Correlation between plaque neovascularization, 18 FDG-PET plaque uptake and dynamic contrast enhanced MRI perfusion parameters in a rabbit model of atherosclerosis

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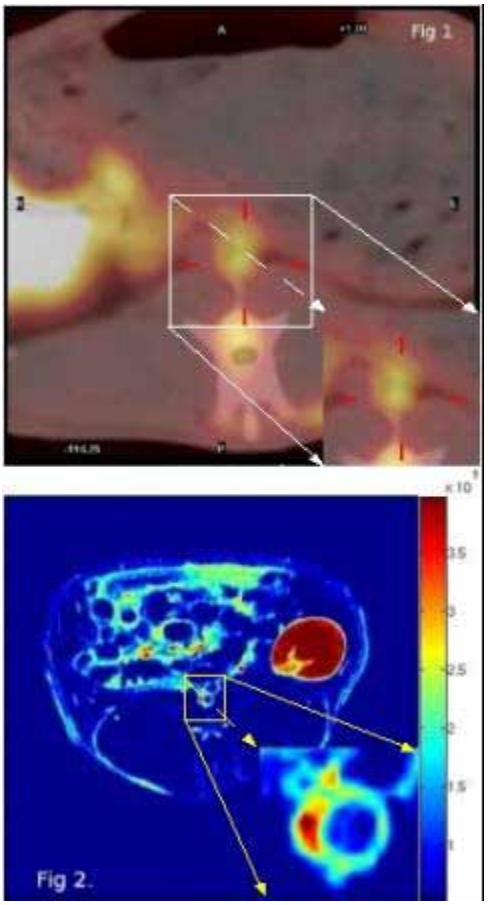
Introduction: High-risk atherosclerotic plaques can be defined as lesions with a high level of inflammation and increased neovascularization [1]. Both those features could thus be measured as markers of high risk disease. The activation of macrophages in high-risk plaques has been previously correlated to the vessel wall uptake of fluorine 18 fluorodeoxyglucose (18F FDG), a non metabolized glucose analog which accumulates in the cell in proportion to metabolic activity. Recent reports have shown that FDG positron emission tomography (PET) can quantify plaque inflammation in rabbits and humans. Additionally, studies have indicated that parameters of atherosclerotic plaque perfusion (such as blood volume, blood flow and Ktrans) may be evaluated by Dynamic Contrast Enhanced (DCE) MRI. These studies show that blood volume values obtained by DCE-MRI correlates with plaque neovessel density [2-3] as evaluated by antiCD31 antibody staining in histological sections. In this study we aim to assess the correlation between DCE MRI and neovessel count and to compare it to the correlation between neovessel count and 18FDG uptake evaluated with PET in the aorta of atherosclerotic New Zealand White rabbits.



Methods: *Atherosclerosis Induction:* 11 New Zealand White rabbits 3-4 months old were fed an atherogenic diet for 5 weeks (1% cholesterol, 6% peanut oil) and then shifted to a normal-chow diet for 8 weeks. After the first week, lesion formation was accelerated in the abdominal aorta by baloon-induced injury using a 4F Fogarty embolectomy catheter. *MR Imaging*: 6 animals were imaged approximately 14 weeks after diet initiation in a 1.5 T clinical system (Siemens, Sonata) after sedation with Ketamine/Xylazine. To allow for plaque characterization, we performed DCE-MRI with a Black Blood TSE sequence (TE = 5.6, TR = 250, slice thickness=3mm, time resolution = 4.8s, number of images=150). After the 5th image, 0.2 mmol/Kg of Gd-DTPA were injected at a rate of 2mL/s followed by saline flush. *PET data acquisition:* 5 rabbits were imaged on a combined GE Lightspeed scanner. Images were acquired 3 hours after FDG injection (1mCi/Kg) in 2D mode, in a single bed position (FOV 15.5cm), over 15 minutes. Images were reconstructed using OSEM algorithm, and analysed on the GE Xeleris workstation. Plaque FDG SUV values were estimated by drawing ROI around the artery wall using the combined PET/CT dataset. Fig 1 shows one representative PET/CT image of the aorta of one animal. *Histological analysis:* Following MRI, rabbits were euthanized by saline perfusion. Aortas were excised, fixed in 4 % Para formaldehyde and embedded in paraffin. 5-µm-thick slices were sectioned and stained with hematoxylin-eosin. An additional section from each location was stained with antiCD31 antibody for neovessels identification. Using a magnification of X40, neovessels were identified in plaque and adventitia; plaque and total neovessels density were calculated. *DCE-MRI Parameters*: Semi-quantitative pixel-by-pixel maps of Blood Volume (BV) were calculated. BV was calculated as the area under the signal intensity versus time curve (AUC). Fig 2 shows a representative pixel-by-pixel BV map of one rabbit; BV values are represented in absolute units. A single region of interest covering the entire plaque was selected. Average values of BV in the ROI were extracted and correlated to plaque, adventitia and total neovessel counts using Pearson's test.(See Table 1)

Results: Statistical analyses showed positive correlation between the number of plaque neovessels and blood volume calculated by analysis of DCE-MRI acquisitions. The correlation between blood volume and plaque neovessels was significant (P< 0.05; R = 0.858). Moreover, blood volume positively correlated with the total neovessel count (R=0.8, p=0.56). No correlation was observed between the DCE-MRI parameters and the neovessel count in the adventitia [see Table 1]. Additionally, statistical analyses showed positive correlation between 18FDG-PET uptake and both plaque and total neovessel count. No correlation between FDG uptake and neovessel count of the adventitia was observed.

Conclusions: The correlation found in this study between perfusion parameters extracted from DCE-MRI and neovessels count in plaques confirms that this technique is able to assess the extent of neovascularization in atherosclerotic plaques. Furthermore, the positive correlation between neovessel count and 18FDG uptake in the plaque strengthen the hypothesis that MRI may be a valuable instrument in assessing the inflammatory burden of the atherosclerotic lesion and, more broadly, in the evaluation of plaque vulnerability.

References:

1. Moreno et al, *Radiology. 2005 Oct;237(1):181-8.*);
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3. Kerwin W et al, I *Radiology. 2006*

Table 1

	Neovessels in Plaque	Neovessels in Adventitia	Total Neovessels
BV (d.f.=5)	**R=0.858 (p=0.029)**	R = 0.186 (p=0.724)	R = 0.8 (p=0.056)
18-FDG (d.f. = 27)	**R = 0.5051(p=0.006)**	R = 0.3401(p=0.077)	**R = 0.5217(p=0.004)**