Generating Positive Contrast from Magnetic Nanoparticles Using a SubShortTE Method with Conventional Spin Echo Sequences

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Target Audience. MR physicists, chemists and molecular imaging scientists who are interested in applications of iron oxide nanoparticle contrast agents.

	3 nm	10 nm	20 nm
r1 ($mM^{-1}s^{-1}$)	4.5	7.3	9.9
r2 ($mM^{-1}s^{-1}$)	16.4	77.7	222.8
ρ	620	590	360

Table 1 Measured values of IONPs with three core sizes.

Purpose. Magnetic iron oxide nanoparticles (IONPs) are primarily used to generate prominent signal decrease or "negative contrast" of targeted tissue on T2 or T2* weighted images. To improve the detection, and even quantification of IONP in the targeted tissue, there have been great interest in generating positive contrast from IONPs, i.e., signal brightening (1-5). Recently, a new SubShortTE method, i.e. subtraction of a later echo signal from an earlier echo signal, was proposed (2,5), but to our knowledge, has not been validated. The purpose of this study was to apply SubShortTE to the widely available SE/TSE sequence, to perform an evaluation of this approach with theoretical simulation and phantom scan using well characterized IONP with different core sizes and iron concentrations.

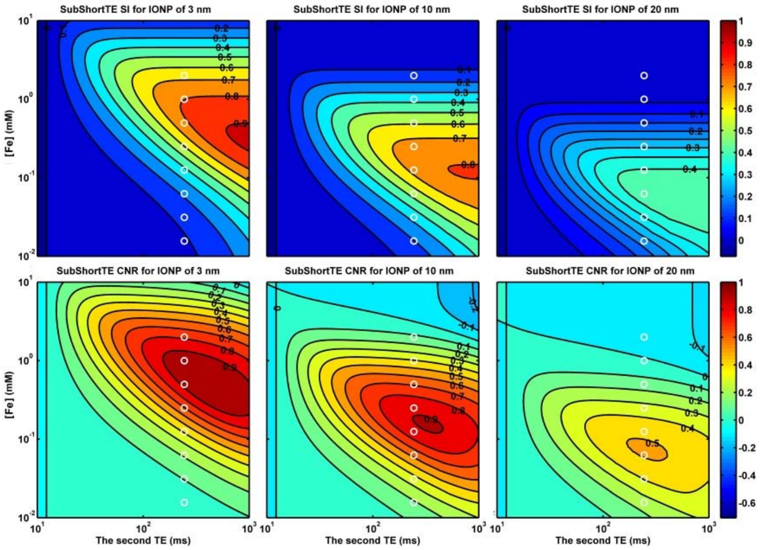

Figure 1 Simulated SI and CNR as a function of TE and [Fe]. The three plots on each row are normalized, respectively. The white circles correspond to the 8 tested [Fe] values, with TE = 12.2 ms as the ShortTE and TE = 244 ms selected as the second TE to calculate SubShortTE.

Methods. IONPs with core sizes of 3, 10 and 20 nm (measured by transmission electron microscopy), and coated with oligosaccharides were prepared (6). IONP colloidal solution phantoms at each core size were prepared with iron concentrations ([Fe]) of 0.0157, 0.0313, 0.0625, 0.125, 0.25, 0.5, 1 and 2 mM, respectively. All MRI experiments were performed on a 3 Tesla MR scanner (Siemens Tim Trio, Erlangen, Germany) using a phased array volumetric wrist coil. The relaxivities of each IONP were determined using a multi-echo SE sequence and an inversion recovery TSE sequence with a turbo factor of 3, which were available on the vendor provided sequence library. For R1 mapping, the inversion recovery TSE sequence with TE of 13 ms and TR of 1500 ms was used to obtain images at TI of 23, 46, 92, 184, 368, 650, 850, 1100 and 1400 ms, respectively. For both R2 mapping and SubShortTE, the multi-echo SE sequence was performed with TR of 2520 ms and 20 TEs starting at 12.2 ms with increments of 12.2 ms.

