

An evaluation of non-invasive vascular assessment methods for detecting peripheral arterial disease in the lower limb

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Statement of originality

I declare that this work is wholly original and is all my own work and to the best of my knowledge contains no materials previously written or published by other persons. Any and all assistance in the preparation of this work has been acknowledged. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository**, subject to the provisions of the Copyright Act 1968.

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Statement of Collaboration

I hereby certify that the work embodied in this thesis has been done in collaboration with other researchers. I have included as part of the thesis a statement clearly outlining the extent of collaboration, with whom and under what auspices.

15th April 2016

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Overall I hope that this work encourages podiatrists in all areas of practice, public and private, to complete more accurate and timely non-invasive vascular assessments to ensure better outcomes in our patients and in turn reduce the number of preventable amputations. Although it may not be the most glamorous aspect of podiatry, I have always felt passionate about this area of practice, as ultimately what can be more rewarding than saving someone’s feet from amputation? I hope this thesis enables more podiatrists to do just that.

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Synopsis

This thesis provides an examination of the current evidence base regarding the diagnostic accuracy of non-invasive vascular assessment examination of the lower limb. This project comprised of a systematic review and a further four studies investigating the comparative diagnostic accuracy of non-invasive vascular assessment methods in cohorts at risk of peripheral arterial disease (PAD), the current vascular assessment techniques of Podiatrists in Australia and New Zealand and the reliability of continuous wave Doppler (CWD) assessment performed by Podiatrists. The results of these studies were then used to develop a modified method of lower limb vascular assessment designed to reduce the time burden of performing assessment in clinical practice. The diagnostic accuracy of this method for PAD was then compared to existing international guidelines.

Systematic review of studies investigating the diagnostic accuracy of the toe-brachial index (TBI) for detecting PAD, using diagnostic imaging as a reference standard, identified a lack of existing data. Furthermore, of the studies that have been done, we found that there are significant variations in TBI value used to indicate pathology, making results difficult to interpret. Additionally no studies had undertaken investigations of comparative diagnostic accuracy of the TBI and the more widely used ankle-brachial index (ABI) using a valid reference standard. Therefore undertaking a study evaluating the comparative diagnostic accuracy of the TBI and the ABI for detecting PAD was necessary. The diagnostic accuracy of the TBI and ABI were determined in a population at risk of PAD and demonstrated the TBI was a better clinical tests for PAD while the ABI was highly likely to fail to detect the presence of disease.

As vascular assessment is also known to be particularly challenging in diabetes cohorts due to the specific clinical presentation of diabetes related PAD. Therefore a case-control diagnostic accuracy study of the ABI, TBI and CWD for diagnosing PAD was performed.

Compared to a control group, all tests had lower sensitivity in the group with diabetes with CWD superior diagnostic accuracy in both cohorts.

To further explore the nature of lower limb vascular assessment in clinical Podiatry practice a survey of self-reported lower limb vascular screening techniques used by Podiatrists in Australia and New Zealand was undertaken. From this survey, poor alignment of clinical assessment techniques with existing international guidelines was identified. The most commonly employed vascular assessment techniques used by Podiatrists was reported to be CWD using hand-held Doppler while lack of time was reported to be a significant barrier to undertaking objective vascular assessment tests in clinical practice. As a result of these findings, an inter and intra-tester reliability study of hand-held Doppler examination by performed by Podiatrists was undertaken. This showed that the inter and intra-tester reliability of clinical Doppler examination by podiatrists is low and therefore likely to be of limited value for ongoing monitoring of lower limb vascular function.

Finally, using the research completed in this thesis combined with the current evidence base, a modified lower limb vascular screening method was devised. The diagnostic accuracy of this modified method for detecting PAD was then compared to the diagnostic accuracy of current international guidelines (American Heart Association Guidelines). This showed that the method had similar diagnostic accuracy to the current guideline, however may be more time effective.

The studies presented in this thesis re-enforce the difficulties with non-invasive vascular assessment of the lower limb, particularly in diabetes. The studies also demonstrate that the TBI has good clinical applicability and has good diagnostic accuracy and therefore may be a screening test of choice in populations at risk of PAD.

Chapter 1 Introduction

1.1 Peripheral Arterial Disease

Peripheral arterial disease (PAD) is the progressive stenosis of arterial beds which impedes the delivery of essential nutrients to the tissue (1). The process involves fatty streaking within the arterial lumen (2) which initiates an inflammatory process. This process promotes cholesterol deposition and leads to the development of atherosclerotic plaques (Figure 1.1) (2). These lesions can be stable or unstable in nature, with unstable lesions being vulnerable to ulceration and leading to thrombotic occlusion or embolization (3).

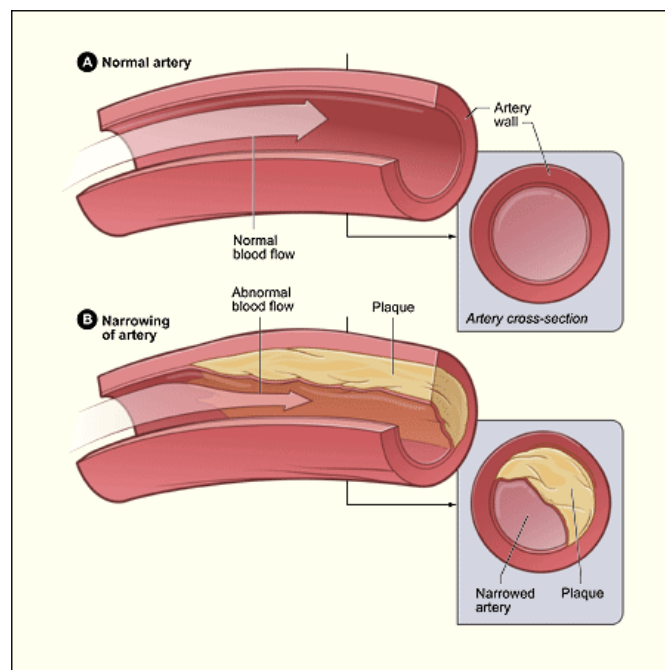


Figure 1.1 A depiction of a normal artery and an artery affected by atherosclerosis (4).

PAD is a broad term which describes disease altering the structure and function of non-coronary arteries(5). The non-coronary arteries are those which supply the brain, visceral organs, and the limbs (5). This thesis will focus on PAD affecting the lower limbs.

1.2 Epidemiology of PAD

PAD most commonly occurs in the sixth and seventh decade of life with prevalence estimated to be 20% of people over the age of 70 [(6, 7)]. Limited data exists on the prevalence of PAD in Australia, but it is predicted to be similar to other developed countries (6). In the presence of chronic disease such as diabetes, the clinical presentation of PAD is variable with a large proportion of PAD sufferers being asymptomatic(8). Current screening practices are inconsistently applied therefore the overall prevalence of PAD is estimated to be higher than what is currently reported and the costs associated with treatment and management are very high(9).

1.3 Risk Factors

A large number of modifiable and non-modifiable risk factors are implicated in the development of PAD (7). Undertaking an assessment of patient risk factors is essential for identification of modifiable risk factors that can be controlled to reduce the incidence and/or severity of PAD. Tobacco use is the most significant modifiable risk factor for PAD, increasing the chance of the disease by up to three-fold (Figure 1)(10) and resulting in much earlier onset of the disease (11). Hypertension and dyslipidaemia also pose significant risk and often occur concurrently (12).

The most significant non-modifiable risk factor for PAD is increasing age (5). Older populations have higher rates of PAD and are more likely to have concurrent risk factors for atherosclerosis, such as dyslipidaemia, hypertension and hyperviscosity. Male gender is also associated with higher prevalence of PAD (12, 13) while diabetes increases the risk of the disease by four fold and is associated with a more aggressive presentation and early large vessel involvement (Figure 1.2) (12). Chronic hyperglycaemia exacerbates risk of

developing diabetes related PAD by 26% for every 1% increase in glycosylated haemoglobin levels (14).

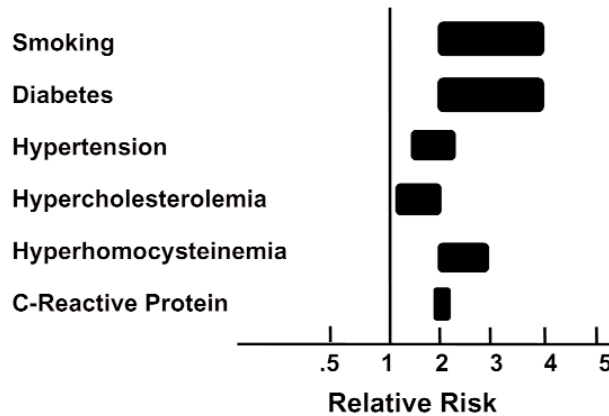


Figure 1.2: Relative Risk of PAD in relation to risk factors(15)

1.4 Anatomical Distribution of Peripheral Arterial Disease

The anatomical distribution of PAD depends on the risk factors involved (Figure 1.3) and affects the accuracy of non-invasive vascular screening methods. Smokers and younger age groups have a higher prevalence of proximal disease (16) whereas older age and diabetes more commonly have a more distal disease distribution. Distal disease presents a range of diagnostic challenges. The presence of conditions such as peripheral oedema, fibrosis, adipose tissue and the presence of ulceration and medial arterial calcification can interfere with the use of commonly used testing equipment. In addition, medial arterial calcification (MAC) which causes stiffening of the arterial wall of vessels in the lower limb can prevent the arterial compression required to obtain accurate systolic pressure readings used in the calculation of the ankle-brachial index (ABI). With this condition prevalent populations typically at risk of PAD including the elderly and those with diabetes, accurate vascular screening in these populations can be difficult to achieve (17).

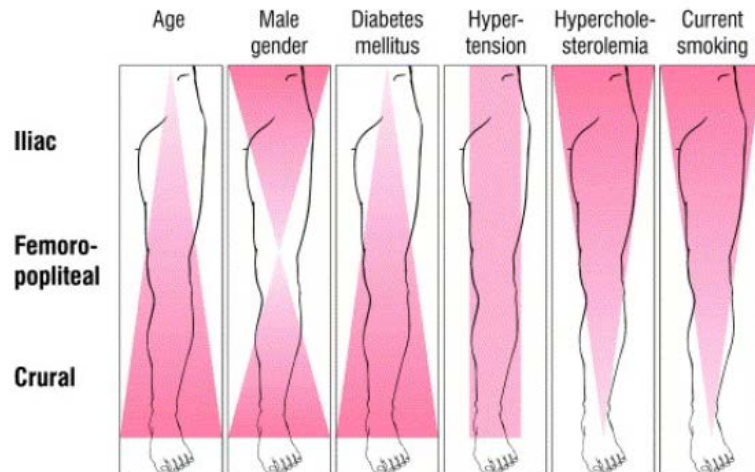


Figure 1.3 Association of risk factor with pattern of atherosclerotic lesions (16))

1.5 Clinical presentation of peripheral arterial disease

Diagnosis of PAD is frequently overlooked in clinical practice as PAD sufferers may be asymptomatic in the early stages of the disease or present with symptoms which are atypical or non-specific (18). Additionally, common symptoms of PAD including distal pain, numbness and coldness are often confused with other conditions such as arthritis or nerve disorders (19). In people with diabetes, presence of peripheral sensory neuropathy can mask the signs and symptoms of advanced PAD including claudication pain and ischaemic rest pain (20).

The most widely recognised symptom of PAD is intermittent claudication, which presents as muscle pain or cramp-like pain evoked by activity (15). Generally patients report pain occurs after walking a specific distance and typically subsides within 2-5 minutes of rest (21). Symptoms are normally reported distal to the location of the obstruction (i.e. toe pain could indicate an occlusion in the midfoot) with distance walked before onset of pain reflective of the severity of the disease process (19). Other signs and symptoms of more severe cases of PAD include trophic changes such as subcutaneous atrophy, dependant rubor, hair loss, nail dystrophy and cool skin (21, 22).

Advanced cases of PAD present as critical limb ischemia- a severe foot pain occurs with elevation or exercise and relieved by dependency. These symptoms indicate significant tissue hypoxia and necessitates vascular intervention to avoid amputation(21). With severe disease such as this, the smallest amount of pressure or trauma in the distal limb can result in ischaemic ulceration and/or gangrene.

Typically ischaemic ulcerations are ulcerations that will not heal due to impaired blood flow and are readily identified by their characteristic appearance, symptoms and location. Ischaemic ulcerations generally appear with a dull wound base, have necrotic areas and are surrounded by atrophic skin (23). They also present with pain, absence of bleeding, and usually occur secondary to trauma, therefore have a tendency to occur on the pretibial areas and the distal feet (24). However, other forms of ulceration such as neuropathic ulceration may have an ischaemic component which is not so readily identified (25, 26). Ischaemic ulcerations generally require vascular intervention in order to heal as the primary aetiology is arterial insufficiency(27). The end stage symptom of PAD is the presence of gangrene (Figure 1.4) which indicates severe tissue hypoxia and frequently results in surgical amputation in addition to requiring vascular intervention (25).



Figure 1.4: A foot affected by gangrene

1.6 Outcomes of PAD

The prognosis of a limb affected by PAD is dictated largely by the extent and location of disease. It is estimated that 25% of symptomatic PAD sufferers require vascular intervention and suffer irreversible tissue loss (28). It has also been reported that patients who undergo distal vascular intervention are more likely to require amputation than those who have had proximal interventions (29). This is significant as patients with distal disease are often the most difficult to diagnose, as well as manage.

Whilst the amputation rate for patients with PAD is relatively low (30), the risk of death from a cardiovascular event is high (30%)(31). The significantly increased risk of death is due in part to the strong relationship between the presence of PAD and other forms of macroangiopathy such as coronary artery disease. Coronary artery disease is said to be present concurrently in 40% of symptomatic PAD sufferers (32). In severe cases of PAD, it has been reported that there is a 60% incidence of significant coronary artery disease (33) with the renal arteries and cerebrovascular system also affected but to a lesser extent (17).

Due to the morbidity and mortality associated with PAD, accurate vascular screening of at risk patients on a regular basis is essential to ensuring correct management of the

condition. Management of PAD includes early identification, intervention and aggressive risk factor modification(31) including smoking cessation and pharmacological and exercise interventions (31).

1.7 Diagnosis of peripheral arterial disease

1.7.1 Non-invasive screening methods for PAD

There are many different non-invasive screening methods for PAD, including subjective testing techniques such as pedal pulse palpation, capillary refill time and Buerger's elevation/dependency test. Dorsalis pedis and posterior tibial pulses are normally palpated and assessed for presence, rate, regularity, strength and equality (23). Capillary refill is performed by compressing the skin with the thumb on the plantar great toe leading to blanching in skin colour. On release of the thumb the capillaries should refill returning the skin to a normal colour within three seconds(23). Buerger's elevation/dependency test is determined by elevating the limb at 45 degrees and observing for colour changes, in an ischemic limb the foot/limb will have severe and widespread pallor (34). The limb is then lowered into dependency and the time taken for the limb to return to the colour on the contralateral limb is noted. A normal foot should regain its colour in 15-20 seconds with a delayed time suggesting inadequate blood flow (34). These tests have been shown to have varying levels of sensitivity, specificity and reliability. Pedal pulse palpation has adequate sensitivity (73%) and specificity (92%) (35), however has highly variable reliability (κ 0.20 to 0.92)(36, 37). Buerger's test has been shown to have perfect sensitivity (100%) however low specificity (54%) and reliability is unknown whereas capillary refill time has low sensitivity (25%) good specificity (84%) but unknown reliability (38).

1.7.1.1 Ankle Brachial Index

Current vascular screening guidelines recommend that people over the age of 65, or over the age of 50 with a history of smoking or diabetes be screened every 2 years for the presence of PAD using an ABI (7). The ABI is a simple, cost-effective test that is available to most practitioners as no specialised equipment is necessary. An ABI is calculated by taking the highest systolic pressure of either the dorsalis pedis or posterior tibial artery and dividing it by the highest of the left and right systolic brachial pressures (Figure 1.5) (7). In a normal limb, systolic pressure at the ankle should be slightly higher than the brachial pressure due to pulse wave reflection resulting in a normal ABI of above 1.0 (7). In the presence of arterial stenosis, the ABI should drop below 1.0, with <0.9 considered definitive of PAD (12).



Figure 1.5 An ankle pressure being measured

The reliability of the ABI has been demonstrated to be high when performed by doctors, nurses and vascular technologists (39). However the reliability of the ABI performed by podiatrists has not been investigated. The ABI has been demonstrated to be sensitive and specific for detecting PAD in the general population, however there is research to suggest that in specific populations there is a reduction in diagnostic accuracy(40). This loss of diagnostic accuracy has largely been attributed to medial arterial calcification (MAC) (41). MAC is a condition where calcification occurs in the tunica media in large and medium size

arteries (42). This results in a reduction in the elastic compliance of the artery, increase in pulse-pressure and artificially inflated ABI values (43). MAC is also associated with an increased risk of lower extremity amputation, myocardial infarction and stroke (42) and populations including people with diabetes, renal disease and in advanced age are more prone to MAC (42). Currently it is assumed if an ABI measurement is above 1.4 the vessels being tested are affected by MAC (5). In cases such as this, a toe pressure and calculation of a toe-brachial index is recommended to assess distal tissue perfusion (7). However recent research has also shown that co-existence of both MAC and PAD can result in an ABI value that may fall within the normal range and fail to indicate the presence of either condition or the need for further testing (8).

1.7.1.2 Toe Pressures

Toe pressures (Figure 1.6) are a measure of systolic blood flow in the great or second toe. The pressure is measured using an occlusive pneumatic cuff that is placed around the proximal hallux and inflated. Pressure is gradually released and the subsequent return of blood flow (systolic pressure) detected, most commonly using photoplethysmography (PPG) or laser Doppler. Normal toe pressures should be approximately 6-10mmhg less than a brachial pressure(44) and are used clinically to determine healing capacity. A toe pressure of less than 50mmhg has been associated with symptomatic PAD (45), and a pressure of less than 30mmhg has been associated with poor healing outcomes(46) (45). Toe pressures reliability has been shown to have good reliability (47, 48) and high sensitivity (85%) and specificity (88%) for detecting PAD (45).

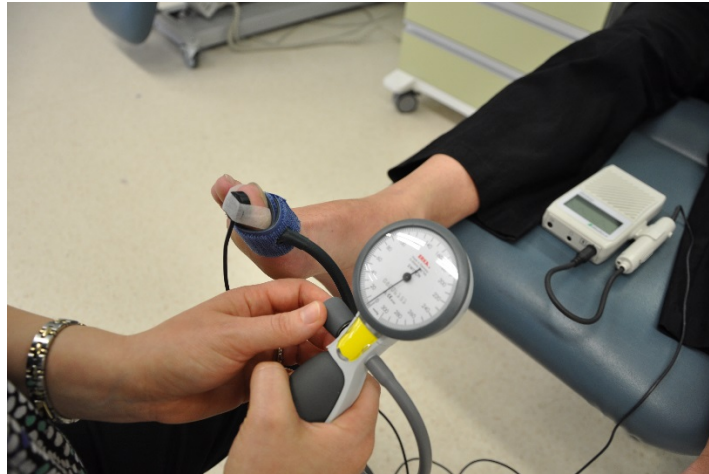


Figure 1.6: A toe pressure being measured

1.7.1.3 Toe Brachial Index

The toe-brachial index (TBI), calculated in a similar manner to the ABI, is the ratio between the systolic toe and brachial pressures and is determined by dividing the toe systolic pressure by the highest brachial systolic pressure. Current recommendations for interpreting the TBI are heterogeneous with normal values reported in the literature varying from >0.6 to >0.75 (49). Current guidelines (7) recommend a TBI be used in the presence of an elevated ABI (>1.4) secondary to MAC as digital arteries are less commonly affected by this pathology (7). In populations at risk of MAC, such as those with diabetes, the ABI has been demonstrated to have reduced diagnostic utility(8). However whilst there is some evidence that the TBI can be performed reliably in the general population and in people with diabetes (50, 51), there has been little investigation of the diagnostic accuracy of this test for PAD in any population.

1.7.1.4 Continuous Wave Doppler Ultrasound

Continuous wave Doppler ultrasound examination is commonly performed in the foot and ankle using hand-held Doppler often as an adjunct to the ABI (7) and, most frequently of the dorsalis pedis and posterior tibial arteries. Normal artery signals are classified as either bi- or triphasic (52, 53), with pathological waveforms monophasic with

classification based on clinical interpretation of audio data and visual interpretation of waveforms.

Qualitative analysis of visual waveforms includes assessing the shape and contour of the waveform (Figure 1.7)(54). This method has potentially significant diagnostic value, as waveforms are altered depending on location and severity of PAD (55). A delay in acceleration time or a serration in the systolic peak is indicative of an obstruction proximal to the Doppler site, whereas disease distal to the Doppler placement will see an elongation of the systolic down slope. Disease within a run-off vessel can be seen as low amplitude and low resistance and multi-level disease will be demonstrated by a rounded monophasic waveform with slow acceleration, prolonged deceleration and an absence of reverse flow(54).

Quantitative Doppler of visual waveform analysis can include measurement of systolic rise time, pulse transit time, velocity measurements and peak-to-peak pulsatility indexes. However, quantitative analysis has been demonstrated to be not as accurate as other methods, requires specialist software applications and is rarely used in clinical practice (20, 55).

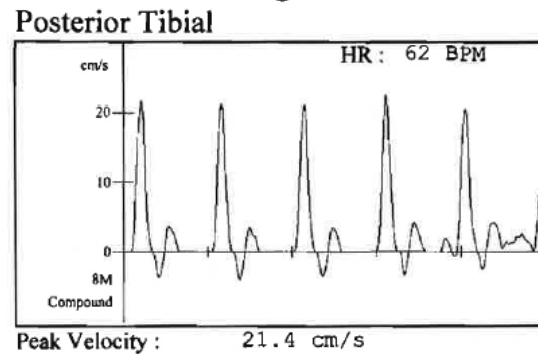


Figure 1.7: Triphasic Doppler waveform in posterior tibial artery

However despite widespread use of this form of testing for vascular screening and on-going monitoring in the Podiatry profession, there is little evidence available regarding the accuracy or reliability of what is fundamentally a subjective test (56)

1.7.2 Non-invasive vascular assessment in Podiatry practice

Podiatrists are responsible for the assessment, diagnosis and management of pathology in the lower extremity(57). This includes regular assessment of peripheral blood flow and identification and monitoring of PAD in populations considered at risk (58). However current methods for performing vascular assessment in Podiatry clinical practice are in Australia are largely unknown. Currently there is only one national evidence based guideline relating to vascular assessment in the lower limb for people with diabetes(4) and there is a lack of profession specific protocols for the general population at risk of PAD.

The scant research that does exist assessing the use of the ABI by Podiatrists in clinical practice suggests this testing method is not widely adopted, with approximately only half of all Podiatrists not performing an ABI as part of a routine vascular assessment (59). Lacks of available equipment, time constraints and limited financial incentive have been suggested as reasons for failure to perform an ABI. In addition clinical techniques for performing the test have been demonstrated to be inconsistent with current guidelines

and are a further limitation to current clinical practice (59). Whilst alternate methods of vascular assessment may be used in place of the ABI, no investigation of current practices has been undertaken. However the high rates of undiagnosed PAD suggest improved clinical screening is needed. Further research is required to determine current levels of knowledge of clinical indicators for, and application of, vascular assessment amongst practicing clinicians. The extent of use of other vascular screening techniques including the TBI and CWD also needs to be evaluated before effective strategies can be implemented to improve clinical practice.

1.8 Management of PAD

Due to patients with PAD having multiple atherosclerotic risk factors and extensive atherosclerotic disease, their initial management is aimed at managing their atherosclerotic risk factors(12) . Given the association of smoking and a marked increase in PAD, smoking cessation is strongly advised. Whilst smoking cessation may not lead to a decrease or reversal of symptoms associated with PAD, it has been shown to increase survival (12). Management of hyperlipidaemia through reduction on low-density lipoproteins (LDLs) has been demonstrated to reduce cardiovascular events in patients with PAD. Reduction of LDLs can be made through diet modification or pharmacological therapy (12). Given the three fold increased risk of PAD for patients with hypertension, aggressive treatment of blood pressure is currently recommended(12). Thiazides and ACE inhibitors are generally considered as first line treatment options to reduce blood pressure in PAD (12). In patients with diabetes, aggressive blood glucose control is recommended and has been shown to reduce the risk of cardiovascular events (60).

Exercise rehabilitation is generally prescribed in symptomatic PAD where patients undergo supervised exercise therapy(12). Exercise therapy in claudicants has been shown to improve walking efficiency, endothelial function and metabolic adaptations in skeletal muscle (61) . However, many patients have contraindications for exercise, be unwilling to

undertake exercise, or there may not be an appropriate program of supervised exercise available to them (12). Pharmacological management of symptomatic PAD may then be considered. First line pharmacological management of claudication generally includes cilostazol, a vaso-dilatory drug which relieves symptoms of PAD. Antiplatelet therapy is also commonly used in patients with symptomatic PAD to effectively reduce the risk of cardiovascular morbidity and mortality(12)

Surgical intervention for PAD is reserved for the most severe cases of PAD, and surgical candidates first need vascular imaging performed in order to isolate the lesions in the affected limb/s. This is generally in the form of CFDU and digital subtraction angiography. Revascularisation may consist of either endovascular procedure or open surgical procedure, dependant on the site, type and length of the atherosclerotic lesion/s (12).

1.9 Aims of thesis

The aims of this thesis was to evaluate non-invasive vascular assessment methods for detecting peripheral arterial disease in the lower limb. Investigations were undertaken to determine the diagnostic accuracy of non-invasive vascular assessment techniques for detecting PAD in a community-based population meeting current guidelines for PAD screening and in a diabetes cohort. Current vascular assessment techniques used by Podiatrists in Australia and New Zealand were established and reliability of CWD in clinical podiatry practice was determined. Based on these findings the diagnostic accuracy of a modified method of vascular assessment, designed to reduce time required for assessment to be performed, compared to testing performed in accordance with current guidelines, was investigated.

1.10 Objectives of Thesis

- To systematically evaluate the current evidence base as to the diagnostic accuracy of TBI for PAD
- To determine the diagnostic accuracy of the TBI and the ABI for PAD in a mixed population at risk of PAD
- To determine the diagnostic accuracy of the TBI, the ABI and continuous wave Doppler for PAD in people with diabetes.
- To establish current vascular assessment practice amongst Australian and New Zealand podiatrists
- To assess the inter and intra tester reliability of hand-held Doppler use when performed by Podiatrists
- To determine the diagnostic accuracy of a modified, more time efficient method of performing vascular screening for PAD compared to diagnostic accuracy of assessment conducted in accordance with current guidelines.

Chapter 2 A systematic review of the sensitivity and specificity of the toe-brachial index for detecting peripheral arterial disease

2.1 Preface

The TBI is currently recommended as an alternative test to the ABI for screening for PAD. However there have been few investigations of the diagnostic accuracy of this test for PAD and there has been no consolidated review of these data. . A systematic review of the literature is presented in this chapter. The results suggest that the TBI may be an accurate test in specific populations but more evidence is required, using gold standard imaging as a reference standard.

There was no ethics approval required for this study. This study has been accepted for publication to the peer-reviewed journal *Vascular Medicine*. The accepted manuscript is located in Appendix 1. In addition a meta-analysis was conducted for studies included in this review. Although the study populations were subsequently deemed too heterogeneous for inclusion of the meta-analysis in the final version of the accepted paper. It has been included in this thesis in Appendix 18.

This study was also presented as a poster presentation for the 2015 Society of Podiatrists and Chiropodists Annual Conference in Harrogate, United Kingdom.

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2.3 Abstract

2.3.1 Objectives

The toe-brachial index (TBI) is used as an adjunct to the ankle-brachial index (ABI) for non-invasive lower limb vascular screening. With increasing evidence suggesting limitations of the ABI for diagnosis of vascular complications, particularly in specific populations including diabetes cohorts, the TBI is being used more widely. The aim of this review was to determine the sensitivity and specificity of the TBI for detecting peripheral arterial disease (PAD) in populations at risk of this disease

2.3.2 Methods

A database search was conducted to identify current work relating to the sensitivity and specificity of toe brachial indices up to July 2015. Only studies using valid diagnostic imaging as a reference standard were included. The QUADAS-2 tool was used to critically appraise included articles.

2.3.3 Results

Seven studies met the inclusion criteria. Sensitivity of the TBI for PAD was reported in all seven studies; sensitivity ranged from 45% to 100% and specificity was reported by five studies only; ranging from 16% to 100%.

2.3.4 Conclusions

This review suggests that the TBI has variable diagnostic accuracy for the presence of PAD in specific populations at risk of developing the disease. There was notable lack of large scale diagnostic accuracy studies determining diagnostic accuracy of the TBI in detecting PAD in different at risk cohorts. However, standardised normal values need to be established for the TBI to conclusively determine the diagnostic accuracy of this test.

2.4 Introduction

Traditionally, the ankle-brachial index (ABI) has been used as a large vessel screening tool for clinical assessment of peripheral arterial disease (PAD) (62). The ABI has been shown to be a sensitive and specific measure of detecting PAD in the general population (63). However, there is increasing evidence to suggest that in specific populations there is a decrease in the diagnostic accuracy of the test (20, 41). Medial arterial calcification (MAC), a stiffening of the arterial wall most commonly in infragenicular arteries used for the calculation of the ABI (64), is prevalent in the diabetic population, particularly in men and in older age groups, and is thought to reduce the diagnostic accuracy of the ABI (41). Although MAC artificially inflates the ABI this cannot always be detected during routine clinical assessment as co-existent PAD may result in the ABI ratio presenting as normal or even low despite its presence (43).

Assessment of the small vessels within the foot and distal extremities also presents an issue for clinicians, as an ABI is not sensitive to occlusions and arterial disease below the ankle (8). Current international guidelines recommend the toe brachial index (TBI) as an alternate screening method for PAD in the presence of an elevated ABI (12, 65); however, the evidence base for the use of the TBI as a stand-alone diagnostic test remains low. The TBI is a ratio of the systolic toe pressure divided by the highest systolic brachial pressure. Systolic toe pressure can be performed by placing an appropriately sized occlusive pneumatic cuff (between 15 and 25mm) around the base of the proximal great or second toe, and a photoplethysmography (PPG) probe affixed to the distal pulp of the toe with adhesive tape (Figure 1.6). A continuous wave Doppler probe may also be used on the digital arteries in lieu of a PPG probe. Once a steady signal is obtained, the occlusive cuff is inflated by sphygmomanometer 20 mmHg above the last visual PPG waveform. The occlusive cuff is then slowly deflated with the pressure reading recorded when a consistent waveform returns (7, 66). Normal values for TBI are universally lower than the ABI, with

normal being considered between >0.6 - >0.75 (45, 49, 67, 68), with recent research suggesting that in normal populations the mean TBI is between 0.94 and 0.98 (69).

Accurate measurement of systolic toe pressure is dependent on a number of factors, including the control of ambient temperature. Similar to the ABI, strict control of patient factors needs to be undertaken to ensure test accuracy. Patients need to avoid smoking immediately prior to testing and lie completely flat with the legs and feet at the same level as the heart. In addition the TBI is affected by ambient temperature and room temperature needs to be maintained at 23 and 25 degrees Celsius (46). Unlike the ABI, the TBI is also affected by Raynaud's disease or scleroderma and the measurements lacks utility in these populations(67). When premeasurement protocols are adhered to the TBI can be performed reliably in clinical environments with both automated and manual devices(47). The measurement has also been shown to be an accurate indicator of PAD in populations prone to MAC including those with diabetes-related PAD, sensori-motor neuropathy, and patients undergoing haemodialysis for end stage renal failure (20, 70, 71). However there is currently no consensus on the diagnostic accuracy of this test for identifying PAD across populations at risk of the disease.

The aim of this paper is to systematically review the evidence evaluating diagnostic accuracy of the TBI in detecting PAD in at risk populations.

2.5 Materials and Methods

2.5.1 Search strategy

A database search was conducted by the primary researcher (PT) up to July 2015 using Ovid Medline (1946-2015), CINAHL Plus (1982 – 2015), Amed (Ovid), Web of Science, Scopus and Embase.

Search terms were derived (Table 2.1) and truncated versions using wildcard symbols were included to help broaden the search. No language restrictions were used. Reference lists of suitable articles were also hand searched for suitable work (Search strategy Figure 2.1)

Table 2.1: Search terms

| | |
|-----|---|
| S1 | Toe brachial ind* |
| S2 | Toe brachial ind* AND sensitivity |
| S3 | Toe brachial ind* AND specificity |
| S4 | Toe brachial ind* AND peripheral arterial disease |
| S5 | Toe brachial ind* AND ischemia |
| S6 | Toe brachial ind* AND lead |
| S7 | Toe brachial ind* AND lower extremity |
| S8 | S2 AND S3 AND S4 |
| S9 | Toe brachial ind* AND peripheral arterial* |
| S10 | S2 AND S3 AND S9 |
| S11 | Toe brachial* |
| S12 | Toe brachial* AND sensitivity AND specificity |
| S13 | S2 AND S3 AND S5 |
| S14 | S2 AND S3 AND S6 |
| S15 | S2 AND S3 AND S7 |

2.5.2 Inclusion and exclusion criteria

Original articles that diagnosed PAD using valid diagnostic imaging as a reference standard were included. Studies which used symptoms as a primary indicator of the severity of PAD, or, where PAD was diagnosed by ABI, TBI or Doppler waveform analysis alone were excluded. Studies which included participants with vasospastic disorders were not included as this is known to affect the accuracy of toe pressure measurements (67).

2.5.3 Study selection and data extraction

Literature searching was undertaken by a single reviewer (PT) who independently searched each database using the search terms and retrieved abstracts. Abstracts were then reviewed independently by two reviewers (PT and VC) and relevant articles were assessed according to the selection criteria. If any difference of opinion arose, the study in question was referred to a third party. Articles considered relevant were then obtained in full text. Reference lists of retrieved articles were searched for further potentially relevant studies. Data on sensitivity and

specificity of the toe-brachial index in detecting peripheral arterial disease along with reference standards, room temperature, pre-rest time and demographic data were extracted by two researchers (PT and VC) independently, with disagreements resolved by a third researcher (DS). In cases where journal articles contained insufficient information, attempts were made to contact authors to obtain missing details.

Methodological quality was assessed using the QUADAS-2 tool for systematic reviews of diagnostic accuracy (72).

2.6 Results

A total of 939 articles were retrieved for abstract review (Table 2.2). Of these, 922 were excluded for lack of relevance. Seventeen articles in total were deemed relevant and full text versions were acquired. One study was excluded (73) as it was determining inter and intra tester reliability alone, and not diagnostic accuracy. One study (67) was excluded as it compared ankle-toe pressures rather than the TBI. Five studies (74-78) were excluded as they did not diagnose PAD using diagnostic imaging for the reference standard. One study was excluded (79) as it reported correlation only and data examining sensitivity and specificity in this group were reported in another included study (20). One study was excluded as it examined patients with vasospastic disorders (75) and one other study was excluded as it diagnosed calcification and not PAD [25]. Seven studies met all inclusion criteria for this review (20, 70, 71, 80-84).

All seven included studies were appraised for risk of bias using the Quality assessment of diagnostic accuracy studies (QUADAS-2) tool (Table 2.2, Figure 2.2).

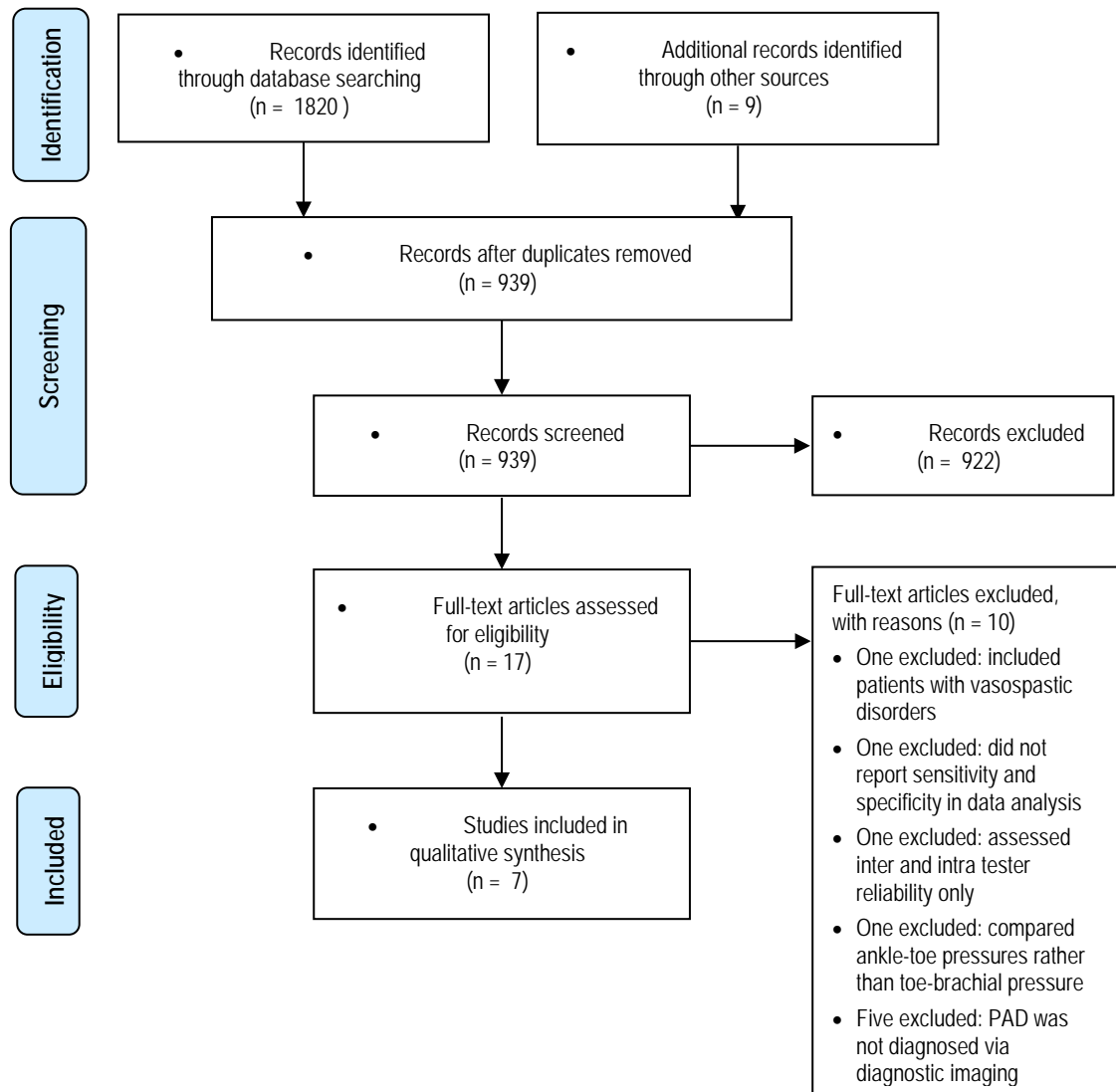


Figure 2.1 Search Strategy

2.6.1 Characteristics and overview of included studies

2.6.1.1 General

The studies included in this review examined sensitivity and specificity of TBI for detecting PAD in different cross sections of participants (Table 2.2). A total of 566 lower limbs were included in the seven studies. Of the 566 limbs, diagnostic imaging demonstrated 340 with PAD and 210 without PAD (16 limbs missing data(84)). Reported participant age varied significantly (Table 3) with most of the studies examining an older age group, with the exception of one study (71) which had a range of 35 – 89 years and one study which did not report age at all(80). Both men and women were included in most studies, with all reporting a higher number of male

participants (20, 80-84). One study did not specify gender of participants (71). Sample sizes varied amongst the seven studies ranging between 30 and 130 (Table 3). Most studies used paired data(20, 71, 80, 81), one was unclear (70, 83) and two studies used one limb per person(82, 84).

Table 2.2: Summary of studies for sensitivity and specificity of the TBI for detecting PAD

| Study | Year | Limbs | Mean age (SD ^a) | Population | Reference standard | PAD Diagnosis | TBI Method | Sensitivity % | Specificity % | With Disease (n) | Without Disease (n) | TBI normal limit | Room Temperature (°c) | Pre-measurement rest time (minutes) |
|---------------|------|-------------|-----------------------------|--|--------------------|---------------------------|------------|---------------|---------------|------------------|---------------------|------------------|-----------------------|-------------------------------------|
| Bunte (83) | 2015 | 31 (n=31) | 66 | Critical limb ischemia | Angiography | Stenotic >50% or occluded | Manual | 92 | 16.7 | 25 | 6 | ≥0.7 | - | 5-10 |
| Okamoto (71) | 2006 | 72 (n= 36) | Range 35-89 | Renal patients | MDCT ^c | Stenosis >75% | Automated | 45.2 | 100 (98.1) | 46 | 26 | ≥0.6 | 23 | - |
| Park (80) | 2012 | 30 (n=15) | - | Diabetes, claudicating +/- gangrene | Angiography | - | Automated | 100 (96.3) | 100 (97.8) | 13 | 17 | ≥0.6 | 22 | 15 |
| Suominen (84) | 2008 | 68 (n=68) | 69.5 (11.7) | Patients with elevated ABI | DSA ^d | Stenosis >50% | Automated | 99 | - | 68 | - | ≥0.6 | Controlled | 10 |
| Tehan (82) | 2015 | 119 (n=119) | 73.1 (7.2) | Patients at risk of PAD | CDU ^b | Stenosis >50% | Manual | 71 | 79 | 51 | 68 | ≥0.7 | 23 - 25 | 10 |
| Weinberg (81) | 2013 | 116 (n=92) | 71.2 (11.2) | Patients attending vascular laboratory | DSA ^d | TASC II | - | 92 | - | 100 | - | ≥0.7 | - | - |
| Williams (20) | 2005 | 130 (n=68) | Range 63 - 69 | Diabetes and control | CDU ^b | Stenosis >50% | Manual | 100 | 76 | 37 | 93 | ≥0.75 | 25 | 3-5 |

^aStandard Deviation, ^bColour duplex ultrasound, ^cMulti-detector computed tomography, ^ddigital subtraction angiography

TBI = toe-brachial index, ABI = ankle brachial index. Corrected values for sensitivity and specificity in parentheses. TASC II= TASC II classification scheme

2.6.1.2 TBI Method

Details of methodological procedures of included studies are provided in Table 3. All of the included studies used the photoplethysmography method to measure the toe pressure included in the TBI and included a mix of manual and automated measurements. Pre-measurement rest time varied between three and fifteen minutes. Most studies used only one toe pressure measurement in the calculation of the TBI (70, 71, 80, 82, 84) whereas one study(20) took a mean of two measurements, taken at three and five minute intervals. Two studies did not describe the TBI method in sufficient detail to determine how many measurements were taken (81, 83). Cut-offs for abnormal TBI values indicating PAD diagnosis also differed between the studies (<0.6, <0.7 and <0.75). Room temperature was controlled in most studies and only varied by a few degrees, two studies did not detail room temperature(81, 83) and one study stated it was controlled but did not specify the temperature(84).

2.6.1.3 Quality Assessment

A QUADAS-2 checklist was used to assess methodological quality and risk of bias of the included studies (Table 2.3, Figure 2.2). In all of the included studies it was unclear if the results of the index test were interpreted without knowledge of the reference standard. It was also unclear in all of the studies if the reference standard results were interpreted without knowledge of the index test. Details of the methodological quality assessed by the QUADAS-2 tool are provided in Table 2.3 and Figure 2.2.

A range of different diagnostic imaging methods were utilised by the included studies to diagnose PAD, all of which have varying levels of diagnostic accuracy. Four of the included studies used the gold standard angiography as a reference standard, two used colour duplex ultrasound and one used multi-detector row computed tomography. The diagnosis of PAD using these reference standards also differed significantly between studies. Several different anatomic criteria for diagnosis of PAD were used including >50% stenosis, >75% stenosis and

one paper utilising the TASC classification system for interpretation of lower limb angiography. The index test, the TBI was also interpreted differently between studies with definition of a normal value ranging from >0.6 to >0.75 .

The sample populations studied all included groups representing people either at risk of, or with current PAD (Table 3). However, the diagnosis of haemodynamically significant PAD, disease severity and presence of underlying comorbidities varied significantly between studies. Only one of the included studies recruited a non-diseased control group with a further four studies including non-diseased single limbs and/or participants from different at-risk or symptomatic cohorts. Two studies were stated to be performed retrospectively and included diseased limbs only. Underlying co-morbidities included diabetes, renal disease and mixed populations at risk of PAD that were symptomatic or non-symptomatic.

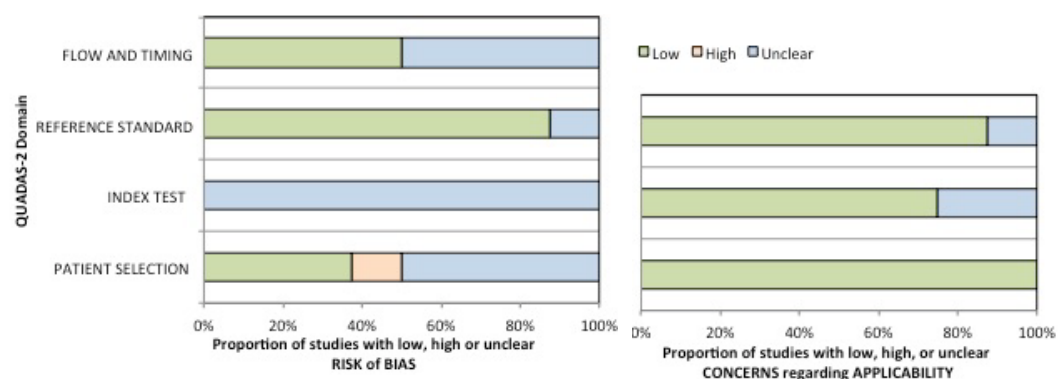





Figure 2.2: QUADAS-2 Risk of bias tool

Table 2.3: Risk of bias of included studies using QUADAS-2 tool

| Study | Risk of Bias | | | | Applicability Concerns | | | |
|---|-------------------|------------|--------------------|-----------------|------------------------|------------|--------------------|-----|
| | Patient Selection | Index Test | Reference Standard | Flow and Timing | Patient Selection | Index Test | Reference Standard | |
| Bunte | • ? | • ? | • ? | • ? | • ? | • ? | • ? | • ? |
| Okamoto | • ? | • ? | • ? | • ? | • ? | • ? | • ? | • ? |
| Park | • ? | • ? | • ? | • ? | • ? | • ? | • ? | • ? |
| Suominen | • ? | • ? | • ? | • ? | • ? | • ? | • ? | • ? |
| Tehan | • ? | • ? | • ? | • ? | • ? | • ? | • ? | • ? |
| Weinberg | • ? | • ? | • ? | • ? | • ? | • ? | • ? | • ? |
| Williams | • ? | • ? | • ? | • ? | • ? | • ? | • ? | • ? |
|  Low Risk  High Risk  Unclear Risk | | | | | | | | |

2.6.1.4 Sensitivity and specificity of the TBI

Sensitivity was reported in all seven studies and ranged from 45% to 100% (Table 2.2) with the highest reported sensitivity by Park et al (80) who demonstrated 100% sensitivity of the TBI for detecting PAD in a population of thirty claudicating limbs with and without gangrene. The lowest sensitivity was reported by Okamoto et al (71) who demonstrated the TBI had 45% sensitivity for detecting PAD in a sample of seventy-two participants undergoing haemodialysis. Specificity of the TBI for diagnosing PAD was reported by five studies and ranged from 16% to 100% (Table 2.2). The highest reported specificity (100%) was also by Park et al (80) and the lowest specificity (16%) was demonstrated by Bunte et al (83).

