

Feasibility of Monitoring Vascular Ageing by Multi-Site Photoplethysmography

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Abstract

The aim of this pilot study was to determine the expected normative values of two main features from multi-site photoplethysmography (PPG) waveforms, namely the pulse transit times to foot (PTTf) and to peak (PTTp), and explore their overall trends with ageing. These measures reflect the presence of arterial stiffness and peripheral arterial disease, important factors in cardiovascular risk.

PPG waveforms were acquired from the right and left ear lobes, index fingers, and great toes in 31 healthy subjects (19 males and 12 females, mean age 50 years old and range 30-70 years). The electrocardiogram was also simultaneously recorded to provide a cardiac timing reference for the computation of PTTf and PTTp. Values from right and left sides were averaged for subsequent analysis. Linear regressions with age were investigated utilising Pearson's correlation analysis.

PTTf for ear, finger and toe sites were 139±10 ms, 192±14 ms, and 282±24 ms, respectively. For PTTp the values were 460±67 ms, 431±40 ms, and 510±29 ms, respectively. Toe PTTf significantly decreased with age ($r=-0.59$, $p<0.001$). In contrast, finger PTTp significantly increased with age ($r=0.46$, $p<0.01$).

In conclusion, multi-site PPG shows potential to assess the increase in cardiovascular risk linked to physiological or early vascular ageing.

1. Introduction

Ageing is associated with a number of profound changes in the vascular system. Since the pioneering work carried out by Bramwell and Hill at the beginning of the 20th century [4], the number of studies focussing on this topic has been increasing over the last decades. Vascular ageing results from an underlying process of gradual hardening of the medium and large-sized arteries, denominated arteriosclerosis. Two most common clinical manifestations of arteriosclerosis are arterial stiffness (AS) and peripheral arterial disease (PAD). Both AS and

PAD are now recognized as independent cardiovascular risk factors [9, 10]. Notwithstanding, these conditions are often neglected and only identified on the occurrence of a cardiovascular event. Research studies demonstrated that only about 50% of patients affected by PAD are aware of their condition [9, 13]. Risk factors such as smoking, lack of exercise, hypertension, diabetes, and renal dysfunction can cause premature vascular ageing and are associated with accelerated arteriosclerosis. However, it has also been acknowledged that vascular deterioration is actually pathological and is not an inevitable and irreversible ageing process [6, 11].

The most common technologies utilized for the non-invasive assessment of the vascular system are ultrasound, magnetic resonance imaging (MRI), and arterial pressure waveforms [10]. Recently, an optical technology called photoplethysmography (PPG) has been receiving increasing interest for this specific use. PPG has the advantage of being low-cost, quick and operator-independent and it has already shown several potential clinical applications [3]. PPG uses an LED (usually in the near infrared region) and a matched photo-detector to measure the blood volume changes (related to the heart beating) at peripheral body sites, with the most common ones being the tissue pads of the ear lobes, finger tips, and great toes.

Imaging-based techniques such as ultrasound and MRI allow assessing structural characteristics of the main arteries, mainly diameter and wall thickness. This information, combined with blood pressure and blood flow measurements, permits the calculation of regional mechanical properties of arterial segments, such as Young's modulus, compliance, distensibility, Peterson's elastic modulus, characteristic impedance, and β stiffness index [5]. Lumped properties of the entire arterial tree can be extracted by using Windkessel models [14]. Two gold standard measures for the global property of specific arterial segments are the carotid-femoral pulse wave velocity (PWV) and the ankle-brachial pressure index (ABPI). PWV is commonly used for the assessment of AS, and ABPI is used in PAD to assess the presence of occlusion in the lower limbs arteries. Recently, the pulse transit time (PTT) has been studied in arteriosclerotic

populations for the assessment of both AS [1, 12] and PAD [2, 7]. Its attraction is motivated by its simplicity and its relationship with the PWV. PTT has also shown potential for other possible clinical applications in respiratory sleep studies, cardiac function, autonomic function, and hypertension [8].

PTT is usually considered as the time delay for the pulse wave to travel to a peripheral site such as the finger, toe, or ear lobe. The peripheral arrival point is often taken as the foot of the pulse shape, as the point where the pulse reaches a certain percentage of its peak value, or from the intersecting tangent method. Although these landmarks are generally preferred because their computation is more reliable than the pulse peak and they are minimally affected by wave reflections, the clinical value of the pulse transit time to the peak of the pulse has also been demonstrated by one previous study from our group [2].

The aim of this pilot study was to determine the expected normative values for both timing measures, pulse transit time to foot (PTTf) and to peak (PTTp), in a healthy group, and to explore their overall trends with ageing.

2. Methods

2.1. Subjects

The study recruited 31 healthy subjects (19 males and 12 females, age mean±SD 50±12 years old and range 30-70 years). Each gave their written informed consent prior to the measurements commenced.

