

## Ankle-Brachial Index Testing at the Time of Stress Testing in Patients Without Known Atherosclerosis

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### ABSTRACT

**Background:** Individuals referred for stress testing to identify coronary artery disease may have nonobstructive atherosclerosis, which is not detected by stress tests. Identification of increased risk despite a negative stress test could inform prevention efforts. Abnormal ankle-brachial index (ABI) is associated with increased cardiovascular risk.

**Hypothesis:** Routine ABI testing in the stress laboratory will identify unrecognized peripheral arterial disease in some patients.

**Methods:** Participants referred for stress testing without known history of atherosclerotic disease underwent ABI testing ( $n = 451$ ). Ankle-brachial index was assessed via simultaneous arm and leg pressure using standard measurement, automated blood-pressure cuffs at rest. Ankle-brachial index was measured after exercise in 296 patients and 30 healthy controls. Abnormal postexercise ABI was defined as a  $>20\%$  drop in ABI or fall in ankle pressure by  $>30$  mm Hg.

**Results:** Overall, 2.0% of participants had resting ABI  $\leq 0.90$ , 3.1% had ABI  $\geq 1.40$ , and 5.5% had borderline ABI. No patient with abnormal or borderline ABI had an abnormal stress test. Participants who met peripheral arterial disease screening criteria (age  $\geq 65$  or 50–64 with diabetes or smoking) tended toward greater frequency of low ABI (2.9% vs 1.0%;  $P = 0.06$ ) and were more likely to have borderline ABI (0.91 to 0.99; 7.8% vs 2.9%;  $P = 0.006$ ). Postexercise ABI was abnormal in 29.4% of patients and 30.0% of controls ( $P$  not significant).

**Conclusions:** Ankle-brachial index screening at rest just before stress testing detected low ABI in 2.0% of participants, all of whom had negative stress tests.

### Introduction

The ankle-brachial index (ABI) is a very sensitive and specific method for the diagnosis of peripheral arterial disease (PAD).<sup>1</sup> In addition, abnormal ABI is a prognostic marker for future cardiovascular events and functional impairment,

even in the absence of symptoms.<sup>2–4</sup> American College of Cardiology/American Heart Association (ACC/AHA) guidelines for management of PAD recommend ABI screening for lower-extremity PAD among asymptomatic individuals at increased risk (age  $\geq 65$  or age 50–64 with history of smoking or diabetes mellitus [DM]). The reference standard for ABI is measurement via handheld Doppler, with separate measurements of the posterior tibial and dorsalis pedis arteries, as well as both brachial arteries. Measurement of ABI using automated blood pressure cuffs, which relies on the principle of oscillometry, offers an easier and more convenient way to implement screening. Oscillometric determination of ABI correlates well with Doppler in multiple studies, especially in patients with normal ABI or mild PAD; in more severe PAD, oscillometry tends to underestimate the severity of disease.<sup>1,5–7</sup>

The sensitivity of ABI for obstructive PAD may be increased by addition of a measurement immediately

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after exercise.<sup>1</sup> The ACC/AHA guidelines suggest it is reasonable to perform exercise ABI measurement in at-risk patients with normal ABI without classic symptoms or other evidence of atherosclerosis.<sup>8</sup> The guidelines do not specify the type of exercise to be used.

Patients referred for stress testing represent an at-risk group in whom detection of subclinical atherosclerosis could alter the risk-reduction approach. It is well known that myocardial infarction is frequently caused by rupture of plaques that were not obstructive before the event, and therefore are not detected by routine stress testing, and that atherosclerosis is a diffuse process.<sup>9,10</sup> We hypothesized that the addition of resting ABI measurements, and subsequent postexercise ABI measurements in those who were normal, to participants referred for stress testing would identify participants with abnormal ABI among those with normal stress tests.

