Early Identification of Asymptomatic Peripheral Arterial Disease in Smokers
Christian Ellul, BSc, Anabelle Mizzi, MSc, and Cynthia Formosa, PhD

ABSTRACT
This study investigated whether daily tobacco smoking affects peripheral artery insufficiency in a cohort of middle-aged individuals. A matched nonexperimental study was used. Twenty smokers and 20 nonsmokers not suffering from any cardiovascular disease were recruited. The Huntleigh Dopplex Assist was used to measure the ankle brachial pressure index (ABPI) and quantitatively analyze the Doppler arterial waveforms. There was no significant difference in mean ABPI scores between smokers and nonsmokers; however, significant difference was noted in the Doppler waveforms on all arteries assessed between groups. Doppler waveforms should be used to assess smokers to screen for peripheral arterial disease.

Keywords: ankle brachial pressure index, peripheral arterial disease, smoking, spectral arterial waveforms

According to the World Health Organization, there are 1.1 billion tobacco smokers worldwide. Epidemiologic studies strongly support the assertion that cigarette smoking increases the incidence of myocardial infarction and fatal coronary artery disease and is known to cause 11% of cardiovascular deaths. Of all the risk factors of cardiovascular disease (CVD), smoking is considered as the most potent modifiable risk factor. Its pathophysiological mechanisms in the human body are numerous and may promote atherosclerosis through vascular inflammation and oxidative stress. Atherosclerosis is described as the principal cause of peripheral arterial disease (PAD), and several authors have explained that lower-extremity PAD is thought to be a marker of widespread atherosclerosis affecting a high prevalence of patients, thus stressing the need for early diagnosis.

PAD is a significant public health problem; however, as many as 50% of patients living with PAD are asymptomatic. Only approximately 30% of people with PAD live up to 15 years after their initial diagnosis, with those at highest risk being over the age of 50 years, and have risk factors including obesity, dyslipidemia, diabetes, and smoking history. It has been estimated that only approximately 25% of patients living with PAD receive treatment because most people are not aware that they have it. Despite the lack of symptoms, such patients still share the same prognosis as symptomatic patients, showing a risk profile comparable with patients with symptomatic lower-extremity PAD or chronic heart disease. The most widely used test for diagnosing PAD in a clinical setting is the ankle brachial pressure index (ABPI). It has been reported to be almost 100% specific in identifying healthy individuals, and an ABPI < 0.9 is approximately 95% sensitive in detecting arteriogram-positive PAD. This consists of a noninvasive, quantitative measurement of the patency of the lower-extremity arterial system. It is regarded as a validated and reproducible test, which consists of a simple measurement that can be performed in any health care professional clinic with inexpensive equipment consisting of a blood pressure cuff and a Doppler ultrasonic sensor. The American Diabetes Association Consensus statement reported ABPI as a noninvasive method for evaluating PAD and that, in contrast to the variability of pulse assessment, information obtained via history, and other components of physical examination, the ABPI is reproducible and reasonably accurate, although errors may occur in some cases because the reliability of any diagnostic test is dependent on the prior probability of disease (Bayes’ theorem). This is mainly a result of poorly compressible arteries caused by medial arterial calcification, thus rendering the diagnosis of PAD by ABPI alone less reliable and inaccurate because of artifactually raised occlusion pressures, especially in patients with diabetes mellitus or end-stage renal failure and smokers.
This pilot study aimed to evaluate the occurrence of PAD in middle-aged smokers and nonsmokers using ABPI measurements and arterial waveform interpretation.

**METHODS**

This study used a quantitative nonexperimental frequency-matched subject design. A convenient cohort of 40 participants was recruited in this pilot study. Twenty smokers and 20 nonsmokers with no history of smoking were included. Both men and women between the ages of 40 and 60 years were included. Participants were matched for sex, body mass index (BMI, kg/m^2^), and age using frequency distribution matching. This allowed the close comparison of the experimental and control group through relevant variables. Participants were excluded from the study if they were found to suffer from any high-risk factors known to cause PAD, including any CVD, diabetes mellitus, hypertension, or hyperlipidemia.

