Discrepancies in Prevalence of Peripheral Arterial Disease between Lower Extremities at Rest and Postexercise

Kevin P. Cohoon, DO, MSc^{1,2} Guillaume Mahe, MD, PhD^{1,3} David A. Liedl, RN^{1,2}
Thom W. Rooke, MD^{1,2} Paul W. Wennberg, MD^{1,2}

¹ Department of Cardiovascular Diseases and Gonda Vascular Center, Mayo Clinic, Rochester, Minnesota

² Department of Internal Medicine; Mayo Clinic, Rochester, Minnesota

³ Univ Rennes 1, University Hospital of Rennes, France and Inserm, Clinical Investigation Center (CIC) 1414, Rennes, France

Address for correspondence Paul W. Wennberg, MD, Gonda 4

Divisions of Cardiovascular Diseases, Mayo Clinic and Foundation for Education and Research, 200 First Street, SW, Rochester, MN 55905 (e-mail: wennberg.paul@mayo.edu).

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Abstract

Background Lower extremity peripheral arterial disease (PAD) is a common medical condition causing substantial morbidity. Limited data exist on whether discrepancies in PAD prevalence exist between the lower extremities using resting ankle-brachial indices (ABIs) and postexercise pressures.

Objective We predicted the prevalence of PAD between the lower extremities.

Methods and Results Consecutive patients who had undergone a noninvasive arterial lower extremity study at Mayo Clinic, Rochester, MN, between January 1996 and December 2012 with suspected PAD were retrospectively reviewed. We identified 12,312 consecutive patients who underwent an arterial lower extremity and an exercise treadmill study. Prevalence of PAD was assessed at rest and after exercise using two criteria: a resting ABI ≤ 0.90 and a postexercise pressure decrease of > 30 mm Hg. Mean age was 67 ± 12 years and there were 4,780 (39%) women studied. At rest, we found a higher prevalence of PAD on the left extremity (27.4%) compared with the right (24.6%) ($p < 0.0001$). After exercise, we found a higher prevalence of PAD on the right extremity (25.1%) compared with the left (19.0%) ($p < 0.0001$). These discrepancies between the prevalence of PAD at rest and after exercise were present in women and men.

Conclusion Using validated criteria of a resting ABI of ≤ 0.90 and postexercise ankle pressure decrease > 30 mm Hg, our results suggest that there is a significantly higher prevalence of PAD in the left lower extremity at rest, in contrast to a greater prevalence of abnormal postexercise testing in the right lower extremity. The reason(s) of these discrepancies remain to be studied.

Keywords

- peripheral arterial disease
- ankle-brachial index
- postexercise ankle-brachial index
- American Heart Association criteria

Lower extremity peripheral arterial disease (PAD) is a common disorder affecting approximately 8 to 12 million people in the United States.^{1,2} PAD is a strong predictor of systemic atherosclerosis with substantial morbidity and mortality.³ The 10-year risk of mortality in people diagnosed with PAD

has remained largely unchanged since the advent of the resting ankle-brachial index (ABI) and has been reported as high as 40%.⁴

The ABI is a commonly used noninvasive test for PAD that is easy to measure and economical.⁵ This index accounts for the

ratio of the systolic blood pressure measured at the ankle to that measured at the brachial artery and, if abnormal, is predictive of PAD.^{6,7} A normal resting ABI does not exclude PAD, and when combined with exercise treadmill testing, the sensitivity of the ABI can be significantly increased.⁸ The postexercise ABI has been shown to be predictive of future major adverse cardiac events.^{8,9} However, reports on the lower normal resting ABI threshold used to diagnose PAD vary widely, with abnormal cutoff points ranging from 0.80 to 1.04.^{1,2,5,10} Furthermore, in those with resting ABI > 0.90, a postexercise ankle pressure decrease of > 30 mm Hg or increase fall of > 20% has been suggested to diagnose PAD.^{10,11} We have previously shown that in a population, the ABI fall is more sensitive.¹²

A previous study has demonstrated a significantly lower resting and postexercise ABI in the left extremity when compared with the right, which could reflect a unilateral lower extremity predisposition to PAD.² Given the scarcity of literature on lower extremity discrepancies in suspected PAD patients, we conducted a retrospective analysis to assess the prevalence of PAD at rest (ABI ≤ 0.90) and after exercise (postexercise ankle pressure decrease of >30 mm Hg) between lower extremities.