2.7 Discussion

This review assessed the sensitivity and specificity of the TBI in detecting PAD. Seven studies were included which examined sensitivity and five studies examined specificity of the TBI for detecting PAD in a range of different populations. The TBI had varying degrees of sensitivity ranging from 45% to 100% and specificity from 16% to 100% depending on the population studied. The heterogeneity of the included populations was notable. Overall the TBI had good

test performance in patients with diabetes, claudicants and those at risk of PAD and therefore may be a useful adjunct for vascular screening in these cohorts (65). Lower sensitivity was reported in a population with renal disease, and poor specificity in a cohort with critical limb ischemia. Overall the variable results of measures of diagnostic accuracy of the TBI for PAD in the existing literature make it difficult to determine the clinical utility of this test. The variable diagnostic accuracy reported in the included studies is likely to have been influenced by both the heterogeneity of included participants groups and the methodological differences between studies.

Methodological quality was varied across the seven studies with a significant amount of heterogeneity across multiple domains. The QUADAS-2 assessment demonstrated that a large amount of information was unclear across the studies, particularly in relation to risk of bias with patient selection and the index test. Only one of the seven included studies recruited non-diseased participants, with two studies only including a diseased populations. The lack of equitable non-diseased groups in the majority of studies creates significant spectrum bias (85). In addition it was unclear if there was appropriate operator blinding between the index and reference testing in all of the included studies which was also likely to lead to an increased risk of bias.

The interpretation of the TBI value for normal was also a likely factor in the varying levels of reported accuracy. Studies which used the lower value for normal of >0.6 were likely to have overestimated the presence of disease compared to those using a much higher cut-off of >0.75 . Unlike the ABI, the TBI does not have a well-established grading system or an agreed normal value which is correlated with gold standard diagnostic imaging. Currently there are discrepancies in the literature and any of the values used in the included studies i.e. 0.6, 0.7 or 0.75 can be considered as a cut-off for to differentiate normal and abnormal findings (20, 67, 68, 75). Recent research has shown that in normal populations mean TBI values are 0.94 to

0.98, suggesting that the current cut-offs are too low and that under diagnosis of PAD is likely (69). The differing cut-offs used in the included studies are certain to have influenced the sensitivity and specificity.

The range of reference standards used by the included studies and differing anatomic criteria for diagnosis of PAD may also account for the varied levels of reported diagnostic accuracy. One study used multi-detector row computed tomography(70, 71), four used angiography(80, 81, 83, 84) and two used colour duplex ultrasound(20, 82). Although angiography remains the gold standard in imaging for PAD the studies using this method used differing criteria to diagnose PAD making comparison between studies difficult. Whilst duplex ultrasound is the gold standard non-invasive imaging method for diagnosing PAD, and is used extensively clinically, it is operator-dependent. Both studies using duplex ultrasound reported high test-retest reliability; however, testing was conducted in a small sample and this form of imaging is known to have has reduced diagnostic accuracy particularly in infragenicular vessels (86) and those affected by extensive MAC (87).

Methodological differences in performing the TBI measurement between studies may also have had an effect on the reported sensitivity and specificity outcomes of studies included in this review. The TBI is highly influenced by environmental factors and has limited utility in some populations such as those with vasospastic disorders(67). External variables known to influence toe pressure measurement such as ambient temperature varied in the included studies. Limb temperature which is also known to influence toe pressure measurement was also not demonstrated by any of the included studies (88). The included studies also reported differences in rest times prior to taking toe pressures, and use of serial (an average of two or more) and single measurements. There is evidence to suggest that toe pressures do not stabilise for the first 10 minutes (89) possibly affecting the accuracy of studies using shorter pre-measurement rest time frames. Furthermore use of one versus an average of two TBI

measurements may also have affected measures of diagnostic accuracy. Although one measurement has been shown to have adequate diagnostic accuracy of the TBI for PAD(82), there has been no comparative investigation of the effect of single or serial TBI measurements.

Our systematic review has demonstrated a paucity of data relating to the diagnostic accuracy of the TBI for PAD. Current international PAD screening guidelines recommended the TBI be used in the presence of an elevated ABI value(7). It is possible the TBI can also provide additional information on small vessel PAD and disease below the ankle, which is not detected by large vessel screening methods such as the ABI. Furthermore co-existence of PAD and MAC have been demonstrated to reduce the ABI to a normal value, failing to detect either disease process (8) and may render the ABI less accurate in specific populations including those with renal disease and diabetes. However based on current literature the value of the TBI for diagnosing PAD across populations at risk of the disease is inconclusive.

2.7.1 Limitations

We performed an exhaustive search for relevant literature, however the volume of articles retrieved from database searches may have led to accidental omissions of relevant research. Six databases were utilised in the search, however researchers in the field were not contacted for any unpublished work. Authors were only contacted where information from included articles were missing and in only one case responded. Furthermore, strict exclusion criteria meant that multiple studies were not included as they did not use valid diagnostic imaging as a reference standard or did not calculate sensitivity and specificity. Overall there was a lack of high level evidence for determining diagnostic accuracy of the TBI for PAD. All of the included studies had small sample sizes with large variations in methodology and very specific populations. More extensive investigation is required using larger sample sizes and including more general populations at risk of PAD in order to determine the true value of the TBI as a potential diagnostic tool.

2.8 Conclusions

This review highlights the lack of high level evidence available investigating the diagnostic accuracy of the TBI for PAD. Based on current literature it is not possible to determine the extent of the effectiveness of this test for diagnosing PAD in a clinical setting. We have also demonstrated there is a need for standardised normal values to be established for the TBI before diagnostic accuracy for PAD can be conclusively determined.

2.9 Acknowledgements

This research received funding from the national research training scheme (Australia) and a University of Newcastle Faculty of Health and Medicine PhD exchange grant

2.10 Conflict of interest statement

None of the authors have any conflicts of interest to declare

Chapter 3 The sensitivity and specificity of the toe-brachial index in detecting peripheral arterial disease: initial findings

3.1 Preface

The results of the systematic review presented in Chapter two demonstrated there are scant data investigating the diagnostic accuracy of the TBI for PAD. A preliminary investigation of measures of diagnostic accuracy of the TBI is presented in this chapter. The results demonstrate that in an older, community based population at risk of PAD, the TBI is more sensitive but less specific than the ABI for detecting PAD and overall is a better diagnostic test.

The advertising, consent forms, authority to release healthcare information, information statement, and ethics approval relating to this study are available in Appendices 2, 3, 4, 5 and 6.

The study presented in Chapter 3 was conducted in accordance with ethical approval granted by: University of Newcastle Human Research Ethics Committee (reference number H-2010-1230).

This study has been published in the peer-reviewed journal *Journal of Ultrasound in Medicine* (Appendix 7).

Tehan, PE. Bray, A, Carruthers, A., Keech, R., Rounsley, R., Chuter, VH. The sensitivity and specificity of the toe-brachial index in detecting peripheral arterial disease: Initial findings. *Journal of Ultrasound in Medicine* 2015, 34: 1737-1743. doi:10.7863/ultra.15.14.09071

The initial findings of this study were presented as a poster presentation at the Australian Podiatry Conference in 2013 and is also a published abstract:

Craike, PE. Bray, A, Carruthers, A., Keech, R., Rounsley, R., Chuter, VH. The sensitivity and specificity of the toe-brachial index in detecting peripheral arterial disease. *Journal of Foot and Ankle Research* 2013, 6(Suppl1):P3 doi:10.1186/1757-1146-6-S1-P3

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3.3 Abstract

Objectives –The toe-brachial index (TBI) is an alternative to the ankle-brachial index (ABI) to screen for peripheral arterial disease (PAD) however, there is limited evidence comparing their diagnostic accuracy. This study compared the diagnostic accuracy of the ABI and TBI in a population at risk of PAD.

Method –Sensitivity and specificity of the ABI and TBI were determined using colour duplex ultrasound. Receiver operating characteristic (ROC) analysis was performed.

Results – 119 participants were recruited (M: 75 F: 44). Sensitivity for PAD was highest for the TBI (TBI: 70%, ABI: 45%) and specificity highest for the ABI (ABI: 92%, TBI: 78%). ROC analysis indicated the TBI (ROC area: 0.77 p=0.0001) had greater clinical efficacy for the diagnosis of PAD than the ABI (ROC area: 0.65, p=0.005).

Conclusion - In specific populations the TBI may have greater clinical efficacy than the ABI for the diagnosis of PAD

3.4 Introduction

Peripheral arterial disease (PAD) involves the progressive stenosis and, potentially, occlusion of arterial beds supplying the lower extremity through the development of atherosclerosis. The risk of PAD increases with age, affecting 21% of those over the age of 65, and in the presence of risk factors such as smoking, diabetes, dyslipidaemia and hypertension (16, 90). As many PAD sufferers are asymptomatic, the condition is highly under-recognised (91) and if untreated can ultimately lead to the development of wounds, gangrene and amputation (92). Presence of PAD is also an indicator of systemic arterial disease and is associated with an increased risk of a cardiovascular event (30) and associated mortality (32).

Traditionally, the ankle brachial index (ABI) has been used as a non-invasive method of assessing peripheral vascular status in patients at risk of PAD. An ABI is calculated by taking the higher of the systolic pressure of the dorsalis pedis or posterior tibial artery and dividing it by the highest systolic brachial pressure (7). A normal ABI is considered to be above 1.0 (7) with a ratio less than 0.90 is diagnostic of PAD (12).

The ABI is a highly sensitive and specific screening tool for PAD (12, 65). The relative simplicity of application and low cost make the ABI an easily accessible assessment tool for many clinicians. However, recent research suggests the diagnostic accuracy of the ABI is reduced in specific populations. Decreased sensitivity and specificity of the ABI for the presence of PAD has been demonstrated in the elderly and in the presence of renal disease or diabetes (20, 71). It is widely recognised that higher rates of medial arterial calcification (MAC) in these populations leads to stiffening of the arterial wall, preventing full compression of the lower extremity arteries, inflating the ABI value and reducing the clinical efficacy of the test (8, 20). An elevated ABI (>1.4), is generally accepted to be indicative of MAC (12). However, further complicating lower extremity vascular testing in these patients, presence of MAC is also associated with significant lower extremity atherosclerosis (93). The combination of these two pathologies may

result in a normal ABI result in the presence of significant PAD due to partial loss of compressibility of the artery, leading to undiagnosed PAD. Additionally, more distal anatomical distribution of atherosclerotic lesions occurring both in people with diabetes and advanced age (16) further affects the ABI, with a stenosis of arteries at the level of, or distal to, the ankle unable to be detected with ankle pressure measurements (8).

Alternative methods of non-invasive vascular assessment may be performed using small vessel testing methods such as the toe-brachial index (TBI). The TBI is a ratio of the systolic toe pressure divided by the highest systolic brachial pressure (7). Normal values for the TBI are lower than the ABI, with 0.7 and above considered normal (45, 67, 68). The TBI has been shown to be an accurate indicator of PAD in specific populations who are prone to medial calcification including those with diabetes-related PAD, sensorimotor neuropathy (20), and patients undergoing haemodialysis for end-stage renal failure (70, 71). The TBI is by no means a new assessment method however its use remains limited, particularly in the vascular laboratory.

Despite the potentially wide applicability of the TBI as a test for PAD, evidence evaluating its diagnostic accuracy is limited. There is also a lack of comparative data assessing the relative diagnostic accuracy of the TBI and the ABI for the presence of PAD using diagnostic imaging as the reference standard. The aim of this study is to examine the sensitivity and specificity of the TBI, and comparative diagnostic accuracy of the TBI versus the ABI in detecting PAD in a population of patients at risk of PAD.

3.5 Methods

This study was undertaken at a private vascular clinic in Lake Macquarie, New South Wales, Australia. Ethical approval was obtained from the University of Newcastle Human Research Ethics Committee. All participants provided written informed consent prior to participation.

Over a period of twenty-eight months (August 2011- December 2013) participants were recruited on a volunteer basis from a private vascular clinic and a podiatry service in Newcastle. Inclusion criteria were set in accordance with current guidelines for lower extremity vascular screening (12): participants aged over 65 years; or aged over 50 years with a history of diabetes or current smoking; or with exertional leg pain or non-healing wounds. Exclusion criteria were: contraindications to ankle, toe, and brachial pressure measurements including active hallux or leg ulceration preventing cuff placement; history of deep vein thrombosis, lymphoedema and previous bilateral mastectomy or vasospastic disorders.

All participants attended a single testing session at the vascular clinic with one of three ultrasonographers. During the testing session ABI and TBI measurements, colour duplex ultrasound (CFDU) and neurological testing were performed on the right leg. CFDU was chosen as it has been demonstrated to be a valid imaging technique in non-invasive vascular diagnostic testing (91, 94). The right limb only was used to comply with the assumption of independence of data in statistical testing (95). Medical history was obtained each participant. Participants were asked to avoid alcohol, smoking, exercise and caffeine one hour prior to the testing session to avoid influencing pressure measurement (96). Participants were placed in a supine position and rested for at least 10 minutes prior to pressure measurements being taken. A subset of 10 participants randomly selected returned within one week of the initial testing session. At the second testing session all tests (vascular and neurological) were repeated by a different clinician blinded to the results of the initial test, to establish inter-tester reliability.

CFDU was performed with either a Phillips CX-50 or GE Logiq-I. All ankle and brachial pressures and CW Doppler tracings of pedal arteries were taken using the Parks Vascular Mini Lab 1050c with 8.2 MHz CW Doppler, a Parks standard 10 cm inflatable cuff and ERKA switch blood pressure gauge. Toe pressures were obtained with a photoplethysmography (PPG) probe,

Hokinson toe pressure cuff (2.5cm, 1.9cm or 1.6cm) and ERKA switch blood pressure gauge. Size of cuff used was in accordance with current guidelines for cuff size (7)

Room temperature was monitored with a thermometer and was maintained between 23°C and 25°C (88). Bilateral brachial systolic pressures were obtained in all participants using a Parkes CW Doppler and hand-held sphygmomanometer. Ankle systolic pressures of the right leg only were taken by placing the brachial pressure cuff around the lower leg, proximal to the medial and lateral malleoli. Both dorsalis pedis and posterior tibial artery pressures were recorded, with the higher of the two being used in calculation of the ABI. Toe systolic pressures were obtained by placing a PPG probe directly on the distal pulp of the right great toe affixed with adhesive tape. Once a clear signal was obtained, a toe cuff was placed immediately proximal to the PPG probe. In the event of the great toe being too large for the toe cuff, the second toe was used. The cuff was then inflated to 20 mmHg above the last visual PPG signal. The cuff was then slowly deflated - the pressure reading was recorded when a consistent waveform returned. The TBI was calculated by dividing the toe pressure by the highest brachial pressure.

CFDU was performed following pressure measurements, from the abdominal aorta to the distal ankle on the right side as the reference standard. For calculations relating to diagnostic accuracy, presence of PAD was defined as one or more arteries with >50% stenosis (86, 97). Distal disease was defined as disease distal to and including the proximal popliteal artery and proximal disease was disease from the common iliac artery to the distal superficial femoral artery. Sensitivity, specificity, diagnostic accuracy and positive predictive value of the ABI and TBI for the presence of PAD were calculated using the standard cut-off score for an abnormal ABI of ≤ 0.90 or greater than 1.4, consistent with current screening guidelines(7) and the suggested cut-off score for the TBI of <0.70 (5, 65). Ankle pressures exceeding 200 mmHg were considered incompressible (7). Receiver Operating Characteristic (ROC) analysis was performed for ABI and TBI and was calculated using SPSS version 19 statistical software. Standard

deviations (SD) were derived for all means, sensitivities, specificities and positive and negative predictive values. Calculations of diagnostic accuracy were performed using Microsoft Excel.

Inter-tester reliability of CFDU scanning was calculated using the presence or absence of PAD as a dichotomous variable and an unweighted Cohen's Kappa (K) statistic. Intra-class correlation coefficients (ICC) with 95% confidence intervals (CI) were calculated to determine level of agreement between test and retest for the ABI and the TBI. All ICC values for inter-tester reliability were interpreted according to cut-offs suggested by Fleiss (98). Interpretation of the Cohen's K statistic was performed using the method proposed by Landis and Koch (99). All reliability analyses were conducted using SPSS version 19.

3.6 Results

A total of 119 participants were recruited. One participant was excluded as the CFDU scan was performed on a different day to the remainder of the vascular examination. Participant characteristics are included in **Table 3.1**.

Table 3.1: Participant Characteristics

| | |
|-------------------------------------|----------------------------|
| Total Participants (N) | 119 |
| Males n (%) | 75 (63.02) |
| Females n (%) | 44 (36.97) |
| Age Range (Years) | 53 – 92 |
| Diabetes n (%) | 73 (61.34) |
| Mean Age (years) | 73.1 (SD ^A 7.2) |
| Incompressible ankle pressure n (%) | 16 (13.44) |
| Distal PAD n (%) | 37 (31.09) |
| Proximal PAD n (%) | 7 (5.88) |
| Distal & Proximal PAD n (%) | 7 (5.88) |
| PAD n (%) | 51 (42.85) |
| Proximal Occlusions n (%) | 1 (0.84) |
| Distal Occlusions n (%) | 40 (33.61) |

^A=standard deviation, PAD= Peripheral arterial disease

Mean ABI was 1.13 (SD 0.23). The mean falls within the normal range for an ABI measurement. The ABI results ranged from 0.34 to 2.0 that indicated participant peripheral arterial status included both those with significant PAD and significant MAC. The ABI was more likely to fail to

diagnose the presence of PAD. Diagnostic accuracy of the ABI was 72% (Table 3.2). ROC analysis showed that sensitivity for an ABI set at <0.9 or >1.4 for detecting PAD was only 65.2% (95%CI 0.54-0.77) (Figure 3.1). This indicates in this population the ABI was a poor test {Akobeng, 2007 #36}. The sensitivity and negative predictive value of the ABI of 45% and 69% reflects an increased risk of failure to diagnose existing disease (Table 3.2). However the specificity (93%) and positive predictive value (82%) were high, indicating that the ABI is relatively unlikely to falsely diagnose people without PAD.

Table 3.2: Table of results

| | <i>Analysis</i> | |
|------------------------------------|-----------------------------|---------------------------|
| | <i>Ankle Brachial Index</i> | <i>Toe Brachial Index</i> |
| Mean (SD) | • 1.13 (0.23) | • 0.71 (0.21) |
| Sensitivity (95% CI) | • 45 (32-59) | • 71 (57-81) |
| Specificity (95% CI) | • 93 (84-97) | • 79 (67-87) |
| Positive predictive value (95% CI) | • 82% (63-93) | • 72% (57-83) |
| Negative predictive value (95% CI) | • 69% (58-78) | • 77% (65-86) |
| ROC area (p value) | • 0.65 (p=0.005) | • 0.77 (p=0.0001) |

The mean TBI was 0.71 (SD 0.21), which is within a normal range for TBI measurement. ROC analysis was 77.7% (95%CI 0.69-0.87) indicating the TBI was a fair test in this population (99). The sensitivity of the TBI for detecting PAD was 71% indicating that the TBI was quite likely to accurately detect PAD in this population (Table 3.2). The specificity was 79%, which while lower than the ABI result, suggests that the TBI is relatively unlikely to falsely detect PAD.

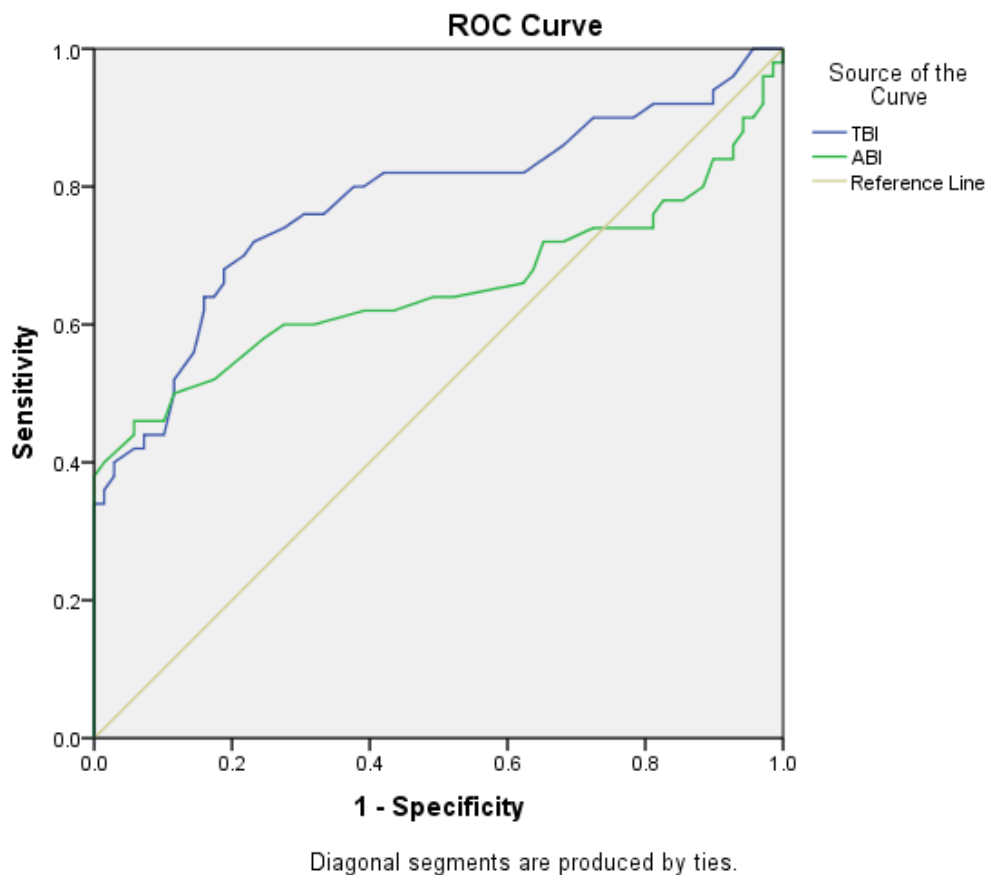


Figure 3.1: ROC analysis ABI vs TBI

Inter-tester reliability of the CFDU scans between the three ultra-sonographers was high (K 0.78, $p < 0.01$)(99). ICCs demonstrated good test-retest reliability of the toe pressures (ICC: 0.80, 95% CI: 0.39-0.95) and moderate reliability of brachial pressures (ICC: 0.66, 95% CI: 0.09-0.90) and ankle pressures (ICC 0.62, 95% CI: 0.03-0.89)(100).

3.7 Discussion

The results of this study indicate that overall the TBI has much higher sensitivity (71%) for the presence of PAD than the ABI (45%). However, the ABI demonstrated slightly higher specificity (93%) than the TBI (79%). The negative predictive value of the ABI (69%) together with poor ROC analysis (65.2%) has significant clinical implications, leaving approximately one third of participants falsely undiagnosed.

Previous research studies have reported a range of results regarding sensitivity of the ABI, depending on the cohort of subjects studied. In healthy patients, the ABI has been demonstrated to be highly sensitive (95%) (101-104) however in patients with diabetes or renal disease sensitivity of the ABI has been shown to be considerably lower (29.9-53%)(20, 71). The population in this present study met current criteria for lower extremity vascular screening and consisted of an older age group with a large number of people with diabetes. The findings of our study suggest that there may be a high prevalence of concurrent MAC and PAD within the general population requiring peripheral vascular screening. This is expected as this population is older, and at higher risk of comorbidities such as diabetes which are both associated with the development of MAC. Although MAC is known to affect the accuracy of the ABI in people with diabetes, renal disease and in older age, the prevalence of clinical and subclinical MAC within the general population remains controversial.

MAC has been estimated to affect approximately 13.3% of males and 6.9% of females in a population at risk of PAD (17). However cut off points for the diagnosis of MAC by the ABI have been questioned. Further complicating matters, the presence of a sub-clinical MAC has been proposed, which goes undetected by the ABI (92). It is therefore difficult to determine the extent to which the accuracy of the ABI may be affected and the efficacy of using the measurement as a screening tool. Current recommendations suggest a toe pressure be used only in the presence of an ABI elevated to beyond 1.40, however this does not address the presence of PAD coexisting with MAC which may reduce ABI to within a normal range (8, 43, 105, 106). This study supports previous findings indicating that the ABI had decreasing levels of sensitivity in a population at risk of PAD and concurrent MAC. Conversely, the specificity of the ABI (93%) in this study was higher than the TBI (79%). Previous studies in different populations have demonstrated the ABI had differing specificity rates (88 – 100%)(20, 71), however this study was a mixed population with a larger sample size, and participants were rested for 10

minutes which has been demonstrated as the ideal rest time for ankle pressures(107). This may have resulted in higher specificity rates.

Previous research in small cohorts of people with diabetes has demonstrated that the TBI had a superior sensitivity for the presence of PAD compared to the ABI (20). In this study, the TBI also had a superior sensitivity and ROC analysis when compared to the ABI. Whilst the TBI's specificity was lower than the ABI, the TBI still fared better overall demonstrating a more significant result with ROC analysis. This suggests that the TBI has a wider applicability to a broader population at risk of PAD than previously believed.

In this study 61% of the participants had diabetes and the average age was older than previously reported. As both advanced age and diabetes are associated with more distally distributed atherosclerotic lesions(16) these participants demonstrated higher rates of distally located stenoses. Our findings of increased sensitivity of the TBI for PAD in our sample is congruent with previous suggestions that the TBI has high sensitivity for more distally distributed disease and should therefore be a test of choice in populations at risk of such disease patterns. However it is important to note that in this study that a PPG probe was used to measure TBI. There are other methods of obtaining toe pressures including strain gauge plethysmography, oscillometric plethysmography and laser Doppler, therefore our study applies only to the PPG method.

In addition to being highly sensitive, our results also suggest that the TBI had higher specificity (79%) than previously reported in small groups of people with diabetes (61-65%) (20). However this may be due to the effect of diabetes on microcirculation and impairment of vasodilatory capacity which would remain undetected by large vessel screening methods such as the ABI and CFDU (88). The presence of microvascular disease dropping the TBI without co-existent PAD would reduce specificity of the test for PAD. Conversely, in studies examining people with

chronic renal failure, the specificity of both the TBI and the ABI has been shown to be up to 100% potentially due to the high rates of MAC in this population without the presence of peripheral microvascular disease (71).

3.7.1 Potential Limitations

To the authors' knowledge this is the first study to assess the sensitivity and specificity of the TBI across a mixed population at risk of PAD. However, the findings of this study need to be considered carefully due to some potential limitations. CFDU, while a valid form of non-invasive vascular assessment, is heavily dependent on operator skill, and while an inter-tester reliability study was performed, and shown to be adequate, the results are never the less subjective and dependant on clinician skill and experience. The inter-tester reliability testing of CFDU was limited to ten due to financial restraints and may not be statistically robust, however, has similar participant numbers to another study of diagnostic accuracy using CFDU as a reference standard (10). Our convenience sample consisted of a large proportion of people with diabetes, and an older mean age, however this reflects the sample population who were attending a podiatry and vascular clinic at risk of PAD. People over the age of 75 have a higher prevalence of PAD (91). People with diabetes are at increased risk of PAD, with disease occurring earlier, and more aggressively with a more distal distribution frequently reported (108). Results of this study therefore reflect a population at significant risk of PAD with more distally located stenoses.

3.8 Conclusion

This study demonstrated that the TBI had greater sensitivity than the ABI in participants at risk of PAD. Specificity of TBI was lower than the ABI, but higher than previously reported. These results suggest that the TBI may be more clinically effective forms of vascular assessment in this population. Further research is required in larger cohorts to further elucidate the sensitivity and specificity of the TBI in broad populations at risk of PAD.

Chapter 4 Non-invasive vascular assessment in the foot with diabetes: sensitivity and specificity of the ankle brachial index, toe brachial index and continuous wave Doppler in detecting peripheral arterial disease

4.1 Preface

Non-invasive vascular assessment in the lower limb in diabetes cohorts is particularly challenging due to the nature of vascular pathology affecting both large and small blood vessels. Clinicians regularly use ABI, TBI and CWD to perform vascular assessment in diabetes cohorts, however little evidence exists evaluating the diagnostic accuracy of these tests using diagnostic imaging as a reference standard. An investigation of the sensitivity and specificity of the ABI, TBI and qualitative waveform analysis is presented in this chapter. The results highlight both the difficulties completing lower limb vascular assessment in this population and the need for a multi-faceted approach to vascular assessment in the presence of diabetes.

The advertising, consent forms, information statements, and ethics approval relating to this study are available in Appendices 2, 3, 4, 5 and 6. The study presented in Chapter 4 was conducted in accordance with ethical approval granted by: University of Newcastle Human Research Ethics Committee (reference number H-2010-1230).

This chapter has been published in the peer-reviewed journal *Journal of Diabetes and its complications*. (Appendix 8).

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This chapter was also accepted as an oral presentation at the Society of Podiatrists and Chiropodists Conference in Harrogate, United Kingdom, November 2015. The conference abstract will be published in the Journal of Foot and Ankle Research in 2016.

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4.3 Abstract

4.3.1 Background & Aims

Non-invasive lower limb vascular assessment in people at risk of peripheral arterial disease (PAD) including those with diabetes is crucial. There is evidence that standard assessment techniques such as the ankle-brachial index (ABI) may be less effective in people with diabetes. However there is limited evidence for other frequently used tests including continuous wave Doppler (CWD), and the toe-brachial index (TBI). The aim of

this study was to determine the sensitivity and specificity of CWD, ABI and TBI in a population with, and without diabetes.

4.3.2 Methods

Participants with and without diabetes who met current guidelines for vascular screening were recruited and CWD waveforms, an ABI and a TBI were obtained from the right lower limb. Diagnostic accuracy was determined using colour duplex ultrasound (CFDU).

4.3.3 Results

One hundred and seventeen participants were recruited, seventy-two with diabetes and forty-five without diabetes. CWD had the highest sensitivity in people with diabetes (74%) and without (84%). CWD also had the highest specificity in people with diabetes (74%) and without (84%) compared to both TBI and ABI. In participants with diabetes, the ABI was a poor test ROC: 0.58(p= 0.27).

4.3.4 Conclusions

CWD waveform is more likely to detect significant PAD compared to ABI and TBI in people with and without diabetes.

4.4 Introduction

Non-invasive lower limb vascular assessment is essential for detecting peripheral arterial disease (PAD). Early detection and on-going monitoring of PAD through routine screening facilitates effective management of the condition and, can ultimately prevent foot complications such as wounds, gangrene and amputation(109). As PAD commonly occurs with systemic atherosclerosis (60), timely diagnosis is also necessary to ensure cardiovascular risk factors are managed to avoid more serious complications such as heart attack and stroke.

People with diabetes are at a four-fold increased risk of developing PAD. In this cohort the condition also progresses more quickly, is more severe than in the general population, tends to affect distal rather than proximal arteries and is more likely to result in ischaemic ulceration and amputation (12, 110, 111). Due to the heightened risk of foot complications associated with diabetes-related PAD, accurate non-invasive vascular assessments of the lower limb are essential in this population.

Both the ankle-brachial index (the ratio of ankle arterial pressure to that in the brachial artery) and toe-brachial index (the ratio of toe arterial pressure to that in the brachial artery) are non-invasive vascular assessment techniques used to quantitatively evaluate arterial status of the lower limb (7, 65). Although the ankle-brachial index (ABI) is used more widely, it has been demonstrated to have significant limitations in the presence of diabetes-related PAD including inability to detect distally located PAD and poor accuracy in the presence of medial arterial calcification, a condition associated with diabetes resulting in incompressible lower leg arteries (41).

As the toe-brachial index (TBI) measurement is taken more distally in the lower limb there is a greater likelihood of detecting arterial pressure changes caused by stenosis located below the knee as occur in the presence of diabetes(59). The digital arteries are also less likely to be affected by MAC (62, 68, 112), and these factors potentially make the TBI a more sensitive test for PAD than the ABI across diabetes cohorts. However, there are varying levels of diagnostic accuracy of the TBI in the limited current literature. Although there is some evidence that the TBI has superior sensitivity in the presence of diabetic neuropathy, in groups with diabetes alone, the TBI has shown lower sensitivity and specificity compared to ABI. In control populations, the TBI has demonstrated lower levels of specificity compared to ABI, but higher sensitivity (20). However as these findings varied significantly between small groups (n=7 to n=41) and the study eligibility criteria were tightly controlled- most significantly excluding people with a smoking history or

significant cardiovascular disease which are known to be associated with PAD, there is a need for more investigation in larger samples which reflect patients that clinicians encounter in clinical practice.

Continuous wave Doppler ultrasound (CWD) is frequently used alongside pressure measurement in non-invasive lower limb vascular assessment to assist in diagnosis of PAD, monitor disease progression and estimate severity (110). CWD is a low cost screening tool that is accessible and quick to use. However, diagnostic accuracy of CWD for detecting PAD is not well known in people with diabetes, with a single small study demonstrating that CWD has high sensitivity and specificity for diabetes-related PAD than the ABI or TBI(20). As interpretation of the CWD waveform relies upon the skill of the operator, and is considered more subjective than pressure measurements, further larger scale investigation of the utility of the assessment in a diabetes-cohort is required.

The aim of this study was to determine individual sensitivity and specificity of the ABI, TBI and CWD for detecting significant PAD in people with and without diabetes to further inform clinical use of non-invasive lower limb vascular assessments.

4.5 Methods

This was a prospective, single centre, cross sectional case-control study to determine the diagnostic accuracy of three non-invasive lower limb vascular assessment techniques in people with and without diabetes. This study was undertaken at Vascular Health Care, a private vascular clinic in Lake Macquarie, New South Wales, Australia. Ethical approval was obtained from the University of Newcastle Human Research Ethics Committee. All participants provided written informed consent prior to participation.

Over a period of twenty-eight months (August 2011- December 2013) a volunteer convenience sample was recruited via flyer advertising from a private vascular clinic and a community health service in Newcastle. The following inclusion criteria were set in

accordance with current guidelines for lower extremity vascular screening (7, 65): participants aged over 65 years; or aged over 50 years with a history of diabetes; or aged over 50 years currently smoking; or with exertional leg pain or non-healing wounds. Exclusion criteria were: known allergy to coupling gel, presence of a wound preventing Doppler probe or ankle cuff placement or previous bilateral mastectomy preventing bilateral brachial blood pressure examination.

All participants attended a single testing session at the vascular clinic with one of three ultrasonographers (RK, RR, and AC). During the testing session CWD waveforms, ankle pressures and the hallux toe pressure were taken from the right side. Brachial pressures were performed bilaterally. Colour duplex ultrasound (CFDU) was performed on the right side from the distal aorta to the foot and used as the reference standard. CFDU was chosen as it has been demonstrated to be a valid imaging technique in non-invasive vascular diagnostic testing (91, 94). The right limb only was used to reduce the incidence of type 1 error (95). Following the initial testing session medical history was obtained from the general practitioners of individual participants. A subset of 10 participants randomly selected returned within one week of the initial testing session. At the second testing session, all vascular tests were repeated by a different clinician blinded to the results of the initial test to establish inter-tester reliability.

Sonographers were trained in performing a basic neurological assessment by an experienced Podiatrist. The neurological assessment was performed by testing for protective sensation with the 10 gram Semmes-Weinstein monofilament at 10 points on the plantar surface of both feet. The 128Hz tuning fork was applied at the apex of the hallux bilaterally to assess vibration perception (113). Participants were classified as insensate if they failed either examination – more than four sites were undetected for the test of protective sensation or there was absent vibration perception.

CFDU was performed with either a Phillips CX-50 or GE Logiq-I. Pressures and CW Doppler tracings of pedal arteries were taken using the Parks Vascular Mini Lab 1050c, 8.2 MHz continuous wave Doppler, Parks standard 10 cm inflatable cuff, and ERKA switch blood pressure gauge. Size of cuff used was in accordance with current guidelines for cuff size (7). Room temperature was monitored with a thermometer and was maintained between 23°C and 25°C (88). Participants were asked to avoid alcohol, smoking, exercise and caffeine one hour prior to the testing session to avoid influencing pressure measurement (96). Participants were placed in a supine position and rested for at least 10 minutes prior to pressure measurements being taken. Bilateral brachial systolic pressures were obtained in all participants using a Parkes continuous wave Doppler and hand-held sphygmomanometer. Ankle systolic pressures of the right leg only were taken by placing the brachial pressure cuff around the lower leg, proximal to the medial and lateral malleoli. Both dorsalis pedis and posterior tibial artery pressures were recorded, with the higher of the two being used in calculation of the ABI. A single toe systolic pressure was obtained by placing a PPG probe directly on the distal pulp of the right great toe affixed with adhesive tape. Once a clear signal was obtained, a toe cuff was placed immediately proximal to the PPG probe. In the event of the great toe being too large for the toe cuff, the second toe was used. The cuff was then inflated to 20 mmHg above the last visual PPG signal. The cuff was then slowly deflated - the pressure reading was recorded when a consistent waveform returned. The TBI was calculated by dividing the toe pressure by the highest brachial pressure. CFDU was performed following pressure measurements, from the abdominal aorta to the distal ankle on the right side as the reference standard.

For calculations relating to diagnostic accuracy, PAD was defined as one or more arteries with $\geq 50\%$ stenosis indicating the presence of significant PAD (61, 86, 97). Sensitivity, specificity, positive and negative predictive values and ratios of the ABI for the presence of PAD were calculated using the standard cut-off score for an abnormal ABI of ≤ 0.90 or

greater than 1.4, consistent with current screening guidelines (7, 65). TBI normal values were considered ≥ 0.70 . CWD waveforms were analysed by a single researcher who assessed each waveform, blinded to the results of CFDU and pressure measurement. Loss of multi-phasic pattern (i.e. bi-phasic or tri-phasic) demonstrated by low resistance, slow systolic acceleration and no diastolic flow reversal were considered positive for PAD(54). Standard deviations ([SD]) were derived for all means. 95% confidence intervals were calculated for sensitivities, specificities and positive and negative predictive values and ratios. Calculations of diagnostic accuracy were performed using Microsoft Excel. Receiver Operating Characteristic (ROC) analysis was performed for ABI and TBI and was calculated using SPSS version 22 statistical software.

Inter-tester reliability of CFDU scanning was calculated using the presence or absence of PAD as a dichotomous variable and an unweighted Cohen's Kappa (K) statistic. Inter-tester reliability of the neurological examination was also calculated using the presence or absence of sensorimotor neuropathy as a dichotomous variable and an unweighted Cohen's Kappa (K) statistic. Intra-class correlation coefficients (ICC) with 95% confidence intervals (CI) were calculated to determine level of agreement between test and retest for the ABI. All ICC values for inter-tester reliability were interpreted according to cut-offs suggested by Fleiss (98). Interpretation of the Cohen's K statistic was performed using the method proposed by Landis and Koch (99) and interpretation of positive and negative predictive values was using the guide proposed by Geyman et al (114). To compare the groups with and without diabetes, independent samples t-tests will be performed for age, ABI and TBI. Fisher's exact test compared history of smoking and severity of PAD, and Pearson's chi-square compared gender, known history of cardiovascular disease and neurological status. P values were calculated for all comparative data. All reliability and comparative analyses were conducted using SPSS version 22 statistical software.

4.6 Results

A total of 117 participants were recruited. Participants were categorised into the diabetes (n=72) or no diabetes group (n=45) post-hoc. The no diabetes group served as the control group. Comparison of the two groups, with and without diabetes showed that overall there were no significant differences in gender (p=0.56), neurological status (p=1.00), age (p=0.20), severity of PAD (p=0.75), known cardiovascular disease (p=0.90) and smoking history (p=0.37) (Table 4.1). Inter-tester reliability of the CFDU scans between the three ultra-sonographers was high (K 0.78, p<0.01) (99). ICCs demonstrated good test-retest reliability of the toe pressures (ICC: 0.80, 95% CI: 0.39-0.95), moderate reliability of brachial pressures (ICC: 0.66, 95% CI: 0.09-0.90), and ankle pressures (ICC 0.62, 95% CI: 0.03-0.89).

Table 4.1 Participant Characteristics

| | DM Group | No DM group | Comparison |
|-------------------------------------|-------------|-------------|-----------------------------|
| Total Participants N | 73 | 46 | |
| Males n (%) | 48 (65) | 27 (58) | 0.338 ^B (p=0.56) |
| Females n (%) | 25 (34) | 19 (41) | |
| Age Range (Years) | 53 -86 | 65 - 91 | 1.28 ^D (p=0.20) |
| Mean Age (years) | 72.47 | 74.21 | |
| Neuropathy n (%) | 9 (12) | 6 (13) | 0.000 ^B (p=1.00) |
| History of smoking (%) | 43 (58) | 21 (46) | 2.112 ^C (p=0.37) |
| Currently smoking (%) | 2 (02) | 3 (6) | |
| Known CVD (%) | 23 (31) | 15 (32) | 0.01 ^B (p=0.90) |
| Mean ABI (^A) | 1.16 (0.24) | 1.08 (0.22) | 1.67 ^B (p=0.09) |
| Mean TBI (^A) | .70 (0.23) | 0.67 (0.24) | 0.67 ^B (p=0.51) |
| Incompressible ankle pressure n (%) | 8 (10) | 2 (4) | |
| Distal PAD n (%) | 27 (36) | 17 (36) | |
| Proximal PAD n (%) | 10 (13) | 4 (8) | |
| PAD n (%) | 36 (49) | 19 (41) | |
| >50% stenosis n (%) | 4 (5) | 1 (2) | 1.382 ^C (p=0.75) |
| >75% stenosis n (%) | 4 (5) | 1 (2) | |
| Occlusion n (%) | 24 (33) | 17 (37) | |

^A=standard deviation, PAD= Peripheral arterial disease, DM= Diabetes Mellitus CVD= Cardiovascular disease ^BPearson's chi-square ^CFishers exact test ^DIndependent samples t test

Means for ABI and TBI were comparable in both groups. Mean ABI was 1.16 in the diabetes group, and 1.08 in the group without diabetes, both within normal range and not significantly different between groups (p=0.97). The mean was TBI 0.70 in the diabetes

group which was also within normal range however was slightly below normal for the group without diabetes but not significantly different between groups (0.67, $p=0.50$).

Sensitivity and specificity results of the three methods of assessment (CWD, ABI and TBI) for the presence of significant PAD in people with and without diabetes are shown in table 2, along with positive and negative predictive values. Overall CWD had the higher sensitivity, specificity, positive and negative predictive values for detecting significant PAD in both groups. The TBI was more sensitive than the ABI in both groups but had notably better sensitivity in the group of people without diabetes (83.33%) compared to the group with diabetes (63.63%). The sensitivity of the ABI was low in both groups but specificity was high and similar for both groups (approximately 92%). Likelihood ratios revealed important (114) positive likelihood ratios for the ABI and CWD in people with (ABI 6.17, CWD 10.39) and without diabetes (ABI 6.39, CWD 22.74) (Table 4.2). Negative likelihood ratios were important for CWD in people without diabetes (0.16). The TBI had somewhat important positive likelihood ratios in people with (3.21) and without diabetes (3.55).

Table 4.2 Validation Table All Groups

| | Participants with Diabetes | | | Participants without Diabetes | | |
|------------------------------------|----------------------------|-------------------------|------------------------|-------------------------------|--------------------------|------------------------|
| | Ankle Brachial Index | Continuous Wave Doppler | Toe-Brachial index | Ankle Brachial Index | Continuous Wave Doppler | Toe-Brachial index |
| Sensitivity (95% CI) | 45.16 (27.33 to 63.96) | 74.19 (55.38 to 88.11) | 63.64 (45.13 to 79.58) | 47.37 (24.49 to 71.10) | 84.21 (60.40 to 96.43) | 83.33 (58.56 to 96.23) |
| Specificity (95% CI) | 92.68 (80.05 to 98.38) | 92.86 (80.49 to 98.42) | 82.05 (66.46 to 92.43) | 92.59 (75.67 to 98.88) | 96.3 (80.97 to 99.38) | 74.07 (53.71 to 88.84) |
| Positive likelihood ratio (95% CI) | 6.17** (1.94 to 19.62) | 10.39** (3.42 to 31.52) | 3.55* (1.73 to 7.28) | 6.39** (1.55 to 26.33) | 22.74** (3.29 to 157.15) | 3.21* (1.64 to 6.28) |
| Negative likelihood ratio (95% CI) | 0.59 (0.43 to 0.82) | 0.28 (0.15 to 0.51) | 0.44 (0.28 to 0.71) | 0.57 (0.37 to 0.88) | 0.16** (0.06 to 0.46) | 0.22 (0.08 to 0.65) |
| Positive predictive value (95% CI) | 82.35 (56.55 to 95.99) | 88.46 (69.82 to 97.42) | 75.00 (55.12 to 89.26) | 81.82 (48.24 to 97.18) | 94.12 (71.24 to 99.02) | 68.18 (45.13 to 86.08) |
| Negative predictive value (95% CI) | 69.09 (55.19 to 80.85) | 82.98 (69.18 to 92.33) | 72.73 (57.21 to 85.03) | 71.43 (53.69 to 85.34) | 89.66 (72.62 to 97.69) | 86.96 (66.38 to 97.07) |

**Important likelihood ratio, *relatively important likelihood ratio

ROC analysis in the group without diabetes indicated similar clinical efficacy for both the ABI (ROC area: 0.81, $p=0.0001$) and TBI (ROC area: 0.81, $p=0.0001$) (Figure 4.1). In the group with diabetes, the TBI had greater clinical efficacy (ROC area: 0.75 $p=0.0001$) than the ABI (ROC area: 0.58, $p=0.27$) (Figure 4.2).

