The Role of Ankle-Brachial Index for Predicting Peripheral Arterial Disease

Marius RAC-ALBU\textsuperscript{a}; Luminita ILIUTA\textsuperscript{b}; Suzana Maria GUBERNA\textsuperscript{c}; Crina SINESCU\textsuperscript{d}

\textsuperscript{a}Intern in Cardiology, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
\textsuperscript{b}“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
\textsuperscript{c}Department of Cardiology, Bagdasar Arseni Emergency Clinical Hospital, Bucharest, Romania
\textsuperscript{d}Department of Cardiology, Bagdasar Arseni Emergency Clinical Hospital, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

\textbf{ABSTRACT}

The presence of peripheral arterial disease (PAD) is associated with higher cardiovascular morbidity and mortality, regardless of gender or its clinical form of presentation (symptomatic or asymptomatic). PAD is considered an independent predictor for cardiovascular mortality, more important for survival than clinical history of coronary artery disease.

The ankle brachial index (ABI) is a sensitive and cost-effective screening tool for PAD. ABI is valuable for screening of peripheral artery disease in patients at risk and for diagnosing the disease in patients who present with lower-extremity symptoms.

Compared to other diagnostic methods, ABI is superior because it is a simple, noninvasive test, which could be routinely determined in all patients.

Normal cut-off values for ABI are between 0.9 and 1.4. An abnormal ankle-brachial index - below 0.9 - is a powerful independent marker of cardiovascular risk.

There is an inverse correlation between ABI values, non-fatal cardiac events (myocardial infarction, stroke and heart failure exacerbation) and mortality (cardiovascular and global), the relation being nonlinear, patients with very low ABI (<0.3) having a significantly higher additional risk. Also, ABI values over 1.3-1.4 correlate with major adverse cardiovascular events.

Therefore, ABI can be considered a generalized atherosclerotic predictor, identifying patients at high risk for developing cardio- or cerebrovascular events and should be incorporated into routine clinical practice.

\textbf{Address for correspondence:}
Marius Rac-Albu, 21 Octavian Goga Boulevard, 3\textsuperscript{rd} District, Bucharest, Romania.
E-mail: racalbu@yahoo.com

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INTRODUCTION

Peripheral arterial disease (PAD) is a disorder characterized by decreased blood flow to the limbs, due to an obstruction or narrowing of the vessels tributaries (1). The concept of PAD has a broader meaning, including the impairment of the carotid arteries, vertebral, renal and mesenteric, but not including aortic diseases (2).

The presence of PAD is associated with higher cardiovascular morbidity and mortality, regardless of gender or its clinical form of presentation (symptomatic or asymptomatic), mostly in patients who need peripheral revascularization (these patients having more severe impairment of vascular territories and an increased preoperative risk with frequently associated comorbidities such as age greater than 70 years, diabetes mellitus, renal dysfunction or smoking) (1,3,4). PAD is actually considered an independent predictor for cardiovascular mortality, of paramount importance, more important for survival than clinical history of coronary artery disease (3).

Underlying causes of arterial lesions are heterogeneous, the most frequent being atherosclerosis (characterized by a chronic process, slowly unfolding in intimal thickening and plaque and finally causing stenosis, sometimes complicated with thrombus), and others such as vasculitis, vasospasm, embolism, thrombosis, fibromuscular dysplasia or compartment syndrome (2,5). Depending on the degree of obstruction of the affected vessel, clinical manifestations vary from atypical symptoms or intermittent claudication until the critical ischemia (rest pain, ulceration and gangrene), which, in the absence of proper treatment, can lead to amputation. Most patients with PAD (almost two thirds), however, are asymptomatic or with mild symptoms - atypical symptoms, such as tingling, numbness of the affected limb, atypical pain and decreased mobility due to comorbidities, which, in turn can result in difficulties diagnosing PAD and increasing the time until the correct diagnostic (2,6,7).

Often, the diagnosis of PAD is difficult to be established, especially in subclinical stages of the disease, requiring a special attention from the doctor regarding the disease’s diagnosis and its management (5).

Optimization and standardization of methods of diagnostic and screening, use of available screening methods and better management of patients at risk could lead to a decrease of undiagnosed cases and early diagnosis of PAD. Consequently, optimal multimodal therapy (measures regarding quality of life, rehabilitation, medication and interventional therapy) and strict control of risk factors may reduce the risk of major cardiovascular events and amputations. It should be noted that although revascularization procedures have a positive impact on the functional status of the patient, they do not affect the survival (8).

