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Photoplethysmography detection of lower limb peripheral arterial occlusive disease: a comparison of pulse timing, amplitude and shape characteristics

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Abstract

The assessment and diagnosis of lower limb peripheral arterial occlusive disease (PAOD) is important since it can lead progressively to disabling claudication, ischaemic rest pain and gangrene. Historically, the first assessment has been palpation of the peripheral pulse since it can become damped, delayed and diminished with disease. In this study we investigated the clinical value of objective photoplethysmography (PPG) pulse measurements collected simultaneously from the right and left great toes to diagnose disease in the lower limbs. In total, 63 healthy subjects and 44 patients with suspected lower limb disease were studied. Pulse wave analysis techniques extracted timing, amplitude and shape characteristics for both toes and for right-to-left toe differences. Normative ranges of pulse characteristics were then calculated for the healthy subject group. The relative diagnostic values of the different pulse features for detecting lower limb arterial disease were determined, referenced to the established ankle-brachial pressure index (ABPI) measurement. The ranges of pulse characteristics and degree of bilateral similarity in healthy subjects were established, and the degrees of pulse delay, amplitude reduction, and damping and bilateral asymmetry were quantified for different grades of disease. When pulse timing, amplitude and shape features were ranked in order of diagnostic performance, the shape index (SI) gave substantial agreement with ABPI (>90% accuracy, kappa 0.75). SI also detected higher grade disease, for legs with an ABPI less than 0.5, with a sensitivity of 100%. The simple-to-calculate timing differences between pulse peaks produced a diagnostic accuracy of 88% for all grades of arterial disease (kappa 0.70), and 93% for higher grade disease (kappa 0.77). These contrasted with the limited discriminatory value of PPG pulse amplitude. The low-cost and simplicity of this optical-based technology could offer significant benefits to healthcare, such

as in primary care where non-invasive, accurate and simple-to-use (de-skilled) diagnostic techniques are desirable.

Keywords: pulse, peripheral arterial occlusive disease, vascular, artery, ankle-brachial pressure index, photoplethysmograph

1. Introduction

Peripheral arterial occlusive disease (PAOD) of increasing severity can lead progressively to disabling claudication, ischaemic rest pain and gangrene. It is therefore important to detect it early (AbuRhama and Diethrich 1988, Belcaro *et al* 1998). Historically, the first assessment has been palpation of the peripheral pulse since it becomes delayed, diminished and damped with arterial disease (Kester and Leveson 1981, Allen and Murray 1995, 2000, Carter and Tate 1996). However, manual palpation can be inaccurate, even by those trained in vascular assessment. In addition, current ultrasound-based vascular assessment techniques such as the ankle-brachial pressure index and colour duplex ultrasound do not always agree (Allen *et al* 1996, Oates 2001).

The pulse can be measured easily and non-invasively using low-cost optical-based photoplethysmography (PPG) (Hertzman 1937a, 1937b, Jago and Murray 1988, Insall 1991, Allen and Murray 1993, 1995, Nitzan *et al* 1998, Spigulis and Rubins 1998, Millasseau *et al* 2000, Kyriacou *et al* 2001, Loukogeorgakis *et al* 2002). PPG comprises a pulsatile ('ac') physiological waveform attributed to cardiac synchronous changes in skin microvascular blood volume with each heart beat (Challoner 1979), and superimposed on a slowly varying ('dc') baseline with various lower frequency components attributed to respiration, sympathetic nervous system activity and thermoregulation (Buchs *et al* 2005). We have extended basic single site PPG measurements by developing a novel system with capability to simultaneously acquire pulse measurements from the right and left body sites, with PPG amplifier matching to enable true physiological differences to be detected with confidence (Allen and Murray 2002, 2003). The multi-site PPG concept has considerable clinical potential; we have previously shown that bilateral (right-to-left side) similarity in higher frequency PPG characteristics is usually found in healthy subjects compared with the bilateral asymmetry often found in patients with vascular disease (Allen and Murray 2000), and recently Buchs *et al* (2005) have demonstrated the potential value of finger and toe PPG low frequency characteristics for assessing autonomic dysfunction in diabetic patients.

