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Can multi-slice or navigator-gated R2*-MRI replace single-slice breath-hold acquisition for hepatic iron quantification?

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Abstract

Background—Liver R2* values calculated from multi-gradient echo (mGRE) magnetic resonance images (MRI) are strongly correlated with hepatic iron content (HIC) as shown in several independently derived biopsy calibration studies. These calibrations were established for axial single-slice breath-hold imaging at the location of the portal vein. Scanning in multi-slice mode makes the exam more efficient, since whole-liver coverage can be achieved with two breath-holds and the optimal slice can be selected afterward. Navigator echoes remove the need for breath-holds and allow use in sedated patients.

Objective—To evaluate if the existing biopsy calibrations can be applied to multi-slice and navigator-controlled mGRE imaging in children with hepatic iron overload, by testing if there is a bias-free correlation between single-slice R2* and multi-slice or multi-slice navigator controlled R2*.

Materials and methods—This study included MRI data from 71 patients with transfusional iron overload, who received an MRI exam to estimate HIC using gradient echo sequences. Patient scans contained 2 or 3 of the following imaging methods used for analysis: single-slice images ($n=71$), multi-slice images ($n=69$) and navigator-controlled images ($n=17$). Small and large, blood corrected region of interests were selected on axial images of the liver to obtain R2* values for all data sets. Bland-Altman and linear regression analysis were used to compare R2* values from single-slice images to those of multi-slice images and navigator-controlled images.

Compliance with ethical standards

Conflicts of interest None

Results—Bland-Altman analysis showed that all imaging method comparisons were strongly associated with each other and had high correlation coefficients (0.98 r 1.00) with P -values 0.0001. Linear regression yielded slopes that were close to 1.

Conclusion—We found that navigator-gated or breath-held multi-slice R2*MRI for HIC determination measure R2* values comparable to the biopsy-validated single-slice, single breath-hold scan. We conclude that these three R2* methods can be interchangeably used in existing R2*-HIC calibrations.

Keywords

Children; Hepatic iron content; Iron; Iron quantification; Liver; Magnetic resonance imaging; R2* quantification; T2*

Introduction

Patients with sickle cell disease, thalassemia major and other bone marrow failure syndromes with ineffective erythropoiesis (e.g., Blackfan-Diamond anemia) are dependent on blood transfusions to maintain healthy levels of red blood cells or prevent disease complications [1, 2]. Iron from repeated transfused blood accumulates in several organs, as there is no physiological mechanism to discard excess iron [3, 4]. The exogenous iron is stored in organs, particularly the liver, and leads to iron overload causing hepatic dysfunction and, in severe cases, organ failure [5, 6]. Chelation therapy can be administered to patients to remove iron from the body, but has its own side effects and toxicities [3, 4, 7]. Therefore, close monitoring of iron concentration in patients is essential to determine the appropriate dose and efficacy of chelation therapy [8]. Needle biopsy was used to determine hepatic iron concentration (HIC) until magnetic resonance imaging (MRI) methods emerged to replace this invasive procedure; needle biopsy is susceptible to sampling variation [9, 10] and can cause pain and infection [11–13].

Hepatic transverse relaxation rates (R2, R2*) have demonstrated excellent correlation with biopsy-based HIC in multiple independent studies [14–17]. Many of these studies quantified R2* during a breath-hold using a multi-gradient echo (mGRE) imaging method for a single, transverse slice through the center of the liver at the level of the main portal vein [15, 17, 18]. However, to provide whole-liver coverage with this single-slice breath-hold approach, repeated breath-hold acquisitions are necessary [19]. Complete liver coverage enhances workflow as the optimal slice for R2* evaluation can be selected retroactively. Further, breath-hold acquisition is impractical for sedated patients or children who are too young or unable to comply with breath-hold instructions. Due to these challenges, there is strong motivation to develop imaging schemes that increase volumetric coverage per unit time and also eliminate the need for breath-holding.

Multi-slice data acquisitions [20] are widely used to increase spatial coverage per unit scan time [21]. They can provide whole-liver coverage in only two breath-holds. Independently, to eliminate the need for breath-holding and allow free breathing acquisitions, navigator echoes [22], which monitor the diaphragm motion and trigger acquisition only when the diaphragm is within a certain acceptance window [23], have become increasingly utilized in

MRI [24–27]. Incorporating navigator echoes into a multi-slice or 3D technique can minimize motion artifacts significantly, allowing whole-liver coverage during free breathing [28].