Materials and Methods

Study Design, Setting, and Population

A retrospective, population-based, cohort study of consecutive patients with suspected PAD referred to the vascular center (both locally and remotely) for an arterial lower extremity study was conducted at a single tertiary care institution (Mayo Clinic, Rochester, MN) for the period January 1996 through December 2012. All patients referred for arterial lower extremity study were eligible for inclusion. We excluded patients who: (1) did not provide research authorization; (2) did not perform a treadmill exercise test; and (3) were aged < 18 years at the time of the arterial assessment. The Mayo Clinic Institutional Review Board approved the study.

Ankle-Brachial Index Measurements

Ankle-Brachial Index at Rest

After a 10-minute resting supine period, a registered vascular technician used a pressure cuff and a handheld Doppler probe to obtain systolic pressures in the right and left brachial, posterior tibial (PT), and dorsalis pedis (DP) arteries. The ABI was calculated by dividing the DP or PT pressures in each leg by the highest arm pressure. For each lower extremity, we considered the highest resting ABI to classify patients according to established categories: ABI ≤ 0.90 defined PAD; 0.90 < resting ABI; ≤ 1.00 defined borderline; 1.00 < resting ABI; < 1.40 defined normal; and resting ABI ≥ 1.40 defined a noncompressible artery.

Postexercise Ankle-Brachial Index

Participants who performed an exercise treadmill test had a postexercise ABI measured at the completion of the exercise

protocol or after stopping due to symptoms. At the termination of exercise, patients returned to the supine position and arm and ankle pressures at 1, 3, and 5 minutes after exercise were measured. Given the need to rapidly obtain pressure measurements after exercise, two technicians simultaneously measured systolic pressures of the aforementioned arteries. One technician measured the arm pressure whereas the other measured leg pressures. The arm with the highest systolic resting pressure at rest was used for the postexercise measurements.

Resting Doppler Waveform Analysis

Continuous Doppler waveform analysis is evaluated by a trained technician using a 4- to 8-MHz Doppler probe. Patients are examined in the supine position, and waveform analysis is evaluated at PT and DP arteries. The Doppler waveforms of each arterial segment, which were evaluated and recorded at rest and categorized into four grades: triphasic, biphasic, reduced biphasic, and monophasic. Reduced biphasic and monophasic were considered as abnormal waveforms.

Ankle-Brachial Index Classification Criteria Used to Determine Peripheral Arterial Disease

Positive lower extremity PAD were defined by criteria proposed by the 2012 American Heart Association (AHA) as a postexercise ankle pressure decrease > 30 mm Hg, whereas negative lower extremity PAD was defined as a postexercise ankle pressure decrease ≤ 30 mm Hg. At the leg level, the best Doppler signal between the PT and DP arteries was also recorded and determined which extremity was used to calculate the postexercise ABI. Postexercise ankle pressure difference was calculated as resting ankle pressure minus postexercise ankle pressure on the same artery. When the Doppler signal was not found at the leg level, although it was present at rest, a systolic pressure of 0 mm Hg was reported to calculate either the postexercise ABI or postexercise ankle pressure.

Treadmill Testing

Exercise testing was performed on a motor-driven treadmill with continuous electrocardiographic monitoring. Different treadmill test protocols were used depending on the patients' ability to walk. Walking speed used ranged from 0.8 to 2 mph with a 10% treadmill grade for all tests. The maximal duration for the treadmill test was 5 minutes, which corresponds to a maximal walking distance of ≈ 259 m.

Statistical Analysis

Data analyses (DAL and GCM) were conducted using JMP (version 9.0.1, SAS Institute Inc., Cary, NC) and MedCalc software (version 12.6.1.0, Belgium). Continuous variables were reported as means ± standard deviation (SD) and compared between groups using a *t*-test. The right and left ABI was measured in the same patient; therefore, a paired *t*-test was used. Categorical variables were reported as percentages and compared between groups using Pearson's chi-squared test for independent variables and McNemar test for

dependent variables. *p* Value using the two-tailed α level of ≤ 0.05 was considered statistically significant.

