Gadofosveset monitors the effects of different interventions on endothelial permeability and plaque progression

Alkystis Phinikaridou[1], Marcelo E Andia[2], and Rene M Botnar[2]
[1]*Imaging Sciences, King's College London, London, United Kingdom,* [2]*King's College London*

Introduction: Studies have demonstrated that endothelial dysfunction precedes and promotes atherosclerosis development because of increased endothelial permeability, circulating lipoproteins, inflammatory cells and molecules. We have previously shown that contrast enhanced MRI using gadofosveset, an albumin binding gadolinium contrast agent, can detect endothelial damage associated with atherosclerotic plaque formation and progression in high-fat fed apoE $^{-/-}$ mice [1]. In this study, we explored whether imaging with gadofosveset could be used to monitor the effects of different interventions on endothelial permeability and plaque progression.

Materials and Methods: Animal model: Starting at 8 weeks of age, male apoE $^{-/-}$ mice were fed a high-fat diet that contained 21% fat from lard and 0.15% (wt/wt) cholesterol for 12 weeks. Male C57BL/6J mice (n=4) were fed a normal diet and were used as controls. Simultaneously with the commencement of the high-fat diet mice received Ebselen (n=4) (5 mg/kg body weight dissolved in 5% CM-cellulose), minocycline (n=4) (1.5mg/kg) and clopidogrel (n=4) (25 mg/kg) dissolved in drinking water. Ebselen, a lipid-soluble selenoorganic compound and a known glutathione peroxidase-1 mimetic has been shown to improve endothelial function and reduce atherosclerotic burden in different animal models [2, 3]. Minocycline is a broad-spectrum tetracycline antibiotic shown to reduce the activity of matrix metalloproteinases in atherosclerotic rabbits [4]. Finally clopidogrel is an anti-platelet agent. *In vivo* MRI was performed using a 3T Philips Achieva system. Images were acquired before and after intravenous administration of 0.03mmol/kg gadofosveset. Mice were placed prone on a single loop microscopy surface coil (diameter=23mm). Following a 3D GRE scout scan, time-of-flight (TOF) images were acquired for visualization of the aortic arch, the brachiocephalic and carotid arteries with a FOV=20x20x10mm, matrix=160, in-plane resolution=0.3x0.3mm (reconstructed 0.13x0.13mm), slice thickness=0.5mm, TR/TE=37/7.7ms and flip angle=60°. The maximum intensity projection images were used to plan the subsequent delayed enhancement (DE) and T1 mapping scans. A 2D-Look-Locker sequence planned perpendicular to the ascending aorta, was used to determine the optimal inversion time (TI) for blood signal nulling. Acquisition parameters were: FOV=30mm, matrix=75, in-plane spatial resolution=0.4x0.4mm, slice thickness=2mm, TR/TE=19/8.6ms, TR between subsequent IR pulses=1000ms, and flip angle=10°. An inversion-recovery 3D fast-gradient echo sequence was acquired 30 minutes post injection and was used for DE-MRI and visualization of contrast uptake. Imaging parameters were: FOV=30x8x30mm, matrix=300, in-plane resolution=0.1x0.1mm, slice thickness=0.5mm, slices=32, TR/TE=27/8ms, 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=22x8x36mm, matrix=180x171, in-plane resolution=0.2x0.2mm, slice thickness=0.5mm, slices=16, TR/TE=9.2/4.7ms, flip angle=10°. T1 values were computed on a pixel-by-pixel basis using an in house software (Matlab, Natick, MA).

Results and Discussion: The uptake of gadofosveset in control, atherosclerotic and treated mice is illustrated in **Fig. 1**. Cross-sectional DE-MR images **(Fig. A_1, B_1, D_1, E_1)** and DE-MR images fused with the TOF images **(Fig. A_2, B_2, D_2, E_2)** of the brachiocephalic arteries showed increased vessel wall enhancement corresponding to plaque progression after 12 weeks of HFD. Conversely, mice treated with ebselen and minocycline showed deceased vessel wall enhancement whereas clopidogrel treated mice showed an intermediate enhancement. The uptake of gadofosveset within the vessel wall was quantified using the relaxation rate (R1) maps **(Fig. A_3, B_3, D_3, E_3;** yellow coloration indicates a high R1) and results are shown in **Fig. 2**. Treatment with ebselen and minocycline significantly reduced the leakage of gadofosveset into the vessel wall, and thus decreased the R1, compared to 12 weeks HFD animals *(P<0.001)*. Treatment with clopidogrel decreased the uptake of gadofosveset but to a lesser extent *(P<0.01)* compared to non-treated animals.

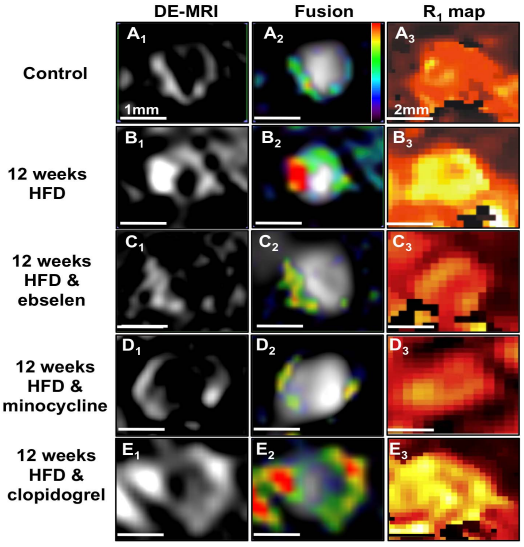

Figure 1: Effects of interventions on the uptake of gadofosveset in the brachiocephalic artery of apoE $^{-/-}$ mice.

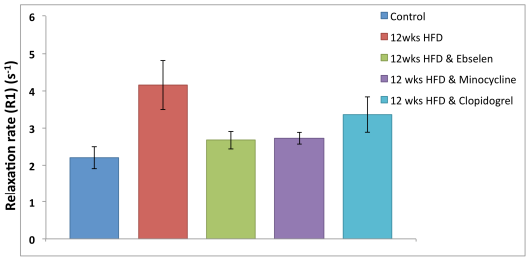

Figure 2: Quantitation of the relaxation rate in the vessel wall of the brachiocephalic artery of apoE $^{-/-}$ mice.

Conclusions: Contrast enhanced MRI with gadofosveset appears promising for the non-invasive monitoring of different medical interventions on endothelial permeability and plaque progression.

References:

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