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New Approach to Measuring the Ankle and Toe Brachial Indices as New Markers for Early Detection of Lower Extremity Peripheral Artery Disease

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Abstract

Background: Lower extremity Peripheral artery disease (PAD) is caused by atherosclerosis, or Plaque buildup, that reduces the blood flow to the legs and feet. PAD affects approximately 230 million adults worldwide and is associated with an increased risk of coronary heart disease, stroke, and leg amputation. The first-line method for diagnosis of PAD is the Ankle Brachial Index (ABI), which is the ratio of ankle to brachial higher systolic pressure measured in ankles and arms. The Toe Brachial Index (TBI), which is the ratio of the toe systolic pressure to brachial higher systolic pressure measured in both arms, is considered to be an alternative to the ABI in screening for PAD. The ABI and TBI are measured on the right and left side, and the lower of these numbers is the patient's overall ABI and TBI. Clinical studies and meta-analysis reviews have shown that the conventional ABI measurement, which uses a cuff, and handheld sphygmomanometer and continuous-wave Doppler tracings, provides an acceptable-to-high specificity level but low sensitivity when compared with vascular color Doppler ultrasound, and/or angiography methods. Another study has shown that the TBI measurement has greater sensitivity but lower specificity than the ABI when compared with vascular color Doppler ultrasound diagnostic based on waveforms. The aim of this clinical study was to evaluate the specificity and sensitivity of the VasoPad System comparing its results to the vascular color doppler ultrasound waveforms. **Materials and Methods:** The VasoPad System is an automated device using the pulse wave method to measure the arms and ankles dorsalis and tibial posterior artery blood pressures, the photoplethysmography second derivative (PTGSD) to estimate the toe systolic pressure, a patented photoplethysmography (PTG) index marker and volume plethysmography via cuffs during deflation. Vascular Color Doppler ultrasound can diagnose stenosis

through the direct visualization of atherosclerosis or plaques and through waveform analysis. The vascular color Doppler ultrasound provides 3 waveform types. The type 1, triphasic waveform is normal blood flow and no atherosclerosis or plaque, the type 2, diphasic waveform is seen when there are atherosclerosis plaques, but normal blood flow, and the type 3, monophasic waveform reflects stenosis with diameter reduction > 50%. **Results:** The sum of the overall ABI and TBI VasoPad values, called Sum of Brachial Indices (SBI), gave a specificity of 88.89% and sensitivity of 100% for detecting vascular color Doppler ultrasound biphasic and monophasic waveforms versus triphasic waveforms with a cutoff ≤ 1.36 ($P < 0.0001$, area under the receiver operating characteristic(ROC) curve of 0.960). The average of the SBI to detect the Doppler waveform triphasic, biphasic and monophasic is respectively 1.57, 1.29 and 1.20. The toe PTG Index, returned a specificity of 83.3% and a sensitivity of 100% compared with vascular color Doppler ultrasound biphasic and monophasic waveforms versus triphasic waveforms with a cutoff ≤ 26 ($P = 0.001$ and AUC = 0.917). The average of the PTG index to detect the Doppler waveform triphasic, biphasic and monophasic is respectively 29, 21.5 and 20 Volt per second (V/s). **Conclusion:** The VasoPad was useful for detecting PAD, which is fully defined as having vessel stenosis > 50% (Doppler monophasic waveforms) but also early stage of atherosclerosis plaque of the lower extremities (Doppler biphasic waveforms). The VasoPad method provided a remarkable sensitivity of 100% and a specificity level similar to those of the conventional ABI test method compared with the vascular color Doppler ultrasound. In addition to being useful to screen and detect PAD, the VasoPad offers early detection of lower extremity atherosclerosis, with normal blood flow (Doppler biphasic waveforms), which could provide greater treatment options and thus reduce the overall number of lower extremity complications.