Results

General Characteristics

In our database, we identified 31,663 consecutive patients at Mayo Clinic, Rochester, MN, who underwent an arterial lower extremity study between January 1996 and December 2012 for suspected lower extremity PAD (**Fig. 1**). Of these, 12,312 patients (mean age: 67 ± 12 years) underwent an exercise treadmill study and were included for analysis. The main indication for an exercise treadmill study was for intermittent claudication ($n = 10,064$, 74%). The mean age was significantly different between women (mean age: 65 ± 14 years) and men (mean age: 68 ± 11 years) ($p < 0.0001$). There was no difference between women ($n = 1217$, 25%) and men ($n = 2,218$, 29%) who were aged ≥ 75 years ($p = 0.8687$). The sex distribution was different for the overall group (39% of women; 61% of men; $p < 0.0001$).

Ankle-Brachial Index and Doppler Waveforms at Rest

According to the AHA criteria for resting ABI, our cohort was made up of 4,317 (35%) with PAD, 1,554 (13%) were "borderline," 162 (1%) had noncompressible arteries, and 6,279 (51%) were normal. Comparisons of resting ABI, postexercise ABI, and postexercise ankle pressures between lower extremity and sexes are presented in **Table 1**. In the overall studied cohort, the mean resting ABI was 1.03 ± 0.23 for the right lower extremity and 1.02 ± 0.23 for the left lower extremity ($p \leq 0.0001$). The left lower extremity resting ABI remained

significantly lower in both sexes; the average overall resting ABI was 0.02 lower in the left extremity compared with the right. Differences in the resting ABI remained significantly lower for the left extremity compared with the right even when the overall group was subdivided into those with a resting ABI > 0.90 and ≤ 0.90 . There was no significant sex difference in the lower extremity resting ABI for individuals with an ABI > 0.90 . However, for the resting ABI ≤ 0.90 group, only the men continued to have a significantly lower resting ABI on the left extremity compared with right.

Resting Doppler waveforms analyses were also found to have significantly more abnormal than normal (triphasic/biphasic) waveforms in the left extremity compared with the right in each sex and between sexes. Significant Doppler waveform differences were observed in both the left PT ($n = 12,291$; missing 21) and DP arteries (DP) ($n = 12,292$; missing 20) when compared with their same right extremity artery (PT: $n = 12,299$, missing 13; DP: $n = 12,297$, missing 15) ($p < 0.05$) (**Fig. 2**). Furthermore, the DP artery was found to have significantly more abnormal Doppler waveforms when compared with the PT artery on the same lower extremity ($p < 0.001$).

Postexercise Ankle-Brachial Index and Ankle Pressures

Conversely, after exercise, the average overall postexercise ABI was at least 0.02 lower in the right extremity compared with the left (**Table 1**). In each extremity, the average overall postexercise ABI was at least 0.01 higher for women compared with men. The overall mean postexercise ABI of the left lower extremity was 0.95 ± 0.30 in those with an ankle pressure

Fig. 1 Flow diagram on the identification and selection of patients with suspected lower extremity peripheral arterial disease who underwent an exercise treadmill study and were included for analysis.

Table 1 Comparisons of resting ABI, postexercise ABI, and postexercise ankle pressures between lower extremity and sexes in the overall group

