Relation of Magnetic Resonance Imaging Based Arterial Signal Enhancement to Markers of Peripheral Artery Disease

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Peripheral artery disease (PAD) is associated with impaired lower extremity function. We hypothesized that contrast-enhanced magnetic resonance imaging (CE-MRI) based arterial signal enhancement (SE) measures are associated with markers of PAD. A total of 66 participants were enrolled, 10 were excluded due to incomplete data, resulting in 56 participants for the final analyses (36 PAD, 20 matched controls). MR imaging was performed postreactive hyperemia using bilateral thigh blood-pressure cuffs. First pass-perfusion images were acquired at the mid-calf region with a high-resolution saturation recovery gradient echo pulse sequence, and arterial SE was measured for the lower extremity arteries. As expected, peak walking time (PWT) was reduced in PAD patients compared with controls (282 [248 to 317] sec, vs 353 [346 to 360] sec; p = 0.002), and postexercise ankle brachial index (ABI) decreased in PAD patients but not in controls (PAD: 0.75 ± 0.2, 0.60 [0.5 to 0.7]; p <0.001; vs Controls: 1.17 ± 0.1, 1.19 [1.1 to 1.2]; p = 0.50). Intraclass correlation coefficients were excellent for inter- and intraobserver variability of arterial tracings (n = 10: 0.95 (95%-confidence interval [CI]: 0.94 to 0.96), n = 9: 1.0 (CI: 1.0 to 1.0). Minimum arterial SE was reduced in PAD patients compared with matched controls (128 [110 to 147] A.U. vs 192 [149 to 234] A.U., p = 0.003). Among PAD patients but not in controls the maximum arterial SE was associated with the estimated glomerular filtration rate (eGFR), a marker of renal function (n = 36, ß = 1.37, R^2 = 0.12, p = 0.025). In conclusion, CE-MRI first-pass arterial perfusion is impaired in PAD patients compared with matched controls and associated with markers of lower extremity ischemia. **© 2020 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2021;140:140−147)**

Peripheral artery disease (PAD) is associated with impaired blood flow in the lower extremities.[1,2] It is estimated that more 200 million people have PAD worldwide[3] including about 12% of the adult U.S. population and PAD is significantly associated with adverse cardiovascular outcomes.[4−6] Previous studies demonstrated that contrast-enhanced MRI (CE-MRI) is suitable to visualize functional or pathologic changes in the lower extremity arteries.[7,8] CE-MRI can visualize arterial anatomy with high sensitivity and specificity[8,9] and quantitatively assess first-pass perfusion of the major lower extremity arteries.[10,11] [12] Previously, researchers have demonstrated that peak-exercise measurement of lower limb perfusion with first-pass MRI distinguishes PAD from controls independent of exercise workload[13] and that tissue perfusion correlates with walking distance.[14] [15] [16] For this study, we have hypothesized that CE-MRI-based arterial signal enhancement (SE) is associated with markers of PAD. We used a validated peak detection algorithm to identify physiological and fixed time points in the arterial input function taken from the more symptomatic leg during first-pass CE-MRI for the posterior tibialis (PT), anterior tibialis (AT), and peroneal (PE) arteries.[17] We have determined associations between CE-MRI arterial signal enhancement measures and markers of PAD in both PAD patients and matched controls.

Methods

Men and women with a resting ankle brachial index (ABI) <0.9 and life-style limiting intermittent claudication (IC) were recruited[18] between July 2013 and July 2016 from the Houston Methodist Hospital and the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC), Houston, TX. All study participants received standard of care during this observational imaging study. Patients with contraindications to MRI or with an estimated glomerular filtration rate (eGFR) ≤40 mL/min/1.73.m^2 were excluded from this study. Matched controls without PAD were also

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recruited at the same sites. In all 66 participants were enrolled. The target leg was defined as the one with the lower ABI or as the more symptomatic leg. This study obtained approval from the local institutional review board (IRB) and all participants provided informed consent.

CE-MR imaging was performed with a 3.0T system (Siemens Magnetom Trio or Verio, Erlangen, Germany) with a 36-element bilateral lower extremity coil. Participants were positioned on the MRI table feet first in the supine position and imaging was performed at the mid-calf level. Initial localizers were performed with a field of view (FOV) of 19.9 × 39.9 cm. A previously described reactive hyperemia protocol was implemented. Briefly, bilateral MRI compatible blood-pressure cuffs were placed above the knee and inflated to supra systolic levels (170 mm Hg) for 3.5 minutes.[17] Subsequently imaging was commenced and a gadolinium-based contrast agent (GBCA) was administered and blood pressure cuffs were deflated rapidly, as described previously.[17] Briefly, CE-MRI was performed with high resolution saturation recovery gradient echo (GRE) pulse sequence (repetition time [TR] = 2.7 ms; echo time [TE] = 1.23 ms; slice thickness [ST] = 10 mm; bandwidth = 1021 Hz/px; flip angle [FA] = 30; FOV= 17.5 × 35.0 cm; matrix = 144 × 288, number of averages = 1, temporal resolution = 409 ms). A GBCA was administered intravenously (gadopentetate dimeglumine [Magnevist, Bayer Inc.] at 0.2 mmol/kg, or gadobutrol [Gadavist, Bayer Inc.] at 0.1 mmol/kg) with flow rates of 2 to 4 ml/s which was followed by a 20 ml saline flush.

