INITIAL FINDINGS IN THE SENSITIVITY AND SPECIFICITY OF THE TOE BRACHIAL INDEX IN DETECTING PERIPHERAL ARTERIAL DISEASE

ORIGINAL ARTICLE

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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.

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 (1, 2). As many PAD sufferers are asymptomatic, the condition is highly under-recognised (3) and if untreated can ultimately lead to the development of wounds, gangrene and amputation (4). Presence of PAD is also an indicator of systemic arterial disease and is associated with an increased risk of a cardiovascular event (5) and associated mortality (6).

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 (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 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 (10, 11). 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 (10, 12). An elevated ABI (>1.4), is generally accepted to be indicative of MAC (8) . However, further complicating lower extremity

vascular testing in these patients, presence of MAC is also associated with significant lower extremity atherosclerosis (13). 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 (2) 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 (12).

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 (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 haemodialysis 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 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.

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 (18): 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 (3, 19). The right limb only was used to comply with the assumption of independence of data in statistical testing (20). 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 (21). 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 guage. Toe pressures were obtained with a photoplythsmograph (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 (22). 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 (24, 25). 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 (26, 27). 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 (28). Interpretation of the Cohen's K statistic was performed using the method proposed by Landis and Koch (29). All reliability analyses were conducted using SPSS version 19.

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 1.

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 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) (Fig 1). This indicates in this population the ABI was a poor test (30). The sensitivity and negative predictive value of the ABI of 45% and 69% reflects an increased risk of failure to diagnose existing disease (Table 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.

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 (Fig.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 while lower than the ABI result, suggests that the TBI is relatively unlikely to falsely detect PAD.

Inter-tester reliability of the CFDU scans between the three ultra-sonographers was high (K 0.78, $p<0.01$)(29). 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)(31).

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%) (32-35) however in patients with diabetes or renal disease sensitivity of the ABI has been shown to be considerably lower (29.9-53%)(10, 11). 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

192 to affect the accuracy of the ABI in people with diabetes, renal disease and in older age, the
193 prevalence of clinical and subclinical MAC within the general population remains controversial.

194 MAC has been estimated to affect approximately 13.3% of males and 6.9% of females in a
195 population at risk of PAD (36). However cut off points for the diagnosis of MAC by the ABI have been
196 questioned. Further complicating matters, the presence of a sub-clinical MAC has been proposed,
197 which goes undetected by the ABI (4). It is therefore difficult to determine the extent to which the
198 accuracy of the ABI may be affected and the efficacy of using the measurement as a screening tool.
199 Current recommendations suggest a toe pressure be used only in the presence of an ABI elevated to
200 beyond 1.40, however this does not address the presence of PAD coexisting with MAC which may
201 reduce ABI to within a normal range (12,37-39). This study supports previous findings indicating that
202 the ABI had decreasing levels of sensitivity in a population at risk of PAD and concurrent MAC.
203 Conversely, the specificity of the ABI (93%) in this study was higher than the TBI (79%). Previous
204 studies in different populations have demonstrated the ABI had differing specificity rates (88 –
205 100%)(10, 11), however this study was a mixed population with a larger sample size, and participants
206 were rested for 10 minutes which has been demonstrated as the ideal rest time for ankle
207 pressures(40). This may have resulted in higher specificity rates.

208 Previous research in small cohorts of people with diabetes has demonstrated that the TBI had a
209 superior sensitivity for the presence of PAD compared to the ABI (10). In this study, the TBI also had
210 a superior sensitivity and ROC analysis when compared to the ABI. Whilst the TBI's specificity was
211 lower than the ABI, the TBI still faired better overall demonstrating a more significant result with
212 ROC analysis. This suggests that the TBI has a wider applicability to a broader population at risk of
213 PAD than previously believed.

214 In this study 61% of the participants had diabetes and the average age was older than previously
215 reported. As both advanced age and diabetes are associated with more distally distributed
216 atherosclerotic lesions(2) 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%) (10). 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 (22). 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 (11).