Variable	Overall (n = 12,312)		Women (n = 4,780)		Men (n = 7,532)	
	Right	Left	Right	Left	Right	Left
Lower extremity						
At rest						
Overall						
Number of extremity	12,308	12,306	4,778	4,779	7,530	7,527
Resting ABI	1.03 ± 0.23 ^a	1.02 ± 0.23 ^a	1.03 ± 0.21 ^{a,b}	1.01 ± 0.21 ^{a,b}	1.04 ± 0.26 ^{a,b}	1.02 ± 0.26 ^{a,b}
Patients with ABI > 0.90						
Number of extremity	9,280	8,930	3,735	3,599	5,545	5,331
Resting ABI	1.14 ± 0.10 ^a	1.13 ± 0.09 ^a	1.12 ± 0.12 ^{a,b}	1.11 ± 0.12 ^{a,b}	1.16 ± 0.15 ^{a,b}	1.15 ± 0.15 ^{a,b}
Patients with ABI ≤ 0.90						
Number of extremity	3,028	3,376	1,043	1,180	1,985	2,196
Resting ABI	0.72 ± 0.17 ^a	0.71 ± 0.12 ^a	0.71 ± 0.13 ^b	0.72 ± 0.14 ^b	0.72 ± 0.13 ^{a,b}	0.71 ± 0.14 ^{a,b}
After exercise						
Overall						
Number of extremity	12,305	12,305	4,778	4,779	7,527	7,526
Postexercise ABI	0.82 ± 0.35 ^a	0.85 ± 0.34 ^a	0.83 ± 0.32 ^{a,b}	0.85 ± 0.31 ^a	0.81 ± 0.37 ^{a,b}	0.84 ± 0.36 ^a
Postexercise ankle pressure difference (mm Hg)	-4.6 ± 37.3 ^a	1.7 ± 35.2 ^a	-1.4 ± 34.2 ^{a,b}	4.1 ± 32.2 ^{a,b}	-6.6 ± 39.0 ^{a,b}	0.3 ± 37.0 ^{a,b}
Patients with postexercise decrease ≤ 30 mm Hg						
Number of extremity	9,216	9,965	3,803	4,061	5,413	5,904
Postexercise ABI	0.96 ± 0.26 ^a	0.95 ± 0.27 ^a	0.94 ± 0.24 ^b	0.94 ± 0.24 ^b	0.97 ± 0.27 ^b	0.96 ± 0.29 ^b
Postexercise ankle pressure difference (mm Hg)	12.3 ± 24.3 ^a	14.6 ± 24.1 ^a	11.8 ± 22.8 ^a	14.1 ± 22.3 ^a	12.6 ± 25.3 ^a	15.0 ± 25.2 ^a
Patients with postexercise decrease > 30 mm Hg						
Number of extremity	3,089	2,340	975	718	2,114	1,622
Postexercise ABI	0.40 ± 0.23 ^a	0.38 ± 0.22 ^a	0.41 ± 0.22 ^a	0.38 ± 0.21 ^a	0.40 ± 0.23 ^a	0.38 ± 0.23 ^a
Postexercise ankle pressure difference (mm Hg)	-54.8 ± 20.3 ^a	-53.0 ± 19.1 ^a	-52.8 ± 19.2 ^b	-52.1 ± 18.2	-55.7 ± 20.7 ^{a,b}	-53.3 ± 19.4 ^a

Abbreviation: ABI, ankle-brachial index.

At rest, four right lower extremities had absent data (three with prosthesis, one with a deep vein thrombosis) whereas four left lower extremities were absent (four with prosthesis). After exercise, three pressure measurements on right and left extremities were not done due to the technician's discretion.

^ap value < 0.05 using t-test when comparing right extremities between left extremities.^bp value < 0.05 using t-test when comparing right extremities of women to men and left extremities of women to men.

Fig. 2 Comparison between the percentage of abnormal lower extremity Doppler waveforms within the posterior tibial and dorsalis pedis artery within the right and left extremities.

drop ≤ 30 mm Hg and 0.38 ± 0.24 in those > 30 mm Hg ($p < 0.0001$) at 1 minute postexercise measurements.

Prevalence of Peripheral Arterial Disease at Rest and After Exercise between Lower Extremities

Comparisons between the prevalence of PAD at rest and after exercise are presented in ►Fig. 3. In the overall population, at rest, we found a higher prevalence of PAD on the left extremity (27.4%) compared with the right (24.6%) ($p < 0.0001$). Conversely, after exercise, we found a higher prevalence of PAD on the right extremity (25.1%) compared with the left (19.0%) ($p < 0.0001$). In women, the prevalence of PAD was significantly higher in their left extremity (24.7%) when compared with their right extremity (21.8%) ($p < 0.0001$) at rest, whereas the prevalence of PAD was significantly lower in their left extremity (15.0%) when compared with their right extremity (20.4%) after exercise ($p < 0.0001$). Similarly, the prevalence of PAD in men was significantly higher in their left extremity (29.2%) when compared with their right extremity (26.4%) ($p < 0.0001$) at rest, whereas the prevalence of PAD was significantly lower in their left extremity

Fig. 3 Comparisons of the percentage of PAD (ankle-brachial index [ABI] ≤ 0.90) at rest and after exercise (postexercise decrease > 30 mm Hg) between the right and left extremities.