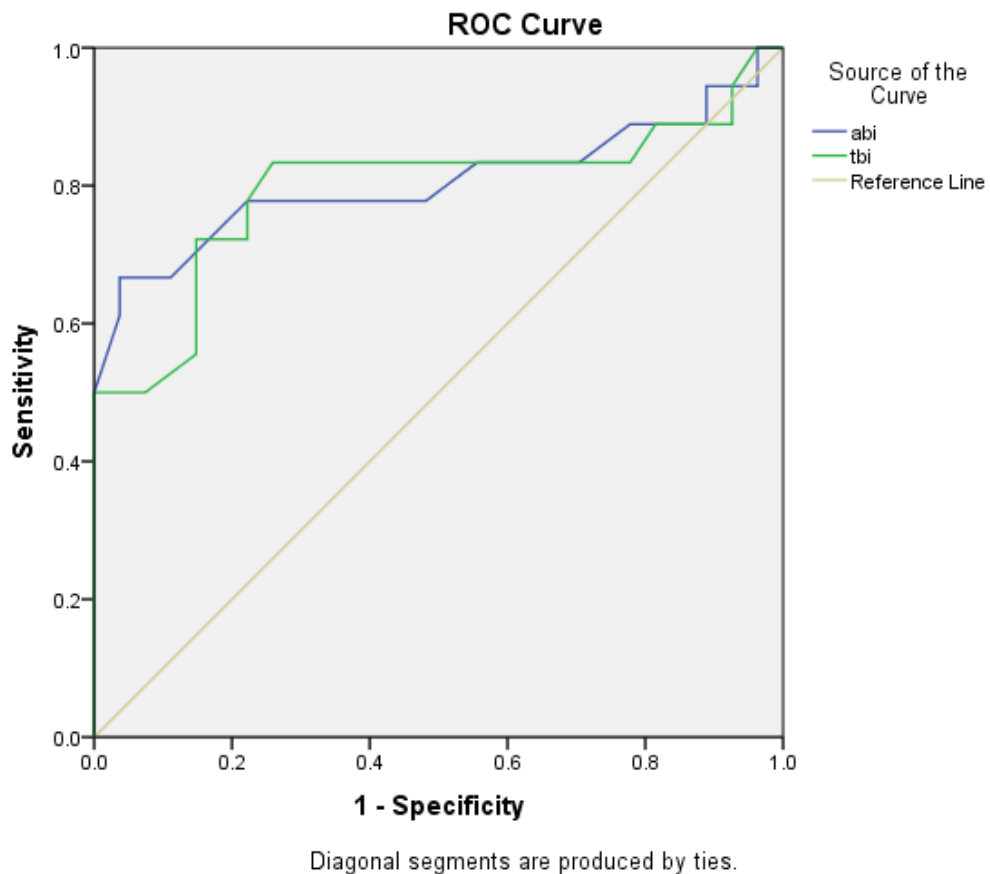


Figure 4.1: ROC Analysis of TBI and ABI for detecting PAD in people without diabetes

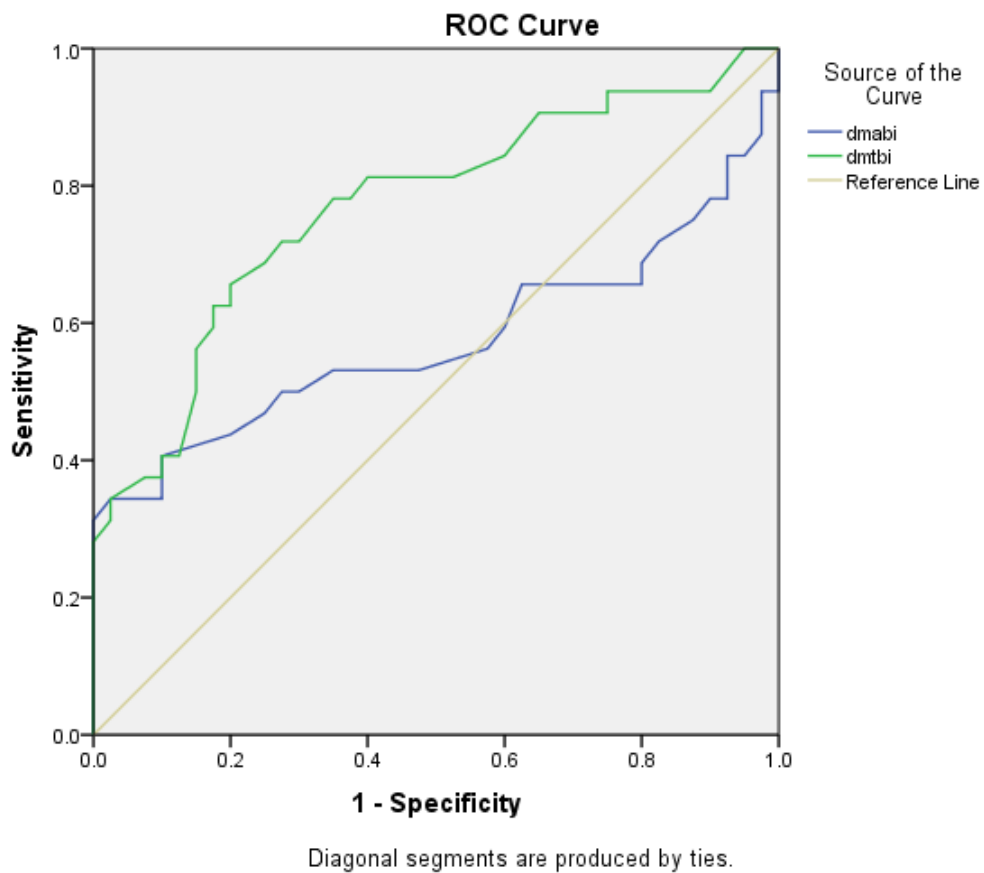


Figure 4.2: ROC Analysis of TBI and ABI for detecting PAD in people with diabetes

4.7 Discussion

To the best of our knowledge, this is the largest prospective diagnostic accuracy study examining the most commonly used non-invasive vascular assessment methods in diabetes. This study is unique in that the sample is substantial, and the participants are reflective of those encountered in clinical practice.

The specificity of the ABI was high in participants with (92.68%) and without diabetes (92.59%) and important positive likelihood ratios were also present in those with (6.17) and without diabetes (6.39), which was consistent with previous studies involving similar populations (20, 115, 116). The sensitivity of the ABI was poor in both groups, with (45.16%), and without diabetes (47.37%). This was slightly lower than previous studies (115, 116) however this may have occurred as a result of the characteristic of the

population we recruited. The participants in our study were older (mean age 72 and 74 years for participants with and without diabetes respectively), and there was also a large proportion of people with distally distributed PAD (36% in both groups). Our sample included a larger number of individual participants than previous studies (20) and represented a community-based population requiring non-invasive vascular screening including people with smoking history, significant cardiovascular disease and any form of neuropathy. This suggests these findings are reflective of the utility of this test in clinical practice. Based on our results the ABI was unlikely to yield false positive results in those with and without diabetes, however, it was highly likely to produce false negatives, which has significant clinical implications, particularly as PAD is frequently asymptomatic(117).

The sensitivity of the TBI for detecting PAD was lower in people with diabetes (63%) than those without diabetes (83%). Although sensitivity of the TBI for PAD in the diabetes cohort was lower than reported in a previous research (20), our findings of superior sensitivity with a TBI than an ABI in this population is consistent with existing evidence. The specificity of the TBI in detecting PAD was higher in the group with diabetes (82%), than without (74%). ROC analysis demonstrated that overall the TBI was a superior test in the group with diabetes (ROC area: 0.75) compared to ABI which had limited diagnostic utility (ROC area 0.58). Both ABI and TBI demonstrated equal diagnostic utility in the group with no diabetes (both ROC area: 0.81).

The most sensitive test in both groups was CWD, which was more sensitive (74.19%) for the presence of PAD in people with diabetes than both the TBI (63.64%) and ABI (45.16%). Important positive likelihood ratios in both participants with (10.39) and without diabetes (22.74) also indicated good test performance. These results are fairly consistent with a previous study (20) which showed CWD to have high sensitivity in populations with diabetes. We also defined PAD as a single lesion of >50% stenosis or more as diagnosed by CFDU, which has also been used in a previous study (20). However,

this cut-off for defining PAD may lead to increased sensitivity of CWD, as a minor stenosis proximally may be sufficient to alter the distal CWD, but not cause a significant drop in pressure at rest. Therefore peripheral pressure measurements may not be able to detect minor degrees of PAD.

4.7.1 Potential Limitations

The findings of this study should be considered in light of some potential limitations. This study used CFDU as the reference standard, and whilst this method is used extensively clinically, and considered an accurate method of non-invasive testing, it is operator dependant. We conducted an inter-tester reliability study, which whilst yielded good results, was limited to ten due to financial restraints. However, this was similar to previous studies utilising CFDU as a reference standard (20). Diagnosis of PAD by CFDU below the knee is known to be problematic. However, the participants in this study with distally located stenoses demonstrated more severe PAD, with almost all participants with distal PAD having complete occlusions in vessels below the knee. This makes the likelihood of a false positive unlikely. The post-hoc categorisation of the two groups may limit the generalizability of the results, however, statistical analysis revealed there were no significant differences between the groups so this is not likely. Although signs and symptoms that may indicate PAD were collected by the vascular sonographers at the time of scanning rigorous investigation and classification of these using the widely accepted Rutherford-Becker classification system was not performed. Therefore from our data it was not possible to determine the relationship between symptom severity and the ABI, TBI and CWD in this cohort, limiting the clinical utility of our results

The prospective nature and sample population of this study did not allow for more accurate and more invasive methods of vascular assessment as the reference standard. People with any form of neuropathy were included in this study population. A previous study has shown that diabetic neuropathy affected sensitivity of the ABI. However due to

the small number of neuropathic participants recruited for our present study (only 15 out of the 117 participants) a separate sub analysis was not conducted on this group. It is possible that this may have affected our results as although incidence of peripheral neuropathy was evenly distributed between the groups, currently it is only diabetic peripheral neuropathy that is known to sensitivity of the ABI, and there is no data for peripheral neuropathy of other causes. This warrants investigation in a larger cohort.

4.8 Conclusion

All non-invasive testing was less sensitive in the group with diabetes, which draws attention to the difficulties of performing accurate vascular assessment in this population. Perhaps most striking was the low sensitivity of the ABI in both groups, suggesting this may not be the most appropriate vascular test even in the absence of diabetes, particularly where PAD is suspected. The results of this study suggest that relying on an individual test such as an ABI or TBI for vascular screening is likely to be problematic.

4.9 Acknowledgements

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Chapter 5 Vascular assessment techniques of podiatrists in Australia and New Zealand: A web-based survey

5.1 Preface

International guidelines exist for performing vascular assessments to diagnose presence of PAD. However the adherence of Podiatrists in Australia and New Zealand to existing guidelines and the broader vascular assessment techniques that are used in clinical practice have not yet been established. A cross-sectional survey of vascular assessment habits of Podiatrists in Australia and

New Zealand is presented in this chapter. The results provide initial data on the most frequently used methods of performing assessment and barriers to undertaking comprehensive vascular assessments in clinical practice.

The advertising, survey (containing information statement and consent) and ethics approval relating to this study are available in Appendices 9, 10 and 11. The study presented in Chapter 5 was conducted in accordance with ethical approval granted by the Hunter New England Local Health District ethics committee and University of Newcastle Human Research Ethics Committee

This study was published in the Journal of Foot and Ankle Research in August 2015. DOI 10.1186/s13047-015-0130-5. The manuscript is located in appendix 12.

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5.3 Abstract

5.3.1 Background

Podiatrists play a central role in conducting non-invasive vascular assessment in the lower extremity. This involves screening for signs and symptoms of peripheral arterial disease (PAD) and ongoing monitoring of the condition. Podiatric vascular assessment practices in Australia and New Zealand are currently unclear. Determining the clinical habits of Podiatrists is essential in identifying if there is a need for further education or support in performing accurate vascular assessments.

5.3.2 Methods

A web-based, secure, anonymous questionnaire was conducted of registered Podiatrists in Australia and New Zealand between 1 April and 31 July 2013. The questions examined clinician's regular practices in vascular assessment, clinical indicators to perform and barriers in completing vascular assessment. Nominal logistic regression was performed to further examine years of experience and practice setting on clinical indicators to perform vascular assessment and types of assessment performed.

5.3.3 Results

Four hundred and forty-seven podiatrists participated in the survey. Clinical indicators for vascular assessment, along with barriers and available equipment were examined and the results varied depending on the podiatrists' geographical location, practice setting, and experience. Palpation of pedal pulses was the most frequently reported assessment (97%) along with Doppler assessment (74%). Pressure measurement was the least frequently reported vascular assessment method, with only 34% undertaking ankle-brachial indices and 19% completing toe-brachial indices. Public podiatrists reported more varied and complete vascular assessment compared to those in private practice. Lack of time was identified as the most frequently reported barrier (66%) in performing vascular assessment, followed by lack of

equipment (28%). In New Zealand podiatrists, lack of equipment was much more of an issue than in Australian podiatrists.

5.3.4 Conclusion

Large variations exist in vascular assessment methods amongst Australian and New Zealand podiatrists. Some assessments being undertaken are potentially inadequate for accurate screening for PAD. There is a need for continuing education in vascular assessment to address the deficiencies in technique reported by some Podiatrists. A podiatry-relevant summary of broad international guidelines for PAD screening may be of use to improve utilisation and accuracy of screening methods to improve patient management.

5.4 Introduction

Podiatrists play a central role in conducting non-invasive vascular assessment in the lower extremity. This involves screening for signs and symptoms of peripheral arterial disease (PAD) and ongoing monitoring of the condition following diagnosis(7). Given that people with PAD are not only at higher risk of wounds and limb loss, but are at far greater risk of cardiovascular events and death (118),effective routine vascular screening is integral to improving clinical outcomes through early identification of the presence of the disease to facilitate effective intervention, and for ongoing monitoring (119).

A number of tests are currently used for lower limb vascular assessment including pulse palpation, systolic toe pressures, toe-brachial index (TBI), ankle-brachial index (ABI) and Doppler examination. While generally these tests have been shown to have high reliability and diagnostic accuracy (20, 39, 48, 50, 56, 63, 73, 120, 121), there has been little investigation of the frequency of use and practicality of performing these assessments in clinical practice generally, with most evidence relating to the most widely recommended test, the ABI(122).

In general medical practice, time constraints and lack of financial reimbursement have been reported to contribute to reduced utility of the ABI for vascular screening (123) with general practitioners also reporting a lack of confidence in ability to perform the measurement (124). Only 32% of general practitioners are reported to perform ABI on a regular basis most commonly prior to the application of compression bandaging and for determining the aetiology of chronic wounds (123). Podiatrists also have reported time constraints and lack of financial reimbursement as barriers in performing ABI, with approximately half of practitioners reporting using ABI regularly (59). However the clinical indicators used by clinicians to complete this assessment or conduct other forms of lower limb vascular assessment including the TBI and Doppler waveform assessment have not been investigated (59, 124).

The primary aim of this study was to determine current practices in performing lower limb vascular assessments of Podiatrists in Australia and New Zealand. The secondary aims of this study were to investigate factors influencing lower limb vascular assessment practices including levels of clinical experience and education, practice location and resources and to establish perceived barriers to performing lower limb vascular assessments Podiatry practice.

5.5 Methods

This was a cross-sectional observational study performed using a web –based, secure anonymous self-administered survey reading lower limb vascular assessment habits of Podiatrists from Australia and New Zealand that was conducted between 1 April and 31 July 2013.

Recruitment of participants was via their affiliated professional body – The Australian Podiatry Association or PodiatryNZ. Invitations to participate were sent via e-mail advertising in the weekly bulletin or a small advertisement in the paper based bulletin with a link to the survey. External clinical supervisors participating in the University of Newcastle external placement

program were also invited to take part via email invitation containing a survey overview with a hyperlink to the survey. Inclusion criteria were Podiatrists registered and currently practicing in Australia and New Zealand. Ethical approval was obtained from the University of Newcastle Human Research Ethics Committee (Ethics approval: H-2012-0384). All participants provided informed consent prior to participation in this study.

The survey was delivered online via the online survey software Survey Monkey®. The questions examined clinician's regular practices in vascular assessment, factors prompting performance of an assessment and availability of equipment (Appendix 10). The first seven questions elicited demographic and descriptive data from the participants. Questions eight to 15 related to clinicians vascular assessment habits and 16 and 17 related to provision of patient education. The majority of questions were closed with three open ended questions, which related to time spent in practice and topics covered in education provision. A mix of nominal polytomous, ordinal polytomous and dichotomous questions were used. Pilot testing of the survey was performed at a University of Newcastle continuing professional development event attended by a mix of 35 private and public sector podiatrists. Based on feedback from podiatrists some small amendments were made from open ended to ordered polytomous and phrasing of the questions was slightly altered to allow for further clarity.

5.5.1 Data Analysis

The primary data analyses were descriptive statistics of the cohort including geographical practice location, years of experience, qualifications held and practice sector. Nominal logistic regression was performed and relative risk ratios calculated for possible factors affecting clinical indications to perform vascular assessment and the type of vascular testing that was performed. These clinical indicators included combinations of the type of referral received, clinical signs and symptoms of PAD and patient medical history. Vascular assessment performed included combinations of clinical observations, Doppler use and pressure measurements. The fit of the

data to the final nominal logistic regression model was assessed using the Hosmer-Lemeshow test with a p value >0.05 indicating an adequate fit. All data analysis was conducted using Stata data analysis and statistical software version 13. Missing data were excluded case wise.

5.6 Results

5.6.1 Participant Characteristics

Four hundred and forty seven podiatrists were recruited in total, however the number of responses varied slightly per question with some respondents not answering all questions, and some questions allowed for multiple answer options. Overall percentages are reported as the percentage of the total number of participants who answered an individual question and the total number of respondents for the question provided. For comparison of sub groups descriptive statistics are reported as the percentage of the number of respondents identified in that sub group e.g. practitioners in private practice. The total response rate represents approximately 10% of all registered Podiatrists in Australia and New Zealand in 2013. Participant characteristics are included in Table 5.1.

Table 5.1 Survey Participant Characteristics

| Participant Characteristics | |
|-----------------------------|-----------|
| Participants | 447 |
| Private practice | 322 (73%) |
| Public practice | 115 (26%) |
| Research/education | 10 (2%) |
| Metropolitan | 265 (60%) |
| Regional | 137 (31%) |
| Rural | 57 (13%) |
| Years of practice (Range) | 0-42 |
| Years of practice (Mean) | 13 |
| Diploma | 80 (18%) |
| Bachelor or equivalent | 268 (61%) |
| Post graduate/RHD | 91 (21%) |

5.6.2 Indicators to Perform a Vascular Assessment

A history of diabetes was the most frequently reported clinical indicator to complete a vascular assessment (82%, n=367/377), the least frequently reported was presence of thickened nails (14.6%, n=55/377) (Table 5.1). Several other cardiovascular risk factors

for PAD including hypertension and dyslipidaemia were among the least frequently reported clinical indicators. The mean number of vascular assessments performed in the most recent day of practice was 2.35 and ten minutes was the most frequently reported average time taken to complete vascular assessment (Table 5.2). The most commonly reported clinical indicators to perform a vascular assessment were grouped into the patient's medical history, practitioner's clinical observations and the type of referral i.e. Medicare EPC referral, general practitioner referral (Table 5.3

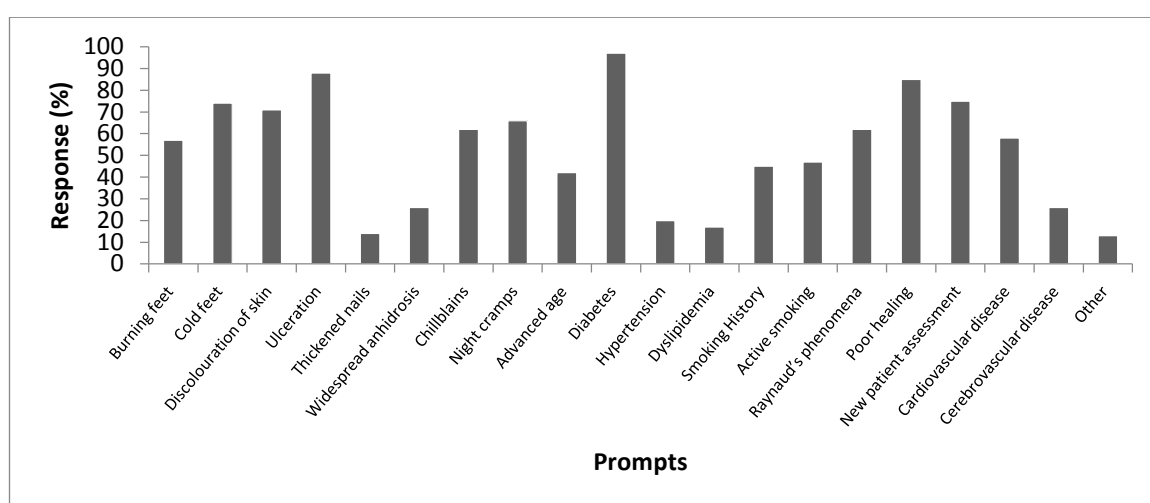


Figure 5.1 Clinical indicators to prompt podiatrists to perform vascular assessment

Table 5.2 General Vascular Assessment Information

| General vascular assessment | | | | |
|---|------------|------------|------------|------------|
| Mean number of vascular assessments performed in most recent day of clinical practice | | | 2.35 | |
| Vascular assessment within standard consultation n (%) | | | 277 (73) | |
| Vascular assessment as separate consultation n (%) | | | 47 (12) | |
| Charge additional fee for vascular assessment n (%) | | | 34 (9) | |
| Do not charge additional fee for vascular assessment n (%) | | | 280 (74) | |
| Time to complete assessment n (%) | | | | |
| 5 minutes | 10 minutes | 15 minutes | 20 minutes | 30 minutes |
| 97 (25) | 130 (34) | 80 (21) | 40 (12) | 26 (7) |

Table 5.3 Clinical Indicators for Vascular Assessment

| Clinical indicators | Medical History, Observations and Referral Type | | | | | | | | | | | | | | | | |
|------------------------------|---|-------|-------------|-------------------|----------------|----------------------------------|-------|-------------|-------------------|---------------|---|-------|-----------------------------------|-------|-------------|--------------|----------------|
| | Medical History | | | | | Medical History and Observations | | | | | Medical History, Observations and Referral Type | | Medical History and Referral Type | | | | |
| | N | % | RRR | P Value | 95% CI | N | % | RRR | P Value | 95% CI | N | % | N | % | RRR | P Value | 95% CI |
| <i>Education Level</i> | | | | | | | | | | | | | | | | | |
| Diploma | 6 | 8.45 | 0.93 | 0.789 | 0.55 to 1.569 | 13 | 18.31 | 0.78 | 0.251 | 0.51 to 1.189 | 47 | 66.2 | 5 | 7.04 | 1.40 | 0.44 | 0.6 to 3.282 |
| Bachelor | 30 | 11.95 | | | | 33 | 13.15 | | | | 150 | 59.76 | 38 | 15.14 | | | |
| Postgrad/RHD | 5 | 5.68 | | | | 11 | 12.5 | | | | 53 | 60.23 | 19 | 21.59 | | | |
| <i>Practice Setting</i> | | | | | | | | | | | | | | | | | |
| Private | 30 | 10.38 | 0.02 | <0.0001 | 0.003 to 0.153 | 52 | 17.99 | 0.38 | <0.0001 | 0.22 to 0.652 | 162 | 56.06 | 45 | 15.57 | 0.10 | 0.028 | 0.01 to 0.782 |
| Public | 9 | 8.82 | | | | 4 | 3.92 | | | | 74 | 72.55 | 15 | 14.71 | | | |
| <i>Geographical location</i> | | | | | | | | | | | | | | | | | |
| Metro | 21 | 8.57 | 2.05 | 0.292 | 0.54 to 7.773 | 40 | 16.33 | 0.96 | 0.945 | 0.27 to 3.430 | 149 | 60.82 | 35 | 14.29 | 2.38 | 0.345 | 0.39 to 14.435 |
| Regional | 16 | 12.21 | 0.71 | 0.609 | 0.2 to 2.592 | 15 | 11.45 | 0.36 | 0.11 | 0.11 to 1.258 | 81 | 61.83 | 19 | 14.5 | 1.35 | 0.731 | 0.24 to 7.640 |
| Rural | 4 | 7.69 | 1.15 | 0.831 | 0.31 to 4.304 | 4 | 7.69 | 0.94 | 0.927 | 0.27 to 3.249 | 33 | 63.46 | 11 | 21.15 | 2.77 | 0.244 | 0.5 to 15.394 |
| <i>Experience</i> | | | | | | | | | | | | | | | | | |
| Years (mean, SD) | 12.01 | 8.96 | 1.04 | 0.018 | 1.01 to 1.073 | 14.82 | 11.14 | 1.04 | 0.004 | 1.01 to 1.066 | 12.14 | 10.04 | 13.60 | 9.73 | 1.06 | 0.039 | 1.00 to 1.117 |

*Values in bold are considered statistically significant, RRR= relative risk ratio,

The reference group of the nominal logistic regression model used a combination of responses of Observations, Medical History and Referral Type. .^A Bachelor or equivalent degree was used as the reference category for education level ^B Private practitioners were used as the reference category for work setting.

Regression analysis showed the clinical indicators used as a basis for performing a vascular assessment were most strongly influenced by the years of clinical experience and practice setting (public of private) (Table 5.3)

Public sector podiatrists were more likely to perform vascular assessment based on a combination of medical history, observations and the type of referral compared to private sector practitioners ($p < 0.0001$). Less experienced podiatrists were more likely to use a combination of multiple factors (referral type, medical history and observations) to prompt for vascular assessment ($p = 0.018$) compared to more experienced podiatrists who reported relying upon one or two clinical indicators alone, rather than a combination of all three clinical indicators. The Hosmer-Lemeshow test was identified as statistically non significant ($p = 0.17$) indicating the model was an adequate fit to the data.

5.6.3 Vascular Assessment Methods

Pedal pulse palpation (97%, $n = 366/377$) and Doppler use (74%, $n = 281/377$) were the most frequently reported vascular assessment tests by respondents (Table 5.4). Use of any type of vascular pressure measurement was substantially lower with 34.2% ($n = 129/377$) of respondents reporting regularly using ABIs and 19.4% ($n = 73/377$) using TBIs. Podiatrists employed in the public sector reported a higher frequency of Doppler use (92%, $n = 101/110$) than private-sector podiatrists (66%, $n = 197/300$). There were also differences in frequency of use of pressure measurement between public and private sector podiatrists.

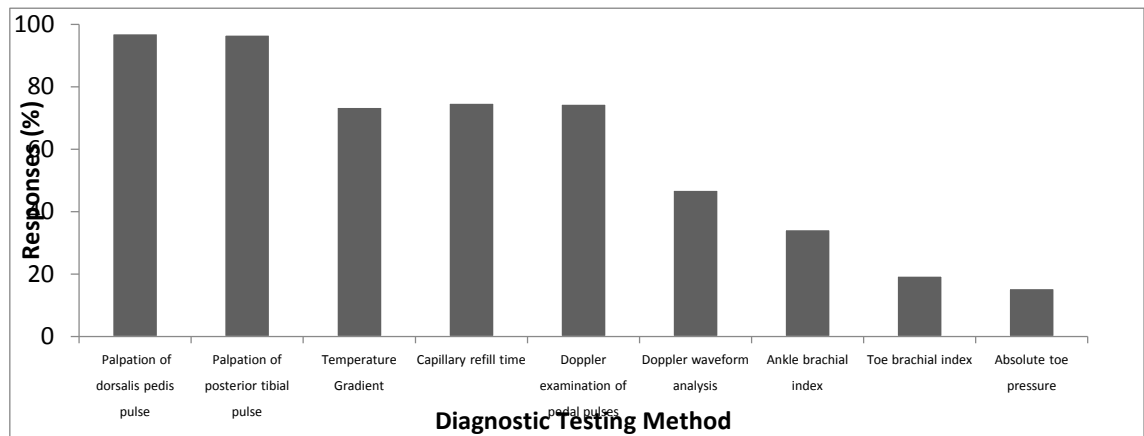


Figure 5.2 Clinical testing performed by podiatrists

Fifty three percent of public sector podiatrists reported regularly using an ABI (n=58/110 and thirty-five percent regularly using a TBI (n=39/110). In the private sector, 25% of podiatrists reported regularly using an ABI (n=75/300) and only 12% regularly used a TBI (n=24/300).

Nominal regression analysis revealed that setting (private or public sector) and years of experience were significant predictors of what testing methods were reported to be performed (Table 5.4). Private sector practitioners were less likely to use multiple assessments that included observations and Doppler ($p < 0.0001$) or observations and pressure measurement ($p = 0.01$), compared to public sector practitioners. More experienced podiatrists were also more likely to report relying on their clinical observations ($p = 0.018$) rather than undertaking clinical testing such as Doppler and pressure measurement to perform a lower limb vascular assessment.

Table 5.4 Types of Testing Utilised by Podiatrists

| Types of testing | Observations Alone | | | | | Observations and Doppler | | | | | Observations Doppler and Pressure | | Observations and Pressure | | | | |
|------------------------------|--------------------|-------|-------------|-------------------|----------------|--------------------------|-------|-------------|-------------------|---------------|-----------------------------------|-------|---------------------------|------|-------------|--------------|----------------|
| | N | % | RRR | P Value | 95% CI | N | % | RRR | P Value | 95% CI | N | % | N | % | RRR | P Value | 95% CI |
| <i>Education Level</i> | | | | | | | | | | | | | | | | | |
| Diploma | 19 | 26.76 | 0.93 | 0.789 | 0.55 to 1.569 | 32 | 45.07 | 0.78 | 0.251 | 0.51 to 1.189 | 17 | 23.94 | 3 | 4.23 | 1.40 | 0.44 | 0.6 to 3.282 |
| Bachelor | 43 | 17.2 | | | | 92 | 36.8 | | | | 107 | 42.8 | 8 | 3.2 | | | |
| Postgrad/RHD | 15 | 17.05 | | | | 24 | 27.27 | | | | 42 | 47.73 | 7 | 7.95 | | | |
| <i>Practice Setting</i> | | | | | | | | | | | | | | | | | |
| Private | 70 | 24.31 | 0.02 | <0.0001 | 0.003 to 0.153 | 115 | 39.93 | 0.38 | <0.0001 | 0.22 to 0.652 | 89 | 30.9 | 14 | 4.86 | 0.10 | 0.028 | 0.01 to 0.782 |
| Public | 1 | 0.98 | | | | 30 | 29.41 | | | | 70 | 68.63 | 1 | 0.98 | | | |
| <i>Geographical location</i> | | | | | | | | | | | | | | | | | |
| Metro | 53 | 21.72 | 2.05 | 0.292 | 0.54 to 7.773 | 98 | 40.16 | 0.96 | 0.945 | 0.27 to 3.430 | 82 | 33.61 | 11 | 4.51 | 2.38 | 0.345 | 0.39 to 14.435 |
| Regional | 20 | 15.27 | 0.71 | 0.609 | 0.2 to 2.592 | 34 | 25.95 | 0.36 | 0.11 | 0.11 to 1.258 | 71 | 54.2 | 6 | 4.58 | 1.35 | 0.731 | 0.24 to 7.640 |
| Rural | 8 | 15.38 | 1.15 | 0.831 | 0.31 to 4.304 | 20 | 38.46 | 0.94 | 0.927 | 0.27 to 3.249 | 21 | 40.38 | 3 | 5.77 | 2.77 | 0.244 | 0.5 to 15.394 |
| <i>Experience</i> | | | | | | | | | | | | | | | | | |
| Years (mean, SD) | 14.4 | 8.3 | 1.04 | 0.018 | 1.01 to 1.073 | 14.5 | 11.4 | 1.04 | 0.004 | 1.01 to 1.066 | 10.1 | 9.0 | 15.5 | 10.1 | 1.06 | 0.039 | 1.00 to 1.117 |

*Values in bold are considered statistically significant, RRR= relative risk ratio,

The reference group of the nominal logistic regression model used a combination of responses of Observations, Doppler and Pressure measurement. ^A Bachelor or equivalent degree was used as the reference category for education level ^B Private practitioners were used as the reference category for work setting.

5.6.4 Barriers in performing vascular assessment

Time constraints were the most frequently nominated barrier to performing a vascular assessment for all respondents (62%, n=233/376), followed by general lack of equipment (28%, n=106/376). Lack of equipment was more frequently reported as a barrier in New Zealand podiatrists 43.8% (n=28/64) than their Australian counterparts (25%, n=78/312). No barriers to completing vascular assessment was reported by 22% (n=99/376) of the responding participants.

Private sector podiatrists reported time constraints were a barrier to performing vascular assessments (64%, n=190/293) more frequently than those in public practice (54%, n=58/108). Lack of equipment and uncertainty about technique were also more frequently reported in by podiatrists in private practice (equipment: 32%, n=93/293, technique: 13%, n=38/293) than in public practice (equipment: 22%, n=24/108, technique: 3.7%, n=4/108).

Geographical location appeared to have an influence on barriers in performing vascular assessment. Although time constraints were the most commonly reported barrier in performing vascular assessment for all respondents (62%, n=233/376), this was highest amongst rural (77%, n=41/53), and regional podiatrists (62%, n=80/129) compared to those in metropolitan areas (58%, n=138/239). The majority of podiatrists unsure of assessment techniques were rurally located (17%, n=9/53), followed by those in metropolitan (10%, n=24/239) and regional (8%, n=11/129) areas.

The lack of financial incentive to perform vascular assessment was noted by 23% (n=86/376) of podiatrists as a significant barrier, with this generally only relevant to private practice (30%, n=87/293).

5.6.5 Patient education

The majority of podiatrists (71.4%, n=269/377) reported to always provide patient education as part of a vascular assessment with very few reporting education was rarely or never provided, (3/377 [0.8%] reported rarely providing education and 1/377 [0.3%] reported never providing education). Main themes of patient education which emerged from open responses given included: footwear, self-care, smoking cessation, foot hygiene, exercise, daily foot inspection, first aid and signs and symptoms of PAD.

5.7 Discussion

This is the first study to investigate the clinical indicators that podiatrists use to undertake lower limb vascular assessment and to establish the current clinical examination techniques most commonly used by podiatrists in Australia and New Zealand. We have demonstrated that pedal pulse palpation and use of Doppler were the most commonly utilised assessment methods, and that practice setting and experience had the most significant influence on performance of assessment and what type of assessment methods were utilised. This study suggests that in Australian and New Zealand podiatrists there is a reliance on subjective vascular assessment testing methods such as pedal pulses palpation and Doppler examination, and a lack of objective measurement such as the ABI and TBI. As objective measurements not only help to identify the presence of PAD but provide indication of severity of disease, when used in combination with signs and symptoms these tests play an essential role in guiding patient management and assessing risk status. This reliance on more subjective testing methods was more evident in private practitioners than public practitioners. This may be due to a number of different factors. The patients seen in each clinical setting tend to differ, generally with more high risk, diabetes and complex vascular pathology patients seen in public practice (125) who require more extensive investigation, which may account for some of the differences reported. In private practice, no financial incentives currently exist to complete vascular assessment and

time is more limited, so practitioners may not perform the more time consuming testing such as pressure measurement.

The overall number of podiatrists reporting using the ABI on a regular basis was lower than previously reported (59) and podiatrists participating in this study reported they were more likely to use the clinical signs and symptoms of PAD present in the lower limb, as a clinical indicator to perform vascular assessment. Systemic factors, such as advanced age, smoking, cardiovascular disease and stroke, which are well-established risk factors for PAD, were much less frequently reported to be used as clinical indicators to perform such an assessment. Given that the signs and symptoms of PAD are frequently unrecognised or even absent (126), it may be likely that relying on subjective testing methods will result in missed or late diagnosis of PAD and/or an inaccurate diagnosis of disease severity. Objective pressure measurements add another important dimension to lower limb vascular assessment, allowing for ongoing monitoring of PAD from year to year. This is particularly important for conditions such as Diabetes where changes can occur quickly and action needs to be undertaken to prevent complications such as wounds, ulceration and gangrene.

This study highlights that a large proportion of reported practices in lower limb vascular assessment being undertaken by podiatrists in Australia and New Zealand do not follow international guidelines(65) for PAD screening. However, it is likely that podiatrists are unaware of this broad guideline, which recommends the use of objective pressure measurement, mainly the ABI when performing vascular assessment in populations deemed at risk of PAD. Our findings demonstrated a need for a podiatry specific summary of these broad international guidelines to assist podiatrists in their daily practice or increased awareness of the international guideline through continuing education.

The barriers to performing vascular assessment reported in this present study were consistent with previous studies (59, 123), with time constraints and lack of equipment most frequently cited. Uncertainty of technique was identified as a barrier to complete an assessment mainly in rural podiatrists, which suggests continuing education provision may be particularly beneficial in rural areas. A lack of equipment was identified as a major barrier in New Zealand podiatrists; however, there are differences in service provision in New Zealand compared to Australia, which may have an influence on the equipment required most frequently in daily clinical practice. Limited ability to obtain financial remuneration for vascular assessments was also a reported barrier in a quarter of all respondents. Given the importance of the task lower limb vascular assessment and its role in preventative care, future lobbying for health fund and/or Medicare rebates may be of use to remove this barrier for podiatrists to more regularly screen for PAD in their patients who are considered at risk.

5.7.1 Potential limitations

This study should be considered in light of some potential limitations. A non-validated survey was used and therefore the findings may have limited external validity and reproducibility. Despite our best efforts, our sample size was limited and may not be representative of the entire population of podiatrists in Australia and New Zealand. Over-reporting and under-reporting are possible, however piloting of the survey assisted in formulating specific answering methods and we believe this may have reduced the likelihood of this. There are also some differences in delivery of podiatric services between Australia and New Zealand, which will differently influence barriers in performing testing which could be explored further in future research.

5.8 Conclusion

Although our study only included a small proportion of practicing podiatrists in Australia and New Zealand, our findings suggest that there is a lack of consistency in the profession regarding

our approach to lower limb vascular assessment. Our results indicate there is greater scope for use of objective assessment techniques within the profession. Assessment methods employed by podiatrists appear to be guided by practice setting, practitioner experience and geographical location, rather than diagnostic utility of testing methods. There is a need for continuing education for podiatrists in the area of lower limb vascular assessment to increase awareness of accurate and appropriate vascular assessment requirements for populations at risk of PAD.

5.8.1 Acknowledgments

Thank you to the Podiatry Associations of Australia and New Zealand for their assistance with distributing the survey to their members. Thank you to all the podiatrists who gave their valuable time to complete the survey. Thank you to Alan Ho who assisted with the statistical analysis.

Chapter 6 Use of hand-held Doppler ultrasound examination by Podiatrists: A reliability study

6.1 Preface

This chapter evaluates the inter- and intra-tester reliability of hand-held Doppler use in Podiatrists. This is the first study to evaluate the reliability of all aspects of Doppler use in podiatrists, including the clinical utility, the audio output and the visual analysis of printed waveforms. The results of this study suggest reliability of clinical use of this form of assessment is low and therefore may have limited value as a diagnostic test for PAD in Podiatry clinical practice.

The consent forms, information statement and ethics approval relating to this study are available in Appendices 13, 14 and 15. The study presented in this chapter was conducted in accordance with ethical approval granted by: University of Newcastle Human Research Ethics

Committee (reference number H-2013-0152); and Hunter New England Area Health Research Ethics Committee 13/02/20/5.05 and NSW HREC LNR/13/HNE/18.

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This chapter was also presented at the National Podiatry Conference at the Gold Coast in May 2015 and is a published conference abstract in the Journal of Foot and Ankle Research. Financial support for this study was provided by an early career researcher grant from the University of Newcastle.

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6.3 Abstract

6.3.1 Background

Hand held Doppler examination is a frequently used non-invasive vascular assessment utilised by podiatrists. Despite this, the reliability of hand-held Doppler has not been thoroughly investigated. Given the importance of Doppler in completing a vascular assessment of the lower limb, it is essential to determine the reliability of the interpretation of this testing method in practicing podiatrists.

6.3.2 Methods

This was a multi-centre inter and intra-rater reliability study. Four podiatrists (the raters) participated in this study, two public and two private practitioners. Three aspects of Doppler use were examined; (i) use of Doppler (i.e. technique and interpretation), (ii) interpretation of Doppler audio sounds, and (iii) interpretation of visual Doppler waveforms (i.e. tracings). Participants meeting current guidelines for vascular screening attended two testing sessions, one week apart at either the private practice (n=32), or the public practice (n=31). To assess use of Doppler, the raters evaluated the Doppler waveforms that they collected, rating them as mono-phasic or multi-phasic. To assess Doppler audio sounds and visual Doppler waveforms, raters were required to evaluate 30 audio recordings of Doppler sounds and 30 waveform tracings, respectively, that were previously recorded and chosen at random by the researchers. Cohen's kappa (κ) statistics were used to calculate inter and intra-rater reliability using SPSS version 19.

6.3.3 Results

Use of Doppler demonstrated the lowest reliability for both pairs of clinicians (inter-rater reliability κ 0.20 to 0.24 and intra-rater reliability κ 0.27 to 0.42). The public podiatrists showed

higher reliability in audio interpretation (inter-tester reliability κ 0.61, intra-tester reliability κ 1.00) compared to the private podiatrists (inter-tester reliability κ 0.31, intra-tester reliability κ 0.53). Evaluation of Doppler waveform tracings demonstrated highest reliability, with inter-rater reliability ranging from κ 0.77 to 0.90 and intra-rater reliability from κ 0.81 to 1.00.

6.3.4 Conclusions

There is a need for ongoing education for podiatrists using Doppler in clinical practice, as the reliability for the clinical use of the Doppler was low. This indicates that technique could be an issue. There is also a need to further evaluate if hand-held Doppler equipment, using the examinations that we evaluated, is suitable for use in the contexts examined in this study.

6.4 Introduction

Peripheral arterial disease (PAD) is associated with cardiovascular morbidity and mortality (127) and the development of lower limb wounds, gangrene and amputation. The condition becomes increasingly prevalent in older age, renal disease and inflammatory arthritis. PAD also occurs earlier, more distally and with more rapid progression in association with diabetes (8, 128). Early detection is essential to ensure that modifiable risk factors are identified and for the conditions to be appropriately monitored and managed to prevent potentially life-threatening complications.

Regular screening of those at risk of PAD is essential as only 22% of people with PAD are symptomatic(129). Current recommendations indicate routine lower limb vascular screening is required for those over the age of 65 years or over 50 years with diabetes or a history of smoking(7). Podiatrists are in an ideal position to carry out vascular screening on a regular basis, as people who are older and have diabetes frequently seek podiatric care(125). With an ageing population and increasing prevalence of diabetes(130), non-invasive vascular screening is becoming increasingly important to prevent lower limb complications related to PAD.

Hand-held Doppler examination (Doppler) of pedal arteries is the most frequently used non-invasive vascular assessment modality utilised by podiatrists(59) for diagnosis and ongoing monitoring of PAD. Podiatrists generally use Doppler in two different ways, as part of an ankle brachial index (ABI) or as a standalone test(59). Doppler examination is a useful method for vascular screening as it has been demonstrated to be effective for detecting and excluding PAD, can be performed at relatively low cost and is non-invasive (56, 131).

In the foot, the dorsalis pedis and posterior tibial arteries are the most frequently examined due to their accessibility (54). Both audio and visual analyses of Doppler waveforms are performed by clinicians to determine the presence of PAD. In audio analysis non-pathological Doppler waveforms are considered multiphasic, which includes bi-phasic (two) or tri-phasic (three) sounds (132, 133). In contrast, a monophasic waveform is a single sound that is considered pathological (54) , indicating the presence of PAD. In visual analysis of a Doppler tracing, a non-pathological waveform has a distinct shape representing high resistance and diastolic flow reversal, which can be classified as multiphasic (bi or tri-phasic). Pathological waveforms generally have low resistance, slow systolic acceleration and no diastolic flow reversal and are classified as monophasic (54).

The accurate use of Doppler relies upon multiple competencies including the skills involved in accurate application of the device, and concurrent interpretation of both audio and visual data to classify the waveform as normal or pathological. For this type of assessment to be useful for ongoing monitoring of PAD in practice, high reliability of the measurement is required.

However, despite its widespread use in the podiatry profession, very little investigation has been completed on the reliability of either clinical measurement or interpretation for this type of assessment.

Currently, evidence of reliability of Doppler use in podiatry practice is isolated to interpretation of audio sound alone, with several studies demonstrating moderate inter-rater reliability (134, 135). In professions other than podiatry, hand-held Doppler has been shown to have high levels of reliability (56). A comprehensive assessment of the three elements of Doppler use (clinical application with waveform interpretation and independent audio and visual interpretation of waveforms) is required to determine the clinical efficacy of using this technique for ongoing peripheral vascular monitoring.

The aim of this study was to investigate the inter- and intra-rater reliability of the use of Doppler ultrasound for collection and interpretation of Doppler waveforms by podiatrists in mixed clinical settings. This included: (i) overall use of Doppler to evaluate the pedal pulses (involving conducting the assessment and interpreting audio and visual outputs), (ii) interpretation of Doppler audio sounds presented independently, and (iii) interpretation of visual Doppler waveforms presented independently.

6.5 Design and Methods

This was an inter- and intra-rater reliability study that took place over a period of six months (June – November 2013). Ethical approval was obtained from the University of Newcastle and Hunter New England Local Health District ethics committees, New South Wales, Australia (Reference number 13/02/20/5.05). All participants signed informed consent prior to being recruited into the study.

6.5.1 Raters

Four podiatrists (i.e. the raters) with varying levels of clinical experience (1-8 years) who studied at three different tertiary institutions across two states of Australia were invited, and subsequently agreed to participate in this study. The raters were selected to ensure varying levels of experience, training and employment sector were included. Written informed consent

was obtained from each participating podiatrist. All raters had previous experience with use of Doppler ultrasound for lower limb vascular assessment and did not receive further instruction on how to perform this task.

6.5.2 Participants

A convenience sample from the patient populations at each respective clinic were recruited for this study. In accordance with current guidelines for lower extremity vascular screening, eligibility criteria were: people aged over 65 years, or, aged over 50 years with a history of diabetes or smoking, or with exertional leg pain or non-healing wounds(65). This group was chosen as it is representative of people who may undergo these tests in clinical practice. Exclusion criteria were contraindications to Doppler testing including active foot or leg ulceration preventing Doppler placement, known allergy to coupling gel and/or an inability to lie supine for more than 20 minutes.

6.5.3 Procedure

Two testing sites were used, one was a podiatry clinic in a community health centre (public practice) in the Newcastle area (New South Wales, Australia) and one was a private podiatry clinic (private practice) in the same catchment. Participants were assessed at the testing site of the service they attended (Figure 1). All participants were instructed to avoid exercise, caffeine and smoking for at least one hour prior to their assessment as these are known to affect vascular assessment(136). All assessments were undertaken in a quiet, private room. Raters were blinded to both their own and each other's results at all times. To ensure consistency with data collection, and minimise measurement and interpretation errors (137) a strict data collection protocol was used (Appendix 1).