2.2. Pulse measurements

PPG signals were acquired utilizing a multi-site PPG system developed at the Medical Physics Department, Freeman Hospital and Newcastle University. This device uses an LED, operating in the infrared region at a wavelength of 950 nm (bandwidth 50 nm), and its photo-detector with a reflection mode set-up. Three pairs of PPG probes were placed at the right and left ear lobes, index fingers, and great toes. The probes were held firmly and comfortably with clips (ears) and Artema black Velcro cuffs (fingers and toes). A diagnostic bandwidth ECG lead I was also recorded to provide a cardiac timing reference. The PPG amplifier (bandwidth 0.5 to 20 Hz) was adjusted at the most suitable gain for each measurement in order to maximize the dynamic range. The ECG and PPG waveforms were digitally and simultaneously recorded to computer at a sample rate of 2 kHz.

The whole measurements lasted 150 s and were undertaken in a temperature controlled room at Freeman Hospital, with room temperature at 23±1 °C. Subjects remained still and quite throughout the measurement and

maintained a supine position.

2.3. Data and statistical analysis

Data were analyzed off-line using bespoke pulse wave analysis software developed with MATLAB.

For each subject, an interval of 60 s from the recording was chosen for analysis, which ensured small measurement error. In the selected intervals, PTTf and PTTp were calculated as the time delay between ECG R-wave and its corresponding pulse foot and peak, respectively (Figure 1). Values were summarised using mean, standard deviation (SD), and coefficient of variation (CoV).

The Wilcoxon test was utilized to investigate the right to left differences in the PPG measures. Gender differences were assessed with the non-parametric Mann-Whitney U test, and possible linear regressions with age were investigated using Pearson's correlation analysis. P-values equal to or lower than 0.05 were considered to indicate statistical significance. All statistical analysis was carried out with Minitab version 16.

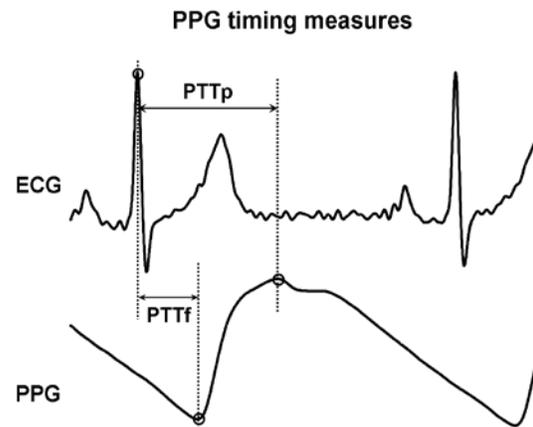


Figure 1. Definition of the PPG timing measures.

3. Results

3.1. Quantification of timing measures

The right to left differences (Figure 2) of PTTf (ears, fingers, and toes) were 0.8±9.1 ms, 1.9±7.5 ms, and 0.2±7.9 ms; for PTTp (ears, fingers, and toes) they were 0±82.6 ms, 2.7±18.7 ms, and 1.5±23.5 ms. These differences were not significantly different from zero and so values from right and left sides were averaged for subsequent analysis.

Averaged PPG timing measures obtained at each body site are summarized in Table 1, for the whole group and also separately for males and females. The Mann-Whitney test did not show any significant difference

between genders in these measures or in the age. Therefore, subsequent linear regression analysis was performed jointly for the entire group.

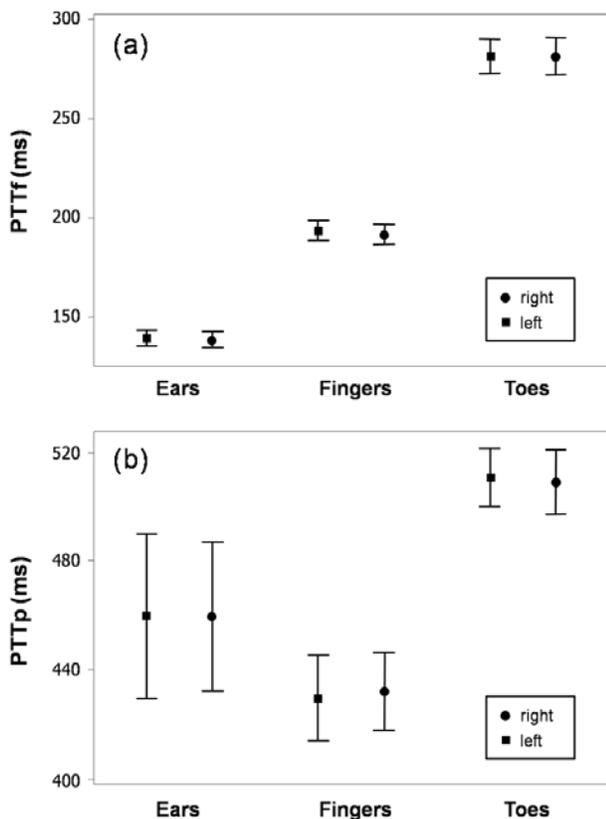


Figure 2. Comparison of values from the right and left sides at each body site for PTTf (a) and PTTp (b). 95% Confidence Intervals of the mean are shown.

