Evaluating anti-inflammatory efficacy of pioglitazone in a rabbit model of atherosclerosis with multimodality imaging

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Introduction: Inflammation is a major contributor to atherosclerotic plaque instability and rupture.1 Pioglitazone, a PPAR-γ agonist, has been shown to delay atherosclerosis progression in mouse models and increase cardiovascular disease survival rates in high-risk human populations.2 Pioglitazone displays positive effects through its anti-inflammatory properties, promotion of reversal cholesterol transport, and lipoprotein profile influence.2 In this study we used a multimodal imaging approach including dynamic contrast enhanced (DCE) MRI and F18 fluorodeoxyglucose (FDG) PET/CT to monitor inflammatory changes of plaque in an atherosclerotic rabbit model3 during and after pioglitazone treatment. Histological analysis of matched aortic sections validated imaging results in order to accurately evaluate therapeutic efficacy.

Methods: Atherosclerosis was induced in 13 New Zealand White (NZW) rabbits with high cholesterol diet and abdominal aortic double balloon injury. Rabbits underwent baseline DCE-MRI, multicontrast (T1, T2, and PD) MRI, and FDG PET/CT 4 weeks following second balloon injury (plaque age = 4 months). Animals were then divided into a control (n=7) and treatment group (n=6). Both groups maintained a high cholesterol diet and the treatment group received 10 mg/kg pioglitazone admixed to diet. DCE-MRI, multicontrast MRI, and FDG PET/CT were again performed after one and three months (Figure 1, 2). DCE-MRI images were analyzed by calculating the area under the signal intensity versus time curve (AUC) of the contrast agent uptake in atherosclerotic plaque. PET/CT images were analyzed by calculating the standard uptake value (SUV) of F18 FDG in aortic sections directly inferior to the left renal bifurcation (0-5 cm) three hours after injection. Both groups were sacrificed after three months and immuno-histochemistry was performed on a 5 cm length of abdominal aorta using macrophage specific RAM11 and ApoB specific MB47 antibodies.

Results: Three months after pioglitazone treatment, DCE-MRI showed a significant reduction in AUC values compared to baseline (p =0.045, Figure 3a) while controls exhibited no difference (p=0.83, Figure 3a). FDG PET/CT showed similar SUVs between control and treated animals at baseline (p=0.97, Figure 3b) and lower SUVs between groups at one month (p=0.010, Figure 3b) and three months (p=0.0025, Figure 3b). Immuno-histochemistry showed decreased LDL plaque density in the treated group as compared to controls (p=0.062) and a significant decrease in macrophage density (p=0.046). No significant change in vessel wall area was detected with multicontrast MRI from baseline to three months in the control group (p=0.48) or treatment group (p=0.77).

Conclusion: In this study we showed the ability of DCE-MRI to detect a decrease in vessel wall inflammation after three months of pioglitazone treatment. Positive changes were also observed with FDG PET/CT. These results were validated with macrophage-targeted immuno-histochemistry, indicating therapeutic efficacy of pioglitazone after three months of treatment in a balloon-injured atherosclerotic rabbit model. This multimodality imaging approach could represent a non-invasive technique for future (pre)clinical cardiovascular drug efficacy evaluation.