Establishing Normative Data for Peripheral Arterial Disease Using Pulse Wave Analysis

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Abstract

Peripheral arterial disease (PAD) affects 10–25% of people over the age of 55. It contributes to foot amputation, morbidity and mortality. Accurate and early diagnosis can lessen this public health burden. A current clinical measure of PAD such as the ankle brachial pressure index (ABPI) has low sensitivity and specificity for asymptomatic disease and calcified arteries especially in the diabetic population. Therefore, a new non-invasive evaluation method for lower limb vasualisation has been investigated. Pulse wave analysis (PWA) including peak blood flow velocity (PBFV) and fractal dimension (FD) of the velocity waveform. A "non pathological" group students and staff was selected using convenience sampling at Charles Sturt University. We observed two and three peak velocity waveforms (51.7%) which indicate normal flow but also a high occurrence (33.33%) of pre-peaks and four peaks in the pulse wave not reported previously. Normative values were determined for PBFV (95% CI 9.9-37.3 cm/sec) and the fractal dimension (95% Cl 1.082-1.261). The results indicate that this study warrants further investigation into the potential for PBFV or FD to be used as a clinical assessment tool to identify early asymptomatic PAD.

1. INTRODUCTION

Within Australia, peripheral arterial disease (PAD) affects 10–25% of people over the age of 55 and can lead to foot ulceration, gangrene, and amputation [1-4]. PAD is also a major risk factor for the development of cardiovascular and cerebrovascular disease that can lead to myocardial infarction and death [2,4]

Several diagnostic methods exist for the detection of PAD. These include angiography, the Ankle Brachial Pressure Index (ABPI) and pulse palpation (PP).

A. Current Methods Used

Angiography is identified as the gold standard for determining the presence of PAD [2,3]. However, angiography is both a costly and an invasive procedure that involves the risk of local complications associated with invasive procedures, anaphylaxis, or renal failure that is associated with the contrast agent [5,6].

The current podiatric method for PAD diagnosis uses the ABPI [7]. This index is derived by dividing the ankle systolic blood pressure by the arm systolic blood pressure [7]. However, there is controversy related to the accuracy, reliability, and validity of this measure [7]. In addition the ABPI is not reliable for calcified vessels, giving falsely elevated readings [6].

In clinical practice, pulse pressure (PP) has been used as an alternative, non-invasive procedure to detect PAD. The predictive power of this method is similar to the ABPI with low sensitivity and specificity and overestimates the presence of PAD because of factors such as anatomic variation of artery location and the absence of the pulse associated with the dorsalis pedis artery in approximately 8% of healthy individuals [2].

B. Pulse Wave Analysis

Pulse Wave Analysis (PWA) relies on detecting changes in blood flow through the vessels and can be used for calcified arteries. Calcification changes compliance of the blood vessel and as a result the flow characteristics are altered and can be recorded using a transducer such as a Doppler ultrasound instrument [8]. Changes in pulse wave morphology may also be present in asymptomatic disease [9].

PWA has been shown to be effective in the early screening for cardiovascular disease using the carotid and/or radial artery [10-11]. This type of analysis has not been researched for the lower limb. The literature also reports on descriptive analysis of the pulse waves for the upper limb (eg number of peaks present), with no reference to the lower limb.

A normal waveform of a lower limb peripheral artery is represented usually by a triphasic waveform as shown in Figure 1 [12].

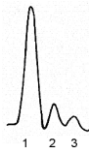


Fig. 1: Example of a triphasic pulse wave
1 = 1st peak
2 =2nd peak
3 = 3rd peak
[14] p. 37

The first peak represents the blood flow velocity due to blood being expelled from the ventricle during systole. The second wave peak represents the reversal flow velocity of early diastole due to the elastic distension in the arteries. The third peak represents the forward flow velocity during late diastole due to the rebound of the arteries [12-13]. The form of the first peak is most often considered clinically, as a teepee indicating a fast flow and an igloo peak indicating a slower flow [14].

Contrary to the theory that only a triphasic waveform represents normal blood flow, Hoffman [14] suggested that a normal waveform can also be biphasic. Table 1 describes possible differences in characteristics of the pulse waveform and what each characteristic indicates.

