A Multi-Echo Technique for Positive Contrast Detection of SPIO-labeled Cells at 9.4T

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Introduction

Therapeutic cell treatments have been applied to a large number of pathological diseases. Tracking the engraftment of cells is key to planning and assessing cell therapies. Migration dynamics and tissue integration are commonly assessed by locating iron-oxide labeled cells with T2* weighted MRI. Interpretation of the resulting signal voids can be challenging in preclinical scanners, especially in regions of magnetic field inhomogeneities or susceptibility. Although techniques exist to obtain positive contrast of iron-oxide labeled cells, such as Off-Resonance Imaging [1] and Inversion-Recovery with ON-Resonant Water Suppression [2], their sensitivity to magnetic field inhomogeneities deter application at high B_0. We present here a multi-echo technique that exploits both the T1 and T2-relaxation effect of iron to achieve positive contrast of SPIO-labeled cells at 9.4T.

Materials and Methods

Pulse sequence: A 2d-multiple-echo ultra-short echo time (MUTE) pulse sequence is implemented on a 400MHz MRI system [3]. It includes a slice excitation scheme that shortens slice-refocusing duration, as well as radial readout for minimum echo-time. The raw data is regridded onto a cartesian grid by Kaiser-Bessel interpolation. Scan parameters are: TR=150ms, TE=0.208ms (UTE), 2.56ms (ECHO1) and 5.12ms (ECHO2) respectively, FOV=40x40mm, regridded matrix=256x256, number of radial projections=403, flip angle=15°. Subtractions between UTE, ECHO1 and ECHO2 images were carried out. Images were cropped to 24x24mm for display.

Cell labeling: Human mononuclear cells (MNCs) were collected by leukapheresis from peripheral blood of G-CSF-stimulated donors. They were washed twice with PBS, centrifugated for 10min, plated in DMEM (Gibco, UK) and incubated at 37°C and 5% CO2 for 2 hours. Cells were subsequently labeled with SPIOs (Endorem, Guerbet Laboratories, UK) by incubation with 45µl/ml media for 24h. They were then trypsinized, washed twice with PBS and re-suspended.

Animal preparation: 1 male Wistar rat (Charles River Ltd, U.K.) aged 7 weeks was anaesthetized with intra-peritoneal injection of Hypnovel-Hypnorm-water mixture (1:1:2, 2.5ml/kg, Roche U.K., VetaPharma U.K.). A thoracotomy procedure was performed in the 4th inter-costal space following blunt dissection of the chest muscles to expose the heart. $5x10^5$ and $2.5x10^5$ of MNCs were directly injected into the left myocardium wall at the apex and mid-ventricle respectively. The rat was sacrificed after 2 hours and its heart was excised, followed by 24h fixation in 4% PFA at 5°C. It was then embedded in 1% agarose. **ROI analysis:** Regions of interest were drawn at the two injection sites and the native myocardium tissue, followed by comparison of their contrast-to-noise ratios (CNR); where CNR = Signal intensity $(SI_{LABELED}.SI_{MYO})/\sigma_{noise}$.

Results and Discussion

Figure 1 illustrates UTE, ECHO1, ECHO2 and their subtraction images in the excised heart. Table 1 presents their measured contrast-to-noise ratios at the APEX and LV injection sites. We observed that the CNR of the UTE image is already positive, albeit with a low CNR. This is partially attributed to the dominant proton density influence over the T1-weighting. In addition, since the apex has higher total iron content, its transverse relaxation effect is more pronounced as well. This is supported by the larger negative contrast seen in ECHO1 and ECHO2 images. Although the short echo-time of 208µs tilted the contrast in favor of T1 relaxation effect of SPIOs, it is still not optimum for positive contrast. Besides, SPIOs induced T1 change at 9.4T is minimal compared to T2*.We can elevate positive contrast with a subtraction, and the resulting difference images highlight the marked increase in CNR that can be achieved with MUTE. Subtraction between UTE and ECHO2 elevated positive contrast by as much as 227 times at the apex. Absolute contrast with MUTE is at least twice that of typical T2*-weighted imaging.

Conclusion

This study has demonstrated the feasibility of a multiple-echo UTE technique to detect SPIO-labeled cells with high positive contrast. To harness the full potential of MUTE, the echo-time in the UTE image has to be minimized. This could be further achieved with a 3D acquisition [4]. Alternatively, when hardware limitation is encountered, subtraction between the UTE and a later ECHO can augment the positive contrast significantly. It appears that lower cell concentration might decrease sensitivity and thus the iron load per cell has to increase. Future work involves exploring larger particles sizes without compromising on cell viability.

Contrast-to-Noise Ratio	LV	APEX
UTE (TE = 0.208ms)	0.2	0.1
ECHO1 (TE = 2.56ms)	-4.9	-9.3
ECHO2 (TE = 5.12ms)	-8.9	-10.6
UTE-ECHO1	2.5	4.5
UTE-ECHO2	19.6	22.7

Table1: Contrast-to-noise ratio comparison between UTE, ECHO1, ECHO2. The boost in positive contrast is clearly depicted in their subtracted images.

References

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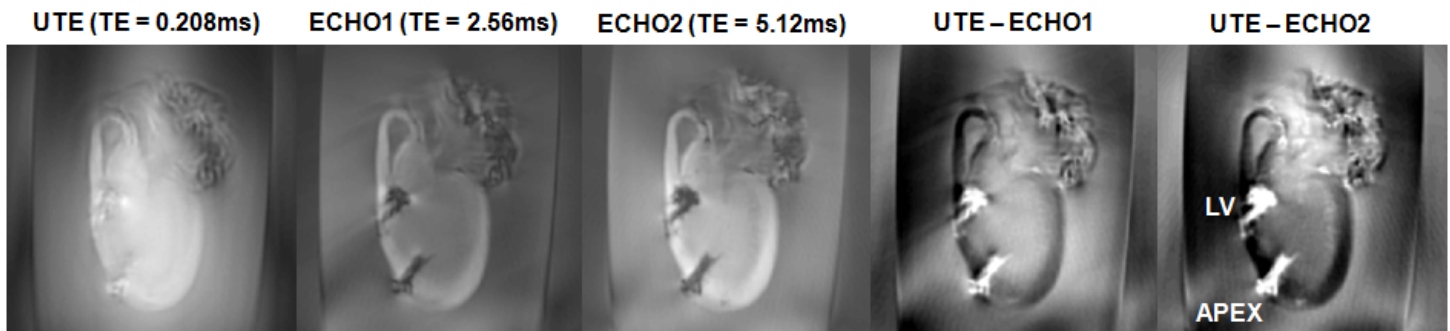[4] Stehning et al. Magn. Reson. Med. 52, 197–203 (2004).

Figure1: UTE and ECHO images with MUTE. Subtraction between UTE and subsequent echoes generate positive contrast of SPIO-labeled cells.