Keywords

Lower Extremity Peripheral Artery Disease, PAD, Ankle Brachial Index, ABI, Toe Brachial Index, TBI, Vascular Color Doppler Ultrasound, Photoplethysmography Second Derivative-PTGSD, Photoplethysmography Index-PTG Index

1. Introduction

Lower extremity peripheral artery disease (PAD) is an atherosclerotic disease of the arteries supplying blood to the legs and feet. The PAD prevalence has been estimated to be ≤19% in people > 55 years old [1], which increases with advancing age and in the presence of risk factors, such as smoking, hypertension, diabetes, inactivity, and obesity [1] [2]. Because it is often asymptomatic, PAD is underdiagnosed; consequently, those who have it may not receive appropriate treatment [3] [4]. PAD is associated with an increased risk of coronary heart disease, stroke, and leg amputation [5]. Diagnosis of PAD is defined as ≥50% stenosis of the lower extremity artery [6].

The first-line method for detection of PAD is the Ankle Brachial Index (ABI). The Toe Brachial Index (TBI) is considered to be an alternative to the ABI in screening for PAD [2] [7]. The other PAD diagnostic methods include Vascular Color Doppler ultrasound, which uses sound waves to image the movement of blood through blood vessels, and angiography, which uses X-rays, magnetic resonance imaging scans, or computed tomography scans to look for blockages in the arteries [6].

The ABI represents the ratio of ankle to brachial systolic pressure and is recommended to be calculated by dividing the higher systolic pressure of the dorsalis pedis and tibialis posterior vessels at the ankle by the higher of the systolic pressures measured in the brachial artery in both arms. The TBI is the ratio of the toe systolic pressure divided by the higher systolic pressure measured in both arms. The ABI and TBI are measured on the right and left side, and the lower of these numbers is the patient's overall ABI and TBI [7] [8].

There are different methods for measuring the ABI and different calculations to obtain the best specificity and sensitivity to detect PAD compared with those of vascular color Doppler ultrasound lower extremity waveforms and/or angiography [9] [10]. Several noninvasive techniques are used to detect limb blood flow or pulse volume for measuring the ABI, primarily the conventional method, which uses a cuff, and handheld sphygmomanometer and continuous-wave Doppler tracings, but the other methods are the oscillometric method, volume plethysmography analysis from the cuff pressure, and photoplethysmography (PTG) analysis [11]. Compared with a variety of imaging methods to determine the presence of PAD, the diagnostic performance of the ABI varies according to the population studied, cutoff threshold, and technique used to detect blood flow through the ankle arteries [6].

Meta-analysis studies of ABI using the cuff and Doppler probe method have achieved reasonably high specificity (83% - 99%) but lower sensitivity (69% - 79%), with a cutoff ≤ 0.9 [6] [12] [13]. A study by Tehan *et al.* found that the sensitivity for PAD was highest for the TBI (71%; ABI, 45%), and the specificity was highest for the ABI (93%; TBI, 78%). The sensitivity and specificity of the ABI and TBI were determined by vascular color duplex ultrasound [14]. That study used the conventional ABI to measure the pressures with a cuff and handheld sphygmomanometer and continuous-wave Doppler tracings at the arms and ankles. Toe pressures were measured with a PTG probe and a Hokanson toe pressure cuff [14]. Fowkes *et al.* [15] reported several factors that contribute to the ABI variability, including the interactions among the subject, subject's leg (right versus left), observer, and delay between measurements.

The aim of this clinical study was to determine the specificity and sensitivity of VasoPad (Manufactured by LD Technology, Florida, USA), compared to the vascular color Doppler ultrasound waveforms to validate the VasoPad for eventual use as an effective screening method to detect PAD and early detection of atherosclerosis plaques at the lower extremities.

Vascular color Doppler ultrasound was chosen as a reference diagnostic be-

cause it has been demonstrated to be a valid imaging technique for noninvasive vascular diagnostic testing [16] [17].

