformation. The cut-off values of the SIC on the 20-min delay hepatocyte-phase were determined using receiver operating characteristic (ROC) curves. The ROC curves and graphs were plotted using MedCalc 9.3.0.0 for Windows (MedCalc Software, Mariakerke, Belgium). A *p*-value less than 0.05 was considered statistically significant.

Results

The SICs of the liver parenchyma in the patient group and control group at each phase are shown in Table 1. There was a statistically significant difference between the two groups on the 10- and 20-min delay images ($p = 0.003$ and $p < 0.0001$, respectively) with the most significant difference being noted on the 20-min delay hepatocyte-phase image. The mean SIC after log transformation on the 20-min delay hepatocyte-phase image was 1.90 ± 0.10 and 2.23 ± 0.13 for the chronic liver

Table 1. Comparison of the Signal Intensity Changes of the Hepatic Parenchyma between the Patient Group with Chronic Liver Disease and the Control Group at Each Phase

Time	Patient Group (*n* = 50)			Control Group (*n* = 30)			*p* value
	Mean LogSIC	S.D.	S.E.	Mean LogSIC	S.D.	S.E.	
2 min	1.84	0.11	0.053	1.96	0.14	0.069	0.203
3 min	1.93	0.10	0.048	2.03	0.12	0.062	0.249
10 min	1.92	0.08	0.045	2.15	0.11	0.057	0.003
20 min	1.90	0.10	0.053	2.23	0.13	0.068	< 0.0001

LogSIC = SIC after Log transtormation, S.D. = standard deviation, S.E. = standard error
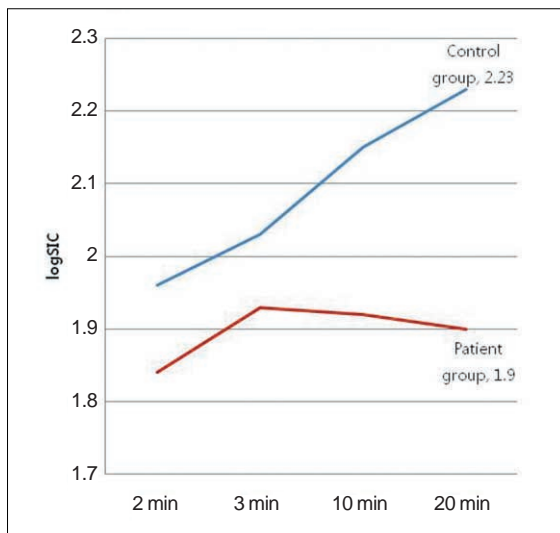

Fig. 2. The temporal profiles of the signal intensity change after log transformation illustrate the relationship between the patient group with chronic liver disease and the control group at each phase.
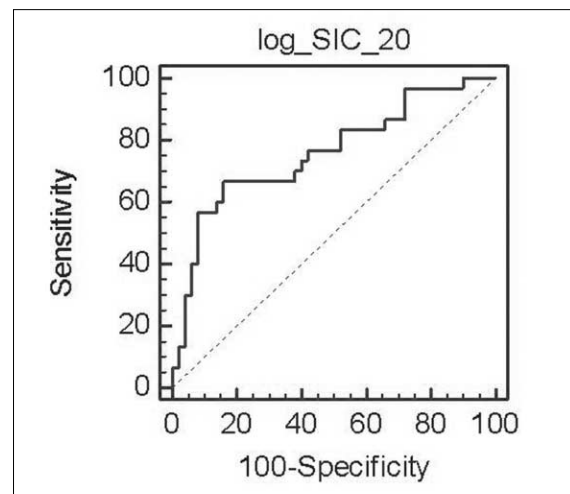

Fig. 3. The receiver operating characteristic curves of the signal intensity change after log transformation between the pre-contrast images and the 20-min delay hepatocyte-phase images. Since the area under the receiver operating characteristic curve and the calculated *p*-value were 0.759 and 0.0001, respectively, this can be interpreted as there was a significant difference between the patient group with chronic liver disease and the control group.

disease group and the normal liver group, respectively. The temporal profiles of the SICs after log transformation showed a difference between the two groups. The mean SICs of the control group showed a continuous increase and the mean SICs were significantly higher at 10 and 20 min after the administration of Gd-EOB-DTPA. In contrast, the mean SICs of the patient group increased up to 3 min and they were slightly decreased after 10 and 20 min (Fig. 2). The optimal cut-off value of the SIC on the 20-min delay hepatocyte-phase was 2.17 (area under the ROC: 0.759, sensitivity: 66.7%, specificity: 84.0%, positive predictive value: 71.4%, negative predictive value: 80.8%). The positive likelihood ratio was 4.17, which means that the patient group was four times more likely to have an optimal cut-off SIC of 2.17 than was the control group (Fig. 3).

Discussion

Many methods have been used for quantitatively analyzing chronic liver disease or focal liver lesions on MRI with various contrast materials (1, 8, 11). The previously published studies of MR elastography demonstrated that patients with liver fibrosis had higher MR elastographic liver stiffness measurements than that of the healthy volunteers, suggesting that the MR elastographic technique might be useful for diagnosing and evaluating diffuse liver fibrosis (11). Whole-liver 3D perfusion MR imaging and MR spectroscopy are also feasible and non-invasive imaging modalities (1); however, these studies need additional equipment and they are complicated processes. For 3D perfusion MR imaging, the extensive post-processing required to obtain the perfusion parameters is a substantial barrier to the widespread clinical use of this technique. Moreover, post-processing entails multiple data transfers, with each transfer requiring its own data conversion. MR elastography requires a new MR sequence and apparatus and it involves complex steps. In contrast, by using the method described here, we can measure the signal intensity of the hepatic parenchyma at ROIs and easily calculate the SIC at a personal PACS monitor as a daily practice. Thus, our method could provide a convenient single-step technique to noninvasively estimate chronic liver disease.