MRI scans were saved in the DICOM format and subsequently transferred to a workstation for further processing. The arterial lumen of the AT, PT, and PE arteries were segmented, as available, with Sante DICOM Editor Version 3.0 (Santesoft LTD, Greece). The lumen was segmented in a single frame and the contours were propagated to all remaining frames. Due to the imaging protocol with a bilateral lower extremity coil, leg motion was limited effectively. Care was taken to account for frames with significant leg motion. In order to determine reproducibility and quality of the lumen segmentations, detailed inter- and intraobserver reproducibility analyses were conducted. The frame numbers (time points) were extracted from the arterial signal enhancement curves (**Figure 1**). The local precontrast arrival frame number (timing) was confirmed visually as the frame before any arterial signal enhancement was apparent. For each of the 3 main arteries (AT, PT, and PE), the peak arterial signal in arbitrary units (A.U.) was extracted as the maximum value across all segmented frames. The minimum post peak enhancement was extracted as the minimum value between the peak and the recirculation peak of the gadolinium bolus. The level of arterial signal enhancement was measured as the difference between the local precontrast arrival signal intensity (SI) and the peak arterial SI. SE was a difference measure and not an absolute quantity. The minimum SE and the maximum SE variables were defined as either the minimum or maximum SE values across the 3 arteries (AT, PT, and PE). Frame numbers were converted to time by multiplying with the temporal resolution (409 ms) of the GRE pulse sequence. Arterial SE slope, or wash-in slope, was calculated as the slope of the line connecting the prearrival arterial SI with the peak (maximum) arterial SI.[19] Cross-sectional leg muscle area (CSLMA) was measured, as describe previously.[17]

All variables were expressed as mean (standard deviation), median (interquartile range [IQR]) for non-normal variables, percentages, or frequencies. Variable normality was determined with the Shapiro-Wilk test. Group

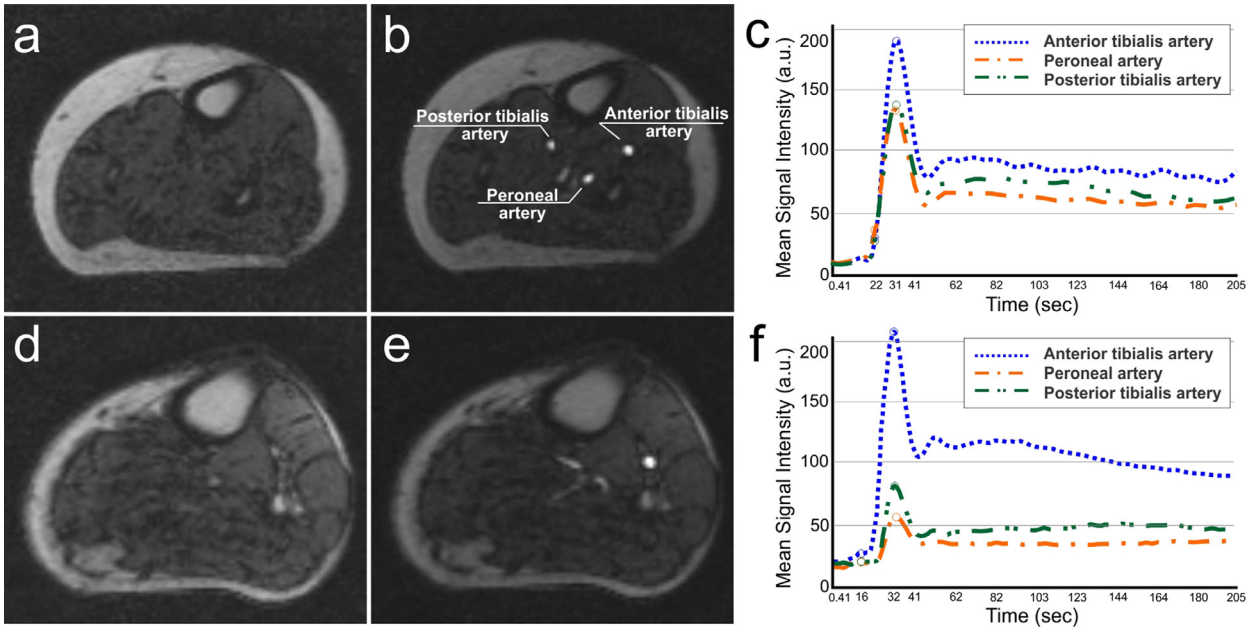

Figure 1. – (a, d): Contrast-enhanced magnetic resonance images of a control and PAD patient at precontrast arrival; (b, e): Contrast-enhanced magnetic resonance images of a control and PAD patient peak arterial signal enhancement; (c, f): arterial signal enhancement from a control and a PAD patient (panels: curves represent the time points before contrast arrival, peak arterial signal enhancement, the minimum before the recirculation peak).