Although breath-hold multi-slice acquisition and navigator-controlled multi-slice acquisition offer great potential for whole-liver $R2^*$ quantification, existing $R2^*$ -HIC calibrations [15, 17, 18] are validated for single-slice, breath-hold sequences. There is good reason not to assume that multi-slice breath-hold and navigator-controlled sequences would provide the same $R2^*$ measurements as the single-slice, breath-hold approach. First, multi-slice acquisitions require additional radio frequency pulses to generate signal from additional slice locations, which can lead to signal interferences (slice cross excitation) [20, 29]. Second, in navigator echo techniques, averaging effects due to slightly different diaphragm positions could lead to bias. Consequently, both effects may influence $R2^*$ quantification. In order to replace existing single-slice breath-hold techniques with multi-slice breath-hold or navigator-controlled imaging approaches, a systematic comparison of liver $R2^*$ measurements is necessary and equivalency must be demonstrated. The purpose of this study was to determine whether multi-slice breath-hold and navigator-controlled sequences provide liver $R2^*$ measurements that are comparable to single-slice breath-hold $R2^*$ values.

Materials and methods

As part of routine clinical care at our institution, HIC is assessed noninvasively with the single-slice imaging method in breath-holding and $R2^*$ -HIC calibration [17]. All measurements were carried out on 1.5-T MRI scanners (Magnetom Avanto; Siemens Medical Solutions, Malvern, PA) using body array and spine array coils for signal reception. In addition to the standard single-slice breath-hold images, interleaved multi-slice breath-hold and navigator-controlled images were acquired. $R2^*$ values obtained with multi-slice breath-hold and navigator-controlled sequences were compared to those obtained with the single-slice breath-hold technique. The following sequence parameters were identical for all three compared mGRE sequences: axial slice orientation, time to repetition (TR)=200 ms, First echo time (TE₁)=0.9–1.1 ms, Inter echo time=1.3 ms, echo train length (ETL)=20, readout bandwidth=1,950 Hz/pixel, slice thickness=10 mm, flip angle=25°, matrix=128×104. The slight changes in TE₁ were due to software upgrades between patients; however, TE₁ was identical for the sequences acquired in a patient. The field of view (and resulting pixel size) was variable depending on patient size (range: 350–450 mm²), but identical for all sequences in each patient.

Only acquisition time and slice number changed between sequences: The acquisition time was 21 s for the single-slice and multi-slice breath-hold sequences, and 1.5 min on average for the multi-slice navigator-supported acquisition. With the chosen bandwidth, a maximum of 7 interleaved slices fit in the repetition time of 200 ms, therefore the multi-slice sequences typically contained 7 slices with a slice gap of 10 mm (equal to slice thickness) between consecutive slices.

Off-line image analysis was performed on a computer workstation using a graphical user interface (GUI) developed in MATLAB (The MathWorks Inc., Natick, MA) [30]. For the

entire image, pixel-wise $T2^*$ values were calculated by fitting a monoexponential decay to the magnitude of the mGRE signal while accounting for Rician noise bias [31, 32].

Region selection was performed within the GUI in two ways by a trained undergraduate student (A.W.W.) in images that showed the main portal vein as described in [30]: (i) Small regions of interest (ROIs) were drawn on the $T2^*$ -weighted source images or $T2^*$ maps in a homogenous region of liver parenchyma excluding large biliary and vascular structures in the right lobe of the liver. This ROI position was selected as described in [30] to ensure that no bias was introduced in the HIC calculation. The average $T2^*$ was subsequently calculated across all pixels within the ROI and the resulting $R2^*$ ($=1/T2^*$) was recorded. (ii) Large ROIs were drawn on the same images to include the entire axial cross-section of the liver. Since the large ROIs included vessels and other structures that would affect the mean liver $R2^*$ value, such pixels were removed from the large ROI via a $T2^*$ histogram analysis as also described in [30] and mean $R2^*$ values derived from the remaining pixels inside the large ROI.

The respective slice from the multi-slice and navigator-supported data set that most closely matched the single-slice position was used for evaluation. If the anatomy matched well, ROI outlines drawn on the single-slice images were saved and mapped onto the multi-slice and navigator-supported data sets (Fig. 1). Otherwise, ROIs were redrawn to encompass visually similar regions.