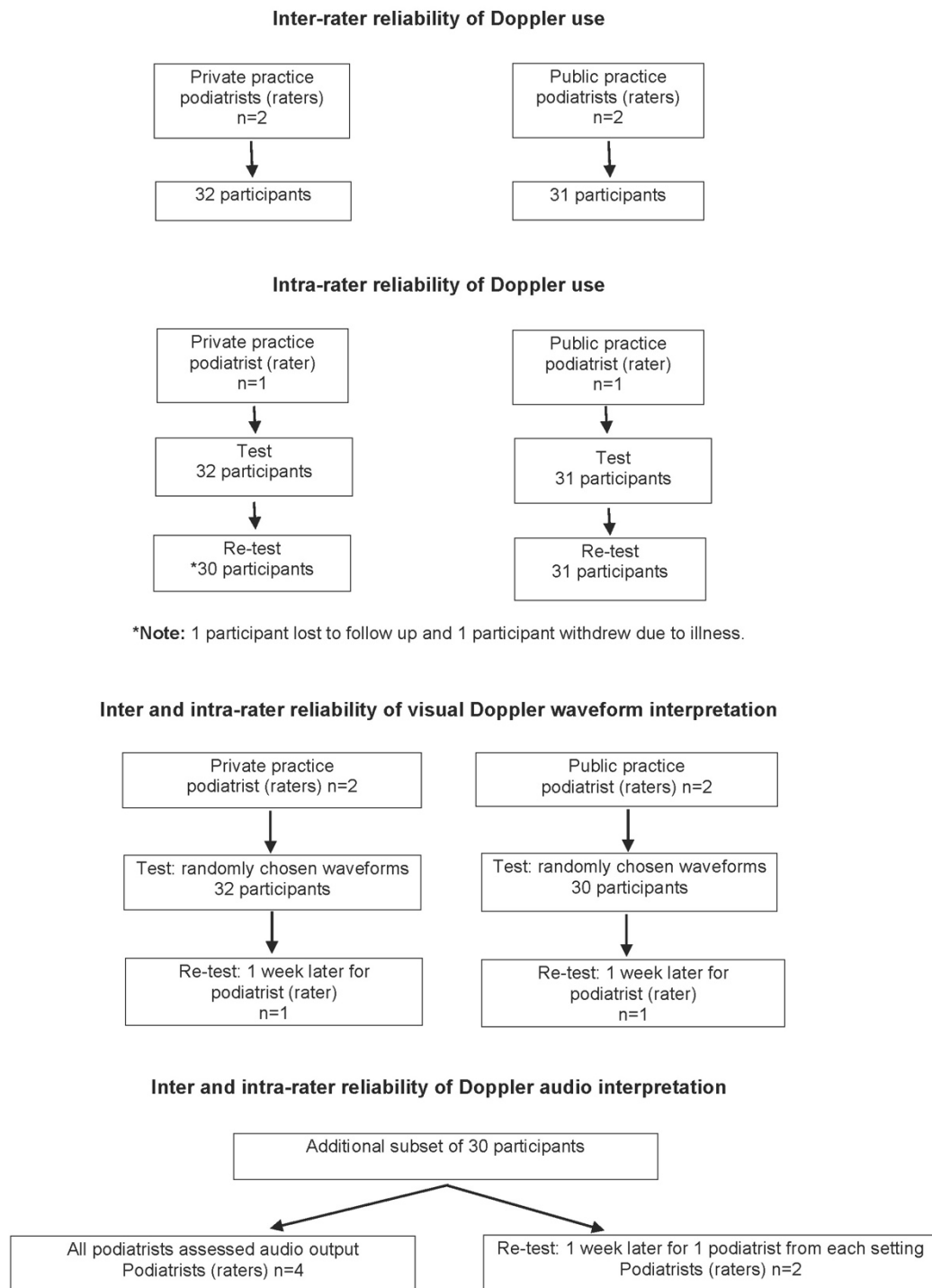


Figure 6.1 Flow chart

6.5.4 Inter- and intra- rater reliability of Doppler use

For this part of the study the inter- and intra-rater reliability of podiatrists performing a Doppler ultrasound assessment of the dorsalis pedis and posterior tibial arteries and the podiatrists

ability to interpret their results (i.e. use of the Doppler) was investigated. Participants at each setting were placed in a horizontal supine position and rested for at least ten minutes prior to the assessment. To assess inter-rater reliability of clinical use of the Doppler, all podiatrists were required to independently assess dorsalis pedis and posterior tibial arterial flow using a Hadeco Smartdop 45® (Hadeco, Kawasaki) and Aquasonic® ultrasound transmission gel (Parker Laboratories, New Jersey). All testing equipment was new at the beginning of the study. The private practice podiatrists undertook assessment on participants attending the private clinic, and the public sector podiatrists undertook assessments on participants attending the community health podiatry clinic. Based on the audio and visual waveforms produced by their own Doppler assessments all podiatrists then graded Doppler waveforms as absent, monophasic or multiphasic. All participants returned one week later to their original test site, either the public or private practice. Following the same test protocol, each participant had their waveforms obtained and graded again by one of the podiatrists from their previous testing session using the same procedure described previously.

6.5.5 Inter- and intra-rater reliability of Doppler audio interpretation

To determine the reliability of interpretation of Doppler audio alone, a single researcher (PT), who was not a rater in this study recorded dorsalis pedis and posterior tibial waveforms using the Hadeco Smartdop 45® from a separate, additional subset of thirty eligible participants recruited to the community health centre. Participants were rested in horizontal supine position for a minimum of ten minutes prior to assessment. Doppler audio were recorded using a digital Dictaphone held approximately ten centimetres from the Doppler speaker. Each set of Doppler audio were recorded for twenty seconds with the Doppler volume set at high. Either the dorsalis pedis or posterior tibial waveform was then randomly selected for each participant. To determine inter-rater reliability the same selected waveform audio files were then separately played to the four participating podiatrists who evaluated them independently as monophasic

or multiphasic. To determine the intra-rater reliability one of the private podiatrists, and one of the public podiatrists repeated the assessment of the same thirty audio files one week later, with the order of presentation of the audio files randomised to avoid order error.

6.5.6 Inter- and intra-rater reliability of visual Doppler waveform interpretation

To isolate reliability of visual interpretation of Doppler waveforms a researcher (PT) who was not a rater in this study, randomly chose thirty printed Doppler waveforms (i.e. tracings) collected by the four raters involved in this study. Each rater was then asked to rate them as monophasic or multiphasic based on the printed waveform. One of the private podiatrists, and one of the public podiatrists repeated the assessment one week later using the same set of printed waveforms with the order randomised.

6.5.7 Data Analysis

Inter-rater reliability of (i) waveform interpretation for clinical use of the Doppler, (ii) interpretation of independently collected audio recordings and (iii) interpretation of independently collected visual wave forms between the two private podiatrists and between the two public podiatrists was calculated by determining the level of agreement between measures using an unweighted Cohen's kappa (κ) statistic with 95% confidence intervals. All waveforms were classified as pathological (absent or monophasic) or non-pathological (multiphasic). Intra-rater reliability was calculated in the same manner for one of the public podiatrists and one of the private podiatrists for the three aspects of Doppler use detailed above.

Results were interpreted in accordance with Landis and Koch: ≥ 0.75 denotes excellent agreement; > 0.40 but < 0.75 denotes fair to good agreement; and < 0.40 denotes poor agreement (99). All reliability analyses were conducted using SPSS version 19.

6.6 Results

Thirty two participants attended the private practice, and 31 participants attended the public practice. Of these, according to the inclusion criteria, 23 (public group) and 15 (private group) were over 50 years of age with diabetes and 9 (public group) and 15 (private group) were over 65 years of age. No participants had active wounds or exertional leg pain, and only one participant was a current smoker (private group). In the public practice participant group, there was a larger age range and lower mean age than the private practice participant group. The public participant group also had higher rates of diabetes than the private participant group. Participant characteristics are listed in Table 6.1.

Table 6.1: Participant demographics

| Participant group characteristics | | | |
|-----------------------------------|---------------------|----------------------|----------------------|
| | Public participants | Private participants | Audio Interpretation |
| Males n (%) | 17 (53) | 18 (58) | 17 (56) |
| Females n (%) | 15 (47) | 13 (42) | 13 (44) |
| Mean age (years) | 70.9 (SD 7.1) | 72.0(SD 5.7) | 71.6 (SD 6.7) |
| Age range (years) | 57-88 | 61-81 | 55 - 82 |
| DM n (%) | 23 (72) | 15 (48) | 19 (63) |
| Total N | 32 | 31 | 30 |

SD: standard deviation, DM: diabetes mellitus

For Doppler use: the public participant group was evaluated by the public practice raters, and private participants were evaluated by private practice raters. For visual Doppler waveform analysis, printed waveforms from both public and private participants were randomly selected and evaluated by all raters. For audio interpretation all raters evaluated the recorded sounds of the sub-group listed above.

6.6.1 Inter- and intra-rater reliability of Doppler use

Inter-rater reliability for clinical use of Doppler was poor between the private podiatrists and between public podiatrists for both dorsalis pedis and posterior tibial arteries (99) with 95% confidence intervals crossing zero. The private podiatrist demonstrated the highest intra-rater reliability for collection and classification of Doppler waveforms for the posterior tibial artery examination (K: 0.42), which corresponds to fair agreement. Intra-rater reliability was poor for

both dorsalis pedis (K: 0.21) and posterior tibial artery waveforms collected and classified by the public podiatrist (K: 0.27).

Table 6.2: Reliability results for use of Doppler examination

| Use of Doppler inter-rater reliability | | | | | Use of Doppler intra-rater reliability | | | |
|--|---------------|---------------|---------------|---------------|--|---------------|---------------|---------------|
| | DP | 95% CI | PT | 95% CI | DP | 95% CI | PT | 95% CI |
| Private | K 0.20 (N:32) | -0.09 to 0.49 | K 0.16 (N:32) | -0.11 to 0.43 | K 0.22 (N:30) | -0.31 to 0.53 | K 0.42 (N:30) | 0.15 to 0.69 |
| Public | K 0.17 (N:31) | -0.14 to 0.48 | K 0.24 (N:31) | -0.07 to 0.55 | K 0.21 (N:31) | -0.16 to 0.58 | K 0.27 (N:31) | -0.06 to 0.60 |

95% CI: 95% confidence intervals, DP: dorsalis pedis artery, PT: posterior tibial artery, Private: private practitioners, Public: public practitioners

6.6.2 Inter- and intra-rater reliability of Doppler audio interpretation

Reliability of Doppler audio interpretation was fair for public podiatrists (κ : 0.61) and poor for the private podiatrists (κ : 0.31) (Table 6.3) Intra-rater reliability of Doppler audio interpretation was excellent for the public podiatrist (κ : 1.00) and fair for the private podiatrist (κ : 0.53).

Table 6.3: Reliability results of audio interpretation of Doppler

| Audio waveforms inter-rater reliability | | | 95% CI | Audio waveforms intra-rater reliability | | | 95% CI |
|--|---|-------------|--------|---|---------|---|-------------|
| Private | • | 0.31 (N:30) | | -0.08 to 0.70 | Private | • | 0.53 (N:30) |
| Public | • | 0.61 (N:30) | | 0.23 to 0.99 | Public | • | 1.00 (N:30) |
| 95% CI: 95% confidence intervals, Private: private practitioners, Public: public practitioners | | | | | | | |

6.6.3 Inter- and intra-rater reliability of visual Doppler waveform interpretation

The inter-rater reliability of visual Doppler waveform interpretation was excellent for both the private and public podiatrist (κ : 0.90 and κ : 0.77 respectively) (Table 6.4). Similarly, intra-rater reliability of visual interpretation of the waveforms for both the private podiatrist and public podiatrist were excellent (κ : 1.00 and κ : 0.81 respectively).

Table 6.4: Reliability results of visual Doppler waveform interpretation

| Visual waveforms inter-rater reliability | | | | 95 % CI | Visual waveforms intra-rater reliability | | | | 95% CI |
|--|---|---------------|---|--------------|--|---|-------------|---|--------------|
| Private | • | K 0.90 (N:32) | • | 0.71 to 1.09 | Private | • | 1.00 (N:32) | • | 1.0 to 1.0 |
| Public | • | K 0.77 (N:30) | • | 0.53 to 1.01 | Public | • | 0.81 (N:30) | • | 0.57 to 1.05 |
| 95% CI: 95% confidence intervals, Private: Private practitioners, Public: Public practitioners | | | | | | | | | |

6.7 Discussion

To the best of the authors' knowledge this is the first study to examine the reliability of the clinical use of Doppler and waveform interpretation skills in podiatrists. Our results demonstrate that the reliability of Doppler use with classification of waveforms was generally poor. Interpretation of independently collected Doppler audio demonstrated moderate inter-rater reliability and moderate to excellent intra-rater reliability. Finally, visual Doppler waveform interpretation of independently

collected waveforms yielded excellent inter-rater and intra-rater reliability in both private and public podiatrists.

These results suggest podiatrists had higher skill level in interpretation of visual waveforms and audio of Doppler waveforms in isolation than when the assessment had to be performed and the visual and audio results interpreted concurrently in a clinical setting. Generally the 95% confidence intervals for inter- and intra- rater reliability of the clinical use of Doppler included a negative lower limit. This suggests the range of plausible values for the “true” value of kappa included levels of agreement less than zero which would be worse than the level of agreement expected from chance alone; that is, if the raters were to guess each rating (138). The poor levels of agreement between and within clinicians for this aspect of the study may have been related to clinical technique in Doppler use or increased difficulty associated with interpreting visual and audio results simultaneously.

From a clinical perspective Doppler use can be difficult, particularly if patients have issues such as peripheral oedema, if there is fibrosis or adipose tissue present and/or there is anatomical variation in artery location. Such factors affecting reliable performance of the assessment may therefore have contributed to poorer reliability seen in this aspect of Doppler use. In addition, the requirement in this present study for clinicians to interpret both visual and audio outputs concurrently to inform their decision on presence or absence of pathology may have resulted in poorer reliability. Higher reliability may have been achieved by reducing the output of the Doppler to one variable, either audio or visual waveform to make the interpretation process more simple. However, as podiatrists are required to do both simultaneously in clinical practice, our results suggest that further training in Doppler use including concurrent interpretation of visual and audio waveforms, is required for this to be an effective component of non-invasive vascular assessment.

Visual Doppler waveform analysis of independently collected waveforms had the most consistently high inter- and intra-rater reliability in this study. As far as we are aware, this is the first study to examine the reliability of visual Doppler waveform analysis in podiatrists. Based on our results, when

visual waveform tracings alone were presented to podiatrists in both private and public practices they were able to reliably classify pathological or non-pathological waveforms between themselves and on a test-retest basis. However interpretation of Doppler audio of waveforms showed much more variable reliability between the two tester groups. Whilst public podiatrists had reasonable inter-rater reliability for interpretation of audio data (κ : 0.61) and perfect intra-rater reliability (κ : 1.00), the private podiatrists had lower inter- and intra- rater reliability (ranging for κ : 0.31 to κ : 0.53).

Previous studies have shown much higher levels of reliability in analysis of audio waveforms in podiatrists (134, 135). The differences in reliability between private and public sector podiatrists may be due in part, to the differences between the public and private participant groups. Although this study did not include any assessment of diagnostic accuracy of the Doppler for PAD, the participant group assessed by the public podiatrists had double the incidence of diabetes. Given increased rates and severity of PAD in this population(139) it is possible that more severe disease was present which was more easily detected and interpreted resulting in higher reliability.

The low reliability of clinical use of Doppler for peripheral arterial assessment demonstrated in this present study poses significant implications for ongoing patient care. Vascular assessments of patients tend to occur annually and are interpreted relative to previous results. The reliability of assessments is essential for accurate and appropriate management. Given the poor reliability of Doppler use that we found in this study, reliance on this test in isolation is problematic. Our results suggest that, in the small sample of podiatrists we studied, Doppler assessments are of limited use as a tool for ongoing monitoring in clinical practice and, at the very least, it is essential for other objective vascular tests (e.g. Ankle Brachial Index) to be incorporated in the annual screening process. Research has demonstrated that reliability of use and interpretation of Doppler has been achieved in other professions supporting the use of this form of assessment for ongoing monitoring in clinical practice (56, 140). Although Australia does not currently have any specific guidelines for lower limb vascular assessment in the general population at risk of PAD, the United Kingdom currently use

National Institute for health Care Excellence (NICE) guidelines, which recommend documentation and analysis of Doppler waveforms as part of an overall vascular assessment(141). Our results suggest that further skill development is required specifically for podiatrists to ensure clinical utility of Doppler use within the profession.

The results of this study need to be interpreted in light of several limitations. Firstly, the type of Doppler used may have influenced this study and it is unknown if similar results would be achieved if Doppler ultrasound units from alternative manufacturers had been or if participating podiatrists had used their regular equipment. However, the style of Doppler used in this study is one commonly used in clinical practice. Secondly, it was assumed that participating podiatrists had previously been trained in Doppler ultrasound assessment, so additional training was not provided. A training session provided prior to the study may have improved reliability, but we avoided this as we wanted results to be an accurate reflection of current skills of practicing clinicians. Nonetheless, raters were given a strict protocol for data collection, which realistically would be expected to improve the reliability of the assessment. Thirdly, clinical experience levels of raters ranged from one to eight years, which may have affected reliability. Although the least experienced podiatrist demonstrated the highest intra-rater reliability for clinical use of Doppler, so this seems unlikely. Finally, despite our best efforts to include podiatrists with a range of experience and undergraduate training from the two main areas of clinical practice (public and private), the clinicians participating in this study may not have been representative of the podiatry profession as a whole. Further investigation in other samples may assist in establishing the true reliability within the podiatry profession generally.

6.8 Conclusion

This study demonstrated that in Australian podiatrists in private and public practice visual Doppler waveform interpretation is the most reliable aspect of Doppler use, followed by Doppler audio interpretation. The poor reliability of the use of Doppler in the small cohort of practitioners in this study suggests that this form of assessment may be of limited use for ongoing monitoring. This finding

highlights the need for clinicians to engage in regular and ongoing continuing education in order to improve both collection of Doppler data and interpretation of visual waveforms and audio sounds concurrently. In addition our results suggest that reliance on only qualitative Doppler assessment for ongoing assessment of lower limb arterial status is problematic and that multiple methods of assessing vascular status should be employed.

6.8.1 Acknowledgments

This project was funded through a University of Newcastle New Staff Grant and Early Career Researcher Grant. Thank you to Port Stephens Podiatry and Hunter New England Area Health Service for volunteering their valuable staff for assistance with data collection for this project.

Chapter 7 Modified Method for Screening for Peripheral Arterial Disease

7.1 Preface

This chapter explores the diagnostic accuracy of a modified method for screening for PAD compared to the standard American (AHA) Heart Association Guidelines for screening for PAD. The modified method was developed based on results diagnostic accuracy and reliability studies included in this thesis and the survey of current vascular assessment techniques of Podiatrists which revealed that time taken for objective testing to be performed was a significant barrier to vascular assessments in clinical practice.

The advertising, consent forms, information statements and ethics approval relating to this study are available in Appendices 2, 3, 4, and 5. The study presented in Chapter 7 was conducted in accordance with ethical approval granted by: University of Newcastle Human Research Ethics Committee (reference number H-2013-0152).

The initial findings of this study were presented as an oral presentation at the Australian Podiatry Conference in 2015 and was a published abstract in the *Journal of Foot and Ankle Research*. This paper has been submitted to peer reviewed journal *The Foot* and is currently under review. The manuscript under review is located in Appendix 17.

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7.3 Abstract

7.3.1 Background

Routine lower limb vascular assessment is fundamental to ensuring early intervention and preventing complications related to PAD. Vascular assessment techniques vary widely in Podiatry practice with time required for undertaking objective pressure testing cited as a major barrier to performing assessment in accordance with current international guidelines. The aim of this study was to investigate the diagnostic accuracy of a modified version of current vascular assessment guidelines for detecting PAD. The modifications were made to reduce the time required to complete assessments to encourage more widespread application of accurate vascular assessment in Podiatry practice.

7.3.2 Method

Non-invasive vascular assessment objective tests including the ankle and toe brachial index and continuous wave Doppler were performed in a population at risk of PAD. CFDU was performed from the distal aorta into the foot as a reference standard. Diagnostic accuracy of tests conducted in accordance with American Heart Association (AHA) guidelines for the presence of PAD was compared to that of a modified version of the guidelines.

7.3.3 Results

One hundred and nineteen participants were included. Sensitivity of the targeted screening method (62%, 95%CI 47.17-75.35) was higher than the AHA method (49%, 95%CI 34.75 – 63.40), however specificity of the AHA method (94%, 95%CI 85.62 – 98.37) was higher than the targeted screening method (85%, 95%CI 74.26 – 92.60). Diagnostic accuracy of the AHA guidelines (74%) and modified method (73%) were similar.

7.3.4 Conclusion

Compared to current guidelines the modification used in this study did not significantly affect diagnostic accuracy and reduced the number of cases of undiagnosed disease in the study population and could reduce time taken for vascular assessment to be performed. This study highlights the difficulties in obtaining accuracy in lower limb vascular assessment in general.

7.4 Introduction

Identifying the presence and extent of peripheral arterial disease (PAD) through accurate lower limb vascular assessment is essential for reducing morbidity and mortality associated with the disease{Vaidya, 2014 #325}. Through early identification of PAD, complications such as ulceration, gangrene and amputation can be reduced or avoided using aggressive risk factor modification, provision of ongoing foot care and foot care education [2, 3, and 4]. It has been estimated that up to 90% of amputations are preventable [2, 3, 4] with adequate foot screening including vascular assessment playing a vital role in reducing complications and improving clinical outcomes [1]. Accurate and effective vascular assessment requires a complex reasoning process which takes into account a patient's vascular risk factors as well as an awareness of the effect of co-morbidities on the clinical efficacy of assessments techniques, and, subsequent interpretation of results to formulate an evidence-based management plan.

Podiatrists play a central role in conducting non-invasive lower limb vascular assessments in the general population. We have recently demonstrated that on average, podiatrists perform two vascular assessments per day however the type of the testing that is conducted during the assessments is extremely varied and, potentially inadequate for accurate PAD screening (142). Based on these findings, although there are several available international guidelines for performing screening for PAD, the uptake of these recommendations into clinical practice appears to be inconsistent(142). Time required to

perform recommended objective testing, particularly the ankle-brachial index (ABI) is the most widely nominated barrier to conducting appropriate vascular assessment (59, 142) with clinicians often relying on more quickly applied assessments including continuous wave Doppler (CWD) and pulse palpation. In addition there is growing evidence of the reduced accuracy of the ABI for detecting PAD in specific populations including those at risk of medial arterial calcification (MAC) particularly when co-existing with PAD and of a more distal distribution of atherosclerotic lesions including diabetes, renal disease, and older aged cohorts (8). In such patient populations further alternate testing including the toe brachial index (TBI) is frequently required, adding to the time required to complete an assessment. Our recent research suggests more quickly applied vascular assessment techniques such as the TBI and CWD may be suitable for use as first line assessment techniques for PAD assessment, particularly in older people and those with diabetes (66, 82). The aim of this study was to determine if a modified version of current guidelines in which the TBI was used initially in patient populations in which the ABI is known to be problematic could achieve similar diagnostic accuracy to testing protocols outlined in current guidelines where the ABI is used as the primary objective testing method for all people at risk of PAD.

7.5 Method

An extensive review of the literature was performed. Combined with recent research completed by the researchers(66, 82) which examined the diagnostic accuracy of the ABI, TBI and CWD in different populations at risk of PAD, a modified vascular assessment method was developed that is applied based on a patient's medical history. The modified method used the patient's risk factors for PAD combined with the known limitations of the ABI to assist the clinician choose the most accurate vascular test in the specific patient population being assessed. In the modified method the presence of diabetes and/or renal disease, or being of advanced age were used as a prompt for the clinician to perform a TBI

due to the reduced diagnostic accuracy of the ABI in these populations (8, 20, 66). In the modified method all other risk factors for PAD led the clinician to perform an ABI as this has been demonstrated to be an adequate test in the general population at risk of PAD and, in the absence of diabetes, renal disease or advanced age (40). All patients had CWD performed as this is an accessible, quick and relatively simple test to perform which has been shown to be reliable and accurate in populations requiring vascular screening and a useful adjunct to peripheral pressure testing (20, 56, 66, 110). The modified method was then directly compared to the American Heart Association (AHA) guideline(7) to determine relative diagnostic accuracy of both screening techniques for PAD. Ethics approval was obtained through the University of Newcastle ethics committee.

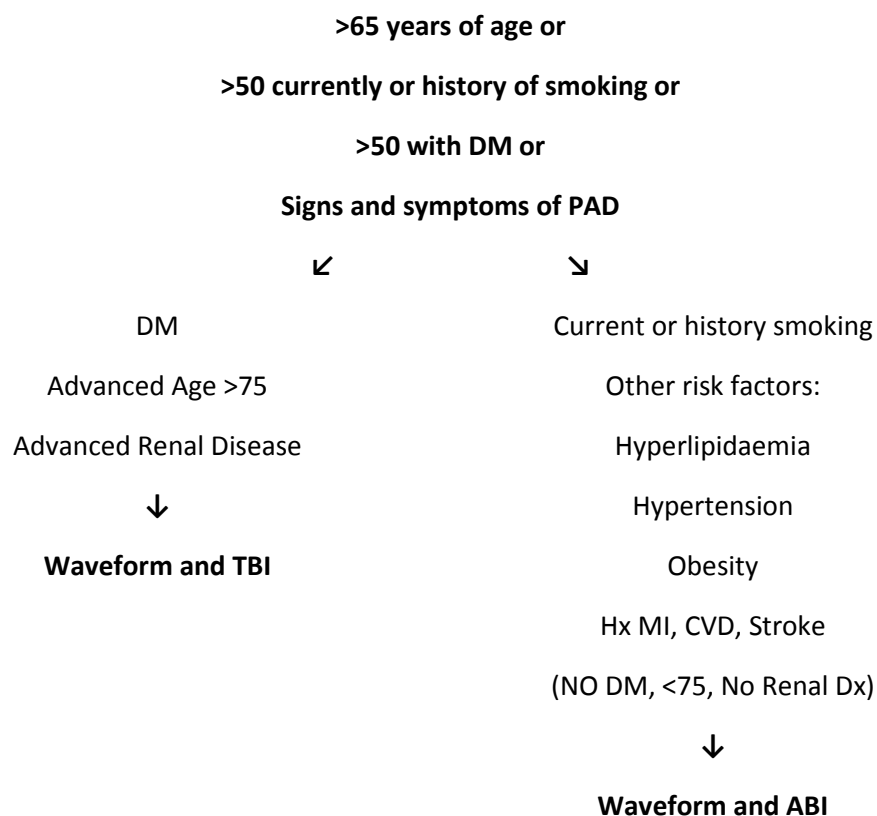


Figure 7.1 Flow chart of targeted screening method

Participants were recruited on a volunteer basis from two different locations, a community health centre in Newcastle, NSW, and a private podiatry practice in Nelson Bay NSW. Participants who fitted the AHA guidelines for peripheral vascular screening were

eligible to participate; i.e. patients over the age of 65, patients above the age of 50 with the presence of diabetes or currently smoking or patients with exertional leg pain.

Participants who were unable to comply with the testing protocol or who had a vasospastic disorder preventing TBI measurement were excluded. Testers included three vascular sonographers who performed colour duplex ultrasounds (CFDU) at a private clinic in Newcastle. CFDU reliability has previously been assessed (82) and found to be acceptable.

7.5.1 Experimental Procedure

All participants then attended a testing session at the vascular clinic with one of three ultra sonographers. During the testing session ABI and TBI measurements, Doppler waveform tracings and CFDU were performed on the right leg using methods and equipment described previously(66). CFDU was chosen as it has been demonstrated to be a valid imaging technique in non-invasive vascular diagnostic testing (91, 94). The right limb only was used to comply with the assumption of independence of data in statistical testing (95). Participants were asked to avoid alcohol, smoking, exercise and caffeine one hour prior to the testing session to avoid influencing pressure measurement (96). Participants were placed in a supine position and rested for at least 10 minutes prior to pressure measurements being taken. Room temperature was monitored with a thermometer and was maintained between 23°C and 25°C (88).

The AHA guideline was applied to the entire data set by a single researcher (PT) i.e. the ABI result was used unless it exceeded 1.4 in which case it was replaced by the TBI. These results were used to determine the diagnostic accuracy of the AHA guidelines for detecting PAD using CFDU as the reference standard. The modified method was also applied to the entire data set by a single researcher (PT) i.e. the ABI was used unless diabetes or renal failure was present or participants were aged over 75 years in which case the TBI value

was used. These results were used to determine the diagnostic accuracy of the targeted screening method for detecting PAD using CFDU as a reference standard.

For statistical calculations relating to diagnostic accuracy, presence of PAD was defined as one or more arteries with >50% stenosis (86, 97). Sensitivity, specificity, positive and negative predictive values and likelihood ratios were calculated with 95% confidence intervals for the AHA screening method and the targeted screening method. Calculations of diagnostic accuracy were performed using Microsoft Excel.

7.6 Results

A total of 120 participants were recruited (Table 7.1) however one participant was excluded as the CFDU scan was performed on a different day to the remainder of the vascular examination. An additional two participants were excluded from the targeted screening method due to missing toe pressure data. Generally the population was older, in accordance with the inclusion criteria. There were a high number of participants with diabetes (61%). Sensitivity of the modified method (62%, 95%CI 47.17-75.35) was higher than the AHA method (49%, 95%CI 34.75 – 63.40), however specificity of the AHA method (94%, 95%CI 85.62 – 98.37) was higher than the targeted screening method (85%, 95%CI 74.26 – 92.60) (Table 7.2). Overall the diagnostic accuracy of both methods were similar, with the AHA screening method 74% diagnostic accuracy and the targeted screening method 73% diagnostic accuracy.

Table 7.1: Participant Characteristics

| | |
|-------------------------------------|----------------|
| Total Participants (N) | 119 |
| Males n (%) | 75 (63.02) |
| Females n (%) | 44 (36.97) |
| Age Range (Years) | 53 – 92 |
| Diabetes n (%) | 73 (61.34) |
| Mean Age (years) | 73.1 (SDA 7.2) |
| Incompressible ankle pressure n (%) | 16 (13.44) |
| Distal PAD n (%) | 37 (31.09) |
| Proximal PAD n (%) | 7 (5.88) |
| Distal & Proximal PAD n (%) | 7 (5.88) |
| PAD n (%) | 51 (42.85) |
| Proximal Occlusions n (%) | 1 (0.84) |
| Distal Occlusions n (%) | 40 (33.61) |

^A=standard deviation, PAD= Peripheral arterial disease

Table 7.2: Results Table

| | Targeted Screening Method | | | AHA | | |
|---------------------------|---------------------------|---|-------------------------|--------|---|-------------------------|
| | % | • | 95% Confidence Interval | % | • | 95% Confidence Interval |
| Sensitivity | 62.00 | • | 47.17 to 75.35 | 49.02 | • | 34.75 to 63.40 |
| Specificity | 85.07 | • | 74.26 to 92.60 | 94.12 | • | 85.62 to 98.37 |
| Positive predictive value | 75.61 | • | 2.25 to 7.66 | 86.21 | • | 68.34 to 96.11 |
| Negative Predictive Value | 75.00 | • | 0.31 to 0.65 | 71.11 | • | 60.60 to 80.18 |
| Positive likelihood ratio | 4.15* | • | 2.25 to 7.66 | 8.33** | • | 3.09 to 22.45 |
| Negative likelihood ratio | 0.45* | • | 0.31 to 0.65 | 0.54 | • | 0.41 to 0.71 |
| Diagnostic Accuracy | 73.94 | • | | 74.78 | • | |

**Important likelihood ratio *May be important likelihood ratio

7.7 Discussion

This study investigated whether diagnostic accuracy of lower limb vascular screening for PAD can be achieved using a modified version of current guidelines designed to reduce the time taken to perform a vascular assessment. The results of this study indicate that the modified method had a higher sensitivity for PAD than when tests were conducted in accordance with the AHA guidelines, however lower specificity. Overall the two methods

had almost identical diagnostic accuracy (AHA method 74%, modified method 73%).

Although the ABI has been shown to have good sensitivity and excellent specificity across the general population (40) our recent research suggests uptake of the test by Podiatrists is poor with the time associated with performing the test cited as one of the most common reasons for this (142). Performing an ABI requires two ankle pressures per limb (dorsalis pedis and posterior tibial). The modified method we have proposed increases the number of people who have a TBI performed as the initial screening test. A TBI test is quicker to perform due to the need for only one toe pressure per limb to be taken. In addition the modified method ensures there will rarely be a time that clinicians will need to perform more than one form of lower limb pressure measurement in a single testing session. Both changes are likely to reduce the amount of time needed to perform objective non-invasive vascular testing.

Currently evidence suggests podiatrists rely on subjective findings including pulse palpation and visual appearance to identify PAD, while object assessment is often limited to continuous wave Doppler which we have shown to have poor reliability (142, 143). The modified method we have developed offers a potential mechanism to improve the diagnostic accuracy of vascular assessments performed by podiatrists by targeting the type of objective test to be used using medical history. In addition increasing the use of the TBI, which has been shown to have high reliability in diabetes and non-diabetes cohorts for initial testing for PAD (51), offers a more time efficient objective test that may be more widely adopted in clinical practice. There is also growing evidence that tests such as the TBI may be a valuable adjunct to clinical practice and could be more widely used. The TBI has been shown to have superior predictive capability than the ABI, with recent research showing that both toe pressures and TBI to be accurate predictors of wound healing and foot complications (46).

Of note our study demonstrates that neither screening method yielded a very high level of diagnostic accuracy, which re-enforces the difficulty of non-invasive lower limb vascular assessment in populations at risk of PAD. Further investigation into the diagnostic accuracy of non-invasive vascular assessment testing methods should be undertaken to ascertain what testing should be performed in populations at risk of PAD. The diagnostic accuracy of both the ABI and TBI should be elucidated using gold standard imaging as a reference standard. Further research that helps guide clinical practice could facilitate increased efficiency and increased accuracy when conducting vascular assessments, reducing the number of undiagnosed cases of PAD and ensuring timely intervention and appropriate management to prevent complications such as ulceration and infection and amputation.

7.7.1 Limitations

The results of this pilot study need to be considered in light of some significant limitations. The accuracy of both screening tools relies upon the individual accuracy of each diagnostic test. Each of the included tests, ABI and TBI have their own limitations with accuracy. The ABI in particular has been shown to have limited diagnostic accuracy in populations at risk of PAD. The reference standard used, CDFU, whilst a valid form of diagnostic imaging, has its limitations. Ideally angiography would be used as a reference standard however due to the prospective nature of the data collection this was not possible. Future research should use the gold standard in vascular imaging, angiography as a reference standard.

7.8 Conclusion

Modification of current international guidelines based on medical history to reduce the time burden of lower limb vascular assessment in clinical practice yields similar diagnostic accuracy to assessment undertaken in accordance with the guidelines. This study

highlights the difficulties in obtaining accuracy in lower limb vascular assessment in at risk populations and clinicians should consider using the TBI as an alternate screening tool given its high level of accuracy and predictive capabilities.

Chapter 8 Conclusion

This thesis has been an investigation of non-invasive vascular assessment techniques for the lower limb. Firstly, a systematic review was conducted to evaluate the current evidence base on the sensitivity and specificity of the TBI in detecting PAD (Chapter 2). This found that there were limited high quality diagnostic accuracy studies using valid diagnostic imaging as a reference standard. There was also a lack of consistency of TBI values used to represent presence of absence of pathology. This demonstrated the need for a high quality diagnostic accuracy study using diagnostic imaging as a reference standard.

A diagnostic accuracy study was then performed investigating the sensitivity and specificity of the TBI for detecting PAD in a mixed population at risk of the disease (Chapter 3). The population in this study was older, community-based and met current guidelines for undergoing lower limb vascular assessment to screen for PAD. The result of this study demonstrated much higher sensitivity (71%) for the presence of PAD than the ABI (45%). However, the ABI demonstrated slightly higher specificity (93%) than the TBI (79%). Comparative ROC analysis shown the TBI to be a superior clinical test (AUC0.77) with the negative predictive value of the ABI (69%) together with an AUC of 0.65 suggesting that the ABI is a test of limited clinical value for diagnosing PAD in a population at risk of the disease.

In the fourth Chapter the sensitivity and specificity of the ABI, TBI and CWD in people with diabetes was performed. This study further highlighted the difficulties that clinicians face when

assessing lower limb vascular status in this population. All three tests had lower levels of sensitivity and specificity in the population with diabetes compared to the control group.

Overall CWD had the highest sensitivity (74%) and specificity (92%) in detecting PAD in people with diabetes, followed by the TBI (63% sensitivity, 82% specificity) and the ABI (45% sensitivity, 92% specificity). ROC analysis demonstrated the TBI had an AUC of 0.75 whereas the AUC of the ABI was 0.58. This indicates that the ABI is a poor test for PAD in a diabetes cohort.

In chapter 5 a survey of Podiatrists in Australia and New Zealand about their vascular assessment techniques was conducted. This study is the first study to investigate clinical vascular assessment techniques used by Podiatrists in these countries. The study demonstrated that there were large variations in practice, depending on a Podiatrists work sector and years of experience. Contrary to current international guidelines for lower limb vascular assessment, less than half of Podiatrist respondents reported completing objective pressure measurements on a regular basis. Performance of vascular assessment was frequently reported to be based upon clinical signs and symptoms of PAD, rather than patient risk factors for PAD. The most commonly employed vascular assessment tool was qualitative hand held Doppler examination with 74% of respondents indicating they used this assessment technique as part of their assessment. Time, lack of financial incentive and concerns about technique were identified as key barriers in performing assessment.

In chapter 6 a reliability study examining hand-held Doppler use in podiatrists was conducted. This was the first study to examine all three aspects of Doppler use; clinical use and audio and visual waveform analysis. This study demonstrated that podiatrists had low levels of inter and intra-tester reliability for the clinical use of Doppler indicating this form of assessment is unacceptable for use of CWD for ongoing monitoring in clinical practice. Notably visual or audio interpretation of waveforms was much more reliable than when interpretation was combined with clinical application, suggesting poor clinical technique may be responsible for these

outcomes. Other health professions including medicine and nursing have demonstrated much higher reliability can be achieved with this form of assessment. Given the high diagnostic accuracy of CWD we demonstrated in a diabetes cohort, further training to improve technique is necessary improve reliability of hand-held Doppler use and therefore CWD amongst Podiatrists due to the clear benefits this method of assessment offers in ease of application, time for application and diagnostic capabilities.

Based on the results of these studies an evidence based, modified method of screening for PAD was formulated, which was presented in Chapter 7. The modified method was developed from the evidence provided from the preceding studies in chapter 2 to 6. Given the low reliability of hand-held Doppler examination, as shown in chapter 6, this was excluded as a testing method. Given the higher AUC of the TBI compared to the ABI in people with diabetes, as demonstrated in chapter 4, the TBI was used as a screening tool in people with diabetes. The targeted pathway was compared to the AHA current international guideline for lower limb vascular screening for PAD. Whilst the targeted screening method was more sensitive for detecting PAD (62%) than the AHA guideline (49%), it was less specific (Targeted 85%, AHA 94%). However, it may be a useful tool for clinicians, as it demonstrated similar diagnostic accuracy (Targeted 73%, AHA 74%) and could save time by avoiding the need for multiple pressure measurements in cases of MAC and reducing the number of pressures required (only one toe pressure instead of two ankle pressures per limb) in people with diabetes and older people which comprise a large proportion of patients requiring vascular assessment.

8.1 Strengths & Limitations

The systematic review presented in chapter 2 is the first to examine the sensitivity and specificity of the TBI for detecting PAD. Included studies were assessed for inclusion using strict criteria and data was extracted by two researchers independently. All studies were assessed for quality, reporting adequacy and risk of bias using the QUADAS-2 appraisal tool. All attempts were made

to promote a robust search strategy and a meta-analysis was employed to quantify the conclusions drawn. An exhaustive search for relevant literature was performed, however the volume of articles retrieved from database searches may have led to accidental omissions of relevant research. Six databases were utilised in the search, however researchers in the field were not contacted for any unpublished work. Authors were only contacted where information from included articles were missing and in only one case responded. Furthermore, strict exclusion criteria meant that multiple studies were not included as they did not use valid diagnostic imaging as a reference standard or did not calculate sensitivity and specificity. Overall there was a lack of high level evidence for determining diagnostic accuracy of the TBI for PAD. All of the included studies had small sample sizes with large variations in methodology and very specific populations. More extensive investigation is required using larger sample sizes and including more general populations at risk of PAD. This may lead to wider applicability of the test.

The study presented in chapter 3 was the first to examine the diagnostic accuracy of the ABI and TBI in a broad cross-section of patients at risk of PAD. These results have significant clinical relevance. The population used in this study were an older community based population at risk of PAD making the results highly generalizable to clinical practice and representing a cohort for which there are currently scant data available. The study was cross –sectional and included non-disease individuals reducing the risk of spectrum bias. Prior to our study existing research investigating the diagnostic accuracy of the TBI for PAD was restricted to specific populations, such as those with diabetes, or renal disease. The use of CFDU as the reference standard is also clinically relevant, as CFDU is the most commonly employed non-invasive imaging technique for detecting PAD. However, this also represents a limitation of this study as while CFDU is a valid form of non-invasive vascular assessment, is operator dependant. Although this study demonstrated in a small sample that inter-tester reliability was between sonographers involved in this study was acceptable, the results are never the less subjective and dependant

on clinician skill and experience. These findings therefore need to be substantiated with further research in a larger cohort and research in a diseased cohort where angiography can be used as the reference standard. The inter-tester reliability testing of CDFU was limited to ten due to financial restraints and may not be statistically robust, however, has similar participant numbers to another study of diagnostic accuracy using CDFU as a reference standard (10). The 95% confidence intervals demonstrate a wide range within which a repeated score can be expected to lie suggests variability inherent in the measurement. This is likely to be associated with the small sample size used for reliability testing with data likely to be too variable to make a precise estimate. Our convenience sample consisted of a large proportion of people with diabetes, and an older mean age, however this reflects the sample population who were attending a Podiatry and vascular clinic at risk of PAD.

The study presented in chapter 4, examined the diagnostic accuracy of non-invasive screening techniques in people with diabetes. The results of this study will guide clinical assessment as the accuracy of the three most commonly employed vascular assessment tools in clinical practice. This is the first study to undertake a comparative diagnostic accuracy evaluation of these tests in a population with diabetes against imaging as a reference standard. This study had a larger sample size than previous studies in this area and did not include the use of paired data. In addition this study was cross-sectional in nature and included non-diseased individuals reducing the risk of spectrum bias inflating the diagnostic accuracy of the tests.

Limitations of this study are similar to that of the study presented in chapter 3, however there are some specific additions. The post-hoc categorisation of the two groups may have limited the generalizability of the results, however, statistical analysis revealed there were no significant differences between the groups so it was unlikely to be the case. Although signs and symptoms that may indicate PAD were collected by the vascular sonographers at the time of scanning rigorous investigation and classification of these using the widely accepted Rutherford-Becker

classification system was not performed. Therefore from our data it was not possible to determine the relationship between symptom severity and the ABI, TBI and CWD in this cohort, limiting the clinical utility of our results. People with any form of neuropathy were included in the study population. A previous study has shown that diabetic neuropathy affected sensitivity of the ABI. However due to the small number of neuropathic participants recruited for our present study (only 15 out of the 117 participants) a separate sub analysis was not conducted on this group. It is possible that this may have affected our results as although incidence of peripheral neuropathy was evenly distributed between the groups, currently it is only diabetic peripheral neuropathy that is known to sensitivity of the ABI, and there is no data for peripheral neuropathy of other causes. The findings of this study support the need for a larger scale study investigating the comparative diagnostic accuracy of the ABI, TBI and CDW using angiography as the reference standard in a diabetes cohort.

The survey presented in chapter 5 was the first to examine the broader vascular assessment techniques of Podiatrists in Australia and New Zealand. The survey provided useful information about what prompts Podiatrists to perform vascular assessment and what constitutes a vascular assessment in Podiatric practice. The survey identified that time was the most significant barrier in completing a vascular assessment for most practitioners and also identified that rural practitioners would benefit most from continuing education as they were the most likely to identify as being unsure of technique.

Limitations of this study include the use of a non-validated survey which may have limited the external validity and reproducibility of the findings and the relatively small sample size compared to the total number of practicing Podiatrists which potentially reduces the extent to which our results are representative of the entire population of Podiatrists in Australia and New Zealand. Over-reporting and under-reporting are also possible, however piloting of the survey assisted in formulating specific answering methods including of nominal polytomous, ordinal

polytomous and dichotomous to reduce the likelihood of this. There are also some differences in delivery of Podiatric services between Australia and New Zealand, which will differently influence barriers in performing testing which could be explored further in future research.

The reliability study presented in chapter 6 was the first to examine all three aspects of hand-held Doppler examination when performed by Podiatrists. It also provided the first Australian-based reliability data for the most commonly employed vascular test reported by Australian and New Zealand Podiatrists. The use of four Podiatrists, with varying levels of clinical experience, and covering the two main areas of clinical practice (private and public practice) was a strength of the study. The study identified problems with the reliability of the test, which need to be targeted with ongoing clinical education.

Limitations of the study include the type of Doppler equipment used. Although the brand of Doppler used in this study is widely available this may which may have affected the ability of Podiatrists to perform the assessment reliably, particularly if it differed from the equipment they usually used involved. . It was assumed that participating Podiatrists had previously been trained in Doppler ultrasound assessment, so additional training was not provided. A training session provided prior to the study may have improved reliability, but this was avoided to ensure the results were an accurate reflection of current skills of practicing clinicians.

Nonetheless, the Podiatrists involved were given a strict protocol for data collection, which realistically would be expected to improve the reliability of the assessment. Finally, despite our best efforts to include Podiatrists with a range of experience and undergraduate training from the two main areas of clinical practice (public and private), the clinicians participating in this study may not have been representative of the Podiatry profession as a whole. Further investigation in other samples may assist in establishing the true reliability within the Podiatry profession generally.

The modified screening method presented in chapter 7 is the first of its kind to assist podiatrists in their non-invasive lower limb vascular assessment in populations in need of vascular screening. A large sample size reflective of patients seen in clinical practice was used and CDFU, a valid diagnostic imaging technique was used as a reference standard.

Limitations of this study include the accuracy of both the current guidelines and the modified method for diagnosing PAD relied upon the individual accuracy of each diagnostic test. Both the ABI and TBI have limitations with accuracy. The ABI in particular has been shown to have limited diagnostic accuracy in populations at risk of PAD. The reference standard used, CDFU, whilst a valid form of diagnostic imaging, has its limitations including operator error. Ideally angiography would be used as a reference standard however due to the cross sectional nature of nature of this study, this was not possible. Future research should use the gold standard in vascular imaging, angiography as a reference standard.

8.2 Recommendations and directions for future research

Based on the results of this thesis, there are some further studies, which should be pursued. A systematic review of the diagnostic accuracy of all commonly utilised non-invasive vascular tests in the lower limb should be undertaken, including the ABI, TBI and CWD and potentially a meta-analysis to quantify the results, if possible. This will further guide clinical practice for people requiring vascular screening to improve overall diagnostic accuracy of testing techniques.

Further diagnostic accuracy studies should be undertaken, including ABI, TBI and CWD using angiography as the reference standard. This will offer more conclusive evidence of the comparative diagnostic accuracy of these three commonly used screening tests compared to the gold standard diagnostic imaging technique. These studies will need to be retrospective due to the invasive nature of angiography.

Future directions for research may also include investigating other allied health professionals clinical assessment methods and reliability in performing non-invasive vascular assessment methods. Other vulnerable populations which are at risk of PAD, such as those with rheumatoid arthritis require further diagnostic accuracy studies, due to the complex vascular pathology demonstrated in this group.

The podiatry profession may benefit from the findings in this thesis to firstly inform their clinical practice. A podiatry-specific guideline, or practice brief may be of use regarding non-invasive vascular assessment of the lower limb. Secondly, lobbyists may be able to use the evidence in this thesis to inform government and private health insurers regarding gaining access to rebates for appropriate and timely non-invasive vascular assessments.

8.3 Concluding statement

The findings of this thesis add to the overall knowledge of non-invasive lower limb vascular assessment. The six original aims of this thesis have been addressed. The TBI has good test performance in detecting PAD in a mixed population at risk of the disease. In populations with diabetes, CWD waveforms yielded the highest diagnostic accuracy, followed by the TBI, while the ABI had poor performance. The vascular assessment techniques of Podiatrists are varied, not generally aligned with current lower limb vascular assessment guidelines and are potentially inadequate for accurate screening and ongoing monitoring for PAD in the lower limb.

Podiatrists demonstrate low reliability with clinical hand-held Doppler use, with our results suggesting this commonly used form of vascular assessment is of limited use in the ongoing monitoring of lower limb vascular function. Finally, a targeted screening method for lower limb vascular assessment yielded similar accuracy to the current international standard screening guideline.