differences for categorical variables were analyzed with the Chi-square or Fisher exact test. Continuous variables were analyzed with an independent samples Student's *t* test and the Mann-Whitney-Wilcoxon test was used for non-normal variables. Associations between MRI signal enhancement measures and markers of PAD were determined with linear regression analyses. Correlation analyses were performed and the strength of the correlation was described as weak ($r < 0.3$), medium ($0.3 \leq r < 0.5$), or strong ($r \geq 0.5$).[20] Inter-observer and intraobserver variability was measured with the intraclass correlation coefficient (ICC) using a 2-way random-effects model.[21] All tests were 2-sided and a p-value <0.05 was considered statistically significant. The statistical analyses were performed with Stata Statistical Software: Release 13 (College Station, Texas, StataCorp LP).

Results

A total of 66 participants were enrolled and 5 PAD patients among them did not return for the baseline MRI visit, 4 more were excluded due to incomplete MRI exams, protocol deviations, or poor image quality, and 1 more was excluded due to not performing the exercise ABI, resulting in 56 participants included in the final analysis (36 PAD, 20 controls). PAD patients and controls without PAD were matched appropriately and there were no differences in age, gender, race, or body mass index (BMI, **Table 1**). Compared with controls, PAD patients were more likely diabetic (47% vs 15%, p = 0.021), with a history of smoking (89% vs 40%, p <0.001), hypertensive (92% vs 60%, p = 0.011), hyperlipidemic (94% vs 60%, p = 0.002), be on lipid lowering therapy (89% vs 45%, p = 0.001), and have a history of lower extremity revascularization (61% vs 0%, p = 0.001).

Resting ABIs were significantly lower (0.75 ± 0.2 vs 1.17 ± 0.1, p <0.001) and peak walking time (PWT) was shorter (282 [248 to 317] sec vs 353 [346 to 360] sec, p = 0.002) in PAD patients compared with matched controls (**Table 1**). The changes between rest and exercise ABI showed that post-treadmill walking ABIs were significantly decreased in PAD patients (0.76 ± 0.2, 0.60 [0.5 to 0.7]; p <0.001) but remained unchanged in controls (1.17 ± 0.1, 1.19 (1.1 to 1.2); p = 0.50), as expected.

In a subgroup analysis, PAD patients were divided into 2 groups, (1) those who completed the 6-minute treadmill walking test (treadmill completers, n = 19) and (2) those who did not (treadmill noncompleters, n = 17). Noncompleters compared with treadmill completers had significantly lower resting ABIs (0.65 ± 0.2 vs 0.84 ± 0.2, p = 0.011), shorter PWT (190 (148 to 232) sec. vs 360 (360 to 360) sec., p <0.001), and claudication onset time (COT, 122 [80 to 164] sec. vs 232 [163 to 301] sec., p = 0.005).

Interobserver variability was assessed for 2 readers using 10 scans and intraobserver reproducibility was assessed for 9 scans. Intraobserver and interobserver variability of the arterial tracings, as measured with ICC coefficients, was excellent for both. Similarly, inter- and intraobserver reproducibility was assessed for CSLMA for 2 readers, using 20 scans each. ICCs of CSLMA were excellent for both inter- and intraobserver variability (**Table 2**).

Minimum SE and maximum SE were significantly reduced in PAD patients compared with matched controls