2. Materials and Methods

VasoPad system description (**Figure 1** Drawing of the unit)

The VasoPad system (marketed as Smart-ABI Plus in the USA) is a combination of devices, TBL-ABI and OXI_W, and the 2 devices are FDA cleared.

The TBL-ABI comprises:

- ✓ Four Bluetooth blood pressure devices with integrated regular-sized cuffs for left and right arms and ankles.
- ✓ One Bluetooth blood pressure device with a large-arm cuff.
- ✓ A USB charger and cable for charging the blood pressure devices.

The OXI_W is a plethysmography device.

The VasoPad System is an automated device using:

- ✓ The pulse wave method [18] to measure the arms and ankles dorsalis and tibial posterior artery blood pressures.
- ✓ The volume plethysmography via the blood pressure cuffs. During deflation, the air displacement is used to measure blood volume changes at the measuring site [19] (**Figure 2**).
- ✓ A patented photoplethysmography (PTG) index marker (US 9,668,701 B2) [20] (**Figure 3**).
- ✓ The Daisuke Fujita method that proposes a cuff-less systolic pressure estimation from the contour lines of the second-derivative photoplethysmography (SDPTG) waveform to estimate the toe systolic pressure. The toe cuffless systolic pressure estimation method using partial least-squares (PLS) and level-crossing feature shows good agreement with the cuff systolic pressure measurement. The systolic pression absolute error was ≤5 mmHg [21].

Figure 1. Unit drawing.

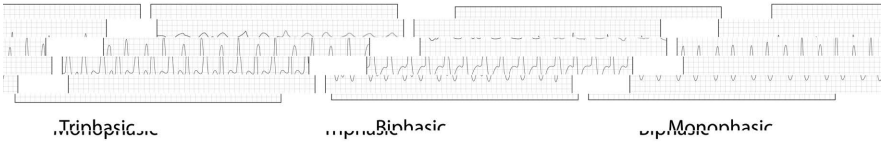

Figure 2. Screen shot of the VasoPad volume plethysmography types. The volume plethysmography waveforms are converted using the first derivative in order to display a record matching with the Vascular color Doppler ultrasound waveforms.

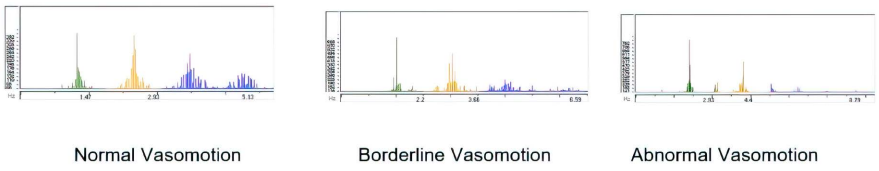

Figure 3. Screen shot of the PTG Index types. The PTG spectral analysis marker, called the PTG Index is calculated from the amplitude of the vasomotion of the spectral analysis. The less vasomotion seen in the graphic is indicated by a lower PTG Index value expressed in Volts per second (V/s) units.

In addition, the device can be used for Post Exercise (PE) measurements. Comparing the measurements at rest with the PE is useful to detect PAD when the ABI is acceptable or borderline (>0.8 to 0.99) according to the American Heart association guidelines. This feature was not used during the study since this PE procedure is well established. [8]

VasoPad system measurement process

The patients were placed in the supine position and rested ≥ 5 minutes before measurements (**Figure 4**).

The four Bluetooth blood pressure devices with different colors and labeling are placed on each arm and ankle. The Bluetooth photoplethysmograph sensor is connected to an external sensor wrapped first around the toe.

Sequence of the measurement:

1) Left-toe PTG.

2) Right-toe PTG. The external sensor is switched to the right toe.

3) Synchronized blood pressure measurement of the left arm and dorsalis pedis artery of each ankle. The arrow of each cuff is placed toward the dorsalis pedis artery.

