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Usefulness of Cardiovascular Magnetic Resonance Imaging of the Superficial Femoral Artery for Screening Patients with Diabetes Mellitus for Atherosclerosis

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Abstract

Cardiovascular magnetic resonance (CMR) of the superficial femoral artery (SFA) allows direct visualization of atherosclerotic plaque burden noninvasively. We examined atherosclerosis in 3 groups of patients without a history or symptoms of peripheral arterial disease (PAD) with varying expected burdens: those with diabetes mellitus (DM) and known coronary artery disease (CAD) (n=24); DM and a high prevalence of CAD risk factors (n=20); and controls of similar age without DM or CAD and few CAD risk factors (n=15). We also assessed the diagnostic accuracy of this technique to differentiate between these 3 groups. T1-weighted spin-echo images were used to measure the mean wall thickness (WT) and total wall volume indexed to total vessel volume (IWV). Diagnostic accuracy was assessed by area under the receiver operating characteristic (ROC) curve analysis. Individuals with DM+risk factors and DM+CAD had higher mean WT (1.28mm and 1.37mm) and mean IWV (0.53 and 0.56) compared with controls (mean WT 1.16mm and mean IWV 0.45), all p<0.010. Both mean WT and IWV showed good diagnostic accuracy in discriminating controls from those with DM+CAD (AUCs of 0.85 and 0.87 with p<0.001, respectively), while only IWV discriminated DM+risk factors from controls (AUC=0.82, p<0.001). Neither could discriminate between DM+risk factors and DM+CAD. In conclusion, patients with DM+risk factors and DM+CAD had significantly higher atherosclerotic burden in the SFA on CMR than controls of similar age, with good diagnostic accuracy in differentiating these groups. The high reproducibility and reliability of CMR of the SFA may facilitate improved assessment of atherosclerosis prevalence as well as progression/regression in studies of novel therapies.

Keywords

therosclerosis; cardiovascular magnetic resonance; diabetes mellitus

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The presence and extent of peripheral arterial disease (PAD) correlates closely with coronary atherosclerosis and cardiac events.¹ Ankle-brachial indices (ABIs) are specific for disease but are insensitive and fail to quantify the degree of peripheral atherosclerosis.² This is especially true in patients with diabetes mellitus (DM), who frequently have stiff, calcified vessels that can lead to a false-negative study. PAD has a high prevalence in diabetic patients; and those with both DM and PAD have a 3.6-fold increase in cardiac events compared to those with DM alone.^{3,4} Cardiovascular magnetic resonance (CMR) can quantify atherosclerotic plaque volume in the superficial femoral artery (SFA) with high spatial resolution and excellent reproducibility.⁵ Accordingly, the purpose of this study was: 1) to establish the extent of superficial femoral atherosclerosis in 3 asymptomatic cohorts with varying estimated atherosclerotic burdens, and 2) to determine the diagnostic accuracy of CMR of the SFA to differentiate between these 3 cohorts.

METHODS

Study approval was obtained from the University of Virginia Institutional Review Board in compliance with the Helsinki Declaration, and written consent was obtained from all subjects prior to enrollment.

The study population consisted of 3 cohorts expected to have high, intermediate, and low atherosclerotic burdens: patients with DM and known CAD; subjects with DM and a high prevalence of risk factors for CAD but no known disease (DM+Risk Factors); and a group of similarly-aged controls without DM or CAD and a low prevalence of CAD risk factors (Controls). Study subjects were prospectively recruited from the University of Virginia Diabetes and Cardiovascular Care clinic, the general cardiovascular clinics, and the general internal medicine clinics (figure 1). Consenting individuals age 18 to 85 with DM were included unless they had a history of PAD, claudication, arterial insufficiency ulcers, or a contraindication to CMR (such as a pacemaker or an inability to lie flat). Similar proportions of subjects with and without CAD were sought. ABIs were obtained in the majority of patients, and those with an index <0.90 for either leg were excluded, as this study was designed to assess global atherosclerotic burden rather than focal obstructive disease. Similarly aged controls without DM or CAD and a low prevalence of CAD risk factors were also recruited.

Extensive clinical information was prospectively collected from participants at the time of their CMR study, including basic demographics, type and severity of DM, presence of vascular disease and its risk factors, medication usage, and relevant laboratory data such as lipids and hemoglobin A1c.