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Appendix 1

A systematic review of the toe-brachial index for detecting peripheral arterial disease

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| Journal: | <i>Vascular Medicine</i> |
| Manuscript ID | VMJ-16-2135.R2 |
| Manuscript Type: | Review |
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| Complete List of Authors: | Tehan, Peta; University of Newcastle, Health and Medicine Santos, Derek; Queen Margaret University, Podiatry Chuter, Vivienne; University of Newcastle, Health and Medicine |
| Keywords: | Arterial Occlusive Diseases, Blood Pressure, Blood Pressure Determination, Peripheral Vascular Diseases, Peripheral Arterial Disease, Peripheral Vascular, Toes |
| Abstract: | <p>Objectives The toe-brachial index (TBI) is used as an adjunct to the ankle-brachial index (ABI) for non-invasive lower limb vascular screening. With increasing evidence suggesting limitations of the ABI for diagnosis of vascular complications, particularly in specific populations including diabetes cohorts, the TBI is being used more widely. The aim of this review was to determine the sensitivity and specificity of the TBI for detecting peripheral arterial disease (PAD) in populations at risk of this disease.</p> <p>Methods A database search was conducted to identify current work relating to the sensitivity and specificity of toe brachial indices up to July 2015. Only studies using valid diagnostic imaging as a reference standard were included. The QUADAS-2 tool was used to critically appraise included articles.</p> <p>Results Seven studies met the inclusion criteria. Sensitivity of the TBI for PAD was reported in all seven studies; sensitivity ranged from 45% to 100% and specificity was reported by five studies only; ranging from 16% to 100%.</p> <p>Conclusions This review suggests that the TBI has variable diagnostic accuracy for the presence of PAD in specific populations at risk of developing the disease. There was notable lack of large scale diagnostic accuracy studies determining diagnostic accuracy of the TBI in detecting PAD in different at risk cohorts. However, standardised normal values need to be established for the TBI to conclusively determine the diagnostic accuracy of this test.</p> |

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A systematic review of the sensitivity and specificity of the toe-brachial index for detecting peripheral arterial disease

ORIGINAL ARTICLE: REVIEW

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Objectives

The toe-brachial index (TBI) is used as an adjunct to the ankle-brachial index (ABI) for non-invasive lower limb vascular screening. With increasing evidence suggesting limitations of the ABI for diagnosis of vascular complications, particularly in specific populations including diabetes cohorts, the TBI is being used more widely. The aim of this review was to determine the sensitivity and specificity of the TBI for detecting peripheral arterial disease (PAD) in populations at risk of this disease.

Methods

A database search was conducted to identify current work relating to the sensitivity and specificity of toe brachial indices up to July 2015. Only studies using valid diagnostic imaging as a reference standard were included. The QUADAS-2 tool was used to critically appraise included articles.

Results

Seven studies met the inclusion criteria. Sensitivity of the TBI for PAD was reported in all seven studies; sensitivity ranged from 45% to 100% and specificity was reported by five studies only; ranging from 16% to 100%.

Conclusions

This review suggests that the TBI has variable diagnostic accuracy for the presence of PAD in specific populations at risk of developing the disease. There was notable lack of large scale diagnostic accuracy studies determining diagnostic accuracy of the TBI in detecting PAD in different at risk cohorts. However, standardised normal values need to be established for the TBI to conclusively determine the diagnostic accuracy of this test.

Introduction

Traditionally, the ankle-brachial index (ABI) has been used as a large vessel screening tool for clinical assessment of peripheral arterial disease (PAD) [1]. The ABI has been shown to be a sensitive and specific measure of detecting PAD in the general population [2]. However, there is increasing evidence to suggest that in specific populations there is a decrease in the diagnostic accuracy of the test [3, 4]. Medial arterial calcification (MAC), a stiffening of the arterial wall most commonly in infragenicular arteries used for the calculation of the ABI [5], is prevalent in the diabetic population, particularly in men and in older age groups, and is thought to reduce the diagnostic accuracy of the ABI [3]. Although MAC artificially inflates the ABI this cannot always be detected during routine clinical assessment as co-existent PAD may result in the ABI ratio presenting as normal or even low despite its presence [6].

Assessment of the small vessels within the foot and distal extremities also presents an issue for clinicians, as an ABI is not sensitive to occlusions and arterial disease below the ankle [7]. Current international guidelines recommend the toe brachial index (TBI) as an alternate screening method for PAD in the presence of an elevated ABI [8, 9], however the evidence base for the use of the TBI as a stand-alone diagnostic test remains low. The TBI is a ratio of the systolic toe pressure divided by the highest systolic brachial pressure. Systolic toe pressure can be performed by placing an appropriately sized occlusive pneumatic cuff (between 15 and 25mm) around the base of the proximal great or second toe, and a photoplethysmography (PPG) probe affixed to the distal pulp of the toe with adhesive tape (Figure 1). A continuous wave Doppler probe may also be used on the digital arteries in lieu of a PPG probe. Once a steady signal is obtained, the occlusive cuff is inflated by sphygmomanometer 20 mmHg above the last visual PPG waveform. The occlusive cuff is then slowly deflated with the pressure reading recorded when a consistent waveform returns [10, 11]. Normal values for TBI are universally

lower than the ABI, with normal being considered between $>0.6 - >0.75$ [12-15], with recent research suggesting that in normal populations the mean TBI is between 0.94 and 0.98 [16].

Accurate measurement of systolic toe pressure is dependent on a number of factors, including the control of ambient temperature. Similar to the ABI, strict control of patient factors needs to be undertaken to ensure test accuracy. Patients need to avoid smoking immediately prior to testing and lie completely flat with the legs and feet at the same level as the heart. In addition the TBI is affected by ambient temperature and room temperature needs to be maintained at 23 and 25 degrees Celsius [17]. Unlike the ABI, the TBI is also affected by Raynaud's disease or scleroderma and the measurements lacks utility in these populations[12]. When premeasurement protocols are adhered to the TBI can be performed reliably in clinical environments with both automated and manual devices[18]. The measurement has also been shown to be an accurate indicator of PAD in populations prone to MAC including those with diabetes-related PAD, sensori-motor neuropathy, and patients undergoing haemodialysis for end stage renal failure [4, 19, 20]. However there is currently no consensus on the diagnostic accuracy of this test for identifying PAD across populations at risk of the disease.

The aim of this paper is to systematically review the evidence evaluating diagnostic accuracy of the TBI in detecting PAD in at risk populations.

Materials and Methods

Search strategy

A database search was conducted by the primary researcher (PT) up to July 2015 using Ovid Medline (1946-2015), CINAHL Plus (1982 – 2015), Amed (Ovid), Web of Science, Scopus and Embase.

Search terms were derived (Table 1) and truncated versions using wildcard symbols were included to help broaden the search. No language restrictions were used. Reference lists of suitable articles were also hand searched for suitable work (Search strategy Figure 2).

Inclusion and exclusion criteria

Original articles that diagnosed PAD using valid diagnostic imaging as a reference standard were included. Studies which used symptoms as a primary indicator of the severity of PAD, or, where PAD was diagnosed by ABI, TBI or Doppler waveform analysis alone were excluded. Studies which included participants with vasospastic disorders were not included as this is known to affect the accuracy of toe pressure measurements [12].

Study selection and data extraction

Literature searching was undertaken by a single reviewer (PT) who independently searched each database using the search terms and retrieved abstracts. Abstracts were then reviewed independently by two reviewers (PT and VC) and relevant articles were assessed according to the selection criteria. If any difference of opinion arose, the study in question was referred to a third party. Articles considered relevant were then obtained in full text. Reference lists of retrieved articles were searched for further potentially relevant studies. Data on sensitivity and specificity of the toe-brachial index in detecting peripheral arterial disease along with reference standards, room temperature, pre-rest time and demographic data were extracted by two researchers (PT and VC) independently, with disagreements resolved by a third researcher (DS). In cases where journal articles contained insufficient information, attempts were made to contact authors to obtain missing details.

Methodological quality was assessed using the QUADAS-2 tool for systematic reviews of diagnostic accuracy [21].

Results

A total of 939 articles were retrieved for abstract review (Figure 2). Of these, 922 were excluded for lack of relevance. Seventeen articles in total were deemed relevant and full text versions were acquired. One study was excluded [22] as it was determining inter and intra tester reliability alone, and not diagnostic accuracy. One study [12] was excluded as it compared ankle-toe pressures rather than the TBI. Five studies [23-27] were excluded as they did not diagnose PAD using diagnostic imaging for the reference standard. One study was excluded [28] as it reported correlation only and data examining sensitivity and specificity in this group were reported in another included study [4]. One study was excluded as it examined patients with vasospastic disorders [24] and one other study was excluded as it diagnosed calcification and not PAD [25]. Seven studies met all inclusion criteria for this review [4, 20, 29-34].

All seven included studies were appraised for risk of bias using the Quality assessment of diagnostic accuracy studies (QUADAS-2) tool (Table 2, Figure 3).

Characteristics and overview of included studies

General

The studies included in this review examined sensitivity and specificity of TBI for detecting PAD in different cross sections of participants (Table 3). A total of 566 lower limbs were included in the seven studies. Of the 566 limbs, diagnostic imaging demonstrated 340 with PAD and 210 without PAD (16 limbs missing data[34]). Reported participant age varied significantly (Table 3) with most of the studies examining an older age group, with the exception of one study [20] which had a range of 35 – 89 years and one study which did not report age at all[30]. Both men and women were included in most studies, with all reporting a higher number of male participants [4, 30-34]. One study did not specify gender of participants[20]. Sample sizes varied amongst the seven studies ranging between 30 and 130 (Table 3). Most studies used

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4 paired data[4, 20, 30, 31], one was unclear [29, 33] and two studies used one limb per
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6 person[32, 34].
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10 11 12 **TBI Method** 13

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15 Details of methodological procedures of included studies are provided in Table 3. All of the
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17 included studies used the photoplethysmography method to measure the toe pressure included
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19 in the TBI and included a mix of manual and automated measurements. Pre- measurement
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21 rest time varied between three and fifteen minutes. Most studies used only one toe pressure
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23 measurement in the calculation of the TBI [20, 29, 30, 32, 34] whereas one study[4] took a
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25 mean of two measurements, taken at three and five minute intervals. Two studies did not
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27 describe the TBI method in sufficient detail to determine how many measurements were taken
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29 [31, 33]. Cut-offs for abnormal TBI values indicating PAD diagnosis also differed between the
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31 studies (<0.6 , <0.7 and <0.75). Room temperature was controlled in most studies and only
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33 varied by a few degrees, two studies did not detail room temperature[31, 33] and one study
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35 stated it was controlled but did not specify the temperature[34].
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39 40 **Quality assessment** 41

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43 A QUADAS-2 checklist was used to assess methodological quality and risk of bias of the
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45 included studies (Table 2, Figure 3). In all of the included studies it was unclear if the results of
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47 the index test were interpreted without knowledge of the reference standard. It was also
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49 unclear in all of the studies if the reference standard results were interpreted without
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51 knowledge of the index test. Details of the methodological quality assessed by the QUADAS-2
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53 tool are provided in Table 2 and Figure 3.
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57 A range of different diagnostic imaging methods were utilised by the included studies to
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59 diagnose PAD, all of which have varying levels of diagnostic accuracy. Four of the included
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studies used the gold standard angiography as a reference standard, two used colour duplex ultrasound and one used multi-detector row computed tomography. The diagnosis of PAD using these reference standards also differed significantly between studies. Several different anatomic criteria for diagnosis of PAD were used including >50% stenosis, >75% stenosis and one paper utilising the TASC classification system for interpretation of lower limb angiography. The index test, the TBI was also interpreted differently between studies with definition of a normal value ranging from >0.6 to >0.75.

The sample populations studied all included groups representing people either at risk of, or with current PAD (Table 3). However, the diagnosis of haemodynamically significant PAD, disease severity and presence of underlying comorbidities varied significantly between studies. Only one of the included studies recruited a non-diseased control group with a further four studies including non-diseased single limbs and/or participants from different at-risk or symptomatic cohorts. Two studies were stated to be performed retrospectively and included diseased limbs only. Underlying co-morbidities included diabetes, renal disease and mixed populations at risk of PAD that were symptomatic or non-symptomatic.

Sensitivity of TBI & Specificity of TBI

Sensitivity was reported in all seven studies and ranged from 45% to 100% (Table 3)-with the highest reported sensitivity by Park et al [30] who demonstrated 100% sensitivity of the TBI for detecting PAD in a population of thirty claudicating limbs with and without gangrene. The lowest sensitivity was reported by Okamoto et al [20] who demonstrated the TBI had 45% sensitivity for detecting PAD in a sample of seventy-two participants undergoing haemodialysis. Specificity of the TBI for diagnosing PAD was reported by five studies and ranged from 16% to 100% (Table 3). The highest reported specificity (100%) was also by Park et al [30] and the lowest specificity (16%) was demonstrated by Bunte et al [33].

Discussion

This review assessed the sensitivity and specificity of the TBI in detecting PAD. Seven studies were included which examined sensitivity and five studies examined specificity of the TBI for detecting PAD in a range of different populations. The TBI had varying degrees of sensitivity ranging from 45% to 100% and specificity from 16% to 100% depending on the population studied. The heterogeneity of the included populations was notable. Overall the TBI had good test performance in patients with diabetes, claudicants and those at risk of PAD and therefore may be a useful adjunct for vascular screening in these cohorts [9]. Lower sensitivity was reported in a population with renal disease, and poor specificity in a cohort with critical limb ischemia. Overall the variable results of measures of diagnostic accuracy of the TBI for PAD in the existing literature make it difficult to determine the clinical utility of this test. The variable diagnostic accuracy reported in the included studies is likely to have been influenced by both the heterogeneity of included participants groups and the methodological differences between studies.

Methodological quality was varied across the seven studies with a significant amount of heterogeneity across multiple domains. The QUADAS-2 assessment demonstrated that a large amount of information was unclear across the studies, particularly in relation to risk of bias with patient selection and the index test. Only one of the seven included studies recruited non-diseased participants, with two studies only including a diseased populations. The lack of equitable non-diseased groups in the majority of studies creates significant spectrum bias [35]. In addition it was unclear if there was appropriate operator blinding between the index and reference testing in all of the included studies which was also likely to lead to an increased risk of bias.

The interpretation of the TBI value for normal was also a likely factor in the varying levels of reported accuracy. Studies which used the lower value for normal of >0.6 were likely to have

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The interpretation of the TBI value for normal was also a likely factor in the varying levels of reported accuracy. Studies which used the lower value for normal of >0.6 were likely to have

overestimated the presence of disease compared to those using a much higher cut-off of >0.75. Unlike the ABI, the TBI does not have a well-established grading system or an agreed normal value which is correlated with gold standard diagnostic imaging. Currently there are discrepancies in the literature and any of the values used in the included studies i.e. 0.6, 0.7 or 0.75 can be considered as a cut-off for to differentiate normal and abnormal findings [4, 12, 14, 24]. Recent research has shown that in normal populations mean TBI values are 0.94 to 0.98, suggesting that the current cut-offs are too low and that underdiagnosis of PAD is likely [16]. The differing cut-offs used in the included studies are certain to have influenced the sensitivity and specificity.

The range of reference standards used by the included studies and differing anatomic criteria for diagnosis of PAD may also account for the varied levels of reported diagnostic accuracy. One study used multi-detector row computed tomography[20, 29], four used angiography[30, 31, 33, 34] and two used colour duplex ultrasound[4, 32]. Although angiography remains the gold standard in imaging for PAD the studies using this method used differing criteria to diagnose PAD making comparison between studies difficult. Whilst duplex ultrasound is the gold standard non-invasive imaging method for diagnosing PAD, and is used extensively clinically, it is operator-dependent. Both studies using duplex ultrasound reported high test-retest reliability however testing was conducted in a small sample and this form of imaging is known to have reduced diagnostic accuracy particularly in infragenicular vessels [36] and those affected by extensive MAC [37].

Methodological differences in performing the TBI measurement between studies may also have had an effect on the reported sensitivity and specificity outcomes of studies included in this review. The TBI is highly influenced by environmental factors and has limited utility in some populations such as those with vasospastic disorders[12]. External variables known to influence toe pressure measurement such as ambient temperature varied in the included

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4 studies. Limb temperature which is also known to influence toe pressure measurement was
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6 also not demonstrated by any of the included studies [38]. The included studies also reported
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8 differences in rest times prior to taking toe pressures, and use of serial (an average of two or
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10 more) and single measurements. There is evidence to suggest that toe pressures do not
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12 stabilise for the first 10 minutes [39] possibly affecting the accuracy of studies using shorter
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14 pre-measurement rest time frames. Furthermore use of one versus an average of two TBI
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16 measurements may also have affected measures of diagnostic accuracy. Although one
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18 measurement has been shown to have adequate diagnostic accuracy of the TBI for PAD[32],
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20 there has been no comparative investigation of the effect of single or serial TBI measurements.
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24 Our systematic review has demonstrated a paucity of data relating to the diagnostic accuracy
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26 of the TBI for PAD. Current international PAD screening guidelines recommended the TBI be
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28 used in the presence of an elevated ABI value[10]. It is possible the TBI can also provide
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30 additional information on small vessel PAD and disease below the ankle which is not detected
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32 by large vessel screening methods such as the ABI. Furthermore co-existence of PAD and MAC
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34 have been demonstrated to reduce the ABI to a normal value, failing to detect either disease
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36 process [7] and may render the ABI less accurate in specific populations including those with
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38 renal disease and diabetes. However based on current literature the value of the TBI for
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40 diagnosing PAD across populations at risk of the disease is inconclusive.
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43 44 **Limitations**

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47 We performed an exhaustive search for relevant literature, however the volume of articles
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49 retrieved from database searches may have led to accidental omissions of relevant research.
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51 Six databases were utilised in the search, however researchers in the field were not contacted
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53 for any unpublished work. Authors were only contacted where information from included
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55 articles were missing and in only one case responded. Furthermore, strict exclusion criteria
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57 meant that multiple studies were not included as they did not use valid diagnostic imaging as a
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reference standard or did not calculate sensitivity and specificity. Overall there was a lack of high level evidence for determining diagnostic accuracy of the TBI for PAD. All of the included studies had small sample sizes with large variations in methodology and very specific populations. More extensive investigation is required using larger sample sizes and including more general populations at risk of PAD in order to determine the true value of the TBI as a potential diagnostic tool.

Conclusions

This review highlights the lack of high level evidence available investigating the diagnostic accuracy of the TBI for PAD. Based on current literature it is not possible to determine the extent of the effectiveness of this test for diagnosing PAD in a clinical setting. We have also demonstrated there is a need for standardised normal values to be established for the TBI before diagnostic accuracy for PAD can be conclusively determined.

Conflict of Interest Statement

None of the authors have any conflicts of interest to declare

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Table 1: Search Terms

| | |
|----|---|
| S1 | Toe brachial ind* |
| S2 | Toe brachial ind* AND sensitivity |
| S3 | Toe brachial ind* AND specificity |
| S4 | Toe brachial ind* AND peripheral arterial disease |
| S5 | Toe brachial ind* AND ischemia |
| S6 | Toe brachial ind* AND lead |
| S7 | Toe brachial ind* AND lower extremity |
| S8 | S2 AND S3 AND S4 |
| S9 | Toe brachial ind* AND peripheral arterial* |

| | |
|-----|---|
| S10 | S2 AND S3 AND S9 |
| S11 | Toe brachial* |
| S12 | Toe brachial* AND sensitivity AND specificity |
| S13 | S2 AND S3 AND S5 |
| S14 | S2 AND S3 AND S6 |
| S15 | S2 AND S3 AND S7 |

Table 2: Risk of bias of included studies using Quadas-2 tool

| Study | Risk of Bias | | | | Applicability Concerns | | |
|---|-------------------|------------|--------------------|-----------------|------------------------|------------|--------------------|
| | Patient Selection | Index Test | Reference Standard | Flow and Timing | Patient Selection | Index Test | Reference Standard |
| Bunte | ? | ? | 😊 | ? | 😊 | ? | 😊 |
| Okamoto | ? | ? | 😊 | 😊 | 😊 | 😊 | 😊 |
| Park | 😞 | ? | 😊 | ? | 😞 | 😊 | 😊 |
| Suominen | 😊 | ? | 😊 | ? | 😊 | ? | ? |
| Tehan | 😊 | ? | 😊 | 😊 | 😊 | 😊 | 😊 |
| Weinberg | ? | ? | ? | 😊 | 😊 | 😊 | 😊 |
| Williams | 😊 | ? | 😊 | 😊 | 😊 | 😊 | 😊 |
| 😊 Low Risk 😞 High Risk ? Unclear Risk | | | | | | | |

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Table 3: Summary of studies of sensitivity and specificity of the toe-brachial index in detecting peripheral arterial disease

| Study | Year | Limbs | Mean age (SD) ^a | Population | Reference standard | PAD Diagnosis | TBI Method | Sensitivity % | Specificity % | With Disease (n) | Without Disease (n) | TBI normal limit | Room Temperature (°C) | Pre-measure ment rest time (minutes) |
|--------------|------|-------------|----------------------------|--|--------------------|---------------------------|------------|---------------|---------------|------------------|---------------------|------------------|-----------------------|--------------------------------------|
| Bunte[33] | 2015 | 31 (n=31) | 66 | Critical limb ischemia | Angiography | Stenotic >50% or occluded | Manual | 92 | 16.7 | 25 | 6 | ≥0.7 | | 5-10 |
| Tomoto [20] | 2006 | 72 (n= 36) | Range 35-89 | Renal patients | MDCT ^c | Stenosis >75% | Automated | 45.2 | 100 (98.1) | 46 | 26 | ≥0.6 | 23 | - |
| Park[30] | 2012 | 30 (n=15) | - | Diabetes, claudicating +/- gangrene | Angiography | - | Automated | 100 (96.3) | 100 (97.8) | 13 | 17 | ≥0.6 | 22 | 15 |
| Sigmenin[33] | 2008 | 68 (n=68) | 69.5 (11.7) | Patients with elevated ABI | DSA ^d | Stenosis >50% | Automated | 99 | - | 68 | - | ≥0.6 | Controlled | 10 |
| Lehan[32] | 2015 | 119 (n=119) | 73.1 (7.2) | Patients at risk of PAD | CDU ^b | Stenosis >50% | Manual | 71 | 79 | 51 | 68 | ≥0.7 | 23 - 25 | 10 |
| Wahberg [31] | 2013 | 116 (n=92) | 71.2 (11.2) | Patients attending vascular laboratory | DSA ^d | TASC II | - | 92 | - | 100 | - | ≥0.7 | - | - |
| Williams [4] | 2005 | 130 (n=68) | Range 63 - 69 | Diabetes and control | CDU ^b | Stenosis >50% | Manual | 100 | 76 | 37 | 93 | ≥0.75 | 25 | 3-5 |

^aStandard Deviation, ^bColour duplex ultrasound, ^cMulti-detector computed tomography, ^ddigital subtraction angiography

TBI = toe-brachial index, ABI = ankle brachial index. Corrected values for sensitivity and specificity in parentheses. TASC II= TASC II classification scheme

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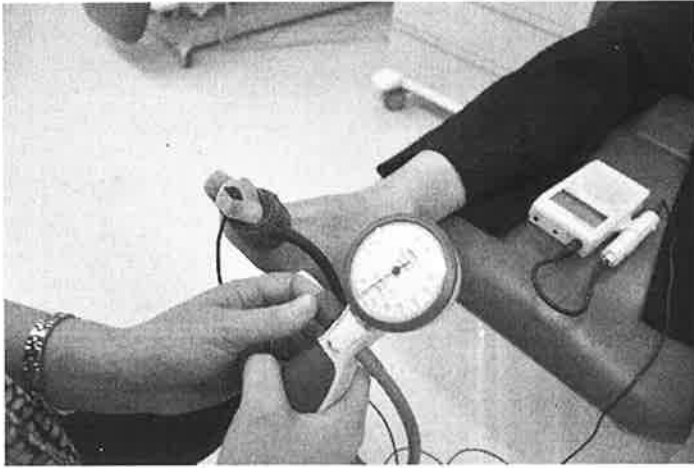


Figure 1: A systolic toe pressure being measured using the manual hand-held photoplethysmography (PPG) method. Continuous wave Doppler can also be used on the digital arteries in lieu of a PPG probe.

Appendix 2



THE UNIVERSITY OF
NEWCASTLE
AUSTRALIA

Do you have problems with your circulation??

Would you like to be involved in clinical research?

The University of Newcastle Podiatry Discipline is conducting research examining different methods of assessing circulation in the lower limb.

We need approximately 100 people with circulation issues.

We are currently looking for members of the community who would be willing to volunteer to participate in this study. If you are interested in being involved in this research please ask for an information sheet from reception. Thankyou.

Research project: The ability of toe pressure to detect the presence of peripheral arterial disease

HREC Approval:

Chief Investigator: Dr. Vivienne Chuter

Contact: Vivienne.Chuter@newcastle.edu.au

Appendix 3

Appendix 4

AUTHORITY TO RELEASE HEALTHCARE INFORMATION

Project Title: The sensitivity and specificity of the Toe-Brachial Index (TBI) as a measure of blood flow in the presence of peripheral arterial disease, and development of a more comprehensive TBI value classification system.
HREC Approval: H-2010-1230

Dr. Vivienne Chuter, Ms Peta Craike & Dr Alan Bray
Document Version 1 dated: 23/03/11

Patient's Name: _____ Date of Birth: _____

I request _____ (General Practitioner) _____ to

release healthcare information of the patient named above to:

Name: _____ Peta Craike _____

Address: _____ University of Newcastle, Health Precinct, PO Box 127, Ourimbah, New South Wales _____

Postcode: _____ 2258 _____

This request and authorisation applies to:

Healthcare information relating to the following treatment, condition, or dates:

_____ Medical History, medications summary and results of most recent blood tests. _____

This information is required as part of a research project investigating clinical evaluation of peripheral arterial supply entitled: The sensitivity and specificity of the Toe-Brachial Index (TBI) as a measure of blood flow in the presence of peripheral arterial disease, and development of a more comprehensive TBI value classification system.

(Please note that any information provided will be held in accordance with the University of Newcastle's policies and procedures regarding the storage and protection of confidential data)

I authorise the release of release of information detailed above, which is relevant to this research project

Patient Signature: _____ Date Signed: _____

Print Name: _____

Appendix 5



Information Statement for the Research Project:

The sensitivity and specificity of the Toe-Brachial Index (TBI) as a measure of blood flow in the presence of peripheral arterial disease, and development of a more comprehensive TBI value classification system.

HREC Approval: H-2010-1230

Dr. Vivienne Chuter, Ms Peta Craike, Dr Alan Bray
Document Version 1 dated: 23/3/11

You are invited to participate in the research project identified above which is being conducted by Dr. Vivienne Chuter, Senior Lecturer, Ms Peta Craike, Lecturer, from the Discipline of Podiatry at the University of Newcastle and Dr Alan Bray, Vascular Surgeon.

Why is the research being done?

The purpose of the research is to determine the reliability and accuracy of a toe pressure to detect arterial disease in the legs and feet.

Who can participate in the research?

We are seeking men and women with or without Type 2 diabetes and have no history of major heart or kidney problems and do not have any other systemic illnesses such as scleroderma or rheumatoid arthritis etc.

Unfortunately if you currently smoke or have a disease which causes problems with your blood supply to your feet such as vasculitis, if you have problems with your veins or suffer regularly from very swollen feet or ankles, if you have widespread numbness in your feet NOT related to diabetes, if you have heart or kidney disease, or, if you have Raynaud's disease, you are not eligible to participate in this study.

What choice do you have?

Participation in this research is entirely your choice. Only those people who give their informed consent will be included in the project. Whether or not you decide to participate, your decision will not disadvantage you.

If you do decide to participate, you may withdraw from the project at any time without giving a reason and have the option of withdrawing any data which identifies you.

What would you be asked to do?

If you agree to participate, you will be asked to:

- Release the results of your vascular exam to researchers.
- Undergo a non-invasive, painless neurological assessment to test the nerve function in your feet. This will involve measuring your ability to feel light touch on the skin of your foot and to detect vibration of a tuning fork when it is applied to various parts of your foot.
- Provide consent for researchers to request relevant information from your medical records relating to your history of diabetes mellitus (if applicable) and other chronic diseases and current medications.

How much time will it take?

Participation in this project will add an additional 15 minutes to your vascular exam. The vascular exam will take approximately 90 minutes.

What are the risks and benefits of participating?

There are no risks associated with participating in this research. The benefits are that you will have a thorough assessment of the blood supply and nerves in your legs which may help to prevent future complications.

How will your privacy be protected?

All data will be stored securely at the University of Newcastle by the Principal Researcher and only members of the research team will have access to this data. Data will be retained for at least 5 years. Following completion of the three parts of this study your name will be replaced by a code ensuring all your data is unidentifiable. Data will only be saved on electronic file in a coded form which de-identifies you. All data will be deleted/destroyed after 5 years. All data will be stored securely at the University of Newcastle by the principal researcher. Electronic data will be stored on a password protected computer, paper-based records will be stored in a locked filing cabinet. Information obtained from medical records will not feature in the reporting of this research. Disposal of data will be performed in accordance with university policy (Research Data and Materials Management Procedure document number 000870)

How will the information collected be used?

The results of this study will disseminated via national and international conferences and for papers in scientific journals. Medical information will not feature in the reporting of this research.

All participants in the study will receive a summary of the results in hard copy. Individual test results will be provided to each participant or their medical practitioner if preferred.

What do you need to do to participate?

Please read this Information Statement and be sure you understand its contents before you consent to participate. If there is anything you do not understand, or you have questions, contact the researcher.

Appendix 6

HUMAN RESEARCH ETHICS COMMITTEE

APPROVAL TO CONDUCT HUMAN RESEARCH

| | |
|--|---|
| To Chief Investigator or Project Supervisor: | Doctor Viv Chuter |
| Cc Co-investigators / Research Students: | Miss Alex Barwick Mr Sean Lanting Miss Jennifer Sonter Ms Peta Craike Mrs Sarah Casey Mr Priten Solanki Doctor Fiona Hawke |
| Re Protocol: | The validity, reliability and predictive value of the Toe-Brachial Index as a measure of peripheral blood flow in people with diabetes mellitus |
| Date: | 15-Oct-2013 |
| Reference No: | H-2010-1230 |

Thank you for your recent application to the University of Newcastle Human Research Ethics Committee (HREC) for approval of the protocol identified above.

Details of previous approvals for Initial, Renewal and Variation applications are available upon request.

A *Certificate of Approval* is enclosed.

**THE CERTIFICATE AND THIS ADVICE ARE TO BE RETAINED
THEY ARE IMPORTANT DOCUMENTS**

- Note any comments related to the approval.
- **Where the HREC is the lead or primary HREC, if the research requires the use of an Information Statement, ensure the Reference No. is inserted into the complaints paragraph in the approved document(s) prior to distribution to potential participants.**
- Where the research is the project of a higher degree candidate, it is the responsibility of the project supervisor to ensure that the candidate receives this approval advice.

Conditions of Approval

This approval has been granted subject to you complying with the requirements for *Monitoring of Progress*, *Reporting of Adverse Events*, and *Variations to the Approved Protocol* as detailed below.

PLEASE NOTE:

In the case where the HREC has "noted" the approval of an External HREC, progress reports and reports of adverse events are to be submitted to the External HREC only. In the case of Variations to the approved protocol, you will apply to the External HREC for approval in the first instance and then Register that approval with the University's HREC.

- **Monitoring of Progress**

Other than above, the University is obliged to monitor the progress of research projects involving human participants to ensure that they are conducted according to the protocol as approved by the HREC. The *Certificate of Approval* identifies the period for which approval is granted and your progress report schedule. A progress report is required on an annual basis, you will be advised when a report is due.

- **Reporting of Adverse Events**

1. It is the responsibility of the person **first named on the Certificate** to report adverse events.
2. Adverse events, however minor, must be recorded by the investigator as observed by the investigator or as volunteered by a participant in the research. Full details are to be documented, whether or not the investigator, or his/her deputies, consider the event to be related to the research substance or procedure.
3. Serious or unforeseen adverse events that occur during the research or within six (6) months of completion of the research, must be reported by the person first named on the Certificate to the (HREC) by way of the Adverse Event Report form within 72 hours of the occurrence of the event or the investigator receiving advice of the event.
4. Serious adverse events are defined as:
 - Causing death, life threatening or serious disability.
 - Causing or prolonging hospitalisation.
 - Overdoses, cancers, congenital abnormalities, tissue damage, whether or not they are judged to be caused by the investigational agent or procedure.
 - Causing psycho-social and/or financial harm. This covers everything from perceived invasion of privacy, breach of confidentiality, or the diminution of social reputation, to the creation of psychological fears and trauma.
 - Any other event which might affect the continued ethical acceptability of the project.
5. Reports of adverse events must include:
 - Participant's study identification number;
 - date of birth;
 - date of entry into the study;
 - treatment arm (if applicable);
 - date of event;
 - details of event;
 - the investigator's opinion as to whether the event is related to the research procedures; and
 - action taken in response to the event.
6. Adverse events which do not fall within the definition of serious, including those reported from other sites involved in the research, are to be reported in detail at the time of the annual progress report to the HREC.

- **Variations to approved protocol**

If you wish to change, or deviate from, the approved protocol, you will need to submit an *Application for Variation to Approved Human Research*. Variations may include, but are not limited to, changes or additions to investigators, study design, study population, number of participants, methods of recruitment, or participant information/consent documentation. **Variations must be approved by the (HREC) before they are implemented** except when Registering an approval of a variation from an external HREC which has been designated the lead HREC, in which case you may proceed as soon as you receive an acknowledgement of your Registration.

Linkage of ethics approval to a new Grant

HREC approvals cannot be assigned to a new grant or award (ie those that were not identified on the application for ethics approval) without confirmation of the approval from the Human Research Ethics Officer on behalf of the HREC.

With best wishes for a successful project.

Professor Allyson Holbrook
Chair, Human Research Ethics Committee

For communications and enquiries:
Human Research Ethics Administration

Research Services
Research Integrity Unit
The Chancellery
The University of Newcastle
Callaghan NSW 2308
T +61 2 492 17894
F +61 2 492 17164
Human-Ethics@newcastle.edu.au

RIMS website - <https://RIMS.newcastle.edu.au/login.asp>

Linked University of Newcastle administered funding:

| Funding body | Funding project title | First named investigator | Grant Ref |
|--|---|--------------------------|-----------|
| University of Newcastle/New Staff Grant(**) | The sensitivity of the Toe-Brachial Index as a measure of blood flow and predictor of peripheral arterial disease-related morbidity in diabetes mellitus | Casey Sarah, | G1100060 |
| Ramaciotti Foundations/Establishment Grant(**) | The reliability of the toe-brachial index as a measure of blood flow and predictor of peripheral arterial disease-related morbidity and mortality in diabetes mellitus | Chuter Viv, | G0190501 |
| University of Newcastle/New Staff Grant(**) | The sensitivity and specificity of the Toe-Brachial Index (TBI) as a measure of blood flow in the presence of peripheral arterial disease, and development of a more comprehensive TBI value classification system. | Craike Peta, | G1100272 |

HUMAN RESEARCH ETHICS COMMITTEE

Certificate of Approval

| | |
|---|---|
| Applicant: (first named in application) | Doctor Viv Chuter |
| Co-Investigators / Research Students: | Miss Alex Barwick Mr Sean Lanting Miss Jennifer Sonter Ms Peta Craike Mrs Sarah Casey Mr Priten Solanki Doctor Fiona Hawke |
| Protocol: | The validity, reliability and predictive value of the Toe-Brachial Index as a measure of peripheral blood flow in people with diabetes mellitus |

In approving this protocol, the Human Research Ethics Committee (HREC) is of the opinion that the project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research, 2007*, and the requirements within this University relating to human research.

Note: Approval is granted subject to the requirements set out in the accompanying document **Approval to Conduct Human Research**, and any additional comments or conditions noted below.

| | |
|--|---------------------------------------|
| Details of Approval | |
| HREC Approval No: H-2010-1230 | Date of Initial Approval: 16-Dec-2010 |
| Approval <i>Approval will remain valid subject to the submission, and satisfactory assessment, of annual progress reports. If the approval of an External HREC has been "noted" the approval period is as determined by that HREC.</i> | |
| Progress reports due: Annually. <i>If the approval of an External HREC has been "noted", the reporting period is as determined by that HREC.</i> | |
| Approval Details | |
| Initial Application 16-Feb-2011 Approved The Committee ratified the approval granted by the Chair on 16/12/10 under the provisions for expedited review. | |
| Variation 17-Aug-2011 Variation to: | |
| 1. Add Peta Craike (student researcher) to the research team. | |
| 2. Add an additional participant group (100) to the project comprised of people with varying extents of peripheral arterial disease being managed a vascular clinic. This group will provide additional information about | |

the sensitivity of the toe brachial index to the extent of arterial disease. Participants will be recruited via a study advertisement in the vascular clinic.

3. Link the project to a new source of funding (G1100272).

- Vascular Clinic Recruitment Poster
- Consent Form for Peripheral Arterial Disease Cohort (v1, dated 23/3/11)
- Authority to Release Healthcare Information form for Peripheral Arterial Disease Cohort (v1, dated 23/3/11)

Approved

The Committee ratified the approval granted by the Chair on 22/07/11 under the provisions for expedited review.

Variation

22-Feb-2012

Variation to:

1. Introduce a new participant group to be recruited from people attending the University of Newcastle Podiatry Clinic at Wyong Hospital. Participants will visit the clinic on three occasions and will have their ankle, arm and tow pressures tested after a designated resting period of 5-15 minutes.

2. Add the University of Newcastle Podiatry Clinic at Hunter Street as a new research site.

3. Reduce the number of exclusion criteria for Participant Group 6 (people with varying degrees of peripheral arterial disease). Exclusion criteria to be removed include pyrexia and skin changes associated with significant venous disease.

4. Update the address provided for the University of Newcastle Podiatry Clinic from Kanwal Medical Centre to Wyong Hospital.

5. Update the address provided for the Alan Bray Vascular Clinic to 9 Sydney St, Gateshead

6. Add Dr Jennifer Sonter to the research team

- Participant Information Statement (Alan Bray Vascular Clinic), Version 2 dated 28.11.2011

-Participant Information Statement, (UoN Podiatry Clinic/ Central Coast Radiology), Version 3 dated 28.11.2011

-Participant Information Statement ('Resting Measurement Group') Version 1 dated 28.11.2011

- Consent Form, Version 1 dated 28.11.2011

Approved

The Committee ratified the approval granted by the Deputy Chair on the 20th of December 2011 under the provisions for expedited review.

Variation

20-Jun-2012

Variation to:

1. Add Mr Sean Sadler (student researcher) and Mrs Fiona Blinkhorn (co-supervisor) to the research team.

2. Recruit an additional 70 participants. The testing undertaken by this group will be to determine the effect of rest time prior to testing (5, 10 or 15 minutes) and the reliability of toe pressure measurements using an automated device (Systoe, Atys Medical). Inclusion criteria for this participant group will be amended to align with American Heart Association guidelines for vascular testing (50-65 smoker and/or diabetics, or, 65+ non-smoker/non-diabetic).

2. Recruit a further 30 participants to undergo comparison of toe pressure measurement using a hand held non-automated pressure device to tow pressures using an automated device. Inclusion criteria are again adjusted to

align with American Heart Association guidelines for vascular testing.

3. The sources of recruitment have been expanded to include clients from:

- Berkeley Vale and Long Jetty Podiatry;
- University of Newcastle Podiatry Clinics at Wyong Hospital and Hunter St ,Newcastle; and
- University of Newcastle Ourimbah Campus.

- Information Statement and Consent Form for Toe Brachial Pressure Measurements at 5, 10 and 15 minutes of Rest (v2, dated 26/04/2012)
- Information Statement and Consent Form for Reliability of Toe Pressure Taken by an Automated Device (v2, dated 26/04/2012)
- Information Statement and Consent Form for Reliability of Two Different Techniques for Measuring Toe Pressure (v2, dated 26/04/2012)
- Recruitment Flyers

Approved

Variation

17-Apr-2013

Variation to:

1. Add Sean Lanting and Alex Barwick to the research team.
2. Recruit a new participant group made up of an additional 30 participants from the same population as the existing protocol
3. Invite the new participant group to undertake measurements of resting toe pressure and reactive hyperaemia. Reactive hyperaemia will be measured first using a photoplethysmographic probe and then a laser Doppler.
4. Conduct a second measurement of toe pressure following a period of occlusion. (blocking of the blood vessels)

This process will occur twice with two different clinicians in session one and will then repeated at session two, 7-10 days later

- Participant Information Statement, version 2 dated 27.2.2013

Approved

The Committee ratified the approval granted by the Human Research Ethics Officer on 19 March 2013 under the provisions for expedited review.

Authorised Certificate held in Research Services

Professor Allyson Holbrook
Chair, Human Research Ethics Committee

Appendix 7

Sensitivity and Specificity of the Toe-Brachial Index for Detecting Peripheral Arterial Disease

Initial Findings

Peta Tehan, B Health Sc (Pod) G Cert Wound Care, Alan Bray, MBBS, FRACS (Vascular Surgery), MD, DDU, Ruth Keech, Grad Dip Ultrasonography, DMU (Vascular), Richard Rounsley, Dip Health Sc (Pathology), B Med Sc, DMU (Vascular), Angela Carruthers, B Health Sc, RN, Vivienne Helaine Chuter, B Pod (Hons), PhD

Objectives—The toe-brachial index (TBI) is an alternative to the ankle-brachial index (ABI) in screening for peripheral arterial disease (PAD); however, there is limited evidence comparing their diagnostic accuracy. This study compared the diagnostic accuracy of the ABI and TBI in a population at risk of PAD.

Methods—The sensitivity and specificity of the ABI and TBI were determined by color duplex sonography. Receiver operating characteristic (ROC) analysis was performed.

Results—A total of 119 participants were recruited (75 male and 44 female). The sensitivity for PAD was highest for the TBI (71%; ABI, 45%), and the specificity was highest for the ABI (93%; TBI, 78%). Receiver operating characteristic analysis indicated that the TBI (ROC area, 0.77; $P = .0001$) had greater clinical efficacy for diagnosis of PAD than the ABI (ROC area, 0.65; $P = .005$).

Conclusions—In specific populations, the TBI may have greater clinical efficacy than the ABI for diagnosis of PAD.

Key Words—ankle-brachial index; peripheral arterial disease; sensitivity; specificity; toe-brachial index; vascular ultrasound

Received October 1, 2014, from the School of Health Sciences, Faculty of Health, University of Newcastle, Ourimbah, New South Wales, Australia (P.T., V.H.C.); and Vascular Health Care, Gateshead, New South Wales, Australia (A.B., R.K., R.R., A.C.). Revision requested November 5, 2014. Revised manuscript accepted for publication December 23, 2014.

This project was funded by a University of Newcastle new staff grant and early career researcher grant.

Address correspondence to Peta Tehan, B Health Sc (Pod) G Cert Wound Care, School of Health Sciences, University of Newcastle, PO Box 127, Ourimbah NSW 2258, Australia.

E-mail: peta.craike@newcastle.edu.au

Abbreviations

ABI, ankle-brachial index; CI, confidence interval; ICC, intraclass correlation coefficient; PAD, peripheral arterial disease; ROC, receiver operating characteristic; TBI, toe-brachial index

doi:10.7863/ultra.15.14.09071

Peripheral arterial disease (PAD) involves progressive stenosis and, potentially, occlusion of arterial beds supplying the lower extremity through the development of atherosclerosis. The risk of PAD increases with age, affecting 21% of those older than 65 years, and in the presence of risk factors such as smoking, diabetes, dyslipidemia, and hypertension.^{1,2} As many people with PAD are asymptomatic, the condition is highly under-recognized³ and if untreated can ultimately lead to the development of wounds, gangrene, and amputation.⁴ The presence of PAD is also an indicator of systemic arterial disease and is associated with an increased risk of a cardiovascular event⁵ and associated mortality.⁶

Traditionally, the ankle-brachial index (ABI) has been used as a noninvasive method for assessing peripheral vascular status in patients at risk of PAD. An ABI is calculated by taking the higher of the systolic pressure of the dorsalis pedis or posterior tibial artery and dividing it by the highest systolic brachial pressure.⁷ An ABI of greater than 1.0 is considered normal,⁷ with a ratio of less than 0.90 considered diagnostic for PAD.⁸

The ABI is a highly sensitive and specific screening tool for PAD.^{8,9} The relative simplicity of application and low cost make the ABI an easily accessible assessment tool for many clinicians. However, recent research suggests that the diagnostic accuracy of the ABI is reduced in specific populations. Decreased sensitivity and specificity of the ABI for the presence of PAD have been demonstrated in the elderly and in the presence of renal disease or diabetes.^{10,11} It is widely recognized that higher rates of medial arterial calcification in these populations leads to stiffening of the arterial wall, preventing full compression of the lower extremity arteries, inflating the ABI value, and reducing the clinical efficacy of the test.^{10,12} An elevated ABI (>1.4), is generally accepted to be indicative of medial arterial calcification.⁸ However, further complicating lower extremity vascular testing in these patients, the presence of medial arterial calcification is also associated with substantial lower extremity atherosclerosis.¹³ The combination of these two conditions may result in a normal ABI in the presence of substantial PAD due to partial loss of compressibility of the artery, leading to undiagnosed PAD. Additionally, more distal anatomic distribution of atherosclerotic lesions occurring in both people with diabetes and those of advanced age² further affects the ABI, with an inability to detect stenosis of arteries at the level of, or distal to, the ankle by ankle pressure measurements.¹²

Alternative methods of noninvasive vascular assessment may be performed using small vessel-testing methods such as the toe-brachial index (TBI). The TBI is a ratio of the systolic toe pressure divided by the highest systolic brachial pressure.⁷ Normal values for the TBI are less than those for the ABI, with 0.7 and greater considered normal.^{14–16} The TBI has been shown to be an accurate indicator of PAD in specific populations who are prone to medial calcification, including those with diabetes-related PAD, sensorimotor neuropathy,¹⁰ and patients undergoing hemodialysis for end-stage renal failure.^{11,17} The TBI is by no means a new assessment method; however, its use remains limited, particularly in the vascular laboratory.

Despite the potentially wide applicability of the TBI as a test for PAD, evidence evaluating its diagnostic accuracy is limited. There is also a lack of comparative data assessing the relative diagnostic accuracy of the TBI and ABI for the presence of PAD using diagnostic imaging as the reference standard. The aim of this study was to examine the sensitivity and specificity of the TBI and the comparative diagnostic accuracy of the TBI versus the ABI for detecting PAD in a population of patients at risk of PAD.

Materials and Methods

This study was undertaken at a private vascular clinic in Lake Macquarie, New South Wales, Australia. Ethical approval was obtained from the University of Newcastle Human Research Ethics Committee. All participants provided written informed consent before participation.

Over 28 months (August 2011–December 2013), participants were recruited on a volunteer basis from a private vascular clinic and a podiatry service in Newcastle. Inclusion criteria were set in accordance with current guidelines for lower extremity vascular screening¹⁸: participants older than 65 years or older than 50 years with a history of diabetes, current smoking, exertional leg pain, or nonhealing wounds. Exclusion criteria were contraindications to ankle, toe, and brachial pressure measurements, including active hallux or leg ulceration preventing cuff placement, history of deep venous thrombosis, lymphedema, and previous bilateral mastectomy or vasospastic disorders.

All participants attended a single testing session at the vascular clinic with 1 of 3 sonographers. During the testing session, ABI and TBI measurements, color duplex sonography, and neurologic testing were performed on the right leg. Color duplex sonography was chosen, as it has been demonstrated to be a valid imaging technique for noninvasive vascular diagnostic testing.^{3,19} The right limb only was used to comply with the assumption of independence of data in statistical testing.²⁰ The medical history was obtained from each participant. Participants were asked to avoid alcohol, smoking, exercise, and caffeine 1 hour before the testing session to avoid influencing pressure measurements.²¹ Participants were placed in a supine position and rested for at least 10 minutes before pressure measurements. A subset of 10 participants randomly selected returned within 1 week of the initial testing session. At the second testing session, all tests (vascular and neurologic) were repeated by a different clinician blinded to the results of the initial test to establish intertester reliability.