4) Synchronized blood pressure measurement of the right arm and posterior tibial artery of each ankle. The ankle cuffs are rotated to place the arrow toward the posterior tibial arteries.

Vascular Color Doppler ultrasound

The Vascular Color Doppler ultrasound (GE Voluson TM S8 with Touch Panel located in Sunflower Laboratory and Diagnostic Center, Mumbai, India) is accredited by the National Accreditation Board for Testing & Calibration Laboratories).

It can diagnose stenosis through the direct visualization of atherosclerosis or plaques and through waveform analysis [15] [16]. The vascular color Doppler ultrasound provides 3 waveform types. The type 1, triphasic waveform is normal blood flow and no atherosclerosis or plaque or calcification, the type 2, diphasic waveform is seen when there are atherosclerosis plaques but normal blood flow, and the type 3, monophasic waveform reflects a stenosis with a diameter reduction > 50% [22] [23] [24] (**Figure 5**).

Study design and setting

The study was conducted according to the ethical principles of the Declaration of Helsinki. All of the subjects provided written informed consent and their

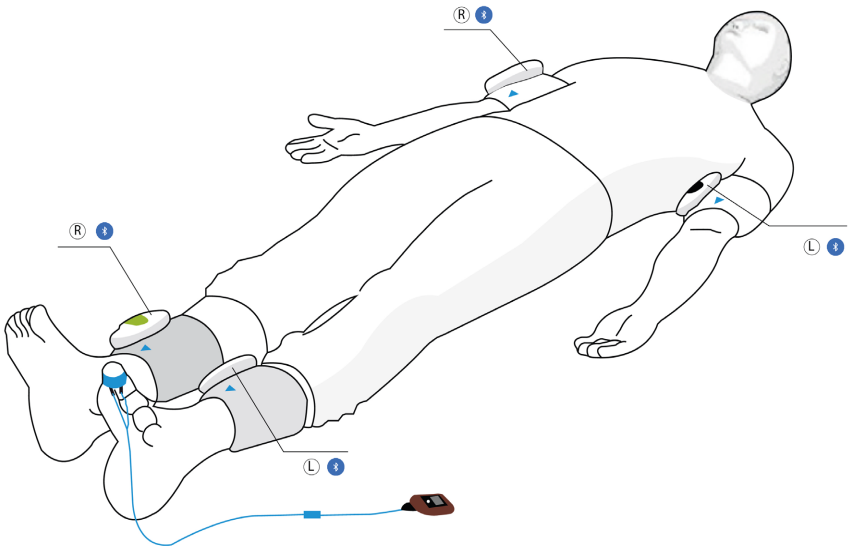

Figure 4. Patient setup.

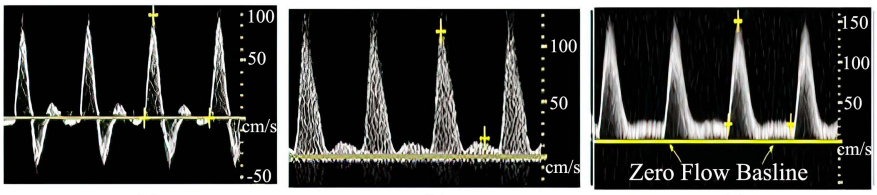

Figure 5. Vascular color doppler ultrasound images for lower extremity arteries [22]. (a) Triphasic: Normal blood flow and no atherosclerosis or plaque or calcification. Three phases—forward flow, flow reversal, and a second forward component. (b) Biphasic: Light to moderate. Atherosclerosis plaques but normal blood flow. Two phases—one forward flow and one reverse. (c) Monophasic: Abnormal. stenosis with a diameter reduction > 50%. One phase, No flow reversal, and no second forward component.

confidentiality was maintained. Subjects who were >18 years old and had the ability to provide written informed consent were included in this study.

