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Clinical correlates of size and number of collateral vessels in peripheral artery disease

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Abstract

We studied associations of the number and size of magnetic resonance angiography (MRA)-assessed lower extremity collateral vessels with the ankle–brachial index (ABI), severity of superficial femoral artery (SFA) plaque, and leg symptoms in participants with peripheral artery disease (PAD). A total of 303 participants with PAD underwent time-resolved MRA at the thigh station. Collaterals were categorized by number (Category 1: 0–3 collaterals; Category 2: 4–7 collaterals; Category 3: ≥ 8 collateral vessels) and size (Grade 1: ≤ 5 small collaterals; Grade 2: > 5 small vessels; Grade 3: ≤ 5 large collaterals; Grade 4: > 5 large collaterals). Adjusting for age, sex, race, comorbidities and other covariates, more numerous collateral vessels were associated with lower ABI values (Category 1: 0.79; Category 2: 0.67; Category 3: 0.60; p trend < 0.001). Similarly, larger collateral vessels were associated with lower ABI values (Grade 1: 0.75; Grade 2: 0.65; Grade 3: 0.62; Grade 4: 0.59; p trend < 0.001). More numerous ($p < 0.001$) and larger ($p < 0.001$) collateral vessels were associated with greater mean SFA plaque area (p trend < 0.001). More numerous (p trend = 0.007) and larger (p trend = 0.017) collateral vessels were associated with a lower prevalence of asymptomatic PAD. In conclusion, among participants with PAD, larger and more numerous collaterals, measured by MRA, were associated with lower ABI values, greater plaque area in the SFA, and a lower prevalence of asymptomatic PAD. Further study is needed to determine the role of collateral vessels in maintaining functional performance in PAD.

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Conflict of interest

None declared.

Keywords

ankle–brachial index; intermittent claudication; magnetic resonance angiography; peripheral artery disease

Introduction

Peripheral artery disease (PAD) affects 8 million Americans and is associated with greater lower extremity functional impairment and faster functional decline compared to people without PAD.[1–4] Critical limb ischemia is relatively uncommon in PAD.[5] The relatively low incidence of critical limb ischemia in PAD is thought related to the large and numerous collateral vessels that typically develop in people with PAD. However, the clinical characteristics associated with the number and size of collateral vessels in people with PAD are not established.

We used magnetic resonance angiography (MRA) to identify collateral vessels within the lower extremity of people with PAD and studied specific clinical characteristics associated with larger, more numerous collateral vessels. We aimed to determine whether more severe PAD, as measured by lower ankle–brachial index (ABI) values and greater atherosclerotic plaque in the superficial femoral artery (SFA), were associated with larger and more numerous lower extremity collateral vessels. We also studied associations of the number and size of MRA-measured lower extremity collateral vessels with leg symptoms. Because limb ischemia serves as a stimulus to development of lower extremity collateral vessels,[6,7] we hypothesized that participants with lower ABI values and greater atherosclerotic plaque in the SFA would have larger and more numerous lower extremity collateral vessels. Because collateral vessels may restore blood flow to ischemic tissue,[6,7] we hypothesized that asymptomatic PAD participants would have larger and more numerous MRA-measured collateral vessels than those with intermittent claudication symptoms.

Methods

Subjects

The Institutional Review Boards of Northwestern University Feinberg School of Medicine and all participating sites approved the protocol. Participants gave written informed consent. Participants were identified from the Walking and Leg Circulation Study III (WALCS III), a prospective, observational study designed to establish associations of magnetic resonance imaging (MRI)-measured atherosclerotic plaque characteristics with functional impairment and functional decline in PAD.[8] Between 1 January 2008 and 1 June 2008, MRA was performed in WALCS III participants without a history of renal disease. After 1 June 2008, MRA was performed in WALCS III participants with a glomerular filtration rate (GFR) ≥ 30 ml/min/1.73 m^2. A total of 303 participants with PAD in WALCS III underwent MRA. Participants were identified from among consecutive PAD patients in the non-invasive vascular laboratories at Northwestern Memorial Hospital, Jesse Brown Veterans Administration, Rush Medical Center, and Mt Sinai Hospital in Chicago, USA.[8] Consecutive patients diagnosed with PAD in the vascular surgery, cardiology, endocrinology,

general medicine, and geriatric practices at the Northwestern Medical Faculty Foundation and in the vascular surgery practice at the Jesse Brown VA were contacted and invited to participate.[8] A small number of participants were identified from among men and women aged 70 years and older in Northwestern's largest general internal medicine practice who were screened using the ABI and found to have an ABI < 1.00.

