

The Importance of Early Identification of Atherosclerotic Vascular Disease

Formosa C¹, Mizzi A¹, Ellul C¹, Mizzi S¹ and Gatt A¹

¹Faculty of Health Sciences, University of Malta, Malta

***Corresponding author:** Cynthia Formosa, PhD, Faculty of Health Sciences, University of Malta, Tal-Qroqq, Msida, Malta, Tel: 00356 99861396; Email: Cynthia.formosa@um.edu.mt

Published Date: February 26, 2016

ABSTRACT

Peripheral Arterial Disease [PAD] is a significant public-health problem. It has been estimated that only approximately 25% of patients living with PAD receive treatment since most people are not aware that they are living with this condition. Despite the lack of symptoms such patients still share the same prognosis as symptomatic patients showing a risk profile comparable to patients with symptomatic lower extremity PAD or with chronic heart disease. It is imperative that this condition is diagnosed as early as possible in order to avoid devastating further complications including atherosclerotic cardiovascular complications.

The aim of this chapter is to report studies evaluating the occurrence and diagnosis of peripheral arterial disease using different non-invasive modalities in specific diverse populations namely patients living with Type 2 diabetes mellitus, smokers and non-smokers. A further aim is to compare these modalities in order to determine whether a correlation between them exists. Although large clinical randomized studies on arterial disease are limited, this chapter provides evidence from recently published studies on the importance of using different non-invasive modalities when assessing patients with arterial disease and when results do not concur, further extensive evaluations should be performed.

These findings reported in this chapter have important implications for both clinical practice and future research. The findings from our present studies suggest that use of ABPI alone in patients with Type 2 diabetes mellitus or smokers is likely to yield high false negative results. We recommend that peripheral arterial perfusion in patients with diabetes or smokers should be assessed utilizing ABPIs, Doppler waveforms and toe pressures and toe brachial pressure indices. When the findings from these modalities do not correlate these patients should be monitored or further evaluated accordingly. One possible alternative when inconsistencies occur between modalities could include further physiological testing including duplex scanning, high resolution CT and magnetic resonance imaging to establish whether PAD is actually present.

Keywords: Atherosclerosis, Peripheral arterial disease, Non invasive diagnostic testing, Ankle brachial pressure indices, Toe pressure indices, Qualitative spectral waveforms

INTRODUCTION

Structural and functional abnormalities of arteries manifest clinically in a broad spectrum of disorders, including atherosclerosis, micro vascular complications and lower limb ulcerations and amputations [1].

Peripheral Arterial Disease [PAD] is a significant public-health problem. It is a common and clinically relevant manifestation of atherosclerosis characterized by narrowing or blockage of arteries known to carry blood to legs and arms [2]. Peripheral arterial disease is said to affect 200 million adults worldwide and is becoming an increasingly important health problem across both low and high income countries [3]. Peripheral arterial disease [PAD] most commonly affects the superficial femoral artery in the thigh or the common and external iliac artery in the lower abdomen which carry blood to the legs, however in people with diabetes it is not uncommon for PAD to affect distal extremity arteries [4].

The prevalence of PAD has been estimated in several epidemiological studies and found to be in the range of 3-10% in the general population, increasing to 15-20% in individuals over 70 years of age [5] and up to 26% in persons living with diabetes mellitus. With improving life expectancy, the prevalence of PAD is increasing, presenting an important public health challenge [6]. Furthermore it has been reported that Mediterranean countries have a higher prevalence of PAD than other western and northern European counterparts [7].

Sudden loss of arterial blood supply to the lower limbs is a clinical emergency. Arterial ischaemia is known to lead to ulcerations, tissue necrosis and ultimately the need for possible amputations of the limb [1]. Atheromatous material from atherosclerotic plaques in the arteries is usually the cause of acute or chronic lower limb ischaemia. Atheroma tends to form where arteries are fixed posteriorly by branching. It has been estimated that only approximately 25% of patients living with PAD receive treatment since most people are not aware that they are living with this condition. Despite the lack of symptoms such patients still share the same prognosis

as symptomatic patients, showing a risk profile comparable to patients with symptomatic lower extremity PAD or with chronic heart disease [8].

