

Monitoring of endothelial permeability and plaque progression in a rabbit model of atherothrombosis using an albumin-binding MR contrast agent

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Introduction: Endothelial dysfunction, characterized by increased vascular permeability and impaired endothelial-dependent vasodilation, precedes and portends the development of atherosclerosis. Recent advances in MRI acquisition protocols allowed the non-invasive assessment of endothelial function by MRI. Such studies showed that impaired focal endothelial dysfunction, measured as impaired vasodilation after isometric handgrip exercise, correlates with the extent of focal plaque burden in the coronary arteries (1,2). In addition, leakage of blood albumin into the vessel wall has been used as a surrogate marker to assess focal endothelial cell integrity and vascular permeability. We have previously reported that gadofosveset, an albumin-binding MR contrast agent, can be used to non-invasively assess endothelial permeability, plaque burden progression (3) and regression (4) in a murine model of accelerated atherosclerosis. To expand our previous findings we investigated the interplay between endothelial dysfunction, plaque progression and instability in a bigger animal (rabbit) model of accelerated disease.

Materials and Methods: Aortic atherosclerosis was induced in New Zealand White rabbits (n=10) by cholesterol-diet and endothelial denudation. *In vivo MRI* of the abdominal aorta was performed at 1 and 10-weeks after endothelial denudation using a 3T Philips Achieva scanner and a 32-channel cardiac coil. Native and contrast enhanced images were acquired before and 40min after intravenous administration of 0.03 mmol/kg of gadofosveset. 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 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). **Histology:** Immunohistochemistry for albumin and electron microscopy were used to corroborate the MRI findings.

Results and Discussion: DE-MRI images acquired post administration of gadofosveset at 1 and 10 weeks after endothelial denudation are shown in **Figure 1**. Leakage of gadofosveset in the vessel wall 1-week after surgical removal of the endothelium resulted in a circumferential enhancement of the vessel wall (**Fig. 1A**). At 10-weeks, the enhancement was eccentric and a region of significant vessel wall thickening due to plaque formation was observed (**Fig. 1B**). Quantification of the vessel wall relaxation rate (R₁) showed significantly higher gadofosveset uptake in the presence of established atherosclerosis compared to the earlier time point (**Fig. 1C**). Immunohistochemistry for albumin showed accumulation of albumin within the plaque (**Fig. 1D**) that was significantly higher compared to the control aorta (**Fig. 1E**). Finally, electron microscopy (**Fig. 1F**) showed morphological changes of endothelial cells and denudation of the vessel wall overlying atherosclerotic lesions.

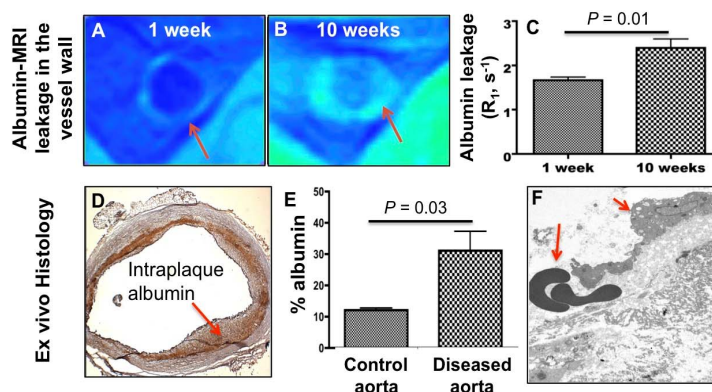


Figure 1: DE-MRI of the rabbit aorta after administration of gadofosveset.

Conclusions: *In vivo* MRI can be used to assess both endothelial permeability and function. Assessment of these two features within a single MRI examination could collectively be used as a “barometer” of endothelial health and provide a more accurate stratification of atherosclerotic disease.

References:

(1) Hays AG. et al. JACC 2010, (2) Hays AG. et al. Circ. Cardio. Img. 2012. (3) Phinikaridou A. et al. Circ. 2012. (4) Phinikaridou A. et al. JAHA, 2013.