Participants

There were 27 patients (12 women, 15 men) ranging in age from 29 to 79 years. The patients were examined with the VasoPad at IPC Heart Care Centers in Mumbai and by vascular color Doppler ultrasound at the Sunflower Diagnostics Radiologic center in Mumbai, India.

Patients were asked to avoid alcohol, smoking, exercise, and caffeine for ≥1 hour before the examination.

Fontaine classification of the four stages of PAD:

- **Stage I:** Asymptomatic

Stage I includes patients who are asymptomatic most of the time, but in whom a careful history may reveal non-specific, subtle symptoms, such as paresthesia. Physical examination may reveal cold extremities, reduced peripheral pulse, or murmurs in the peripheral arteries.

- **Stage II:** Intermittent claudication. Patients usually note the appearance of

pain after walking a constant distance:

- **Stage IIa:** Intermittent claudication after walking > 200 m.
- **Stage IIb:** Intermittent claudication after walking < 200 m.

- **Stage III:** Rest pain. Rest pain appears especially during the night when the legs are raised up on the bed, which diminishes the gravitational effect present by day; during the night, the lack of sensory stimuli also allows patients to focus on their legs.
- **Stage IV:** Ischemic ulcers or gangrene (which may be dry or humid).

Sociodemographic characteristics of the sample (**Table 1**).

Inclusion and exclusion criteria

The inclusion criteria were 1) 18+ years of age for patients with symptoms of PAD and 2) ability to provide written informed consent.

The exclusion criteria were the following contraindications: 1) bilateral mastectomy, 2) arterial catheters (access or therapy) on arm or leg or an arteriovenous (AV) fistula or shunt. 3) venous pulsations (e.g., tricuspid valve regurgitation), 4) patients that have low perfusion, and 5) more than one extremity missing.

Statistical analysis

Statistical analysis was performed using receiver operating characteristic curves to determine the specificity and sensitivity of the device to detect the patient with abnormal vascular color Doppler waveform (diphasic and triphasic) and normal waveform (triphasic). MedCalc software [25] was used to perform the statistical analyses.

Table 1. Sociodemographic characteristics of the sample.

Mean Age (average and range, years)	55.5	29 - 79
Number of males (n, %)	15	55.5%
Number of females (n, %)	12	44.5%
Fontaine classification		
Stage I Stage IIa Stage IIb Stage III Stage IV	4 10 7 6 0	14.8% 37% 26% 22.2% 0%
Doppler waveform results		
Monophasic number (n, %)	4	14.8%
Diphasic number (n, %)	5	18.53%
Triphasic number (n, %)	18	66.67%
Dyslipidemia number (n, %)	21	77.7%
Smoker number (n, %)	5	18%
Diabetes mellitus (n, %)	16	59%
Hypertension (n, %)	13	48%
Under medications (n, %)	23	85%
Systolic pressure (average and range, mmHg)	121.8	87 - 158
Diastolic pressure average (average and range, mmHg)	72.07	52 - 107

3. Results

Overall ABI sensitivity and specificity

The overall ABI gave the same specificity and sensitivity values of 77.8%, with a cutoff ≤ 0.9 (P = 0.024 and AUC = 0.747) for detecting vascular color Doppler ultrasound biphasic and monophasic waveforms versus triphasic waveforms (Figure 6).

Overall TBI sensitivity and specificity

The overall TBI gave a specificity of 55.6% and sensitivity of 100%, with a cutoff ≤ 0.55. (P = 0.001 and AUC = 0.824) for detecting vascular color Doppler ultrasound biphasic and monophasic waveforms versus triphasic waveforms (Figure 7).

Overall PTG Index marker sensitivity and specificity

The overall PTG index marker gave a specificity of 83.3% and a sensitivity of 100%, with a cutoff ≤ 26 (P = 0.001 and AUC = 0.917) for detecting vascular color Doppler ultrasound biphasic and monophasic waveforms versus triphasic waveforms (Figure 8).