Inclusion criteria

The inclusion criterion was an ABI < 1.00.[8] This inclusion criterion was selected because truly normal ABI values are 1.10–1.40[9–11] and because this inclusion criterion ensured a broad range of PAD severity.

Exclusion criteria

Potential participants with dementia and those with a mini-mental status examination score < 23 were excluded because of concern about the reliability of their questionnaire responses.[12] Nursing home residents, wheelchair-bound patients, and patients with foot or leg amputations were excluded because of their severely impaired functioning. Non-English-speaking patients were excluded because investigators were not fluent in non-English languages. Patients who had undergone major surgery during the past 3 months were also excluded. To identify participants primarily limited in their walking performance by PAD, potential participants who required oxygen therapy were excluded. In addition, potential participants unwilling to undergo MRI testing and those with contraindications to MRI were excluded.

Ankle–brachial index measurement

After participants had rested supine for 5 minutes, a hand-held Doppler probe (Nicolet Vascular Pocket Dop II; Golden, CO, USA) was used to measure systolic pressures in this order: right brachial, dorsalis pedis, and posterior tibial arteries and left dorsalis pedis, posterior tibial, and brachial arteries.[2–4] Pressures were repeated in reverse order. The ABI was calculated in each leg by dividing the average pressures in each leg by the average of the four brachial pressures.[13,14] The average brachial pressures in the arm with the highest pressure were used when one brachial pressure was higher than the opposite brachial pressure in both measurement sets, and the two brachial pressures differed by 10 or more mmHg in at least one measurement set, since in such cases subclavian stenosis was possible.[14] Data from undetectable or incompressible dorsalis pedis and posterior tibial arteries were excluded. The lowest ABI was selected for analyses.

Leg symptoms

We used the San Diego Claudication Questionnaire to classify participants into one of five leg symptom categories, based on prior study:[2,4,15] (1) intermittent claudication (exertional calf pain that does not begin at rest, causes the participant to stop walking, and resolves within 10 minutes of rest); (2) atypical exertional leg pain/carry on; (3) atypical exertional leg pain/stop; (4) leg pain on exertion and rest; and (5) asymptomatic (no exertional leg symptoms).[4]

Magnetic resonance angiography technique

A 1.5 Tesla Siemens Espree (Siemens Medical Solutions, Erlangen, Germany) MRI scanner was employed for MRA image acquisition. A 12-channel surface array coil (Siemens Medical Solutions) was used for signal reception. We imaged atherosclerotic plaque in the SFA because the SFA is the most common site of atherosclerosis below the inguinal ligament,[16] and because the SFA supplies calf muscle, which is typically symptomatic in patients with PAD.

Dynamic MRA images from one station, the groin to the knee, were acquired from both legs, including the common femoral artery, the profunda femoris, the SFA, and the popliteal artery. Dynamic images were acquired with the TWIST (Time resolved angiography With Interleaved Stochastic Trajectories) pulse sequence.[17] Parallel imaging with Generalized Autocalibrating Partially Parallel Acquisitions[18] image reconstruction provided a twofold increase in frame rate. Following a three-plane localizer image, the TWIST sequence was applied in the coronal orientation. A 10-ml bolus of non-diluted gadopentetate dimeglumine (0.5 mmol/ml, Magnevist; Berlex, Montville, NJ, USA) was administered intravenously at 2 ml/second. Imaging parameters were: TR/TE/Flip angle = 3.3 ms/TE, 1.3 ms/25°; rectangular field of view (rFOV), 246 × 375 mm; matrix, 210 × 320; 88 partitions; voxel size after zero interpolation, 1.2 × 1.2 × 1.2 mm^3 (true voxel size, 1.2 × 1.2 × 2.0 mm^3); acceleration factor: 2. Figure 1 shows examples of MRA images from study participants.