Peripheral pulses can be described in various ways, including timing, amplitude and shape characteristics to represent delay, diminishing and damping respectively, with arterial disease. There are few data in the literature, however, quantifying the normal ranges of pulse characteristics and how these change in vascular patients. Furthermore, it is not known which pulse features are most accurate at detecting disease. In this study we investigated the clinical value of PPG measurements of lower limb arterial disease where accurate gold standard assessments were available. The aims of this study were (a) to determine the normative ranges of PPG pulse characteristics at the great toes, and (b) to compare patient pulse data with these normative ranges and estimate the accuracy of lower limb arterial disease detection for different measures of pulse timing, amplitude and shape.

2. Methods

2.1. Subjects

Two separate study groups were formed: a healthy control group from which the normal ranges of peripheral pulse characteristics were determined and a patient group which had been referred for investigation of suspected significant lower limb PAOD. Since this disease usually affects older subjects, we studied only those who were over 40 years of age in both groups. Those having an obvious cardiac arrhythmia, limb tremor, skin problems (e.g. those with cuts or bruising at a measurement site or photosensitive skin), and Raynaud's phenomenon were excluded. Healthy subjects were recruited from staff at the Newcastle upon Tyne Hospitals NHS Trust and patients recruited from Freeman Hospital Northern Vascular Centre out-patient clinics and the Vascular Ultrasound Laboratory. The study was approved by the Local Research Ethics Committee. All subjects gave their written informed consent.

2.2. Multi-site PPG pulse measurement system

The pulse measurement system is described in earlier publications (Allen and Murray 2000, 2002, 2003). Only brief details are therefore provided here. The system simultaneously acquired PPG pulses using electronically matched pairs of right and left pulse amplifier channels so that any differences detected between legs are likely to be due to physiological or anatomical reasons. The PPG pulse reflectance mode transducers (Artema, Denmark; ear type 75331-9, finger and toe type 75333-5) had an operating wavelength 950 nm and used constant low level tissue illumination (output power 2.5 mW). Data were recorded to computer using 16-bit analog-to-digital conversion at a sampling rate of 2500 Hz (Drinnan *et al* 2001). The PPG pulse amplifier bandwidth was 0.15–20 Hz. In addition, a single lead diagnostic bandwidth electrocardiogram (ECG) was recorded to provide a cardiac timing reference.

2.3. Measurement protocol

2.3.1. Vascular diagnostic reference. All subjects had a 'gold standard' ankle-brachial pressure index (ABPI) vascular assessment (Oates 2001). The ABPI reference measurements defined lower limbs as having normal arteries when the ankle systolic blood pressure was at least 90% of the brachial artery systolic blood pressure (i.e. an ABPI $\geqslant 0.9$) (Kester and Leveson 1981). Generally, the ankle arterial blood pressure falls relative to the arm pressure with increasing severity of disease, and when less than 90% it is classed as clinically significant. Two sub-classifications of disease were also included in the analysis: lower grade disease (LG, $0.9 >$ ABPI $\geqslant 0.5$) and higher grade disease (HG, ABPI < 0.5).

2.3.2. Physiological measurements. All subjects underwent physiological measurements in a warm, temperature-controlled room (25 ± 1 °C) with at least 10 min given for thermal acclimatization and relaxation. Measurements were made with subjects in the supine position. Bilateral great toe pulses and ECG were then captured to computer for 150 s. The gain of each pulse amplifier channel was also recorded.

2.4. Comparison of pulse characteristics in health and vascular disease

2.4.1. Pulse wave characterization. The PPG pulse waveforms were digitally filtered using high pass filters (type zero phase Butterworth with cut-off frequency 0.5 Hz 4 pole; Matlab, MathWorks Inc) to reduce the low-frequency variations in baseline and enable reliable

detection of the pulse feet and peaks (Allen 2002). Poor quality beats, i.e. those affected by movement artefact, were then removed using a semi-automated approach. The good quality pulses were then characterized in terms of timing in seconds (pulse transit time from ECG R wave to pulse foot [PTTf] and to pulse peak [PTTp] and the foot-to-peak rise time [RT]), foot-to-peak amplitude [AMP] calibrated by normalizing with the respective PPG amplifier gain setting, and normalized pulse shape waveform of height between 0 (pulse foot) and 1 (pulse peak) and a width of unity with 100 equally spaced points computed using cubic spline interpolation (Allen and Murray 2003). Since PPG characteristics vary slightly from beat-to-beat then average time, amplitude and shape waveforms were computed for the toes of each subject from a total of 60 consecutive heart beats from the 150 s recording. Bilateral differences in toe timing and shape waveforms were obtained from their absolute differences. Bilateral amplitude differences were obtained from the ratio of largest to smallest pulse size.