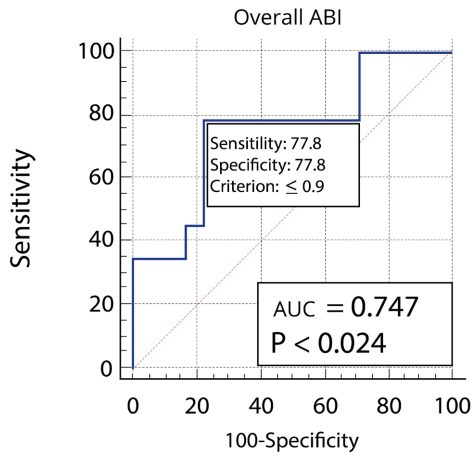

Figure 6. Overall ABI sensitivity and specificity.

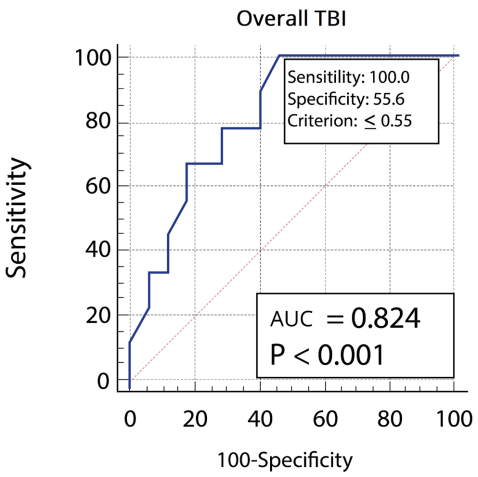

Figure 7. Overall TBI sensitivity and specificity.

The sum of the overall ABI plus TBI (SBI) specificity and sensitivity

The overall sum the ABI and TBI (SBI) values gave a specificity of 88.9% and a sensitivity of 100% with a cutoff ≤ 1.36 (P = 0.001 and AUC = 0.960) for detecting vascular color Doppler ultrasound biphasic and monophasic waveforms versus triphasic waveforms (Figure 9).

Notes: Any patient in the study returned a non-compressible (ABI > 1.40).

The SBI has not be evaluated in case of non-compressible result, therefore, the SBI cannot be used in case of ABI ≥ 1.4.

Overall algorithm ABI plus TBI average compared with the Doppler ultrasound waveform types

The patients with a vascular color Doppler monophasic waveform had an SBI average of 1.20, those with a biphasic waveform had an SBI average of 1.29, and those with a triphasic waveform had an SBI average of 1.57 (Figure 10).

Overall PTG Index marker average compared with the color Doppler waveform types

The patients with a vascular color Doppler monophasic waveform had an overall PTG Index average of 20, those with a biphasic waveform had an overall PTG Index marker average of 21.5, and those with a triphasic waveform had an overall PTG Index marker average of 29 (Figure 11).

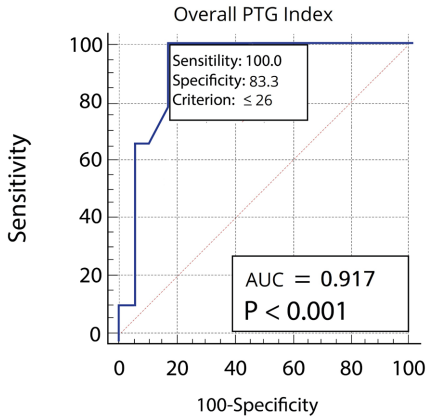

Figure 8. Overall PTG Index marker sensitivity and specificity.