Subjects underwent CMR of the bilateral SFAs on a 1.5 Tesla Siemens Avanto scanner using a linear, flexible, 4-element (10cm ×10cm square) surface coil array (Nova Medical, Wilmington, MA). Contiguous, interleaved, ungated, 3.0mm axial, black-blood, fat-suppressed, T1-weighted spin-echo images were obtained for each extremity (figure 2 shows representative images). Imaging parameters included a repetition time (TR) 1100ms, echo time (TE) 7.6ms, echo spacing 7.5ms, turbo factor 9, 4 signal averages, and scan time 1 minute and 23 seconds for a 7 slice image set. The image resolution was 0.5 × 0.5 × 3.0mm. Images were obtained for 15–20cm of the SFA, starting at the femoral bifurcation and continuing through the adductor canal. Total imaging time for both lower extremities was typically 60 minutes.

All images were processed by one of two operators using VesselMass software (Version 5.1, University of Leiden). Interobserver agreement with this approach is excellent.⁵ The luminal and adventitial borders of the SFA were manually-delineated in each 3mm slice. The length

of interpretable SFA for each subject extremity was obtained by summing the thicknesses of the slices in which contours could be adequately drawn. The depth of the artery from the skin surface and signal to noise ratio (SNR) were measured at the level of the first analyzed slice for each leg.⁶ The mean wall thickness and wall cross-sectional area for each axial slice were determined by VesselMass. Mean wall thickness (WT) normalized to vessel cross-sectional area was also assessed. The vessel wall volume for each slice was calculated as the cross-sectional area multiplied by the slice thickness. The indexed wall volume (IWV) was obtained by dividing the vessel wall volume of each slice by the total vessel volume in the same slice. The WT, normalized WT, and IWV values were averaged across all slices to give mean values.

For data analysis, continuous variables were given as means $\pm$ standard deviation (SD) or as medians with 25th and 75th percentiles, and categorical variables were given as percentages. Baseline characteristics, medications, analyzed vessel length, artery depth, signal to noise ratio, mean WT, normalized WT, and mean IWV were compared with analysis of variance (ANOVA) and Tukey's studentized range testing for continuous variables and Chi-square analysis or Fisher's exact testing for categorical variables. Data from both the left and right legs were combined when the mean WT and IWV were calculated. For all testing, P-values less than 0.05 were considered to be statistically-significant. Receiver operating characteristic (ROC) curves and their associated areas under the curve (AUC) were used to assess the diagnostic accuracy of the mean WT and IWV to differentiate the SFAs from patients with DM, DM+CAD, or neither. The values of the WT and IWV between the left and right legs were compared using Pearson correlation coefficients. All analyses were prospectively designed and performed using SAS version 9.1 (SAS, Cary, NC).

RESULTS

The derivation of the study cohort is given in figure 1. Consent was obtained from 47 individuals with DM (1 of whom was excluded for an ABI <0.9) and 15 similarly-aged controls. CMR was performed, and 2 subjects were subsequently excluded for incomplete data and uninterpretable images due to patient movement. The remaining 59 patients made up the final study cohort.

The baseline characteristics of the study subjects are provided in table 1, subdivided by presence or absence of DM+CAD. As expected, the median (25th, 75th percentile) number of CAD risk factors from table 1 was highest in the high prevalence DM group 6 (5,6), intermediate in the low prevalence DM group, 4 (3,4.5), and lowest in the control group 2 (1,2)($p<0.001$). There was no difference between those with DM alone and DM+CAD in the mean HgA1c (8.2 vs. 7.3, $p=0.264$) or proportion treated with oral hypoglycemic agents or insulin. The mean duration of DM (93% type 2) was very similar (10.3 ± 9.8 years for DM alone versus 10.0 ± 7.8 years for DM+CAD, $p=0.938$). The mean LDL values were 128 for those with DM alone, 74 for those with DM+CAD, and 109 for control patients ($p<0.001$); the HDL values were 47 mg/dL, 41 mg/dL, and 53 mg/dL ($p=0.023$) for these groups, respectively. Both diabetic groups had high rates of statin and ACE-inhibitor/ARB use, with no significant differences between them. Beta-blockers and aspirin were taken more often by those with known CAD.

Subjects with CAD had a 75% prevalence of prior myocardial infarction (MI) (18 of 24), and 67% (16 of 24) had prior revascularization (7 with prior bypass surgery (29%) and 11 (46%) with prior percutaneous coronary intervention). A history of heart failure was only found in those with known CAD.