Early identification of PAD and atherosclerotic plaques in the arteries is important if complications are to be avoided. A non-viable limb needs to be recognized and managed appropriately. Today the accessibility and accuracy of non-invasive investigations makes it possible to diagnose ischaemia promptly. The literature reports that compared with patients with cardiovascular and cerebrovascular disease, patients with PAD had the highest death rates at one year [9]. Evidence-based medicine has shown that reducing cardiovascular risk in patients with symptomatic PAD improves survival, with the major risk factors being diabetes and cigarette smoking amongst others.

Methods of Arterial Assessment

Recent developments in non-invasive imaging have revolutionized the identification of early disease in the arteries. The most widely used test for diagnosing PAD in a clinical setting is the ankle brachial pressure index [ABPI]. The ABPI has been reported to be almost 100% specific in identifying healthy individuals and an ABPI <0.9 is approximately 95% sensitive in detecting arteriogram positive PAD [10]. The ABPI consists of a noninvasive, quantitative measurement of the patency of the lower extremity arterial system. This is a validated and reproducible test which consists of a simple measurement which can be performed in any health care professional clinic with inexpensive equipment consisting of a blood pressure cuff and a Doppler ultrasonic sensor [11]. This involves measuring the systolic blood pressure in the ankles and arms and then calculating a ratio. The American Diabetes Association Consensus statement [12], reported the ABPI as a non-invasive method for evaluating PAD and that in contrast to the variability of pulse assessment and the nonspecific nature of information obtained via history and other components of physical examination, the ABPI is reproducible and reasonably accurate. However, it should be noted that in the evaluation of the individual patient there may be errors and that the reliability of any diagnostic test is dependent on the prior probability of disease [Bayes' Theorem][13]. This is mainly a result of poorly compressible arteries due to the presence of medial arterial calcification due to smoking or underlying disease, thus rendering the diagnosis of PAD by ABPI alone less reliable and inaccurate due to artefactually raised occlusion pressures especially in patients with diabetes mellitus and end stage renal failure. Due to this factor TBI's, toe pressures and spectral waveforms at the ankle have been reported to be better predictors of arterial insufficiency in the foot [14], and the authors suggest that ABPI's alone should not be relied on in these specific populations.

METHODS

The studies reported in this chapter were approved by the University Research Ethics Committee and all participants provided informed consent before any data collection. All investigations were carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000.

The testing modalities and examination methods were carried out by same two investigators to ensure uniformity. The screening process involved review of the patient's medical history and a lower-extremity physical examination. Each individual's personal lifestyle characteristics and clinical history including duration of diabetes, recent HbA1c, weight, height, current medications and smoking history were recorded. Individual assessments took approximately 20 minutes.

Peripheral arterial disease

Peripheral Arterial Disease [PAD] was assessed using the documentation of history of intermittent claudication, rest pain and palpation of peripheral pulses. Palpation of pulses was done using the fingertips by two experienced clinicians. Dorsalis pedis and posterior tibial pulses were recorded. Cyanosis, cold feet, skin thinning and hair anomalies were also recorded. Claudication was evaluated from information supplied by the patient with regard to exercise-induced calf, thigh and/or buttock pain.

Measurement of ABPI's

Measurement of ABPI was performed using a portable hand held Doppler and blood pressure cuffs. Apart from ABPI assessment qualitative pedal waveform analysis was obtained from all recruited subjects utilizing the continuous wave Doppler. The Doppler waveforms and the measurement of the ankle brachial pressure index were obtained using the 'Huntleigh® Dopplex Assist vascular package (Cardiff, UK)' as the principal study tool.

The Huntleigh® hand held continuous wave Doppler with an 8MHz probe, part of the Dopplex Assist vascular package, was used to measure the waveforms of the dorsalis pedis and the posterior tibial. The probe was held steadily on the anatomical artery location at an angle between 45 to 60 degrees against the flow of arterial blood. Interpretation of arterial pressure waveform results was based on standards from the literature [15]. Waveforms were classified as triphasic, biphasic, monophasic discontinuous and monophasic continuous. The triphasic waveforms were considered as normal, whereas the biphasic and monophasic discontinuous and monophasic continuous waveforms were interpreted as abnormal.