MRA image analysis

A validated scoring system was used to grade the number and size of collateral vessels, based on a previous study by Baumgartner et al. for grading calf collateral vessels.[19] Baumgartner et al. categorized collateral vessels as large if they were visible for more than 25% of the imaged calf length and estimated to be at least 50% as large as the corresponding infra-popliteal arteries.[19] This method has excellent intra-rater reliability (mean 85.7% agreement).[19] We adapted this scale for the thigh and defined small collaterals as occupying less than 25% of the length of the imaged thigh and less than 50% of the diameter of the SFA, with large collaterals occupying more than 25% of the length of the imaged thigh and greater than 50% of the diameter of the SFA. The number of collateral vessels was counted. Categories were used to classify the number and size of collateral vessels, based on previous study[19] (Table 1). In addition, we required that the full length of the collateral vessel be visible for analyses. MRA images were reviewed on a workstation (GE Healthcare, Milwaukee, WI, USA) by a radiologist who was blinded to all other participant characteristics.

Measurement of atherosclerotic plaque

Previously described methods were used to image atherosclerotic plaque in the SFA.[8] Atherosclerotic plaque was imaged using a 1.5 Tesla Siemens Espree (Siemens Medical Solutions) with four-element phased-array surface coils. Twelve sequential 2.5-mm cross-sectional images of the SFA were obtained, beginning at the bifurcation of the common femoral artery and moving distally without gap using two-dimensional bright-blood time-of-flight and proton density-weighted images. Data were collected using standard, turbo-spin echo acquisition proton density-weighted images (TR/TE = 2160 ms/8 ms, bandwidth 230

Hz/pixel, turbo factor 15). The FOV was 120 × 120 mm^2 and images were acquired in matrix 192, yielding an in-plane spatial resolution of 0.625 × 0.625 mm^2. Three signal averages were acquired. Regional signal saturation bands were played out superiorly and inferiorly to suppress signal from inflowing blood, ensuring dark blood contrast. Chemically selective lipid saturation pulses eliminated signal from peri-adventitial fat. Bright-blood two-dimensional time-of-flight images (TR/TE = 31.0 ms/7.2 ms) were registered to the proton density images and acquired using an identical FOV, slice thickness, and imaging matrix. We have demonstrated excellent test–retest reliability for this method.[8]

Two physicians used CASCADE software (Seattle, WA, USA) to trace the outer boundary and lumen of each cross-sectional image, to quantify plaque and the lumen area. The lumen was identified in time-of-flight images and was copied onto the proton density-weighted image, where the artery outer wall boundary was traced. Images for each participant were assigned to one primary physician reviewer and were assessed by the second physician reviewer to ensure accuracy. Disagreement was resolved by discussion between the reviewers.

Based on prior study, plaque measurements were adjusted (normalized) for artery size.[8] The mean plaque area was normalized by dividing the average plaque area by the median of the outer wall area. The mean percent lumen area was normalized by dividing the mean lumen area by the outer wall area for each arterial slice. The leg with the lowest ABI was imaged.

Comorbidities

Medical record review, participant questionnaires, and a primary care physician questionnaire were used to identify and confirm comorbidities using established methods.[20] Hypertension was defined as participant report of physician-diagnosed high blood pressure or physician report of hypertension on the primary care physician questionnaire. Diabetes mellitus was defined as (a) use of a diabetes medication or (b) participant report of diabetes mellitus that was confirmed by the primary care questionnaire or medical record review.

Other measures

Height and weight were measured at the study visit. Body mass index (BMI) was calculated as weight (kg)/[height (m)]^2. Cigarette smoking history was measured with self-report.

Statistical analyses

Characteristics of WALCS III participants with versus without MRA data were compared using chi-squared tests for categorical variables and analysis of variance for continuous variables. MRA results were analyzed from the limb with the lowest baseline ABI. Associations of clinical characteristics with collateral number (Categories 1–3) and collateral size (Grades 1–4) were determined using chi-square tests for categorical variables and analysis of variance for continuous variables.