Table 1. Summary of PPG timing measures.

	females	males	all	CoV
Age (years)	54±13	47±12	50±12	
PTTf ears (ms)	137±14	139±7	139±10	7.3%
PTTf fingers (ms)	189±16	194±11	192±14	7.0%
PTTf toes (ms)	273±29	287±19	282±24	8.6%
PTTp ears (ms)	443±47	470±76	460±67	14.5%
PTTp fingers (ms)	438±29	426±46	431±40	9.3%
PTTp toes (ms)	511±31	509±28	510±29	5.6%

Values are reported as mean±SD for females, males, and the entire group (all). CoV is the coefficient of variation for the entire group.

3.2 Pulse transit time changes with ageing

Table 2 shows the results from regression analysis. Toe PTTf significantly decreased with age ($r=-0.59$,

$p<0.001$), whilst finger PTTp significantly increased with age ($r=0.46$, $p<0.01$). Other PPG timing measures did not correlate significantly with subject age. Regressions of PTT measures that significantly correlated with age are plotted in Figure 3.

Table 2. Results from regression analysis.

PPG measure	r	slope	p-value
PTTf ears	0.160	n/a	NS
PTTf fingers	-0.262	n/a	NS
PTTf toes	-0.591	-1.15	<0.001
PTTp ears	-0.146	n/a	NS
PTTp fingers	0.464	1.50	0.009
PTTp toes	-0.143	n/a	NS

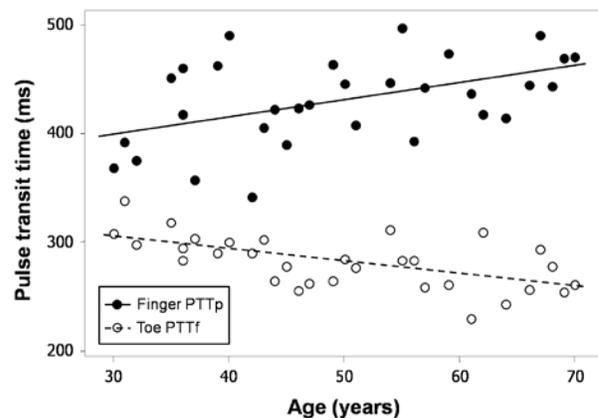


Figure 3. PPG timing measures significantly correlating with age. Regression equations were (1) Toe PTTf = 339 - 1.15*Age (2) Finger PTTp = 356 + 1.5*Age.

4. Discussion

PPG timing measures showed high similarity between right and left side and this was expected in a healthy population, whilst bilateral asymmetry would be expected in PAD [2, 7].

The relationship between gender and arterial stiffness, at least when measured in the aorta, is still controversial. However, most studies have found no difference in age-related aortic stiffening between men and women [10]. Our study did not find significant differences in PTTf between genders. PTTf is a measure of the overall arterial stiffness in the specific vascular segment, and this is expected to be correlated with the aortic stiffness at each body site. No difference between males and females was either found in PTTp, but no previous results about this have been found in the literature.

The values measured for PTTf and PTTp agreed well with those found in our previously published work [1, 2]. PTTf values from other groups may systematically differ from ours because different methods were used for its

computation. It is worth noting that for PTTf a relatively low and similar level of CoV was found at the three body sites, suggesting good reliability in the identification of the foot of the pulses at all sites. A similar CoV was also found for PTTp at the fingers and toes, indicating that at these sites the peak of the pulses could be identified with a similar reliability as for the foot. However, CoV was exaggerated for ear PTTp and also the mean value at this site was higher than that at the fingers. This was probably a consequence of increased complexity of the PPG pulse shape at this site [3]. For example, the second peak at the more proximal sites is often higher than the first one and hence becomes the measured dominant peak. Also the large SD in the right to left difference for ear PTTp may be a consequence of this.

Toe PTTf significantly decreased with age as a consequence of the increasing arterial stiffness which makes the pulse wave travel faster along the arteries. Our previous study in 2002 [1] also showed finger and ear PTTf to significantly decrease with age. This different result is probably a statistical effect due to the fact that that study considered a larger number of subjects (namely 116). In fact, also in that study, toe PTTf provided the highest correlation coefficient and with much lower correlation for the ears and fingers.

Finger PTTp showed an opposite trend, increasing with age. It may be related to the increasing arterial stiffness, as speculated by Zahedi *et al.* [15], but also the atherosclerosis and its associated PAD may play a role in dampening the rising edge of the PPG pulse, hence resulting in larger PTTp. Although PAD is commonly manifest in the lower limbs, it is in fact an expression of generalized atherosclerosis, and therefore it may contribute in dampening the PPG pulse at the finger as it has been shown to happen at the toe [2].

This pilot study has quantified the expected normative values of two characteristic timing measures (PTTf and PTTp). Finger PTTp showed a different trend with age when compared to toe PTTf. However, the actual physiological reasons for the changes in PTTp are still not well understood. Further research is warranted to quantify the ageing effects in relation to clinical variables and also to explore pulse rise time changes with subject age. The contribution of the pre-ejection period should also be taken into account in future studies.

5. Conclusions

Expected normative values for PTTf and PTTp have been quantified. Multi-site PPG technology shows potential to assess the increase in cardiovascular risk linked to physiological or premature vascular ageing.

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