TABLE 1: DESCRIPTION AND SIGNIFICANCE OF A PERIPHERAL ARTERY WAVEFORM

Description of Waveform	What it signifies
Monophasic (1 peak)	Usually suggests a serious perfusion problem and is usually associated with ischaemia
Biphasic (2 peaks)	Can indicate initial problems eg a proximal obstruction or at least an altered perfusion Can be seen with ageing as vessels lose compliability May also indicate tachycardia as the heart is beating too rapidly for reverse flow to occur Hoffman [14] suggests that this can also be classed as normal
Triphasic (Narrow peak with two smaller peaks)	Classed as a normal artery
Flattening of peaks	Indicates severe disease
Shakiness (Complex peaks)	Turbulence
Undetectable peaks	May indicate critical limb ischaemia
Any of the above descriptions	Can also be reflective of poor signal, operator error or artefact

[12-14]

C. Measurement of the Peripheral Arterial Waveform

There is no standardised approach for measurements of the waveform characteristics. However, the amplitude of the peaks and time delays between peaks, have both been measured in the past. The main purpose of these measurements is establishing points to serve as markers that can aid in comparison of data collected from the same equipment/individual over time. However, no normative data has been published on these measurements for a clinical standard.

It has also been suggested that arterial stiffness can be measured by pulse wave velocity, although reliable normative data is lacking here also [15]. Inter-observer comparisons are difficult without some standardisation to obtain a scale-free measure. One way to address this issue is to measure the characteristics of the waveform directly. This can be done using the approximate entropy or fractal dimension (FD).

D. Approximate Entropy and Fractal Dimension

Approximate entropy is a non-linear method for measuring the characteristics of a waveform. However, it has been criticised as being heavily reliant on the length of recordings as shorter recordings result in lower than expected values [16]. Other non-linear methods include the fractal dimension which may be more appropriate to use on pulse waveforms [17].

2. METHOD

This study was granted ethics approval from the Charles Sturt University School of Community Health Ethics Committee. Participants were recruited from staff and students of the Albury campus and participants of the Diabetes Complication Screening Initiative at Charles Sturt University.

All participants had to be healthy without any known previous or current pathology such as diabetes, kidney disease, stroke, cardiovascular, or peripheral vascular disease. The inclusion criteria also stated that the participants had to be 18+ years of age and that informed consent had been attained. Additional exclusion criteria included the following; participants with skin allergies associated with tapes, gels etc; smoking more than 5 cigarettes a day (vasoconstrictor) and consuming more than 2 alcoholic drinks per day (standard glasses) (vasodilator). Participants with who have areas of skin breakdown or had recent lower limb surgery in the lower limb which is contraindicated for the ABPI were also excluded. After completing the information and consent process, participants completed a medical history form and were examined using the ABPI and PWA.

The ABPI was determined using a Doppler ultrasound with an 8MHz probe and sphygnomometer after a 10 minute rest. The systolic blood BP was taken on both arms and both legs. The ABPI was calculated by dividing the ankle systolic pressure by the arm (brachial) systolic pressure for both the

left and the right side [7]. The results were recorded for each limb.

The pulse waves were recorded during the Doppler ankle measurements for the ABPI on a paper recording strip for the left and right foot before the cuff was inflated. The characteristic of the waveform was noted by examining the number of wave peaks and waveform characteristics. For this study the following categories were used; 2 waves, 3 waves, 4 waves, pre wave and complex waveform. Due to the inclusion of currently unclassified waveforms (Table 1) a pilot study was done on the first eleven people for the pulse wave analysis to see if the same waveforms were obtained when testing two to four weeks later to rule out spurious results.

