Qualitative and quantitative estimation of high risk atherosclerotic plaques in WHHL animals with Gadofluorine M – enhanced MRI at 3T

H. Ittrich[1], A. N. Priest[1], T. Nielsen[2], T. Schaeffter[2], C. Weber[1], B. Misselwitz[3], H-J. Weinmann[3], G. Adam[1]

[1]Department of Diagnostic and Interventional Radiology, University Hospital Hamburg Eppendorf, Hamburg, Germany, [2]Philips Research Laboratories Hamburg, Hamburg, Germany, [3]CRBA Diagnostics & Radiopharmaceuticals, MRI and X-Ray Research, Schering AG, Berlin, Germany

Introduction

Early stages of atherosclerosis without luminal stenosis cannot be detected with angiographic techniques like conventional, computed tomography (CT) or magnetic resonance (MR) angiography, because these early stages of atherosclerotic plaques are a process within the vessel wall. Complications of these unstable, vulnerable and high risk plaques are plaque rupture, local thrombus-formation and acute arterial occlusion, which lead to severe clinical events, like stroke, myocardial infarction or acute peripheral occlusion. The risk of such an event is more correlated to the composition of the plaques than to the degree of luminal stenosis. Therefore techniques are needed which are able to characterize the components of the arterial wall and the composition of atherosclerotic plaques [1]. Encouraging results in MR Imaging of the vessel wall have forced the interest in development new techniques for detection of early stages in atherosclerosis [2-4]. Enhancement of lipid plaques using high doses (100 µmol) of Gadofluorine M (GdF, Schering AG, Germany) has been shown in previous studies [5,6], however toxicity for a future administration in humans increases with dosage.
The purpose of this study was to detect the lowest plaque-enhancing concentration as well as to quantify the uptake of Gadofluorine M in atherosclerotic plaques of the aorta using Look-Locker (LL) measurements in an animal model using a 3T clinical MR scanner.

Material and Methods

The aortic arch of 12 Watanabe heritable hyperlipidemic (WHHL) rabbits (ages 16 to 28 months) and 8 New Zealand White (NZW) rabbits (control, age 16 months) was scanned before (baseline), immediately and 24 after administration of GdF (4 groups, injection dosages of 100, 50, 25, 12.5 µmol GdF/kg body weight) in a 3 Tesla clinical MRI scanner (Philips Intera) by using an 6-channel head array coil. MR Angiographies, 3D Inversion Recovery (IR)-TurboFLASH and T1 relaxation measurements were performed. Acquisition parameters for the 3D MRA were TR/TE 5.6/2.1 ms, flip angle 25°, acquisition matrix 256×179×70, 12 NSA, effective voxel volume: 0.7×0.7×0.7mm^3, for the 3D IR-TurboFLASH sequence TR/TE=7.2/2.2 ms, TI 120 ms, flip angle 20°, acquisition matrix 256×195×19, effective voxel volume: 0.55×0.72×1.6mm^3, shot repetition time 300 ms, 15 excitations per shot, 6 NSA and for the T1 relaxation measurements (Look-Locker sequence) TR/TE 8.7/4.6, FA 10°, TFE factor 8, 16 images, NSA 6, resolution 0.63×0.63×3.0mm^3, which all covered the aortic arch. We investigated the luminal diameters and the qualitative and quantitative uptake of GdF in aortic wall. SNR measurements before and after administration of contrast agent (GdF) were performed using ImageJ (NIH). T1 relaxation data analyses were performed using a software tool (RelaxFit, Philips Research Laboratories Hamburg, Germany). After euthanasia histological correlations (HE, macrophages antibody RAM11) were performed and matched with MRI images. Statistical differences between WHHL and NZW groups were test by Student's t-test.

Results

In all animals (WHHL/NZW) the luminal diameters of the aortic arch showed no significant differences or severe stenosis ($p>0.05$). Enhancement of the aortic wall 24h after administration of Gadofluorine could be detected in all WHHL rabbits of the 100, 50 and 25 µmol group (*Fig. 1, 2*) with significant differences of SNR before and after GdF application ($p<0.05$). No significant uptake could be shown in WHHL rabbits of the 12.5 µmol group and in all animals of the NZW group. Histological cross sections showed a strong correlation between the bright, contrast-enhanced regions in the aorta of WHHL animals in MRI and the prominent, lipid-rich plaques within the aortic wall. Corresponding to the missing aortic enhancement in the NZW control animals a histologically normal layering of the aorta was observed, without wall thickening (*Fig. 3*).