2.4.2. Normative ranges of multi-site pulse characteristics. Normative toe pulse characteristics were summarized for the healthy control subject group using median and 95% confidence interval (i.e. between 2.5 and 97.5 percentiles) ranges. For normalized pulse shape waveforms these ranges defined the boundaries of the pulse contour for legs with healthy arteries. A shape index measure (SI) then quantified the total area of the pulse falling outside these normal limits, i.e. the area below the lower boundary limit plus the area above the upper boundary limit. For healthy subjects SI values should be close to zero, however pulses from vascular patients should have significantly greater values to reflect the distortion, i.e. the rounding in shape, with disease (Allen and Murray 1995). Furthermore, it is expected that legs with different disease severity should also give a large value of SI in bilateral shape comparisons.

2.4.3. Pulse characteristics in vascular patients. Pulse timing, amplitude and shape waveform characteristics were also summarized for the vascular patient group using median and 95% confidence interval ranges.

2.4.4. Diagnostic accuracy. The diagnostic accuracy of pulse measurements for detecting lower limb PAOD was determined by comparing patient toe pulse data with the normative pulse ranges, referenced to the ABPI. When right-to-left side differences were studied the lowest side ABPI measurement was used. The pulse timing (PTTf, PTTp, RT), amplitude (AMP) and shape (SI) features were analysed separately for individual legs and also for bilateral leg differences so that their diagnostic accuracies could be ranked to show which performed best overall.

The diagnostic performances were determined from contingency tables for (a) the detection of arterial disease (ABPI < 0.9) and (b) the detection of higher grade arterial disease (HG, ABPI < 0.5). Here, specificity (Sp), sensitivity (Se), overall accuracy (A) and the kappa statistical coefficient of agreement (Cohen 1960, Bland 1995) were calculated. Kappa agreements beyond chance have been graded by Landis and Koch (1977): greater than 0.8 as almost perfect agreement, 0.61–0.80 as substantial, 0.41–0.60 as moderate, 0.21–0.40 as fair, 0.01–0.20 as slight, and zero as chance agreement.

3. Results

A total of 63 healthy control subjects (38 male) and 44 vascular patients (40 male) were included in the study, with age ranges of 40–72 and 40–85 years, respectively. Their mean (standard

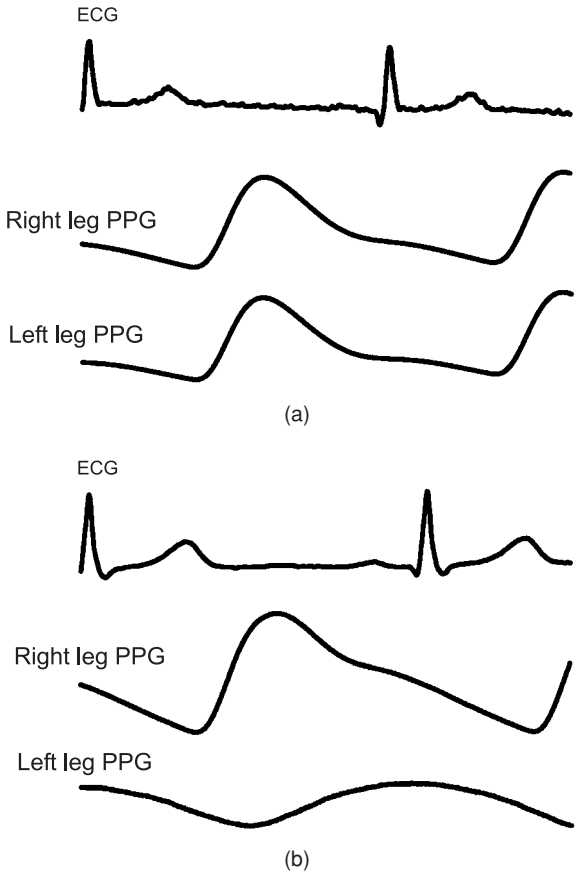

Figure 1. Examples of bilateral toe pulse waveforms over 1.25 s, with (a) a normal healthy control subject, and (b) a vascular patient with significant unilateral lower limb PAOD (left leg disease only). In each case the ECG cardiac timing reference is shown alongside. The bilateral similarity of timing, amplitude and shape characteristics can be seen in the healthy subject. However, asymmetry between toe measurements can clearly be seen for the patient.

deviation) heights were 1.70 (0.10) and 1.72 (0.07) m, and heart rates were 62 (9) and 70 (10) beats per minute, respectively. There were no lower limb amputees, giving toe pulse data from 126 legs in the healthy control group and from 88 legs in the patient group. All healthy control subjects had an ABPI of at least 0.9 for each leg. Using the ABPI classification of arterial disease the patient group had 36 normal legs and 52 legs with disease (22 with higher grade disease), and for the bilateral comparisons 12 patients were classed as normal and 32 patients with disease (14 with at least one leg having higher grade disease).