The peak blood flow velocity (PBFV) (cm/sec) was calculated by the Doppler and printed on the tracing. To obtain the FD's the printout of the waveform was converted to a digital image using a WACOM digitisation tablet and software (Intuos.3 Graphics tablet –PTZ-631W, WACOM) in Combination with a drawing programme from NIH (Image J http://rsb.info.nih.gov/ij/download.html). The waveform was then analysed in NIH Image using a purpose written dilation FD macro (copyright H Jelinek). Once the dilation measurements were complete the results were imported into EXCEL and a graph was plotted using log B (The counts of the result of each measurement with each kernel diameter) vs. log A (The kernel diameter). Data was removed until an r^2 of greater than 0.999 was achieved. The gradient (S) of the slope was calculated as FD = 2 – S to give the FD [18].

The data for the PWA (PBFV and FD) is shown as minimum and maximum values as well as mean and standard deviation. For an indication of a possible normal range, the 5th and 95th percentile was determined. The pulse waveform characteristics were compared with the corresponding ABPI, PBFV and FD.

Within the literature there is variation in the cut-off values for the ABPI. For this research the ABPI cut-off values of between 0.9 and 1.3 were used.

The results for the piot study were analysed using Chi-square. Differences between wave morphology groups were analysed using ANOVA followed by a Fisher's Least Significant Difference (LSD) post hoc test. Significance was set at $p \leq 0.05$.

3. RESULTS

A total of 60 participants were included in this analysis. In the age range of <30 (n= 31) there were 9 males and 22 females and in the age range of >30 (n=29) there were 9 males and 20 females. Both a left and right result was recorded. In this study, all participants recorded normal ABPI results (0.9-1.3).

A. Pilot Study

The pilot study included the first 11 participants and the results are listed in Table 2. There is statistically no significant difference between the tests (p=0.29 for left and right).

TABLE 2: CONSISTENCY FOR PULSE WAVEFORM CHARACTERISTICS

	N	% Consistency	Df	Chi-Squared Statistic	p-value
Left Pulse Wave Characteristic	11	81.8%	1	1.1	0.29
Right Pulse Wave Characteristic	11	81.8%	1	1.1	0.29

B. Normative Range for PBFV and FD

The normative ranges using the 5^{th} and 95^{th} percentile for PBFV and FD as the lower and upper bounds for normal are 9.9-37.3 cm/sec for PBFV and 1.082-1.261 for FD.

C. Descriptive Statistics

The descriptive statistics for the data are displayed in Table 3.

TABLE 3: DESCRIPTIVE STATISTICS FOR ABPI, PBFV and FD

	Age	ABPI^	PBFV^^ (cm/sec)	FD^^^
N	60	120	120	120
Mean	36	1.03	21.18	1.19
Std. Deviation	15.62	0.05	9.36	0.05
Minimum	20	0.91	7.60	1.01
Maximum	64	1.17	51.8	1.3

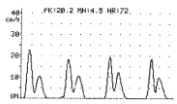
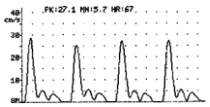
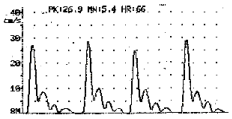
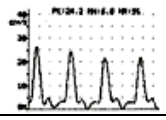
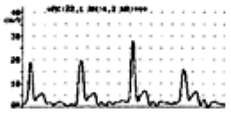
^ Ankle Brachial Pressure Index
^^ Peak Blood Flow Velocity
^^^ Fractal Dimension

D. Pulse Wave Characteristic

The percentage of recordings that represented the different pulse wave characteristics was calculated. The results are in Table 4. Three peaks are indicators of normal function and

account for 45% of the recordings. Four peaks are the next most common occurrence with 38.3%.

TABLE 4: COMPARISON OF THE PULSE WAVE CHARACTERISTIC WITH THE CORRESPONDING FD and PBFV

Pulse Wave Characteristic	Pulse Wave Characteristic Examples	% of Pulse Wave Characteristic (N=120)
2 peaks		6.7%
3 peaks		45%
4 peaks		38.3%
Unclassified – Pre-peak Preceding the First Wave		2.5%
Unclassified – Complex Wave		7.5%

E. Comparison of PBFV and FD for the different pulse wave characteristic groups

An ANOVA test was used to determine if there were any differences between the pulsewave morphologygroups and the tests of PBFV and FD (Table 5). There was no significant differences between the groups for PBFV, yet a statistical difference was found for the FD (p=0.05). A LSD post hoc analysis was completed for FD (Table 6) indicating a significant difference between 2 peak and 3 peak waveforms as well as between 3 peak and complex categories.