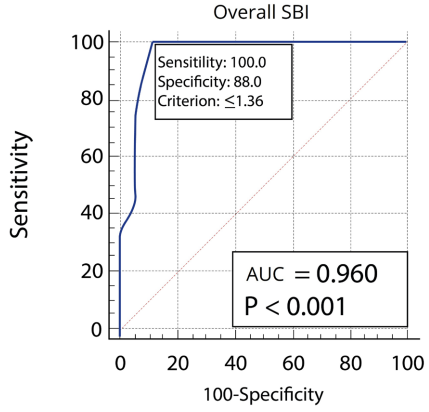

Figure 9. The sum of the overall ABI plus TBI (SBI) specificity and sensitivity

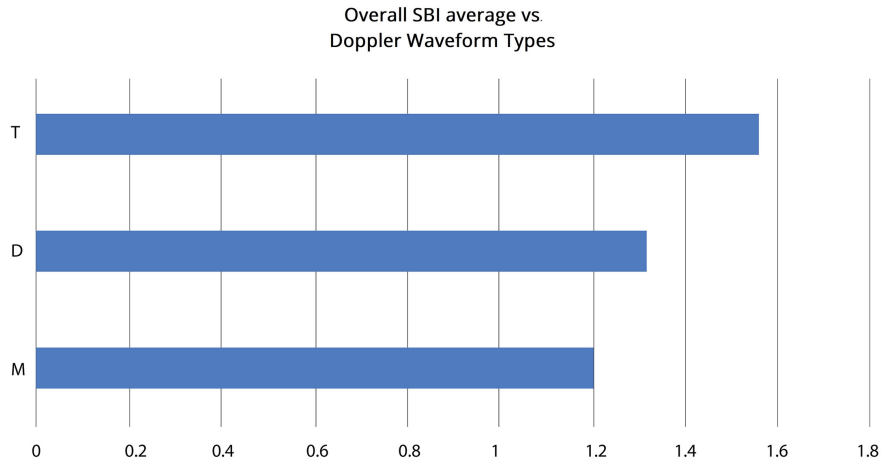

Figure 10. M = Monophasic, B = Biphasic, T = Triphasic.

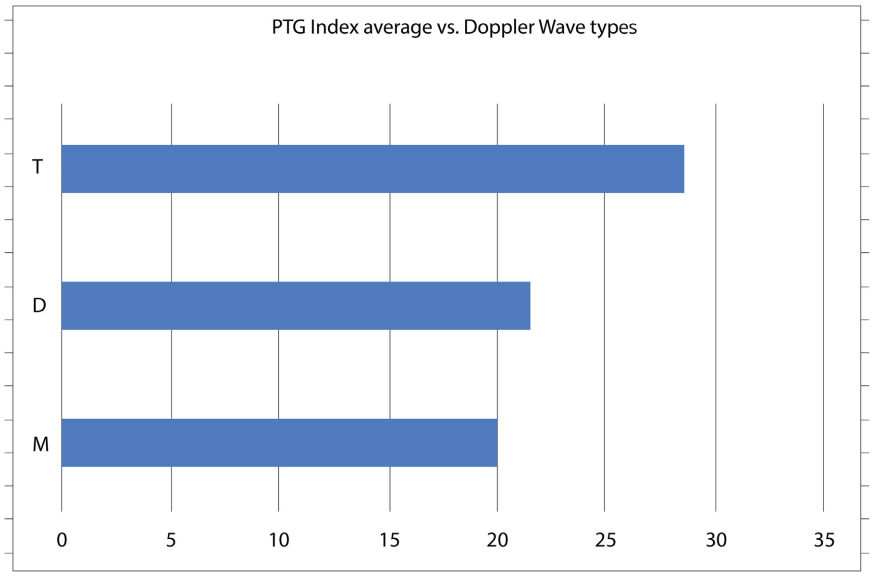

Figure 11. M = Monophasic, B = Biphasic, T = Triphasic.