## Methods

Participants who were referred for stress testing at the New York University Langone Medical Center and Bellevue Hospital Center for suspected coronary artery disease (CAD) were screened and approached for participation between October 2012 and March 2014. The New York University institutional review board approved the study protocol, and all participants provided informed consent. Participants were excluded if they were referred for stress testing for an indication other than suspected CAD and if they had a known history of atherosclerotic vascular disease, including CAD, carotid artery disease, PAD, or abdominal aortic aneurysm, whether or not they had a prior clinical event. Demographics and relevant history were collected from the medical record. Cardiac risk factors were based on appearance in the medical record as entered by the referring provider or if the patient reported the risk factor during preprocedure evaluation. Participants were characterized as meeting ACC/AHA guideline criteria for ABI screening (age  $\geq 65$  or 50–64 with history of DM or current or former tobacco use) or not meeting these criteria. The Edinburgh Questionnaire, a 6-question screen for symptoms of claudication, was administered to all participants.<sup>11</sup>

Ankle-brachial index measurements were obtained with the patient lying supine with the use of 3 separate automated blood pressure cuffs (Philips Healthcare, Andover, MA). Resting measurements were obtained simultaneously in the right arm and both legs, followed by the left arm. Resting ABI for each leg was calculated as the ankle pressure divided by the higher of the 2 brachial pressures.<sup>1</sup> Normal ABI was defined as 1.00 to 1.39 in both legs. Peripheral arterial disease was defined as ABI  $\leq 0.90$  in either leg. Abnormally high ABI was defined as ABI  $\geq 1.40$  in either leg. Borderline ABI was defined as ABI between 0.91 to 0.99 in either leg in participants without PAD or abnormally high ABI.<sup>1</sup>

Stress testing was carried out using the symptom-limited Bruce protocol. Postexercise measurements were obtained in participants with normal or borderline resting ABI as soon as the patient was able to lie down in recovery. Blood pressure was measured simultaneously in both legs and the right arm with the patient lying flat to calculate postexercise ABI. If automated measurement of blood pressure in either

leg was not complete by the time the arm pressure measurement was complete, a second arm pressure was obtained that was simultaneous with leg pressure measurement. In such cases, the simultaneous arm measurement was used for ABI calculation for that leg. Some enrolled participants (132 participants in total) did not undergo measurement of postexercise ABI because an insufficient number of automated blood pressure cuffs were available at the time of testing.

A group of 30 healthy individuals age  $\leq 40$  years free of all risk factors for cardiovascular disease (CVD) were enrolled as a control group for resting and exercise ABI measurement. These control participants also exercised according to the symptom-limited Bruce protocol.

Abnormal post-exercise ABI was defined as a  $>20\%$  decrease in ABI or a  $>30$  mm Hg decrease in ankle pressure as defined by the AHA Scientific Statement on measurement and interpretation of ABI.<sup>1</sup>

## Statistical Analysis

Continuous variables are represented by means and SDs and were compared using the Student *t* test or analysis of variance, depending on the number of groups in the comparison. All analyses were performed using Microsoft Excel 2011, version 14.0.6112.5000.<sup>4</sup> When a *P* value  $< 0.05$  was obtained during  $2 \times 3$   $\chi^2$  testing or ANOVA, we tested  $2 \times 2$  comparisons and report these in the tables. *P*  $< 0.05$  was considered statistically significant.

## Results

A total of 1255 patients referred for stress testing were screened for participation. Four hundred fifty-one eligible participants were enrolled, with average age  $58.9 \pm 12.4$  years (Table 1). The remaining patients were excluded due to known atherosclerotic disease or an indication for stress testing other than for the suspected diagnosis of CAD. Among enrolled participants, 34.4% had a history of current or former tobacco use, 49.1% had a history of hypertension, and 12.9% had a history of DM. Participants' medication use is shown in Table 1; about one-third were taking aspirin, statins, and angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs).

