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Original Article

Quantitative evaluation of gadoxetate hepatocyte phase homogeneity: potential imaging markers for detection of early cirrhosis☆,☆☆,★

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ABSTRACT

Objective: Does quantitative analysis of the gadoxetate hepatocyte phase homogeneity, measuring percent standard deviation of hepatocyte phase (SDHP) and liver-to-kidney enhancement ratio (LiKER) detect early hepatic fibrosis?

Materials and methods: Retrospective review of gadoxetate liver MRI plus biopsy-proven fibrosis within 6 months included 31 reversible hepatic fibrosis, 33 irreversible hepatic fibrosis, and 15 donors. Parenchymal and vascular SDHP and LiKER were measured on the 20-min hepatocyte phase using region of interest.

Results: Parenchymal SDHP, vascular SDHP and LiKER measurements differentiate early hepatic fibrosis from controls ($P<.01$).

Conclusion: Quantitative analysis of gadoxetate hepatocyte phase homogeneity using SDHP and LiKER is a promising imaging biomarker for diagnosis of early liver fibrosis.

1. Introduction

Cirrhosis is the 12th leading cause of death in the United States, accounting for nearly 32,000 deaths each year with a mortality rate of 9.7 per 100,000 patients [1]. Patients with end-stage cirrhosis have a 5-year cumulative risk of 17–30% for development hepatocellular carcinoma [2], which is higher than in those with no or mild fibrosis. In addition, there is significant morbidity associated with cirrhosis including encephalopathy, malnutrition, ascites, varices and variceal bleeding [3–6]. Thus, the early detection and accurate staging of liver fibrosis is a critical clinical issue.

The drawbacks of liver biopsy, the gold standard for assessment of liver fibrosis, include risk of morbidity and mortality [7] and potential sampling error [8]. Conventional imaging, including MRI, can detect cirrhosis with qualitative evaluation of typical morphological features but has variable sensitivity and is of limited value especially in the detection of reversible cirrhosis [9]. New technologies including elastography are a promising surrogate but require an extra imaging sequence that is not widely available [10,11]. The search for a noninvasive marker to assess liver fibrosis and cirrhosis is important.

Newer hepatocyte-specific contrast agents (HSA) such as gadoxetate disodium are gradually taken up by hepatocytes and increase liver signal intensity [12] due to their T1 shortening properties. Fibrosis in the liver appears relatively hypointense [13] compared to normal healthy tissue and the hepatic parenchymal intensity on hepatocyte phase MR images using an HSA is affected by the severity of fibrosis [14], giving the liver a qualitatively heterogeneous appearance. This parenchymal heterogeneity can be readily quantified with the widely available, signal standard deviation (SD) on the region of interest (ROI) analysis tool, recently validated by Choi et al. [15], and correlated with fibrosis severity.

After recognizing the change in the liver vascularity in cirrhotic patients [16], we explored the signal SD of the liver parenchyma and blood vessels together. We postulated that the signal intensities would vary over a narrower range in cirrhosis compared to normal liver, taking into account the multiple simultaneous changes occurring in the liver contributing to the signal variation.

Lastly, gadoxetate is equally eliminated via the renal and hepatobiliary routes following intravenous administration [17]. A compensatory mechanism of increased renal excretion of HSA was reported in animals with impaired biliary excretion [18], which was recently confirmed clinically in humans with cirrhotic liver and impaired hepatic function relative to normal subjects [19]. This observed difference in

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Table 1
Summary flow chart of the study population section from patient cohort based on the inclusion and exclusion criteria

Total number of liver biopsies: $n=887$ (03/01/2011–03/30/2014)
Inclusion Criteria:
• Dynamic spiral MRI + <6 months duration from tissue diagnosis **($n=86$)**
Exclusion Criteria:
• Patients with dynamic spiral MRI + 6–12 months duration from liver biopsy **($n=22$)**
• Patients with dynamic spiral MRI + >12 months duration from liver biopsy **($n=16$)**
• Patients with nonspiral acquisition MRI **($n=385$)**
• Patients with MRI at other institution **($n=378$)**
• Suboptimal Studies **($n=7$)**
o Poor image quality: **$n=2$**
o Lack of delayed phase imaging: **$n=2$**
o Liver failure with no fibrosis: **$n=2$**
o Portal vein thrombosis: **$n=1$**
Study Population ($n=79$):
Inclusion criteria ($n=86$) − suboptimal studies ($n=7$)]
• Reversible fibrosis + liver biopsy: ($n=31$)
• Irreversible fibrosis + liver biopsy: ($n=33$)
• Donors + liver explant: ($n=15$)

excretion is dependent on the relative function of the liver and kidneys and is a reflection in the difference in uptake of gadoxetate. As a result, we hypothesize that the manifestation of this relative uptake of HSA and relative parenchymal enhancement of the liver to the kidney [liver-to-kidney enhancement ratio (LiKER)] during the hepatocyte phase MRI may be a quantitative method to assess hepatic dysfunction related to fibrosis.

The primary aim of this retrospective study is to improve detection of hepatic fibrosis by utilizing simple quantitative ROI analysis in the hepatocyte phase of gadoxetate MRI compared to qualitative morphologic assessment. A secondary aim is to assess the utility of this ROI technique for discriminating grades of fibrosis severity.

