Molecular MRI of Vascular Remodeling in a Swine Model of Coronary Injury using an Elastin-Binding Contrast Agent

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Introduction:

Extracellular matrix (ECM) synthesis and degradation plays an important role in the initiation, progression and complication of atherosclerosis and in-stent restenosis as well as in aneurysm formation/degradation and graft disease. Enhanced synthesis of ECM typically leads to expansive or constrictive vessel wall remodeling resulting in plaque stability but also arterial stenosis or in-stent restenosis. In contrast, advanced ECM degradation can lead to plaque instability and subsequent plaque rupture as typically observed in patients with acute coronary syndromes. In this study we sought to demonstrate the feasibility of non-invasive MR imaging of vascular remodeling in a swine model of coronary injury using a novel elastin-binding low molecular weight contrast agent, BMS753951 (Bristol Myers Squibb, Billerica, MA).

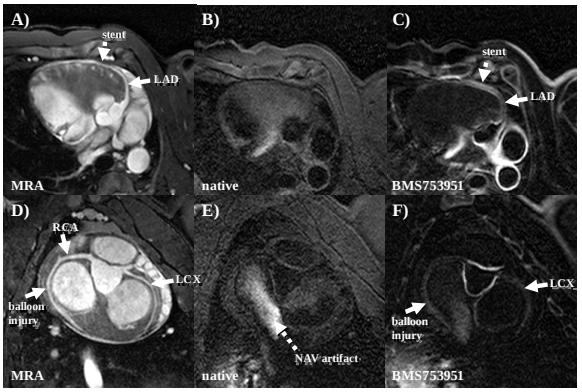

Figure 1: (A, D) Coronary MRA of control (RCA), balloon injured (LCX), and stented vessel (LAD). Corresponding delayed enhancement images pre (B, E) and post (C, F) injection of and BMS753951.

Methods:

Vascular injury was induced in 6 female landrace pigs (30-35kg) by endothelial denudation and stent placement in the left anterior descending (LAD) and left circumflex (LCX), followed by a 28 day normal diet. The RCA served as control vessel. Lasered MR-lucent prototype stents (Aachen Resonance, Aachen, Germany) were used to allow artifact free imaging of the stent lumen and vessel wall. At day 28, free-breathing coronary MRA and delayed enhancement imaging of the coronary vessel walls was performed using a 1.5T MR scanner (Achieva, Philips Medical Systems, NL) pre and post injection of 0.2mmol/kg Gd-DTPA. Imaging parameters of the free-breathing ECG triggered and navigator (NAV) gated inversion recovery (IR) segmented gradient echo vessel wall sequence included FOV=320mm, matrix=256x256, in-plane resolution=1.25x1.25mm, slice thickness=3mm, acquisition window=50ms, TR/TE=4.7ms/1.4ms, flip angle=30º, inversion time=285ms (@ 90bpm), and slices=24. Two days later, coronary MRA and delayed enhancement coronary vessel wall imaging were repeated pre and post (until to 2 hours) injection of 0.1mmol/kg BMS753951. After completion of MR imaging, x-ray coronary angiography was performed to assess the degree of luminal stenosis in the stented and balloon injured vessel segment. Subsequently, animals were euthanized and hearts were harvested for histological analysis. Sirius red (collagen) and Elastica van Gieson (elastin) staining was performed in the stented coronary segments while Movat pentachrome (elastin) staining was performed for the control and balloon injured segments. For objective image analysis, signal-to-noise (SNR) of the vessel wall and contrast-to-noise ratio (CNR) between vessel wall and blood was determined by manual segmentation of the coronary vessel wall in the stented, balloon injured and control vessels on reformatted images.

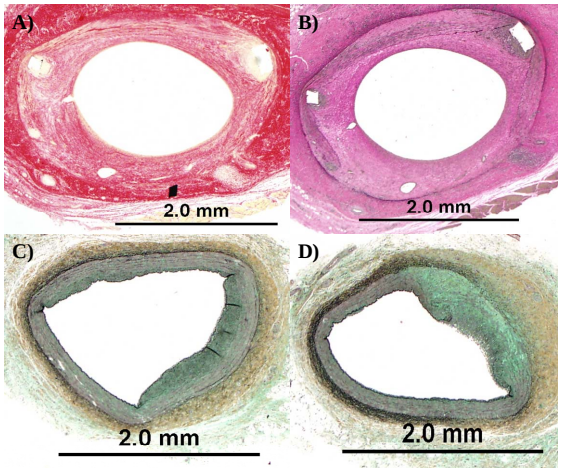

Figure 2: (A, B) Sirius red and Elastica van Gieson (EvG) stain of the stented LAD coronary vessel segment demonstrating severe remodeling of the injured vessel wall. (C, D) Movat stain of the balloon injured RCA vessel wall segment demonstrating little remodeling from 12 to 6'o clock.

Results:

Coronary MRA allowed good visualization of the stented and balloon injured vessel segments (Figure 1a, d). No enhancement of the stented, balloon injured and control coronary vessel segments was observed on native inversion recovery images (Figure 1b, e). In contrast, after administration of BMS753951, strong enhancement of the stented and intermediate enhancement of the balloon injured coronary vessel segment were observed suggestive for vascular remodeling in the injured vessel segments (Figure 1c, f). There was no to little visually apparent enhancement in the control coronary artery (Figure 1f). Histological analysis revealed severe remodeling in the stented segments (Figure 2a, b) and only minor remodeling in the balloon injured segments (Figure 2c, d). Quantitative analysis of vessel wall enhancement yielded a 3-fold higher CNR (Figure 3) in the stented coronary artery when compared to the balloon injured and control artery ($p<0.001$). SNR remained at a consistently high level in the stented coronary vessel wall segment suggesting specific binding to the vessel wall with no wash-out tendency up to 2 hours after of BMS753951 injection (Figure 4). In addition, strong aortic and pulmonary vessel wall enhancement was seen after BMS753951 administration, which is in agreement with the high elastin content in those vessels, while no apparent enhancement was observed after Gd-DTPA injection ($p<0.001$).

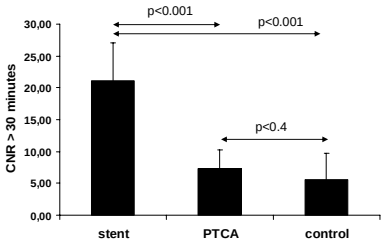

Figure 3: Contrast-to-noise ratio (CNR) between coronary vessel wall and blood in stented, balloon injured, and control vessel after administration of BMS753951.

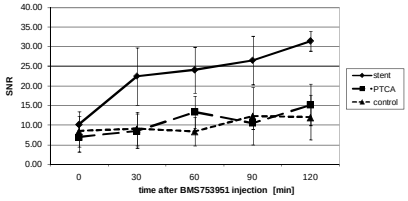

Figure 4: Signal-to-noise ratio (SNR) in the stented, balloon injured and control coronary artery vessel wall pre and post injection of BMS753951. SNR in the stented coronary vessel wall rapidly increased after BMS753951 injection and even slightly increased over a 2 hour period suggestive for specific binding to elastin in the injured vessel wall.

Conclusions:

This is the first MRI study to demonstrate the detection of ECM synthesis non-invasively in an animal model of coronary vessel wall injury using an elastin-specific contrast agent. This novel approach may be useful for in-vivo monitoring of vascular remodeling post stent placement or for the assessment of plaque burden in patients with suspected coronary artery disease.