CMR of both SFAs was performed in all except one patient whose study had to be terminated for claustrophobia. The mean ($\pm$ SD) length of SFA measured per leg was 16.2 ± 2.3 cm and did not differ significantly between the 3 subgroups. There was no difference in SNR ($p=0.210$) despite a greater artery depth as the expected burden of atherosclerosis increased. Moreover, there was no discernible qualitative difference in image quality between groups.

Box and whisker plots for the mean wall thickness (WT) and wall-volume index (IWV) dichotomized by subgroup are provided in figure 3. There was a statistically-significant difference in mean WT between the control subjects and those with DM+CAD (increase of 0.20 mm (95% CI: 0.07–0.34), $p<0.001$), but not between controls and those with DM and a high prevalence of CAD risk factors (increase of 0.11 mm (95% CI: –0.02–0.25), $p=0.093$) or between those with DM and a high prevalence of CAD risk factors and DM+CAD (decrease of 0.08 mm (95% CI: –0.21–0.03), $p=0.120$). Similar results were found when the mean WT was normalized to vessel cross-sectional area.

The mean IWV was a better differentiator between groups than the mean WT, with statistically-significant differences between control subjects and both those with DM and a high prevalence of CAD risk factors (increase of 0.07 mm (95% CI: 0.02–0.12), $p<0.001$) and DM+CAD (increase of 0.10 (95% CI: 0.06–0.15), $p<0.001$). As with mean WT, the mean IWV did not differ significantly between the DM and high CAD risk factor prevalence and DM+CAD subgroups (decrease of 0.03 (95% CI: –0.07–0.01), $p=0.085$).

The ROC curves and AUC analyses are provided for mean WT and mean IWV in figure 4. Mean WT showed good diagnostic accuracy in differentiating control subjects from those with DM+CAD but was more limited in other discrimination. On the other hand, the mean IWV showed good diagnostic accuracy for differentiating between controls and both those with DM and a high CAD risk factor prevalence and DM+CAD. As with the mean WT, discrimination by the mean IWV was only fair between individuals with DM and high CAD risk factor prevalence and DM+CAD.

The correlation between the SFAs in the right and left leg for both mean WT ($R=0.81$) and mean IWV ($R=0.89$) were good ($p<0.001$).

DISCUSSION

CMR is an emerging technique for the evaluation of atherosclerosis and has unique advantages over other imaging modalities such as echocardiography or invasive angiography.^{5,7,8} Unlike invasive angiography, CMR allows direct visualization of atherosclerotic plaque and the vessel wall. Components of atherosclerotic plaque (lipid, calcium, hemorrhage, thrombosis, and fibrous cap) have been identified on CMR and correlated with pathologic specimens.^{9,10} Calcium scoring is useful but has high test-retest variability (10–15%) and uses radiation, reducing its utility for repeat testing.^{11,12} Carotid intima-media thickness testing (CMT) has been used in large trials of atherosclerosis regression but has important limitations including lack of methodological standardization, a weak association with the degree of coronary atherosclerosis, limited data that progression of CMT increases cardiac events, high inter-observer variability; and large sample sizes required to show differences between groups.^{13–15} Moreover, the limited resolution of CMT minimizes its usefulness for individual patient assessment. Bots et al. have estimated that 468 patients would be required to have 80% power to detect a treatment effect as large as 30% by CMT.¹⁶

Using CMR, the SFA is an ideal location for atherosclerosis assessment. It is easily accessible to surface coils receiving the CMR signal compared with the aorta. It has

decreased motion and a larger vessel wall volume compared with the carotid.^{17,18} Accordingly, the inter-observer agreement ($R=0.987$) and test-retest reproducibility ($R=0.996$) are excellent. Isbell et al. have shown that only 27 subjects are needed to show changes in wall volume of as little as 2%, compared to 10% in the carotid distribution.^{5,17,18} This precision in measurement is especially important for use as a surrogate endpoint in studies of the effects of novel therapies to reduce adverse cardiac outcomes.^{19–21} Its noninvasive nature facilitates repeat testing. CMR has been employed to monitor statin-induced regression of aortic, carotid, and peripheral atherosclerotic plaques.^{22,23} The correlation of wall thickness and volumes with atherosclerosis of the SFA is well-established.²⁴

In this study, we have shown that CMR of the SFA identifies progressively-increased atherosclerotic burden, as measured by higher wall thicknesses and indexed wall volume, in subgroups with higher expected disease burdens. The mean IWV appears to be superior to mean WT in this population, as it can differentiate control subjects with few CAD risk factors from both those with DM and a high prevalence of CAD risk factors and those with DM+CAD. Neither WT nor IWV differentiates those with DM and a high prevalence of CAD risk factors from patients with DM+CAD, with relatively poor diagnostic accuracy ($AUC < 0.7$) for both. This suggests that these groups have comparable levels of atherosclerosis in the SFA.

