Monitoring statin therapy in atherosclerotic rabbits using USPIO-enhanced MRI and FDG-PET on a new PET/MRI system

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Introduction: Rupture of atherosclerotic plaques may trigger clinical events like myocardial infarction or stroke. Macrophages are inflammatory cells that have been demonstrated to play a critical role in plaque formation and contribute to plaque instability/rupture. Thus, visualization of the macrophage burden could be a beneficial tool to monitor the efficacy of therapeutic interventions. Fluorodeoxyglucose positron emission tomography (FDG-PET) and contrast-enhanced magnetic resonance imaging (MRI) are two imaging techniques that have shown potential in visualizing the inflammation/macrophage burden in atherosclerotic plaques via uptake of FDG and ultra-small superparamagnetic iron oxide (USPIO) respectively (1). Recently, Phillips introduced a PET/MRI hybrid system that allows sequential in vivo acquisition of PET and MRI scans. It permits the fusion of these complementary modalities with MRI providing superior soft-tissue contrast and high spatial resolution, while PET offers high sensitivity. In the current study, we aim to monitor the effects of statins, a lipid-lowering therapy proven to diminish the inflammation burden, in atherosclerotic rabbits using PET/MRI. A newly developed USPIO (P904, Guerbet, France) will be used to obtain contrast-enhanced MR images of the inflammation burden of atherosclerotic plaques while FDG-PET/MRI will be used to assess their macrophage metabolic activity.

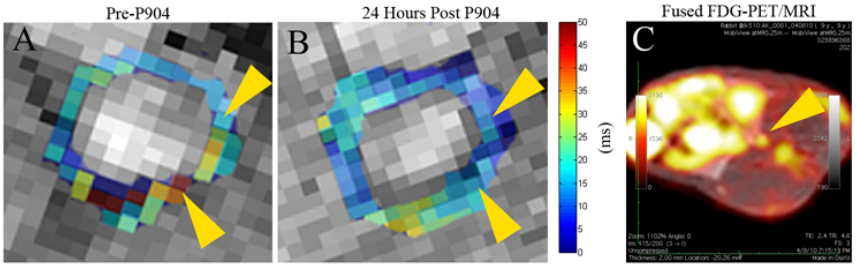
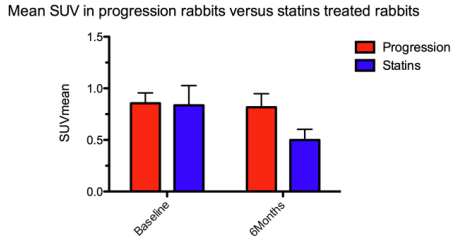


Figure1 A-B T2* maps calculated in the aortic wall at baseline before and after injection of USPIO. **C -** Fused FDG-PET/MRI showing increased FDG uptake in the corresponding slice.

Methods: Atherosclerotic plaques were induced in rabbits as previously described (2). All the animals underwent USPIO contrast enhanced MRI and FDG-PET/MRI at baseline and were divided in a control (n=3) and treatment group (n=4). The control group maintained a high cholesterol diet while the treatment group received 90 mg/kg atorvastatin mixed with a regular chow diet. Both group were scanned again 6 months after plaque induction. The imaging protocol included a 3T MRI of the abdominal aorta prior and 24 hours after P904 injection (50 µmol Fe/kg, both groups). We applied a high-resolution gradient echo T2*-weighted sequence (T2*-w) with 16 echo times (TE) ranging from 4.8 ms to 38.5 ms. FDG-PET/MRI was performed immediately before the 24h post-P904 MRI. After the last imaging time point, animals were sacrificed for immunohistochemistry. T2*-maps were generated in the aortic wall using a Matlab. R2* values (R2*=1/T2*) were calculated and averaged in the vessel wall over the entire aorta after P904 injection and were compared at baseline and at 6 months in both the progression and statin group. PET/MRI data were analyzed by measuring and averaging the mean SUV over the entire abdominal aorta and compared between both groups.

A



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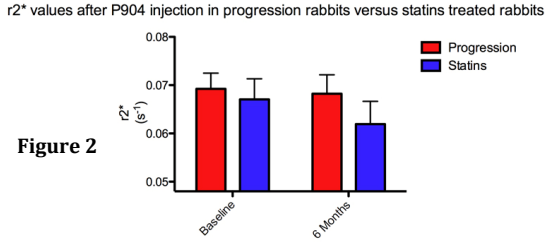

Figure 2

Results: At baseline, P904 injection induced a strong darkening of the vessel wall area compared to pre-injection imaging. An increase in the R2* average values confirmed these observation with values increasing from 0.041±0.001 s^{-1} pre-P904 to 0.067 s^{-1}±0.004 post-P904 in the statin group and 0.047±0.006 s^{-1} to 0.069±0.006 s^{-1} in progression animals. This increase reflects a shortening in T2* relaxation times due to the presence of iron in the vessel wall area (Figure 1A, B). FDG-PET/MRI performed at baseline revealed a strong uptake of FDG in the abdominal aorta (Figure 1C). At 6 months, mean SUV values measured in the statin group showed less FDG uptake in the abdominal aorta with a mean SUV value 36% decreased compared to baseline (Figure 2A). In comparison, the progression group showed a similar mean SUV compared to baseline ($p<0.05$). These findings are consistent with previously published studies (3,4) and reflect a decrease of macrophage metabolic activity in plaques after statin treatment. Although not significant, R2* values calculated after the injection of P904 at 6 months showed a similar decreasing trend (Figure 2B), suggesting less iron uptake in the aortic wall of statin treated animals. Further analysis and more animals will be included to improve the power of the study and achieve statistical difference.

Conclusion: This study describes the use of FDG-PET/MRI and USPIO-enhanced MRI to monitor the effects of statin therapy in atherosclerotic rabbits. FDG/PET and USPIO MRI on a combined PET/MRI system allow the (semi)-quantitative evaluation of plaque inflammation.

(1) Tang et al. J Am Coll Cardiol. 2009. (2) Sirol et al. Circ. 2009. (3) Rudd et al. Circ. 2002. (4) Sakalihasan et al. Eur J Vasc Endovasc Surg. 2002.