This study was approved by the research ethics committee, and all participants provided informed consent before any data collection. All investigations were performed in accordance with the principles of the Declaration of Helsinki as revised in 2000.

The testing modalities and examination methods were performed by the same 2 investigators to ensure uniformity. The screening process involved a review of the patient’s medical history and a lower-extremity physical examination. Each individual’s personal lifestyle characteristics and clinical history, including weight, height, current medications, and smoking history, were recorded. Individual assessments took approximately 20 minutes.

**PAD**

PAD was assessed using the documentation of history of intermittent claudication, rest pain, and palpation of peripheral pulses. Palpation of pulses was conducted by using the fingertips of 2 experienced clinicians. Dorsalis pedis and posterior tibial pulses were recorded. Cyanosis, cold feet, skin thinning, and hair anomalies were also recorded. Claudication was evaluated from information supplied by the patient regarding exercise–induced calf, thigh, and/or buttock pain. Measurement of ABPI was performed using a portable handheld Doppler and blood pressure cuffs. Apart from ABPI assessment, quantitative pedal waveform analysis was obtained from all recruited subjects using the continuous wave Doppler. The Doppler waveforms and the measurement of the ABPI were obtained using the Dopplex Assist Vascular package (Huntleigh, Cardiff, UK) as the principal study tool.

The Huntleigh handheld continuous wave Doppler with an 8-MHz probe, part of the Dopplex Assist Vascular package, was used to measure the waveforms of the dorsalis pedis and the posterior tibial. The probe was held steadily on the anatomic artery location at an angle between 45 and 60 degrees against the flow of arterial blood. Interpretation of arterial pressure waveform results was based on standards from the literature. Waveforms were classified as triphasic, biphasic, monophasic discontinuous, and monophasic continuous. The triphasic waveforms were considered as normal, whereas the biphasic and monophasic discontinuous and monophasic continuous waveforms were interpreted as abnormal.

Measurements were performed after a 5-minute rest in the supine position with the upper body as flat as possible because measurements in the sitting or semisitting position can result in a substantial blood increase in the tibial arteries. Patients were also asked to undo all tight clothing around the waist and the arm. The Huntleigh Dopplex Assist Series was used to measure the resting ABPI. According to the company specifications, ABPI measurement is one of the instrument’s principal applications apart from waveform analysis. The series used for this study included an electric pump, which deflates the pressure cuffs, requiring the investigator to simply press a button. An optimum Doppler signal is achieved at an angle of 45 to 60 degrees. When measured, the systolic blood pressures are automatically saved onto the system’s software, with the saved results then used to calculate the ABPI ratios by the system.

A blood pressure cuff was applied to the arm (to measure the brachial systolic pressure) and the ankle (to measure the dorsalis pedis and posterior tibial pressures) to determine the ankle pressure. The cuff was inflated to occlude the arterial pressure. The systolic pressure was obtained by listening and noting the pressure on the manometer. The systolic pressure
was noted, and the higher values of the brachial and the ankle pressures were used to calculate the ABPI. Values were interpreted according to the criteria proposed by the American Heart Association and the American Diabetes Association. In this research, ABPI calculations were interpreted as normal if they were between 0.9 and 1.29, and lower-extremity vascular disease was defined as an ankle brachial index < 0.90 in either foot. An ABPI of > 1.3 was considered significantly elevated and indicative of vascular calcification.

RESULTS
A total of 40 subjects, 24 women and 16 men, with a mean age of 49.93 years (smokers 49.75 vs non-smokers 50.10, standard deviation [SD] = 5.92) were included in the study. BMI was calculated in kg/m². The mean BMI for all participants was 25.00, with 25.01 (SD = 3.80) for smokers and 24.99 (SD = 3.31) for nonsmokers. For the smokers (n = 20), the packet years of smoking for each individual was calculated as the number of packets of cigarettes consumed per day multiplied by the duration of smoking in years. The mean packet years for this study group was 31.0 (SD = 20.22).

