In-Vivo MR Microscopy Efficacy of A Novel Imaging Agent P947, a Marker That Molecularly Targets Matrix Metalloproteinases in Atherosclerotic Plaque of Apolipoprotein E Knockout Mice

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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 atherosclerotic plaque. The latest developments in magnetic resonance (MR) molecular imaging agents have focused on specific targets that can detect and evaluate tissue biological activity more accurately. P947 (Guerbet, France) represents a new class of molecular imaging agents made of a peptide covalently bound to a Gd-DOTA moiety (the peptide is a ligand for MMPs). It is a candidate agent that may potentially target matrix metalloproteinases (MMPs). MMPs have been implicated in the development and complications of atherosclerosis. The purpose of the study was to investigate the in-vivo efficacy of P947 in detecting atherosclerotic plaque using Apolipoprotein E knockout (KO) mice.

Methods:

Fifteen-month-old KO mice (n=6) 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 1, 2, 3, and 24 hours post injection using a T1W black blood sequence. Sixteen contiguous 500 µm thick slices with an in-plane resolution of 101 µm were acquired in 34 minutes. P947 (100 µmol/kg) was injected via the tail vein. For control, another group of KO mice (n=3) was injected with Gd-DOTA (Dotarem, a standard extracellular Gadolinium contrast agent - Guerbet, France) using an equivalent dose of Gadolinium (100 µmol/kg). After MRM, the aortas were isolated, fixed and immunohistochemistry was performed for various MMPs. MRM images of the matched (pre and post) slices were used for analysis.

Results:

In the P947 group, there was heterogeneous enhancement seen on MRM, with significant increase in contrast-to-noise ratio (CNR) for wall/lumen and wall/muscle in the post-CE images (at 1, 2 and 3 hours post injection) with no significant increase at 24 hours vs. pre-CE images [ANOVA, $p < 0.05$](Figure 1). In the Gd-DOTA control group, there was no significant enhancement of the wall, with no increase in CNR for wall/lumen and wall/muscle at all 4 timepoints. The ratio of the post to the pre contrast signal intensity of the wall (normalized to muscle) with P947 was 1.91 ± 0.19(enhancement of 91%) in KO group at 1 hour, 1.52 ± 0.14(enhancement of 52%) at 2 hours, 1.22 ± 0.13(enhancement of 22%) at 3 hours, and 1.14 ± 0.06 (enhancement of 14%) at 24 hours. Figure 2 shows a graph of the comparison of the enhancement ratio (normalized to muscle) between the two groups at various timepoints.

Conclusions:

P947 showed good contrast enhancement of aortic atherosclerotic plaque in KO mice. CE MRM with P947 offers a potential for a novel noninvasive diagnostic tool in the detection of atherosclerosis. Further work is ongoing to evaluate whether P497 has the ability to identify high-risk plaque and predict complications of atherosclerosis.

Acknowledgements:

This work was partially supported by the NIH/NHLBI HL071021 and HL078667, Guerbet, France and The Stanley J. Sarnoff Endowment for Cardiovascular Science (VA).

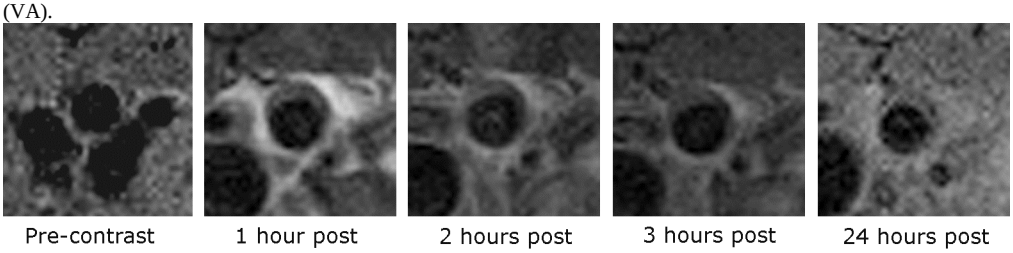

Figure 1. Matched axial MR images of the abdominal aorta of ApoE KO mice at various timepoints using P947.

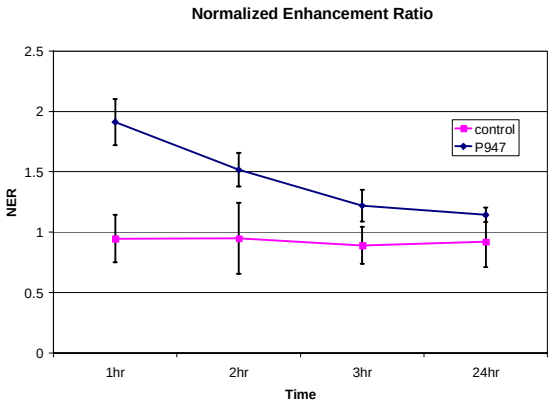

Figure 2. Comparison of the NER (normalized to muscle) between the P947 and the control group (Gd-DOTA) at different timepoints.