Borderline peripheral arterial disease

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Peripheral arterial disease (PAD), along with coronary artery disease and cerebrovascular disease, is a manifestation of systemic atherosclerosis. These cardiovascular diseases (CVDs) are the leading cause of death in the world, representing 30% of all global deaths. Although population-based studies indicate that PAD has a relatively benign course in the legs, patients with PAD show more cardiovascular comorbidity and have at least twofold risk of fatal coronary artery disease and cerebrovascular accidents compared with the general population. These studies suggest that noninvasive testing using the ankle-brachial index (ABI) is also an accurate marker of subclinical CVD and thus may hold promise for early identification of individuals at the greatest risk for major CVD events.

The Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) defines a cutoff ABI value of 0.90 or less for diagnosing PAD at rest. This threshold value has been reported to be 95% sensitive in detecting angiogram-positive PAD and almost 100% specific in identifying apparently healthy individuals. In persons without PAD, arterial pressures increase with greater distance from the heart, resulting in higher systolic blood pressures at the ankle than at the the brachial arteries. Thus, persons without atherosclerosis typically have an ABI greater than 1.00. But what is the significance of ABI values between 0.91 to 1.00, which are conventionally regarded as 'no disease'? The present article gives an overview of current knowledge of borderline PAD (ie, an ABI of 0.91 to 1.00).

Key Words: *Ankle-brachial index; Borderline peripheral arterial disease; Cardiovascular disease; Cardiovascular risk; Peripheral arterial disease*

THE PREVALENCE AND ASSOCIATED RISK FACTORS OF BORDERLINE PERIPHERAL ARTERIAL DISEASE

Few population-based studies have reported the prevalence of peripheral arterial disease (PAD) and borderline PAD (Table 1). These epidemiological studies have used slightly different cutoff values to indicate PAD and borderline PAD. The study populations of the Framingham Offspring Study (1) and the 1999 to 2002 National Health and Nutrition Examination Survey (NHANES) (2) were unselected samples of United States adults, whereas the participants of the Multi-Ethnic Study of Atherosclerosis (MESA) (3) were free of clinically evident cardiovascular disease (CVD).

The prevalence of borderline PAD at the population level is almost twofold higher than that of PAD. According to the results of NHANES and MESA, women have a twofold higher age-adjusted prevalence of borderline PAD than men (2,3). Within the ethnic groups of MESA, prevalences of PAD and borderline PAD are highest in African-Americans, and lowest among Chinese men and Hispanic women (3).

The risk factors associated with borderline PAD seem to be the same as those with CVD. In the cohort of NHANES, the prevalences of current smoking, hypertension, diabetes, abdominal obesity, chronic kidney disease, physical inactivity and an elevated C-reactive protein level were higher at lower ankle-brachial index (ABI) levels than in participants with normal ABIs (defined as 1.10 to 1.29). After adjustment for these potential confounders and hypercholesterolemia, higher age-, race/ethnicity- and sex-adjusted ORs of CVD were present at lower than normal ABI levels. Additionally, the multivariate-adjusted OR of stroke was significantly increased for those with borderline PAD (2).

Measurements in MESA included ABI, carotid artery intima-media thickness, and coronary artery calcium assessed with computed tomography. These investigations revealed that compared with normal ABIs (defined as 1.10 to 1.29), borderline ABIs were associated with greater subclinical atherosclerosis in the internal carotid artery in both sexes, and also in common carotid and coronary arteries in men, independent of confounders. Among women, inverse associations between ABI and subclinical atherosclerosis were less strong in Chinese than in Caucasians and African-Americans (3).

In the Rotterdam Coronary Calcification Study (4), borderline ABI (defined as 0.90 to 0.99) was associated with a higher degree of subclinical coronary atherosclerosis than were ABIs of 1.20 or greater, but only in men (4).

TABLE 1
The population-based studies reporting the prevalence of peripheral arterial disease (PAD) and borderline PAD

Study	Participants	Prevalence of PAD (definition)	Prevalence of borderline PAD (definition)
Framingham Offspring Study (1)	n=3313; ≥40 years	3.60% (ABI <0.9)	7.10% (ABI 0.9–1.0)
NHANES (2) 1999–2002	n=4895; ≥40 years	5.00% (ABI <0.90)	8.70% (ABI 0.90–0.99)
MESA (3)	n=6570; 45–84 years; free of CVD	3.70% (ABI <0.90)	7.60% (ABI 0.90–0.99)

ABI Ankle-brachial index; CVD Cardiovascular disease; MESA Multi-Ethnic Study of Atherosclerosis; NHANES National Health and Nutrition Examination Survey

PROGNOSIS OF BORDERLINE PAD

Due to the cross-sectional nature of the studies described above, they cannot answer the question of whether persons with borderline PAD have a higher incidence of CVD events than persons with normal ABIs. The best evidence regarding

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the risk of CVD associated with different ABI categories is provided from prospective cohort studies among patients initially free of clinical CVD.

The Ankle Brachial Index Collaboration recently published a meta-analysis of 16 cohort studies (5), in which participants 47 to 78 years of age were derived from a general population. ABI was measured at baseline, and participants were followed up to detect total and cardiovascular mortality. In men with ABIs of 0.91 to 1.00, compared with reference ABIs of 1.11 to 1.20, the hazard ratios for total mortality, cardiovascular mortality and major coronary events were 1.61 (95% CI 1.47 to 1.77), 1.68 (95% CI 1.40 to 2.00) and 1.43 (95% CI 1.23 to 1.66), respectively. The corresponding figures in women were 1.52 (95% CI 1.38 to 1.67), 1.84 (95% CI 1.53 to 2.22) and 1.53 (95% CI 1.30 to 1.79), respectively. The magnitudes of the increased risk in persons with borderline PAD were much lower than in those with ABIs of 0.90 or less, but substantially higher than in those with ABIs greater than 1.40.