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

A blood pressure cuff was applied to the arm [to measure the brachial systolic pressure]

and the ankle [to measure the dorsalis pedis and posterior tibial pressures] to determine the ankle pressure. The cuff was inflated to occlude the arterial pressure. The systolic pressure was obtained by listening and noting the pressure on the manometer. The systolic pressure was noted and the higher values of the brachial and the ankle pressures were used to calculate the ABPI. Values were interpreted according to the criteria proposed by the American Heart Association and the American Diabetes Association [12]. In this research, ABPI calculations were interpreted as 0.9– 1.29 normal, lower-extremity vascular disease was defined an ankle brachial index < 0.90 in either foot. An ABPI of >1.3 was considered significantly elevated and indicative of vascular calcification.

Measurements for Toe Pressures

The procedure for obtaining toe pressures and TBI's involved applying a cuff of approximately 1.5cm width on the proximal aspect of the hallux or 2nd toe (when the hallux had been amputated) and the photoplethysmography probe was applied to the pulp of the hallux. Patients were examined in the supine position. When a regular waveform was observed, the sphygmomanometer was pumped up slowly to inflate the digital cuff and occlude digital blood flow. Upon slow release, the point at which the waveform was observed the toe systolic pressure was measured. Using PPG, the actual TBI was obtained during gradual deflation of the cuff at the moment the pulsatile signal reappeared. Toe pressures and the TBI were automatically calculated by the dopplex unit and a print out was obtained.

DISCUSSION

The three studies reported in this chapter [14,16,17] aimed to identify any significant differences in different non-invasive physiological test results when evaluating the occurrence of peripheral arterial disease in people with possible Atherosclerotic Vascular Disease.

According to the World Health Organization (WHO), there are currently 1.1 billion tobacco smokers worldwide [18]. The literature suggests that cigarette smoking increases the incidence of myocardial infarction and fatal coronary artery disease and is known to cause 11% of cardiovascular deaths [19]. Smoking is considered as the most potent modifiable risk factor of cardiovascular disease. Its pathophysiological mechanisms in the human body are numerous and may promote atherosclerosis through vascular inflammation and oxidative stress [20]. The first study presented in this chapter compares the incidence of peripheral arterial disease diagnosis using ankle-brachial pressure index and printed arterial waveforms in a cohort of 20 smokers and 20 non-smokers. No significant difference was observed in the APBI scores and cumulative smoking exposure [measured in packet years]. However, although no significant difference was obtained for the ABPI readings further quantitative analysis of Spectral Doppler waveforms revealed an important significant difference in waveforms between smokers and non-smokers on all pedal pulses of the study population. This finding may shed light on arterial dysfunction associated with smoking at subclinical level and in the presence of normal ABPI scores [17].

These findings have important implications for clinical practice. Early diagnosis and treatment of PAD is crucial in smokers. This study has shown that ABPI readings in smokers could be falsely elevated due to arterial calcification which is common in smokers since ABPI readings and spectral waveforms were not consistent. Smoking has been reported as a principal risk factor for calcification of the coronary arteries, aortic arch calcification and carotid calcification [21]. This study [17] has shown that despite 'normal' ABPI's in smokers, there may be early indications of altered arterial hemodynamics due to abnormal waveforms, increasing the risk of atherosclerosis and cardiovascular events. PAD is strongly associated with early death in cardiovascular disease. This study highlights the importance of increased vigilance coupled with strengthening of existing screening structures with regards to PAD assessment in smokers in order to reduce the incidence of PAD and allow initiation of appropriate secondary risk factor control measures. Combining Doppler waveforms and measurement of ABPI's could yield more reliable results without significantly increasing time required for testing. When these two tests do not concur, further evaluation of peripheral perfusion should be performed [16]. Early detection of abnormal blood flow in the lower limb may lead to early treatment and advice with regards to smoking cessation. It will also aid in timely preventative measures to avoid deterioration and development of serious complications such as lower limb loss and consequently death. This study recommends non-invasive physiological testing of peripheral perfusion in all smokers in order to facilitate the early identification of asymptomatic peripheral arterial disease in smokers.