4. DISCUSSION

Peripheral arterial disease is not only a major risk factor for the development of cardiovascular and cerebrovascular disease, but can result in foot ulceration, gangrene and amputation [2-4]. The best non-invasive method to detect PAD is debated within the literature. A new method involving PWA was therefore investigated in this study.

TABLE 5:ANOVA TEST FOR PULSE WAVE CHARACTERISTICS FOR PBFV AND FD

Parameter	PBFV^	FD^^
2 peaks (6.7%)	18.5±14.34	1.15±0.08
3 peaks (45%)	22.01±9.98	1.2±0.04
4 peaks (38.3%)	21.95±8.12	1.18±0.05
Pre-Peak (2.5%)	15±1.25	1.18±0.03
Complex Waves (7.5%)	16.72±6.71	1.16±0.06
df	4	4
F Value	1.03.82	.007
p-value	0.318	0.05*

* Significance at the 0.05 level
^ Peak Blood Flow Velocity
^^ Fractal Dimension

TABLE 6:LSD POST HOC ANALYSIS FOR FD

Groups	Mean Difference	Std. Error	p-value
2 peak and 3 peak	0.05	0.02	0.01**
3 peak and complex	0.04	0.02	0.03**

** Significance at the 0.01 level

A. Pilot Study

During collection of data for the first eleven participants, waveform characteristics were apparent that did not fit into the current accepted classification of one, two, or three complex pulse wave peaks. The pilot study 81.8% consistency for both left and right side recordings There was no significant differences between tests for the left or the right (p=0.29) suggesting that the waveforms displayed repeatable peak characteristics over a period of time.

B. Pulse Wave Characteristics

The most common pulse wave characteristic was a waveform with 3 peaks (45% of study population). This was an expected result from the participant history and APBI measures There were no waveforms that were undetectable or had 1 wave, which can indicate abnormal blood flow [12].

Waveforms with four peaks were observed in 38.3% of the study population. This is of interest as this group of participants represents a "normal and healthy" sample population as defined by ABPI and from previous medical history but four peak waveforms have not been described in the literature. These waveforms may indeed be normal considering the large percentage seen in this healthy population. However these multiple wave peaks may also be related to turbulence caused in the vessels due to obstructions associated with early changes in the blood vessel lumen due to atherosclerosis or due to good elasticity in the young. If the former is true, this is of concern as it may mean that a large percentage of "normal and healthy" people may not be "healthy" but have asymptomatic/preclinical atherosclerosis. Another reason may be that the Doppler was picking up background noise, such as emanating from the veins. During the gap between one peak and the next the background noise may have been traced. This is unlikely as the method used

was checked by an experienced podiatrist in the Allied Health Clinic and venous influence on the tracing was deemed unlikely.

Waveforms with a pre-peak preceding the first peak of the pulse wave (2.5% of sample) were also observed. This waveform morphology is also not mentioned in the literature. One possibility why these were seen is arrhythmia where the pre-peak indicates an ectopic beat. Future study may involve selecting a cohort with known cardiac arrhythmia and recording the pulse wave flow velocity to determine the characteristic flow velocity pattern in the lower limbs.

Katz [19] has stated that the FD from ECG waveforms was used to distinguish different cardiac pathologies. Different pulse wave characteristics in the radial artery also indicate pathology or at least different functional capacities within the normal range. Our study indicates that abnormal waveform morphology such as pre-peak or 4 peaks have a lower FD, which could identify abnormal function. As the FD is a measure of complexity, it seems that the lack of complexity may be an indicator of pathology. Further investigation is however needed to provide understanding of what a 4 peak or pre-peak waveform signifies.

