

# Inflammatory Atherosclerotic Plaque Can Be Reproducibly Assessed By 3T Dynamic Contrast Enhanced MRI for Multi-Center Studies

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## Introduction

Inflammation plays an important role in both atherosclerotic plaque progression and rupture [1], which has led to an interest in treatments with anti-inflammatory effects. To assess and monitor inflammation *in vivo*, dynamic contrast-enhanced (DCE) MRI has been previously demonstrated [2]. Kinetic parameters derived from DCE-MRI, including the transfer constant ( $K^{trans}$ ) and partial plasma volume ( $v_p$ ), correspond to permeability and blood supply, which are related to inflammatory processes. Histological investigations have shown that  $K^{trans}$  and  $v_p$  correlate with macrophage and neovessel content of atherosclerotic plaque when measured in either the plaque [2] or adventitia [3]. However, the inter-scan reproducibility of these kinetic parameters has not been investigated for multi-center studies, which is essential for prospective studies. In this study, we sought to establish the reproducibility of  $K^{trans}$  and  $v_p$  in atherosclerotic plaque using 3T scanners in a multi-center design.

## Methods and Materials

**Population** For this investigation, 26 subjects were recruited from 6 clinical sites under substudies (NCT00880178 and NCT01178320) of the AIM-HIGH study (NCT00120289). AIM-HIGH inclusion criteria are age >45, documented vascular atherosclerosis, and dyslipidemia. Although the AIM-HIGH study randomizes subjects to simvastatin alone or in combination with extended release niacin, this study was conducted prior to treatment.

**MR Imaging** All subjects were scanned twice within two weeks on 3T scanners (GE HealthCare) to acquire the images of the carotid artery. The imaging protocol included an axial 2D spoiled gradient recalled echo (SGRE) sequence to acquire DCE images (slice thickness 2 mm, FOV 160\*160 mm, matrix 256\*256, reconstructed image size 512\*512, TR= 117ms, TE=5ms). Images were acquired at 8 slices centered on bifurcation of index carotid artery. The index side was defined as the side with more severe plaque. Coincident with the second dynamic scan in the sequence, 0.05 mmol/kg of a gadolinium-based contrast agent was injected at a rate of 2 ml/s by a power injector. After bolus arrival, images were acquired at 18 time points separated by a repetition interval of 18s. Other contrast weightings acquired with a standard protocol [4] included time of flight (TOF), T1, contrast enhanced T1 (CET1), T2, and proton density (PD).

**Image Analysis** Two trained reviewers analyzed each scan blinded to the other scan and subject information. For each acquired DCE-MRI image, the corresponding TOF, T1, CET1, T2 and PD weighted images were reviewed using custom software (CASCADE) [5] to identify the lumen and outer wall boundaries of the carotid artery. The DCE-MRI images then were automatically processed to produce vasa vasorum (V-V) images [3] that show  $K^{trans}$  and  $v_p$  as a color-coded parametric image (Fig.1). Then, the boundaries of lumen and outer wall were mapped to the V-V image by an automatic registration algorithm [3], which allows further manual adjustment. Lastly, the artery-based average  $K^{trans}$  and  $v_p$  values for the plaque and the adventitia were reported for each scan.

Plaque measurements were obtained by averaging all pixels inside the outer wall boundary and outside the lumen boundary in all matched slices of the two scans for each artery. Adventitial measurements were calculated by averaging pixels along the outer wall boundary with distance of less than 2 reconstructed pixels. Notably, to minimize the signal influence from the high intensity lumen caused by partial volumes, blurring, and motion of the bright vessel lumen, a region with width of 0.625 mm adjacent to the lumen was excluded for all the measurements.

**Data Analysis** The reproducibility of the  $K^{trans}$  and  $v_p$  measurements for plaque and adventitia was evaluated by the Intra Class Correlation (ICC) (one-way random, single measures in SPSS). The coefficient of variation for the measurement error (CV) of each parameter was also reported. Variability estimates from the data were used to calculate the sample size that would be needed to detect a 25% within-subject decrease of each kinetic measurement with 80% power, assuming a constant CV and that measurement error is the primary source of variability (two-sided paired t-test with a significance level of 0.05).

## Results

Of 26 subjects, 7 were excluded because of poor image quality in at least one scan. Fig 1. shows an example of the resulting V-V images with good image quality, showing  $K^{trans}$  in green and  $v_p$  in red for two scans of the same carotid artery. For the 19 subjects with acceptable image quality, ICCs and CVs are summarized in Table 1. The sample sizes needed to detect a 25% decrease of each kinetic parameter are shown in Table 2. Although  $K^{trans}$  exhibits somewhat lower ICC than  $v_p$  (Table 1), its CV for the measurement error is smaller, causing a smaller sample size to detect changes within-subject. The  $K^{trans}$  ICC is lower despite a smaller CV because there is less inter-subject variability in this population, relative to the measurement error.

## Conclusion

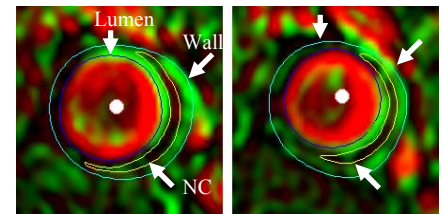
This study demonstrates, for the first time, that the inflammatory atherosclerotic plaque can be reproducibly assessed by kinetic parameters ( $K^{trans}$  and  $v_p$ ) generated from DCE-MRI using 3T MR scanners for multi-center studies. This result suggests that the kinetic parameters generated from DCE-MRI are suitable for studies to test the effectiveness of new anti-inflammatory, anti-atherosclerotic agents currently in development. The result of the power analysis indicates that  $K^{trans}$  of the plaque or adventitia would be useful parameters to detect changes with a relatively modest sample size.

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## References:

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**Fig 1.** An example of the V-V images with  $K^{trans}$  in green and  $v_p$  in red for two scans of the same artery. The points label the carotid lumen. The white arrows point to the outlined contours of lumen, outer wall and necrotic core (NC).

**Table 1.** ICCs and CVs of the kinetic parameters of atherosclerotic plaque in carotid artery from 19 subjects from 4 clinical sites

ICC (CV)	$K^{trans}$	$v_p$
Plaque	0.444* (25.03%)	0.738* (39.67%)
Adventitial	0.427* (24.41%)	0.740* (39.94%)

\*: p value < 0.05.

**Table 2.** Sample sizes needed to detect 25% within-subject decrease of kinetic parameters in carotid plaque with 80% power and significance level of 0.05 using a paired t-Test.

Sample size	$K^{trans}$	$v_p$
Plaque	18	42
Adventitial	17	43