At rest, 2.0% of participants had ABI  $\leq 0.90$ , consistent with undiagnosed PAD. Ankle-brachial index was  $\geq 1.40$  in 3.1% of participants, consistent with poorly compressible arteries (Figure 1). An additional 5.5% had borderline ABI (0.91–0.99).

On chart review, 244 (54.1%) of participants met criteria for ABI screening according to the PAD guidelines. Participants who met guideline criteria for PAD screening trended toward having higher rates of low ABI than participants who did not meet screening criteria (2.9% vs 1.0%; *P* = 0.06). Participants who met screening criteria were more likely to have a borderline ABI (7.8% vs 2.9%; *P* = 0.005; Table 2). There was no difference in the frequency of abnormal ABI, high or low, in men compared with women (Table 2).

Overall, 11 participants had claudication as assessed by the Edinburgh Questionnaire, including 1 of 9 participants with low ABI (11%) and 2 of 25 with borderline ABI (8%). Among participants with low or high ABI, none had a positive stress test for ischemia.

Table 1. Comparison of Participant Characteristics by Resting ABI Results

Characteristic	Total, N = 451	ABI $\leq$ 0.90, n = 9	ABI $\geq$ 1.40, n = 14	Borderline ABI, 0.91–0.99, n = 25	Normal, n = 403	P Value <sup>a</sup>
Age, y, mean $\pm$ SD	58.9 $\pm$ 12.4	62.8 $\pm$ 14	61.6 $\pm$ 11.1	61.4 $\pm$ 11.3	58.6 $\pm$ 12.5	0.43
Male sex, %	49.7	44.4	57.1	40.0	50.1	0.71
Hypertension, %	49.1	100.0	50.0	76.0	46.2	<0.001 <sup>b</sup>
Hyperlipidemia, %	51.8	77.8	50.0	52.0	51.1	0.47
DM, %	12.9	44.4	0.0	20.0	12.2	0.01 <sup>c</sup>
Tobacco use (current or former), %	34.4	44.4	35.7	36.0	34.0	0.93
Family history of CAD, %	32.9	66.7	28.6	28.0	32.5	0.17
BMI $\geq$ 30 kg/m <sup>2</sup> , %	63.6	77.8	71.4	80.0	61.8	0.10
Race = white, %	75.4	77.8	78.6	84.0	74.7	0.75
Definite claudicant (Edinburgh), %	2.4	11.1	0.0	8.0	2.0	0.08
Positive stress test, %	6.2	0.0	0.0	0.0	7.0	0.31
Peak exercise METs, n = 418	9.5	7.6	9.3	9	9.6	0.06
Attained $\geq$ 85% maximal predicted HR, n = 426, %	88.3	62.5	100	66.7	89.7	<0.0001 <sup>d</sup>
Medications, %						
ASA	35.3	66.7	42.9	44.0	33.7	0.14
Statin	40.4	66.7	28.6	44.0	40.0	0.31
ACEI or ACEI/ARB	30.0	55.6	28.6	52.0	28.0	0.03 <sup>e</sup>
$\beta$ -Blocker	18.2	55.6	21.4	24.0	16.9	0.02 <sup>f</sup>

Abbreviations: ABI, ankle-brachial index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, aspirin; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; HR, heart rate; MET, metabolic equivalent; SD, standard deviation.  
<sup>a</sup>P value for comparison of all 4 groups. <sup>b</sup>Normal vs low ABI  $P = 0.001$ ; normal vs borderline ABI  $P = 0.004$ ; normal vs high ABI  $P = 0.78$ . <sup>c</sup>Normal vs low ABI  $P = 0.004$ ; normal vs borderline ABI  $P = 0.25$ ; normal vs high ABI  $P = 0.16$ . <sup>d</sup>Normal vs low ABI  $P = 0.01$ ; normal vs borderline ABI  $P < 0.001$ ; normal vs high ABI  $P = 0.21$ . <sup>e</sup>Normal vs low ABI  $P = 0.07$ ; normal vs borderline ABI  $P = 0.01$ ; normal vs high ABI  $P = 0.97$ . <sup>f</sup>Normal vs low ABI  $P = 0.002$ ; normal vs borderline ABI  $P = 0.36$ ; normal vs high ABI  $P = 0.66$ .