Data analysis was performed offline using an in-house Matlab program (Mathworks, Natick, MA, USA). R1 and R2 maps were calculated by performing a non-linear fitting to the signal intensities (SI): $\mathrm{SI} = \mathrm{K1}(1 - 2e^{-TI \cdot R1} + e^{-TR \cdot R1})$ and $\mathrm{SI} = \mathrm{K2} \cdot e^{-TE \cdot R2}$, respectively, where K1, K2, R1 and R2 are parameters to fit. In conjunction with the known [Fe] values, empirical linear relaxivity approximation equations $\mathrm{R1} = R1_0 + r1 \cdot [Fe]$ and $\mathrm{R2} = R2_0 + r2 \cdot [Fe]$ were then used to fit r1 and r2, the longitudinal and transverse IONP relaxivities (2). The SE image with TE = 12.2 ms was selected as the ShortTE image. A rough effective proton density ρ map was calculated by compensating the R2 exponential term on the ShortTE image. SubShortTE images were calculated by subtracting images of all other echoes from the ShortTE image. When necessary, regions of interest (ROIs) were assessed on phantoms using ImageJ (National Institutes of Health, Bethesda, MD).

A simulation analysis similar to that was reported in (2,5) was performed in Matlab to help understand and optimize the contrast change of SubShortTE. With $R1_0$ of 0.33 s^{-1} and $R2_0$ of 0.4 s^{-1} being the baseline transverse relaxation rates of water, the linear relaxivity approximation equations were used to calculate R1 and R2 at any given [Fe] of these three IONP sizes. SI of general SE/TSE images was simulated for different combinations of TE and [Fe] based on $\mathrm{SI} = \rho e^{-TE \cdot R2}(1 - e^{-TR \cdot R1})$, and subsequently SI of SubShortTE images were calculated. The definitions of contrast (C) and contrast-to-noise ratio (CNR) per unit time were the same as defined in (2): $\mathrm{C} = SI_{[Fe]} - SI_{[Fe]=0}$ and $\mathrm{CNR} \propto \mathrm{C}/\sqrt{TR}$.

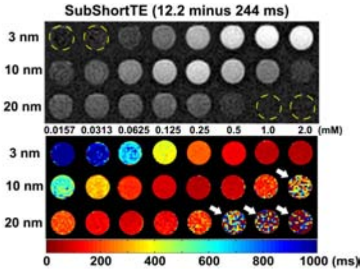

Figure 2 Experimental SubShortTE image (top) and T2 map (bottom).

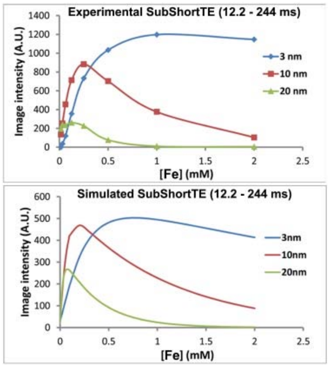

Figure 3 Experimental and Simulated SI of SubShortTE image as a function of [Fe].

Results and Discussions. The measured relaxivities and effective proton density values are listed in Table 1. The simulated SI and CNR as a function of TE and [Fe] are shown in Figure 1, which reveals that using a later echo with TE = 244 ms is generally near optimal. Example SubShortTE image (subtraction of SI of TE = 244 ms from SI of TE = 12.2 ms) is shown in Figure 2, with the corresponding T2 map as a reference. Good consistency is found between the simulated and experimental SI of the SubShortTE image, as shown in Figure 3.

For the sizes and concentrations tested in this study, IONP with 3 nm core size exhibited well described monotonic correlation between SI of SubShortTE and [Fe] (Figure 1-3). However, IONPs with larger sizes, such as 10 and 20 nm, only showed monotonic increasing trends for a smaller [Fe] range (Figure 1-3), but then experienced SI or CNR drop, as predicted by the results from the simulation which are demonstrated in Figure 1 and 3. It should be pointed out that due to the strong T2 effects of IONPs with large sizes at high concentrations, correct measurement of T2 values in the T2 map (arrows in Figure 2) become difficult as the original SE images did not have enough signal-to-noise ratio (data not shown). Therefore, sub-5 nm IONP that was reported recently (6) may be the optimal IONP to work with the proposed SubShortTE method in order to obtain a positive contrast. Such sub-5 nm IONP may also allow one to use higher concentrations than IONPs with large sizes.

Conclusions. This preliminary study demonstrated that positive contrast could be obtained using a SubShortTE approach based on the conventional SE/TSE sequences. With future *in vitro* and *in vivo* test and evaluation, the SubShortTE method can potentially serve as an alternative approach to other positive contrast methods without the need of any special sequences.

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