Rapid and Reproducible Measurement of Atherosclerotic Plaque Volume in Peripheral Arterial Disease by MRI

D. C. Isbell[1], C. H. Meyer[2], W. J. Rogers[3], F. H. Epstein[3], J. M. DiMaria[3], N. L. Harthun[4], H. Wang[5], C. M. Kramer[3]

[1]Medicine, University of Virginia Health System, Charlottesville, VA, United States, [2]Biomedical Engineering, University of Virginia Health System, Charlottesville, VA, United States, [3]Radiology, University of Virginia Health System, Charlottesville, VA, United States, [4]Surgery, University of Virginia Health System, Charlottesville, VA, United States, [5]Public Health Sciences, University of Virginia Health System, Charlottesville, VA, United States

Introduction. Peripheral arterial disease (PAD) is an increasingly common condition characterized by atherosclerotic obstruction of the arteries supplying the lower limbs. Although PAD is now recognized as an important manifestation of systemic atherosclerosis, it remains underdiagnosed and undertreated. The ankle-brachial index (ABI) is an excellent test for identifying peripheral arterial obstruction, but limited in its utility for assessing disease severity and predicting clinical events. Direct measurement of plaque and peripheral arterial remodeling may be better suited for defining disease burden and predicting clinical progression. Because of the inherent limitations of lumenographic techniques in evaluating and assessing the extent of atheroma, novel approaches for directly evaluating the vessel wall are needed. MRI could be an ideal approach for the noninvasive assessment of atherosclerotic plaque burden in the peripheral circulation. While MRI has been used for measuring and characterizing plaque in the coronary, carotid, and aortic circulations, few studies have rigorously investigated its role in PAD. The goal of this study was to develop and refine a practical technique for quantifying plaque in the superficial femoral artery (SFA) of patients with mild to moderate PAD that would allow for determination of plaque burden and noninvasive, serial monitoring of plaque progression in patients treated with both established and novel therapies.

Methods.

Study Population. Patients between 30-85 years with symptoms of intermittent claudication without critical limb ischemia and an ankle-brachial index (ABI) between 0.4 and 0.9 were eligible. All were placed supine in a 1.5T Siemens scanner with the calf at the isocenter of the magnet. A custom-built flexible, linear four-element (10 cm x 10cm square element) surface coil array (Nova Medical, Wilmington, MA) was placed over the thigh and SFA. A multi-slice turbo-spin-echo pulse sequence with fat presaturation was used. Flowing blood was suppressed using a combination of periodic excitation of upstream slices and spatial presaturation slabs. Additional flow suppression for downstream slices was provided by the imaging excitations themselves, so that blood was suppressed throughout the multislice data set. Other imaging parameters included: repetition time 715ms, echo time 7.6ms, echo spacing 7.5ms, turbo factor 9, voxel size 0.5 x 0.5 x 3mm, 3mm gap between slices, 4 signal averages, and scan time 1minute 23 seconds, with interleaved image sets used to cover the length of the SFA. Imaging began above the femoral bifurcation and continued through the adductor canal. Contiguous images of the SFA are shown in **Figure 1.**

Image Analysis. A total of 20 patients were imaged and 14 had image quality suitable for analysis. In 4 of the 6 excluded data sets, complete occlusion of the SFA precluded analysis. In 2 subject, obesity led to poor image quality. In the 14 patients with adequate image quality, atherosclerotic plaque volume (APV) of the SFA was contoured by two independent operators using VesselMASS software (University of Leiden). For each individual slice, both the luminal and adventitial borders were manually delineated and cross-sectional area (CSA) of the vessel wall measured. Total vessel volume was calculated as $\text{Volume} = \sum_{i=1}^{n} \text{CSA}_i \times H$ where H is the slice thickness and n the number of slices in the 3-D data set. Volume measurements were initiated at the bifurcation of the common femoral artery and total vessel distance covered for each analysis was predefined. Nine patients returned (at a mean of 45 ± 60 days) for evaluation of test-retest reliability using anatomic landmarks and matched number of acquired slices. Imaging time was measured from acquisition of the first scouts to completion of the imaging protocol. *Statistical analysis.* Subject characteristics are summarized as mean ± standard deviation. The intraclass correlation coefficients of reliability were calculated for the interobserver, intraobserver, and reproducibility data using the output of analysis of variance from SAS statistical software (SAS 9.0, Cary, NC). Reproducibility and both inter- and intraobserver variability were analyzed using the method of Bland and Altman. MedCalc software (version 8.1.0.0) was used to generate Bland-Altman plots. Using the test-retest reliability obtained, we estimated the sample sizes needed to detect the true difference between the means of APV with 80% power. Assuming a two-tailed test, a significant level of 0.05, and using the estimated standard deviation, the sample sizes needed to detect the true mean differences ranging from 1% to 5% of the mean APV were calculated.