Compared with patients without peripheral vascular damage, patients with PAD have additional lesions in other vascular territories (such as coronary or carotid artery disease), with incidence and prevalence varying from study to study depending on the diagnostic criteria used. Thus, 60-80% of patients have at least one significant coronary artery stenosis detected by angiography (9), two thirds have changes suggestive of ischemia on stress tests and between a third and a half have suggestive elements for coronary artery disease on physical examination or electrocardiogram at rest (9). Prevalence of significant carotid damage varies in studies between 12-25%, depending on the authors (10). In the SMART study (Second Manifestation of ARTerial disease), which identified the prevalence of asymptomatic internal carotid artery stenosis (ICAS) in patients with PAD and characteristics that are associated with ICAS, the percentage was much higher, up to 50% if patients had one or more risk factors, such as age >65 years, hypertension or pathological ankle-brachial index (ABI) <0.9, whether peripheral arterial disease was symptomatic or not (11).

The relative risk for cardiovascular morbidity and mortality is higher in patients with peripheral vascular disease compared to controls, and this risk does not depend on the presence of concomitant coronary artery disease (6). Patients with PAD have an increased risk of fatal or non-fatal cardiovascular events, the incidence of coronary artery disease, myocardial infarction, stroke and death being similar (4-5% per year) and not influenced by gender or presence of intermittent claudication.

On the other hand, cardiovascular risk is significantly increased in patients with severe symptoms of ischemia (Fontaine stages III-IV) and is inversely proportional with the value of ankle-brachial index. These patients have a
very high mortality, both short-term (15 to 20% per year) and long-term (5-year mortality of approximately 44% - almost two times higher than in asymptomatic patients) (12). Patients with critical limb ischemia have a much higher risk of mortality (up to 80% in patients with pain at rest, respectively 95% in patients with trophic lesions) compared with asymptomatic patients (with a mortality rate of 50% to 10 years in asymptomatic patients) (13).

Risk factors involved in the pathogenesis of PAD are similar to those involved in coronary atherosclerotic processes. The traditional risk factors such as smoking, diabetes, hypertension, dyslipidemia, obesity, physical inactivity and increased age are associated with PAD, the strongest correlation being with smoking and diabetes (14). Data from observational studies revealed that the risk for developing PAD in smokers was 2-3 times higher than in non-smokers, and it was both correlated with the number of cigarettes per day and the number of years the patient has smoked. On the other hand, the prevalence of PAD increases with age, being relatively rare before 40-50 years, more frequent in the next decades of life (2), especially after 70 years. Also, the race influences the distribution of PAD, Caucasians and Blacks in particular having more frequent peripheral vascular injury (15,16).

Most epidemiological studies have used ankle-brachial index (ABI) as a diagnostic method for PAD (5) and PAD prevalence derived from abnormal ABI values measurements.

**Prognostic role of ankle-arm index**

Besides the diagnostic role, ABI has a prognostic role, identifying patients with very high cardiovascular risk, independently of the presence or absence of symptoms. Compared to other diagnostic methods, ABI is superior because of its simplicity, being very easy to routinely determine in all patients and because it is a noninvasive test.

Almost all major studies and international guidelines included PAD as major cardiovascular risk factor with independent role in risk stratification in patients with coronary artery disease (2,17). Normal cut-off values for ABI, adopted by most studies and by the accepted guidelines of cardiology societies are between 0.9 (0.85) and 1.4 (2). An abnormal ankle-brachial index below 0.9 is a powerful independent marker of cardiovascular risk. Also, there is an inverse correlation between ABI value, non-fatal cardiac events (myocardial infarction, stroke and heart failure exacerbation) and mortality (cardiovascular and global), the relation being nonlinear, patients with very low ABI (<0.3) having an additional risk significantly higher (18-21). Also, a decrease in ABI was found as an independent prognostic factor for these patients (22).

In general, a lower ABI was found mostly in male patients, with older age, former smokers and having more frequent alterations in renal function. Among the risk factors associated with PAD, hypertension and diabetes mellitus have the strongest correlation with lower ABI values (lower ABI values in diabetes patients having additive value for the risk of death) (23,24). On the other hand, ABI value is predictive for target organ damage in hypertensive patients, and generally identifies a subgroup of patients who associate major comorbidities, such as coronary heart disease with severe and extensive coronary lesions, history of stroke and left ventricular hypertrophy (24). Patients with hypertension and a history of acute coronary syndrome have a significantly higher prevalence of asymptomatic PAD and an ABI value <0.9 was associated with a higher risk of developing heart failure, angina and in and out-hospital mortality (24).