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 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 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 (3). People with diabetes are at increased risk of PAD, with disease occurring earlier, and more aggressively with a more distal distribution frequently reported(41). Results of this study therefore reflect a population at significant risk of PAD with more distally located stenoses.

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.

Acknowledgments

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Tables

Table 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)

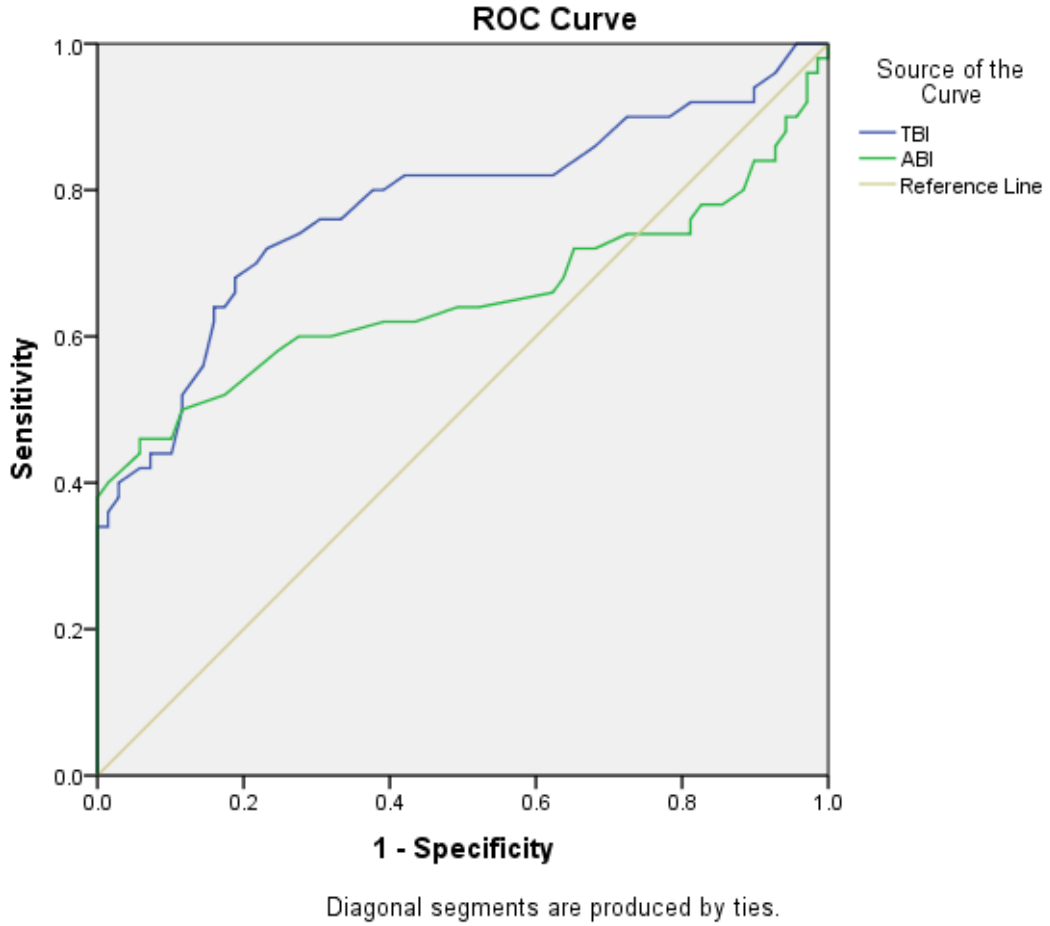
[A]=standard deviation, PAD= Peripheral arterial disease

Table 2: Table of Results

	Analysis	
	Ankle Brachial Index	*Toe Brachial Index*
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)

Figures

Figure 1: Roc analysis TBI vs ABI



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