Agreement between $R2^*$ values from small and large blood-corrected ROIs of the single-slice breath-hold data set was compared to those of the multi-slice and navigator-supported images using three analytic methods. First, Pearson C\correlation coefficients were used to quantify correlation between each comparison, and P -values were obtained to test against the null hypothesis that the coefficients are zero. A significant correlation is a necessary but insufficient condition for agreement. Second, a linear regression model with no intercept was fit for each pair of variables, which forces the fit through the origin to test the agreement between the two variables (single-slice and multi-slice/navigator). The slope is expected to be close to 1 when methods are interchangeable. Therefore, the estimates of the slope with a 95% confidence interval were calculated and it was assessed if 1 was within the confidence intervals. Finally, agreement was assessed between techniques using Bland-Altman plots [33] with estimates of the bias and the 95% limits of agreement. Analyses were conducted using SAS Version 9.3 (SAS Institute, Inc., Cary, NC). P -values less than 0.05 were considered statistically significant. MRI data were retrospectively collected with Institutional Review Board approval.

Results

The study cohort consisted of 71 patients with a median age of 14 years (minimum: 3, 25th percentile: 10, 75th percentile: 17, maximum: 44). Of these, 37 (52%) were females and 34 (48%) were males. These patients had diagnoses of sickle cell anemia (Hb SS) ($n=39$), beta thalassemia major ($n=19$), Blackfan-Diamond anemia ($n=3$), acute lymphoblastic leukemia ($n=2$), bone marrow failure ($n=2$), and one each of the following conditions: metastatic neuroblastoma, sideroblastic anemia, pyruvate kinase deficiency, glioblastoma multiforme,

Fanconi anemia, and congenital dyserythropoietic anemia. All patients had a history of transfusional iron overload and underwent MRI R2* assessment for iron chelation or phlebotomy monitoring or to aid in the decision to initiate therapy.

Fifteen patients had all three measurements performed during the same test: single-slice breath-hold, multi-slice breath-hold and navigator-controlled multi-slice. An additional 54 patients had single-slice and multi-slice paired breath-hold data sets available, and single-slice breath-hold and navigator-controlled multi-slice paired data sets were available for 2 patients. The number of data sets used for each comparison, the correlation coefficients (r), and the P -values are reported in Table 1.

Agreement analysis of small and large ROI R2* values from images acquired with single-slice, multi-slice and navigator control demonstrated strong correlation with Pearson correlation coefficients close to 1 ($0.98 \leq r \leq 1.00$). The P -values indicated significance in all cases (P -values < 0.0001). The data scatter plots and Bland-Altman plots with limits of agreement for the single-slice vs. multi-slice comparison are displayed in Fig. 2 and show good agreement with negligible bias (-0.1 1/s for small and -1.3 1/s for large ROI). Figure 3 shows the respective plots for the comparison of single slice vs. navigator control. The Bland-Altman plot for the small ROI analysis shows a small bias (6.1 1/s), whereas the large ROI exhibits a bias of -19.0 1/s. Finally, the slopes and 95% confidence intervals from the best-fit regression lines are reported in Table 1. The slopes were all close to 1, indicating nearly a one-to-one relationship between R2* values acquired from different imaging methods. This level of agreement was especially high for the single-slice vs. multi-slice comparison (slopes of 0.99 and 1.00 for small and large ROIs, respectively). The 95% confidence intervals for all slopes included 1.

Discussion

Comparisons of R2* values measured with single-slice breath-hold and multi-slice breath-hold or multi-slice navigator-controlled imaging protocols showed strong correlations, indicating that multi-slice methods, with or without navigators, are a viable alternative to single-slice breath-hold imaging for HIC estimation. This was observed for both small and large ROI measurements, with large ROI single-slice vs. multi-slice breath-hold demonstrating the least variability. No systematic bias in R2* was observed with either the multi-slice breath-hold or navigator approach, indicating that any existing slice cross-talk is negligible.

In this study, we performed two multi-slice scans back-to-back for multi-slice breath-hold and navigator-controlled imaging; the first one acquired multiple interleaved slices with 100% gap between slices and the second one collected the missing slices within the gaps. This allows for whole-liver coverage while minimizing potential cross-talk between slices due to sufficiently large gaps. In addition, the full coverage allows selection of an optimal slice at the level of the portal vein for the final R2* analysis. The selection of optimal slices permits the use of published R2*-HIC calibrations, which are based on single-slice breath-hold acquisition at the level of the portal vein [15, 17].