Participants with low ABI tended to achieve lower metabolic equivalents (METs) during stress compared with those with normal ABI (7.6 vs 9.6 METs;  $P = 0.06$ ). Participants with low or borderline ABI less frequently achieved  $\geq 85\%$  of the maximum predicted heart rate during exercise compared with those with normal ABI (normal vs low,  $P = 0.01$ ; normal vs borderline,  $P < 0.001$ ).

Among 296 patients with normal resting ABI in whom postexercise ABI was obtained, 87 patients (29.4%) met  $\geq 1$  criterion for abnormal ABI after exercise (Table 3). Of those 87 patients, 73 met only the criterion of 20% drop in ABI after exercise, 2 had a 30 mm Hg drop in their ankle pressure with exercise but not a 20% drop in ABI, and 12 patients met both criteria. Patients with abnormal postexercise ABI were younger than those with normal postexercise ABI (mean age,  $56.0 \pm 12.2$  years vs  $59.3 \pm 12.3$  years;  $P = 0.05$ ). There was no difference in rates of hypertension, DM, dyslipidemia, or current or former smoking between the 2 groups. There was no significant difference in exercise capacity as measured by peak METs achieved between those with abnormal postexercise ABI vs those without (9.9 vs 9.5 METs;  $P = 0.11$ ).

Among 30 healthy controls without any cardiovascular risk factors or symptoms of PAD, the average age was  $26 \pm 3$  years. All had normal resting ABIs. Nine controls (30%) met criteria for abnormal postexercise ABI, 7 of whom had a 20% drop in ABI with exercise, 1 of whom had a decrease in ankle pressure of 30 mm Hg, and 1 of whom met both criteria. There was no difference in rates of abnormal exercise ABI among patients screened and healthy controls (29.4% vs 30%;  $P = 0.94$ ).

## Discussion

We added ABI screening via oscillometric determination with the aim of detecting subclinical atherosclerosis in patients referred for stress testing for suspected CAD. We found abnormal resting ABI at the time of stress testing in 5.1% of participants without prior history of atherosclerotic disease, with 2.0% of patients having low ABI consistent with PAD and 3.1% of patients having high ABI suggestive of poorly compressible arteries. An additional 5.5% of participants had borderline ABI. Although the likelihood of abnormal or borderline resting ABI was higher among the 54% of participants who met guideline

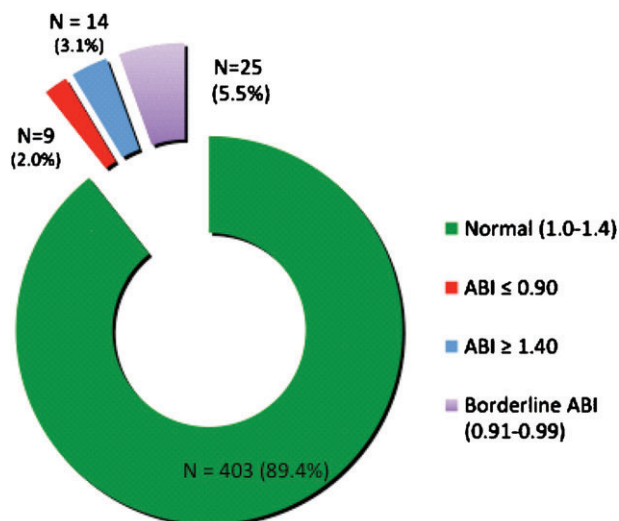


Figure 1. Distribution of ABI results in all participants. Abbreviations: ABI, ankle-brachial index.

