Atherosclerotic plaques MRI detection in ApoE -/- mice using the blood pool agent B22956/1

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Purpose

Development of new, non-invasive, diagnostic tools aimed to detect the occurrence of atherosclerotic plaques is a primary task in medical research, due to the impact of atherosclerosis-induced diseases, such as myocardial infarction or stroke, on the world population health. MRI contrast agents (CA) with a long persisting time in blood may, potentially, accumulate into atherosclerotic lesions possibly through an altered endothelial permeability and thus increase the contrast with respect to non pathologic vessels.. Cornily et al. have successfully used the blood pool CA B22956/1 (Bracco Imaging SpA) to detect lesions in rabbits maintained on a high fat diet followed by artificial injury of the aorta.

In this study the efficacy of B22956/1 in enhancing the MRI sensitivity for plaque detection has been investigated, using apolipoprotein E knockout (ApoE -/-) mice, an animal model that, under proper diet conditions, spontaneously developes significant human-like lesions with high vulnerability at the brachiocephalic artery.

Materials and Methods

ApoE -/- mice (genetically modified C57BL/6 to lack apolipoprotein-e) 8 to 16 weeks old have been maintained for 0 to 12 weeks on a high fat diet containing 21% fat from lard and 0.15% cholesterol. At the end of the dietary treatment, MR images were acquired before and until 2 hours post injection of the paramagnetic contrast agent B22956/1 administered at the dose of 0.1 mmol/Kg (i.v.). B22956/1 (gadocoletic acid trisodium salt) is a Gadolinium-based molecule with a high albumin binding level, that ensures a blood pool behavior.

MRI experiments were performed on a 7T-16cm PharmaScan system (Bruker BioSpin), using a 3D T_1-weighted fast spin echo sequence with T_R=400 ms, T_E=13 ms, a slice thickness TH of 0.5 mm and an in-plane resolution of 0.1x0.1 mm^2. In order to avoid flux artifacts due to unsaturated spins flowing through the observed axial slice, the black-blood effect was maximized by triggering on the systolic phase of the ECG.

Animals were then sacrificed and, after perfusion with 4% formalin, brachiocephalic arteries were removed. Serial paraffin sections were stained with hematoxylin and eosin.

Results and discussion

Examples of histology and MRI results, for two animals with different plaque degrees are reported in Fig.1.

Hystologic analysis, performed on 34 animals revealed lesions areas up to 70% of the entire lumen section, confirming that the brachiocephalic artery of ApoE -/- is a good target to test the capabilities of *in-vivo* techniques for imaging atherosclerotic lesions. In parallel to *ex-vivo* analysis, the plaque occurrence in MRI images have been evaluated by three blinded researchers, either pre and post-injection of B22956/1. The diagnostic test revealed that the MRI-based method performs poorly in detecting the presence of the plaque before CA-administration: the sensitivity and specificity values were equal to 24% and 100%. After the administration of B22956/1 the sensitivity of the method increased up to 85% while the specificity was not affected.

Conclusions

Using ApoE -/- mice as animal model and hystologic analysis as reference standard, we confirmed that the blood pool contrast agent B22956/1 strongly improves the sensitivity of MRI in detecting spontaneously occurring human-like atherosclerotic lesions. The winning feature of this Gd-based molecule must be searched in its strong albumin binding which increases the intravascular persisting time and thus the chance to permeate altered endothelial tissues.

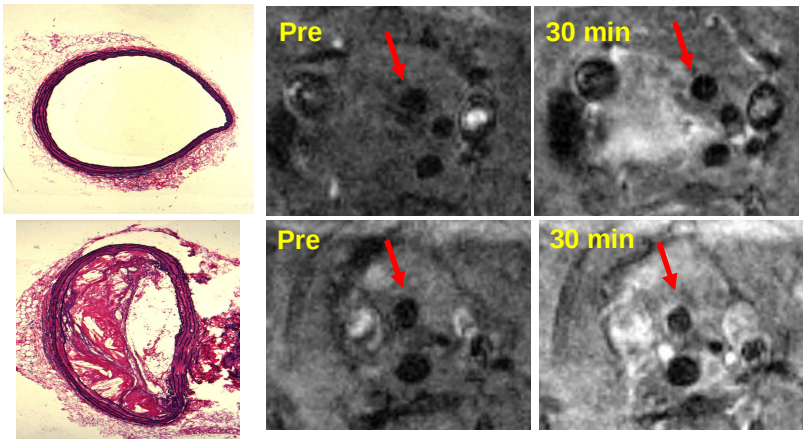

Figure 1. Hematoxylin-eosin sections and RARE 3D T_{1w} images acquired on ApoE (-/-) mice pre- and post-injection of B22956/1.