In vivo detection of vulnerable atherosclerotic plaque by magnetic resonance imaging

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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. The ability to identify specific atherosclerotic plaque regions with a high risk for sudden disruption prior to an ACS event is presently not possible and would be of great utility. We used a rabbit model of pharmacologically controlled atherothrombosis to test whether *in vivo* MRI can noninvasively distinguish vulnerable plaques from those that do not support atherothrombosis (stable).

Materials and Methods: Aortic atherosclerosis was induced in 17 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* MR experiments 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. Pre-triggered images were assessed for features of vulnerability following identification of vulnerable plaque regions by thrombosis noted on the post-triggered images and corresponding histology. Un-gated coronal 3D phase contrast MR angiograms (PC-MRA) acquired with a T1-weighted, fast-filed echo sequence were used as scout images. Then 2D T1-weighted black-blood (T1BB) images were acquired with a double inversion recovery turbo spin echo sequence and cardiac gating. T1BB parameters were: TR=2 cardiac cycles, TE=10ms, TSE=15, axial slice thickness = 4mm, inversion recovery delay = 350 ms, NEX=2, MTX= 384x362 (in-plane resolution=0.23x0.23 mm), scan time= 8 min. Subsequently, un-gated axial 3D PC-MRA images were acquired immediately after a bolus injection of Gd-DTPA (0.1 mmol/kg, IV). For every axial T1BB slice (4 mm), eight 0.5mm PC-MRA slices were acquired. Scan parameters were: TR=17ms, TE=7.4, flip angle=15°, NEX=2, flow velocity=75 cm/s, MTX=128x122 (in-plane resolution=0.19x0.19mm) and scan time=8 min. Post-contrast enhanced (post-CE) T1BB images were acquired 10-15 min after Gd-DTPA injection. Image analysis was done on the pre-triggered MR images using ImageJ. Pre-CE T1BB images were used to calculate the plaque area [PA= adventitial area - lumen area] and the % cross-sectional narrowing [% CSN = (plaque area/vessel area)*100]. The anatomical/flow compensated PC-MRA images were used to calculate the remodeling ratio [RR = vessel area $_{lesion}$/ vessel area $_{reference}$] and the corresponding flow-encoded images were used to calculate the % stenosis: [% stenosis=1-[lumen area $_{lesion}$/lumen area $_{reference}$]*100]. Three remodeling categories were defined as previously described (Pasterkamp et al. J Am Coll Cardiol 1995;26(2):422-8): positive if RR>1.05, intermediate if $0.95 \leq RR \leq 1.05$ and negative if RR <0.95. Post-CE T1BB images were visually compared to the pre-CE T1BB images to evaluate the presence or absence of a circumferential (full ring) or crescent-shape enhancement pattern of the vessel wall. Histology was performed on transverse (10µm) cryo-sections which were 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: Atherosclerosis was identified by the pre-triggered images in all rabbits, and thrombosis was identified in 9/17 animals (53%) by post-trigger MRI. After sacrifice, a total of 95 plaques were analyzed, of which 28 (29.5%) had thrombi (vulnerable) and 67 did not (stable) (70.5%). Pre-triggered MRI revealed that stable and vulnerable plaques had comparable degrees of stenosis despite the fact the vulnerable plaques had larger plaque areas. Interestingly, vulnerable plaques more frequently exhibited: (1) positive remodeling, in which the plaque is hidden within the vessel wall instead of occluding the lumen **(Figure 1)**; and (2) enhanced gadolinium uptake associated with histological findings of neovascularization, inflammation, and tissue necrosis **(Figure 2)**.

Conclusions: We demonstrate that *in vivo* MRI at 3.0 Tesla detects features of vulnerable plaque in an animal model of controlled atherothrombosis. These findings suggest that MRI may be useful as a non-invasive strategy for localization of plaques that are prone to disruption.
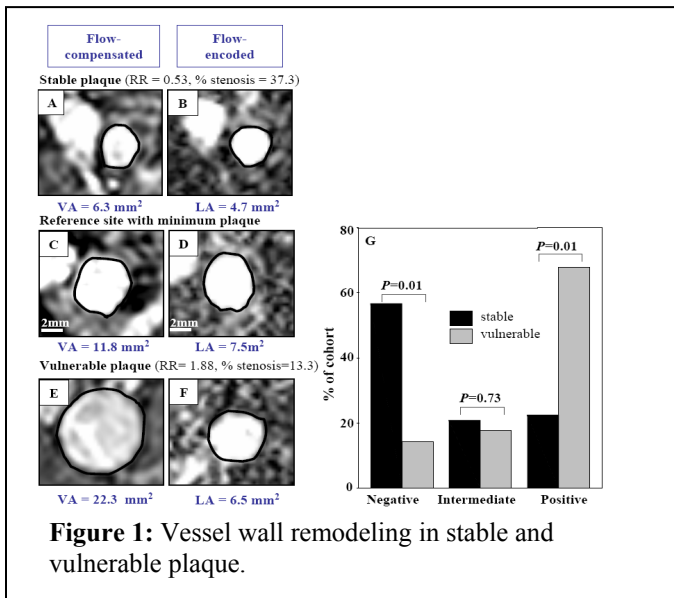

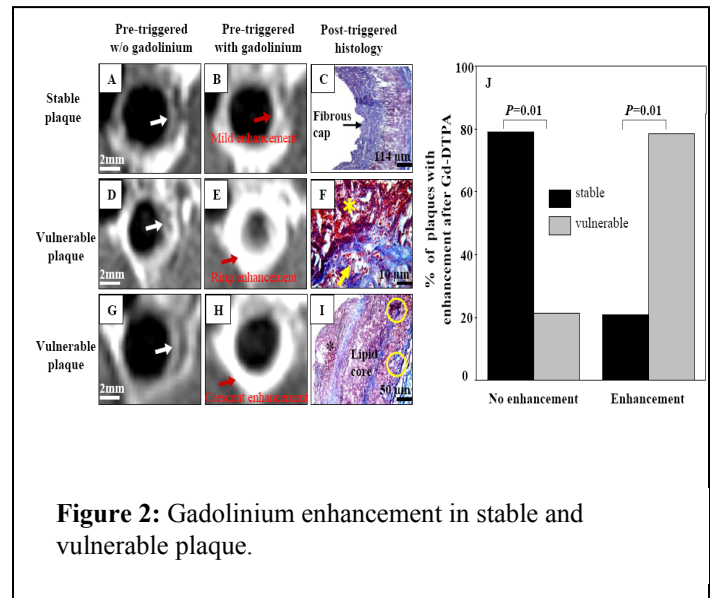**Figure 1:** Vessel wall remodeling in stable and vulnerable plaque.

Figure 2: Gadolinium enhancement in stable and vulnerable plaque.