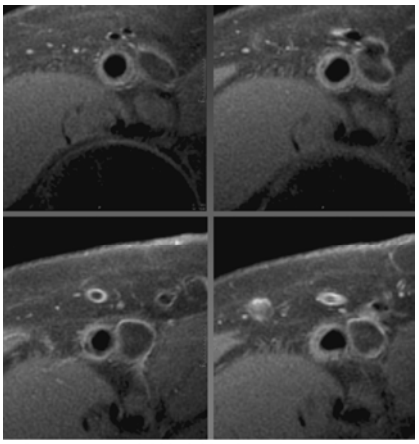
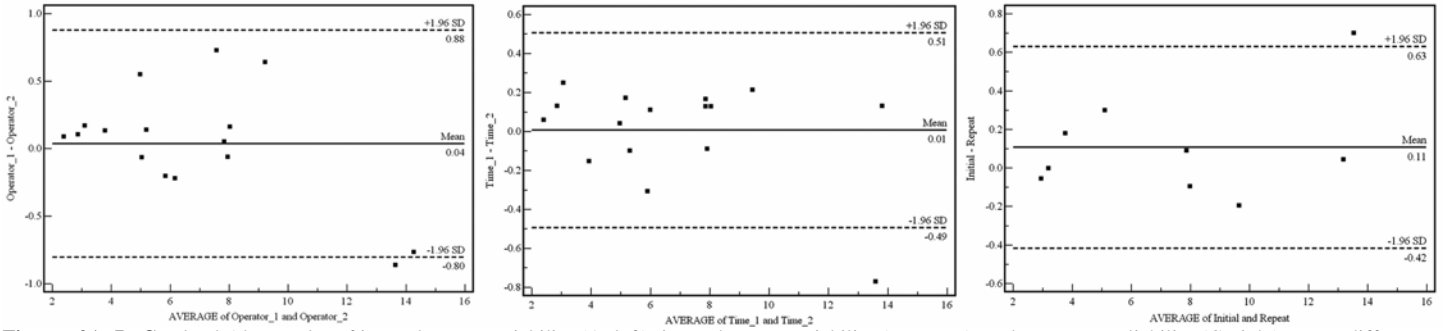


Figure 1. Sequential black blood TSE images (upper L to lower R) in a PAD patient.

Results. Fourteen patients (age 61±9 yrs) with mild to moderate PAD (ankle brachial index 0.70±0.11) were studied. Sixteen SFA vessels in the 14 patients were studied (mean length 16.7±5.5 cm) with total image acquisition time of 12.8±2.9 minutes per vessel. Mean APV on initial exam was 6.76 ± 3.36 cm^3. For the inter-observer data, intraclass correlation coefficient R=0.993. The Bland-Altman plot for inter-observer variability is shown in **Figure 2A.** A single operator performed repeat analysis of the 16 vessel segments at a mean of 22±16 days later. For intra-observer data, intraclass correlation coefficient R=0.997. The Bland-Altman plot for intra-observer data is shown in **Figure 2B**. For reproducibility data, intraclass correlation coefficient R=0.996. The Bland-Altman analysis of test-retest reliability (n=9) is shown in **Figure 2C.** Sample size estimates, assuming all patients enrolled will have adequate image quality for analysis demonstrated that for a change in atherosclerotic plaque volume of 1%, 123 patients would be needed; for 2%, 31 patients; for 5%, 5 patients.



Figures 2A, B, C. Bland-Altman plot of inter-observer variability (A, left), intra-observer variability (B, center), and test-retest reliability (C, right). Mean differences were 0.04 cm^3, 0.01 cm^3, and 0.11 cm^3 respectively.

Conclusions. High resolution, high volume black blood, MR measurement of atherosclerotic plaque volume in the superficial femoral artery in peripheral arterial disease is feasible, rapid, and highly reproducible. Potential applications include diagnosing preclinical vascular disease, assessing disease severity in those with established PAD, and monitoring atherosclerotic plaque progression in response to both established and novel therapies. Furthermore, this noninvasive approach could reduce required sample sizes for clinical studies using atherosclerotic plaque progression rate as a surrogate efficacy endpoint.