Table 1 shows the mean ABPI and P values for smokers versus nonsmokers using 1-way analysis of variance. No significant difference was found between smokers and nonsmokers in this study group (left limb 1.051 vs 1.063, P = .729 [SD = 0.061]; right limb 1.070 vs 1.086 [SD = 0.188], P = .730).

Doppler waveform analysis of the right and left dorsalis pedis artery in the smoking group versus the nonsmoking group was analyzed using the chi-square test (Table 2). A significant difference was noted in the Doppler waveforms on both right and left dorsalis pedis arteries assessed between the 2 groups (P ≤ .05). Doppler waveform analysis of the right and left posterior tibial arteries in the smoking group versus the nonsmoking group was analyzed using the chi-square test. A significant difference was noted in the Doppler waveforms on both right and left posterior tibial arteries assessed between the 2 groups (P ≤ .05).

DISCUSSION
This pilot study compared the incidence of PAD diagnosis using the ABPI and printed arterial waveforms in a cohort of 20 smokers and 20 nonsmokers. No significant difference was observed in the ABPI scores and cumulative smoking exposure (measured in packet years). However, although no significant difference was obtained for the ABPI readings, further quantitative analysis of Doppler waveforms revealed an important significant difference in waveforms between smokers and nonsmokers on all pedal pulses of the study population. This finding may shed light on arterial dysfunction associated with smoking at the subclinical level and in the presence of normal ABPI scores.

One of the limitations of this study could be the sample size. For this reason, this study should be considered as a pilot study with the authors recommending repeating the same study with a larger

Table 1. Mean Ankle Brachial Pressure Index Scores and P Values for Smokers and Nonsmokers as Generated by 1-way Analysis of Variance

<table>
<thead>
<tr>
<th></th>
<th>Mean ABPI score</th>
<th>SD</th>
<th>SE</th>
<th>95% CI for Mean</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower Bound</td>
<td>Upper Bound</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>1.063</td>
<td>0.061</td>
<td>0.014</td>
<td>1.034</td>
<td>1.091</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.051</td>
<td>0.141</td>
<td>0.031</td>
<td>0.985</td>
<td>1.116</td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>1.086</td>
<td>0.066</td>
<td>0.015</td>
<td>1.054</td>
<td>1.117</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.070</td>
<td>0.188</td>
<td>0.042</td>
<td>0.982</td>
<td>1.158</td>
</tr>
</tbody>
</table>

ABPI = ankle brachial pressure index; CI = confidence interval; SD = standard deviation; SE = standard error.
A cohort of subjects in order to increase statistical power of the study results. Furthermore, a power analysis should be calculated to ensure recruitment of the correct sample size. Although the sample size (N = 40) may be considered relatively small because ABPI values below 0.9 are clearly indicative of PAD according to the Eurodialie Study,17 the authors are confident that patients in this study were correctly diagnosed. ABPI thresholds of less than 0.9 and more than 1.3 are highly suspicious for PAD. However, when there is concomitant high risk of arterial calcification (Monckeberg sclerosis), the efficiency of ABPI seems to be limited because a falsely elevated ABPI can be produced.17

Although there is a clear lack of reported studies that made a direct comparison of continuous Doppler in conjunction with ABPI in order to evaluate PAD in high- or intermediate-risk individuals, Stephens et al18 reported that a substantial number of their participants had normal ABPI scores but biphasic and monophasic discontinuous waveforms. In their study, these authors recruited 58 patients between 51 and 88 years old, and both ABPI and waveform Doppler analysis were performed. Results indicated that although an ABPI index was normal, waveform analysis was abnormal (either monophasic discontinuous or biphasic) in 44% of the patients, which led to the conclusion that some of the recruited subjects with a normal ABPI index but abnormal waveforms could mistakenly be classified as normal. In another recent study conducted by Formosa et al,19 the authors also reported inconsistencies between ABPI and waveform interpretations in their study population. The authors reported that approximately 35% of their subjects had inconsistencies between their ABPI result and waveform interpretation in their right or left foot. Although “normal” ABPIs were recorded, this was not consistent with the waveform analysis because subjects showed biphasic, monophasic, or continuous monophasic waveforms in 1 or both feet. The authors postulate that both ABPIs and Doppler waveforms should be assessed in people with a high risk of arterial calcification because the efficiency of ABPI is limited because a falsely elevated ABPI can be produced.17

