High Resolution In Vivo Magnetic Resonance Imaging and Image Quantitation of the Progression of the Murine Aortic Atherosclerotic Plaque

H. Tang[1], H. Liu[1], S. E. Rex_Rabe[2], R. Rosa[2], C. Miller[1], D. S. Williams[1], L. Peterson[2], R. Hargreaves[1]

[1]Imaging, Merck Research Laboratories, Rahway, NJ, United States, [2]Pharmacology, Merck Research Laboratories, Rahway, NJ, United States

Introduction

MRI is becoming an important imaging modality for detecting and characterizing atherosclerosis because of its non-invasive and high-resolution capability [1]. *In vivo* serial measurements of atherosclerosis with MRI could reduce the number of animals and permit tracking changes in lesion size, therefore facilitating disease progression and regression studies [2]. Atherosclerotic plaque detection requires imaging protocols with high spatial resolution and high contrast-to-noise ratio. Our purpose was to establish a high resolution *in vivo* MRI technique for the evaluation and quantitation of the progression of atherosclerosis in a transgenic mouse model based on Ldlr null.

Methods

All experiments were approved by the Institutional Animal Care and Use Committee. The Ldlr knockout mice were fed a 0.15% cholesterol-containing Western diet to induce atherosclerosis at 8 weeks of age, and imaged after 2-months diet (n=6) and 6-months diet (n=6) in comparison with wild type control mice fed normal chow (n=2). MRI was performed on a Bruker Biospin 500WB spectrometer (Bruker NMR, Inc., Billerica, MA) with an 89 mm vertical bore magnet of 11.7 T and a shielded gradient system up to 100 G/cm. Mice were anesthetized with 1.5% isoflurane/O_2 gas mixture during imaging scan within a birdcage coil of 25-mm ID. A cardiac triggered 64-slice T1-weighted 3D-FSE sequence with fat saturation and sufficient blood flow suppression was implemented to allow detecton of plaque in aortic root (AR), aortic arch (AA), innominate artery (IA), right carotid artery (RC), left carotid artery (LC), and left subclavian (LS). A three-slice FSE sequence (ECG trigger at each slice) was employed to acquire high resolution cross-sectional images of aortic arch. Images were acquired with an in-plane resolution 50μm×100μm, and through-plane resolution 300μm. The FSE RARE factor was 2. Paramagnetic contrast agent Gd-DTPA (Gadopentetate Dimeglumine) was injected IP (0.4ml, 2mM/kg) to the mice to enhance the plaque contrast, increase the image SNR, and improve MRI plaque detection sensitivity.

Results

Figure 1 (a) shows high resolution image of the AR, AA, IA, RC, and LC arteries. Figures 1 (b-c) and (e) show the typical high resolution cross sectional images of AA and AR of a mouse with plaque burden after 6 months on Western diet. In comparison, figures 1 (d) and (f) show the AA and AR images of a mouse after 2 months on the Western diet. Atherosclerotic plaques indicated by red arrows were seen in the aortic wall, appearing brighter than the surrounding tissues. MRI 3-dimensional (3D) plaque visualizations (fig. 1 (g) and (i)) were comparable to that of the same mice seen by conventional microscopy (fig. 1 (h) and (j)). The maximum aortic arch wall thickness (mm), total plaque volume (mm^3) in aortic area, and 3D visualization of aortic plaques were obtained using in-house developed software tools containing interactive segmentation, image quantification, and 3D reconstruction functions. High resolution MRI allows 3D visualization of atherosclerotic plaque from different orientations. No plaques were seen from the MRI of the control mice (aortic arch wall thickness: 0.06mm). Significant plaque progressions were seen in the 6-month diet group (0.27±0.017mm, 7.76±1.28 mm^3), and plaque could be detected in aortic root in the 2-month diet group (0.15±0.018mm, 2.27±0.49mm^3).

