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A semiautomatic postprocessing of liver R2* measurement for assessment of liver iron overload

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Abstract

Purpose: The purpose was to propose and evaluate a semiautomatic postprocessing method to measure liver R2* values in patients with a broad range of liver iron content.

Materials and Methods: Multiecho gradient echo magnetic resonance images were acquired in patients diagnosed with thalassemia or other types of congenital anemias. Liver R2* values were measured using a routine manually defined region-of-interest (mROI) method and a semiautomatic (SA) method. In the semiautomatic method, pixelwise (pSA) and averaged (aSA) signal fitting was performed on the segmented liver tissues after hepatic vessel extraction. The pixelwise fitting approach resulted in a liver R2* map with an overlay of nonfitted pixels associated with noise performance. The following aSA approach derived overall R2* by fitting the averaged signal intensities of all pixels within the liver ROI excluding vessels and nonfitted pixels. The measurement accuracy and interobserver agreement using mROI and the two semiautomatic approaches (pSA and aSA) were evaluated.

Results: In a total of 45 exams with R2* ranging from 30 to 1500 s^{-1}, the R2* measurements using all three methods were overall highly correlated and concordant with each other. R2* values measured by aSA were consistently higher than those measured by mROI. At lower R2* (<1000 s^{-1}), R2* values measured by pSA were consistent with aSA but higher than mROI; with increasing R2*, the pSA method became less stable and underestimated R2* due to increased noise level. The interobserver agreement was higher for the aSA method compared to pSA and mROI.

Conclusion: The semiautomatic postprocessing method provides a promising tool for reliable liver R2* measurement with additional information for overall evaluation of iron distribution and measurement confidence. This method may offer the potential of reducing interoperator variability and improving diagnostic confidence in patients with liver iron overload.

Keywords: Liver iron; MRI; R2*; Semiautomatic; Postprocessing

1. Introduction

Patients with severe anemia, such as β-thalassemia, sickle cell anemia and Diamond–Blackfan anemia, are treated with multiple blood transfusions over their lifetimes. Since the hemoglobin in red blood cells is an iron-rich protein, repeated blood transfusion may result in organ iron overload with risks of liver fibrosis, cardiac dysfunction and pathology in other organs [1–4]. Iron chelation therapy to remove excess iron from the body is essential to control tissue iron concentration and reduce the risks of iron-overload-related disease in these patients [5]; therefore, repeated monitoring of tissue iron concentration is important for assessing the therapeutic efficacy and minimizing the toxicity of iron chelation therapies [6].

Because liver iron concentration [7] is an accurate predictor of total body iron store [8], liver biopsy has been used as the most direct clinical method for measuring liver iron concentration (LIC) [9] through chemical analysis. However, biopsy is an invasive procedure with sampling variability due to the small sample size relative to the whole liver; it may also cause patient discomfort and complications. These limitations impede the use of liver biopsy as a long-term monitoring tool.

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It is imperative to exploit noninvasive imaging techniques and accurate analysis methods for LIC measurements.

In the past decade, magnetic resonance imaging (MRI) has been an emerging imaging tool for noninvasive measurement of body iron content [3,10–13]. High correlation between the MRI parameter transverse relaxation rates R2* and biopsy-proven iron concentration (i.e., dry weight iron) has been established [14–18]. Due to the paramagnetic properties of iron, deposits in tissue lead to shortening of T2 and T2* relaxation times (reciprocal of R2*). In MRI exams, multiecho gradient echo [13] sequences are usually performed to acquire images at increasing echo times (TEs), and the signal decay along the echo train is fitted based on a monoexponential model to calculate the T2* relaxation time. Tissues with higher iron concentration result in faster signal decay and darker images due to decreased T2*, whereas normal liver tissues demonstrate slower signal decay and higher signal intensities. LIC can be estimated based on measured R2* by the calibration equation LIC (mg/g)=0.0254×R2*+0.202 [13].

Liver R2* measurement normally utilizes a multiple regions-of-interest (mROI) method: two to three ROIs are placed separately on each liver slice by carefully avoiding large visible blood vessels. Averaged signal intensities within each ROI are fitted to derive the T2* value using a nonlinear curve fitting algorithm. However, this approach may unavoidably include small branches of hepatic vasculature and result in T2* overestimation (R2* underestimation). In addition, this method can only provide an averaged whole liver R2* measurement while lacking an assessment of liver iron distribution.