Figure 1(a) shows an example of toe pulse and ECG recordings over a single heart beat for a healthy subject and figure 1(b) an example for a vascular patient having higher grade arterial disease in one leg only. This loss of bilateral similarity between sides is clearly seen in the patient, with the pulse from the affected (left) leg being damped, delayed and diminished relative to the healthy (right) leg.

Figure 2(a) summarizes the normative ranges of toe pulse characteristics alongside those from vascular patients for different ABPI classifications (separated into normal, lower grade and higher grade disease). Overall, the higher the grade of disease the greater the pulse

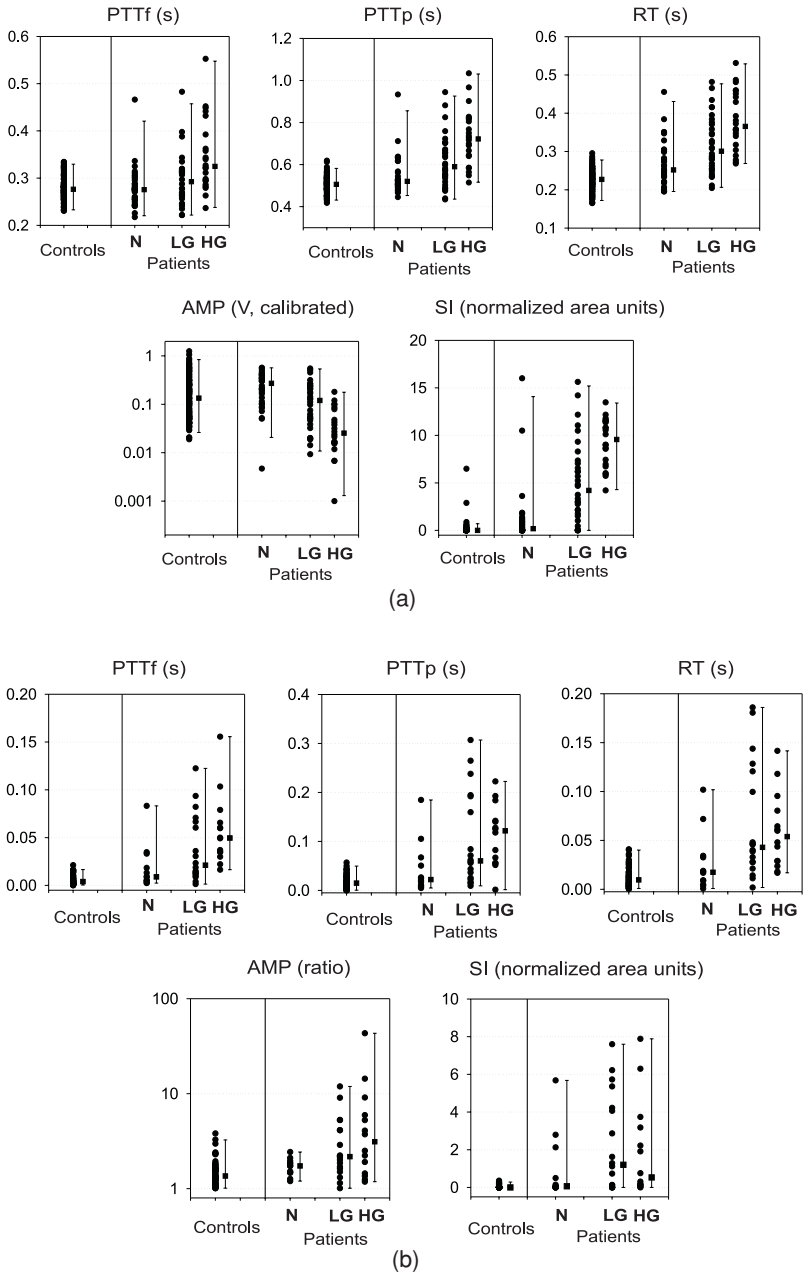

Figure 2. Median and 95% confidence interval ranges for the pulse timing (PTTf, PTTp, RT), amplitude (AMP) and shape (SI) characteristics at the toes. The healthy control subjects are shown alongside the vascular patients for (a) individual legs and (b) the absolute differences between right and left legs. All healthy control subjects had an ABPI $\geqslant 0.9$. Data for patients are shown alongside with legs separated into three ABPI classifications: normal (N, ABPI $\geqslant 0.9$), lower grade arterial disease (LG, $0.9 >$ ABPI $\geqslant 0.5$), and higher arterial disease grade (HG, ABPI < 0.5). The overlap between pulses from normal limbs and patients with the lower grades of disease is evident. It can also be seen from the figures that the three timing measures (PTTf, PTTp, RT) and shape index (SI) tend to increase with disease severity, whereas the pulse amplitude (AMP, $\log_{10}$ scale) tends to decrease.

Table 1. Summary of normative pulse characteristics (95% confidence interval ranges), allowing comparison with patient data.

Pulse measure	Right and left legs	Absolute differences between right and left legs
PTTf (ms)	233–330	0–17
PTTp (ms)	431–582	0–50
RT (ms)	172–278	0–40
AMP (V, and ratio)	0.03–0.84	1.0– 3.3
SI (normalized area units)	0.0–0.71	0.0–0.28

delay (increased timing), diminishing (reduced amplitude), and damping (increased shape distortion), as confirmed from the patient group having statistical correlations between ABPI and each of PTTf, PTTp, RT, $\log_{10}$(AMP), and SI at -0.51 ($r^2 = 0.26$), -0.59 (0.35), -0.58 (0.33), +0.68 (0.46) and -0.74 (0.55), respectively (all $p < 0.0001$). Figure 2(a) also shows the degree of overlap between healthy subjects and the patients with the lower grade disease. Particularly poor separation between the groups can be seen for calibrated pulse amplitude. In contrast, pulse shape (SI) produced very good separation. Figure 2(b) shows the normative ranges of bilateral differences between toes, summarized using the absolute magnitude of side differences displayed against the leg with the lowest side ABPI (most diseased limb). In healthy control subjects the bilateral similarity between legs is demonstrated with only small differences in timing and shape and an amplitude ratio skewed in distribution towards unity. Generally, the median differences between sides and hence bilateral asymmetry increased for the higher grades of disease. The normative toe pulse ranges are also summarized in table 1.