Table 2. ABI Results by Subgroup

	ABI ≤0.90, % (total)	ABI ≥1.40, % (total)	Normal, % (total)	Borderline ABI, % (total)	P Value <sup>a</sup>
Screen <sup>b</sup>	2.9 (7)	3.7 (9)	85.6 (209)	7.8 (19)	0.04 <sup>c</sup>
No screen	1.0 (2)	2.4 (5)	93.7 (194)	2.9 (6)	
M	1.8 (4)	3.6 (8)	90.2 (202)	4.5 (10)	0.52
F	2.2 (5)	2.6 (6)	93.0 (211)	2.2 (5)	

Abbreviations: ABI, ankle-brachial index; DM, diabetes mellitus; F, female; M, male.

<sup>a</sup>P value for comparison among all groups. <sup>b</sup>Patients who met screening criteria by current guidelines<sup>28</sup>: age ≥65 years or age 50–64 with history of DM or tobacco use. <sup>c</sup>Normal vs low ABI  $P = 0.06$ ; normal vs borderline ABI  $P = 0.005$ ; normal vs high ABI  $P = 0.16$ .

indications for screening, the frequency of low ABI identified in our population was lower than expected based on other screening studies. No participant with low ABI had an abnormal stress test. Thus, ABI testing did provide distinct information from stress testing about cardiovascular risk in this group.

Measuring ABI by oscillometry takes less than 5 minutes and is easy to perform. Although Doppler remains the gold standard in measurement of ABI, it is technically more difficult and time-consuming to perform. This may be the reason that many patients at risk go without screening.<sup>12–14</sup> Furthermore, testing in the stress laboratory offers the advantage of convenience for patient and physician, because the patient is already in a noninvasive testing area for the purpose of cardiovascular risk assessment. Based on a large meta-analysis, the specificity of PAD diagnosis as measured by oscillometry compared with Doppler is high, at 96%, whereas sensitivity is lower, at 69%.<sup>6</sup> Thus, patients identified as abnormal using oscillometric ABI are likely

to be truly abnormal, though some patients with true PAD may be missed using this approach. Because oscillometric determination of ABI results in a slightly higher value than Doppler determination, some have suggested that to increase sensitivity in detection of PAD, a threshold of 1.0 might be preferable.<sup>6</sup>

We speculate that the lower-than-expected frequency of low ABI detected in our study may be related to the oscillometric technique, given the known potential for overestimation of ABI by oscillometry as compared with Doppler. We suspect that some of the participants found to have borderline ABI in our study would have low ABI as measured by Doppler. We did not use Doppler to confirm normal oscillometric ABI because the prior literature demonstrates that oscillometry and Doppler are well correlated, especially in patients with normal ABI.<sup>1,5–7</sup>

The demographics of the study population likely also contributed to the lower-than-anticipated prevalence of PAD



Table 3. Postexercise ABI

	Participants, n = 296	Controls, n = 30	P Value
Total abnormal postexercise	87 (29.4)	9 (30.0)	0.94
Abnormal (>20% drop in ABI)	73 (24.7)	7 (23.3)	0.54 <sup>a</sup>
Abnormal (>30 mm Hg drop)	2 (0.7)	1 (3.3)	
Abnormal (>30 mm Hg drop + >20% drop)	12 (4.1)	1 (3.3)	
Normal	209 (70.6)	21 (70.0)	

Abbreviations: ABI, ankle-brachial index.

Data are presented as n (%).

<sup>a</sup>2 × 4 test for comparison among all 4 potential groups.

based on low ABI. In a National Health and Nutrition Examination Survey (NHANES) survey, the prevalence of ABI  $\leq 0.90$  was 4.7% among tested adults without established CVD; and in the Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) study, which screened patients without known CVD age  $\geq 70$  or age 50 to 69 with history of DM or smoking, low ABI was found in 7% of patients.<sup>15,16</sup> Our participants were on average younger than the NHANES and PARTNERS cohorts, with lower rates of smoking and DM, and we examined mostly those undergoing exercise stress testing. Patients referred for pharmacologic stress testing may theoretically have a higher prevalence of undiagnosed PAD. Furthermore, we excluded all patients with known history of any atherosclerosis, including mild carotid plaque, because the goal of this study was to determine the ability of ABI testing at the time of stress testing to identify subclinical atherosclerosis in patients not otherwise known to have this problem.