C. Normative Range for PBFV and FD

Normative ranges are used to diagnose pathology and determine if therapeutic intervention is warranted. Normative data has not been set for PBFV and FD on the lower limb arteries. Therefore normative values were obtained for the posterior tibial artery by calculating the 5^{th} and 95^{th} percentile of the sample data. The 5^{th}-95^{th} percentile range for normal values for the peak blood flow velocity parameter is sufficiently strict for a clinical screening. This sets the normative values at 9.9 - 37.3 cm/sec for PBFV and 1.082 – 1.261 for FD. In using these two methods, some people in the study were identified with asymptomatic disease as the participants that are outside the normal range yet all have normal ABPI values. As both these methods (PBFV and FD) are new, this study has established a set of normative values that provides the framework for further research such as the effect of pathology for example PAD and calcification.

The ABPI lacks sensitivity for vessels that are calcified, which increases the ABPI value but may not reach clinical significance. The FD suggested twelve people with abnormal results similar to the PBFV results. The FD uses more information than any of the other methods and may therefore be more sensitive than the other methods in identifying pathology. However, this needs to be investigated further, by using this method on people with known pathologies such as PAD and calcification to see how these FD's change and relate to the ABPI.

D. Pulse Wave Characteristics, PBFV and FD

There were no statistical differences in PBFV between the pulse wave characteristic groups. This suggests that PBVF is not able to differentiate between the classifications. However, statistical differences occurred between the pulse wave characteristic groups using FD ($p=0.05$). The differences occurred between the 2 and 3 peak groups ($p=0.01$) and the 3 peak and complex waveform groups ($p=0.03$). This may be due to FD being a more sensitive measure of waveform. PBFV only measures the height of the first peak whereas FD takes into consideration the whole of the waveform.

E. Future Research

This research has provided the framework for future studies. As this study has obtained normative values for the new method of PWA including PBFV and FD, further testing of people with known PAD is warranted to observe what happens to these values when calcification or vessel obstruction is present. The sample groups could involve people with angiographically established PAD and calcification of the blood vessels that is evident on X-ray. As some people may have revascularisation procedures shortly after angiographically identified PAD, it would be important to test before revascularisation occurs. Of interest would be to obtain values for people with both PAD and calcified arteries to see whether PWA is sensitive to the calcification as the ABPI gives falsely elevated readings on calcified arteries. Once these groups have been tested, the statistical test of receiver operating characteristic (ROC) curves can be applied, which allows the determination of significant differences between the test procedures and the sensitivity and specificity of each of the instruments.

F. Importance of this Study

Correct and early diagnosis of PAD is essential to prevent complications and morbidity [2]. Within Australia, PAD resulted in 25,432 hospital admissions in 2002/03, and accounted for 2,478 deaths in 2003 [20]. The failure to identify and treat PAD places an enormous economic burden on the health care system [3]. Peak blood flow velocity and FD have the potential to not only detect PAD earlier, but also to detect PAD in calcified vessels that are unable to be identified with the ABPI. Early detection may decrease the need for more complex and risky interventions, and reduce the risk of cardiovascular or cerebrovascular disease.

5. CONCLUSION

Due to the seriousness of PAD, there is a need for easy, accurate, and early diagnosis. The associated costs and inherent risks connected with angiography imply that a more sensitive, non-invasive technique than the current ABPI needs to be found. There is controversy related to the sensitivity and validity of the ABPI. This may impair clinical decision making as patients may be misdiagnosed as a false negative,

and not be offered the required treatment or as a false positive, and receive unnecessary treatment. An alternative method, PWA, was therefore investigated. This is the first study to provide normative data for the parameters of PBFV and FD on a lower limb artery such as the posterior tibial artery. These normative values will provide the framework for further research to investigate the accuracy of this parameter in identifying people with asymptomatic disease and angiographically identified PAD. Both PBFV and FD values suggest that some of the healthy cohort used in this study may have asymptomatic disease.

In light of these findings, further research is warranted for the method of PWA. An easy and accurate diagnosis should ensure identification and commencement of appropriate treatment and may have the impact of improving quality of life and decreasing the health care costs that are associated with PAD.

ACKNOWLEDGEMENT

Assistance by Cheryl Kolbe and Bev de Jong is gratefully acknowledged. The research discussed in this paper was part of LT's honours thesis.

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