Color duplex sonography was performed with either a CX-50 ultrasound system (Philips Healthcare, Best, the Netherlands) or a LOGIQ I system (GE Healthcare, Little Chalfont, England). All ankle and brachial pressures and continuous wave Doppler tracings of pedal arteries were taken with a Parks 1050c Vascular Minilab (Parks Medical Electronics, Inc, Aloha, OR) equipped with 8.2-MHz continuous wave Doppler, a Parks standard 10-cm inflatable cuff, and an ERKA switch blood pressure gauge (ERKA Kallmeyer Medizintechnik GmbH & Co. KG, Bad Tölz, Germany). Toe pressures were obtained with

a photoplethysmograph probe, a Hokanson toe pressure cuff (1.6, 1.9, or 2.5 cm; D. E. Hokanson, Inc, Bellvue, WA), and an ERKA switch blood pressure gauge. The size of the cuff used was in accordance with current guidelines for cuff size.⁷

Room temperature was monitored with a thermometer and was maintained between 23°C and 25°C.²² Bilateral brachial systolic pressures were obtained in all participants with a Parks continuous wave Doppler system and a handheld sphygmomanometer. Ankle systolic pressures of the right leg only were taken by placing the brachial pressure cuff around the lower leg, proximal to the medial and lateral malleoli. Both dorsalis pedis and posterior tibial artery pressures were recorded, with the higher of the two being used for calculation of the ABI. Toe systolic pressures were obtained by placing a photoplethysmograph probe directly on the distal pulp of the right great toe, affixed with adhesive tape. Once a clear signal was obtained, a toe cuff was placed immediately proximal to the photoplethysmograph probe. If the great toe was too large for the toe cuff, the second toe was used. The cuff was then inflated to 20 mm Hg above the last visual photoplethysmograph signal. The cuff was then slowly deflated, and the pressure reading was recorded when a consistent waveform returned. The TBI was calculated by dividing the toe pressure by the highest brachial pressure.

Color duplex sonography was performed after pressure measurements, from the abdominal aorta to the distal ankle on the right side as the reference standard. For calculations relating to diagnostic accuracy, the presence of PAD was defined as 1 or more arteries with greater than 50% stenosis.^{23,24} Distal disease was defined as disease distal to and including the proximal popliteal artery, and proximal disease was defined as disease from the common iliac artery to the distal superficial femoral artery. The sensitivity, specificity, diagnostic accuracy, and positive predictive value of the ABI and TBI for the presence of PAD were calculated by using the standard cutoff scores for an abnormal ABI of 0.90 or less and greater than 1.4, consistent with current screening guidelines,⁷ and the suggested cutoff score for the TBI of less than 0.70.^{9,25} Ankle pressures exceeding 200 mm Hg were considered incompressible.⁷

Receiver operating characteristic (ROC) analysis was performed for the ABI and TBI and was calculated with SPSS version 19 statistical software (IBM Corporation, Armonk, NY). Standard deviations were derived for all means, sensitivities, specificities, and positive and negative predictive values. Calculations of diagnostic accuracy were performed with Microsoft Excel (Microsoft Corporation, Redmond, WA).

Intertester reliability of color duplex sonography was calculated by using the presence or absence of PAD as a dichotomous variable and an unweighted Cohen κ statistic. Intraclass correlation coefficients (ICCs) with 95% confidence intervals (CIs) were calculated to determine the level of agreement between test and retest for the ABI and TBI. All ICC values for intertester reliability were interpreted according to cutoffs suggested by Fleiss.²⁶ Interpretation of the Cohen κ statistic was performed by the method proposed by Landis and Koch.²⁷ All reliability analyses were conducted with SPSS version 19 software.

Results

A total of 120 participants were recruited. One participant was excluded, as the color duplex sonographic scan was performed on a different day from the remainder of the vascular examination. Participant characteristics are included in Table 1.

The mean ABI was 1.13 (SD, 0.23). The mean fell within the normal range for an ABI measurement. The ABI results ranged from 0.34 to 2.0, which indicated that the participants' peripheral arterial status included both those with substantial PAD and substantial medial arterial calcification. The ABI was more likely to fail to diagnose the presence of PAD. Receiver operating characteristic analysis showed that the ROC area for an ABI set at less than 0.9 or greater than 1.4 for detecting PAD was only 0.65 (95% CI, 0.54–0.77; Figure 1). This result indicates that the ABI was a poor test in this population.²⁸ The sensitivity and negative predictive value of 45% and 69%, respectively, for the ABI reflect an increased risk of failure to diagnose existing disease (Table 2). However, the specificity (93%) and

Table 1. Participant Characteristics

| Characteristic | Value |
|--------------------------------------|------------|
| Total participants, n | 119 |
| Male, n (%) | 75 (63.02) |
| Female, n (%) | 44 (36.97) |
| Age range, y | 53–92 |
| Diabetes, n (%) | 73 (61.34) |
| Mean age (SD), y | 73.1 (7.2) |
| Incompressible ankle pressure, n (%) | 16 (13.44) |
| Distal PAD, n (%) | 37 (31.09) |
| Proximal PAD, n (%) | 7 (5.88) |
| Distal and proximal PAD, n (%) | 7 (5.88) |
| PAD, n (%) | 51 (42.85) |
| Proximal occlusions, n (%) | 1 (0.84) |
| Distal occlusions, n (%) | 40 (33.61) |

positive predictive value (82%) were high, indicating that the ABI is relatively unlikely to falsely diagnose PAD.

The mean TBI was 0.71 (SD, 0.21) which was within the normal range. The ROC area was 0.77 (95% CI, 0.69–0.87), indicating that the TBI was a fair test in this population (Figure 1). The sensitivity of the TBI for detecting PAD was 71%, indicating that the TBI was quite likely to accurately detect PAD in this population (Table 2). The specificity was 79%, which, whereas lower than the ABI result, suggests that the TBI is relatively unlikely to falsely detect PAD.

The intertester reliability of the color duplex sonographic scans between the 3 sonographers was high ($\kappa = 0.78$; $P < .01$).²⁷ The ICCs showed good test-retest reliability of the toe pressures (ICC, 0.80; 95% CI, 0.39–0.95) and moderate reliability of the brachial pressures (ICC, 0.66, 95% CI, 0.09–0.90) and ankle pressures (ICC, 0.62; 95% CI, 0.03–0.89).²⁹

Discussion

The results of this study indicate that overall the TBI has much higher sensitivity (71%) for the presence of PAD than the ABI (45%). However, the ABI had slightly higher specificity (93%) than the TBI (79%). The negative predictive value of the ABI (69%) together with poor ROC analysis (0.65) has significant clinical implications, leaving approximately one-third of participants falsely undiagnosed.

Previous research studies have reported a range of results regarding the sensitivity of the ABI, depending on the cohort of participants studied. In healthy individuals, the ABI has been shown to be highly sensitive (95%)^{30–33}; however, in patients with diabetes or renal disease, the sensitivity of the ABI has been shown to be considerably lower (29.9%–53%).^{10,11} The population in this study met current criteria for lower extremity vascular screening and consisted of an older group with a large number of people with diabetes. The findings of our study suggest that there may be a high prevalence of concurrent medial arterial calcification and

PAD within the general population, requiring peripheral vascular screening. This prevalence is expected, as this population is older and at higher risk of comorbidities such as diabetes, which are both associated with the development of medial arterial calcification. Although medial arterial calcification is known to affect the accuracy of the ABI in people with diabetes, renal disease, and older age, the prevalence of clinical and subclinical medial arterial calcification within the general population remains controversial.

Medial arterial calcification has been estimated to affect approximately 13.3% of men and 6.9% of women in a population at risk of PAD.³⁴ However, cutoff points for diagnosis of medial arterial calcification by the ABI have been questioned. Further complicating matters, the presence of subclinical medial arterial calcification has been proposed, which goes undetected by the ABI.⁴ It is therefore difficult to determine the extent to which the accuracy of the ABI may be affected and the efficacy of using the measurement as a screening tool. Current recommendations suggest that a toe pressure be used only in the presence of an ABI elevated to greater than 1.40; however, these recommendations do not address the presence of PAD coexisting with medial arterial calcification, which may reduce the ABI to within a normal range.^{12,35–37} This study supports previous findings indicating that the ABI has decreasing levels of sensitivity in a population at risk of PAD and concurrent medial arterial calcification. Conversely, the specificity of the ABI (93%) in this study was higher than that of the TBI (79%). Previous studies in different populations have shown that the ABI had differ-

Figure 1. Receiver operating characteristic analysis: TBI versus ABI. Diagonal segments are produced by ties.

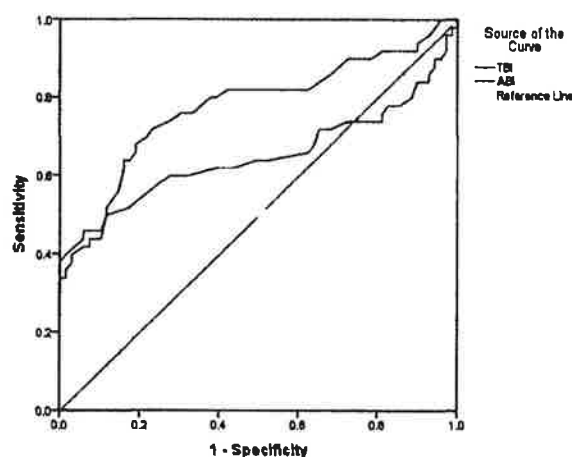


Table 2. Diagnostic Results

| Characteristic | ABI | TBI |
|---------------------------------------|-------------|--------------|
| Mean (SD) | 1.13 (0.23) | 0.71 (0.21) |
| Sensitivity (95% CI), % | 45 (32–59) | 71 (57–81) |
| Specificity (95% CI), % | 93 (84–97) | 79 (67–87) |
| Positive predictive value (95% CI), % | 82 (63–93) | 72 (57–83) |
| Negative predictive value (95% CI), % | 69 (58–78) | 77 (65–86) |
| ROC area (<i>P</i>) | 0.65 (.005) | 0.77 (.0001) |

ing specificity rates (88%–100%)^{10,11}; however, this study included a mixed population with a larger sample size, and participants rested for 10 minutes, which has been shown to be the ideal rest time for ankle pressures.³⁸ This factor may have resulted in higher specificity rates.

Previous research in small cohorts of people with diabetes has shown that the TBI had superior sensitivity for the presence of PAD compared to the ABI.¹⁰ In this study, the TBI also had superior sensitivity and ROC results compared to the ABI. Although the specificity of the TBI was lower than that of the ABI, the TBI still fared better overall, showing a more significant result with ROC analysis. This finding suggests that the TBI has a wider applicability to a broader population at risk of PAD than previously believed.

In this study, 61% of the participants had diabetes, and the average age was older than previously reported. As both advanced age and diabetes are associated with more distally distributed atherosclerotic lesions,² these participants had higher rates of distally located stenoses. Our finding of increased sensitivity of the TBI for PAD in our sample is congruent with previous suggestions that the TBI has high sensitivity for more distally distributed disease and should therefore be a test of choice in populations at risk of such disease patterns. However it is important to note that in this study, a photoplethysmograph probe was used to measure the TBI. There are other methods of obtaining toe pressures, including strain gauge plethysmography, oscillometric plethysmography, and laser Doppler imaging; therefore, our study applies only to the photoplethysmograph method.

In addition to being highly sensitive, our results also suggest that the TBI had higher specificity (79%) than previously reported in small groups of people with diabetes (61%–65%).¹⁰ However, this difference may be due to the effect of diabetes on microcirculation and impairment of vasodilatory capacity, which would remain undetected by large vessel–screening methods such as the ABI and color duplex sonography.²² The presence of microvascular disease that drops the TBI without coexistent PAD would reduce the specificity of the test for PAD. Conversely, in studies examining people with chronic renal failure, the specificity of both the TBI and the ABI has been shown to be up to 100%, potentially due to the high rates of medial arterial calcification in this population without the presence of peripheral microvascular disease.¹¹

To our knowledge, a study assessing the sensitivity and specificity of the TBI across a mixed population at risk of PAD has not been reported previously. However, the findings of this study need to be considered carefully

because of some potential limitations. Although a valid form of noninvasive vascular assessment, color duplex sonography is heavily dependent on operator skill, and whereas an intertester reliability study was performed and shown to be adequate, the results are nevertheless subjective and dependant on clinician skill and experience. The intertester reliability testing for color duplex sonography was limited to 10 participants due to financial restraints and may not have been statistically robust; however, it had a similar participant number as another study of diagnostic accuracy using color duplex sonography as a reference standard.¹⁰ Our convenience sample consisted of a large proportion of people with diabetes and an older mean age; however, this factor reflects the sample population, who were attending a podiatry and vascular clinic and were at risk of PAD. People older than 75 have a higher prevalence of PAD.³ People with diabetes are at increased risk of PAD, with disease occurring earlier and more aggressively, with a more distal distribution frequently reported.³⁹ The results of this study therefore reflect a population at substantial risk of PAD with more distally located stenoses.

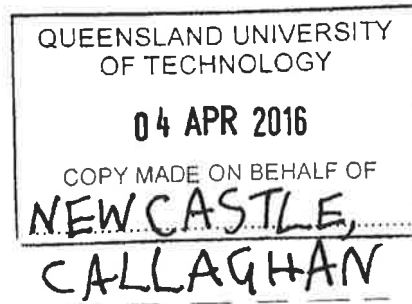
In conclusion, this study demonstrated that the TBI had greater sensitivity than the ABI in participants at risk of PAD. The specificity of the TBI was lower than that of the ABI but higher than previously reported. These results suggest that the TBI may be a more clinically effective form of vascular assessment in this population. Further research in larger cohorts is required to further elucidate the sensitivity and specificity of the TBI in broad populations at risk of PAD.

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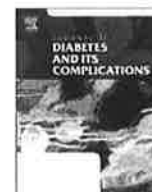
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Appendix 8



Non-invasive vascular assessment in the foot with diabetes: sensitivity and specificity of the ankle brachial index, toe brachial index and continuous wave Doppler for detecting peripheral arterial disease

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ABSTRACT

Background & Aims: Non-invasive lower limb vascular assessment in people at risk of peripheral arterial disease (PAD) including those with diabetes is crucial. There is evidence that standard assessment techniques such as the ankle-brachial index (ABI) may be less effective in people with diabetes. However there is limited evidence for other frequently used tests including continuous wave Doppler (CWD), and the toe-brachial index (TBI). The aim of this study was to determine the sensitivity and specificity of ABI, CWD and TBI in a population with, and without diabetes.

Methods: Participants with and without diabetes who met current guidelines for vascular screening were recruited, and CWD waveforms, an ABI and a TBI were obtained from the right lower limb. Diagnostic accuracy was determined using colour duplex ultrasound (CFDU). Receiver operating characteristic curves were calculated.

Results: 117 participants were recruited, seventy-two with diabetes and forty-five without diabetes. CWD had the highest sensitivity in people with diabetes (74%) and without (84%). CWD also had the highest specificity in people with diabetes (74%) and without (84%) compared to both TBI and ABI. In participants with diabetes, the ABI was a poor test, area under the curve: 0.58 ($p = 0.27$).

Conclusions: CWD waveform is more likely to detect significant PAD compared to ABI and TBI in people with and without diabetes.

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1. Introduction

Non-invasive lower limb vascular assessment is essential for detecting peripheral arterial disease (PAD). Early detection and on-going monitoring of PAD through routine screening facilitates effective management of the condition and can ultimately prevent foot complications such as wounds, gangrene and amputation (Singh, 2005). As PAD commonly occurs with systemic atherosclerosis (Mukherjee & Cho, 2009), timely diagnosis is also necessary to ensure cardiovascular risk factors are managed to avoid more serious complications such as heart attack and stroke.

People with diabetes are at a four-fold increased risk of developing PAD. In this cohort the condition also progresses more quickly, is more severe than in the general population, tends to affect distal rather than proximal arteries and is more likely to result in ischaemic ulceration and amputation (Jude, Oyibo, Chalmers, & Boulton, 2001; Norgren et al.,

2007; Rodu et al., 2013). Due to the heightened risk of foot complications associated with diabetes-related PAD, accurate non-invasive vascular assessments of the lower limb are essential in this population.

Both the ankle-brachial index (the ratio of ankle arterial pressure to that in the brachial artery) and toe-brachial index (the ratio of toe arterial pressure to that in the brachial artery) are non-invasive vascular assessment techniques used to quantitatively evaluate arterial status of the lower limb (Hirsch et al., 2006; Rooke et al., 2011). Although the ankle-brachial index (ABI) is used more widely, it has been demonstrated to have significant limitations in the presence of diabetes-related PAD including inability to detect distally located PAD and poor accuracy in the presence of medial arterial calcification, a condition associated with diabetes resulting in incompressible lower leg arteries (Potier, Halbron, Bouilloud, Dadon, & Le Doeuff, 2009).

As the toe-brachial index (TBI) measurement is taken more distally in the lower limb there is a greater likelihood of detecting arterial pressure changes caused by stenosis located below the knee as occur in the presence of diabetes (Chen, Lawford, Shah, Pham, & Bower, 2012). The digital arteries are also less likely to be affected by MAC (Brooks et al., 2001; Sacks et al., 2002; Sahli et al., 2004), and

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these factors potentially make the TBI a more sensitive test for PAD than the ABI across diabetes cohorts. However, there are varying levels of diagnostic accuracy of the TBI in the limited current literature. Although there is some evidence that the TBI has superior sensitivity in the presence of diabetic neuropathy, in groups with diabetes alone, the TBI has shown lower sensitivity and specificity compared to ABI. In control populations, the TBI has demonstrated lower levels of specificity compared to ABI, but higher sensitivity (Williams, Harding, & Price, 2005). However as these findings varied significantly between small groups ($n = 7$ to $n = 41$) and the study eligibility criteria were tightly controlled, most significantly excluding people with a smoking history or significant cardiovascular disease which are known to be associated with PAD, there is a need for more investigation in larger samples which reflect patients that clinicians encounter in clinical practice.

Continuous wave Doppler ultrasound (CWD) is frequently used alongside pressure measurement in non-invasive lower limb vascular assessment to assist in diagnosis of PAD, monitor disease progression and estimate severity (Rodu et al., 2013). CWD is a low-cost screening tool that is accessible and quick to use. However, diagnostic accuracy of CWD for detecting PAD is not well known in people with diabetes, with a single small study demonstrating that CWD has higher sensitivity and specificity for diabetes-related PAD than the ABI or TBI (Williams et al., 2005). As interpretation of the CWD waveform relies upon the skill of the operator, and is considered more subjective than pressure measurements, further larger scale investigation of the utility of the assessment in a diabetes-cohort is required.

The aim of this study was to determine individual sensitivity and specificity of the ABI, TBI and CWD for detecting significant PAD in people with and without diabetes to further inform clinical use of non-invasive lower limb vascular assessments.

2. Materials and methods

This was a prospective, single centre, cross sectional case-control study to determine the diagnostic accuracy of three non-invasive lower limb vascular assessment techniques in people with and without diabetes. This study was undertaken at Vascular Health Care, a private vascular clinic in Lake Macquarie, New South Wales, Australia. Ethical approval was obtained from the University of Newcastle Human Research Ethics Committee. All participants provided written informed consent prior to participation.

Over a period of twenty-eight months (August 2011–December 2013) a volunteer convenience sample was recruited via flyer advertising from a private vascular clinic and a community health service in Newcastle. The following inclusion criteria were set in accordance with current guidelines for lower extremity vascular screening (Hirsch et al., 2006; Rooke et al., 2011): participants aged over 65 years; or aged over 50 years with a history of diabetes; or aged over 50 years currently smoking; or with exertional leg pain or non-healing wounds. Exclusion criteria were: known allergy to coupling gel, presence of a wound preventing Doppler probe or ankle cuff placement or previous bilateral mastectomy preventing bilateral brachial blood pressure examination.

All participants attended a single testing session at the vascular clinic with one of three ultrasonographers. During the testing session CWD waveforms, ankle pressures and the hallux toe pressure were taken from the right side. Brachial pressures were performed bilaterally. Colour duplex ultrasound (CFDU) was performed on the right side from the distal aorta to the foot and used as the reference standard. CFDU was chosen as it has been demonstrated to be a valid imaging technique in non-invasive vascular diagnostic testing (Collins et al., 2007; Criqui, 2001). The right limb only was used to reduce the incidence of type 1 error (Menz, 2005). Following the initial testing session medical history was obtained from the general practitioners of individual participants. A subset of 10 participants randomly selected returned within one week of the initial testing session. At the second testing session all vascular

tests were repeated by a different clinician blinded to the results of the initial test to establish inter-tester reliability.

Sonographers were trained in performing a basic neurological assessment by an experienced Podiatrist. The neurological assessment was performed by testing for protective sensation with the 10 gram Semmes-Weinstein monofilament at 10 points on the plantar surface of both feet. The 128 Hz tuning fork was applied at the apex of the hallux bilaterally to assess vibration perception (Boulton et al., 2008). Participants were classified as insensate if they failed either examination – more than four sites were undetected for the test of protective sensation or there was absent vibration perception.

CFDU was performed with either a Phillips CX-50 or GE Logiq-I. Pressures and CW Doppler tracings of pedal arteries were taken using the Parks Vascular Mini Lab 1050c, 8.2 Mhz continuous wave Doppler, Parks standard 10 cm inflatable cuff, and ERIKA switch blood pressure gauge. Size of cuff used was in accordance with current guidelines for cuff size (Hirsch et al., 2006). Room temperature was monitored with a thermometer and was maintained between 23 °C and 25 °C (Sawka & Carter, 1992). Participants were asked to avoid alcohol, smoking, exercise and caffeine one hour prior to the testing session to avoid influencing pressure measurement (Campbell, Chockalingham, Fodor, & McKay, 1990). Participants were placed in a supine position and rested for at least 10 minutes prior to pressure measurements being taken. Bilateral brachial systolic pressures were obtained in all participants using a Parks continuous wave Doppler and hand-held sphygmomanometer. Ankle systolic pressures of the right leg only were taken by placing the brachial pressure cuff around the lower leg, proximal to the medial and lateral malleoli. Both dorsalis pedis and posterior tibial artery pressures were recorded, with the higher of the two being used in calculation of the ABI. A single toe systolic pressure was obtained by placing a photoplethysmograph (PPG) probe directly on the distal pulp of the right great toe affixed with adhesive tape. Once a clear signal was obtained, a toe cuff was placed immediately proximal to the PPG probe. In the event of the great toe being too large for the toe cuff, the second toe was used. The cuff was then inflated to 20 mmHg above the last visual PPG signal. The cuff was then slowly deflated – the pressure reading was recorded when a consistent waveform returned. The TBI was calculated by dividing the toe pressure by the highest brachial pressure. CFDU was performed following pressure measurements, from the abdominal aorta to the distal ankle on the right side as the reference standard.

For calculations relating to diagnostic accuracy, PAD was defined as one or more arteries with $\geq 50\%$ stenosis indicating the presence of significant PAD (Koelemay et al., 1996; Olin & Sealove; Sacks, Robinson, Marinelli, & Perlmutter, 1992). Sensitivity, specificity, positive and negative predictive values and ratios of the ABI for the presence of PAD were calculated using the standard cut-off score for an abnormal ABI of ≤ 0.90 or greater than 1.4, consistent with current screening guidelines (Hirsch et al., 2006; Rooke et al., 2011). TBI normal values were considered ≥ 0.70 . CWD waveforms were analysed by a single researcher who assessed each waveform, blinded to the results of CFDU and pressure measurement. Loss of multi-phasic pattern in either the dorsalis pedis or posterior tibial arteries (i.e., bi-phasic or tri-phasic) demonstrated by low-resistance, slow systolic acceleration and no diastolic flow reversal were considered positive for PAD (Poe, 2012). Standard deviations (SD) were derived for all means and 95% confidence intervals were calculated for sensitivities, specificities and positive and negative predictive values and ratios. Calculations of diagnostic accuracy were performed using Microsoft Excel. Receiver operating characteristic (ROC) analysis was performed for ABI and TBI and area under the curve (AUC) was using SPSS version 22 statistical software.

Inter-tester reliability of CFDU scanning was calculated using the presence or absence of PAD as a dichotomous variable and an unweighted Cohen's Kappa (κ) statistic. Inter-tester reliability of the neurological examination was also calculated using the presence or absence of sensorimotor neuropathy as a dichotomous variable and

Table 1
Participant characteristics.

| | DM group | No DM group | Comparison |
|--------------------------------------|-------------|-------------|-------------------------------|
| Total participants, N | 73 | 46 | |
| Males, n (%) | 48 (65) | 27 (58) | 0.338 ^a (p = 0.56) |
| Females, n (%) | 25 (34) | 19 (41) | |
| Age range (years) | 53–86 | 65–91 | 1.28 ^b (p = 0.20) |
| Mean age (years) | 72.47 | 74.21 | |
| Neuropathy, n (%) | 9 (12) | 6 (13) | 0.000 ^a (p = 1.00) |
| History of smoking (%) | 43 (58) | 21 (46) | 2.112 ^c (p = 0.37) |
| Currently smoking (%) | 2 (02) | 3 (6) | |
| Known CVD (%) | 23 (31) | 15 (32) | 0.01 ^a (p = 0.90) |
| Mean ABI (^A) | 1.16 (0.24) | 1.08 (0.22) | 1.67 ^b (p = 0.09) |
| Mean TBI (^A) | .70 (0.23) | 0.67 (0.24) | 0.67 ^b (p = 0.51) |
| Incompressible ankle pressure, n (%) | 8 (10) | 2 (4) | |
| Distal PAD, n (%) | 27 (36) | 17 (36) | |
| Proximal PAD, n (%) | 10 (13) | 4 (8) | |
| PAD, n (%) | 36 (49) | 19 (41) | |
| >50% stenosis, n (%) | 4 (5) | 1 (2) | 1.382 ^c (p = 0.75) |
| >75% stenosis, n (%) | 4 (5) | 1 (2) | |
| Occlusion, n (%) | 24 (33) | 17 (37) | |

^A = Standard deviation, PAD = peripheral arterial disease, DM = diabetes mellitus, CVD = cardiovascular disease.

^a Pearson's chi-square.

^b Independent samples t test.

^c Fisher's exact test.

an unweighted Cohen's Kappa (K) statistic. Intra-class correlation coefficients (ICC) with 95% confidence intervals (CI) were calculated to determine level of agreement between test and retest for the ABI. All ICC values for inter-tester reliability were interpreted according to cut-offs suggested by Fleiss (1986). Interpretation of the Cohen's K statistic was performed using the method proposed by Landis and Koch (1977), and interpretation of positive and negative predictive values was using the guide proposed by Geyman, Deyo, and Ramsey (2000). To compare the groups with and without diabetes, independent samples t-tests will be performed for age, ABI and TBI. Fisher's exact test compared history of smoking and severity of PAD, and Pearson's chi-square compared gender, known history of cardiovascular disease and neurological status. P values were calculated for all comparative data. All reliability and comparative analyses were conducted using SPSS version 22 statistical software.

3. Results

A total of 117 participants were recruited. Participants were categorised into the diabetes (n = 72) or no diabetes group (n = 45) post-hoc. The no diabetes group served as the control group. Comparison of the two groups, with and without diabetes showed that overall there

were no significant differences in gender (p = 0.56), neurological status (p = 1.00), age (p = 0.20), severity of PAD (p = 0.75), known cardiovascular disease (p = 0.90) and smoking history (p = 0.37) (Table 1). Inter-tester reliability of the CFDU scans between the three ultra-sonographers was high (K 0.78, p < 0.01) (Landis & Koch, 1977). ICCs demonstrated good test–retest reliability of the toe pressures (ICC: 0.80, 95% CI: 0.39–0.95), moderate reliability of brachial pressures (ICC: 0.66, 95% CI: 0.09–0.90), and ankle pressures (ICC 0.62, 95% CI: 0.03–0.89).

Means for ABI and TBI were comparable in both groups. Mean ABI was 1.16 in the diabetes group, and 1.08 in the group without diabetes, both within normal range and not significantly different between groups (p = 0.97). The mean TBI was 0.70 in the diabetes group which was also within normal range however was slightly below normal for the group without diabetes (0.67) but was not significantly different between groups (p = 0.50).

Sensitivity and specificity results of the three methods of assessment (CWD, ABI and TBI) for the presence of significant PAD in people with and without diabetes are shown in Table 2, along with positive and negative predictive values. Overall CWD had the higher sensitivity, specificity, positive and negative predictive values for detecting significant PAD in both groups. The TBI was more sensitive than the ABI in both groups but had notably better sensitivity in the group of people without diabetes (83.33%) compared to the group with diabetes (63.63%). The sensitivity of the ABI was low in both groups, but specificity was high and similar for both groups (approximately 92%). Likelihood ratios revealed important (Geyman et al., 2000) positive likelihood ratios for the ABI and CWD in people with (ABI 6.17, CWD 10.39) and without diabetes (ABI 6.39, CWD 22.74) (Table 2). Negative likelihood ratios were important for CWD in people without diabetes (0.16). The TBI had somewhat important positive likelihood ratios in people with (3.21) and without diabetes (3.55).

ROC analysis in the group without diabetes indicated similar clinical efficacy for both the ABI (AUC: 0.81, p = 0.0001) and TBI (AUC: 0.81, p = 0.0001) (Fig. 1). In the group with diabetes, the TBI had greater clinical efficacy (AUC: 0.75 p = 0.0001) than the ABI (AUC: 0.58, p = 0.27) (Fig. 2).

4. Discussion

To the best of our knowledge, this is the largest prospective diagnostic accuracy study examining the most commonly used non-invasive vascular assessment methods in diabetes. This study is unique in that the sample is substantial, and the participants are reflective of those encountered in clinical practice.

The specificity of the ABI was high in participants with (92.68%) and without diabetes (92.59%), and important positive likelihood ratios were also present in those with (6.17) and without diabetes

Table 2
Validation table: all groups.

| | Participants with diabetes | | | Participants without diabetes | | |
|------------------------------------|----------------------------|-------------------------|------------------------|-------------------------------|--------------------------|------------------------|
| | Ankle–Brachial index | Continuous wave Doppler | Toe–Brachial index | Ankle–Brachial index | Continuous wave Doppler | Toe–Brachial index |
| Sensitivity (95% CI) | 45.16 (27.33 to 63.96) | 74.19 (55.38 to 88.11) | 63.64 (45.13 to 79.58) | 47.37 (24.49 to 71.10) | 84.21 (60.40 to 96.43) | 83.33 (58.56 to 96.23) |
| Specificity (95% CI) | 92.68 (80.05 to 98.38) | 92.86 (80.49 to 98.42) | 82.05 (66.46 to 92.43) | 92.59 (75.67 to 98.88) | 96.3 (80.97 to 99.38) | 74.07 (53.71 to 88.84) |
| Positive likelihood ratio (95% CI) | 6.17** (1.94 to 19.62) | 10.39** (3.42 to 31.52) | 3.55* (1.73 to 7.28) | 6.39** (1.55 to 26.33) | 22.74** (3.29 to 157.15) | 3.21* (1.64 to 6.28) |
| Negative likelihood ratio (95% CI) | 0.59 (0.43 to 0.82) | 0.28 (0.15 to 0.51) | 0.44 (0.28 to 0.71) | 0.57 (0.37 to 0.88) | 0.16** (0.06 to 0.46) | 0.22 (0.08 to 0.65) |
| Positive predictive value (95% CI) | 82.35 (56.55 to 95.99) | 88.46 (69.82 to 97.42) | 75.00 (55.12 to 89.26) | 81.82 (48.24 to 97.18) | 94.12 (71.24 to 99.02) | 68.18 (45.13 to 86.08) |
| Negative predictive value (95% CI) | 69.09 (55.19 to 80.85) | 82.98 (69.18 to 92.33) | 72.73 (57.21 to 85.03) | 71.43 (53.69 to 85.34) | 89.66 (72.62 to 97.69) | 86.96 (66.38 to 97.07) |

** Important likelihood ratio.

* Relatively important likelihood ratio.

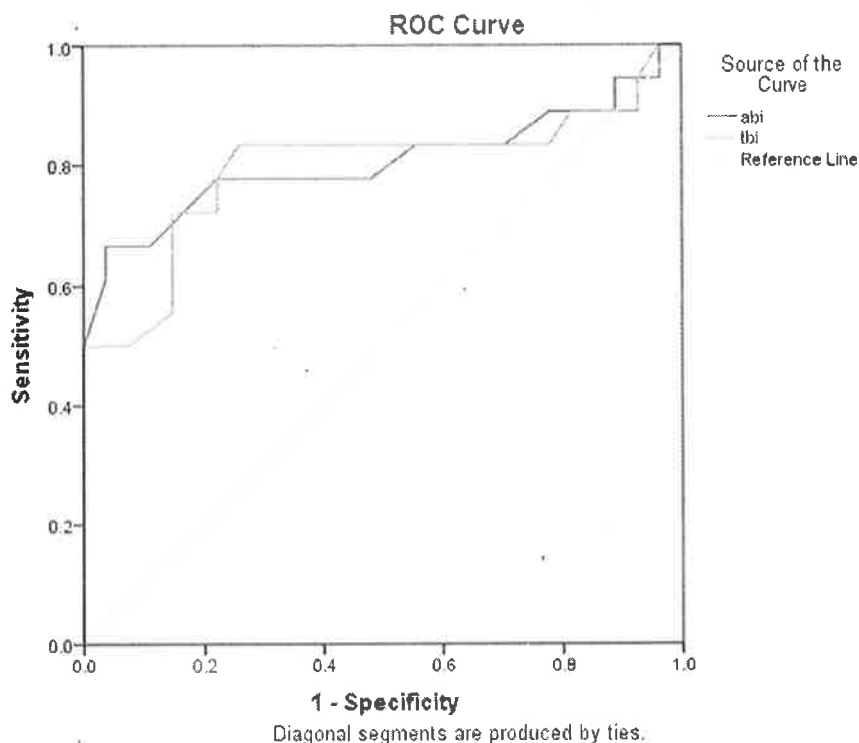


Fig. 1. ROC analysis of TBI and ABI for detecting PAD in people without diabetes.

(6.39) which was consistent with previous studies involving similar populations (Chung et al., 2009; Parameswaran & Dolan, 2005; Williams et al., 2005). The sensitivity of the ABI was poor in both groups, with (45.16%), and without diabetes (47.37%). This was

slightly lower than previous studies (Chung et al., 2009; Parameswaran & Dolan, 2005); however, this may have occurred as a result of the characteristics of the population we recruited. The participants in our study were older (mean age 72 and 74 years for participants with and

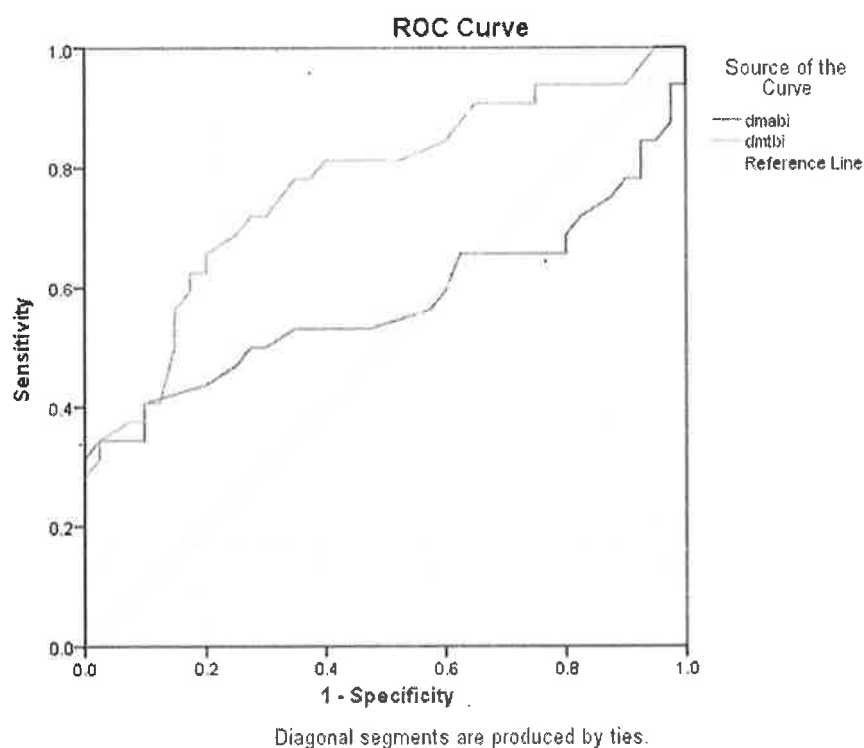


Fig. 2. ROC analysis of ABI and TBI in detecting PAD in people with diabetes.

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Appendix 9



THE UNIVERSITY OF
NEWCASTLE
AUSTRALIA

Would you like to participate in research on clinical practice?

The University of Newcastle Podiatry Discipline is conducting research into current practice in vascular foot assessment.

We are looking for registered Podiatrists in Australia and New Zealand to participate in our 10 minute online survey. If you wish to participate simply type in the link below into your web browser to start the survey.

<http://www.surveymonkey.com/s/footsurvey>

Participants are eligible to go into the draw to win one of five \$100 Westfield gift vouchers.

If you would like more information regarding the study please contact Peta Craike via email – Peta.Craike@newcastle.edu.au

Appendix 10

Participant information statement

You are invited to participate in the research project "Vascular assessment techniques amongst Podiatrists" which is being conducted by Dr Vivienne Chuter, and Ms Peta Craike from the Discipline of Podiatry at the University of Newcastle.

Why is the research being done?

The purpose of the research is to ascertain what current practice is amongst Podiatrists completing vascular assessments. This will help determine if a standard assessment is necessary in the future. This survey forms part of a Masters degree for Peta Craike, from the University of Newcastle. Dr Vivienne Chuter and Dr Alan Bray are involved in supervision of the project.

Who can participate in the research?

We are seeking registered Podiatrists in Australia and New Zealand who are currently practicing.

What choice do you have?

Participation in this research is entirely your choice. Only those people who give their informed consent will be included in the project. Whether or not you decide to participate, your decision will not disadvantage you.

If you do decide to participate, you may withdraw from the project at any time without giving a reason and have the option of withdrawing any data which identifies you.

What would you be asked to do?

If you agree to participate, you will be asked to complete the following survey.

How much time will it take?

Participation in this project will take approximately 10 minutes of your time.

What are the risks and benefits of participating?

There are no risks associated with participating in this research. At the completion of the survey you will be redirected to a separate page where, if you wish, you can enter your name and email address to enter the draw for one of 5 Westfield \$100 gift vouchers. This information is kept separate to your survey responses to maintain anonymity.

How will your privacy be protected?

All data will be stored securely at the University of Newcastle by the Principal Researcher and only members of the research team will have access to this data. Data will be retained for at least 5 years. Following completion of this study your name will be replaced by a code ensuring all your data is unidentifiable. Data will only be saved on electronic file in a coded form which de-identifies you. All data will be deleted/destroyed after 5 years. Electronic data will be stored on a password protected computer, paper-based records will be stored in a locked filing cabinet. Disposal of data will be performed in accordance with university policy (Research Data and Materials Management Procedure document number 000870)

How will the information collected be used?

The results of this study will disseminated via national and international conferences and for papers in scientific journals. Identifying information will not feature in the reporting of this research.

What do you need to do to participate?

Please read this Information Statement and be sure you understand its contents before you consent to participate. If there is anything you do not understand, or you have questions, contact the researcher.

Further information

Thank you in advance for your co-operation with this important effort. Your answers will make a significant contribution to understanding current Podiatry practice in Australia & New Zealand. If you would like a summary of the survey results, or if you have any questions about this research, please do not hesitate to contact me via email - Peta.Craike@newcastle.edu.au

***1. I have read the participant information statement and am eligible and willing to participate**

☐ Yes

☐ No

***2. Are you a registered Podiatrist and currently practicing Podiatry in Australia or New Zealand?**

☐ Yes

☐ No

Participant Information

***3. In the past week, the majority of your work has taken place in what kind of Podiatry setting?**

☐ Private practice

☐ Public sector

☐ Research/education

☐ Other (please specify)

***4. How many years have you been practicing as a Podiatrist?**

***5. Which of the following best describes your primary place of practice?**

☐ Metropolitan

☐ Regional

☐ Rural

***6. Which state or territory does the majority of your practice take place in?**

☐ Queensland

☐ New South Wales

☐ Victoria

☐ South Australia

☐ Western Australia

☐ Tasmania

☐ Australian Capital Territory

☐ Northern Territory

☐ New Zealand

***7. What is the highest level of education you have completed?**

☐ Diploma

☐ Bachelor degree or graduate entry Masters degree

☐ Post Graduate Coursework

☐ Research Higher Degree

Assessment practices

***8. In your most recent day of clinical practice, how many vascular assessments did you perform?**

***9. Which of the following would prompt you to perform a vascular assessment? You may select multiple boxes**

- | | |
|---|--|
| <input type="checkbox"/> Burning feet | <input type="checkbox"/> Hypertension |
| <input type="checkbox"/> Cold feet | <input type="checkbox"/> Dyslipidemia |
| <input type="checkbox"/> Discolouration of skin | <input type="checkbox"/> Smoking history |
| <input type="checkbox"/> Ulceration | <input type="checkbox"/> Active smoking |
| <input type="checkbox"/> Thickened nails | <input type="checkbox"/> Raynaud's phenomena |
| <input type="checkbox"/> Widespread anhidrosis | <input type="checkbox"/> Poor healing |
| <input type="checkbox"/> Chilblains | <input type="checkbox"/> New patient assessment |
| <input type="checkbox"/> Night cramps | <input type="checkbox"/> Cardiovascular disease |
| <input type="checkbox"/> Advanced age | <input type="checkbox"/> Cerebrovascular disease |
| <input type="checkbox"/> Diabetes | |
| <input type="checkbox"/> Other (please specify) | |

***10. Which of the following vascular assessment equipment do you have access to in your clinic? You may select multiple boxes**

- ☐ Stethoscope
- ☐ Blood Pressure Cuff
- ☐ Toe pressure cuff
- ☐ Doppler without waveform display
- ☐ Doppler with waveform display
- ☐ Doppler with waveform display and print out
- ☐ Doppler with waveform display and software application
- ☐ Photoplethysmography probe (PPG)
- ☐ Automated toe pressure machine
- ☐ Automated ankle brachial index machine
- ☐ Other (please specify)

***11. What type of diagnostic testing do you usually use when performing a vascular assessment? You may select multiple boxes**

- ☐ Palpation of dorsalis pedis pulse
- ☐ Palpation of posterior tibial pulse
- ☐ Temperature gradient
- ☐ Capillary refill time
- ☐ Doppler examination of pedal pulses
- ☐ Doppler waveform analysis
- ☐ Ankle brachial index
- ☐ Toe brachial index
- ☐ Absolute toe pressure

Other (please specify)

12. What is/are the main barriers in performing a vascular assessment in your practice?

- ☐ Time constraints
- ☐ No financial incentive
- ☐ Lack of equipment
- ☐ Lack of interest
- ☐ Unsure of techniques
- ☐ There are no barriers

***13. How much time do you estimate it takes you to complete a vascular assessment?**

- ☐ 5 minutes
- ☐ 10 minutes
- ☐ 15 minutes
- ☐ 20 minutes
- ☐ 30 minutes

Other (please specify)

***14. Do you book a vascular assessment as a separate appointment, or is it performed within a routine visit?**

- ☐ As part of routine visit
- ☐ As a separate appointment
- ☐ Other (please specify)

***15. Do you charge an additional fee for a vascular assessment?**

- ☐ Yes
- ☐ No
- ☐ Not Applicable

***16. Do you routinely provide patient education as part of your vascular assessment?**

- ☐ Always
- ☐ Most of the time
- ☐ Sometimes
- ☐ Rarely
- ☐ Never

***17. Which topics do you cover as part of your patient education?**

Case Study

Please read the following short case study and answer the questions below.

You have just completed a diabetes foot assessment on your patient Bruce. Bruce is a 66 year old man whose medical history includes hyperlipidemia, hypertension and non insulin dependent diabetes (diagnosed 2003). He is currently taking Lipitor, Diabex and Atacand. He reports that is diabetes is well controlled. He checks his BSL's sparingly and reports his levels are always under 10mmol/L. His most recent HbA1c was 8.5%.

Your results are as follows:

Neurological Assessment: Monofilament 10/10 bilaterally. Vibration perception – absent bilaterally. Achilles reflexes – within normal limits.

Vascular Assessment: Dorsalis pedis pulses not palpable bilaterally, and tibialis posterior pulses palpable bilaterally. Doppler reveals monophasic dorsalis pedis pulses and biphasic posterior tibial pulses. Ankle brachial index is 1.4 on the right foot, and 1.2 on the left foot.

Musculoskeletal Assessment: Muscle testing within normal limits. Ankle joint range of motion reduced bilaterally. Midtarsal joint and 1st metatarso-phalangeal joint within normal limits. No deformities noted.

Footwear: Jogger. Outsole is well worn. Upper in fair condition. Fit well.

18. Based on these results, how would you classify Bruce's risk status?

- ☐ Low Risk
- ☐ Medium Risk
- ☐ High Risk

19. Is there any further vascular testing you would have performed in your clinic?

- ☐ Yes
- ☐ No

If yes, please specify

*20. Based on the results provided above, what is your management plan?

Appendix 11

HUMAN RESEARCH ETHICS COMMITTEE



Notification of Expedited Approval

| | |
|--|--|
| To Chief Investigator or Project Supervisor: | Doctor Viv Chuter |
| Cc Co-investigators / Research Students: | Ms Peta Craike |
| Re Protocol: | Clinician Variation in Diabetes Foot Assessment amongst Podiatrists in Australia and New Zealand. |
| Date: | 30-Jan-2013 |
| Reference No: | H-2012-0384 |
| Date of Initial Approval: | 30-Jan-2013 |

Thank you for your **Response to Conditional Approval** submission to the Human Research Ethics Committee (HREC) seeking approval in relation to the above protocol.

Your submission was considered under **Expedited** review by the Chair/Deputy Chair.

I am pleased to advise that the decision on your submission is **Approved** effective **30-Jan-2013**.

For noting: Within the Participant Information Statement, please amend the 'privacy' section by changing the wording to '...you may withdraw from the project at any time prior to submitting your survey without giving a reason...'

In approving this protocol, the Human Research Ethics Committee (HREC) is of the opinion that the project complies with the provisions contained in the National Statement on Ethical Conduct in Human Research, 2007, and the requirements within this University relating to human research.

Approval will remain valid subject to the submission, and satisfactory assessment, of annual progress reports. *If the approval of an External HREC has been "noted" the approval period is as determined by that HREC.*

The full Committee will be asked to ratify this decision at its next scheduled meeting. A formal *Certificate of Approval* will be available upon request. Your approval number is **H-2012-0384**.

If the research requires the use of an Information Statement, ensure this number is inserted at the relevant point in the Complaints paragraph prior to distribution to potential participants You may then proceed with the research.

Conditions of Approval

This approval has been granted subject to you complying with the requirements for *Monitoring of Progress, Reporting of Adverse Events, and Variations to the Approved Protocol* as detailed below.

PLEASE NOTE:

In the case where the HREC has "noted" the approval of an External HREC, progress reports and reports of adverse events are to be submitted to the External HREC only. In the case of Variations to the approved protocol, or a Renewal of approval, you will apply to the External HREC for approval in the first instance and then Register that approval with the University's HREC.