Multi-slice and navigator-controlled $R2^*$ quantification offer the potential for whole-liver assessment in short scan times. A realistic breath-hold scan time estimate adds about 15 s for execution of breath-hold commands and 15–20 s for the patient to resume normal breathing to the acquisition time, resulting in about 50 s–1 min total. Thus, two multi-slice data sets would provide full liver coverage with 14 slices in about 2 min; alternatively, continuous navigator acquisition would accomplish equal coverage in about 3 min. In contrast, the most recently published $R2^*$ biopsy calibration study acquired 5 single slices in 5 breath-holds [19] (i.e. roughly a 5-min table time).

Although the planned slice for single-slice acquisition was positioned at the level of the portal vein as determined on scout or other images, the acquired slice in some children differed from the desired location due to the patients' inability to hold their breath consistently at the same position when performing breath-hold maneuvers. In such cases, multiple scans had to be acquired to obtain the desired slice position. It was therefore advantageous to perform multi-slice scans for whole-liver coverage and then select the desired slice; this reduced the scan time and optimized the workflow. Whole-liver coverage could also be potentially advantageous in patients with a heterogeneous distribution of liver iron for a more complete evaluation of the $R2^*$ values in different regions of the liver [34]. However, it needs to be noted that B_0 field gradients can introduce variations in $R2^*$, especially near the dome of the liver [35–37]. Therefore, whole-liver iron evaluation needs to be corrected for potential regional susceptibility effects (e.g., background gradients at liver-lung interfaces) by means of more complex analyses than the fitting routines presented here [35, 37]. Fortunately, background gradient induced susceptibility changes become marginal toward the central area of the liver [37, 38] so that corrections are usually not necessary for slices at the locations of the portal vein. This allows for continued use of existing single-slice breath-hold based HIC calibrations and fitting algorithms, which have been established at this anatomical location [16, 17, 19].

The slope estimates for the single-slice vs. multi-slice comparison are very close to 1 for both ROI methods. In addition, the 95% confidence intervals are very tight, which is a very strong indication that these methods are interchangeable. The slopes for the comparison between navigator and single slice for either small (slope=1.05) and large ROI (slope=0.94) are not as close to 1 and the 95% confidence intervals just included 1 in both cases. Also, the 95% confidence intervals are not as small. Therefore, the maps obtained with the navigator technique may not estimate $R2^*$ values that are perfectly interchangeable with those measured by the current clinical single-slice breath-hold method. This may be partly due to the fact that only 17 data sets were available. Another possible explanation is that $R2^*$ quantification has been impacted by residual artifacts in the navigator-controlled images (Fig. 1): As the patients breath freely during navigator-controlled imaging, the navigator acquisition allows the diaphragm to be within a certain acceptance window for a single scan to be included into the entire data set. Therefore, the individual scans might be collected at slightly different positions during the scan, which would result in minor blurring artifacts at tissue interfaces, e.g., blood vessels would “smear” across several voxels leading to blood contamination in liver parenchyma. In addition, other potential artifacts could manifest in phase encoding direction because of residual motion. All of these effects might lead to altered $R2^*$ values.

Still, the use of navigator echoes for mGRE based $R2^*$ quantification would be particularly advantageous when imaging young patients because they might require sedation during the MRI exam or are noncompliant with breath-hold instructions. Although $R2^*$ values from navigator-gated images may not be perfectly interchangeably with $R2^*$ values collected during breath-hold, they may still offer a clinically effective means to obtain a good HIC estimate when breath holding based protocols (single- or multi-slice) are unattainable.

While only a single reviewer performed ROI analysis to avoid interobserver variation, placement of small and large ROIs varied slightly between single-slice, multi-slice and navigator-controlled images due to patient motion between the individual scans. Also, the exclusion of $T2^*$ values from unwanted structures, e.g., blood vessels, via histogram analysis of large ROIs is dependent on the judgment of the observer. Both effects -- inconsistent ROI placement and observer-biased histogram thresholding -- might impact the comparison of single-slice, multi-slice and navigator-controlled $R2^*$ data. However, McCarville et al. [30] found that $R2^*$ measurements based on small hepatic ROIs and blood-corrected ROIs covering the whole cross section of the liver were very consistent when ROIs were drawn by three separate reviewers [30] using the same methods as employed in our study.