The inverse linear relationship between ABI and CVD outcomes, which included ABI values of 0.9 to 1.1, was also observed in two German follow-up studies (6,7). The getABI Study Group followed a cohort of unselected patients 65 years of age and older, and showed that even individuals with borderline PAD (defined as ABIs of 0.9 to 1.1) carry a 25% increased risk compared with those with ABIs greater than 1.1 (6).

BORDERLINE PAD CORRELATION WITH VASCULAR EVENTS IN THE LEG

The Edinburgh Artery Study (8) was the first population-based study to evaluate changes in ABI over time. At the baseline examination in 1987/1988, 1592 subjects 55 to 74 years of age were studied, and 695 of them had further ABI measurements five and 12 years later. During the follow-up period, the incidence of new cases of intermittent claudication, vascular surgery or leg amputation was inversely related to ABI at baseline within the whole population. These new vascular events occurred in 16% of the patients who had borderline PAD (defined as ABIs of 0.90 to 0.99) at baseline. The incidence rates were 19% in those with ABIs of 0.80 to 0.89, and 22% in those with ABIs of 0.79 or less. Compared with the 11% incidence of new vascular events in those with ABIs between 1.00 and 1.09 at baseline, borderline PAD seems to carry a substantially poorer prognosis.

The investigators of the Edinburgh Artery Study (8) also found that, in the entire study population, there was little change in mean ABI over 12 years in the leg with the lower ABI at baseline. In contrast, the leg with the higher mean baseline ABI showed a significant drop from 1.15 to 1.09 during the 12 years of follow-up (8). The more rapid progression of atherosclerosis in the leg that had a higher ABI at baseline is consistent with the results of Walsh et al (9). They performed two arteriographic evaluations in a group of patients with clinically progressive PAD, and found that 60% of occlusions in the superficial femoral artery originated from areas of mild (less than 50%) stenosis on the initial arteriogram. Therefore, in the long run, clinically significant PAD is more likely to arise from less diseased regions and progress more rapidly than the pre-existing stenotic lesions.

CALCULATION OF ABI TO DETECT PERSONS AT CARDIOVASCULAR RISK

According to the guidelines of TASC II (10) and the American Heart Association (11), ABI is correctly calculated as the ratio of the higher of the systolic blood pressures of the two ankle arteries and the higher of the two systolic blood pressures of the arms. This method is thought to assess the leg perfusion reliably. However, Espinola-Klein et al (12) have recently shown that a modification of ABI, in which the lower instead of the higher ankle pressure is used to calculate ABI, identifies more patients at risk for CVD. They measured ABI using both modifications in 831 patients admitted with chest pain for diagnostic heart catheterization. During the median follow-up of 6.6 years, cardiovascular event rates were comparable (28% versus 25%) for patients with diagnosed PAD (defined as ABI less than 0.9) calculated by either way. The prevalence of PAD was 25% when the higher ankle pressure was used and 36% when the lower pressure was used. Thus, with the modified definition (using the lower ankle pressure to calculate ABI), more patients at risk for CVD can be identified.

SIGNIFICANCE OF BORDERLINE PAD

On the basis of the current evidence, there is no doubt that borderline PAD is a strong and independent predictor of cardiovascular events. It is at least as powerful a risk factor for CVD as ABIs greater than 1.4, which has been regarded as a marker for incompressible arteries, probably caused by media calcification frequently seen in patients with diabetes and kidney disease (13). The transition from asymptomatic borderline PAD to established PAD with claudication can also be quite rapid unless preventive measures are used.

The recognition of the importance of borderline PAD is analogous to the data on lifetime risk of hypertension and the increase in the risk of CVD associated with levels of blood pressure previously considered to be normal. Observational studies involving more than one million individuals have indicated that death from coronary artery disease and stroke increases progressively and linearly from blood pressure levels as low as 115 mmHg systolic and 75 mmHg diastolic upward (14). In 2003, the US Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) (15) introduced a new classification of hypertension that includes the term 'prehypertension' for those with blood pressures ranging from 120 mmHg to 139 mmHg systolic or 80 mmHg to 89 mmHg diastolic. Likewise, it has become common to use term 'prediabetes' when referring to impaired glucose tolerance or impaired fasting glucose, the preliminary stages of diabetes mellitus. Cardiovascular mortality among people with impaired glucose tolerance is about twice that among normal controls (16). Considering the significance of borderline PAD on the CVD continuum, the term 'pre-PAD' and a new classification of ABI values including ABI 0.91 to 1.00 as a marker for increased risk of CVD seems to be justified.

CONCLUSIONS

Because PAD or borderline PAD can be detected in at least every 10th person of the general population 40 years of age or older – most patients being asymptomatic – screening for PAD and borderline PAD with an ABI measurement may be a useful

routine practice at the primary care level. On the other hand, when a surgeon measures ABI and detects a borderline PAD, she or he should inform the patient about the increased risk of CVD and advise the patient to have other cardiovascular risk factors such as blood pressure, plasma cholesterol and glucose values measured. Adoption of healthy lifestyles by all persons with borderline PAD is essential for prevention of coronary artery disease, stroke and the progression of atherosclerosis in the leg. An ABI between 0.91 and 1.0 should be considered to be borderline PAD or 'pre-PAD'.

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