- ***Monitoring of Progress***

Other than above, the University is obliged to monitor the progress of research projects involving human participants to ensure that they are conducted according to the protocol as approved by the HREC. A progress report is required on an annual basis. Continuation of your HREC approval for this project is conditional upon receipt, and satisfactory assessment, of annual progress reports. You will be advised when a report is due.

- ***Reporting of Adverse Events***

1. It is the responsibility of the person **first named on this Approval Advice** to report adverse events.
2. Adverse events, however minor, must be recorded by the investigator as observed by the investigator or as volunteered by a participant in the research. Full details are to be documented, whether or not the investigator, or his/her deputies, consider the event to be related to the research substance or procedure.
3. Serious or unforeseen adverse events that occur during the research or within six (6) months of completion of the research, must be reported by the person first named on the Approval Advice to the (HREC) by way of the Adverse Event Report form (via RIMS at <https://rims.newcastle.edu.au/login.asp>) within 72 hours of the occurrence of the event or the investigator receiving advice of the event.
4. Serious adverse events are defined as:
 - Causing death, life threatening or serious disability.
 - Causing or prolonging hospitalisation.
 - Overdoses, cancers, congenital abnormalities, tissue damage, whether or not they are judged to be caused by the investigational agent or procedure.
 - Causing psycho-social and/or financial harm. This covers everything from perceived invasion of privacy, breach of confidentiality, or the diminution of social reputation, to the creation of psychological fears and trauma.
 - Any other event which might affect the continued ethical acceptability of the project.
5. Reports of adverse events must include:
 - Participant's study identification number;

- date of birth;
- date of entry into the study;
- treatment arm (if applicable);
- date of event;
- details of event;
- the investigator's opinion as to whether the event is related to the research procedures; and
- action taken in response to the event.

6. Adverse events which do not fall within the definition of serious or unexpected, including those reported from other sites involved in the research, are to be reported in detail at the time of the annual progress report to the HREC.

- ***Variations to approved protocol***

If you wish to change, or deviate from, the approved protocol, you will need to submit an *Application for Variation to Approved Human Research* (via RIMS at <https://rims.newcastle.edu.au/login.asp>). Variations may include, but are not limited to, changes or additions to investigators, study design, study population, number of participants, methods of recruitment, or participant information/consent documentation. **Variations must be approved by the (HREC) before they are implemented** except when Registering an approval of a variation from an external HREC which has been designated the lead HREC, in which case you may proceed as soon as you receive an acknowledgement of your Registration.

Linkage of ethics approval to a new Grant

HREC approvals cannot be assigned to a new grant or award (ie those that were not identified on the application for ethics approval) without confirmation of the approval from the Human Research Ethics Officer on behalf of the HREC.

Best wishes for a successful project.

Professor Allyson Holbrook
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Appendix 12



Vascular assessment techniques of podiatrists in Australia and New Zealand: a web-based survey

Peta Ellen Tehan* and Vivienne Helaine Chuter

Abstract

Background: Podiatrists play a central role in conducting non-invasive vascular assessment in the lower extremity. This involves screening for signs and symptoms of peripheral arterial disease (PAD) and ongoing monitoring of the condition. Podiatric vascular assessment practices in Australia and New Zealand are currently unclear. Determining the clinical habits of Podiatrists is essential in identifying if there is a need for further education or support in performing accurate vascular assessments.

Methods: A web-based, secure, anonymous questionnaire was conducted of registered Podiatrists in Australia and New Zealand between 1 April and 31 July 2013. The questions examined clinician's regular practices in vascular assessment, clinical indicators to perform and barriers in completing vascular assessment. Nominal logistic regression was performed to further examine years of experience and practice setting on clinical indicators to perform vascular assessment and types of assessment performed.

Results: Four hundred forty-seven podiatrists participated in the survey. Clinical indicators for vascular assessment, along with barriers and available equipment were examined and the results varied depending on the podiatrists' geographical location, practice setting, and experience. Palpation of pedal pulses was the most frequently reported assessment (97 %) along with Doppler assessment (74 %). Pressure measurement was the least frequently reported vascular assessment method, with only 34 % undertaking ankle-brachial indices and 19 % completing toe-brachial indices. Public podiatrists reported more varied and complete vascular assessment compared to those in private practice. Lack of time was identified as the most frequently reported barrier (66 %) in performing vascular assessment, followed by lack of equipment (28 %). In New Zealand podiatrists, lack of equipment was much more of an issue than in Australian podiatrists.

Conclusion: Large variations exist in vascular assessment methods amongst Australian and New Zealand podiatrists. Some assessments being undertaken are potentially inadequate for accurate screening for PAD. There is a need for continuing education in vascular assessment to address the deficiencies in technique reported by some Podiatrists. A podiatry-relevant summary of broad international guidelines for PAD screening may be of use to improve utilisation and accuracy of screening methods to improve patient management.

Keywords: Non-invasive vascular assessment, Podiatrist, Survey, Clinical practice

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Background

Podiatrists play a central role in conducting non-invasive vascular assessment in the lower extremity. This involves screening for signs and symptoms of peripheral arterial disease (PAD) and ongoing monitoring of the condition following diagnosis [1]. Given that people with PAD are not only at higher risk of wounds and limb loss, but are at far greater risk of cardiovascular events and death [2], effective routine vascular assessment and subsequent accurate diagnosis of PAD is integral to improving clinical outcomes and to facilitate effective intervention and ongoing monitoring [3].

A number of tests are currently used for lower limb vascular assessment including pulse palpation, systolic toe pressures, toe-brachial index (TBI), ankle-brachial index (ABI) and Doppler examination. While generally these tests have been shown to have high reliability and diagnostic accuracy [4–12], there has been little investigation of the frequency of use and practicality of performing these assessments in clinical practice generally, with most evidence relating to the most widely recommended test, the ABI [13].

In general medical practice, time constraints and lack of financial reimbursement have been reported to contribute to reduced utility of the ABI for vascular screening [14] with general medical practitioners also reporting a lack of confidence in ability to perform the measurement [15]. Only 32% of general medical practitioners are reported to perform ABI on a regular basis most commonly prior to the application of compression bandaging and for determining the aetiology of chronic wounds [14]. Podiatrists also have reported time constraints and lack of financial reimbursement as barriers in performing ABI, with approximately half of practitioners reporting using ABI regularly [16]. However the clinical indicators used by clinicians to complete this assessment or conduct other forms of lower limb vascular assessment including the TBI and Doppler waveform assessment have not been investigated [15, 16].

The primary aim of this study was to determine current practices in performing lower limb vascular assessments of Podiatrists in Australia and New Zealand. The secondary aims of this study were to investigate factors influencing lower limb vascular assessment practices including levels of clinical experience and education, practice location and resources and to establish perceived barriers to performing lower limb vascular assessments Podiatry practice.

Methods

This was a cross-sectional observational study performed using a web-based, secure anonymous self-administered survey reading lower limb vascular assessment techniques of Podiatrists from Australia and New

Zealand that was conducted between 1 April and 31 July 2013.

Recruitment of participants was via their affiliated professional body—The Australian Podiatry Association or PodiatryNZ. Invitations to participate were sent via e-mail advertising in the weekly bulletin or a small advertisement in the paper based bulletin with a link to the survey. External clinical supervisors participating in the University of Newcastle external placement program were also invited to take part via email invitation containing a survey overview with a hyperlink to the survey. Inclusion criteria were Podiatrists registered and currently practicing in Australia and New Zealand. Ethical approval was obtained from the University of Newcastle Human Research Ethics Committee (Ethics approval: H-2012-0384). All participants provided informed consent prior to participation in this study.

The survey was delivered online via the online survey software Survey Monkey®. The questions examined clinician's regular practices in vascular assessment, factors prompting performance of an assessment and availability of equipment (Additional file 1). The first seven questions elicited demographic and descriptive data from the participants. Questions eight to 15 related to clinicians vascular assessment habits and 16 and 17 related to provision of patient education. The majority of questions were closed with three open ended questions, which related to time spent in practice and topics covered in education provision. A mix of nominal polytomous, ordinal polytomous and dichotomous questions were used. Pilot testing of the survey was performed at a University of Newcastle continuing professional development event attended by a mix of 35 private and public sector podiatrists. Based on feedback from podiatrists some small amendments were made to some of the questioning methods from open ended to ordered polytomous and phrasing of the questions was slightly altered to allow for further clarity.

Data analysis

The primary data analyses were descriptive statistics of the cohort including geographical practice location, years of experience, qualifications held and practice sector. Nominal logistic regression was performed and relative risk ratios calculated for possible factors affecting clinical indications to perform vascular assessment and the type of vascular testing that was performed. These clinical indicators included combinations of the type of referral received, clinical signs and symptoms of PAD and patient medical history. Vascular assessment performed included combinations of clinical observations, Doppler use and pressure measurements. The fit of the data to the final nominal logistic regression model was assessed using the

Homser-Lemeshow test with a p value >0.05 indicating an adequate fit. All data analysis was conducted using Stata data analysis and statistical software version 13. Missing data were excluded case wise.

Results

Participant characteristics

Four hundred and forty seven podiatrists were recruited in total, however the number of responses varied slightly per question with some respondents not answering all questions, and some questions allowed for multiple answer options. Overall percentages are reported as the percentage of the total number of participants who answered an individual question and the total number of respondents for the question provided. Overall percentages are reported as the percentage of the total number of participants who answered an individual question. For comparison of sub-groups descriptive statistics are reported as the percentage of the number of respondents identified in that sub group e.g. practitioners in private practice. The total response rate represents approximately 10 % of all registered Podiatrists in Australia and New Zealand in 2013. Participant characteristics are included in Table 1.

Indicators to perform a vascular assessment

A history of diabetes was the most frequently reported clinical indicator to complete a vascular assessment (82 %, $n = 367/377$) the least frequently reported was presence of thickened nails (14.6 %, $n = 55/377$) (Fig. 1). Several other cardiovascular risk factors for PAD including hypertension and dyslipidaemia were among the least frequently reported clinical indicators. The mean number of vascular assessments performed in the most recent day of practice was 2.35 and 10 min was the most frequently reported average time taken to complete vascular assessment (Table 2). The most commonly reported clinical indicators

Table 1 Survey participant characteristics

| Participant characteristics | |
|--|------------|
| Participants | 447 |
| Private practice | 322 (73 %) |
| Public practice | 115 (26 %) |
| Research/education | 10 (2 %) |
| Metropolitan area | 265 (60 %) |
| Regional area | 137 (31 %) |
| Rural area | 57 (13 %) |
| Years of practice (Range) | 0–42 |
| Years of practice (Mean) | 13 |
| Diploma | 80 (18 %) |
| Bachelor or equivalent | 268 (61 %) |
| Post graduate qualification/Research Higher Degree | 91 (21 %) |

Table 2 General vascular assessment information

| | | | | |
|---|----------|---------|---------|----------|
| General vascular assessment | | | | |
| Mean number of vascular assessments performed in most recent day of clinical practice | | | | 2.35 |
| Vascular assessment within standard consultation <i>n</i> (%) | | | | 277 (73) |
| Vascular assessment as separate consultation <i>n</i> (%) | | | | 47 (12) |
| Charge additional fee for vascular assessment <i>n</i> (%) | | | | 34 (9) |
| Do not charge additional fee for vascular assessment <i>n</i> (%) | | | | 280 (74) |
| Time to complete assessment <i>n</i> (%) | | | | |
| 5 min | 10 min | 15 min | 20 min | 30 min |
| 97 (25) | 130 (34) | 80 (21) | 40 (12) | 26 (7) |

to perform a vascular assessment were grouped into the patient's medical history, practitioner's clinical observations and the type of referral i.e. Medicare EPC referral, general practitioner referral (Table 3).

Regression analysis showed the clinical indicators used as a basis for performing a vascular assessment were most strongly influenced by the years of clinical experience and practice setting (public or private) (Table 3). Public sector podiatrists were more likely to perform vascular assessment based on a combination of medical history, observations and the type of referral compared to private sector practitioners ($p = <0.0001$). Less experienced podiatrists were more likely to use a combination of multiple factors (referral type, medical history and observations) to prompt for vascular assessment ($p = 0.018$) compared to more experienced podiatrists who reported relying upon one or two clinical indicators alone, rather than a combination of all three clinical indicators. The Hosmer-Lemeshow test was identified as statistically non significant ($p = 0.17$) indicating the model was an adequate fit to the data.

Vascular assessment methods

Pedal pulse palpation (97 %, $n = 366/377$) and Doppler use (74 %, $n = 281/377$) were the most frequently reported vascular assessment tests by all respondents (Fig. 2). Use of vascular pressure measurement was substantially lower with 34.2 % ($n = 129/377$) of all respondents reporting regularly using ABIs and 19.4 % ($n = 73/377$) using TBIs. Public sector podiatrists reported a higher frequency of Doppler use (92 %, $n = 101/110$) than private-sector podiatrists (66 %, $n = 197/300$). There were also differences in frequency of use of pressure measurement between public and private sector podiatrists. Fifty three percent of public sector podiatrists reported regularly using an ABI ($n = 58/110$) and 35 % regularly using a TBI ($n = 39/110$) whereas in the private sector, 25 % of podiatrists reported regularly using an ABI ($n = 75/300$) and only 12 % regularly used a TBI ($n = 24/300$). Nominal regression analysis revealed that

| Clinical indicators | Medical history | | | | Medical history and observations | | | | Medical history, observations and referral type | | | | | | | | |
|-------------------------------|-----------------|-------|-------------|-----------------|----------------------------------|-------|-------|-------------|---|---------------|-------|-------|-------|---------|-------------|--------------|----------------|
| | N | % | RRR | P value | 95 % CI | N | % | RRR | P value | 95 % CI | N | % | RRR | P value | 95 % CI | | |
| Education level ^a | | | | | | | | | | | | | | | | | |
| Diploma | 6 | 8.45 | 0.93 | 0.789 | 0.55 to 1.569 | 13 | 18.31 | 0.78 | 0.251 | 0.51 to 1.189 | 47 | 66.2 | 5 | 7.04 | 1.40 | 0.44 | 0.6 to 3.282 |
| Bachelor | 30 | 11.95 | | | | 33 | 13.15 | | | | 150 | 59.76 | 38 | 15.14 | | | |
| Postgrad/RHD | 5 | 5.68 | | | | 11 | 12.5 | | | | 53 | 60.23 | 19 | 21.59 | | | |
| Practice setting ^b | | | | | | | | | | | | | | | | | |
| Private | 30 | 10.38 | 0.02 | < 0.0001 | 0.003 to 0.153 | 52 | 17.99 | 0.38 | < 0.0001 | 0.22 to 0.652 | 162 | 56.06 | 45 | 15.57 | 0.10 | 0.028 | 0.01 to 0.782 |
| Public | 9 | 8.82 | | | | 4 | 3.92 | | | | 74 | 72.55 | 15 | 14.71 | | | |
| Geographical location | | | | | | | | | | | | | | | | | |
| Metro | 21 | 8.57 | 2.05 | 0.292 | 0.54 to 7.773 | 40 | 16.33 | 0.96 | 0.945 | 0.27 to 3.430 | 149 | 60.82 | 35 | 14.29 | 2.38 | 0.345 | 0.39 to 14.435 |
| Regional | 16 | 12.21 | 0.71 | 0.609 | 0.2 to 2.592 | 15 | 11.45 | 0.36 | 0.11 | 0.11 to 1.258 | 81 | 61.83 | 19 | 14.5 | 1.35 | 0.731 | 0.24 to 7.640 |
| Rural | 4 | 7.69 | 1.15 | 0.831 | 0.31 to 4.304 | 4 | 7.69 | 0.94 | 0.927 | 0.27 to 3.249 | 33 | 63.46 | 11 | 21.15 | 2.77 | 0.244 | 0.5 to 15.394 |
| Experience | | | | | | | | | | | | | | | | | |
| Years (mean, SD) | 12.01 | 8.96 | 1.04 | 0.018 | 1.01 to 1.073 | 14.82 | 11.14 | 1.04 | 0.004 | 1.01 to 1.066 | 12.14 | 10.04 | 13.60 | 9.73 | 1.06 | 0.039 | 1.00 to 1.117 |

*Values in bold are considered statistically significant; RRR = relative risk ratio
 The reference group of the nominal logistic regression model used a combination of responses of Observations, Medical History and Referral Type
 †Bachelor or equivalent degree was used as the reference category for education level
 ‡Private practitioners were used as the reference category for work setting

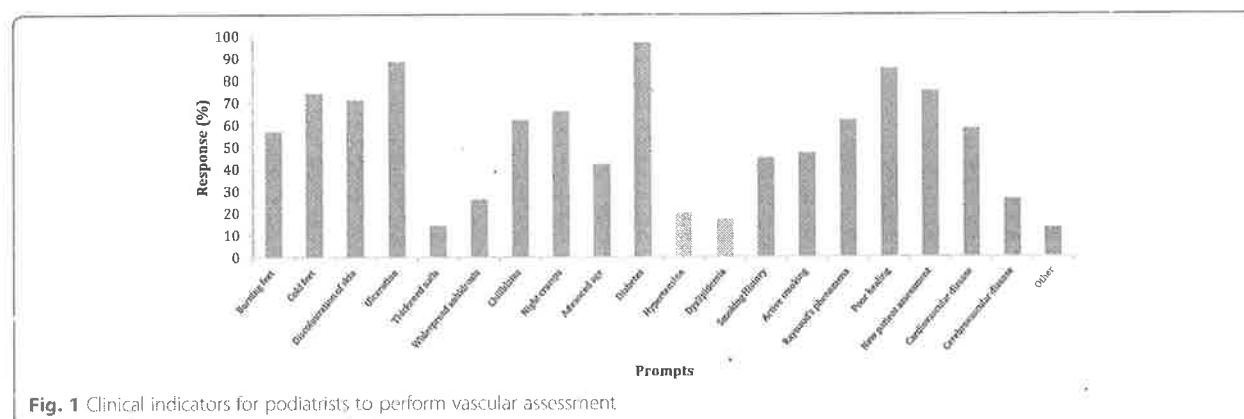


Fig. 1 Clinical indicators for podiatrists to perform vascular assessment

setting (private or public sector) and years of experience were significant predictors of what testing methods were reported to be performed (Table 4). Private sector practitioners were less likely to use multiple assessments that included observations and Doppler ($p = <0.0001$) or observations and pressure measurement ($p = 0.01$), compared to public sector practitioners. More experienced podiatrists were also more likely to report relying on their clinical observations ($p = 0.018$) rather than undertaking clinical testing such as Doppler and pressure measurement to perform a lower limb vascular assessment.

Barriers in performing vascular assessment

Time constraints were the most frequently nominated barrier to performing a vascular assessment for all respondents (62 %, $n = 233/376$), followed by general lack of equipment (28 %, $n = 106/376$). Lack of equipment was more frequently reported as a barrier in New Zealand podiatrists 43.8 % ($n = 28/64$) than their Australian counterparts (25 %, $n = 78/312$). No barriers to completing vascular assessment was reported by 22 % ($n = 99/376$) of the responding participants.

Private sector podiatrists reported time constraints were a barrier to performing vascular assessments (64 %, $n = 190/293$) more frequently than those in public practice

(54 %, $n = 58/108$). Lack of equipment and uncertainty about technique were also more frequently reported in by podiatrists in private practice (equipment: 32 %, $n = 93/293$, technique: 13 %, $n = 38/293$) than in public practice (equipment: 22 %, $n = 24/108$, technique: 3.7 %, $n = 4/108$).

Geographical location appeared to have an influence on barriers in performing vascular assessment. Although time constraints were the most commonly reported barrier in performing vascular assessment for all respondents (62 %, $n = 233/376$), this was highest amongst rural (77 %, $n = 41/53$), and regional podiatrists (62 %, $n = 80/129$) compared to those in metropolitan areas (58 %, $n = 138/239$). The majority of podiatrists unsure of assessment techniques were rurally located (17 %, $n = 9/53$), followed by those in metropolitan (10 %, $n = 24/239$) and regional (8 %, $n = 11/129$) areas.

The lack of financial incentive to perform vascular assessment was noted by 23 % ($n = 86/376$) of podiatrists as a significant barrier, with this generally only relevant to private practice (30 %, $n = 87/293$).

Patient education

The majority of podiatrists (71.4 %, $n = 269/377$) reported to always provide patient education as part of a vascular assessment with very few reporting education

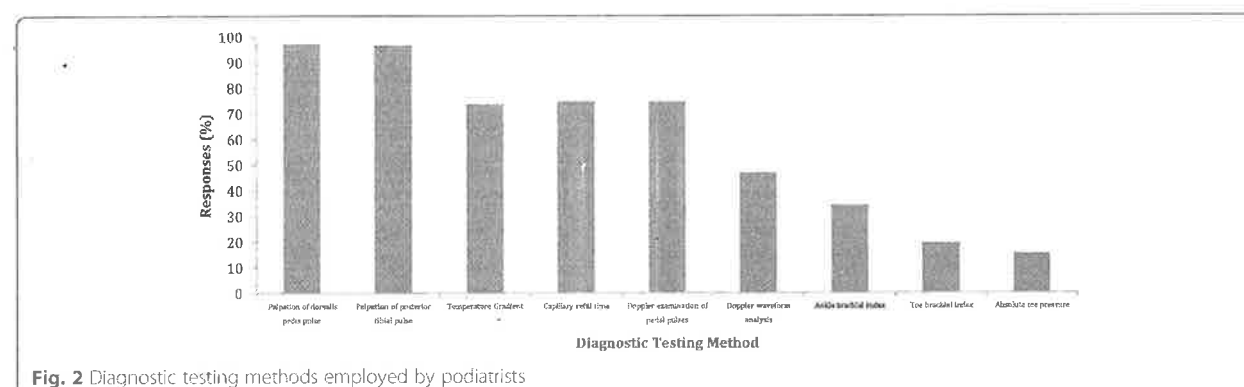


Fig. 2 Diagnostic testing methods employed by podiatrists

Table 4 Types of testing utilised by podiatrists

| Types of testing | Observations alone | | | | | Observations and doppler | | | | | Observations doppler and pressure | | | | | Observations and pressure | | | | |
|-------------------------------|--------------------|-------|-------------|-------------------|----------------|--------------------------|-------|-------------|-------------------|---------------|-----------------------------------|-------|------|---------|-------------|---------------------------|----------------|-----|---------|---------|
| | N | % | RRR | P value | 95 % CI | N | % | RRR | P value | 95 % CI | N | % | RRR | P value | 95 % CI | N | % | RRR | P value | 95 % CI |
| Education level ^a | | | | | | | | | | | | | | | | | | | | |
| Diploma | 19 | 26.76 | 0.93 | 0.789 | 0.55 to 1.569 | 32 | 45.07 | 0.78 | 0.251 | 0.51 to 1.189 | 17 | 23.94 | 3 | 4.23 | 1.40 | 0.44 | 0.6 to 3.282 | | | |
| Bachelor | 43 | 17.2 | | | | 92 | 36.8 | | | | 107 | 42.8 | 8 | 3.2 | | | | | | |
| Postgrad/RHD | 15 | 17.05 | | | | 24 | 27.27 | | | | 42 | 47.73 | 7 | 7.95 | | | | | | |
| Practice setting ^b | | | | | | | | | | | | | | | | | | | | |
| Private | 70 | 24.31 | 0.02 | <0.0001 | 0.003 to 0.153 | 115 | 39.93 | 0.38 | <0.0001 | 0.22 to 0.652 | 89 | 30.9 | 14 | 4.86 | 0.10 | 0.028 | 0.01 to 0.782 | | | |
| Public | 1 | 0.98 | | | | 30 | 29.41 | | | | 70 | 68.63 | 1 | 0.98 | | | | | | |
| Geographical location | | | | | | | | | | | | | | | | | | | | |
| Metro | 53 | 21.72 | 2.05 | 0.292 | 0.54 to 7.773 | 98 | 40.16 | 0.96 | 0.945 | 0.27 to 3.430 | 82 | 33.61 | 11 | 4.51 | 2.38 | 0.345 | 0.39 to 14.435 | | | |
| Regional | 20 | 15.27 | 0.71 | 0.609 | 0.2 to 2.592 | 34 | 25.95 | 0.36 | 0.11 | 0.11 to 1.258 | 71 | 54.2 | 6 | 4.58 | 1.35 | 0.731 | 0.24 to 7.640 | | | |
| Rural | 8 | 15.38 | 1.15 | 0.831 | 0.31 to 4.304 | 20 | 38.46 | 0.94 | 0.927 | 0.27 to 3.249 | 21 | 40.38 | 3 | 5.77 | 2.77 | 0.244 | 0.5 to 15.394 | | | |
| Experience | | | | | | | | | | | | | | | | | | | | |
| Years (mean, SD) | 14.4 | 8.3 | 1.04 | 0.018 | 1.01 to 1.073 | 14.5 | 11.4 | 1.04 | 0.004 | 1.01 to 1.066 | 10.1 | 9.0 | 15.5 | 10.1 | 1.06 | 0.039 | 1.00 to 1.117 | | | |

*Values in bold are considered statistically significant; RRR = relative risk ratio

The reference group of the nominal logistic regression model used a combination of responses of Observations, Doppler and Pressure measurement

^aBachelor or equivalent degree was used as the reference category for education level

^bPrivate practitioners were used as the reference category for work setting

was rarely or never provided, (3/377 [0.8 %] reported rarely providing education and 1/377 [0.3 %] reported never providing education). Main themes of patient education which emerged from open responses given included: footwear, self-care, smoking cessation, foot hygiene, exercise, daily foot inspection, first aid and signs and symptoms of PAD.

Discussion

This is the first study to investigate the clinical indicators that podiatrists use to undertake lower limb vascular assessment and to establish the current clinical examination techniques most commonly used by podiatrists in Australia and New Zealand. We have demonstrated that pedal pulse palpation and use of Doppler were the most commonly utilised assessment methods, and that practice setting and experience had the most significant influence on performance of assessment and what type of assessment methods were utilised. This study suggests that in Australian and New Zealand podiatrists there is a reliance on subjective vascular assessment testing methods such as pedal pulses palpation and Doppler examination, and a lack of use of objective measurement such as the ABI and TBI. As objective measurements not only help to identify the presence of PAD but provide indication of severity of disease, when used in combination with signs and symptoms these tests play an essential role in guiding patient management and assessing risk status. This reliance on more subjective testing methods was more evident in private practitioners than public practitioners. This may be due to a number of different factors. The patients seen in each clinical setting tend to differ, generally with more high risk, diabetes and complex vascular pathology patients seen in public practice [17] who require more extensive investigation, which may account for some of the differences reported. In private practice, no financial incentives currently exist to complete vascular assessment and time is more limited, so practitioners may not perform the more time consuming testing such as pressure measurement.

The overall number of podiatrists reporting using the ABI on a regular basis was lower than previously reported [16] and podiatrists participating in this study reported they were more likely to use the clinical signs and symptoms of PAD present in the lower limb, as a clinical indicator to perform vascular assessment. Systemic factors, such as advanced age, smoking, cardiovascular disease and stroke, which are well-established risk factors for PAD, were much less frequently reported to be used as clinical indicators to perform such an assessment. Given that the signs and symptoms of PAD are frequently unrecognised or even absent [18], it may be likely that relying on subjective testing methods will result in missed or late diagnosis of PAD, and/or an

inaccurate diagnosis of disease severity. Objective pressure measurements add another important dimension to lower limb vascular assessment, allowing for ongoing monitoring of PAD from year to year. This is particularly important for conditions such as Diabetes where changes can occur quickly and action needs to be undertaken to prevent complications such as wounds, ulceration and gangrene.

This study highlights that a large proportion of reported practices in lower limb vascular assessment being undertaken by podiatrists in Australia and New Zealand do not follow international guidelines [19] for PAD screening. However, it is likely that podiatrists are unaware of this broad guideline which recommends the use of objective pressure measurement, mainly the ABI when performing vascular assessment in populations deemed at risk of PAD. Our findings suggest the need for a podiatry specific summary of these broad international guidelines to assist podiatrists in their daily practice or increased awareness of the international guideline through continuing education.

The barriers to performing vascular assessment reported in this present study were consistent with previous studies [14, 16], with time constraints and lack of equipment most frequently cited. Uncertainty of technique was identified as a barrier to complete an assessment mainly in rural podiatrists, suggests that continuing education provision may be particularly beneficial in rural areas. A lack of equipment was identified as a major barrier in New Zealand podiatrists, however, there are differences in service provision in New Zealand compared to Australia, which may have an influence on the equipment required most frequently in daily clinical practice. Limited ability to obtain financial remuneration for vascular assessments was also a reported barrier in a quarter of all respondents. Given the importance of the task lower limb vascular assessment and its role in preventative care, future lobbying for health fund and/or medicare rebates may be of use to remove this barrier for podiatrists to more regularly screen for PAD in their patients who are considered at risk.

Potential limitations

This study should be considered in light of some potential limitations. A non-validated survey was used and therefore the findings may have limited external validity and reproducibility. Despite our best efforts, our sample size was limited and may not be representative of the entire population of podiatrists in Australia and New Zealand. Over-reporting and under-reporting are possible, however piloting of the survey assisted in formulating specific answering methods and we believe this may have reduced the likelihood of this. There are also some differences in delivery of podiatric services between Australia and New Zealand which will differently

influence barriers in performing testing which could be explored further in future research.

Conclusion

Although our study only included a small proportion of practicing podiatrists in Australia and New Zealand, our findings suggest there is a lack of consistency in the profession regarding our approach to lower limb vascular assessment. Our results indicate there is greater scope for use of objective assessment techniques within the profession. Assessment methods employed by podiatrists appear to be guided by practice setting, practitioner experience and geographical location, rather than diagnostic utility of testing methods. There is a need for continuing education for podiatrists in the area of lower limb vascular assessment to increase awareness of accurate and appropriate vascular assessment requirements for populations at risk of PAD.

Additional file

Additional file 1: Copy of survey given to participants. (PDF 262 kb)

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

PT conceived the study and PT and VC created and piloted the survey. PT carried out the survey data collection and PT and VC completed the data analysis. PT wrote the manuscript with the assistance of VC and both authors read and approved the final manuscript.

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Appendix 13

FACULTY OF HEALTH



THE UNIVERSITY OF
NEWCASTLE
AUSTRALIA

Dr. Vivienne Chuter
School of Health Sciences
Health Precinct, Ourimbah Campus
Ph: 02 43494424
Fax: 02 43494538

Email: Vivienne.Chuter@newcastle.edu.au

Consent Form for the Research Project:

Validation of a vascular assessment pathway for Podiatrists

Dr. Vivienne Chuter, Ms Peta Craike
Document Version 1 dated: 28/11/12

I agree to participate in the above research project and give my consent freely.

I understand that the project will be conducted as described in the Information Statement, a copy of which I have retained.

I understand can withdraw from the project at any time and do not have to give any reason for withdrawing.

I consent to:

- Releasing my general practitioner's podiatry referral to this service to the researchers Yes /No (please circle)
- Undergoing a non-invasive, painless assessment for peripheral neuropathy Yes /No (please circle)
- Undergoing a non-invasive, painless assessment for peripheral arterial disease Yes /No (please circle)
- Attending 2 Podiatry testing sessions, and one duplex ultrasound session. Yes /No (please circle)

I have had the opportunity to have questions answered to my satisfaction.

I would like my tests results to be sent directly to my doctor and NOT collect them myself

☐

I would like a summary of the results when they are available via email YES/NO

Email Address: _____

Print Name: _____

Signature: _____ Date: _____

NEWCASTLE | CENTRAL COAST | PORT MACQUARIE | SINGAPORE

The University of Newcastle
Ourimbah NSW 2258 Australia

ourimbah-hub@newcastle.edu.au
CRICOS Provider Number: 00109J

T +61 2 4348 4000
www.newcastle.edu.au

Appendix 14



Information Statement for the Research Project:

Prospective validation of a vascular assessment pathway for Podiatrists
HNEHREC Approval: 13/02/2015.05

Dr. Vivienne Chuter, Ms Peta Craike
Document Version 2 dated: 20/02/13

You are invited to participate in the research project identified above which is being conducted by Dr. Vivienne Chuter, Senior Lecturer, Ms Peta Craike, Lecturer, from the Discipline of Podiatry at the University of Newcastle.

Why is the research being done?

The purpose of the research is to determine the reliability and accuracy of a vascular assessment tool to detect arterial disease in the legs and feet.

Who can participate in the research?

We are seeking men and women with or without Type 2 diabetes and have no history of major heart or kidney problems and do not have any other systemic illnesses such as scleroderma or Raynaud's phenomenon to participate.

What choice do you have?

Participation in this research is entirely your choice. Only those people who give their informed consent will be included in the project. Whether or not you decide to participate, your decision will not disadvantage you.

If you do decide to participate, you may withdraw from the project at any time without giving a reason and have the option of withdrawing any data which identifies you.

What would you be asked to do?

If you agree to participate, you will be asked to:

- Undergo a non-invasive, painless vascular examination to test the circulation in your feet. The examiner will use a Doppler ultrasound to listen to the pulses in your feet, perform a toe blood pressure and an arm blood pressure.
- Undergo a non-invasive, painless neurological assessment to test the nerve function in your feet. This will involve measuring your ability to feel light touch on the skin of your foot and to detect vibration of a tuning fork when it is applied to various parts of your foot.

- Provide consent for researchers to obtain a copy of your general practitioners referral to the podiatry service

How much time will it take?

Participation in this project will require you to attend two 60 minute testing sessions at your Podiatry service, along with attending an ultrasound session at either Gateshead or East Maitland which will take 45 minutes.

What are the risks and benefits of participating?

There are minimal risks associated with participating in this research. Some participants who have painful peripheral neuropathy may experience some mild discomfort during the testing sessions. You may not benefit from participating in this study.

How will your privacy be protected?

All data will be stored securely at the University of Newcastle by the Principal Researcher and only members of the research team will have access to this data. Data will be retained for at least 5 years. Following completion of the three parts of this study your name will be replaced by a code ensuring all your data is unidentifiable. Data will only be saved on electronic file in a coded form which de-identifies you. All data will be deleted/destroyed after 5 years. All data will be stored securely at the University of Newcastle by the principal researcher. Electronic data will be stored on a password protected computer, paper-based records will be stored in a locked filing cabinet. Information obtained from medical records will not feature in the reporting of this research. Disposal of data will be performed in accordance with university policy (Research Data and Materials Management Procedure document number 000870)

How will the information collected be used?

The results of this study will disseminated via national and international conferences and for papers in scientific journals. Medical information will not feature in the reporting of this research.

All participants in the study will receive a summary of the results in hard copy. Individual test results will be provided to each participant or their medical practitioner if preferred.

What do you need to do to participate?

Please read this Information Statement and be sure you understand its contents before you consent to participate. If there is anything you do not understand, or you have questions, contact the researcher.

If you would like to participate, please complete the attached Consent Form and return it in the reply paid envelope provided. You will then be contacted by a member of the research team to organise you testing sessions.

FACULTY OF HEALTH



Further information

If you would like further information please contact Dr. Vivienne Chuter by phone email or post (details below).

Thank you for considering this invitation

Dr. Vivienne Chuter
Senior Lecturer
School of Health Sciences
PO Box 127 Ourimbah, 2258
Ph: 02 43494424
Email: Vivienne.Chuter@newcastle.edu.au

Ms Peta Craike
Lecturer
School of Health Sciences
PO Box 127 Ourimbah, 2258
Ph: 02 43494424
Email: Peta.Craike@newcastle.edu.au

Complaints about this research

This research has been approved by the Hunter New England Human Research Ethics Committee of Hunter New England Local Health District, Reference 13/02/20/5.05

Should you have concerns about your rights as a participant in this research, or you have a complaint about the manner in which the research is conducted, it may be given to the researcher, or, if an independent person is preferred, to Dr Nicole Gerrand, Manager Research Ethics and Governance, Hunter New England Local Health District, Locked Bag 1, New Lambton NSW 2305, telephone (02) 49214950, email Hnehrec@hnehealth.nsw.gov.au

Appendix 15



Health
Hunter New England
Local Health District

8 April 2013

Ms Peta Craike
School Health Sciences
University of Newcastle
PO Box 127
Ourimbah NSW 2258

Dear Ms Craike,

Re: Validation of a Vascular Assessment Pathway for Podiatrists (13/02/20/5.05)

HNEHREC Reference No: 13/02/20/5.05
NSW HREC Reference No: LNR/13/HNE/18

Thank you for submitting the above protocol for single ethical review for a multi-centre study. This project was first considered by the Hunter New England Human Research Ethics Committee at its meeting held on **8 April 2013**. This Human Research Ethics Committee is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research (2007)* (National Statement) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. Further, this Committee has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review. The Committee's Terms of Reference are available from the Hunter New England Local Health District website: http://www.hnehealth.nsw.gov.au/Human_Research_Ethics.

I am pleased to advise that following acceptance under delegated authority of the requested clarifications and revised Information Statement and Consent Form by Dr Nicole Gerrand Manager, Research Ethics & Governance, the Hunter New England Human Research Ethics Committee has granted ethical approval of the above project.

The following documentation has been reviewed and approved by the Hunter New England Human Research Ethics Committee:

- For the Information Statement (Version 2 dated 20 February 2013); and
- For the Consent Form (Version 1 dated 28 November 2012)

For the protocol: **Prospective validation of a Vascular Assessment Clinical Pathway for Podiatrists**

Approval has been granted for this study to take place at the following sites:

- **Newcastle Community Health Centre**

Hunter New England Research Ethics & Governance Unit

(Locked Bag No 1)

(New Lambton NSW 2305)

Telephone (02) 49214 950 Facsimile (02) 49214 818

Email: hnehrec@hnehealth.nsw.gov.au

http://www.hnehealth.nsw.gov.au/research_ethics_and_governance_unit

Approval from the Hunter New England Human Research Ethics Committee for the above protocol is given for a maximum of 3 years from the date of this letter, after which a renewal application will be required if the protocol has not been completed.

The *National Statement on Ethical Conduct in Human Research (2007)*, which the Committee is obliged to adhere to, include the requirement that the committee monitors the research protocols it has approved. In order for the Committee to fulfil this function, it requires:

- A report of the progress of the above protocol be submitted at 12 monthly intervals. Your review date is. A proforma for the annual report will be sent two weeks prior to the due date.
- A final report must be submitted at the completion of the above protocol, that is, after data analysis has been completed and a final report compiled. A proforma for the final report will be sent two weeks prior to the due date.
- All variations or amendments to this protocol, including amendments to the Information Sheet and Consent Form, must be forwarded to and approved by the Hunter New England Human Research Ethics Committee prior to their implementation.
- The Principal Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including:
 - any serious or unexpected adverse events
 - Adverse events, however minor, must be recorded as observed by the Investigator or as volunteered by a participant in this protocol. Full details will be documented, whether or not the Investigator or his deputies considers the event to be related to the trial substance or procedure. These do not need to be reported to the Hunter New England Human Research Ethics Committee
 - Serious adverse events that occur during the study or within six months of completion of the trial at your site should be reported to the Manager, Research Ethics & Governance, of the Hunter New England Human Research Ethics Committee as soon as possible and at the latest within 72 hours.
 - All other safety reporting should be in accordance with the NHMRC's Safety Monitoring Position Statement – May 2009 available at http://www.nhmrc.gov.au/health_ethics/hrecs/reference/files/090609_nhmrc_position_statement.pdf
 - Serious adverse events are defined as:
 - Causing death, life threatening or serious disability.
 - Cause or prolong hospitalisation.
 - Overdoses, cancers, congenital abnormalities whether judged to be caused by the investigational agent or new procedure or not.
 - Unforeseen events that might affect continued ethical acceptability of the project.
- If for some reason the above protocol does not commence (for example it does not receive funding); is suspended or discontinued, please inform Dr Nicole Gerrand, as soon as possible.

Hunter New England Research Ethics & Governance Unit

(Locked Bag No 1)

(New Lambton NSW 2305)

Telephone (02) 49214 950 Facsimile (02) 49214 818

Email: hnehrec@hnehealth.nsw.gov.au

http://www.hnehealth.nsw.gov.au/research_ethics_and_governance_unit

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained.

for submission to the relevant

Research Governance Officer.

Should you have any concerns or questions about your research, please contact Dr Gerrand as per the details at the bottom of the page. The Hunter New England Human Research Ethics Committee wishes you every success in your research.

Please quote **13/02/20/5.05** in all correspondence.

The Hunter New England Human Research Ethics Committee wishes you every success in your research.

Yours faithfully

For: Associate Professor M Parsons
Chair
Hunter New England Human Research Ethics Committee

Hunter New England Research Ethics & Governance Unit

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(New Lambton NSW 2305)

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HUMAN RESEARCH ETHICS COMMITTEE



Acknowledgement of Registration of External HREC Approval

| | |
|--|---|
| To Chief Investigator or Project Supervisor: | Doctor Viv Chuter |
| Cc Co-investigators / Research Students: | Ms Peta Craike |
| Re Protocol: | Validation of a Vascular Assessment pathway for Podiatrists |
| Date: | 15-May-2013 |
| Reference No: | H-2013-0152 |

Thank you for your **Registration of External HREC Approval** submission to the Human Research Ethics Committee (HREC) seeking approval in relation to the above protocol.

Your submission will be considered under **Expedited Review of External Approval** review by the **Chair/Deputy Chair** at the earliest opportunity and you will be advised of the outcome. Meanwhile you may proceed with the research.

Your **protocol reference number** is **H-2013-0152**. Please use this in any correspondence with the HREC in relation to this protocol.

Professor Allyson Holbrook
Chair, Human Research Ethics Committee

For communications and enquiries:
Human Research Ethics Administration

Research Services
Research Integrity Unit
The Chancellery
The University of Newcastle
Callaghan NSW 2308
T +61 2 492 18999
F +61 2 492 17164
Human-Ethics@newcastle.edu.au

RIMS website - <https://RIMS.newcastle.edu.au/login.asp>

Linked University of Newcastle administered funding:

| Funding body | Funding project title | First named investigator | Grant Ref |
|--------------|-----------------------|--------------------------|-----------|
|--------------|-----------------------|--------------------------|-----------|

Appendix 16



RESEARCH

Open Access



Use of hand-held Doppler ultrasound examination by podiatrists: a reliability study

Peta Ellen Tehan* and Vivienne Helaine Chuter

Abstract

Background: Hand held Doppler examination is a frequently used non-invasive vascular assessment utilised by podiatrists. Despite this, the reliability of hand-held Doppler has not been thoroughly investigated. Given the importance of Doppler in completing a vascular assessment of the lower limb, it is essential to determine the reliability of the interpretation of this testing method in practicing podiatrists.

Methods: This was a multi-centre inter and intra-rater reliability study. Four podiatrists (the raters) participated in this study, two public and two private practitioners. Three aspects of Doppler use were examined; (i) use of Doppler (i.e., technique and interpretation), (ii) interpretation of Doppler audio sounds, and (iii) interpretation of visual Doppler waveforms (i.e., tracings). Participants meeting current guidelines for vascular screening attended two testing sessions, 1 week apart at either the private practice ($n = 32$), or the public practice ($n = 31$). To assess use of Doppler, the raters evaluated the Doppler waveforms that they collected, rating them as mono-phasic or multi-phasic. To assess Doppler audio sounds and visual Doppler waveforms, raters were required to evaluate 30 audio recordings of Doppler sounds and 30 waveform tracings, respectively, that were previously recorded and chosen at random by the researchers. Cohen's kappa (κ) statistics were used to calculate inter and intra-rater reliability using SPSS version 19.

Results: Use of Doppler demonstrated the lowest reliability for both pairs of clinicians (inter-rater reliability κ 0.20 to 0.24 and intra-rater reliability κ 0.27 to 0.42). The public podiatrists showed higher reliability in audio interpretation (inter-tester reliability κ 0.61, intra-tester reliability κ 1.00) compared to the private podiatrists (inter-tester reliability κ 0.31, intra-tester reliability κ 0.53). Evaluation of Doppler waveform tracings demonstrated highest reliability, with inter-rater reliability ranging from κ 0.77 to 0.90 and intra-rater reliability from κ 0.81 to 1.00.

Conclusions: There is a need for ongoing education for podiatrists using Doppler in clinical practice, as the reliability for the clinical use of the Doppler was low. This indicates that technique could be an issue. There is also a need to further evaluate if hand-held Doppler equipment, using the examinations that we evaluated, is suitable for use in the contexts examined in this study.

Keywords: Doppler, Reliability, Peripheral arterial disease

Background

Peripheral arterial disease (PAD) is associated with cardiovascular morbidity and mortality [1] and the development of lower limb wounds, gangrene and amputation. The condition becomes increasingly prevalent in older age, renal disease and inflammatory arthritis. PAD also occurs earlier, more distally and with more rapid progression in association with diabetes [2, 3]. Early detection is essential to ensure that modifiable risk factors are

identified and for the conditions to be appropriately monitored and managed to prevent potentially life-threatening complications.

Regular screening of those at risk of PAD is essential as only 22 % of people with PAD are symptomatic [4]. Current recommendations indicate routine lower limb vascular screening is required for those over the age of 65 years, or over 50 years with diabetes or a history of smoking [5]. Podiatrists are in an ideal position to carry out vascular screening on a regular basis, as people who are older and have diabetes frequently seek podiatric care [6]. With an ageing population and increasing

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Ourimbah NSW 2258, Australia



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prevalence of diabetes [7], non-invasive vascular screening is becoming increasingly important to prevent lower limb complications related to PAD.

Hand-held Doppler ultrasound examination (Doppler) of pedal arteries is the most frequently used non-invasive vascular assessment modality utilised by podiatrists [8] for diagnosis and ongoing monitoring of PAD. Podiatrists generally use Doppler in two different ways, as part of an ankle brachial index (ABI) or as a standalone test [8]. Doppler examination is a useful method for vascular screening as it has been demonstrated to be effective for detecting and excluding PAD, can be performed at relatively low cost and is non-invasive [9, 10].

In the foot, the dorsalis pedis and posterior tibial arteries are the most frequently examined due to their accessibility [11]. Both audio and visual analyses of Doppler waveforms are performed by clinicians to determine the presence of PAD. In audio analysis non-pathological Doppler waveforms are considered multiphasic, which includes bi-phasic (two) or tri-phasic (three) sounds [12, 13]. In contrast, a monophasic waveform is a single sound that is considered pathological [11], indicating the presence of PAD. In visual analysis of a Doppler tracing, a non-pathological waveform has a distinct shape representing high resistance and diastolic flow reversal, which can be classified as multiphasic (bi or tri-phasic). Pathological waveforms generally have low resistance, slow systolic acceleration and no diastolic flow reversal and are classified as monophasic [11].

The accurate use of Doppler relies upon multiple competencies including the skills involved in accurate application of the device, and concurrent interpretation of both audio and visual data to classify the waveform as normal or pathological. For this type of assessment to be useful for ongoing monitoring of PAD in practice, high reliability of the measurement is required. However, despite its widespread use in the podiatry profession, very little investigation has been completed on the reliability of either clinical measurement or interpretation for this type of assessment.

Currently, evidence of reliability of Doppler use in podiatry practice is isolated to interpretation of audio sound alone, with several studies demonstrating moderate inter-rater reliability [14, 15]. In professions other than podiatry, hand-held Doppler has been shown to have high levels of reliability [10]. A comprehensive assessment of the three elements of Doppler use (clinical application with waveform interpretation and independent audio and visual interpretation of waveforms) is required to determine the clinical efficacy of using this technique for ongoing peripheral vascular monitoring.