Conclusions and discussions

The study of plaque progression by MRI at monthly intervals from 1-6 months is ongoing, and studies defining aortic cholesterol and cholesterol ester content, microscopic open-chest plaque visualization, and histology are now being conducted to further validate the imaging measurements. The current high resolution *in vivo* MRI protocol measuring plaque progression in small experimental animal models of atherosclerosis may help in the discovery of novel therapeutics that slow or reverse disease and uses a technology that is directly applicable to the clinic. In the future, a selective plaque specific contrast agent that targets plaque in smaller vessels could improve early lesion detection [3].

Reference 1. Weismann F, Szimtenings M, et al., Magn Reson Med 50:69-74, 2003. 2. Trogan E, Fayad ZA, et al., Arterioscler Thromb Vasc Biol. 24:1714-1719, 2004. 3. Choudhury RP, Fuster V. et al., Arterioscler Thromb Vasc Biol. 22:1065-1074, 2002.

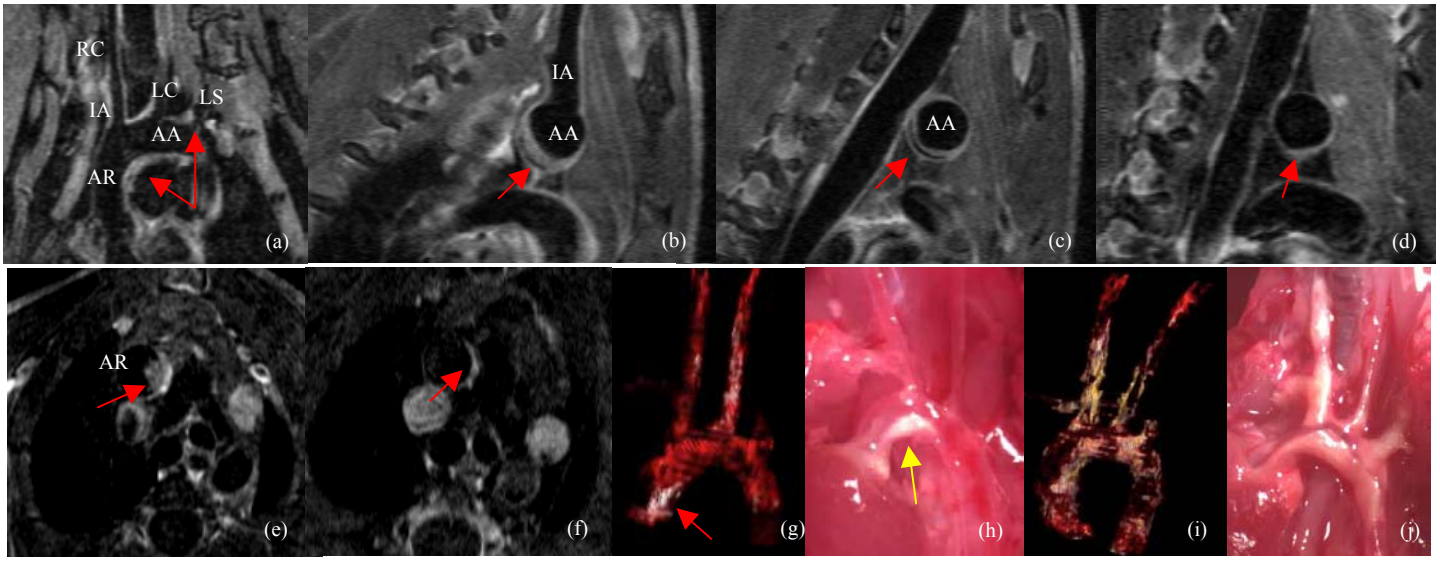

Figure 1. High resolution aortic images. (a) MR image of AR, AA, IA, RC, and LC arteries; (b) High resolution images of AA and IA; (c) AA of a 6-month diet mouse; (d) AA of a 2-month diet mouse; (e) AA of a 6-month diet mouse; (f) AR of a 2-month diet mouse; (g) 3D MRI plaque reconstruction of a 2-month diet mouse; (h) Microscopic plaque visualization of (g); (i) 3D MRI plaque reconstruction of a 6-month diet mouse; (j) Microscopic plaque visualization of (i).