The diagnostic performances are summarized in tables 2(a) and (b) for individual legs and tables 3(a) and (b) for bilateral leg comparisons, each ranked in order of kappa. Shape index performed best overall and separated normal subjects from disease correctly in just over 90% of cases with respect to the ABPI reference. A kappa of 0.75 is consistent with substantial agreement between pulse and ABPI diagnoses. Shape index was also the most sensitive at detecting disease overall, reaching 100% sensitivity for higher grade disease. In contrast, PTTf and AMP performed poorly with sensitivities close to 50% (kappa 0.41 and 0.52, respectively). When bilateral differences were studied the pulse transit time to the peak of the pulse (PTTp) produced an accuracy of approximately 88% for all grades of arterial disease and increasing to 93% for the higher grade disease, each demonstrating substantial agreement between pulse and ABPI.

4. Discussion

We have defined the normative ranges of pulse timing, amplitude and shape characteristics, and their expected changes with peripheral arterial occlusive disease. These are also significantly correlated with the ankle-brachial pressure index, an established measure of lower limb arterial disease. The timing and shape measures increased with disease severity and calibrated amplitude decreased, consistent with the pulse delay, diminishing and damping often seen in vascular patients. The pulse transit times were expected to be elongated because of blood pressure drop across arterial stenoses with subsequent reduction in arterial compliance at a point distal to this. The damping and distortion of pulse shape is attributed to changes in pressure wave reflection and also changes in the resistance and compliance properties of the peripheral arteries (Sherebrin and Sherebrin 1990). The amplitude reductions can be attributed

Table 2. A summary of diagnostic performances for individual great toe measurements, with each table ranked in order of kappa value. The shape index (SI) performed best overall separating healthy control subjects from patients with arterial disease with accuracy (A) of greater than 90%. The specificity (Sp) and sensitivity (Se) are also shown, with the shape index the most sensitive overall. SI gave the highest kappa statistic (0.75) and giving substantial agreement between pulse and ABPI diagnoses. The shape Index was 100% sensitivity in detecting higher grade disease. In contrast pulse amplitude and pulse transit time to foot performed the poorest overall.