These findings have important implications for clinical practice. Early diagnosis and treatment of PAD is crucial in smokers. This study has shown that ABPI readings in smokers could be falsely elevated because of arterial calcification, which is common in smokers because ABPI readings and spectral waveforms were not consistent. Smoking has been

<table>
<thead>
<tr>
<th>Dorsalis Pedis Waveforms</th>
<th>Monophasic, n (%)</th>
<th>Biphasic, n (%)</th>
<th>Triphasic, n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker (n = 20)</td>
<td>0 (0)</td>
<td>3 (15)</td>
<td>17 (85)</td>
<td>.001*</td>
</tr>
<tr>
<td>Smoker (n = 20)</td>
<td>4 (20)</td>
<td>10 (50)</td>
<td>6 (30)</td>
<td></td>
</tr>
<tr>
<td><strong>Right</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker (n = 20)</td>
<td>0 (0)</td>
<td>2 (10)</td>
<td>18 (90)</td>
<td>.000*</td>
</tr>
<tr>
<td>Smoker (n = 20)</td>
<td>8 (40)</td>
<td>8 (40)</td>
<td>4 (20)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Posterior Tibial Waveforms</th>
<th>Monophasic, n (%)</th>
<th>Biphasic, n (%)</th>
<th>Triphasic, n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker (n = 20)</td>
<td>0 (0)</td>
<td>2 (10)</td>
<td>18 (90)</td>
<td>.043*</td>
</tr>
<tr>
<td>Smoker (n = 20)</td>
<td>1 (5)</td>
<td>8 (40)</td>
<td>11 (55)</td>
<td></td>
</tr>
<tr>
<td><strong>Right</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker (n = 20)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>19 (95)</td>
<td>.014*</td>
</tr>
<tr>
<td>Smoker (n = 20)</td>
<td>1 (5)</td>
<td>8 (40)</td>
<td>11 (55)</td>
<td></td>
</tr>
</tbody>
</table>

* P < .05 indicates a significant difference in waveforms between smokers and nonsmokers.
reported as a principal risk factor for calcification of the coronary arteries, aortic arch calcification, and carotid calcification. 20,21 This study has shown that despite “normal” ABPs in smokers, there may be early indications of altered arterial hemodynamics because of abnormal waveforms, increasing the risk of atherosclerosis and cardiovascular events. PAD is strongly associated with early death in CVD. 22 This study highlights the importance of increased vigilance coupled with strengthening of existing screening structures regarding PAD assessment in smokers in order to reduce the incidence of PAD and allow the initiation of appropriate secondary risk factor control measures. Combining Doppler waveforms and measurement of ABP could yield more reliable results without significantly increasing the time required for testing. When these 2 tests do not concur, further evaluation of peripheral perfusion should be performed. 19 Early detection of abnormal blood flow in the lower limb may lead to early treatment and advice regarding smoking cessation. It will also aid in timely preventive measures to avoid deterioration and development of serious complications, such as lower-limb loss and, consequently, death. Recommendations about physiological testing of peripheral perfusion in all smokers should be considered in order to facilitate the early identification of asymptomatic PAD in smokers.

References


Christian Ellul, BSc, is a state-registered podiatrist with the Department of Health in Malta. Anabelle Mizzi, MSc, is a visiting senior lecturer at the Faculty of Health Sciences, University of Malta and assistant principal within the Department of Health. Cynthia Formosa, PhD, is the head of the School of Podiatry at the Faculty of Health Sciences, University of Malta and can be reached at Cynthia.formosa@um.edu.mt. In compliance with national ethical guidelines, the authors report no relationships with business or industry that would pose a conflict of interest.

Acknowledgments

The authors would like to thank all participants who consented to participate in this study.

1555-4155/14/$ see front matter © 2014 Elsevier, Inc. All rights reserved.
http://dx.doi.org/10.1016/j.nurpra.2014.06.020