Table 1
Baseline patient characteristics

Variable	PAD patients (N = 36)	Controls (N = 20)	p Value
Age (years)	69 ± 9.0	65 ± 6.7	0.10
Men	27 (75%)	12 (60%)	0.36
Black	12 (33%)	4 (20%)	0.36
Body mass index (kg/m^2)	27 ± 4.9	29 ± 5.3	0.19
Resting ABI (A.U.)	0.75 ± 0.2	1.17 ± 0.1	<0.001
Post-treadmill ABI (A.U.)	0.60 (0.5−0.7)	1.19 (1.1−1.2)	<0.001
Smoker	32 (89%)	8 (40%)	<0.001
Diabetes mellitus	17 (47%)	3 (15%)	0.021
Hypertension (history)	33 (92%)	12 (60%)	0.011
Hyperlipidemia	34 (94%)	12 (60%)	0.002
Heart rate (bpm)	78 ± 19	71 ± 10	0.13
Hematocrit (%)	41 (39−42)	412 (40−44)	0.46
eGFR (ml/min/1.73m^2)	78 ± 22	78 ± 18	0.95
Anticoagulation	9 (25%)	3 (15%)	0.51
ACE inhibitor	17 (47%)	5 (25%)	0.15
Beta blocker	18 (50%)	7 (35%)	0.40
Claudication onset time (sec)	222 (180−264)	353 (346−360)	<0.001
Peak walking time (sec)	282 (248−317)	353 (346−360)	0.002
Complete 6 min treadmill	19 (53%)	19 (95%)	0.002
Cholesterol-lowering drug use	32 (89%)	9 (45%)	0.001
Coronary artery disease	15 (42%)	5 (25%)	0.26
Low extremities revascularization	22 (61%)	0 (0%)	0.001
Family history of coronary heart disease	14 (39%)	8 (40%)	0.07

Values are reported as mean (standard deviation), medians and interquartile range (IQR), as number (percentage). PAD = peripheral artery disease, BMI = body mass index, eGFR = estimated glomerular filtration rate, ABI = ankle brachial index. Hematocrit controls: n = 15; Post-treadmill ABI PAD patients: n = 35; Claudication onset time PAD patients: n = 35; Peak walking time PAD patients: n = 35.

Table 2
Inter-reader and intra-reader reproducibility

	Variability of arterial			CSLMA tracings		
	N (patients)	ICC	Confidence interval (95%)	N (patients)	ICC	Confidence interval (95%)
Inter-reader correlation	10	0.95	0.94 − 0.96	20	0.91	0.62 − 0.97
Intra-reader correlation	9	1.0	1.0 − 1.0	20	0.99	0.97 − 1.0

ICC and confidence interval were calculated using a two-way model. CSLMA = cross-sectional leg muscle area. ICC = intra-class correlation.

(128 [110 to 147] A.U. vs 192 [149 to 234] A.U., p = 0.003; and 265 ± 81 A.U. vs 314 ± 89 A.U., p = 0.040). When considering individual arteries, the SE of the PE and PT arteries were significantly reduced in PAD patients compared with controls (168 ± 154 A.U. vs 218 ± 87 A.U., p = 0.022; 163 ± 73 A.U. vs 234 ± 110 A.U., p = 0.007) but not for the AT artery (235 ± 201 A.U. vs 289 ± 93 A.U., p = 0.05; **Table 3**).

A categorical analysis by artery showed no significant differences for a preferential artery with minimum and maximum SE between PAD patients and controls (Supplementary Table 1a). However, among PAD patients and among matched controls the AT had the highest frequency of having the maximum SE across the PT, PE, and AT. Conversely, for minimum SE there was no difference in the frequency among the PT, PE, and AT (Supplementary Table 1b).

In PAD patients compared with matched controls there were significant differences of the cross-sectional area of the anterior muscle and the gastrocnemius muscle, but not for the lateral muscle (LM), soleus muscle (SM), deep posterior muscle (DM), and CSLMA (**Table 3**). There were no significant differences in CSLMA between PAD treadmill completers and noncompleters (data not shown).

The maximum arterial SE and the AT arterial SE were significantly associated with the eGFR in a pooled analysis (**Table 4**). The CSLMA was significantly associated with the BMI in the pooled analysis (**Table 5**).

In separate analyses only among PAD patients but not in controls the maximum arterial SE and the AT arterial SE were significantly associated with the eGFR (Supplementary Table 2a). Also in PAD patients but not in controls the slope of the AT arterial SE was significantly associated with eGFR (Supplementary Table 2b). Conversely, the maximum arterial SE and PE arterial SE were inversely associated with the BMI in controls but not in PAD patients (Supplementary Table 2a).

Among treadmill noncompleters the maximum arterial SE and the AT arterial SE were significantly associated with the eGFR (Supplementary Table 3). CSLMA was