Alternatively, a semiautomatic method has been proposed to extract the blood vessels from liver tissues by thresholding the T2* values based on the fact that blood vessels produce higher T2* compared to liver tissues [7,19]. After vessel extraction, pixel-by-pixel R2* values are calculated to generate a R2* map with detection of nonfitted pixels (i.e., noisy pixels that failed fitting or pixels with larger fitting errors). However, the pixel fitting may suffer from low signal-to-noise ratio especially in heavily iron overloaded liver, resulting in inaccurate R2* measurements. Averaged signal intensities from all fitted pixels may provide more accurate overall R2* measurement.

In the present study, we proposed an improved semiautomatic postprocessing method for liver R2* measurements by using both pixel-fitting and averaging approaches with evaluation of pixel-fitting confidence. We evaluated the measurement accuracy of semiautomatic and mROI methods in both phantom and patient studies with a wide range of liver iron concentration.

2. Materials and methods

2.1. Patients

This retrospective study was approved by our Institutional Review Board and was done in accordance with the Health Insurance Portability and Accountability Act. A total of 45 exams (41 patients, 4 patients with two exams on different dates) were included in this study, and informed consent was waived. These transfusion-dependent patients were diagnosed with β-thalassemia major (n=27), alpha thalassemia (n=2), beta thalassemia (n=1), sickle cell disease (n=8), dyserythropoietic anemia (n=1) and Diamond–Blackfan anemia (n=2). The predicted iron concentration based on mROI R2* measurement ranged from 1.1 to 40.5 mg/g dry weight.

2.2. MRI

All imaging studies were performed on a Magnetom Avanto 1.5-T clinical MR scanner (Siemens Medical Solutions, Erlangen, Germany) with maximum gradient amplitude of 45 mT/m and maximum slew rate of 200 T/m/s. Two sets of acquisition protocols of multiecho Gradient Echo (GRE) imaging were set up with the common imaging parameters: field of view=30–40 cm, matrix=128×128, thickness/gap=10/2 mm, repetition time=30 ms and number of slices=4. In Protocol 1 (multislice 12-echo GRE), TE_{min}=1.11 ms, TE_{max}=18.16 ms, echo spacing (ΔTE) =1.55 ms and bandwidth (BW) per pixel=1775 Hz. In Protocol 2 (single-slice interleaved eight-echo GRE), two interleaved eight-echo acquisitions were performed in a row without time delay and resulted in 16 echo images. Protocol 2 allowed lower first echo time (TE_{min}) and echo spacing ΔTE: TE=0.99–7.29 ms for acquisition 1 and TE=1.49–7.99 ms for acquisition 2, combining acquisitions 1 and 2 led to an effective ΔTE=0.5 ms with BW per pixel=1950 Hz.

Measurement accuracy of both protocols was first evaluated on a phantom consisting of 12 vials filled with various concentration of MnCl2 (relaxivity rate: 76 Hz/mM), resulting in a known range of R2*=38–1824 s^{-1}. In patient studies, four center liver slices just above the portal vein were acquired within one breath-hold (using 12-echo protocol) or during four separate breath-holds (using 16-echo protocol). Selection of 12-echo or 16-echo protocol was based on the estimated R2* values. Details of this selection are described below.

2.3. Image postprocessing

Image postprocessing was performed offline using Matlab software (MathWorks, Natick, MA, USA). The multiple ROI (mROI) and semiautomatic (SA) methods were performed on all GRE image series. In the mROI method, three large ROIs were drawn on each liver slice by carefully avoiding visible vessels and obvious image artifacts. Averaged signal intensities within each ROI were plotted as a function of TE, and T2* value was calculated by fitting the monoexponential equation $S(TE)=S(0)\times\exp(-TE/T2^*)$ using the nonlinear Levenberg–Marquardt algorithm. Before fitting, noise baseline was determined as the signal level off at increasing echo times; data points below twice the noise level were not included in the fitting process.