High Resolution MRI of Experimental Atherogenesis: Quantitative Analysis of Vessel Wall Traits Over Time

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Introduction

Atherosclerosis is the underlying cause of both heart disease and stroke. It is defined as the formation of lipid-filled inflammatory lesions in the arteries of vascular system that can narrow the lumen of these arteries and decrease blood flow to downstream tissues. Animal studies designed to follow the progression of atherosclerotic lesion formation have traditionally involved the use of techniques that require animal sacrifice, followed by microscopic evaluation of histological sections. This limits the data collected from any one animal to a single time point. The use of magnetic resonance (MR) imaging, a non-invasive, non-destructive modality with excellent soft tissue contrast, to image the growth of lesions over time has been suggested as an alternative to traditional ways; however, imaging lesion growth over time in rabbit aortae with experimental atherosclerosis has previously been limited by spatial resolution and significant motion. Here we report on a system capable of imaging both the abdominal and thoracic aorta in a relevant model of atherosclerosis at a spatial resolution sufficient to see lesion growth at relatively short (2 months) intervals of time.

Methods

New Zealand White rabbits (n=6) were fed a cholesterol-supplemented (0.25%) diet for 20 months to promote the formation of human-type atherosclerotic lesions. Control rabbits (n=3) were fed a cholesterol free diet. Rabbits were imaged using a 1.5T CV/i GE MR scanner and a customized two-channel phased array RF coil at 12, 14, 16, 18 and 20 months. At each time point 48 contiguous T2-weighted "black-blood" fast-spin-echo (FSE) (TR/TE ~3000/60ms, ETL 5, BW 10 kHz, scan time ~ 20 mins for 10 NEX at 200µm in-plane resolution and 2 mm slice thickness) axial images of the aorta were acquired. Manual tracing of inner and outer vessel wall boundary was used to assess lumen, outer vessel wall/lumen and vessel wall area. Intraobserver variability of the tracing method was assessed using tracings of the same 20 randomly selected sections at two separate time points 6 weeks apart. Data is reported as least square mean value (averages adjusted for all covariates within the system) comparisons of control versus cholesterol-fed rabbits.

Results

Lumen area was significantly lower in cholesterol-fed vs chow-fed rabbits at all time points. It remained fairly static with time in chow-fed rabbits, with a difference only at the 18 month compared to the 12 month time point. In contrast, lumen area was significantly lower than 12 month baseline for all time points in cholesterol-fed rabbits. Outer vessel wall area was significantly lower in cholesterol-fed vs chow-fed rabbits towards the end of the dietary period. It was significantly larger than baseline in chow-fed at the 18 and 20 month time points compared to the 12 month time point. In contrast, outer vessel wall area was significantly lower than baseline in cholesterol-fed rabbits at the 18 month time points compared to the 12 month time point. Vessel wall area was significantly higher in cholesterol-fed vs chow-fed rabbits at all time points. Vessel wall area remained static with time in chow-fed rabbits, with no difference over the time course of the study. In contrast, vessel wall area is significantly higher than 12 month baseline for all time points in cholesterol-fed rabbits (Figure 1 and 2). In addition, lesion burden and growth rate tended to be greatest in the thoracic aorta, indicating the importance of imaging this portion of the aorta. Correlative values for intraobserver variability of tracings for lumen area, outer vessel wall/lumen area and vessel wall area were 0.97, 0.92, 0.86, respectively.

Discussion

High resolution MR imaging of rabbit thoracic aorta at relatively short intervals of time demonstrates significant differences in quantitative vessel wall traits associated with cholesterol- vs chow-feeding. Specifically, adjusted mean lumen area and outer vessel wall area are significantly lower, while adjusted mean vessel wall area was significantly higher in cholesterol-fed compared with chow-fed rabbits. The MR method used to quantify vessel wall morphology in rabbits can thus detect quantitative differences in vessel well traits related to cholesterol feeding. Our MR method showed excellent intra-observer correlation. Furthermore, we believe that the acquired image resolution will be sufficient to monitor changes in lesion composition over time. This robust dynamic system will be helpful for future studies of atherogenesis and/or intervention upon atherosclerosis in this animal model.

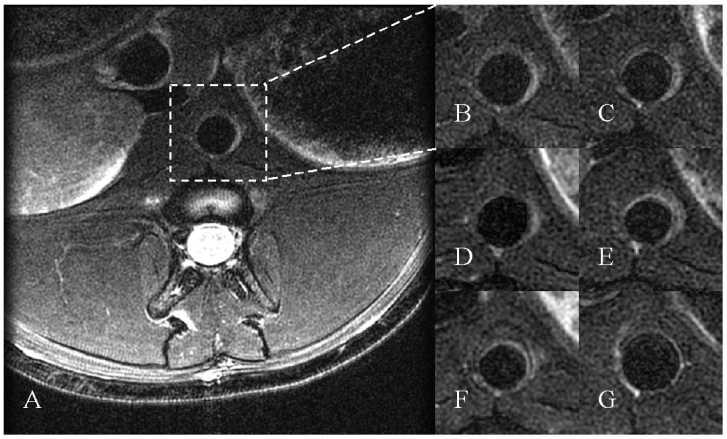

Figure 1: A) Axial T2-weighted "black blood" FSE image (in-plane resolution ~200 mm^2) of cholesterol fed rabbit at 20 months. B-F) Magnified view of aorta at 12, 14, 16, 18 and 20 months, respectively, showing an increase in vessel wall area and complexity over time. Note that vessel wall area was clearly less in control rabbits (G).

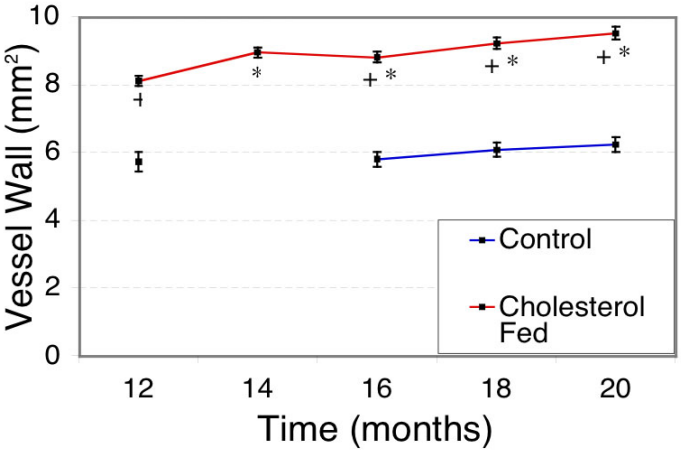

Figure 2: Least square mean comparisions of vessel wall area over an 8 month time period at 2-month intervals in cholesterol-fed versus control animals. Cholesterol-fed animals showed a significant increase in vessel wall area compared to control animals (+ $p<0.001$) and also showed continued growth of lesions over time compared to 12 month values (* $p<0.01$).