Table 3
Magnetic resonance imaging measurements

Variable	PAD patients (N = 36)	Controls (N = 20)	p Value
AT arterial SE (A.U.)	235 ± 201	289 ± 93	0.05
PE arterial SE (A.U.)	168 ± 154	218 ± 87	0.022
PT arterial SE (A.U.)	163 ± 73	234 ± 110	0.007
Minimum arterial SE (A.U.)	128 (110−147)	192 (149−234)	0.003
Maximum arterial SE (A.U.)	265 ± 82	314 ± 89	0.040
AT: SI at pre-contrast arrival	23 ± 7.7	22 ± 4.2	0.37
PE: SI at pre-contrast arrival	21 (19−23)	19 (17−21)	0.09
PT: SI at pre-contrast arrival	22 (20−25)	20 (18−23)	0.29
AT: SE slope	15 (12−18)	17 (11−22)	0.46
PE: SE slope	9.9 (7.5−12)	12 (8.2−15)	0.41
PT: SE slope	6.2 (4.9−7.5)	8.0 (5.6−10)	0.14
Cross sectional leg area (cm^2)	92 ± 24	103 ± 21	0.09
Cross sectional leg muscle area (cm^2)	53 ± 15	62 ± 16	0.05
Cross sectional AM area (cm^2)	9.2 (8.2−10)	11 (9.9−13)	0.013
Cross sectional LM area (cm^2)	4.6 (4.1−5.1)	4.7 (3.8−5.6)	0.82
Cross sectional DM area (cm^2)	3.3 (2.7−3.8)	3.2 (2.5−3.9)	0.91
Cross sectional SM area (cm^2)	21 (19−23)	24 (21−28)	0.12
Cross sectional GM area (cm^2)	15 (13−17)	18 (16−21)	0.036
% muscle of cross-sectional leg area (%)	58 ± 8.6	59 ± 6.6	0.45

Values are reported as mean (standard deviation), medians and interquartile range (IQR). Leg measurements were done on the more symptomatic side. PAD = peripheral artery disease, SE = signal enhancement, A.U. = arbitrary units. PE = peroneal artery, PT = posterior tibialis artery, AT = anterior tibialis artery. Minimum and maximum arterial SE refer to the artery with the lowest and highest SE among PE, PT, AT, respectively. Leg muscle groups: AM = anterior muscle, LM = lateral muscle, DM = deep posterior muscle, SM = soleus muscle, GM = gastrocnemius muscle.

AT arterial SE controls: n = 19; PT arterial SE controls: n = 18; SI at pre-contrast arrival of AT controls: n = 19; SI at pre-contrast arrival of PT controls: n = 18; SE slope of AT controls: n = 19; SE slope of PT controls: n = 18; PE artery SE PAD patients: n = 35; SI at pre-contrast arrival of PE PAD patients: n = 35; SE slope of PE PAD patients: n = 35; SE slope of PT PAD patients: n = 35.

Table 4
Pooled linear regression analyses for signal enhancement parameters with clinical measures

	Independent variable	N	β	Standard error	R2	Adjusted r^2	p Value
Minimum arterial SE (A.U.)	Resting ABI	56	109	34	0.16	0.14	0.002
	Δ of ABI	55	79	53	0.04	0.02	0.15
	Claudication onset time (sec)	24	-0.21	0.12	0.12	0.08	0.09
	Peak walking time (sec)	55	0.12	0.12	0.02	<0.01	0.32
	Body mass index (kg/m^2)	56	-1.93	2.01	0.02	<0.01	0.34
	eGFR ($ml/min/1.73m^2$)	56	-0.01	0.50	<0.01	-0.02	0.99
	Cross-sectional leg muscle area (cm^2)	56	1.12	0.62	0.06	0.04	0.08
Maximum arterial SE (A.U.)	Resting ABI	56	91	41	0.08	0.01	0.032
	Δ of ABI	55	92	61	0.04	0.02	0.13
	Claudication onset time (sec)	24	-0.15	0.20	0.02	-0.02	0.48
	Peak walking time (sec)	55	0.04	0.14	<0.01	-0.02	0.79
	Body mass index (kg/m^2)	56	-0.84	2.33	<0.00	-0.02	0.72
	eGFR ($ml/min/1.73m^2$)	56	1.48	0.54	0.12	0.11	0.008
	Cross-sectional leg muscle area (cm^2)	56	1.86	0.69	0.12	0.10	0.010
AT arterial SE (A.U.)	Resting ABI	55	100	48	0.08	0.06	0.041
	Δ of ABI	54	45	73	0.01	-0.01	0.54
	Claudication onset time (sec)	24	-0.13	0.24	0.01	-0.03	0.60
	Peak walking time (sec)	54	-0.06	0.16	<0.01	-0.02	0.70
	Body mass index (kg/m^2)	55	0.10	2.69	<0.01	-0.02	0.97
	eGFR ($ml/min/1.73m^2$)	55	1.74	0.62	0.13	0.11	0.007
	Cross-sectional leg muscle area (cm^2)	55	2.23	0.81	0.12	0.11	0.008
PE arterial SE (A.U.)	Resting ABI	55	126	35	0.20	0.18	0.001
	Δ of ABI	55	41	56	0.01	-0.01	0.47
	Claudication onset time (sec)	24	-0.23	0.12	0.14	0.10	0.07
	Peak walking time (sec)	55	0.15	0.12	0.03	0.01	0.21
	Body mass index (kg/m^2)	55	-2.52	2.07	0.03	0.01	0.23
	eGFR ($ml/min/1.73m^2$)	55	-0.09	0.52	<0.01	-0.02	0.87
	Cross-sectional leg muscle area (cm^2)	55	0.68	0.66	0.02	<0.01	0.31
PT arterial SE (A.U.)	Resting ABI	54	89	44	0.07	0.05	0.05
	Δ of ABI	53	126	66	0.07	0.05	0.06
	Claudication onset time (sec)	24	-0.18	0.18	0.05	<0.01	0.31
	Peak walking time (sec)	53	0.21	0.14	0.04	0.02	0.16
	Body mass index (kg/m^2)	54	-1.84	2.51	0.01	-0.01	0.47
	eGFR ($ml/min/1.73m^2$)	54	0.12	0.64	<0.01	-0.02	0.85
	Cross-sectional leg muscle area (cm^2)	54	1.57	0.81	0.07	0.05	0.06