The incidence of diabetes is increasing worldwide. Diabetic foot complications and ulcerations remain a global concern since they are said to precede lower extremity amputations, lower the quality of life of individuals living with diabetes and account for a large proportion of hospitalizations and a substantial amount of incurred hospital costs. The second study presented in this chapter [16] aimed at evaluating the occurrence of peripheral arterial disease in a hospital setting using ABPI in patients living with Type 2 diabetes mellitus as recommended by International Working Group on the Diabetic Foot [22]. A further aim was to compare the findings of the arterial waveform interpretation in conjunction with the ABPI readings in order to determine whether a correlation between the two exists [16].

A prospective study was conducted in a tertiary referral hospital setting. A convenient cohort of forty-nine subjects was enrolled to partake in this investigation. The testing modalities and examination methods were carried out by same two investigators to ensure uniformity. Findings from this study also confirm the limitations of use of ABPI in isolation in peripheral arterial assessment and diagnosis in patients with diabetes mellitus. Results from this current study have also demonstrated inconsistencies when comparing ABPI results to arterial waveform interpretation in the recruited subjects. Doppler waveforms were different from ABPI interpretations in most of the recruited subjects. Approximately 35% of the study group were reported to have a 'normal ABPI' however, this was not consistent with the waveform analysis since these subjects demonstrated monophasic discontinuous, biphasic or continuous monophasic waveforms in one or both feet.

These findings have important implications for both clinical practice and future research. The findings of this study suggest that use of ABPI alone in patients with Type 2 diabetes mellitus is likely to yield high false negative results. The authors recommend that peripheral arterial perfusion in patients with diabetes should be assessed utilizing both ABPIs and Doppler waveforms. When the findings from both modalities do not correlate these patients should be monitored or further evaluated accordingly. One possible alternative when inconsistencies occur between the two modalities could include further physiological testing such as toe pressure and toe brachial pressure indices to establish whether PAD is actually present [16]. It has been reported that Doppler analysis offers a particular advantage over the ABPI since the detection of a pulsatile flow using Doppler analysis may be possible even in calcified arteries, which are known to be common in patients living with diabetes, as opposed to recording an ABPI in such patients. Doppler waveform analysis therefore allows the detection of arterial disease when normal ABPI readings are recorded [23].

Earlier diagnosis of PAD in patients with diabetes permits prompt commencement of secondary risk factor control which is known to delay long-term complications, improve outcomes and reduce the financial burden which this condition imposes on both patients and the healthcare system. Accurate identification of PAD in patients with Type 2 diabetes mellitus is essential in order to prevent disability, and limb loss and to help identify those patients at high risk of MI, stroke and death.

Diabetes kills more people annually than breast cancer and AIDS combined [24]. Furthermore, the cost of treating diabetic foot ulcers is greater than that of the 5 most costly forms of cancer and the relative 5-year mortality rate after limb amputation is 68%, when compared with cancer – it is second only to lung cancer (86%) [25]. As the global prevalence of diabetes keeps rising due to population growth, ageing of populations and lifestyle changes associated with urbanization management of the high risk foot needs to keep evolving with the inclusion of the latest advances in technology, biomechanical modelling and other innovations in clinical management in order to prevent amputations and re-amputations.

The prognosis of the limb is determined mainly by the extent of arterial disease. Within one year of diagnosis of peripheral vascular disease, up to 3% of patients develop critical limb ischaemia, whilst 25% of these patients are known to require some form of amputation [8]. The literature suggests that the most important factor in ensuring successful amputation healing is the correct choice of amputation site which is in turn dependent on limb perfusion [26]. Despite improved vascular surgical techniques, revisions of minor amputation sites or higher amputations are still common today. The healing failure rate of minor amputations is approximately 30 - 45% [27]. There is no set of criteria such as toe blood pressure threshold that guarantees healing [28] or that predicts non-healing.

