Detection of Atherosclerotic Plaque Progression: Correlation of Contrast MRI with PET using ^{64}Cu-labeled Natriuretic Peptide

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Purpose

In atherosclerotic plaques, expression of C-Type Natriuretic Peptide (CNP) receptor is known to correlate with the severity of atherosclerosis and its antithrombotic effects are mainly mediated by the activation of Natriuretic Peptide Receptor C (NPR-C) [1,2]. Recently, a PET tracer was developed to target this NPR-C receptor on atherosclerotic plaques [3]. The purpose of this study is to test our hypothesis that contrast enhanced MRI plaque images using a lipophilic yet water-soluble contrast agent can correlate in the signal intensity with the standardized uptake value (SUV) in the PET images acquired with a ^{64}Cu labeled DOTA-C-ANF (C-type atrial natriuretic factor). The aim of this study is to study this correlation in an ongoing project to investigate the progression of plaques in a rabbit atherosclerotic model.

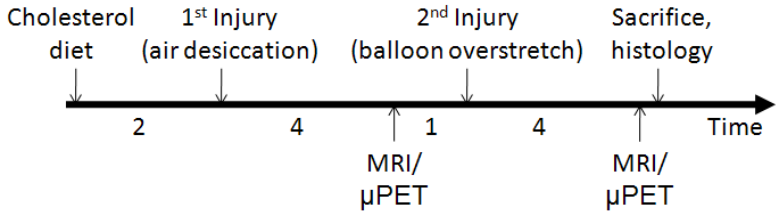

Figure 1. Timeline of rabbit protocol. Numbers equal weeks between events.

Methods

The right femoral artery of four male New Zealand white rabbits (R1-R4) fed a cholesterol-rich diet was double-injured by air desiccation and a balloon overstretching. MRI and MicroPET (µPET) imaging were performed 4 weeks after each injury (Figure 1). MR imaging was performed 1 hour post 0.5 µmol/kg Gadofluorine M injection (Bayer Schering Parma AG, Germany). 16-20 transverse dark-blood T1, T2 and PD-weighted images were acquired with a turbo-spin echo sequence on a clinical 3T system (Trio, Siemens Medical Solutions, Erlanger, Germany). µPET imaging used a ^{64}Cu-DOTA-C-ANF tracer (2-4mCi, 1mCi/nmol) with a 1 hour dynamic scan (Focus 220, Concorde Microsystems, Knoxville, TN). Figure 2 shows sample images from MRI and PET. Volume of interest (VOI) were drawn on PET images, and the averaged SUV for images collected at 5-60 minutes were gathered for the injured artery, control artery (femoral artery on opposite leg), and a leg muscle. Faducials attached to the rabbit scanning bed allowed for regions of interest (ROI) to be drawn on the MR images in the approximate locations that the VOI was drawn on PET images. After the second MR/µPET scan, histopathology and immunohistochemistry (IHC) was performed on both the injured and control femoral arteries.

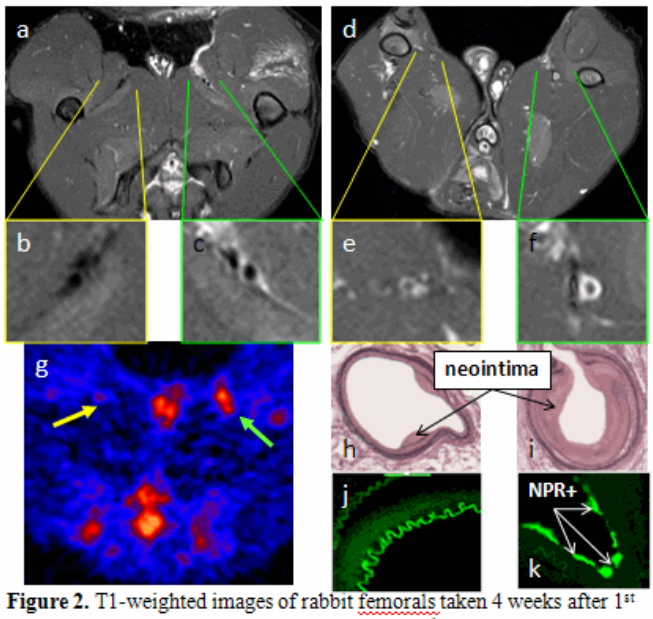

Figure 2. T1-weighted images of rabbit femorals taken 4 weeks after 1st injury (a-c). Same images taken 4 weeks after 2nd injury (d-f), showing increased signal intensity. The PET image (g) corresponds to (d). The VVG stains (h & i) correspond to e & f, as do the immunohistochemistry images (j & k).

Results

Figure 3 shows similar increases in both PET SUV and MRI signal intensity (SI). Values were normalized to the leg muscle [3]. For all rabbits, histopathology confirmed significant plaque growth in the injured femoral, with very little or no neointimal thickening on the control femoral (Figure 2).

Conclusions

Gadofluorine M enhances the extracellular matrix (ECM) of plaques. Such enhancement appears to correlate with PET SUV, indicating that proliferation of ECM is positively linked with CNP-positive plaques. Further studies are needed to understand the mechanism of this correlation.

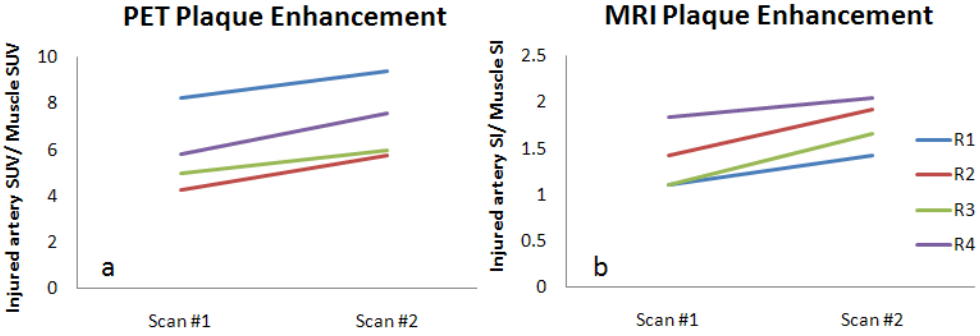

Figure 3. Atherosclerotic plaque progression leads to increases in PET tracer uptake (a) and MRI signal intensity (b). Values are normalized (injured artery/ muscle).

References

1. Hobbs HH et al. Trends Pharmacol Sci 2005;26:162-7.
2. Hobbs HH et al. Proc Natl Acad Sci 2005;102:14452-7.
3. Rossin R, Woodard PK et al. J Nucl Med 2007;48(Suppl. 2):103P.