Our retrospective study has several limitations: No biopsy data were available, so that the HIC correlation is indirect, as the multi-slice and navigator-controlled results were only compared to single-slice acquisition and analysis techniques for which calibration equations exist [17, 30]. Also, due to the retrospective nature of this study, a complete set of measurements was available for only 15 of the 71 measurements, 54 patients had only single-slice and multi-slice paired breath-hold data sets available, and 2 patients had only single-slice breath-hold and navigator-controlled multi-slice paired data sets.

Conclusion

We compared $R2^*$ values obtained from single-slice breath-hold images with $R2^*$ values obtained from multi-slice breath-hold or navigator supported images. Through Bland-Altman and linear regression analysis, we found that these different imaging techniques yield $R2^*$ values that are in strong agreement for both small and large, blood corrected ROIs. We conclude that these alternative MRI techniques for assessment of hepatic iron concentration correlate well with the biopsy-validated single-slice breath-hold imaging method and can be used to improve workflow and to provide increased volumetric coverage. Our findings offer directly benefits to patients, since the table time will be shortened using multi-slice acquisition and data collection could be further simplified using navigator gating for breath-hold non-compliant patients.

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Fig. 1.

Axial source image at minimum echo time (TE) (**a**) and T2* maps of the liver (**b–d**) of a 39-year-old woman with beta thalassemia major. All image series used to calculate the T2* maps were located at the same anatomical position. The same region of interest (ROI) position and shape (blue) was used on all maps to calculate the average T2* value within the ROIs. **b** T2* map from the single-slice breath-hold sequence (T2*=1.4 ms), **(c)** map from the multi-slice breath-hold data set (T2*=1.4 ms), and **(d)** map obtained from the multi-slice navigator-controlled data set (T2*=1.3 ms). Note that there are minor motion artifacts visible in the navigator-controlled data set above the abdomen (white pixels)

Fig. 2.

Scatter plots show the linear relation between $T2^*$ values obtained from single-slice images and those from multi-slice breath-hold images for: (a) small regions of interest (ROIs) and (b) large, blood-corrected ROIs. Scatter plots show the correlation between $R2^*$ values obtained from single-slice and multi-slice breath-hold images for (c) small ROIs (correlation coefficient=0.98, $P<0.0001$) and (d) large ROIs (correlation coefficient=0.99, $P<0.0001$). Bland-Altman plots display the difference versus the average of $R2^*$ values from single-slice images and those of navigator-controlled images together with mean difference (*solid lines*) and 95% limits of agreement (*dashed lines*) for (e) small ROIs (mean difference=0, 95% limits of agreement=-105,105) and (f) large ROIs (mean difference=-1, 95% limits of agreement=-52, 50)

Fig. 3.

Scatter plots show the linear relation between $T2^*$ values from single-slice breath-hold images and multi-slice navigator-controlled images for: **(a)** small regions of interest (ROIs) and **(b)** large, blood-corrected ROIs. Scatter plots show the correlation between $R2^*$ values obtained from single-slice and navigator-controlled acquisition **(c)** small ROIs (correlation coefficient=0.99, $P<0.0001$) and **(d)** large ROIs (correlation coefficient=0.98, $P<0.0001$). Bland-Altman plots display the difference versus the average of $R2^*$ values from single-slice and navigator-controlled images together with mean difference (*solid lines*) and 95% limits of agreement (*dashed lines*) for **(e)** small ROIs (mean difference=6, 95% limits of agreement=-97, 109) and **(f)** large ROIs (mean difference=-19, 95% limits of agreement=-107, 69)

Correlation analysis and linear regression through the origin for three different MRI techniques and two region-of-interest (ROI) selection methods

Table 1

	<i>n</i>	Pearson correlation coefficient	<i>P</i> -value	Slope estimate	95% confidence interval
Multi-slice vs. single-slice breath-hold					
Small ROI	69	0.98	<0.0001	0.99	0.97–1.02
Large, blood corrected ROI	69	0.99	<0.0001	1.00	0.98–1.01
Multi-slice navigator controlled vs. single-slice breath-hold					
Small ROI	17	0.99	<0.0001	1.05	1.00–1.10
Large, blood corrected ROI	17	0.98	<0.0001	0.94	0.90–1.00