Detection of vascular remodeling using an elastin contrast agent in a rabbit model of atherosclerosis

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Introduction: The extracellular matrix protein (ECM) elastin contributes to 30% of the dry weight of the vascular wall. Studies have shown that dysregulation of the balance between elastogenesis and elastolysis leads to the de novo accumulation of elastin fibers in the pathologically altered vessel wall and accompanies the development of atherosclerosis and may contribute to plaque instability [1, 2]. In this study, we employed *in vivo* MRI in a rabbit model of atherosclerosis and controlled plaque disruption to investigate the merits of an elastin-targeted gadolinium-based contrast agent for the detection of vessel wall remodeling and its association with plaque vulnerability.

Materials and Methods: *Animal model:* Aortic atherosclerosis was induced in male New Zealand White (n=6) 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) *[3]*. ***In vivo MRI*** of the abdominal aorta was performed before and after the pharmacological triggering using a 3.0 T Philips Intera Scanner and a 32 channel cardiac coil. Native and contrast enhanced images were acquired before and 2h after intravenous administration of 0.2 mmol/kg of the elastin-targeted gadolinium-based contrast agent, LMI1174 (Lantheus Medical Imaging, No. Billerica, MA), respectively. Following a 3D gradient echo (GRE) scout scan, phase contrast angiography (PCA) images were acquired for visualization of the abdominal aorta, the renal branches, and the iliac bifurcation with a FOV=20x300x150mm, matrix=256x244, reconstructed resolution=0.6x0.6mm, slice thickness=0.3mm, TR/TE=20/3ms and flip angle=15°. The maximum intensity projection images were used to plan the subsequent native and contrast enhanced T1-black blood (T1BB), inversion recovery (IR), and T1 mapping scans. A 2D Look-Locker sequence planned perpendicular to the abdominal aorta, was used to determine the optimal inversion time (TI) for blood signal nulling. IR 3D GRE axial images were then acquired with: FOV=85x100x120mm, acquired matrix=520x521, reconstructed resolution=0.23x0.23mm, slice thickness=4mm, slices=25, TR/TE=19.6/5.4ms, TR between subsequent IR pulses=1000ms, and flip angle=30°. T1 mapping was performed using a sequence that employs two non-selective inversion pulses with inversion times ranging from 20ms to 2000ms, followed by eight segmented readouts for eight individual images. The two imaging trains result in a set of 16 images per slice with increasing inversion times. For T1 mapping the acquisition parameters were: FOV=58x45x80mm, matrix=116x97, reconstructed resolution=0.2x0.2mm, slice thickness=3mm, slices=15, TR/TE=3.5/1.9ms, flip angle=10°. ***Image analysis:*** Contrast enhanced pre-triggered IR images were used to calculate the wall and plaque area by manually tracing the vessel wall contours using Osirix. T1 mapping images were used to calculate the R1 of the vessel wall on a pixel-by-pixel basis using in house software (Matlab, Natick, MA). Post-triggered images were used to identify the presence or absence of thrombi for the classification of plaques to vulnerable and stable, respectively. For the assessment of vascular remodeling, the perpendicular distance of each point illustrated in Figure 1G from the linear regression line was calculated. Subsequently, three remodeling categories were defined as shown in Figure 1H. **Histology**: En face images of the vessels were used to validate the MRI findings.

Results and Discussion: An example of native and CE-MR images acquired in a rabbit that contained both stable and vulnerable aortic plaques is illustrated in **Fig. 1**. The example of the vulnerable plaque showed that vessel wall contours were more readily visualized on the elastin contrast-enhanced IR images **(Fig. 1C)** compared to the native images **(Fig. 1A)**. The R1 maps **(Fig. 1B and 1D)** showed a significant increase in the relaxation rate (R1) of the vessel wall from 1.1 s^{-1} before to 4.7 s^{-1} after the administration of the contrast agent for the vulnerable plaque while it was lower (3.7 s^{-1}) for the stable plaque **(Fig. 1F)**. Comparison of the vessel wall area **(Fig. 1C vs. 1E)**, as demarcated by the adventitial contour of the vessel wall, revealed that the vulnerable plaque had an *increased* vessel wall area whereas the stable plaque had a *decreased* vessel wall area. Note that the enhanced area coming off the left site of the stable plaque is a site branch. The changes in the vessel wall area observed along the aorta starting from the left renal branch (0mm) until the iliac bifurcation (87 mm) are illustrated in **Fig. 1G**. A significant increase in the vessel wall area was observed at two regions outlined by the circles both of which contained vulnerable plaques. The rest of the data points correspond to regions of
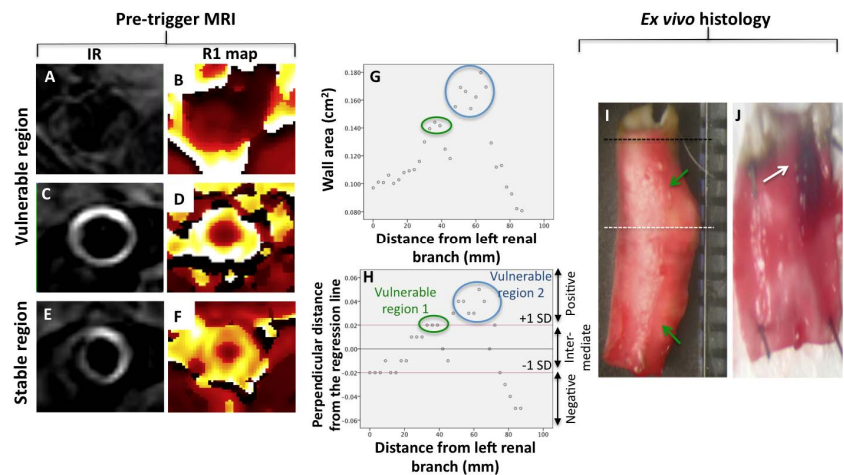

Figure1: Contrast enhanced MRI with the elastin-contrast agent allows better visualization of the vessel wall contours and an accurate assessment of the vessel wall remodeling.

the vessel wall that contained stable plaques. Classification of the type of vessel wall remodeling **(Fig. 1H)** showed that vulnerable plaques clustered within vessel wall regions undergoing *outward/positive* vessel wall remodeling whereas stable plaques undergo either *intermediate or negative remodeling*. The corresponding *ex vivo* histological specimen **(Fig. 1I)** verified the MRI findings showing the localization of the vulnerable plaque (white line) within a region of *outward* remodeling and the stable plaque (black line) in a region of *negative* remodeling. The location of the thrombus (arrow) was verified when the vessel was opened longitudinally **(Fig. 1J)**.

Conclusions: Utilization of the elastin-contrast agent allows accurate detection of the vessel wall contours for the evaluation vessel wall remodeling. Vulnerable plaques cluster within vessel wall regions undergoing *outward/positive* vessel wall remodeling whereas stable plaques undergo *either intermediate or negative remodeling*. The elastin contrast agent may allow the *in vivo* detection of high-risk plaques.

References: 1.Krettek, A., et al. ATVB, 2003. **23**(4): p. 582-7. **2.**Makowski, M.R., et al. Nature medicine, 2011. **17**(3): p. 383-8.