Associations of age, sex, race, comorbidities, smoking, ABI, BMI, and leg symptom categories with collateral number (Categories 1–3) and collateral grade (Grades 1–4) were determined using analyses of variance. Associations of collateral category and grade with

ABI, plaque volume, SFA lumen reduction, and leg symptoms were repeated using analyses of co-variance, adjusting for age, sex, race, diabetes mellitus, current smoking, BMI, hypertension, and ABI. However, analyses of ABI and leg symptoms did not include adjustment for ABI. Pairwise comparisons between the highest collateral category and grade with lower categories and grades, respectively, were made using chi-squared tests or analysis of variance. Because the presence of an occluded artery may drive the formation of collateral vessels, analyses were repeated among the subset of participants without occluded lower extremity vessels. Analyses were performed using SAS Statistical Software version 9.0 (SAS Inc., Cary, NC, USA).

Results

Of the 473 PAD participants included in WALCS III, 303 completed MRA testing. Compared to participants without MRA data, those with MRA data were younger, included higher proportions of participants who were male or current smokers, and included a higher prevalence of participants with intermittent claudication (Table 2).

Table 3 shows the characteristics of participants according to MRA-measured collateral vessel size (grade) and collateral vessel number (category). In unadjusted analyses, greater collateral grade was associated with lower ABI values, greater mean plaque volume, smaller lumen area, and a higher prevalence of men. MRA-measured greater collateral grade was associated with a lower prevalence of asymptomatic PAD and a higher prevalence of intermittent claudication (Table 3). Higher collateral vessel category (i.e. more numerous collateral vessels) was associated with older age, a higher prevalence of males, and a lower prevalence of smoking (Table 3). In unadjusted analyses, more numerous collateral vessels were associated with lower ABI values, greater mean plaque area, and smaller percent lumen area (Table 3).

Table 4 shows associations of MRA-measured collateral grade (size) and collateral category (number of collaterals) with ABI, MRI-measured plaque in the SFA, and leg symptoms, adjusting for covariates. Adjusting for age, sex, race, diabetes mellitus, smoking, BMI, hypertension, and ABI, larger collateral size was associated with lower ABI values (p trend < 0.001), greater mean plaque area (p trend < 0.001), and smaller percent lumen area (p trend < 0.001).

Adjusting for age, sex, race, diabetes mellitus, smoking, BMI, and hypertension, larger collateral size was associated with a higher prevalence of intermittent claudication and a lower prevalence of asymptomatic PAD (Table 4). More numerous collateral vessels were associated with a lower prevalence of asymptomatic PAD (Table 4). After additional adjustment for ABI, associations of collateral size and grade were no longer associated with leg symptoms (data not shown).

Results shown in Tables 3 and 4 were not substantially changed when analyses were repeated in the subset of participants with ($n = 40$) versus without ($n = 251$) any occlusions in the imaged section of the SFA (data not shown). In 12 PAD participants, poor image quality prevented determination regarding presence versus absence of occlusions in the SFA.

Discussion

Among 303 men and women with PAD, larger and more numerous collateral vessels, measured with MRA, were associated with lower ABI values, greater mean plaque volume in the SFA, and a smaller percent lumen area in the SFA. Larger collateral vessels were associated with a higher prevalence of intermittent claudication, while smaller and less numerous collateral vessels were associated with a higher prevalence of asymptomatic PAD. These associations remained statistically significant even after adjusting for age, sex, race, and other covariates. However, these associations of collateral vessel size and number were no longer statistically significant after additional adjustment for the ABI.

Collateral vessels may protect the lower extremity from the adverse effects of ischemia. Thus, recent clinical trials have tested interventions in an effort to increase arteriogenesis in patients with PAD.[21] These clinical trials have not demonstrated a benefit from interventions designed to increase arteriogenesis and improve functional performance among patients with PAD. A better understanding of the clinical characteristics associated with larger collateral size and more numerous collaterals may help target interventions to PAD patients who may achieve greater benefit.