(21.5%) when compared with their right extremity (28.1%) ($p < 0.0001$) measured at 1 minute postexercise.

►Fig. 4A and B provides the subgroup comparison between the prevalence of those with and without PAD according to normal and borderline resting ABI in the right and left extremity. Individuals within the borderline group had a profound leg discrepancy according to postexercise PAD criterion (right: 34% PAD; left 22% PAD) compared with the normal group (right: 10% PAD; left 6% PAD) ($p < 0.0001$). In women, the prevalence of PAD with the borderline subgroup was significantly higher in their right extremity (25%) when compared with their left extremity (16%) after exercise ($p < 0.0001$). Similarly to women, the prevalence of PAD in men within the borderline subgroup was significantly higher in their right extremity (40%) compared with the left (26%) after exercise ($p < 0.0001$). In most cases, the resting ABI and postexercise pressure decrease were studied on the same artery for both extremities (69% for the right extremity and 66% for the left extremity) to calculate the prevalence of PAD. At 3 and at 5 minutes postexercise measurements, the overall prevalence of PAD remained significantly higher in the right extremity when compared with the left extremity (3 minutes; right extremity 10.9% vs. left extremity 9.0%; $p < 0.0001$; 5 minutes right extremity 6.8% vs. left extremity 6.4%; $p < 0.0001$). This remains significant for both postexercise time periods for women and men. Differences in the mean postexercise ankle pressures were discordant to the mean postexercise ABI measurements in these subgroups. The mean postexercise ankle pressure decrease was significant between the right lower extremity compared with the left in those with an ankle pressure drop ≤ 30 mm Hg and > 30 mm Hg. Most postexercise measurements were performed on the posterior tibialis artery on the right ($n = 11,177$; 91%) and left ($n = 11,203$; 91%) lower extremity ($p = \text{nonsignificant}$).

Discussion

In a large retrospective study, we found that there are discrepancies between the lower extremities in the prevalence of PAD at rest and postexercise. When using validated criteria of a resting ABI of ≤ 0.90 and postexercise ankle pressure decrease > 30 mm Hg,¹³ we found a significantly higher prevalence of PAD in the left lower extremity when compared with the right at rest and vice versa postexercise. Resting Doppler waveform analyses confirmed the significant difference in the prevalence of lower extremity PAD demonstrated in the left extremity compared with the right. In contrast to the observed leg discrepancy at rest, the postexercise pressures were significantly lower in the right extremity compared with the left. These differences remained consistent between sexes in the overall population.

Differences of ABI between right and left lower extremities at rest and postexercise ABI has previously been reported,² but there remain limited data in the literature of these discrepancies. In the San Luis Valley Diabetes Study,² the mean ABI at rest and after exercise were assessed in 430 non-insulin-dependent diabetic patients and 1,280 nondiabetic

Fig. 4 (A) Comparisons between overall population, sexes, and right and left extremities among those with normal and borderline resting ankle-brachial index (ABI) and postexercise decreased ≤ 30 mm Hg after exercise. (B) Comparisons between overall population, sexes, and right and left extremities among those with normal and borderline resting ABI and postexercise decreased > 30 mm Hg after exercise.

control patients. This study demonstrated similar findings to the present study in which the resting ABI in the left extremity was 0.02 lower than the right resting ABI.² Although there are statistically significant differences of resting ABI between the lower extremities, this may not represent a clinically significant finding given that the differences ranged from 0.01 to 0.02 in the overall group.² Furthermore, the average resting ABI value was lower in women than in men showing similarity to our study. However, the difference between the resting ABI between sexes was 0.06 greater in the San Luis Valley Diabetes Study compared with ours. They also reported that the resting ABI measured in the DP was 0.04 lower than in the PT artery whereas our difference was smaller (0.01; $p = 0.0007$). To confirm the higher prevalence of PAD at rest on the left lower extremity compared with the right, we used continuous Doppler waveforms. This noninvasive test confirmed the higher prevalence of PAD on the left lower extremity compared with the right, which has not been reported previously. This lower extremity discrepancy observed at rest may represent an anatomical or physiologic variation that predisposes the left extremity to disease, similar to what is seen in May-Thurner disease.

