Contrast kinetics of gadolinium uptake may discriminate stable from vulnerable atherosclerotic plaque

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Introduction: Acute coronary syndromes (ACS), triggered by disruption and thrombosis of vulnerable atherosclerotic plaques, are the leading causes of death in the United States. *In vivo* dynamic contrast enhanced (DCE) MRI of carotid arteries, prior to endarterectomy, has shown a positive correlation of gadolinium uptake with plaque neovascularization and inflammation, two prominent features of vulnerable plaques (1, 2). We employed *in vivo* DCE MRI in a rabbit model of controlled plaque disruption to study the amount and temporal uptake of Gd-DTPA in a quantitative manner in an effort to understand the mechanism of gadolinium uptake and derive standardized criteria that could permit a prospective differentiation of stable from vulnerable plaques prior to acute cardiovascular events.

Materials and Methods: Aortic atherosclerosis was induced in male New Zealand White rabbits by cholesterol diet and endothelial denudation. Plaque disruption and thrombosis was induced with Russell's viper venom (0.15 mg/kg) and histamine (0.02 mg/kg). This procedure was performed twice, within 48 h, in each animal. *In vivo* MRI of the abdominal aorta commenced before (pre) and 24hrs after (post) the second pharmacological triggering using a 3.0 T Philips Intera Scanner and a synergy knee coil with 6 elements. Axial T1-weighted black blood (T1BB) images were acquired with a double inversion recovery, turbo spin echo sequence and cardiac gating. The parameters for the TIBB images were: TR=2 cardiac cycles, TE=10ms, turbo factor=15, inversion delay = 350ms, slices = 23, slice thickness=4mm, NEX=2, MTX=384x362, in-plane resolution=0.23x0.23 mm and scan duration=8min. DCE MRI images were acquired after an intravenous injection of 0.01mmol/kg Gd-DTPA with a fat-suppressed, 3D T1-weighted, ultra-fast gradient echo sequence. Acquisition parameters were**:** TR = 18ms, TE = 7 ms, flip angle = 10°, NEX = 6, slices=23, slice thickness = 4mm, MTX = 400x400, reconstructed resolution = 0.23x0.23 mm, and temporal resolution = 103s. Seven DCE scans were acquired and the total scan duration was 14 min. Inferior and superior radiofrequency saturation pulses were added to null the blood signal. Pre-triggered MRI images were analyzed using ImageJ. Plaques were segmented using the T1BB images and subsequently the region of interest (ROI) was propagated on the DCE images. For each time point, the mean signal intensity of the pixels included within the ROI was recorded. Histology was performed on transverse (10μm) cryo-sections stained with Masson's trichrome to identify cellular components and thrombi. Disrupted (vulnerable) plaques were defined as those with attached platelet and fibrin-rich thrombi. Plaques that had no overlying thrombus were defined as non-disrupted (stable).

Results and Discussion: Examples of T1BB and DCE images for six plaques (3 stable and 3 ruptured) acquired from the aorta of the same rabbit are illustrated in **Figure 1**. The pre-triggered T1BB images reveal the sites of vessel wall thickening whereas the DCE images show the temporal changes of gadolinium uptake. The red arrows indicate the time point after administration of gadolinium at which the maximum signal intensity occurred. Two out of the three stable plaques had peak gadolinium uptake later than the initial 1.5min time point: 4.5 min **(Plaque 1)** and 7.5 min **(Plaque 3)**. Only one of the stable plaques had a peak gadolinium uptake at 1.5 min **(Plaque 2)**. In contrast, all ruptured plaques **(Plaques 4-6)** showed a rapid uptake of gadolinium which peaked at 1.5 min. The absence of luminal thrombi on the histological sections corresponding to plaques 1-3 verified that they were stable plaques. In contrast, plaques 4-6 were vulnerable and ruptured after the pharmacological triggerings forming luminal thrombi. **Figure 2A** demonstrates the kinetic curves for the six plaques presented in Figure 1. Rapid wash-in kinetics and relatively high peak signal was seen in vulnerable plaques **(Plaques 4 and 6; black arrows)**. Histologically these plaques were characterized by extensive vasa vasorum-derived neovessels, and inflammation **(Figure 2B; arrows)**. Interestingly, although **Plaque 2** was a stable plaque, not only was peak signal seen at the initial 1.5min time point as for the vulnerable plaques, but it showed higher peak uptake of gadolinium at 1.5min when compared to Plaque 5 which was a vulnerable plaque. The corresponding histology of Plaque 2 showed abundant new collagen fibers (type III) in addition to neovessels **(Figure 2C; arrow)**. Although the extent of neovascularization was less compared to that observed in vulnerable plaques (4 and 6) it might, together with the increased fibrotic content, this have led to the higher influx of gadolinium into the plaque.

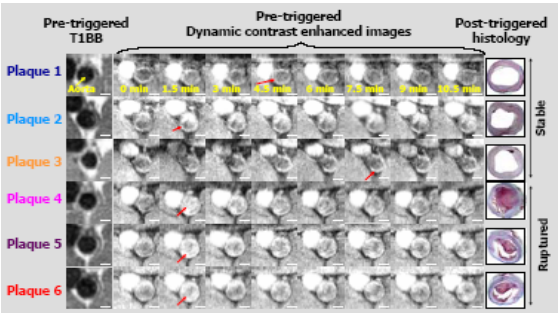

Figure 1: DCE MRI images of stable and ruptured plaques located in the aorta of the same rabbit. Scale bars=2mm.

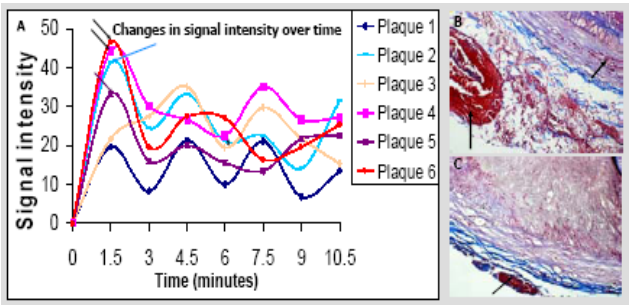

Figure 2: Kinetic curves show the changes in signal intensity over time in stable and ruptured plaques located in the aorta of the same rabbit.

Conclusions: Vulnerable plaques showed rapid wash-in kinetics with higher peak signal after gadolinium contrast administration when compared to stable plaques, which histologically correlated to the extent of vasa vasorum-derived neovessels and inflammation. However, one stable plaque which had abundant fibrosis in addition to neovessels also showed rapid wash-in and high peak gadolinium uptake. Further studies will be performed to establish a mechanism of gadolinium uptake and derive standardized criteria using DCE MRI that could be used to discriminate stable from vulnerable plaques.

References: **1.**Kerwin W, Hooker A, Spilker M, Vicini P, Ferguson M, Hatsukami T, et al. Quantitative magnetic resonance imaging analysis of neovasculature volume in carotid atherosclerotic plaque. Circulation 2003;107(6):851-6.
2. Kerwin WS, O'Brien K D, Ferguson MS, Polissar N, Hatsukami TS, Yuan C. Inflammation in Carotid Atherosclerotic Plaque: A Dynamic Contrast-enhanced MR Imaging Study. Radiology 2006.