Localization of A Novel Contrast Agent Gadofluorine on Atheroslcerotic Plaque of Apolipoprotein E Knockout Mouse Using In Vivo Magnetic Resonance Microscopy

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Introduction:

In vivo MR imaging has been shown to be effective in the study of atherosclerosis. However, there remains a need for a more detailed morphological and functional assessment of the plaque. The latest development in magnetic resonance (MR) contrast agents have focused on targeting specific tissues that can detect and evaluate tissue activity more accurately. Gadofluorine is a new class of contrast agents that is based on a macrocyclic, lipophilic gadolinium complex, and form micelles in aqueous solution, with a potential for specific plaque enhancement. The purpose of the study was to investigate the in vivo localization of Gadofluorine (Schering AG) on atherosclerotic plaques using Apolipoprotein E knockout (KO) mice.

Methods:

Fifteen-month-old KO mice (n=12) and Wild Type (WT) (n=6) group underwent in vivo MR microscopy (MRM) of the abdominal aorta using a 9.4T MR system. Pre-contrast enhanced (CE) and post-CE MRM was performed at 24, 48 and 72 hours post injection using a T1W black blood sequence. Sixteen contiguous 500 μm thick slices with an in-plane resolution of 93 μm were acquired in 30 minutes. Gadofluorine (100 μmol/kg) with fluorescent-labeled carbocyanin was injected via the tail vein. After MRM, the aorta was isolated, frozen sections cut and stained with fluorescently labeled antibodies for macrophages, smooth muscle cells, lymphocytes, and tenascin, including DAPI and imaged by confocal microscopy. MRM images of the matched (pre and post) slices were used for analysis.

Results:

In the KO mouse group, there was a heterogeneous enhancement seen on MRM (Fig. 1), with significant increase in contrast-to-noise ratio (CNR) for wall/lumen and wall/muscle in the post-CE (24 and 48hour post injection) vs. pre-CE images (ANOVA, $p < 0.05$) and no significant increase in CNR for the CE at 72 hours post injection. There was no increase in CNR for wall/lumen and wall/muscle for the WT group in all 3 timepoints. The ratio of the post to the pre contrast signal intensity of the wall (normalized to muscle) was 2.25(enhancement of 125%) in KO group at 24 hours, 1.92(enhancement of 92%) at 48 hours, and 1.75(enhancement of 75%) at 72 hours. Confocal microscopy showed carbocyanin labeled Gadofluorine to be localized to the extracellular regions of plaques (Fig. 2). There was no localization in cells of the plaque.

Conclusions:

Gadofluorine showed good contrast enhancement of aortic atherosclerotic plaques of KO mice. CE MRM with localization of Gadofluorine in atherosclerotic plaque may delineate plaque burden in vivo, improve early detection of atherosclerosis and further our understanding of this disease.

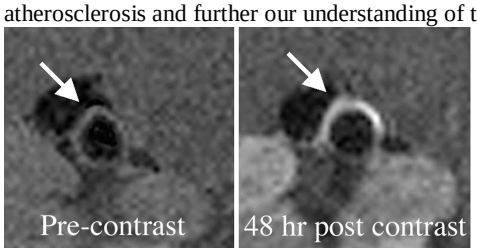

Figure 1. MR image of the abdominal aorta of ApoE KO mouse pre and 48-hour post contrast using Gadofluorine

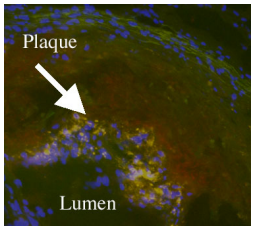

Figure 2. Immunofluorescent staining of Gadofluorine on atherosclerotic plaque using fluorescently labeled antibody to tenascin.

References:

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