In addition to those participants found to have low ABI, 3.1% of our study participants had ABI  $\geq 1.40$ , consistent with poorly compressible arteries. The outcome of patients with high ABI has been inconsistent across different studies. In the Multiethnic Study of Atherosclerosis (MESA), high ABI was associated with incident CVD at similar rates as compared with low ABI. However, this group was a very small fraction of the population and there were a limited number of events in this group.<sup>17</sup> In contrast, in the Atherosclerosis Risk in Communities (ARIC) survey, there was no difference in adjusted CVD event rates between those with high ABI and normal ABI.<sup>18</sup> It has been suggested in one study that the differences in prognosis observed may relate to the actual presence or absence of coexisting occlusive PAD in the populations studied, such that only those with coexisting PAD are at increased risk.<sup>19</sup> We did not perform further testing to assess for occlusive PAD in our patients with high ABI, and it is unclear what the risk associated with this finding in our patients may be. Current guidelines do not specifically address the evaluation and management of this patient population. Future research is warranted in this regard.<sup>8</sup>

We had hypothesized that the addition of postexercise measurements would permit diagnosis of PAD in an additional subset of patients with normal resting ABI. This was of interest because in patients referred to a vascular laboratory, abnormal postexercise ABI is associated with higher long-term mortality in some studies and also an increased rate of incident lower-extremity revascularization.<sup>20–23</sup> In healthy people, the systolic pressure increases with exercise in the central circulation, whereas it decreases at the ankle due to vasodilation in exercising muscle. In the case of PAD, the ankle pressure decreases more than in healthy people and takes longer to recover. Because our patients were referred for exercise stress testing and because exercise ABI recommendations do not specify type of exercise, we assessed postexercise ABI after the Bruce protocol. In clinical practice, exercise ABI is typically performed in patients with a clinical suspicion of PAD when resting ABI is normal. Previous studies that have examined the normal response to exercise have used either 1 minute of treadmill exercise or low-intensity protocols typically carried out in vascular laboratories.<sup>24–26</sup> In our study, about one-third of patients and healthy controls without any risk factors for PAD met criteria for abnormal postexercise ABI. A potential explanation for these findings is that the response in ankle pressure to exercise may vary according to exercise intensity, with more intense exercise protocols leading to the potential for a greater drop in ankle pressure.<sup>27</sup> Though guidelines do not specify type of exercise when performing exercise ABI, we conclude based on our data that the Bruce protocol is not appropriate for this assessment, at least when using oscillometric measurements.

This study demonstrates that clinically relevant information can be obtained with the simple addition of automated oscillometric ABI measurements just before stress testing. Testing in the stress laboratory offers the advantage of convenience for the patient and physician, because the patient is already in a noninvasive testing area for the purpose of cardiovascular risk assessment. However, in this sample of patients, which excluded patients with any known atherosclerosis and who were referred mostly for exercise rather than pharmacologic stress testing, the prevalence of low ABI diagnostic of PAD was low. The prevalence may be higher among patients referred for pharmacologic stress testing; this should be a focus of future study.

One potential application of our findings would be to screen either all referred patients or specifically those who already meet recommended screening guidelines with oscillometric ABIs. Those who were found to have an abnormal or borderline ABI could go onto confirmatory testing with Doppler. The use of sequential Doppler testing in these patients, including the borderline group, would likely increase the identification of patients with PAD.

## Conclusion

Ankle-brachial index screening before stress testing using automated blood pressure cuffs in the stress laboratory led to identification of unsuspected PAD in 2.0% of participants. The yield of oscillometric screening for PAD in this population was low. Postexercise testing using our study methods did not yield reliable results.

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