Our findings suggest that the associations of larger and more numerous collateral vessels with a higher prevalence of intermittent claudication symptoms are related to the presence of more severe lower extremity atherosclerosis among PAD participants with intermittent claudication symptoms.[8] Similarly, our findings suggest that the associations of larger and more numerous collateral vessels with a lower prevalence of asymptomatic PAD are related to less severe lower extremity atherosclerosis among PAD participants who are asymptomatic.[8]

To our knowledge, only one prior study has assessed the clinical characteristics associated with the number or size of collateral vessels in patients with PAD.[22] This prior study of 45 participants with intermittent claudication demonstrated that diabetes mellitus and a shorter duration of symptoms of PAD were each associated with fewer collateral vessels. In unadjusted analyses, we found no associations of number or size of collateral vessels with prevalence of diabetes mellitus. Differences in the characteristics of participants in WALCS III as compared to those in the prior study by De Vivo et al.[22] may explain these disparate findings. For example, the prior study by De Vivo et al. included only participants with intermittent claudication symptoms, while we included PAD participants both with and without classical symptoms of intermittent claudication. A prospective study is needed to determine whether diabetes mellitus is a risk factor for smaller and less numerous collateral vessels.

Our finding in unadjusted analyses that male sex is associated with larger and more numerous collateral vessels is consistent with previous literature demonstrating that men have larger arteries than women.[23] Larger collateral vessels in men may relate to greater calf muscle volume in men as compared to women. Larger calf muscle volume may serve as a larger ischemic stimulus during walking activity in people with PAD.[24] Our finding in unadjusted analyses that older age was associated with larger size and greater numbers of

collateral vessels may relate to a longer duration of PAD in older men and women in this cohort. A previous study suggests that a longer duration of PAD is associated with greater numbers of collateral vessels.[22] However, the duration of PAD is difficult to measure because PAD may be asymptomatic[2] and because PAD is often under-recognized.[25]

This study has limitations. First, only the thigh was imaged in each patient. While the superficial femoral artery is the most common site of lower extremity atherosclerosis,[16] differences in inflow or run-off lesions within the iliac arteries or below-the-knee arteries were not assessed. Second, MRA acquisition was performed at rest and without administration of a vasodilator. Small collateral vessels may have been missed due to under-filling and as a result of the limited spatial resolution of MRI. Third, the patient population consisted of participants with PAD whose ABI was predominately > 0.40. These findings may not be generalizable to individuals with severe PAD. Fourth, data were cross-sectional. Causal inferences cannot be made based on the data presented here. Fifth, MRA has a lower spatial resolution than computed tomographic angiography or digital subtraction angiography. Some collaterals may be too small for identification on MRA.[26] Sixth, although the method used to rate the size and number of collateral vessels has been shown to have excellent intra-rater reliability,[19] we did not re-assess intra-rater reliability in the current study.

In conclusion, among PAD participants, more severe PAD, as measured by the ABI and direct visualization of atherosclerotic plaque with MRI, is associated with larger and more numerous collateral vessels on MRA. Further study is needed to establish the mechanisms of associations reported here.