4. Discussion

In summary the VasoPad results shown that the SBI gave a specificity of 88.89% and sensitivity of 100% for detecting vascular color Doppler ultrasound biphasic and monophasic waveforms versus triphasic waveforms with a cutoff ≤ 1.36 ($P < 0.0001$, area under the receiver operating characteristic (ROC) curve of 0.960). The average of the SBI to detect the Doppler waveform triphasic, biphasic and monophasic is respectively 1.57, 1.29 and 1.20. The toe PTG Index returned a specificity of 83.3% and a sensitivity of 100% compared with vascular color Doppler ultrasound biphasic and monophasic waveforms versus triphasic waveforms with a cutoff ≤ 26 ($P = 0.001$ and AUC = 0.917).

The average of the PTG index to detect the Doppler waveform triphasic, biphasic and monophasic is respectively 29, 21.5 and 20 V/s.

According to the meta-analysis studies using the conventional ABI measure-

ment method, which uses a cuff, and handheld sphygmomanometer and continuous-wave Doppler tracings, returned a specificity of 83% - 99% and a sensitivity of 69% - 79% [6] [11] [12], the VasoPad system gave the same range of sensitivity and slightly lower specificity than those obtained from the ABI conventional method.

The study by Tehan *et al.* gave a sensitivity for PAD that was highest for the TBI (71%; ABI, 45%), and the specificity was highest for the ABI (93%; TBI, 78%). The sensitivity and specificity of the ABI and TBI were determined by vascular color Doppler US [14]. The VasoPad TBI gave a remarkable sensitivity of 100%, but lower specificity.

The underperformance in specificity of the VasoPad ABI and TBI was possibly due to the inclusion of patients with atherosclerosis plaques and normal blood flow (biphasic waveform) which were not included in the reference studies since diagnosis of PAD was defined as stenosis ≥ 50% of the lower extremity artery. However, this approach underestimates the PAD and fails to detect the early phase of arteriosclerotic plaque development [27].

The TBI is usually limited to patients who have vessel stiffness and ABI ≥ 1.40 because of relevant comorbidities associated with elevated ABI [26].

In addition, studies have shown that 14% to 27% of patients referred for distal pressure measurements have a low TBI but a normal ABI [7] [28] [29]. Approximately 60% of these patients were not diagnosed with a disease associated with vessel stiffness, and therefore, would not have been diagnosed with PAD according to the current screening using only the conventional ABI measurement method [30].

Therefore, implementation of the TBI associated with ABI with the VasoPad standard test for PAD could potentially enable detection of patients with undiagnosed PAD.

The VasoPad SBI and the toe PTG Index marker provided high specificities and a remarkable 100% sensitivity compared with Doppler lower extremity waveforms and is therefore a better method for evaluating PAD and early detection of atherosclerosis plaques.

In the case of a non-compressible ABI value (≥1.40), the PTG Index marker will be useful for detecting the presence of atherosclerosis plaques in the lower extremities. The PTG Index marker measured at the finger has been used in several studies for detecting diabetes and coronary artery disease with high specificity and sensitivity [20] [30] [31].

5. Conclusion

The VasoPad was useful for detecting PAD, which is fully defined as having vessel stenosis > 50% (Doppler monophasic waveforms) but also early stage of atherosclerosis plaque of the lower extremities (Doppler biphasic waveforms). The VasoPad method provided a remarkable sensitivity of 100% and a specificity level similar to those of the conventional ABI test method compared with the vascular color Doppler ultrasound. In addition to being useful to screen and

detect PAD, the VasoPad offers early detection of lower extremity atherosclerosis, with normal blood flow (Doppler biphasic waveforms), which could provide greater treatment options and thus reduce the overall number of lower extremity complications.

6. Study Limitations

A limitation of this study was the relatively small sample size.

Acknowledgements

The authors thank LD Technology for providing the medical systems that were used in this study. Dr. Prasad Kamble had the responsibility to enroll the patients, to assure the respect of the study protocol steps and collect the data. Dr. Pratiksha Gandhi performed the data statical analysis and wrote the manuscript.

Conflicts of Interest

The authors report no conflicts of interest related to this study.

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