In patients with normal or borderline ABI at rest, but with risk factors for PAD, it is useful to measure ABI after exercise and to compare it with the nominal value. Thus, a prospective study of 3209 patients (aged 50-75 years, 71% male, the medium follow-up period 8 years), with ABI calculation both at rest and after exercise demonstrated that even in patients with normal ABI at rest, but having a significant reduction in the ABI compared to the reference value, the cardiovascular risk is significantly increased. In these patients, the relative risk value was 1.6 times higher for a decrease in ABI value between 6% and 24%, 3.5 times higher for a reduction between 25-55% and 4.8 times higher in those with ABI after exercise by 55% lower (25). This study reinforces the need for further exploration of patients with risk factors and normal ABI at rest, ABI after exercise being useful in identifying those patients with increased mortality risk (25).

Also, ABI values over 1.3-1.4 correlate with major adverse cardiovascular events. Thus, in a study conducted in an internal medicine clinic
Physiological variations of ankle-brachial index

The force generated by the contraction of the heart is transmitted to the arteries as a pulse wave (ventriculoarterial coupling). It undergoes amplification while crossing the vascular bed, from proximal to distal. The explanation is the retrograde pulse wave reflection arising from arterioles which has an additive effect, stronger in arterial territories characterized by increased peripheral vascular resistance such as limbs. These reflected waves suffer an attenuation process, too. Increased hydrostatic pressure (due to the vertical position of the body) which acts on the lower limb vessels, may cause a physiological thickening of the arterial wall, without changing the inner diameter of the vessel. This is supported by the ABI change, which in the neonate is 1, subsequently increasing to the normal value found in adults around the age of 2-3 years (33). These two mechanisms explain why blood pressure is physiologically higher in the legs than the upper limbs.

Many physiological factors can affect ABI, such as age, height, race or order of the measurements. Two observational studies showed a difference of 0.03 between ABI to the right leg compared to the left lower limb ABI (34,35). This minor difference can be explained through the order of measurements (usually first measured is the right leg), knowing that blood pressure diminishes slightly after the patient is accustomed with the doctor (34,35). Although theoretically ABI should increase with age as a result of increased arterial stiffness, longitudinal population studies have shown the opposite, paradox explained by increased prevalence of PAD in the elderly (34,35). The contribution of the height at ABI value is negligible, about 0.01 per 20 cm (MESA study), although in individuals without cardiovascular impairment, ABI should increase proportionally with height because of the higher systolic blood pressure in the legs due to increased hydrostatic pressure (28). Women have on average a lower ABI with 0.02 to 0.07, according to the study report, independent of other factors such as the height. This applies to populations without PAD / atherosclerosis (15).

Race also influence the ABI value and this may be due to genetic factors (31). The blacks without PAD (MESA study participants) had on average an 0.02 lower ABI compared to the
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Blood pressure in the ankle, brachial blood pressure being not influenced (38).

Methods of measuring the ABI

ABI is commonly used as a method to detect PAD in observational studies. However, the lack of standardized methods widely accepted, may result in discrepancies of ABI and thus to estimate the prevalence of PAD erroneous with negative impact in terms of clinical, social and economic. Thus, a review of 100 articles that used ABI showed many variations in measuring the ABI from the position of the patient and the size of the cuff to the arm/ankle, bilateral measurement of blood pressure and which of distal pulses (tibial or pedis) were used.

Blood pressure measurement methods include oscillometry, Doppler ultrasound, plethysmography, auscultation and pulse measurement, but the main methods remained the oscillometric method and Doppler. Doppler method uses a continuous Doppler probe (typically 5-10 MHz frequency) to detect arterial blood flow. Oscillometry is based on the assumption that maximum oscillations occurring in the vessel in slow cuff deflation correspond to mean arterial pressure from which mathematical formulas can deduct the systolic and diastolic blood pressure. This method was validated from empirical data from healthy subjects for measuring brachial blood pressure (39).

In patients with early PAD, the correlation between Doppler and oscillometric method measurements was acceptable in most studies. On the other hand, in patients with moderate or severe arterial damage, ABI values derived from Doppler measurements were lower and oscillometry overestimates the real values of the arterial blood pressure. Moreover, for low values of blood pressure (<80 mm Hg), most automated oscillometric blood pressure monitors do not detect between 11-44% of readings. Thus, compared with the Doppler method, the sensitivity and specificity of oscillometry varies between 67-97% and 62-96%, respectively (40).

Measurement of ABI after exercise

For increasing the sensitivity of the method, the European Society of Cardiology recommended ABI measurement after exercise in pa-
tients with normal ABI or ABI at the lower limit of normal at rest and a clinical suspicion of PAD (40).