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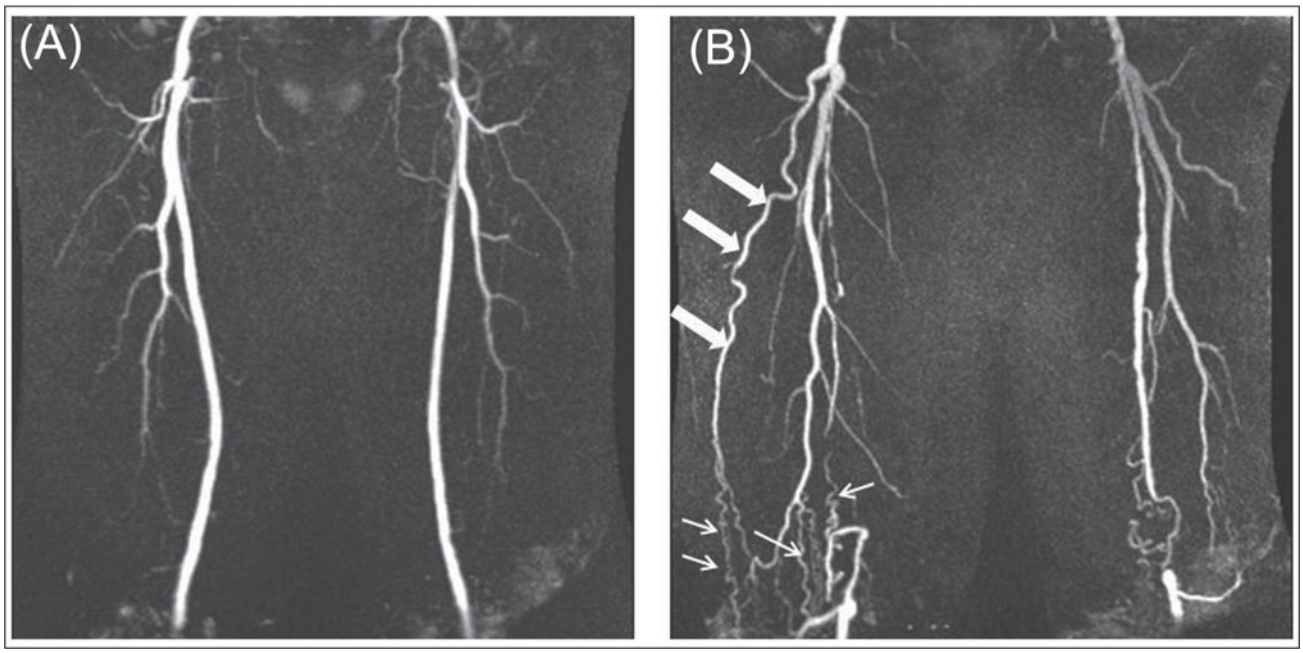

Figure 1.
Examples of magnetic resonance angiogram (MRA) images from (A) a participant with an ankle–brachial index (ABI) of 0.943 and (B) a participant with an ABI of 0.645.

Table 1

Definitions of classification systems used to define collateral vessel number and size

Category	Number of collaterals[a]
Category 1	0–3 collateral vessels
Category 2	4–7 collateral vessels
Category 3	≥ 8 collateral vessels
Collateral vessel grade	Size of collateral vessels
Grade 1	≤ 5 small
Grade 2	> 5 small
Grade 3	≤ 5 large ± small
Grade 4	> 5 large ± small

[a]Small collaterals occupy < 25% of the length of the imaged thigh and < 50% of the diameter of the superficial femoral artery.[19] Large collaterals occupy > 25% of the length of the imaged thigh and ≥ 50% of the diameter of the superficial femoral artery.[19]

Table 2

Characteristics of peripheral artery disease participants with versus without magnetic resonance angiogram (MRA) data[a]

	Without MRA	With MRA	*p*-value
n	170	303	
Age (years)	70.7	68.4	0.017
Male sex (%)	56.5	69.6	0.004
African American (%)	32.9	32.7	0.953
Current smoker (%)	17.1	27.5	0.011
Diabetes (%)	37.7	38.6	0.836
Hypertension (%)	91.8	89.1	0.354
Ankle–brachial index	0.65	0.68	0.135
Body mass index (kg/m2)	29.4	29.4	0.984
Normalized mean plaque area	0.7	0.7	0.811
Mean percent lumen area	0.3	0.3	0.814
Leg symptoms			
Asymptomatic (%)	24.1	17.8	0.101
Intermittent claudication (%)	18.2	26.7	0.037
Pain on exertion and rest (%)	30.6	25.1	0.196
Atypical exertional leg pain (%)	18.2	20.5	0.559
Exertional leg pain carry on (%)	8.8	9.9	0.702

Data shown are mean values.

[a]A total of 241 participants with MRA data and 71 participants without MRA data had a glomerular filtration rate measured as part of the research protocol.

