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Original contribution

Diffusion kurtosis imaging with the breath-hold technique for staging hepatic fibrosis: A preliminary study

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ABSTRACT

Purpose: To evaluate the potential of diffusion kurtosis imaging (DKI) analysis with the breath-hold technique to assess the stage or classify hepatic fibrosis.

Materials and methods: Patients (n = 67) suspected of having a disease of the hepatobiliary system examined by diffusion-weighted imaging (DWI) using a 3.0-T magnetic resonance imaging unit were enrolled in this study. To evaluate hepatic fibrosis, mean kurtosis, Mean apparent diffusion (MD) and apparent diffusion coefficient (ADC) values were compared between groups with varying fibrosis; F0–F1, F2–F3, and F4. The Steel–Dwass test was used for overall comparisons. Correlations between the fibrosis stage and mean kurtosis, MD or ADC values were assessed using Spearman's rank correlation. Discriminative capacities of DKI were evaluated using receiver operating characteristic (ROC) analysis.

Results: There were significant differences in ADC, MD and mean kurtosis values between non-cirrhosis and cirrhosis groups. Moreover, the mean kurtosis value was statistically different between the F0–F1 and F2–F3, F0–F1 and F4, and F2–F3 and F4 groups (all $P < 0.05$). MD value was statistically different between the F0–F1 and F4 groups, and F2–F3 and F4 groups (all $P < 0.05$). However, there was no significant difference in ADC values for all groups (all $P > 0.05$). In addition, mean kurtosis and MD values significantly correlated with the extent of hepatic fibrosis staging (Spearman's rank correlation coefficient, $\rho = 0.851$ and -0.672; $P < 0.0001$). However, ADC values did not reveal a correlation with the extent of hepatic fibrosis staging ($\rho = -0.227$; $P = 0.078$). According to the ROC analysis for the assessment of no fibrosis (F0), fibrosis (≥ F1), and advanced fibrosis (≥ F2) and liver cirrhosis, the DKI cut-off values were 0.923, 0.955, and 1.11, respectively.

Conclusion: Using the DKI method with the breath-hold technique in the liver, the stage of hepatic fibrosis can be classified into normal and early hepatic fibrosis, substantial stages, and advanced hepatic fibrosis.

1. Introduction

Viral hepatitis, alcoholic and nonalcoholic steatohepatitis, and metabolic disorders (e.g., hemochromatosis or Wilson's disease) are the most common types of chronic hepatic disease. These chronic hepatic diseases lead to hepatic fibrosis, which may develop into cirrhosis and hepatocellular carcinoma in the liver parenchyma [1]. Hepatic fibrosis can be cured if detected at an early stage, such as F1 or F2 as per the New Inuyama classification system, and treated immediately; however, advanced hepatic fibrosis, such as F3 or F4 as per the New Inuyama classification system, is difficult to reverse [2,3]. Therefore, early detection and evaluation of hepatic fibrosis is very important.

Thus far, liver biopsy is the reference standard modality for assessing the degree of fibrosis and evaluating necrosis or inflammation. In the New Inuyama classification system, chronic hepatic diseases are classified according to the degree of fibrosis (F) as follows: F0 (no fibrosis), F1 (portal fibrosis widening), F2 (portal fibrosis widening with bridging fibrosis), F3 (bridging fibrosis plus lobular distortion), and F4

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(liver cirrhosis) [2].Chronic hepatic diseases are also classified based on the degree of inflammation of lymphocytes and necrosis of hepatocytes. In hepatic pathology, degeneration by hepatocellular disorder, fatty degeneration, necrosis, and hepatic fibrosis are assessed. These degenerations indicate different pathological structures because of changes in the cellular density and ultrastructure. Pathologists assess the degree of hepatic inflammation and fibrosis using these results. However, liver biopsy is an invasive medical procedure and can result in bleeding, pneumothorax, and procedure-related death [4]. Furthermore, liver biopsy is not used for follow-up assessments because of excessive physical and mental burden on patients. The procedure also has additional limitations including sampling error and inter- or intraobserver variability [5]. Therefore, there is a clinical need for alternative noninvasive methods that are quantitative and reproducible for hepatic fibrosis diagnosis.

Magnetic resonance imaging (MRI), such as MR elastography [6], diffusion-weighted imaging (DWI), and dynamic contrast-enhanced MRI [1], is a noninvasive tool that provides information on the whole liver. Among these methods, DWI has been previously used to evaluate inflammation and fibrosis [7], where a lower apparent diffusion coefficient (ADC) value indicates a tendency of advanced fibrosis and inflammation, such as cirrhotic liver [1,7–13]. The ADC value is calculated using monoexponential analysis of conventional DWI data [14]. However, a limitation of using ADC values to evaluate hepatic fibrosis is the inadequate detection of each stage of hepatic fibrosis [15]. Conventional DWI assumes Gaussian behavior in water molecule diffusion [16]; however, somatic structures are complex and many factors affect the decay of the diffusion signal, such as water restriction by hepatocellular structures, intra- and extracellular water exchange, and variation in tissue compartment sizes.

