Influence of Stimulated Echoes on Iron Quantification with Multi-echo Spin-echo Pulse Sequences

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Introduction: The relaxation and susceptibility properties of phantoms that simulate tissue iron have been measured using a theoretical model[1] that can separately quantify soluble, dispersed (ferritin-like) and insoluble, aggregated (hemosiderin-like) iron using multiple spin echo (MSE) based R_2 images. Here, we examine a large range of these heterogeneous phantoms and a preliminary patient population to determine the effects of stimulated echo (STE) contamination in MSE sequences on the iron quantitation. This study was motivated by a need to calibrate existing *in vivo* clinical measurements which may have been contaminated by STE effects.

Theory: The theory[1] proposes that the signal decay curve of multiple spin echo (MSE) sequences in tissue containing both soluble and insoluble forms of storage iron has the approximate analytic form:

$$S(t) = S_0 e^{-RR_2 * t} \exp\left(-A^{3/4}\Delta t^{3/4}\left(\mathrm{t} - 2\tau\left[1 - \left(\frac{\tau}{\Delta t}\right)^2\right]\right)^{3/8}\right),$$

where S_0 is the initial signal intensity, 2τ is the first spin echo time, and $2\Delta t$ is the inter-echo time. A series of MSE sequences with different inter-echo times can be used to determine a value for RR_2, the reduced relaxation rate (primarily influenced by ferritin iron), and A, the aggregation index (primarily influenced by hemosiderin iron).

Methods: Two types of MSE pulse sequences were performed on a 1.5T Philips MR scanner using a five-element cardiac coil; one with a refocusing RF pulse with flip angle of 160° and slice thickness equal to the excitation slice thickness ("MSE_Original"), the other with a refocusing RF pulse with flip angle 180° and 3 times the excitation slice thickness[2] ("MSE_Improved"). Both sequences otherwise had the same parameters (slice = 10 mm, first echo = 4 ms, interecho = 4, 8, or 16 ms, and SENSE = 1.5). The TR, FOV and resolution for phantoms and patients were 2 s, 250 x 250 mm^2 and 1.95 x 1.95 mm^2, compared to EEG triggered, 37 x 37 cm^2 and 2.9 x 2.9 mm^2, respectively. The cardiac exams were acquired in the short-axis orientation with navigator respiratory gating. Nine patients with transfusional iron-overload (5 males, 4 females, 29 +/- 6 years) had a cardiac MR exam consistent with Institutional Review Board policies. Six phantoms (consisting of six separate tubes) were made using $MnCl_2$ to simulate ferritin and magnetite microspheres to simulate hemosiderin iron cores. All tubes in a single phantom contained constant $MnCl_2$, but variable amounts of microspheres suspended in 2% agarose gel. The $MnCl_2$ concentrations varied from 0 mM to 0.675 mM, while the iron concentrations varied from 0 to 0.1 mg Fe/cm^3. All phantoms were immersed in a cylindrical water bath, doped with 50 mM of $MnCl_2$. For the iron phantoms, a region of interest (ROI) centered on each bottle in the phantom was propagated over all the images in the echo train. For human imaging, an ROI was manually drawn in the septum of the heart and was propagated through all the echoes. RR_2 and A were determined from fitting the three MSE sequences using the standard Levenberg-Marquardt method.

Results: In all cases RR_2 is underestimated and the aggregation index A is overestimated by the sequences that are contaminated by STE. The results of comparing the MSE_Original and MSE_Improved sequences on the entire set of phantom mixtures is shown in *Figures 1a* and *1b*. Linear regression analysis (R^2=0.99) of these data results in the relationships $\boldsymbol{RR_2 = 1.18\ RR_2'}$ and $\boldsymbol{A = 0.78\ A'}$, where the prime refers to the MSE_Original sequence. This indicates that relaxation parameters derived from the MSE_Original sequence can be calibrated for quantification of total as well as compositional iron (ferritin/hemosiderin iron). Results for human subjects were similar to the phantoms. The data from the patients is also plotted in *Figures 1a* and *1b* and is in good agreement, indicating that the patient data acquired with the suboptimal sequence can be easily corrected using the above scaling factors.

Conclusion: It is clear from these results that special attention must be paid to eliminate the effects of stimulated echoes in this method of quantitative R_2-based iron quantification and that, for accurate iron quantification, MSE sequences with minimal stimulated echo must be used. However, based on the agreement between the extensive phantom data and those acquired from patients (and assuming artifacts from cardiac motion during the echo train are minimal) relaxation data acquired using suboptimal sequences can be corrected for iron quantification using this calibration.

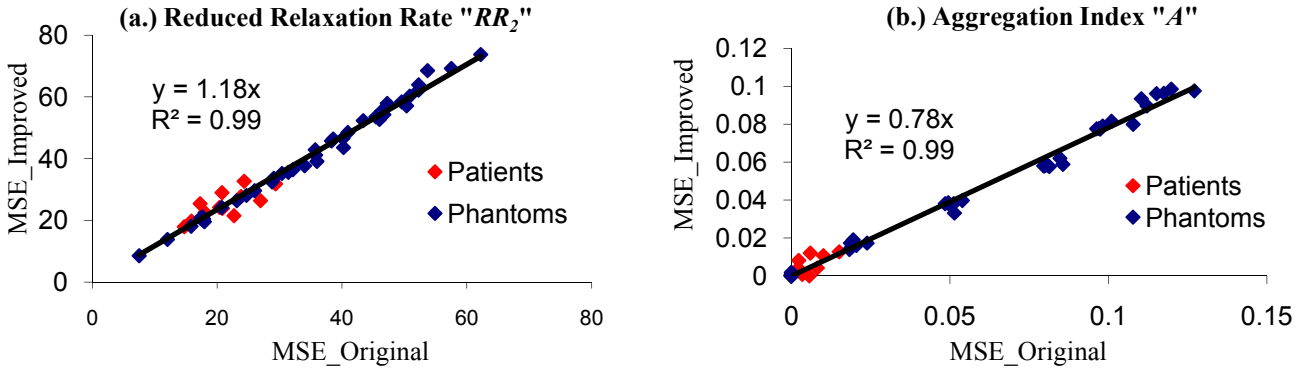

Fig 1. Values for **(a)** RR_2 and **(b)** A from the MSE_Improved sequence versus those from the MSE_Original sequence. Linear regression analysis defines a scaling factor between the values measured with the two sequences.

References 1 Jensen JH, et al. Magn Reson Med 2002;47(6):1131-1138. **2** Pell GS, et al. J Magn Reson Imaging 2006;23(2):248-252.