In vivo carotid plaque magnetic resonance imaging using quantitative T_2* measurments with USPIO particles: a dose-response study to statin therapy

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Introduction

It is well established that carotid atherosclerotic disease and the resulting plaque tissue composition are associated with thromboembolic complications, namely stroke and transient ischemic attacks [1]. MR studies have sought to identify carotid plaque inflammation using Ultra-small Super-Paramagnetic Iron Oxide (USPIO) contrast agents. Ferumoxtran-10, known commercially as Sinerem™ (Guerbet, Roissy, France), originally developed to detect metastatic disease in lymph nodes, has since been repeatedly applied to study atherosclerotic carotid plaques [2, 3]. Previous studies that used USPIO contrast-enhancement to measure carotid-plaque inflammation have measured 'change' as the relative difference in signal intensity in the plaque normalized to the adjacent sternocleidomastoid muscle. A quadruple inversion recovery (QIR) prepared T_2*-weighted spiral sequences has been used to suppress signal from blood over a range of T_1 values post-contrast infusion [4]. 'Change' appears as a hypo-intensity difference in the post-infusion image relative to the pre-infusion image. A recent phase-I randomized double-blinded dose response trial, known as ATHEROMA [Atorvastatin THeraphy: Effects on Reduction of Macrophage Activity], utilized USPIO-contrast enhancement to investigate the interaction of low- and high-dose statin therapy. The clinical outcomes of this trial have been report separately [5]. The work reports USPIO-inflammation as normalized relative changes in signal intensity using the T_2*-weighted spiral sequence. Quantitative issues with this methodology have been discussed [6].

The objectives of this study are two-fold: to present an alternative image acquisition and analysis methodology which derives quantitative T_2* (qT_2*) values directly from atherosclerotic plaques; and to report the results of applying this methodology to the ATHEROMA study data and to investigate if the methodology can detect a dose-response interaction.

Methods

Forty patients [36/40 male, age: 67.6 ±7.7, luminal stenosis: 61.7 ±11.4%, hypertension: 36/40, diabetes: 4/40] were randomized to low-dose (n=20) and high-dose (n=20) statin therapy (10mg and 80mg of Atorvastatin). All patients had both their left and right carotids imaged on a 1.5T whole body clinical machine (Signa HDx, GE Healthcare, Waukesha, WI) using a custom-designed four-channel phased-array surface coil (Flick Engineering Solutions BV, Winterswijk, The Netherlands) held close to the neck. USPIO-enhanced MR imaging was performed pre- and post-infusion at baseline, and at 6 and 12 weeks. The USPIO contrast agent Sinerem™ was diluted in normal saline and administered as a slow infusion through an indwelling large-bore intravenous cannula over 30 minutes with a total dose of 2.6 mg/kg. The post-infusion scan was acquired 36 hours after the contrast administration. QIR prepared multi-echo fast-gradient-echo imaging was performed using an ECG-triggered 8-echo segmented *k*-space sequence (TR/TE/views per segment/flip angle/NEX = 39.8ms/4.0-35.3ms at 4.4ms increments/8/30°/2). Multiple slices, of 3mm slice thickness, were acquired to encompass the extent of the plaque. The adventitia and lumen boundaries of the plaques were delineated, the plaque was then subdivided into 4 quadrants and the mean signal intensity within each quadrant was recorded. Miller's power correction technique was applied using the following equation: $S_c(TE)^2 = S(TE)^2 - S_n(TE)^2$, where S_n is the background noise measurement [7]. Levenberg-Marquardt non-linear least-squares algorithm was used to compute S_o and T_2* after fitting the data from each quadrant to the following equation: $S_c(TE)^2 = S_0^2 \exp(-2TE/T_2^*)$. A linear mixed-effects model was applied to account for the spatial correlation of multiple-plaque measurements from the same patient and to assess dose response differences to statin therapy. The analysis was performed twice: in the first analysis the difference in the derived qT_2* values at each quadrant between pre- and post-USPIO infusion were computed; in the second analysis only the qT_2* values from the post-USPIO session were used.

Results

There was a highly significant difference in inflammation as measured by USPIO plaque uptake over a 12-week follow-up period between the low- and high-dose statin groups. This was observed using direct qT_2* measurements for post USPIO minus pre USPIO ($p<0.001$) and for post USPIO ($p<0.001$) only (shown in figures 1 & 2 respectively). The distributions of the qT_2* values for the low- and high-dose treatment groups at each visit are summarized in the table.

Discussion

Direct qT_2* measurements provide an alternative method of quantifying USPIO uptake; the methodology is free from assumptions made by normalizing signal to the adjacent muscle tissue. These results also demonstrate that change in USPIO can be measured using only the post-USPIO imaging data, negating the need for the pre-imaging sessions in longitudinal studies.

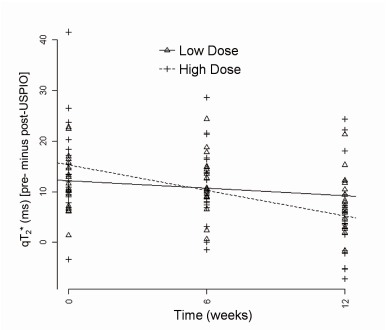

Figure 1 pre minus post

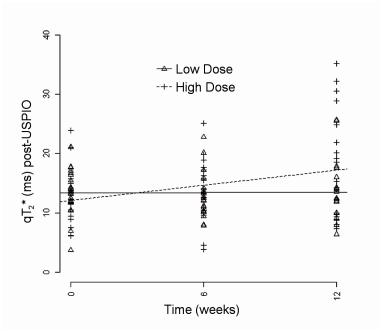

Figure 2 post only

Distributions of qT_2* for the low- and high-dose groups at 0, 6 and 12 weeks

	Pre Infusion [qT_2* (ms)]		Post Infusion [qT_2* (ms)]	
Time (weeks)	Low Dose	High Dose	Low Dose	High Dose
0	24.9 ±10.2	25.7 ±13.9	13.6 ±5.5	12.9 ±6.2
6	24.5 ±11.3	25.0 ±13.0	13.3 ±6.7	14.3 ±7.7
12	22.3 ±11.4	22.5 ±12.9	14.0 ±7.6	18.3 ±11.2

References

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