Non-invasive Quantification of Atherosclerotic Plaque Inflammation and Neovascularity in a Rabbit Model using Bright-Blood Dynamic Contrast-Enhanced MRI

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Introduction - Neovascularization and inflammation are two common features of rupture-prone atherosclerotic plaques, the precursor plaques responsible for heart attacks and stroke **(1,2)**. Development of non-invasive, quantitative imaging techniques to assess these features is of utmost importance to fully understand the natural progression of atherosclerosis, to properly stratify patients in terms of risk of thrombogenic events, and to effectively evaluate new treatments targeting these risk biomarkers. Here we have explored the use of bright-blood dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) for evaluating these features in hypercholesterolemic rabbit aortic plaques that resemble mid-stage plaques in humans. Our study was motivated by three main reasons: 1) relatively few studies have been done with DCE-MRI, particularly bright-blood DCE-MRI, in animal models and therefore further validation is required; 2) novel treatments targeting inflammation and angiogenesis will be evaluated in both humans and animal models and imaging methods that can be applied at both the pre-clinical and clinical stage are advantageous; and 3) to date the DCE-MRI technique has been necessarily validated in very advanced carotid plaques in humans **(3,4,5)**, whereas to allow earlier identification of at-risk patients and improved treatment guidance it is important to show that the method can be used for characterizing earlier plaques such as those found in our rabbit model.

Methods and Results – Atherosclerotic plaques were induced in rabbits by combination of balloon endothelial denudation and 11 months on a hypercholesterolemic diet. In each rabbit, axial images were acquired on a 1.5T scanner using a customized two-channel phased array RF coil between the iliac and left renal bifurcations (4 plaque sections imaged per rabbit). DCE-MRI images were collected prior to and immediately following a 0.1 mmol/kg injection of DTPA-Gd using a fSPGR sequence (TE/TR 3.5/60 ms; FA 40°; BW 10.87 kHz; 40 mm saturation bands placed 5 mm superiorly and inferiorly to the block of images slices; resolution 0.195 x 0.195 x 5 mm^3; scan time per 4 slices = 16 seconds; total scan time = 272 seconds) **(Figure 1)**. Lumenal and adventitial boundaries were traced in each DCE-MRI series and kinetic modeling was performed (5). Briefly, the transfer constant of contrast agent into the extracellular space (K^{trans}) and plasma volume (v_p) were determined, maps of each measure were generated, and a fused colour-coded map of both metrics was generated. Importantly, positive correlations of the transfer constant (K^{trans}) within plaques and histopathological plaque measures of both macrophage percentage and neovessel density were found (r=0.4438, p=0.011 for K^{trans} versus macrophage %; and r=0.4186, p=0.027 for K^{trans} vs. neovessel density) **(Figure 2)**.

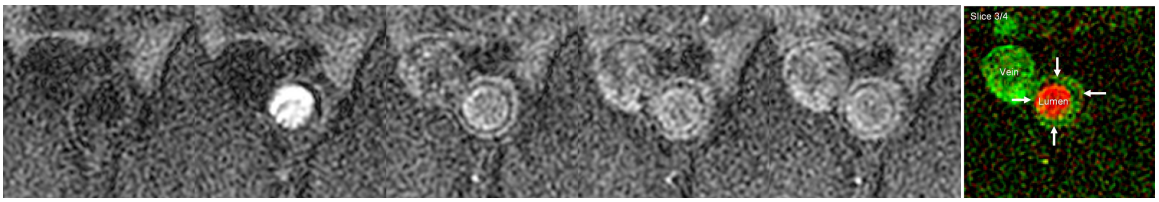

Figure 1 – (Left) DCE-MRI axial images of aortic plaques acquired (from left to right) prior to and 16, 32, 48, 104 seconds after injection of 0.1 mmol/kg DTPA-Gd. (Far Right) Colour-coded parametric map of DCE-MRI kinetic modeling. Red colour represents plasma volume (v_p) and green colour represents transfer constant of agent into extracellular space (K^{trans}).

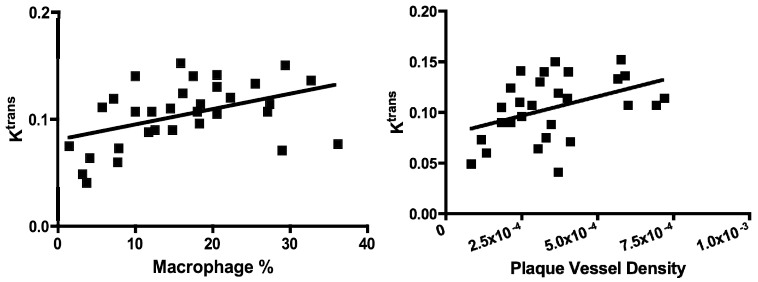

Figure 2 – Linear regression analysis of DCE-MRI transfer constant K^{trans} vs histological measures of both plaque macrophage % (left) and vessel density (right). Line represents linear regression fit. Pearson correlational analysis was performed and revealed r-values of 0.4438 (0=0.011) and 0.4186 (p=0.027) for K^{trans} versus macrophage % and K^{trans} versus vessel density, respectively

Conclusions – We have now shown that bright-blood DCE-MRI is a proven technique that allows quantitative assessment of atherosclerotic plaque neovascularization and inflammation in both animal models and humans. Importantly, since this technique employs clinically-available contrast agents it will allow the effective evaluation and titration of novel anti-inflammatory and anti-angiogenic therapies as they transition from the pre-clinical to clinical stage, ultimately expediting the identification of both high-risk patients and effective treatment strategies.

References - **[1]** Moreno, PR et al. Circulation 2006 ; **[2]** Falk, E. Circulation, 1992**; [3]** Kerwin, WS et al. Circulation, 2003 ; **[4]** Kerwin, WS et al. Radiology, 2006**; [5]** Kerwin WS et al. MRM, 2008.