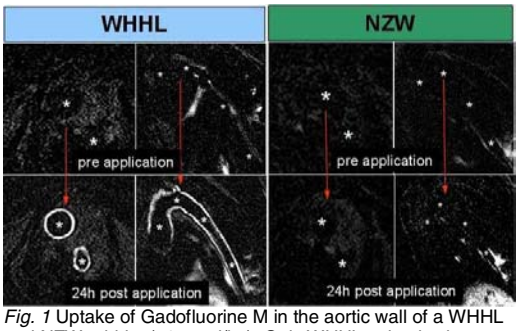

Fig. 1 Uptake of Gadofluorine M in the aortic wall of a WHHL and NZW rabbits (50 µmol/kg). Only WHHL animals show an accumulation of GdF in aortal plaque formations.
(* vessel lumen of aorta)

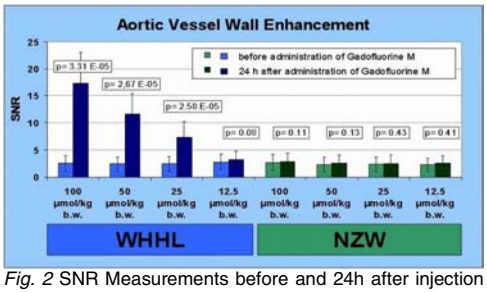

Fig. 2 SNR Measurements before and 24h after injection of GdF demonstrate a significant enhancement of the aortic wall (SNR increase) in WHHL animals of the 100, 50 and 25 µmol group in contrast to the 12.5 µmol WHHL group and all NZW animals without significant SNR changes ($p>0.05$)

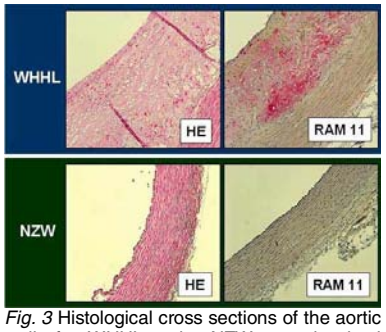

Fig. 3 Histological cross sections of the aortic wall of a WHHL and a NZW control animal with prominent thickening of the intimal layer in WHHL animals

Post-administration in-vivo measurements of R1 [×10^{-3}, in 1/s] in histologically proven (HE, RAM11) inflammatory plaques of WHHL animals correlate strongly with administered GdF dose (100µmol: 1.11/5.88 [ba/pa]; 50µmol: 1.25/3.45; 25µmol: 1.43/2.22; 12.5µmol: 1.25/2.00;R^2=0.9924, *Fig. 4*). No significant R1 changes were measured in NZW controls, suggesting no uptake of GdF, consistent with the absence of plaque formations and macrophages. Relaxivity of GdF in saline was estimated to be 13.5l/mmol×sec^{-1}.

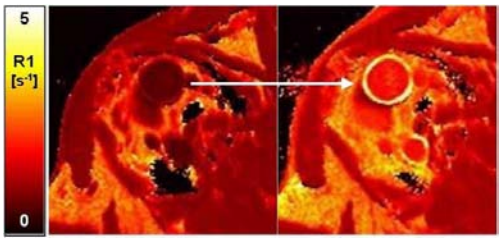

Fig. 4 Example of a R1 measurement within the aortic wall (100 µmol/kg b.w.) demonstrate a significant increase of R1 24h after injection of GdF. R1 correlated linear to GdF application dose (R^2=0.9924).

Discussion and Conclusions

Gadofluorine-enhanced MRI improves detection of early stages in atherosclerosis. In MRI at 3T early, nonstenotic atherosclerotic plaques can be visualized using low dose administration of Gadofluorine M. The Look-Locker sequence allows a quantitative determination of R1 which could be used to estimate of GdF uptake in high risk atherosclerotic plaques. This technique holds promise for detection of initial stages, longitudinal evaluation of plaque progression and monitoring of pharmaceutical therapy in clinical practise.

References

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