The aim of this study was to investigate the inter- and intra-rater reliability of the use of Doppler ultrasound for collection and interpretation of Doppler waveforms

by podiatrists in mixed clinical settings. This included: (i) overall use of Doppler to evaluate the pedal pulses (involving conducting the assessment and interpreting audio and visual outputs), (ii) interpretation of Doppler audio sounds presented independently, and (iii) interpretation of visual Doppler waveforms presented independently.

Methods

This was an inter- and intra-rater reliability study that took place over a period of 6 months (June – November 2013). Ethical approval was obtained from the University of Newcastle and Hunter New England Local Health District Ethics Committees, New South Wales, Australia (Reference number 13/02/20/5.05). All participants signed informed consent prior to being recruited into the study.

Raters

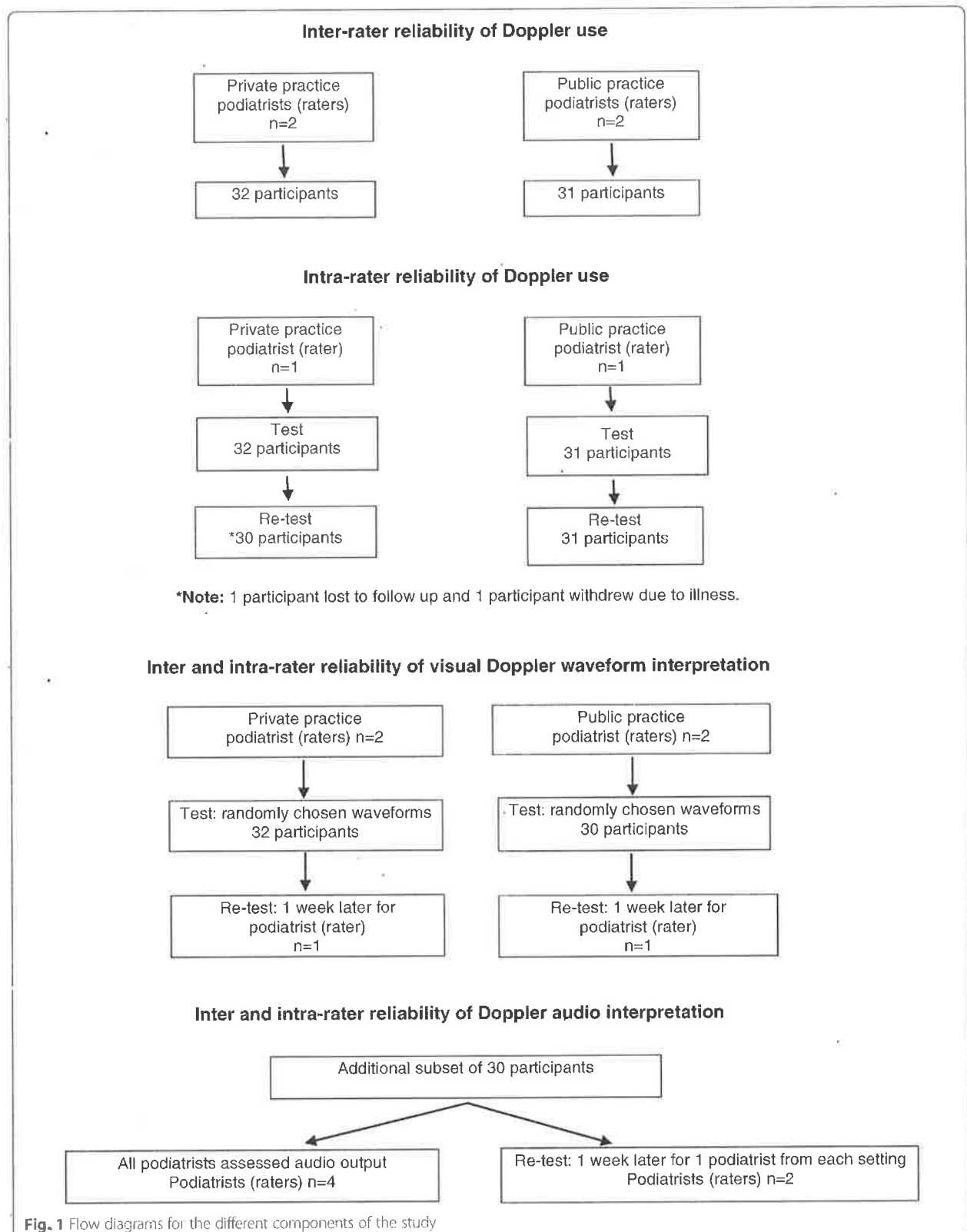
Four podiatrists (i.e., the raters) with varying levels of clinical experience (1–8 years) who studied at three different tertiary institutions across two states of Australia were invited, and subsequently agreed to participate in this study. The raters were selected to ensure varying levels of experience, training and employment sector were included. Written informed consent was obtained from each participating podiatrist. All raters had previous experience with use of Doppler ultrasound for lower limb vascular assessment and did not receive further instruction on how to perform this task.

Participants

A convenience sample from the patient populations at each respective clinic were recruited for this study. In accordance with current guidelines for lower extremity vascular screening, eligibility criteria were: people aged over 65 years, or, aged over 50 years with a history of diabetes or smoking, or with exertional leg pain or non-healing wounds [16]. This group was chosen as it is representative of people who may undergo these tests in clinical practice. Exclusion criteria were: contraindications to Doppler testing including active foot or leg ulceration preventing Doppler placement, known allergy to coupling gel and/or an inability to lie supine for more than 20 min.

Procedure

Two testing sites were used, one was a podiatry clinic in a community health centre (public practice) in the Newcastle area (New South Wales, Australia) and one was a private podiatry clinic (private practice) in the same catchment. Participants were assessed at the testing site of the service they attended (Fig. 1). All participants were instructed to avoid exercise, caffeine and smoking for at least 1 h prior to their assessment as these are



known to affect vascular assessment [17]. All assessments were undertaken in a quiet, private room. Raters were blinded to both their own and each other's results at all times. To ensure consistency with data collection, and minimise measurement and interpretation errors [18], a strict data collection protocol was used (Additional file 1).

Inter- and intra-rater reliability of Doppler use

For this part of the study the inter- and intra-rater reliability of podiatrists performing a Doppler ultrasound assessment of the dorsalis pedis and posterior tibial arteries and the podiatrists ability to interpret their results (i.e., use of the Doppler) was investigated. Participants at each setting were placed in a horizontal supine position and rested for at least 10 min prior to the assessment. To assess inter-rater reliability of clinical use of the Doppler, all podiatrists were required to independently assess dorsalis pedis and posterior tibial arterial flow using a Hadeco Smartdop 45° (Hadeco, Kawasaki) and Aquasonic® ultrasound transmission gel (Parker Laboratories, New Jersey). All testing equipment was new at the beginning of the study. The private practice podiatrists undertook assessment on participants attending the private clinic, and the public sector podiatrists undertook assessments on participants attending the community health podiatry clinic. Based on the audio and visual waveforms produced by their own Doppler assessments, all podiatrists then graded Doppler waveforms as absent, monophasic or multiphasic. All participants returned 1 week later to their original test site, either the public or private practice. Following the same test protocol, each participant had their waveforms obtained and graded again by one of the podiatrists from their previous testing session using the same procedure described previously.

Inter- and intra-rater reliability of Doppler audio interpretation

To determine the reliability of interpretation of Doppler audio alone, a single researcher (PT), who was not a rater in this study recorded dorsalis pedis and posterior tibial waveforms using the Hadeco Smartdop 45° from a separate, additional subset of 30 eligible participants recruited to the community health centre. Participants were rested in horizontal supine position for a minimum of 10 min prior to assessment. Doppler audio were recorded using a digital Dictaphone held approximately 10 cm from the Doppler speaker. Each set of Doppler audio were recorded for 20 s with the Doppler volume set at high. Either the dorsalis pedis or posterior tibial waveform was then randomly selected for each participant. To determine inter-rater reliability the same selected waveform audio files were then separately played to the four participating podiatrists who evaluated them independently as monophasic or multiphasic. To determine

the intra-rater reliability one of the private podiatrists, and one of the public podiatrists repeated the assessment of the same 30 audio files 1 week later, with the order of presentation of the audio files randomised to avoid order error.

Inter- and intra-rater reliability of visual Doppler waveform interpretation

To isolate reliability of visual interpretation of Doppler waveforms a researcher (PT) who was not a rater in this study, randomly chose 30 printed Doppler waveforms (i.e., tracings) collected by the four raters involved in this study. Each rater was then asked to rate them as monophasic or multiphasic based on the printed waveform. One of the private podiatrists, and one of the public podiatrists repeated the assessment 1 week later using the same set of 30 printed waveforms with the order randomised.

Data analysis

Inter-rater reliability of (i) waveform interpretation for clinical use of the Doppler, (ii) interpretation of independently collected audio recordings, and (iii) interpretation of independently collected visual waveforms between the two private podiatrists and between the two public podiatrists was calculated by determining the level of agreement between measures using an unweighted Cohen's kappa (κ) statistic with 95 % confidence intervals. All waveforms were classified as pathological (absent or monophasic) or non-pathological (multiphasic). Intra-rater reliability was calculated in the same manner for one of the public podiatrists and one of the private podiatrists for the three aspects of Doppler use detailed above.

Results were interpreted in accordance with Landis and Koch: ≥ 0.75 denotes excellent agreement; > 0.40 but < 0.75 denotes fair to good agreement; and < 0.40 denotes poor agreement [19]. All reliability analyses were conducted using SPSS version 19.

Results

Thirty two participants attended the private practice and 31 participants attended the public practice. Of these, according to the inclusion criteria, 23 (public group) and 15 (private group) were over 50 years of age with diabetes, and 9 (public group) and 15 (private group) were over 65 years of age. No participants had active wounds or exertional leg pain, and only one participant was a current smoker (private group). In the public participant group, there was a larger age range and lower mean age than the private participant group. The public participant group also had higher rates of diabetes than the private participant group. Participant characteristics are listed in Table 1.

Table 1 Participant characteristics

| | Public participants | Private participants | Audio interpretation |
|-------------------|---------------------|----------------------|----------------------|
| Males n (%) | 17 (53) | 18 (58) | 17 (56) |
| Females n (%) | 15 (47) | 13 (42) | 13 (44) |
| Mean age (years) | 70.9 (SD 7.1) | 72.0 (SD 5.7) | 71.6 (SD 6.7) |
| Age range (years) | 57 - 88 | 61 - 81 | 55 - 82 |
| DM n (%) | 23 (72) | 15 (48) | 19 (63) |
| Total N | 32 | 31 | 30 |

For Doppler use the public participant group was evaluated by the public practice raters, and private participants were evaluated by private practice raters. For visual Doppler waveform analysis, a sub-set of 30 printed waveforms from both public and private participants were randomly selected and evaluated by all raters. For audio interpretation all raters evaluated the recorded sounds of the sub-group listed above
SD standard deviation, DM diabetes mellitus

Inter- and intra-rater reliability of Doppler use

Inter-rater reliability for use of Doppler was poor between the private podiatrists and between public podiatrists for both dorsalis pedis and posterior tibial arteries (Table 2) with 95 % confidence intervals crossing zero. The private podiatrist demonstrated the highest intra-rater reliability for collection and classification of Doppler waveforms for the posterior tibial artery examination (κ : 0.42), which corresponds to fair agreement. Intra-rater reliability was poor for both dorsalis pedis (κ : 0.21) and posterior tibial artery waveforms collected and classified by the public podiatrist (κ : 0.27).

Inter- and intra-rater reliability of Doppler audio interpretation

Reliability of Doppler audio interpretation was fair for public podiatrists (κ : 0.61) and poor for the private podiatrists (κ : 0.31) (Table 3). Intra-rater reliability of Doppler audio interpretation was excellent for the public podiatrist (κ : 1.00) and fair for the private podiatrist (κ : 0.53).

Inter- and intra-rater reliability of visual Doppler waveform interpretation

The inter-rater reliability of visual Doppler waveform interpretation was excellent for both the private and public podiatrist (κ : 0.90 and κ : 0.77 respectively)

(Table 4). Similarly, intra-rater reliability of visual interpretation of the waveforms for both the private podiatrist and public podiatrist were excellent (κ : 1.00 and κ : 0.81 respectively).

Discussion

To the best of the authors' knowledge this is the first study to examine the reliability of the use of Doppler and waveform interpretation skills in podiatrists. Our results demonstrate that the reliability of Doppler use with classification of waveforms was generally poor. Interpretation of independently collected Doppler audio demonstrated moderate inter-rater reliability and moderate to excellent intra-rater reliability. Finally, visual Doppler waveform interpretation of independently collected waveforms yielded excellent inter-rater and intra-rater reliability in both private and public podiatrists.

These results suggest podiatrists had higher skill level in interpretation of visual waveforms and audio of Doppler waveforms in isolation than when the assessment had to be performed and the visual and audio results interpreted concurrently in a clinical setting. Generally, the 95 % confidence intervals for inter- and intra-rater reliability of the clinical use of Doppler included a negative lower limit. This suggests the range of plausible values for the "true" value of kappa included levels of agreement less than zero, which would be worse than the level of agreement expected from chance alone; that is, if the raters were to guess each rating [20]. The poor levels of agreement between and within clinicians for this aspect of the study may have been related to clinical technique in Doppler use or increased difficulty associated with interpreting visual and audio results simultaneously.

From a clinical perspective Doppler use can be difficult, particularly if patients have issues such as peripheral oedema, if there is fibrosis or adipose tissue present and/or there is anatomical variation in artery location. Such factors affecting reliable performance of the assessment may, therefore, have contributed to poorer reliability seen in this aspect of Doppler use. In addition, the requirement in this present study for clinicians to interpret both visual and audio outputs concurrently to inform their decision on presence or absence of pathology may have resulted in poorer reliability. Higher reliability may have been achieved by reducing the output of the Doppler to one variable, either audio or visual

Table 2 Reliability results for use of Doppler

| Table 2. Reliability results for the 30-item Supplier | | | | | | | | | |
|---|--------------------------------|---------------|--------------------------------|---------------|---------|--------------------------------|---------------|--------------------------------|---------------|
| | Inter-rater reliability | | | | | Intra-rater reliability | | | |
| | DP | 95 % CI | PT | 95 % CI | | DP | 95 % CI | PT | 95 % CI |
| Private | κ 0.20 (<i>N</i> = 32) | −0.09 to 0.49 | κ 0.16 (<i>N</i> = 32) | −0.11 to 0.43 | Private | κ 0.22 (<i>N</i> = 30) | −0.31 to 0.53 | κ 0.42 (<i>N</i> = 30) | 0.15 to 0.69 |
| Public | κ 0.17 (<i>N</i> = 31) | −0.14 to 0.48 | κ 0.24 (<i>N</i> = 31) | −0.07 to 0.55 | Public | κ 0.21 (<i>N</i> = 31) | −0.16 to 0.58 | κ 0.27 (<i>N</i> = 31) | −0.06 to 0.60 |

95 % CI 95 % confidence intervals, DP dorsalis pedis artery, PT posterior tibial artery, Private private practitioners, Public public practitioners

Table 3 Reliability results for Doppler audio interpretation

| | Inter-rater reliability | 95 % CI | | Intra-rater reliability | 95 % CI |
|---------|---------------------------|---------------|---------|---------------------------|--------------|
| Private | κ 0.31 (N = 30) | -0.08 to 0.70 | Private | κ 0.53 (N = 30) | 0.16 to 0.91 |
| Public | κ 0.61 (N = 30) | 0.23 to 0.99 | Public | κ 1.00 (N = 30) | 1.00 to 1.00 |

95 % CI 95 % confidence intervals, Private private practitioners, Public public practitioners

waveform to make the interpretation process more simple. However, as podiatrists are required to do both simultaneously in clinical practice, our results suggest that further training in Doppler use including concurrent interpretation of visual and audio waveforms, is required for this to be an effective component of non-invasive vascular assessment.

Visual Doppler waveform analysis of independently collected waveforms had the most consistently high inter- and intra-rater reliability in this study. As far as we are aware, this is the first study to examine the reliability of visual Doppler waveform analysis in podiatrists. Based on our results, when visual waveform tracings alone were presented to podiatrists in both private and public practices they were able to reliably classify pathological or non-pathological waveforms between themselves and on a test-retest basis. However, interpretation of Doppler audio of waveforms showed much more variable reliability between the two tester groups. Whilst public podiatrists had reasonable inter-rater reliability for interpretation of audio data (κ : 0.61) and perfect intra-rater reliability (κ : 1.00), the private podiatrists had lower inter- and intra- rater reliability (ranging from κ : 0.31 to κ : 0.53).

Previous studies have shown much higher levels of reliability in analysis of audio waveforms in podiatrists [14, 15]. The differences in reliability between private and public sector podiatrists may be due in part, to the differences between the public and private participant (i.e., patient) groups. Although this study did not include any assessment of diagnostic accuracy of the Doppler for PAD, the participant group assessed by the public podiatrists had double the incidence of diabetes. Given increased rates and severity of PAD in this population [21], it is possible that more severe disease was

present, which was more easily detected and interpreted resulting in higher reliability.

The low reliability of clinical use of Doppler for peripheral arterial assessment demonstrated in this present study poses significant implications for ongoing patient care. Vascular assessments of patients tend to occur annually and are interpreted relative to previous results. The reliability of assessments is essential for accurate and appropriate management. Given the poor reliability of Doppler use that we found in this study, reliance on this test in isolation is problematic. Our results suggest that, in the small sample of podiatrists we studied, Doppler assessments are of limited use as a tool for ongoing monitoring in clinical practice and, at the very least, it is essential for other objective vascular tests (e.g., Ankle Brachial Index) to be incorporated in the annual screening process. Research has demonstrated that reliability of use and interpretation of Doppler has been achieved in other professions supporting the use of this form of assessment for ongoing monitoring in clinical practice [10, 22]. Although Australia does not currently have any specific guidelines for lower limb vascular assessment in the general population at risk of PAD, the United Kingdom currently use National Institute for health Care Excellence (NICE) guidelines, which recommend documentation and analysis of Doppler waveforms as part of an overall vascular assessment [23]. Our results suggest that further skill development is required specifically for podiatrists to ensure clinical utility of Doppler use within the profession.

The results of this study need to be interpreted in light of several limitations. Firstly, the type of Doppler used may have influenced this study and it is unknown if similar results would be achieved if Doppler ultrasound units from alternative manufacturers had been used or if participating podiatrists had used their regular equipment. However, the style of Doppler used in this study is one commonly used in clinical practice. Secondly, it was assumed that participating podiatrists had previously been trained in Doppler ultrasound assessment, so additional training was not provided. A training session provided prior to the study may have improved reliability, but we avoided this as we wanted results to be an accurate reflection of current skills of practicing clinicians. Nonetheless, raters were given a strict protocol for data collection, which realistically would be expected to improve the reliability of the assessment. Thirdly, clinical experience levels of raters ranged from 1 to 8 years, which may have affected reliability. Although the least experienced podiatrist demonstrated the highest intra-rater reliability for clinical use of Doppler, so this seems unlikely. Finally, despite our best efforts to include podiatrists with a range of experience and undergraduate training from the two main areas of clinical practice

Table 4 Reliability results for Doppler visual interpretation

| | Inter-rater reliability | 95 % CI | | Intra-rater reliability | 95 % CI |
|---------|---------------------------|--------------|---------|---------------------------|--------------|
| Private | κ 0.90 (N = 32) | 0.71 to 1.09 | Private | κ 1.00 (N = 32) | 1.00 to 1.00 |
| Public | κ 0.77 (N = 30) | 0.53 to 1.01 | Public | κ 0.81 (N = 30) | 0.57 to 1.05 |

95 % CI 95 % confidence intervals, Private private practitioners, Public public Practitioners

(public and private), the clinicians participating in this study may not have been representative of the podiatry profession as a whole. Further investigation in other samples may assist in establishing the true reliability within the podiatry profession generally.

Conclusions

This study demonstrated that in Australian podiatrists in private and public practice visual Doppler waveform interpretation is the most reliable aspect of Doppler use, followed by Doppler audio interpretation. The poor reliability of the use of Doppler in the small cohort of practitioners in this study suggests that this form of assessment may be of limited use for ongoing monitoring. This finding highlights the need for clinicians to engage in regular and ongoing continuing education in order to improve both collection of Doppler data and interpretation of visual waveforms and audio sounds concurrently. In addition our results suggest that reliance on only qualitative Doppler assessment for ongoing assessment of lower limb arterial status is problematic and that multiple methods of assessing vascular status should be employed.

Additional file

Additional file 1: Clinical use of Doppler reliability study: Testing protocol for podiatrists. (DOCX 70 kb)

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

PT contributed to the research design, data collection, data analysis and writing of the manuscript. VC guided interpretation of results, assisted with data analysis and provided assistance with writing of the manuscript. Both authors read and approved the final manuscript.

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Appendix 17

Manuscript Number: YFOOT-D-16-00034

Title: A targeted screening method for non-invasive vascular assessment of the lower limb

Article Type: Original Article

Keywords: non-invasive vascular assessment, lower limb, peripheral arterial disease, ankle-brachial index, toe-brachial index

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Abstract: Routine lower limb vascular assessment in podiatry varies widely with time cited as a major barrier to performing assessment in accordance with current international guidelines. The aim of this study was to investigate the diagnostic accuracy of a modified version of current vascular assessment guidelines for detecting PAD.

Method

Non-invasive vascular assessments were performed with CFDU was used as a reference standard. Diagnostic accuracy of tests conducted in accordance with American Heart Association (AHA) guidelines for the presence of PAD was compared to that of a modified version of the guidelines.

Results

119 participants were included. Sensitivity of the modified method (62%, 95%CI 47.17-75.35) was higher than the AHA method (49%, 95%CI 34.75 - 63.40), however specificity of the AHA method (94%, 95%CI 85.62 - 98.37) was higher than the modified method (85%, 95%CI 74.26 - 92.60). Diagnostic accuracy of the AHA guidelines (74%) and modified method (73%) for PAD were similar.

Conclusion

Compared to current guidelines the modification used in this study did not significantly affect diagnostic accuracy and could reduce time taken for vascular assessment to be performed. This study highlights the difficulties in obtaining accuracy in lower limb vascular assessment in general.

FACULTY OF HEALTH



Friday 25th March, 2016
The Foot

Dear Editors,

Please find attached the manuscript: *A targeted screening method for non-invasive vascular assessment of the lower limb*. Routine lower limb vascular assessment is fundamental to ensuring early intervention and preventing complications related to peripheral arterial disease (PAD). Vascular assessment techniques vary widely in podiatry practice with time required for undertaking objective pressure testing cited as a major barrier to performing assessment in accordance with current international guidelines. The aim of this study was to investigate the diagnostic accuracy of a modified version of current vascular assessment guidelines for detecting PAD. The modifications were made to reduce the time required to complete assessments to encourage more widespread application of accurate vascular assessment in Podiatry practice.

Non-invasive vascular assessment objective tests pressure tests including the ankle- and toe-brachial index and continuous wave Doppler were performed in a population at risk of PAD using duplex ultrasound as a reference standard. Diagnostic accuracy of tests conducted in accordance with American Heart Association (AHA) guidelines for the presence of PAD was compared to that of a modified version of the guidelines.

In a sample of one-hundred and nineteen people at risk of PAD, sensitivity of the modified method was higher than the AHA method, however specificity of the AHA method was higher than the modified method. Diagnostic accuracy of the AHA guidelines (74%) and modified method (73%) for PAD were similar. Compared to current guidelines the modification used in this study did not significantly affect diagnostic accuracy and reduced the number of cases of undiagnosed disease in the study population and could reduce time taken for vascular assessment to be performed. similar accuracy. This study highlights the difficulties in obtaining accuracy in lower limb vascular assessment in general.

Both authors were fully involved in the preparation of this manuscript and this manuscript has not been submitted elsewhere. Thank you for your consideration of this manuscript for publication in The Foot.

Kind Regards,

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***Conflict of Interest Statement**

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A targeted screening method for non-invasive vascular assessment of the lower limb

ORIGINAL ARTICLE

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Keywords: non-invasive vascular assessment, podiatrist

Total word count: 2,242

Brief Summary

- A modified method for assessment for PAD yields similar diagnostic accuracy to the current international AHA guideline
- Clinicians may save time by utilising the modified method whilst yielding similar diagnostic accuracy to the AHA guideline therefore removing a major barrier in performing vascular screening
- Both the AHA guideline and the modified method had relatively low sensitivity in detecting PAD reinforcing the difficulty of lower limb non invasive vascular assessment in populations at risk of the disease.

A targeted screening method for non-invasive vascular assessment of the lower limb

ORIGINAL ARTICLE

Keywords: non-invasive vascular assessment, podiatrist

Total word count: 2,242

Introduction

Identifying the presence and extent of peripheral arterial disease (PAD) through accurate lower limb vascular assessment is essential for reducing morbidity and mortality associated with the disease[1]. Through early identification of PAD, complications such as ulceration, gangrene and amputation can be reduced or avoided using aggressive risk factor modification, provision of ongoing foot care and foot care education [2, 3, 4]. It has been estimated that up to 90% of amputations are preventable [2,3,4] with adequate foot screening including vascular assessment playing a vital role in reducing complications and improving clinical outcomes [1]. Accurate and effective vascular assessment requires a complex reasoning process which takes into account a patient's vascular risk factors as well as an awareness of the effect of co-morbidities on the clinical efficacy of assessments techniques, and, subsequent interpretation of results to formulate an evidence-based management plan.

Podiatrists play a central role in conducting non-invasive lower limb vascular assessments in the general population. We have recently demonstrated that on average, podiatrists perform two vascular assessments per day however the type of the testing that is conducted during the assessments is extremely varied and, potentially inadequate for accurate PAD screening [2]. Based on these findings, although there are several available international guidelines for performing screening for PAD, the uptake of these recommendations into clinical practice appears to be inconsistent[2]. Time required to perform recommended objective testing,

1 particularly the ankle-brachial index (ABI) is the most widely nominated barrier to conducting
2 appropriate vascular assessment [2, 3] with clinicians often relying on more quickly applied
3 assessments including continuous wave Doppler (CWD) and pulse palpation. In addition there is
4 growing evidence of the reduced accuracy of the ABI for detecting PAD in specific populations
5 including those at risk of medial arterial calcification (MAC) particularly when co-existing with
6 PAD and of a more distal distribution of atherosclerotic lesions including diabetes, renal disease,
7 and older aged cohorts [4]. In such patient populations further alternate testing including the
8 toe brachial index (TBI) is frequently required, adding to the time required to complete an
9 assessment. Our recent research suggests more quickly applied vascular assessment techniques
10 such as the TBI and CWD may be suitable for use as first line assessment techniques for PAD
11 assessment, particularly in older people and those with diabetes [5, 6]. The aim of this study
12 was to determine if a modified version of current guidelines in which the the TBI was used
13 initially in patient populations in which the ABI is known to be problematic could achieve
14 similar diagnostic accuracy to testing protocols outlined in current guidelines where the ABI is
15 used as the primary objective testing method for all people at risk of PAD.
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34 **Material and methods**

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36 An extensive review of the literature was performed. Combined with recent research completed
37 by the researchers[5, 6] which examined the diagnostic accuracy of the ABI, TBI and CWD in
38 different populations at risk of PAD, a modified vascular assessment method was developed that
39 is applied based on a patient's medical history. The modified method used the patient's risk
40 factors for PAD combined with the known limitations of the ABI to assist the clinician choose
41 the most accurate vascular test in the specific patient population being assessed. In the modified
42 method the presence of diabetes and/or renal disease, or being of advanced age were used as a
43 prompt for the clinician to perform a TBI due to the reduced diagnostic accuracy of the ABI in
44 these populations [4, 5, 7]. In the modified method all other risk factors for PAD led the clinician
45 to perform an ABI as this has been demonstrated to be an adequate test in the general
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1 population at risk of PAD and, in the absence of diabetes, renal disease or advanced age [8]. All
2 patients had CWD performed as this is an accessible, quick and relatively simple test to perform
3 which has been shown to be reliable and accurate in populations requiring vascular screening
4 and a useful adjunct to peripheral pressure testing [5, 7, 9, 10]. The modified method was then
5 directly compared to the American Heart Association (AHA) guideline[11] to determine relative
6 diagnostic accuracy of both screening techniques for PAD. Ethics approval was obtained
7 through the University of Newcastle ethics committee.
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17 Participants were recruited on a volunteer basis from two different locations, a community
18 health centre in Newcastle, NSW, and a private podiatry practice in Nelson Bay NSW.

19 Participants who fitted the AHA guidelines for peripheral vascular screening were eligible to
20 participate; i.e. patients over the age of 65, patients above the age of 50 with the presence of
21 diabetes or currently smoking or patients with exertional leg pain. Participants who were
22 unable to comply with the testing protocol or who had a vasospastic disorder preventing TBI
23 measurement were excluded. Testers included three vascular sonographers who performed
24 colour duplex ultrasounds (CFDU) at a private clinic in Newcastle. CFDU reliability has
25 previously been assessed [6] and found to be acceptable.
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38 **Experimental procedure**

39 All participants then attended a testing session at the vascular clinic with one of three ultra
40 sonographers. During the testing session ABI and TBI measurements, Doppler waveform
41 tracings and CFDU were performed on the right leg using methods and equipment described
42 previously[5]. CFDU was chosen as it has been demonstrated to be a valid imaging technique in
43 non-invasive vascular diagnostic testing [12, 13]. The right limb only was used to comply with
44 the assumption of independence of data in statistical testing [14]. Participants were asked to
45 avoid alcohol, smoking, exercise and caffeine one hour prior to the testing session to avoid
46 influencing pressure measurement [15]. Participants were placed in a supine position and
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rested for at least 10 minutes prior to pressure measurements being taken. Room temperature was monitored with a thermometer and was maintained between 23°C and 25°C [16].

The AHA guideline was applied to the entire data set by a single researcher (PT) i.e. the ABI result was used unless it exceeded 1.4 in which case it was replaced by the TBI. These results were used to determine the diagnostic accuracy of the AHA guidelines for detecting PAD using CFDU as the reference standard. The modified method was also applied to the entire data set by a single researcher (PT) i.e. the ABI was used unless diabetes or renal failure was present or participants were aged over 75 years in which case the TBI value was used. These results were used to determine the diagnostic accuracy of the targeted screening method for detecting PAD using CFDU as a reference standard.

For statistical calculations relating to diagnostic accuracy, presence of PAD was defined as one or more arteries with >50% stenosis [17, 18]. Sensitivity, specificity, positive and negative predictive values and likelihood ratios were calculated with 95% confidence intervals for the AHA screening method and the targeted screening method. Calculations of diagnostic accuracy were performed using Microsoft Excel.

Results

A total of 120 participants were recruited (Table 1) however one participant was excluded as the CFDU scan was performed on a different day to the remainder of the vascular examination. An additional two participants were excluded from the targeted screening method due to missing toe pressure data. Generally the population was older, in accordance with the inclusion criteria. There were a high number of participants with diabetes (61%). Sensitivity of the modified method (62%, 95%CI 47.17-75.35) was higher than the AHA method (49%, 95%CI 34.75 – 63.40), however specificity of the AHA method (94%, 95%CI 85.62 – 98.37) was higher than the targeted screening method (85%, 95%CI 74.26 – 92.60) (Table 2). Overall the

1 diagnostic accuracy of both methods were similar, with the AHA screening method 74%
2 diagnostic accuracy and the targeted screening method 73% diagnostic accuracy.
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5 **Discussion:**

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9 This study investigated whether diagnostic accuracy of lower limb vascular screening for PAD
10 can be achieved using a modified version of current guidelines designed to reduce the time
11 taken to perform a vascular assessment. The results of this study indicate that the modified
12 method had a higher sensitivity for PAD than when tests were conducted in accordance with the
13 AHA guidelines, however lower specificity. Overall the two methods had almost identical
14 diagnostic accuracy (AHA method 74%, modified method 73%). Although the ABI has been
15 shown to have good sensitivity and excellent specificity across the general population [8] our
16 recent research suggests uptake of the test by Podiatrists is poor with the time associated with
17 performing the test cited as one of the most common reasons for this [2]. Performing an ABI
18 requires two ankle pressures per limb (dorsalis pedis and posterior tibial). The modified
19 method we have proposed increases the number of people who have a TBI performed as the
20 initial screening test. A TBI test is quicker to perform due to the need for only one toe pressure
21 per limb to be taken. In addition the modified method ensures there will rarely be a time that
22 clinicians will need to perform more than one form of lower limb pressure measurement in a
23 single testing session. Both changes are likely to reduce the amount of time needed to perform
24 objective non-invasive vascular testing. .
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46 Currently evidence suggests podiatrists rely on subjective findings including pulse palpation
47 and visual appearance to identify PAD, while object assessment is often limited to continuous
48 wave Doppler which we have shown to have poor reliability [2, 19]. The modified method we
49 have developed offers a potential mechanism to improve the diagnostic accuracy of vascular
50 assessments performed by podiatrists by targeting the type of objective test to be used using
51 medical history. In addition increasing the use of the TBI, which has been shown to have high
52 reliability in diabetes and non diabetes cohorts for initial testing for PAD [20], offers a more
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time efficient objective test that may be more widely adopted in clinical practice. There is also growing evidence that tests such as the TBI may be a valuable adjunct to clinical practice and could be more widely used. The TBI has been shown to have superior predictive capability than the ABI, with recent research showing that both toe pressures and TBI to be accurate predictors of wound healing and foot complications [21].

Of note our study demonstrates that neither screening method yielded a very high level of diagnostic accuracy, which re-enforces the difficulty of non-invasive lower limb vascular assessment in populations at risk of PAD. Further investigation into the diagnostic accuracy of non-invasive vascular assessment testing methods should be undertaken to ascertain what testing should be performed in populations at risk of PAD. The diagnostic accuracy of both the ABI and TBI should be elucidated using gold standard imaging as a reference standard. Further research that helps guide clinical practice could facilitate increased efficiency and increased accuracy when conducting vascular assessments, reducing the number of undiagnosed cases of PAD and ensuring timely intervention and appropriate management to prevent complications such as ulceration and infection and amputation.

The results of this pilot study need to be considered in light of some significant limitations. The accuracy of both screening tools relies upon the individual accuracy of each diagnostic test. Each of the included tests, ABI and TBI have their own limitations with accuracy. The ABI in particular has been shown to have limited diagnostic accuracy in populations at risk of PAD. The reference standard used, CFDU, whilst a valid form of diagnostic imaging, and used extensively clinically, also has limitations with diagnostic accuracy. Ideally angiography would be used as a reference standard however due to the prospective nature of the data collection for this study this was not possible. Future research should use retrospective data and use the gold standard in vascular imaging, angiography as a reference standard.

Conclusion

Modification of current international guidelines based on medical history to reduce the time burden of lower limb vascular assessment in clinical practice yields similar diagnostic accuracy to assessment undertaken in accordance with the guidelines. This study highlights the difficulties in obtaining accuracy in lower limb vascular assessment in at risk populations and clinicians should consider using the TBI as an alternate screening tool given its high level of accuracy and predictive capabilities.

Brief Summary

- A modified method for assessment for PAD yields similar diagnostic accuracy to the current international AHA guideline
- Clinicians may save time by utilising the modified method whilst yielding similar diagnostic accuracy to the AHA guideline therefore removing a major barrier in performing vascular screening
- Both the AHA guideline and the modified method had relatively low sensitivity in detecting PAD reinforcing the difficulty of lower limb non invasive vascular assessment in populations at risk of the disease.

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Table

Table 1: Participant Information

| | |
|--|----------------------------|
| Total Participants (N) | 119 |
| Males n (%) | 75 (63.02) |
| Females n (%) | 44 (36.97) |
| Age Range (Years) | 53 – 92 |
| Diabetes n (%) | 73 (61.34) |
| Mean Age (years) | 73.1 (SD ^Δ 7.2) |
| Incompressible ankle pressure n (%) | 16 (13.44) |
| Distal FAD n (%) | 37 (31.09) |
| Proximal PAD n (%) | 7 (5.88) |
| Distal & Proximal PAD n (%) | 7 (5.88) |
| PAD n (%) | 51 (42.85) |
| Proximal Occlusions n (%) | 1 (0.84) |
| Distal Occlusions n (%) | 40 (33.61) |
| ^Δ =standard deviation, PAD= Peripheral arterial disease | |

Table 2: Results

| Results Table | | | | |
|---|---------------------------|-------------------------|--------|-------------------------|
| Participant Group | Targeted Screening Method | | AHA | |
| | % | 95% Confidence Interval | % | 95% Confidence Interval |
| Sensitivity | 62.00 | 47.17 to 75.35 | 49.02 | 34.75 to 63.40 |
| Specificity | 85.07 | 74.26 to 92.60 | 94.12 | 85.62 to 98.37 |
| Positive predictive value | 75.61 | 2.25 to 7.66 | 86.21 | 68.34 to 96.11 |
| Negative Predictive Value | 75.00 | 0.31 to 0.65 | 71.11 | 60.60 to 80.18 |
| Positive likelihood ratio | 4.15* | 2.25 to 7.66 | 8.33** | 3.09 to 22.45 |
| Negative likelihood ratio | 0.45* | 0.31 to 0.65 | 0.54 | 0.41 to 0.71 |
| Diagnostic Accuracy | 73.94 | | 74.78 | |
| **Important likelihood ratio *May be important likelihood ratio | | | | |
| | | | | |

Appendix 18

A meta-analysis was conducted on 6 studies reporting the sensitivity and specificity of the Toe Branchial Index as a diagnostic tool for peripheral arterial disease (Table 1).

A bivariate model was used to analyse pairs of the logit of sensitivity and logit of specificity. These models take into account the heterogeneity between studies (random effects model) and the possible correlation between the two estimates. A correction factor of 0.5 was added to the sample size and sensitivity/specificity recalculated if the reported values equal to 1. Summary measures such as the mean sensitivity and specificity, the diagnostic odds ratio, and Receiver operating characteristic (ROC) curve and the area under the curve will be presented. P-values and confidence intervals for the estimates will be derived based on a normal distribution with a d.f of 1000.

Table 1. Summary of studies used in meta-analysis of TBI.

| Study | Year | Sensitivity (corrected value) | Specificity (corrected value) | # with disease | # without disease | Notes |
|----------|------|-------------------------------------|-------------------------------------|-------------------|----------------------|---|
| Tehan | 2015 | 0.71 | 0.79 | 51 | 68 | Frequencies reported do not match up to sensitivity/specificity - may be missing values. |
| Ohtake | 2011 | 0.826 | 0.86 | 46 | 51 | |
| Okamoto | 2011 | 0.452 | 1 (0.981) | 45 | 26 | |
| Park | 212 | 1 (0.963) | 1 (0.978) | 13 | 22 | |
| Suominen | 2008 | .099 | Not reported | 69 | Not reported | |
| Weinberg | 2013 | 0.92 | Not reported | 100 | Not reported | |
| Williams | 2005 | 1 | 0.76 | 13 | 21 | |

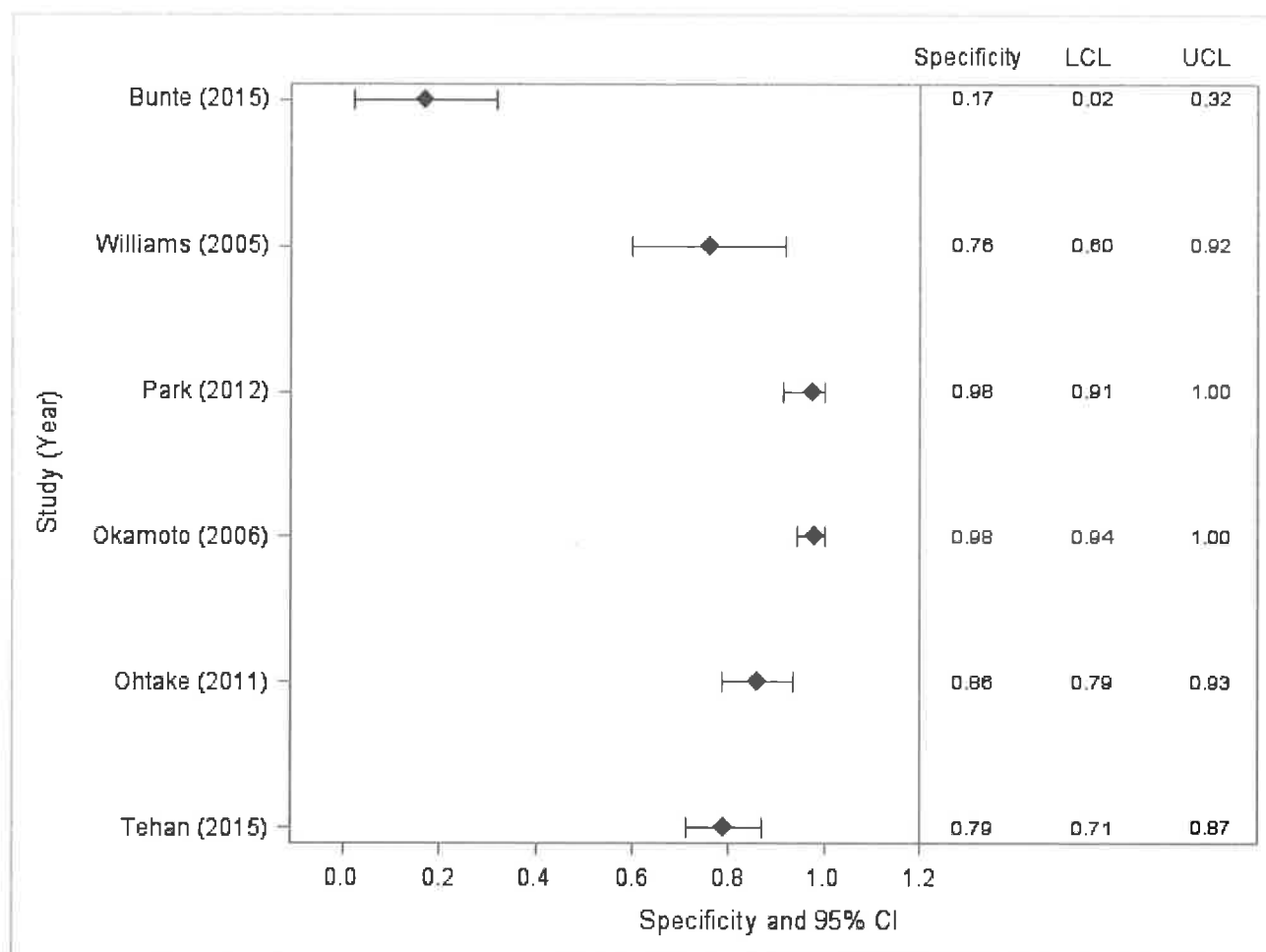


Fig 2: Forrest plot of reported specificities from 6 studies.

Meta analysis of 7 studies show that TBI have a high sensitivity and specificity in detecting PAD. The high diagnostic odds ratio and AUC is indicative of a good test performance.

Table 2. Summary estimates for sensitivity, specificity, and diagnostic odds ratio from the bivariate model

| Estimate | Sensitivity ex Weinberg and Suominen (95% CI) | Specificity ex Weinberg and Suominen (95% CI) | Correlation between Sensitivity and Specificity | Diagnostic Odds Ratio (95% CI) | Sensitivity inc Weinberg and Suominen (95% CI) |
|----------|---|---|---|--------------------------------|--|
| Mean | 0.78 (0.59 – 0.90) | 0.82 (0.56 – 0.94) | -0.89 | 16.8 (6.5 – 43.0) | 0.87 (0.67 – 0.96) |

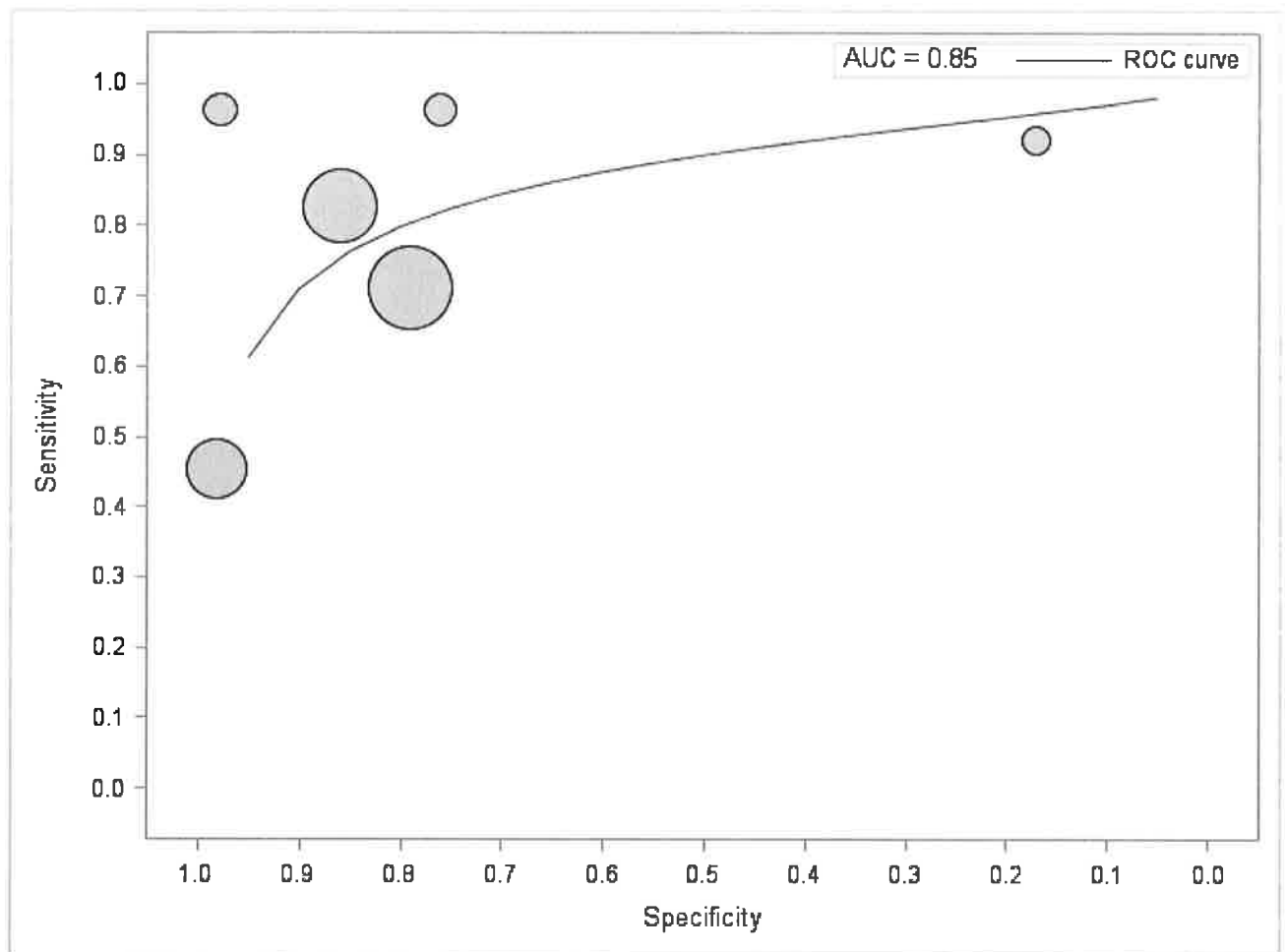


Fig 3. ROC plot of predicted sensitivity against specificity of 6 studies. The size of the points correspond with the total sample size. The ROC curve and AUC were derived from the bivariate model.