The aim of the third study presented in this chapter [14] was to determine whether distal blood

pressure measurements or waveforms could predict wound healing after foot or toe amputations. Study results conclude that TBPIs and toe pressures are better predictors of likelihood of healing after toe amputation than ABPIs. ABPIs alone cannot be relied upon as an indicator of perfusion to the toes in the diabetic population. The distribution of disease in diabetes makes it possible for patients to have relatively adequate ABPIs and yet have very poor perfusion to the toes. Another important finding is that the waveforms are also predictive of wound healing. All patients with triphasic waveforms healed their amputation wounds within six weeks. Patients with monophasic continuous waveforms have a significantly higher risk of developing complications or failing to heal their amputation sites.

As the incidence of lower leg surgical interventions increases the need to establish accurate algorithms to predict the likelihood of wound healing after minor amputations increases. This would help clinicians decide on whether potentially risky revascularization procedures should be performed. Results from this study support the evidence that toe pressures above 30mmHg could predict healing as proposed by the European Consensus Document [29] but also indicate that spectral waveforms at the ankle could be useful in predicting healing and non healing. As importantly it highlights the fact that reliance on ABPIs to predict healing is inadvisable.

CONCLUSION

Early diagnosis and treatment of PAD is crucial. The three studies discussed in this chapter demonstrate that the ABPI in patients with diabetes and in smokers is frequently normal even in the presence of arterial disease and that these cases can be identified through Doppler waveforms analysis or toe pressures. Combining Doppler waveforms and measurement of ABPIs in patients with suspected PAD yields more reliable results without significantly increasing time required for testing. We recommend that all non-invasive modalities should be used in these patients and when results from these investigations do not concur, further evaluation should be performed. This would significantly reduce the proportion of patients who would be falsely identified as having no peripheral arterial disease and subsequently denied the benefit of beneficial and effective secondary risk factor control. Current recommendations about physiological testing of peripheral perfusion should be re-evaluated and consideration to ensure early identification atherosclerotic vascular disease.

References

1. Donnelly R, London NJM. ABC of Arterial and Venous Disease. 2010; 2nd Edition. Wiley-Blackwell, London.
2. Stansby G, Mister R, Fowkes G, Roughton M, Nugara F, Brittenden J, et al. High risk of peripheral arterial disease in the United Kingdom: 2-year results of a prospective registry. *Angiology*. 2011; 62:111-118.
3. Fowkes, FGR, Rudan, D, Rudan I, AboyansV, Denenberg JO, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *The Lancet*. 2013; 282: 1329- 1340.
4. Lapolla A, Piarulli, F, Sartore, G, Ceriello A, Ragazzi E, Reitano R, et al. Advanced glycation end products and antioxidant status in type 2 diabetic patients with and without peripheral artery disease. *Diabetes Care*. 2007; 30, 670-676.
5. Criqui M. Peripheral arterial disease – epidemiological aspects. *Vascular Medicine*. 2001; 6: 3-7.