ABI = ankle brachial index, Δ of ABI = difference between resting ABI and post-treadmill ABI, eGFR = estimated glomerular filtration rate, SE = signal enhancement, A.U. = arbitrary units. AT = anterior tibialis artery, PE = peroneal artery, PT = posterior tibialis artery.

significantly associated with the BMI among treadmill completers, and treadmill noncompleters (**Table 5**).

In a pooled analysis, maximum arterial SE was significantly associated with the CSLMA (**Table 4**).

The slope of the AT arterial SE was significantly associated with the CSLMA in PAD patients but not in controls (Supplementary Table 2b).

Among treadmill noncompleters, the maximum arterial SE was positively associated with the CSLMA (Supplementary Table 3). The slope of the AT arterial SE was significantly associated with the CSLMA among treadmill noncompleters (Supplementary Table 2b) but not in treadmill completers. There were no significant associations between the slopes of the PE and PT arterial SE and CSLMA (Supplementary Table 2b).

The precontrast arrival SI of the AT and PT of the more symptomatic leg were significantly correlated with the contralateral side for PAD patients but not for matched controls ($r = 0.49$, $p = 0.003$ vs $r = 0.51$, $p = 0.002$; and $r = 0.40$, $p = 0.09$ vs $r = 0.36$, $p = 0.12$). Arterial SE between the target and contralateral leg was significantly correlated with the AT artery ($r = 0.73$, $p < 0.001$ vs $r = 0.43$, $p = 0.009$) and the PE artery ($r = 0.68$, $p = 0.001$ vs $r = 0.56$, $p < 0.001$) in both controls and PAD patients, but PT arterial SE was only significant in controls and not in PAD patients ($r = 0.62$, $p = 0.008$ vs $r = 0.15$, $p = 0.42$; Supplementary Table 4).

A pooled analysis of SE variables with clinical measures showed significant associations for the minimum arterial SE ($n = 56$, $= 109$, $R^2 = 0.16$, $p = 0.002$), maximum arterial SE ($n = 56$, $= 91$, $R^2 = 0.08$, $p = 0.032$), the AT arterial SE ($n = 55$, $= 100$, $R^2 = 0.08$, $p = 0.041$), and the PE arterial SE ($n = 55$, $= 126$, $R^2 = 0.18$, $p = 0.001$) with the resting ABI (**Table 4**).

In PAD patients, the PE arterial SE was significantly associated with the resting ABI (Supplementary Table 5). The SE slope of the AT was inversely associated with the changes between resting and exercise ABI (Supplementary Table 6).

Among treadmill noncompleters, the maximum arterial SE was inversely associated with PWT and positively associated with CSLMA (**Table 6,** and Supplementary Table 3).

Table 5
Linear regression analyses for magnetic resonance imaging muscle area parameters with clinical measures