Diffusion kurtosis imaging (DKI), which is a non-Gaussian DWI technique using water diffusion, has emerged as an advanced method for evaluating the tissue microstructure in vivo [17,18]. DKI analysis described by Jensen et al. does not require complete diffusion displacement probability distribution [18]; hence, the technique is less demanding in terms of acquisition time and gradient strengths. Therefore, the DKI method can be easily implemented with the breath-hold technique as an additional sequence to evaluate hepatic fibrosis. Analysis of the liver using the DKI method with the breath-hold technique may enable us to obtain new and more detailed information than conventional DWI.

Therefore, the purpose of this study was to evaluate the potential of DKI analysis with the breath-hold technique for assessing the stage or classifying hepatic fibrosis.

2. Materials and methods

2.1. Subjects

This retrospective study was approved by our Institutional Review Board and informed consent was waived. Between April 2015 and May 2017, 67 patients (31 men and 36 women; mean age, 58 years; range, 24–80 years) suspected of having a disease of the hepatobiliary system and who had undergone liver MRI, including DWI, were enrolled in this study. For the pathologic evaluation of hepatic fibrosis, the liver tissue was obtained by percutaneous or intraoperative excisional liver right lobe biopsy or surgery following liver MRI. On percutaneous liver biopsy, two tissue samples were obtained from the right lobe using an 18-gauge gun. Liver tissues were stained with hematoxylin-eosin (HE) (Fig. 1). All pathologic specimens were reviewed by a pathologist. Fibrosis was scored on a five-point scale according to the New Inuyama classification system [2]: F0, no fibrosis (n = 25); F1, mild and portal fibrosis (n = 7); F2, substantial and periportal fibrosis (n = 4); F3, advanced and septal fibrosis without cirrhosis (n = 9); and F4, widespread fibrosis and cirrhosis (n = 22) [19].

2.2. Diffusional kurtosis analysis

Kurtosis is a dimensionless statistical metric for quantifying the non-Gaussianity of an arbitrary probability distribution. We were able to use the breath-hold method for DKI acquisition because of its short acquisition time, remove artifacts by macroscopic physiological motions, and analyze DKI at the same slice position of each b-value. The value obtained by DKI is represented by the mean kurtosis value, which is related to the properties of the tissue microstructure, such as tissue complexity and tortuosity of the extracellular space [20,21]. All patients underwent MRI using a 3-T unit (Achieva; Philips Medical Systems, the Netherlands) equipped with a six-channel cardiac coil. DKI was acquired using a single-shot, spin echo EPI sequence with two diffusion weightings (b = 1000 and 2000 mm^2/s) along three noncolinear directions and one b = 0 mm^2/s volume (TR, 2500 ms; TE, 58 ms; flip angle, 90°; field of view, 400 × 400 mm^2; matrix, 80 × 80; slice thickness, 5.0 mm; no intersection gap; parallel imaging factor, 2.0; and acquisition time, 22 s). In previous studies, Goshima et al. [22] and Sheng et al. [23] have set the maximum b-value to 2000 mm^2/s. In addition, because we used the breath-hold method for DKI acquisition, few number of b-value was necessary. Hence, we used above b-values, as recommended by Jensen et al. [18] for DKI analysis as a preliminary study. The gradient length (δ) and time between the two leading edges of the diffusion gradient (Δ) were kept constant (Δ/δ = 40/20.5 ms). K map images were generated on a voxel-by-voxel basis with DKE software [24,25] based on following formula [18]:

$$S = S_0 \exp\left(-bD + \frac{1}{6}b^2D^2K\right)$$

where S is the signal intensity at a given b factor, S_0 represents the signal in the absence of any diffusion weighting, D represents the corrected apparent diffusion coefficient accounting for non-Gaussian diffusion behavior, and K represents the apparent kurtosis coefficient. Using this calculation, the program outputs maps for MD (mean apparent diffusion) and mean kurtosis. The mean kurtosis is defined as the average of the kurtosis over all possible diffusion directions. Similarly, MD is defined as the average of the apparent diffusion in all diffusion directions. In this study, ADC values were separately calculated using data from b = 0 and b = 800 s/mm^2 only based on conventional DWI (note: b 800 images were acquired as low b-values except for DKI analysis). ADC values were calculated using the following formula:

$$ADC = \ln\frac{S}{S_0}/(-b)$$

where S is the signal intensity at a given b factor, S_0 represents the signal in the absence of any diffusion weighting.

2.3. Image analysis

Regions of interest (ROI) were placed in the posterior segment of the right hepatic lobe to avoid major vessels, large bile ducts, liver edges, and motion artifacts without knowing the histopathological results. To measure the same areas, all ROI (round shape, at least 10 mm in diameter) were placed in the liver and copied and pasted onto T2-weighted MR and diffusion kurtosis images. The mean kurtosis values were obtained using commercially available software (MRI cro) [26] and calculated from the mean value of five consecutive slices of the liver. The slices were composed of two anterior slices, a center slice, and two posterior slices. The center was determined as the slice at the largest cross-sectional area of the liver.

2.4. Statistical analysis

All statistical analyses were performed using JMP (version 11.0 for Macintosh, SAS) [27]. To evaluate hepatic fibrosis, ADC, MD and mean kurtosis values obtained in three directions (frequency encoding, phase

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