Rank	Pulse measure	Sp (%)	Se (%)	A (%)	Kappa (agreement class)
	(a) Performance of detection of arterial disease (LG and HG, i.e. ABPI < 0.9) using individual toe pulse assessments				
1	Shape index (SI)	90.6	88.9	90.2	0.75 (Substantial)
2	Rise time (RT)	88.8	75.9	85.5	0.63 (Substantial)
3	Pulse transit time to pulse peak (PTTp)	91.3	64.8	84.6	0.58 (Moderate)
4	Calibrated amplitude (AMP)	95.0	33.3	79.4	0.34 (Fair)
5	Pulse transit time to pulse foot (PTTf)	93.8	31.5	78.0	0.30 (Fair)
	(b) Performance in detecting higher grade arterial disease (HG, ABPI < 0.5)				
1	Shape index (SI)	90.6	100.0	91.8	0.70 (Substantial)
2	Pulse transit time to pulse peak (PTTp)	91.3	86.4	90.7	0.64 (Substantial)
3	Rise time (RT)	88.8	86.4	88.5	0.58 (Moderate)
4	Calibrated amplitude (AMP)	95.0	54.5	90.1	0.52 (Moderate)
5	Pulse transit time to pulse foot (PTTf)	93.8	45.5	87.9	0.41 (Moderate)

Table 3. A summary of diagnostic performance for bilateral differences in great toe pulses, with each table ranked in order of kappa value. The pulse transit time to peak PTTp produced an accuracy of close to 88% (kappa 0.70), and giving substantial agreement between pulse and ABPI diagnoses. The bilateral differences in the pulse transit times also detected the higher grades of disease in 93% of patients (kappa 0.77).

Rank	Pulse measure	Sp (%)	Se (%)	A (%)	Kappa (agreement class)
	(a) Performance of detection of arterial disease (LG and HG, i.e. ABPI < 0.9) using absolute bilateral differences in toe pulse assessments				
1	Pulse transit time to pulse peak (PTTp)	93.3	75.0	87.9	0.70 (Substantial)
2	Pulse transit time to pulse foot (PTTf)	93.3	71.9	86.9	0.68 (Substantial)
3	Rise time (RT)	94.7	56.3	83.2	0.56 (Moderate)
4	Shape index (SI)	92.0	59.4	82.2	0.54 (Moderate)
5	Calibrated amplitude (AMP, ratio)	97.3	40.6	80.4	0.45 (Moderate)
	(b) Performance in detecting higher grade arterial disease (HG, ABPI < 0.5)				
1	Pulse transit time to pulse foot (PTTf)	93.3	92.9	93.3	0.77 (Substantial)
2	Pulse transit time to pulse peak (PTTp)	93.3	92.9	93.3	0.77 (Substantial)
3	Rise time (RT)	94.7	64.3	89.9	0.61 (Substantial)
4	Calibrated amplitude (AMP, ratio)	97.3	50.0	89.9	0.55 (Moderate)
5	Shape index (SI)	92.0	57.1	86.5	0.49 (Moderate)

to decreased blood volume in the microvascular bed (Lax *et al* 1956) and also to the smaller pulse pressure resulting from the blood pressure drop across a stenosis (Nichols and O'Rourke 1990).

We have also shown the merits of exploiting different pulse features to obtain diagnostic information. The best overall agreement between 'gold standard' and disease detection for this pilot study was just over 90% for assessments based on shape. This compares to our

