

## Detection of Atherosclerotic plaques in the Aortic Arch using Lipid-based Contrast Agents

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**Introduction:** Atherosclerosis is the main cause of morbidity and mortality in Western societies; however it is usually not identified until a clinical event such as myocardial infarction or stroke occurs. Several MRI studies have shown that atherosclerosis can be successfully assessed both in humans and animal models, yet it remains challenging to discriminate intimal thickening and plaque burden in areas with moving structures like the aortic arch. In the present study we aim to 1) detect and quantify atherosclerotic plaques and 2) determine the optimal time curve for *in vivo* visualization of atherosclerotic in the aortic arch of ApolipoproteinE deficient (ApoE<sup>-/-</sup>) mice, using lipid-based MR contrast agents compared to a conventional contrast agent with retrospectively gated cine MRI.

**Methods:** Meglumine gadoterate (Dotarem®, Guerbet), gadolinium (Gd)-containing NIR<sub>664</sub>-conjugated micelles and liposomes were applied in 3 groups (n=5 per group) of male ApoE<sup>-/-</sup> mice. Mice were imaged with a vertical 9.4T, 89-mm bore Bruker MRI system with a shielded gradient set (1T/m).

Aortic arch of mice were imaged at baseline and 6-12 hour intervals for 6 days following intravenous injection of Dotarem, micelles or liposomes, using equivalent doses of Gd (50 µmol/kg). Using IntraGate software, retrospectively gated cine-FLASH images with 10 cardiac frames were obtained: 6 cross-sectional slices (TR 31 ms/ TE 2.9 ms, NA 400, MTX 128\*128, FOV 18\*18, hermite pulse FA 15°, slice 0.4 mm, res. 141 µm/pixel ).

Immunohistochemistry and confocal microscopy were performed to co-localize and correlate contrast agents with atherosclerotic plaques.

**Results:** Heterogeneous CE in the aortic wall was observed within 6 hours after Dotarem injection. Both micell- and liposome-injected mice, however, showed a bi-phasic CE, with a first, dispersed, peak in contrast-to-noise-ratio (CNR) ± 12 hours after injection. A 2<sup>nd</sup> wave of more focal CE was observed with peak CNR around 60-72 hours (figure 1). Relaxivity measurement of plasma suggests organ retention of micelles and liposomes, and release in the blood ~ 1.5 days post injection. Histological examination demonstrated a topological correlation between the site of MRI enhancement and atherosclerotic plaques. MR signal intensity in the second CE wave after liposome and micell injection was predictive for plaque volume, which was not observed for Dotarem.

**Conclusion:** Retrospective gated imaging of the aortic arch allows visualization of atherosclerotic plaques in mice. Kinetics of contrast enhancement indicates lipid-based contrast agents have a complex biodistribution. Based on our results we suggest that different animal models and contrast agents require longitudinal follow-up to determine the optimal imaging moment, as the standard 24h interval was not suitable in our animal model.

**Figure 1.**