Coronary angiography was not performed to rule out CAD in the groups without known CAD, but our primary goal was to show differences in mean atherosclerotic burden in groups with varying predicted disease and illustrate that this technique can be used in individual patients to measure atherosclerotic burden. A proportion (34%) of the subjects with DM with or without CAD did not have measurement of the ABI prior to imaging to exclude significant PAD. However, none of the patients were symptomatic, and none had obstructive atherosclerosis imaged in their SFA in this analysis. Accordingly, the increased wall thickness and indexed wall volume were felt to represent systemic atherosclerotic burden rather than focal disease. The luminal and adventitial borders were planimetered in axial slices rather than directly perpendicular to the long-axis of the SFA, which may have introduced some error. However, the SFA generally runs perpendicular to the axial plane and thus we expect this error to be small and similar for all subgroups imaged. Imaging of both lower extremities took up to an hour. However, the present study suggests that imaging of both legs is not necessary as there was good correlation between the right and left legs for each patient.

Finally, although this technique has previously been shown to have excellent inter- and intra-observer correlation, the limited sample size may be affecting the differentiation of the three cohorts by SFA CMR, and further study in larger patient populations would be useful.

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Figure 1.

Study cohort derivation flowchart. Abbreviations: ABI=ankle brachial index; CAD=coronary artery disease; DM=diabetes mellitus; MR=magnetic resonance.

Figure 2.

Cross-sectional representative CMR images of the superficial femoral artery in controls (A), patients with diabetes (B), and patients with diabetes and coronary artery disease (C). A stepwise increase in wall thickness and area is appreciated from (A) to (C). Abbreviations: CAD=coronary artery disease; Ctl=control; DM=diabetes mellitus.

Figure 3.

Box and whisker plot analysis comparing the wall volume index and wall thickness.

Abbreviations: CAD=coronary artery disease; DM=diabetes mellitus; IWV=indexed wall volume; WT=wall thickness.

Figure 4.

Area under the curve analysis for mean wall thickness (A) and mean wall volume indexed to vessel volume (B) between controls, patients with diabetes, and those with diabetes and coronary artery disease. Abbreviations: AUC=area under the curve; CAD=coronary artery disease; DM=diabetes mellitus; IWV=indexed wall volume.

Table 1

Study cohort baseline characteristics and medication usage dichotomized by presence of diabetes mellitus and coronary artery disease.

Characteristic	Controls (n=15)	DM Only* (n=20)	DM and CAD* (n=24)	P-value
Age (median, 25 th , 75 th percentiles)	61.0 (58.0, 72.0)	51 (57.5, 61.5)	63.0 (59.0, 68.0)	0.083
Male	11 (73%)	9 (45%)	18 (75%)	0.083
Caucasian	13 (87%)	10 (50%)	23 (96%)	<0.001 [†]
Hypertension [‡]	4 (27%)	17 (85%)	23 (96%)	<0.001 [†]
Hyperlipidemia ^{**}	8 (53%)	15 (75%)	24 (100%)	<0.001 [†]
Current tobacco use	0 (0%)	3 (15%)	8 (33%)	0.025 [†]
Body Mass Index 30 kg/m ²	1 (7%)	13 (65%)	14 (58%)	0.001 [†]
Cerebrovascular Disease	0 (0%)	0 (0%)	1 (4%)	0.476
Heart Failure	0 (0%)	0 (0%)	5 (21%)	0.024 [†]
Aspirin		9 (45%)	23 (96%)	<0.001 [†]
Beta-blocker		3 (15%)	19 (79%)	<0.001 [†]
Statin		14 (70%)	22 (92%)	0.115
Ace-Inhibitor or Angiotensin Receptor Blocker		15 (75%)	21 (87%)	0.284
Oral hypoglycemics		15 (75%)	20 (83%)	0.495
Insulin		8 (40%)	8 (33%)	0.647

* CAD=coronary artery disease; DM=diabetes mellitus.

[†]This p-value represents ANOVA testing. Statistically-significant results have p < 0.05.

[‡]Hypertension was defined as a blood pressure ≥ 135/85 mmHg or a known past history and treatment with an anti-hypertensive.

^{**}Hyperlipidemia was defined as a LDL > 100 mg/dL for patients with DM or > 130 mg/dL for those without DM.