earlier reported data using an artificial neural network based pulse shape classifier of between 80% and 90% (Allen and Murray 1993, 1995). In this study we have shown the relative diagnostic value of the different features of the pulse in detecting disease, including pulse timing and amplitude data. Other workers have also investigated specific characteristics of the PPG toe pulse (Simonson *et al* 1955, Strandness and Bell 1965, Cachovan *et al* 1968, Craxford and Chamberlain 1977, Cohn *et al* 1995). Oliva *et al* (1976) employed frequency analysis to study pulse waveform harmonics to estimate the resistance–compliance changes with disease, reporting a diagnostic accuracy of 89%. Oliva and Roztocîl (1983) found that a measure derived from the relative heights and widths of the pulse could provide an accuracy of 100% in patients with severe grades of vascular disease. In this study the invasive technique of angiography formed the diagnostic 'gold standard' and so only major disease cases would have been studied. More recently, Carter and Tate (1996) described the use of pulse amplitude alone to discriminate between normal subjects and vascular patients, however the overall accuracy of the technique was not clearly stated and therefore cannot be compared with our results. Our data have shown that although pulse amplitude decreases with disease it is a poor discriminatory measure because many healthy subjects also had small PPG pulses. Our results have also shown that the loss of bilateral similarity can give valuable information about the peripheral circulation, achieving overall accuracies close to 88% (93% for higher grade disease) just from very simple timing differences between the right and left side pulse peaks. Furthermore, bilateral difference measurements have been shown to be more repeatable than individual site measurements (Jago and Murray 1988, Allen 2002), an important feature of a diagnostic technique.

The ABPI technique was chosen as the 'gold standard' because it gives a simple quantitative index of vascular impairment and is universally accepted in vascular measurement. However, ABPI can sometimes have problems in detecting the lower grades of disease with knock-on consequences for this pulse system's accuracy. To highlight the inherent uncertainty in current vascular assessment techniques we have shown that the agreement between ABPI and colour duplex ultrasound (CDU) technology to be approximately 83% (kappa 0.66) (Allen *et al* 1996), but with kappa less than 0.4 when least symptomatic limbs were assessed. CDU measurements were not included in this study because of the relative subjectivity of the technique compared to ABPI. However, it is suggested that future assessments of multi-site pulse should include both techniques, as CDU can also provide objective assessments of the more proximal arterial segments, including the detection and grading of upper limb and cerebrovascular disease.

The advantages of bilateral PPG pulse assessments are many. The technique is low cost, easy to use, quick to do, and non-invasive. More pairs of channels can be added to enable the measurement of the right and left ears and fingers in order to enable the assessment of the global circulation, including the detection of proximal disease. We envisage that a multi-site pulse technique could be introduced for first stage peripheral arterial screening, such as in a primary care (GP's clinic) setting. Arguably, the screening of patients for peripheral vascular disease is very important because it has been shown to be an important risk factor for coronary heart disease and stroke (Clement *et al* 1999, Fowkes *et al* 1991). Fowkes *et al* (1991) also showed that the prevalence of major asymptomatic peripheral vascular disease was 8.0% (with symptomatic disease 4.5%) in a group of older adults (age range 55–74 years). Detecting disease early may help in patients with appropriate risk factor modification. Further work is now needed on a larger cohort of healthy subjects and vascular patients to determine the screening accuracy in a community-based population setting. Significantly larger patient numbers would also allow the refinement of the normative ranges to account fully for age, sex, height, body mass index and heart rate, and ultimately with weighted combinations of

pulse timing, amplitude and shape diagnostic information to optimize the overall diagnostic accuracy.

5. Conclusions

We have defined the normative ranges of pulse timing, amplitude and shape characteristics for lower limb photoplethysmography measurements, for individual toes and also for their right-to-left side differences. These data allow comparisons with PPG pulses from patients with suspected vascular disease. We have also quantified the degree of pulse changes in patients with peripheral arterial occlusive disease, representing the increased delay, reduction in amplitude and damping or distortion of shape with disease. Generally, the greatest changes were for the higher grade arterial disease.

We have estimated the accuracy of disease detection at the toes where diagnostic reference data are readily available. The shape index at the toe site agreed with the established ABPI measurement technique in greater than 90% of patients representing substantial agreement. Furthermore, higher grade disease was detected with a sensitivity of 100%. Even simple right–left differences in pulse transit time produced diagnostic accuracies of 88% for all grades of arterial disease, increasing to 93% for higher grade disease. These contrast with PPG pulse amplitude which has very limited diagnostic value for this clinical application.

Further work is now needed to investigate the PPG pulses measured from the right and left finger and ear sites to determine the diagnostic accuracy of proximal disease detection. Further research is also needed to study the accuracy of the multi-site pulse technique in a community-based screening population. Ultimately, the very low-cost and simplicity of this optical-based technology could offer significant benefits to healthcare, such as in primary care where non-invasive, accurate and simple-to-use (de-skilled) diagnostic techniques are desirable.

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