2. Methods

2.1. Patient population

This retrospective study was compliant with the Health Insurance Portability and Accountability Act and was approved by our institutional review board. Study population constituted by all the patients evaluated for suspected fibrosis of native liver between March 2011 and April 2014 and met the inclusion criteria: (1) age: >18 years; (2) dynamic spiral MRI of liver performed with gadoxetate; (3) confirmed tissue diagnosis of liver fibrosis from liver biopsy or explant pathology; and (4) duration between the imaging and tissue diagnosis <6 months. Histopathology evaluation was based on liver biopsy for all patients and on liver explant analysis for all controls/donors. Patient selection is summarized in Table 1.

Patient demographics, underlying liver disease, risk factors (hepatitis, alcohol, HIV), and liver fibrosis stages were collected from hospital electronic medical records. Glomerular filtration rate >60 ml/min within 30 days of the MRI study was used as an indicator of normal renal function. Patients were categorized into two groups based on the fibrosis stage on histopathology evaluation of liver biopsy. Stage 1 fibrosis and stage 2 fibrosis were combined into reversible/early cirrhosis. Stage 3 fibrosis and stage 4 fibrosis were combined as irreversible/late cirrhosis. Liver transplant donors with normal liver evaluation on gadoxetate MRI and explant tissue analysis were used as control group.

2.2. MRI technique

All imaging was performed at 1.5 T (Signa 14.0 or 15.0 EXCITE HDxt, GE Waukesha, WI) using an 8-channel body array coil or an 8-channel cardiac coil for signal reception. The routine liver protocol included in and out of phase gradient echo imaging, dynamic, gadoxetate-enhanced (Gd-EOB-DTPA: Eovist, Bayer Wayne, NJ) spoiled gradient echo imaging with fat suppression, T2-weighted single shot fast spin echo, T2-weighted fast recovery fast spin echo with fat suppression, and diffusion-weighted imaging using *B* values 50 and 500. Delayed imaging with axial and coronal acquisitions was performed at 20 min. Imaging parameters were as follows: repetition time/echo time/flip angle of 4.4 ms/2.1 ms/30°, bandwidth of ±125 kHz, acquisition matrix of 512×512, partial slice encoding factor of 0.7, slice thickness of 4 mm, and field of view of 36–44 cm. Fat suppression was achieved with a spectrally selective inversion pulse combined with a segmented view ordering. All patients were monitored for adverse reactions.

2.3. Image analysis

2.3.1. Typical morphological features

Axial and coronal 20-min delayed phase series were exported and saved to OsiriX DICOM viewer for Macintosh (OsiriX, version 10.5.8; the OsiriX Foundation, Geneva, Switzerland) for analysis. Two radiologists (M.P. and S.B. with 20 years and 4 years of experience, respectively) interpreted the images, and data were agreed on by consensus. The studies were evaluated on the delayed phase imaging for the typical reported morphological features of the cirrhosis [9] such as nodularity of

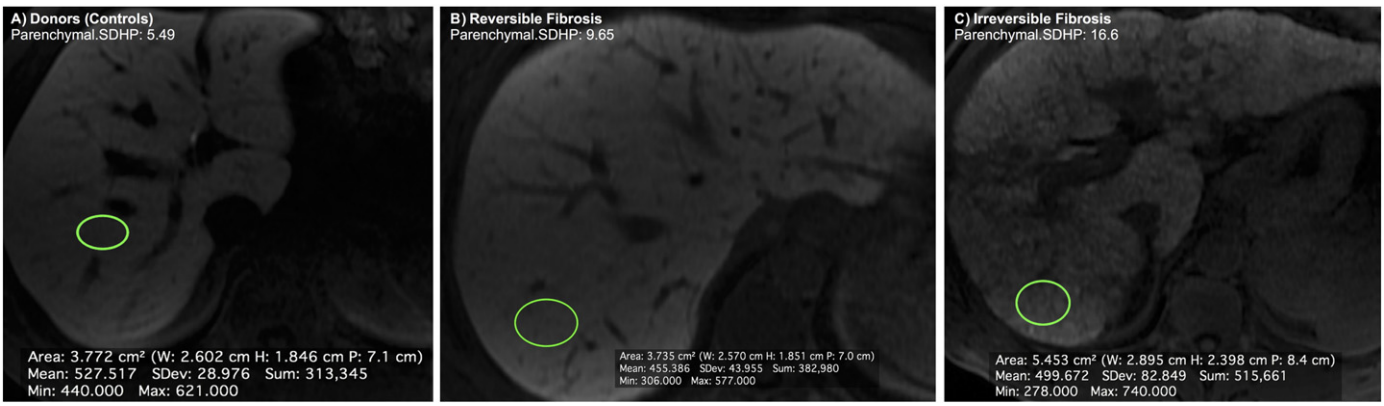

Fig. 1. Parenchymal ROI for measurement of standard deviation of hepatocyte phase (SDHP) Parenchymal ROI for measurement of SDHP in the right lobe posterior hepatic segments: the ROI was drawn to include maximum possible liver parenchyma excluding the hepatic vasculature. The automated ROI generated values from the OSARIX were included at the bottom and the calculated parenchymal SDHP reported at the top left corner for each patient category. Note the increase in "parenchymal SDHP", a quantitative measurement of parenchymal heterogeneity with progression of fibrosis compared to the liver donors.