	Independent variable	N	B	Standard error	R2	Adjusted r^2	p Value
Pooled analyses							
Cross-sectional leg muscle area (cm^2)	Resting ABI	56	11	7.80	0.04	0.02	0.17
	Δ of ABI	55	17	11	0.04	0.02	0.13
	Claudication onset time (sec)	24	0.04	0.04	0.05	0.01	0.28
	Peak walking time (sec)	55	0.03	0.03	0.02	<0.01	0.28
	Body mass index (kg/m^2)	56	1.69	0.37	0.28	0.27	<0.001
	eGFR ($ml/min/1.73m^2$)	56	0.15	0.10	0.04	0.02	0.15
Control group							
Cross-sectional leg muscle area (cm^2)	Resting ABI	20	-44	39.5	0.06	0.01	0.28
	Δ of ABI	20	58	26.5	0.21	0.16	0.043
	Peak walking time (sec)	20	0.29	0.18	0.13	0.09	0.11
	Body mass index (kg/m^2)	20	0.63	0.71	0.04	-0.01	0.38
	eGFR ($ml/min/1.73m^2$)	20	0.27	0.21	0.09	0.04	0.21
PAD group							
Cross-sectional leg muscle area (cm^2)	Resting ABI	36	3.13	12	<0.01	-0.03	0.79
	Δ of ABI	35	-2.67	14	<0.01	-0.03	0.85
	Claudication onset time (sec)	24	0.04	0.04	0.05	0.01	0.28
	Peak walking time (sec)	35	<0.00	0.03	<0.01	-0.03	0.90
	Body mass index (kg/m^2)	36	2.20	0.39	0.49	0.47	<0.001
	eGFR ($ml/min/1.73m^2$)	36	0.12	0.12	0.03	<0.01	0.32
Treadmill completers PAD							
Cross-sectional leg muscle area (cm^2)	Resting ABI	18	1.72	1.23	0.11	0.05	0.18
	Δ of ABI	18	1.72	1.23	0.11	0.05	0.18
	Claudication onset time (sec)	8	0.06	0.08	0.09	-0.06	0.47
	Body mass index (kg/m^2)	19	2.75	0.63	0.53	0.50	<0.001
	eGFR ($ml/min/1.73m^2$)	19	0.28	0.17	0.13	0.08	0.13
Treadmill non-completers PAD							
Cross-sectional leg muscle area (cm^2)	Resting ABI	17	-3.03	24	<0.01	-0.07	0.90
	Δ of ABI	16	-8.61	27	0.01	-0.06	0.75
	Claudication onset time (sec)	16	0.02	0.05	0.01	-0.06	0.74
	Peak walking time (sec)	16	-0.06	0.05	0.09	0.02	0.27
	Body mass index (kg/m^2)	17	1.94	0.48	0.52	0.49	0.001
	eGFR ($ml/min/1.73m^2$)	17	-0.01	0.16	<0.01	-0.07	0.95

PAD = peripheral artery disease, ABI = ankle brachial index, Δ of ABI = difference between resting ABI and post-treadmill ABI, eGFR = estimated glomerular filtration rate.

Among PAD treadmill completers, the PE arterial SE was associated with the resting ABI (Table 6). The SE slope of the AT was inversely associated with the changes between the resting and exercise ABI in PAD treadmill completers (Supplementary Table 6).

Discussion

The primary findings of this study are that CE-MRI-based first-pass arterial perfusion is impaired in PAD patients compared with matched controls and is associated with measures of lower extremity ischemia. The minimum and maximum arterial SE were significantly reduced in PAD patients compared with matched controls. Among PAD patients but not in matched controls, maximum arterial SE was associated with eGFR, an established marker of renal function. In a pooled analysis of PAD patients and controls, CE-MRI-based minimum and maximum arterial SE were significantly associated with the resting ABI. The inter- and intraobserver agreement of the imaging based measures were excellent.

It has been shown that in healthy volunteers MRI-based phase-contrast quantitative flow measurements of the lower extremity arteries depend on age, gender, and calf muscle volume.[22] In our study, maximum arterial SE was positively associated with cross-sectional leg muscle area in PAD treadmill noncompleters but not in matched controls or treadmill completers.

Previous research showed that PAD patients who underwent exercise conditioning had a marked improvement in functional capacity, plethysmograph-based calf blood flow, and peak walking time, however, the change in blood flow did not correlate with the increase in PWT.[23] In this study, maximum arterial SE was significantly reduced in PAD patients compared with matched controls, and we observed an association with CSLMA only in claudicants who did not complete the 6-minute graded treadmill test.

Atkins and Gardner demonstrated that the ABI was not correlated with lower extremity functional strength.[24] In this study linear regression analyses indicate that the ABI is significantly associated with the minimum and maximum arterial SE for the pooled analysis. We also have observed that PAD treadmill noncompleters compared with completers had a significantly lower resting ABI and an earlier onset of claudication pain, indicating a relationship between hemodynamics and leg function.

Table 6
Linear regression analyses for signal enhancement parameters with clinical measures of PAD in PAD treadmill completers and non-completers