Reproducibility of ABI depends on the number of measurements made for its determination, being known that the confidence interval is reduced by the square root of the number of measurements. Thus, the Atherosclerosis Risk in Communities (ARIC) study revealed that a single measurement is associated with ABI variability of ±0.25 from the average, while using three measurements for ABI, the standard deviation from the mean is reduced to only ±0.12 (0.25/sqrt(3)). Also, ABI variability in the same patient can be influenced by physiological factors described above, experience of the observer and the time between measurements. Most studies showed a good reproducibility in measurement of the ankle versus brachial blood pressure, although there are some studies in which there was no difference.

**ABI calculation method and ABI values.**

According to the current guidelines of the American Heart Association (AHA) and the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II), ABI is defined as the ratio of the higher of the systolic blood pressures of the 2 ankle arteries of that limb (either the dorsalis pedis or the tibial artery) and the higher of the 2 systolic blood pressures of the upper limbs (17).

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\text{ABI} = \frac{\text{Highest systolic blood pressures of the 2 ankle}}{\text{Highest systolic blood pressure in both arms}}
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This calculation of ABI using the higher ankle pressure is not widely accepted. Some authors preferred the average of both ankle pressures, and others even recommend that the lower of the 2 ankle pressures be used for ABI calculation. An ABI between 0.9 and 0.4 is interpreted as mild to moderate PAD and an ABI of <0.4 as severe PAD (17).

Some studies recommended to use the average of the two values with the exception of the differences of more than 15 mmHg between the two arms, typically seen in cases of subclavian artery stenosis. Values higher than 15 mmHg can detect a subclavian artery stenosis higher than 50%, with a sensitivity and specificity of almost 100% (41) and are associated with an additional risk for cardiovascular events and positively correlated with vascular damage in other areas, including PAD. False differences may occur between the arms due to patient anxiety, therefore, in case of a large differential it is advisable to repeat the measurements, in order to exclude the confounding factor. Finally, it should be noted that the chosen value of brachial blood pressure should always be the larger of the two arms (2).

The reproducibility of measurements is influenced primarily by the technique used and much less by the artery used to obtain the systolic blood pressure.

The Multi-Ethnic Study of Atherosclerosis (MESA) trial compared ABI using as the numerator either average blood pressure between dorsalis pedis artery and tibial posterior artery, either the minimum/maximum value (cut-off value of 0.9 chosen) regarding the strength of association with cardiovascular risk factors and subclinical systemic atherosclerosis (carotid and coronary). Surprisingly, the ABI obtained using the minimum value of systolic blood pressure has the weakest correlation with atherosclerotic disease (coronary/carotid), probably due to epidemiological peculiarity in the group of patients with PAD who had fewer cardiovascular risk factors (28,42).

In conclusion, the ankle-brachial index is a simple, reproducible, and cost-effective assessment that can be used to detect lower-extremity arterial stenosis in the primary care setting, being an efficient tool for objectively documenting the presence of lower-extremity peripheral arterial disease.

ABI value<0.9 is strongly associated with other cardiovascular risk factors and with PAD occurrence and this cut-off value can be included in the calculation of the cardiovascular risk score for predicting PAD.

An ankle-brachial index greater than 1.40 means that the pedal arteries are stiff and cannot be compressed by the blood pressure cuff. This is considered abnormal, though not necessarily diagnostic of peripheral artery disease.
Noncompressible leg arteries are common among patients with long-standing diabetes mellitus or end-stage renal disease, and also can be found in obese patients (43-46).

Therefore, ABI can be considered a generalized atherosclerotic predictor, identifying patients at high risk for developing cardio- or cerebrovascular events and should be incorporated into routine clinical practice.

Although there are many physiological factors of confusion that can influence ABI, they usually exert a minor effect, which is often questionable (conflicting studies) and not encroaching on its diagnostic power.

The clinical implications of the present review may be summarized as follows:

1. Increase awareness of PAD and its negative consequences
2. Improve the identification of patients with symptomatic and especially asymptomatic PAD, where ABI may have a key role
3. Initiate a screening protocol for patients at high risk for PAD
4. Increase the rates of early detection among the asymptomatic population
5. ABI has a very important role in patients with PAD, not only as a diagnostic tool, but also as a negative predictor
6. Training cardiologists and general practitioners how to measure ABI correctly in order to improve diagnosis of PAD

Also, a large randomized clinical trial is still needed for establishing the role of the simple office-based tool ABI for the diagnosis and determining of the severity of lower extremity PAD and for predicting the associated risk of future cardiovascular events such as fatal myocardial infarction, stroke, and vascular deaths.

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