Molecular MRI of Myeloperoxidase Activity in Experimental Atherosclerosis using a Novel Paramagnetic "Smart" Contrast Agent

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Introduction: Myeloperoxidase (MPO) is secreted by activated macrophages and neutrophils, and is present in high quantities in ruptured atherosclerotic plaques responsible for myocardial infarction and stroke. MPO plays an important role in modulating plaque stability by oxidizing LDL, reversing HDL's protective effects, and activating matrix metalloproteinase to disrupt the plaque. We recently developed the first small-molecule activatable MR contrast agent highly sensitive to MPO activity, Gd(bis-5HT-DTPA). In the presence of MPO, the agent is oligomerized and can bind to proteins, resulting in increased T1-weighted signal and prolonged retention of the agent at sites of increased MPO activity. We hypothesize that this agent can be used to identify plaques with high MPO activity levels in a rabbit model of atherosclerosis.

Methods: A NZW rabbit model of atherosclerosis fed a 0.25%-cholesterol diet for 16 to 18 months was used to test this agent. This model is known to produce lesions in the aorta with human-like compositional elements, including fibrous cap and moderate size lipid-rich necrotic core[1]. Each rabbit (n=5) was scanned at 3T using either a quadruple inversion recovery fast-spin-echo (QIR-FSE) sequence (TE/TR/TI 16.8/800/520 ms; ETL 6; BW +/-11.9 kHz**;** resolution 0.195x0.260x5 mm^3; scan time 8:50; 10 slices) (n=3) or a slab saturation based FSE sequence (TE/TR 18.3/800 ms; ETL 6; BW +/-11.9 kHz; resolution 0.195x0.195x3 mm^3, scan time 20:42; 10 slices) (n=2) pre- and up to 2 to 4 hours post-contrast. Both Gd(DTPA), the nonspecific control agent, and Gd(bis-5HT-DTPA) were used subsequently in each rabbit. One rabbit was additionally scanned with, Gd(bis-tyramine-DTPA), which has a similar structure to Gd(bis-5HT-DTPA) but does not react to the same degree with active MPO. Contiguous frozen tissue sections were histologically stained for macrophages and MPO. MPO-rich regions in tissue sections were compared to areas of increased contrast in the corresponding MR images.

Results: MR imaging of the aorta of these rabbits demonstrated similar initial enhancement pattern of the plaques between the MPO agent and Gd(DTPA). However, delayed images with the MPO agent showed focal areas of enhancement (Figure 1, arrows) 50-100% higher in contrast compared to images from Gd(DTPA). This difference in enhancement persisted for up to 4 hours compared to Gd(DTPA), consistent with MPO activation and agent retention (Figure 2). Preliminary histological validation shows evidence of MPO-rich regions correlating well with regions of increased enhancement with the MPO agent at delayed time points in MR images (Figure 3).

Conclusions: We conclude that Gd(bis-5HT-DTPA) can be used as a highly sensitive MR agent to image and identify MPO-rich plaques. Further development of this class of activatable agents should lead to improved diagnosis of plaque vulnerability and earlier, targeted treatment to decrease the mortality and morbidity associated with cardiovascular and neurovascular diseases.

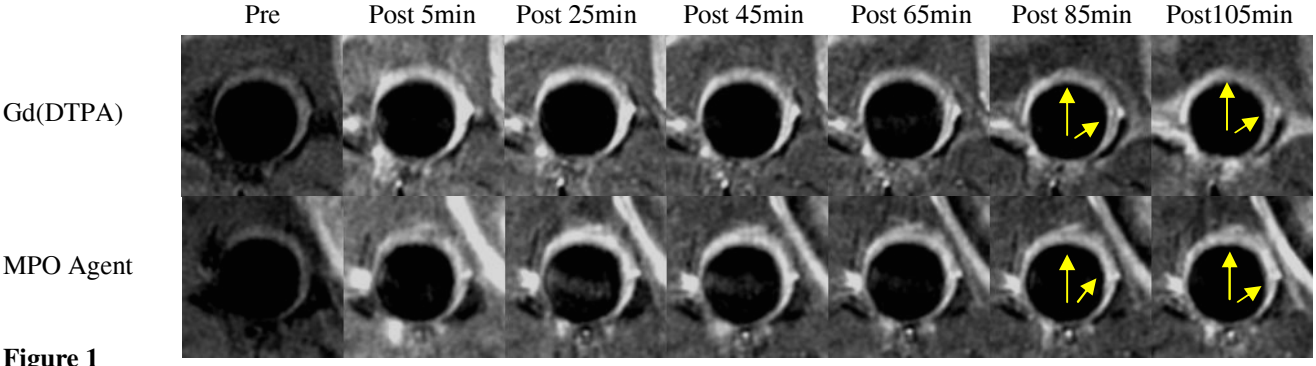

Figure 1

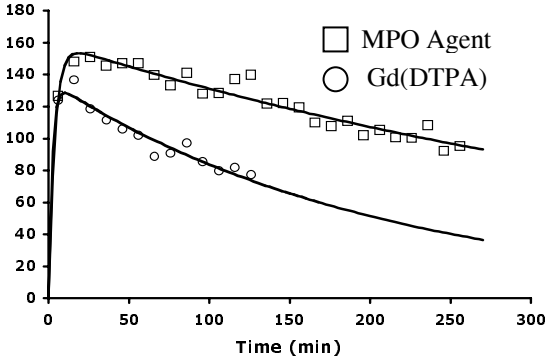

Figure 2

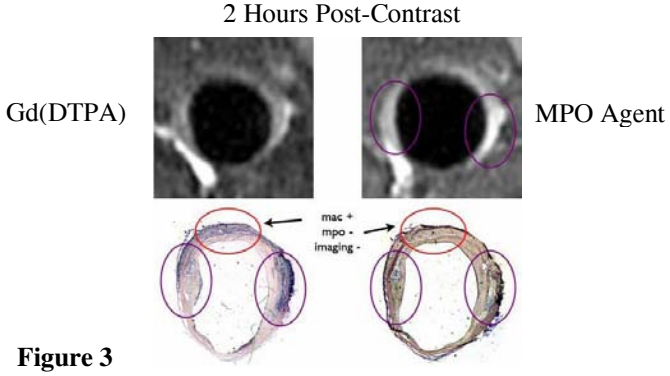

Figure 3

References/Acknowledgments: 1. Daley SJ, Klemp KF, Guyton JR, Rogers KA. Cholesterol-fed and casein- fed rabbit models of atherosclerosis. Part 2: Differing morphological severity of atherogenesis despite matched plasma cholesterol levels. Arterioscler Thromb 1994;14(1):105-141. The authors would like to thank the NIH, Canadian Institutes of Health Research, and the Heart and Stroke Foundation of Canada for grant funding.