	Independent variable	N	β	Standard error	R^2	Adjusted r^2	p Value
Treadmill completers PAD							
Minimum arterial SE (A.U.)	Resting ABI	19	93	48	0.18	0.13	0.07
	Δ of ABI	19	-67	57	0.07	0.02	0.26
	Claudication onset time (sec)	8	-0.28	0.23	0.19	0.05	0.28
Maximum arterial SE (A.U.)	Resting ABI	19	79	74	0.06	0.01	0.30
	Δ of ABI	19	-19	86	<0.01	-0.06	0.81
	Claudication onset time (sec)	8	-0.62	0.43	0.25	0.13	0.20
AT arterial SE (A.U.)	Resting ABI	19	112	98	0.07	0.02	0.27
	Δ of ABI	19	-63	114	0.02	-0.04	0.58
	Claudication onset time (sec)	8	-0.47	0.58	0.10	-0.05	0.45
PE arterial SE (A.U.)	Resting ABI	19	179	53	0.40	0.37	0.003
	Δ of ABI	19	-57	76	0.03	-0.02	0.46
	Claudication onset time (sec)	8	-0.30	0.15	0.39	0.29	0.10
PT arterial SE (A.U.)	Resting ABI	19	-19	78	<0.01	-0.06	0.81
	Δ of ABI	19	-54	87	0.02	-0.04	0.55
	Claudication onset time (sec)	8	-0.56	0.43	0.22	0.09	0.24
Treadmill non-completers PAD							
Minimum arterial SE (A.U.)	Resting ABI	17	74	86	0.05	-0.02	0.40
	Δ of ABI	16	30	97	0.01	-0.06	0.76
	Claudication onset time (sec)	16	-0.21	0.19	0.08	0.01	0.29
	Peak walking time (sec)	16	-0.29	0.18	0.16	0.10	0.13
Maximum arterial SE (A.U.)	Resting ABI	17	24	137	<0.01	-0.06	0.87
	Δ of ABI	16	147	145	0.07	<0.01	0.33
	Claudication onset time (sec)	16	-0.08	0.30	<0.01	-0.07	0.80
	Peak walking time (sec)	16	-0.61	0.26	0.28	0.23	0.033
AT arterial SE (A.U.)	Resting ABI	17	59	158	0.01	-0.06	0.71
	Δ of ABI	16	36	171	<0.01	-0.07	0.84
	Claudication onset time (sec)	16	<0.00	0.34	<0.01	-0.07	1.00
	Peak walking time (sec)	16	-0.74	0.29	0.33	0.28	0.021
PE arterial SE (A.U.)	Resting ABI	16	76	102	0.04	-0.03	0.47
	Δ of ABI	16	47	111	0.01	-0.06	0.68
	Claudication onset time (sec)	16	-0.22	0.22	0.07	<0.01	0.33
	Peak walking time (sec)	16	-0.24	0.22	0.08	0.01	0.30
PT arterial SE (A.U.)	Resting ABI	17	15	107	<0.01	-0.07	0.89
	Δ of ABI	16	121	114	0.07	0.01	0.31
	Claudication onset time (sec)	16	-0.34	0.22	0.15	0.09	0.14
	Peak walking time (sec)	16	-0.22	0.23	0.06	-0.01	0.37

PAD = peripheral artery disease, ABI = ankle brachial index, Δ of ABI = difference between resting ABI and post-treadmill ABI, SE = signal enhancement, A.U. = arbitrary units. AT = anterior tibialis artery, PE = peroneal artery, PT = posterior tibialis artery.

Szuba et al reported that maximal calf blood flow does not predict treadmill walking distance.[25] Our results indicate that treadmill noncompleters versus completers had a significant shorter COT, as expected, and that among all PAD patients, maximum arterial SE was not associated with PWT.

Maximum arterial SE was associated with eGFR, a known marker of PAD, in PAD patients but not in matched controls, suggesting a potential link with kidney function which is a known marker of lower extremity ischemia.[26] The eGFR has also been previously associated with an impaired microvascular circulation in PAD patients, indicating an important link between kidney function and macrovascular and microvascular disease in PAD patients.[17]

Leg muscle area has been previously studied in PAD patients.[27,2] The WALCS II study found that a decrease in calf muscle area, measured by computed tomography over a period of 2 years, was associated with an increased loss of mobility in PAD patients when compared with non-PAD subjects.[2] In this study, CSLMA in PAD patients was associated with the BMI, and the maximum arterial SE was associated with the CSLMA only in treadmill noncompleters but not in completers, or among matched controls.

This study has limitations. The study population was limited to PAD patients with life-style limiting claudication who had no clinical indication for revascularization during the recruitment phase. Participants also had no rest pain or critical limb ischemia, an important group for whom the proposed MR measures have to be assessed in future studies. The proposed technique is subject to all limitations of MR imaging including contraindications to MRI and GBCA. Future work will need to determine the clinical feasibility of incorporating the proposed technique with clinically performed MRI scans with contrast. However, noninvasive CE-MRI may be useful to quantitatively assess PAD.

In conclusion, first-pass arterial perfusion, as measured with CE-MRI, is impaired in PAD patients compared with

matched controls and is associated with clinical measures of lower extremity ischemia. Arterial perfusion measures are highly reproducible and could be of interest as surrogate markers to assess response to clinical management and novel PAD therapies.

Disclosures

There are no conflicts of interest to disclose. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.10.049.

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