Table 3

Baseline WALCS III participant clinical characteristics for those with and without MRA, for collateral grades and collateral number ($n = 303$)

	Collateral grade (size) (1–4 scale, 4 = largest)				*p*-value	Collateral vessel category (number)			*p*-value
	Grade = 1	Grade = 2	Grade = 3	Grade = 4		Category 1 (0–3 collateral vessels)	Category 2 (4–7 collateral vessels)	Category 3 (≥ 8 collateral vessels)	
n[a]	134	51	25	92		65	153	85	
Age (years)	67.9 ± 11.7	68.9 ± 9.2	65.7 ± 9.6	69.5 ± 9.4	0.387	66.4	67.9	70.9	0.020
Body mass index (kg/m2)	29.3	30.2	28.5	29.4	0.646	28.0	29.5	30.2	0.052
Male sex (%)	58.2	82.4	64.0	81.5	0.001	50.8	69.9	83.5	0.001
African American (%)	29.1	33.3	28.0	38.0	0.524	33.9	31.4	34.1	0.887
Current smoker (%)	30.1	23.5	44.0	20.7	0.092	38.5	27.6	18.8	0.028
Diabetes (%)	43.3	31.4	32.0	37.0	0.403	44.6	33.3	43.5	0.161
Hypertension (%)	89.6	88.2	84.0	90.2	0.837	92.3	87.6	89.4	0.588
Ankle–brachial index	0.75	0.66	0.63	0.59	< 0.001	0.78	0.68	0.60	< 0.001
Normalized mean plaque area	0.62 ± 0.11	0.69 ± 16	0.83 ± 22	0.80 ± 0.18	< 0.001	0.62 ± 0.12	0.70 ± 0.18	0.76 ± 0.16	< 0.001
Mean percent lumen area	0.4	0.3	0.3	0.2	< 0.001	0.40 ± 0.09	0.33 ± 0.14	0.26 ± 0.14	< 0.001
Leg symptoms									
Asymptomatic (%)	24.6	11.8	12.0	12.0	0.040	24.6	18.3	11.8	0.122
Intermittent claudication (%)	19.4	35.3	40.0	29.4	0.043	16.9	29.4	29.4	0.131
Pain on exertion and rest (%)	26.9	27.5	16.0	23.9	0.673	32.3	21.6	25.9	0.242
Atypical exertional leg pain (%)	20.9	17.7	20.0	21.7	0.949	21.5	20.3	20.0	0.970
Exertional leg pain carry on (%)	8.2	7.8	12.0	13.0	0.613	4.6	10.5	12.9	0.227

[a]One participant who met criteria for a Grade = 0 was excluded from the analyses on Grade.

Table 4

Adjusted associations of collateral vessel size and collateral vessel number with clinical characteristics in men and women with peripheral artery disease (n = 302)

	Collateral grade (size) (1–4 scale, 4 = largest)				*p*-trend value	Collateral vessel category (number) (1–3 scale, 3 = greatest number of collateral vessels)			*p*-trend value
	Grade = 1	Grade = 2	Grade = 3	Grade = 4		Category 1 (0–3 collateral vessels)	Category 2 (4–7 collateral vessels)	Category 3 (≥ 8 collateral vessels)	
n[a]	133	51	25	92		65	152	85	
Ankle–brachial index	0.75b	0.65	0.62	0.59	< 0.001	0.79b	0.67b	0.60	< 0.001
Normalized mean plaque area	0.63b	0.69b	0.82	0.79	< 0.001	0.64b	0.70	0.74	< 0.001
Mean percent lumen area	0.38b	0.33b	0.26	0.25	< 0.001	0.38b	0.33b	0.28	< 0.001
Leg symptoms									
Intermittent claudication (%)	17.6	35.7	39.9	30.1	0.038	14.9	28.7	30.3	0.077
No pain (%)	20.7	10.3	10.9	9.2	0.017	20.0	16.0	8.3	0.007

Adjusted for age, sex, race, diabetes mellitus, smoking, BMI, hypertension

[a]One participant who met criteria for a Grade = 0 was excluded from the analyses on Grade and one participant without data on smoking was excluded from the adjusted analyses in Table 4.

[b]Analyses of plaque area and lumen area were additionally adjusted for ABI. Pairwise *p*-value < 0.01.