6. Ostchega Y, Paulose-Ram R, Dillon CF, Gu Q, Hughes JP. Prevalence of peripheral arterial disease and risk factors in persons aged 60 and older: data from the National Health and Nutrition Examination Survey 1999-2004. *J Am Geriatr Soc.* 2007; 55: 583-589.
7. Sanna G, Alesso D, Mediati M, Cimminiello C, Botghi C, Fazzari A, et al. Prevalence of peripheral arterial disease in subjects with moderate cardiovascular risk. Italian results from the PANDORA study Data from PANDORA (Prevalence of peripheral Arterial disease in subjects with moderate CVD risk, with no overt vascular Diseases nor Diabetes Mellitus). *BMC Cardiovascular Disorders.* 2011; 11: 59.
8. Hirsch A, Haskal Z, Hertzner NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the Management of Patients with Peripheral Arterial Disease. *Circulation.* 2006; 113: e463-e654.
9. Steg PH, Bhatt D, Wilson PWF, D'Agostino R Sr, Ohman EM, Röther J, et al One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA.* 2007; 297: 1197-1206.
10. Norgren, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. TASC 11 document. *J Vasc Surg.* 2007; 45: Suppl S5A-S67A.
11. Greenland P, Abrams I, Aurigemma GP, Bond MG, Clark LT, Criqui MH, et al. Prevention Conference V: Beyond secondary prevention: identifying the high risk patient for primary prevention: non-invasive tests of atherosclerotic burden: Writing Group III. *Circulation.* 2000; 101: E16-E22.
12. American Diabetes Association. Peripheral Arterial Disease in People with Diabetes. *Diabetes Care.* 2003; 26:12 3333-3341.
13. James J. Bayes' Theorem. *The Stanford Encyclopedia of Philosophy* (Fall 2008 Edition), Edward N. Zalta (ed).
14. Caruana L, Formosa C, Cassar K. Prediction of Wound Healing after Minor Amputations of the Diabetic Foot. *J Diabetes Complications.* 2015; 29: 834-837.
15. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC 11). The worldwide burden of peripheral artery disease. The role of the physician, based on the Inter-Society Consensus. Pocket guide. 2008; Edited by Dr Kenneth Harris.
16. Formosa C, Cassar K, Gatt A, Mizzi A, Mizzi S, Camileri KP, et al. Hidden Dangers revealed by misdiagnosed peripheral arterial disease using ABPI measurement. *Diabetes Res Clin Pract.* 2013; 102 112-116.
17. Ellul C, Mizzi A, Formosa C. Early Identification of Early Asymptomatic Peripheral Arterial Disease in Smokers. *The Journal for Nurse Practitioners.* 2014; 10: 611-615.
18. World Health Organization Report on the Global Tobacco Epidemic, 2013.
19. Centers for Disease Control and Prevention (CDCP) Annual smoking-attributable mortality, years of potential life lost, and economic costs. *MMWR Morb Mortal Wkly Rep.* 5. 2002; 300–303
20. Perlstein TS, Lee RT. Smoking, metalloproteinases, and vascular disease. *Arterioscler Thromb Vasc Biol.* 2006; 26: 250–256.
21. Odink AE, van der Lugt A, Hofman A, Hunink MG, Breteler MM, Krestin GP, et al. Association between calcification in the coronary arteries, aortic arch and carotid arteries: The Rotterdam study. *Atherosclerosis.* 2007; 193; 408- 441.
22. International Working Group on the Diabetic Foot. International Consensus on the Diabetic Foot & Practical and Specific Guidelines on the Management and Prevention of the Diabetic Foot. Launched at the 6th International Symposium on the Diabetic Foot, May 2011.
23. Aboyans V, McClelland LR, Allison AM, McDermott MM, Blumenthal SR, Macura K, et al. Lower extremity peripheral artery disease in the absence of traditional risk factors. The multi-ethnic study of atherosclerosis. *Atherosclerosis.* 2010; 215; 169-173.
24. American Diabetes Association (2009) Fast Facts - Data and Statistics About Diabetes.
25. Armstrong D. Diabetic Foot: Facts and Figures.
26. Bonham P. Measuring Toe Pressures Using a Portable Photoplethysmograph to Detect Arterial Disease in High-risk Patients: An Overview of the Literature. *Ostomy Wound Manage.* 2011; 57: 36-44.
27. MJ. Vitti, DV. Robinson, Hauer-Jensen, Thompson BW, Ranval TJ, Barone G, et al. Wound healing in forefoot amputation: the predictive value of toe pressure. *Ann Vasc Surg.* 1994; 8: 99-106.
28. Holstein P, Lassen NA. Healing of ulcers on the feet correlated with distal blood pressure measurements in occlusive arterial disease. *Acta orthop Scand.* 1980; 51: 995-1006.
29. Second European Consensus. Document on chronic leg ischaemia. *European Journal of Vascular Surgery* 1992; 6 (Suppl 1): 1-32.