Gd-EOB-DTPA is one of the liver-specific MR contrast agents with preferential uptake by hepatocytes, in which gadolinium-diethylenetriaminepentaacetic-acid (Gd-DTPA) is covalently linked to the lipophilic ethoxybenzyl (EOB) moiety ([4S]-4-[4-ethoxybenzyl] -3,6,9-tris[carboxylatomethyl] -3,6,9-triazaundecandioic acid) (12). Gd-EOB-DTPA is taken up into the hepatocytes through passive transport using the receptors on the cell surface and it is excreted into the biliary tract. Approximately half of the injected Gd-EOB-DTPA is taken-up by the hepatocytes and this reaches a plateau after approximately 20 min, and the hepatocyte-phase of Gd-EOB-DTPA-enhanced MRI visualizes the focal hepatic lesion with great contrast. But some patients show limited hepatic enhancement because their hepatic function is reduced. In the liver with impaired function, the receptors on the cell surface might not work as well as those on the normal hepatocytes. Some preclinical studies have reported that the MRI obtained with Gd-EOB-DTPA allowed monitoring of the excretory function of hepatocytes (5, 7, 13-15). These characteristics mean that Gd-EOB-DTPA can be used not only for hepatic imaging, but also for the measurement of hepatic function (7, 12, 16). It is also known that that the signal intensity of the hepatic parenchyma increases when a certain amount of the hepatocyte-specific contrast agent is taken up by the hepatocytes. Moreover, the hepatocyte-phase image obtained approximately 20 minutes after contrast injection allows additional information on the signal intensity changes of the hepatic parenchyma in the normal liver and the liver with chronic disease (17, 18). In this study, we quantified the SICs of the hepatic parenchyma of the normal liver and the liver with chronic disease on both the pre-contrast and post-contrast images using the hepatocyte-specific contrast agent Gd-EOB-DTPA. As shown in this study, insufficient liver enhancement on the hepatocyte-phase image is related to liver dysfunction (5).

In this study, the SICs of the 10- and 20-min delay hepatocyte-phase images were significantly different between the patient and control groups ($p = 0.003$ and $p < 0.0001$, respectively) and the SICs exhibited high specificity (84.0%), but relatively low sensitivity (66.7%). This may be due to the small number of subjects, the various degree of fibrosis and the different Child-Pugh class in the patient group. This study included nine patients with chronic hepatitis and several patients with cirrhosis of Child-Pugh class A, which corresponded to the early stage of liver cirrhosis. It was possible that they had normal liver function, which could lead to an increased false negative rate. Thus, a large-scale confirmation study is needed to validate the significant correlation between estimated SICs in each group.

There were some limitations in this study. First, the

study population in both groups was relatively small. Second, we did not attempt to subclassify the patient group into several subgroups according to the grade of fibrosis or the activity of inflammation because of the number of non-cirrhotic patients was relatively small and a considerable number of cirrhotic patients were of Child-Pugh A. Therefore, this study did not provide helpful information for differentiating chronic liver disease according to degree of fibrosis such as hepatitis and cirrhosis. Third, we used the same dosage of contrast agent irrespective of body weight. Fourth, the control group had no histological proof that the liver parenchyma was normal. Fifth, we did not consider there might be a sample selection bias when measuring the ROIs of the four areas in each image, and especially in the cases of advanced liver cirrhosis with heterogeneous parenchymal signal intensity.

In conclusion, this study revealed that patients with chronic liver disease showed significantly lower SICs on the hepatocyte-phase image using Gd-EOB-DTPA as compared with those SICs of the normal livers. Therefore, MRI using Gd-EOB-DTPA could provide a convenient single-step method to noninvasively diagnose chronic liver disease, although further studies on this are needed.

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Gd-EOB-DTPA MRI를 이용한 만성간질환의 간실질에 대한 정량적 평가: 정상간과 비교[1]

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목적: Gd-EOB-DTPA MRI에서 만성간질환 환자군과 정상군의 간실질의 조영증강률을 비교하여 만성간질환을 진단할 수 있는지를 평가하고자 한다.

대상과 방법: Gd-EOB-DTPA MRI를 시행한 환자 중 수술(n=9) 또는 조직 생검(n=41)을 통해 간경변증(n=41) 또는 만성 간염(n=9)으로 병리학적 진단을 받은 50명의 환자를 대상으로 하였다(환자군). Gd-EOB-DTPA MRI를 시행한 정상 간을 가진 30명을 대조군으로 하여 비교하였다. 조영증강 전 영상과 2분, 3분, 10분, 20분 지연 조영증강 후 영상에서 간실질의 신호대잡음비를 측정하였으며 조영증강 전 영상과 비교하여 각각의 조영증강 후 영상에서의 조영증강률을 구하였다. 모든 측정값은 로그 변환 후 분석하였으며 각 군의 조영증강률의 비교는 Greenhouse-Geisser sphericity correction을 이용하였다.

결과: 두 군간의 조영증강률은 20분 간세포시기영상에서 가장 유의한 차이를 나타내었다(p < 0.0001). 평균조영증강률은 환자군과 정상군에서 각각 1.90 ± 0.10과 2.23 ± 0.13으로 측정되었으며, 20분 지연 간세포시기영상에서의 최적 판별 수치는 2.17로 측정되었다(민감도, 특이도, 양성예측도, 음성예측도는 각각 66.7%, 84.0%, 71.4%, 80.8%).

결론: Gd-EOB-DTPA MRI의 간세포시기영상에서 조영증강률의 측정은 만성간질환을 진단하는데 편리하고 비침습적인 방법으로 유용하게 이용될 수 있다.