In contrast to the San Luis Valley Diabetes Study,² our study demonstrated lower extremity discordance in the prevalence of PAD after exercise compared with rest. However, because there remains debate over specific abnormal postexercise ABI cutoff points, we used validated postexercise pressure decrease > 30 mm Hg.¹³ Using this postexercise criterion, we found a higher prevalence of PAD on the right extremity compared with the left in the overall analysis and within the normal and borderline subgroups. The prevalence of PAD remained consistent between sexes when evaluated within the normal and borderline subgroups. Moreover, individuals within the borderline group had a profound leg discrepancy

compared with the normal group, suggesting that the borderline group may have a hemodynamic component to support these observed leg discrepancies. Because the left lower extremity at rest expressed more PAD (i.e., more arterial stenosis),¹⁴ more collateral vessels may have developed in this lower extremity resulting in improvement of the postexercise pressure. Recent literature in animals and humans suggests that exercise training induces collateral vessel development and enlargement during exercise.^{15–17} It is also plausible that there is a technical explanation. In the present study and as outlined in the AHA ABI measurements scientific statement,¹³ when postexercise pressures are measured, the technicians usually worked from right to left, allowing the left lower extremity slightly more time to recover ankle pressure after exercise than the right extremity. This could falsely decrease the postexercise pressure on the left compared with the right making it appear that there is a higher prevalence of PAD in the opposite extremity than noted at rest. Therefore, we evaluated the postexercise pressure at 3 and at 5 minutes to address this possible technical cause, and the lower extremity discrepancies remained in the overall group and between sexes. To further confirm our novel findings and address this possible technical cause, additional studies are needed. For example, both lower extremities could be simultaneously measured by technicians or automatic pressure devices could be used as it has been suggested for the diagnosis of arterial endofibrosis.¹⁸ Furthermore, the use of postexercise Doppler waveforms tested at the DP or PT arteries could be helpful.^{19,20}

Our study has several strengths. To our knowledge, the present study is one of the largest retrospective cohorts involving all consecutive suspected PAD. This affords us the opportunity to evaluate the associations of PAD by sex variation in a large referral center. Moreover, it allows us to observe if there are lower extremity discrepancies without the need

to adjust for comorbid conditions as one extremity is compared with the other in the same individual.

Our study has several limitations. This is a retrospective analysis and, therefore, bias might influence the results, especially as the reasons for conducting an exercise test might be confounded. The fact that the observed differences are significant may not mean that they are also relevant, as the differences observed are small. The recent AHA recommendation that the same artery (DP or PT) be used for all rest and postexercise measurements was not strictly followed because the dataset predates the recommendation. However, when correcting for this in a second analysis, we found identical results (data not shown). The estimates are for a single tertiary care center, which is predominantly white of non-Hispanic ancestry. Tertiary referral centers often care for patients for multiple complex comorbidities that may differ from community centers. Therefore, our findings may not be generalized to other populations. The identification of PAD is based on retrospective analysis of laboratory records; thus individuals who did not seek medical attention are not included. In addition, this study did not have a control group of participants that were of the general population that were not referred to the noninvasive vascular laboratory, and these results may only be generalizable in patients who are able to perform an exercise treadmill study.

In conclusion, we found a discrepancy between the prevalence of PAD between lower extremities at rest and after exercise. The prevalence of PAD was higher in the left lower extremity at rest whereas it was lower after exercise. The explanation of this difference needs additional studies to identify an anatomical variation or pathophysiologic adaptations versus a technical measurements issue in obtaining postexercise pressure.

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Disclosures

None.

Conflict of Interest

None.

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