Biomed Tech 2008; 53:156–159 © 2008 by Walter de Gruyter • Berlin • New York. DOI 10.1515/BMT.2008.023

Short communication

Effects of poorly perfused peripheries on derived transit time parameters of the lower and upper limbs

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Abstract

A simple and non-intrusive approach termed the pulse transit time ratio (PTTR) has recently been shown to be a potential surrogate of the ankle-brachial index (ABI). PTTR is based on the principle of PTT, which is known to be temperature-sensitive. In this study, 23 healthy adults with normally perfused peripheries and 10 with poorly perfused peripheries were recruited. No significant change in PTTR was observed between those with cold (1.287 ± 0.043) and normal (1.290 ± 0.027) peripheries ($p > 0.05$). A cold periphery may cause pulse waveform changes and indirectly affect PTT owing to poor skin microcirculation, but may have a limited effect on PTTR, which is useful as an ABI alternative.

Keywords: ankle-brachial index; blood pressure; electrocardiogram; non-invasive prolonged monitoring; photoplethysmography; pulse transit time.

Since its introduction, the ankle brachial index (ABI) has been widely used in clinical practice to monitor the pathogenesis of peripheral arterial occlusive diseases such as atherosclerosis and ischemic extremity [1, 18]. Currently, numerous methods to calculate ABI have been proposed in studies of its diagnostic and epidemiological value. In clinical practice, there is consensus that ABI is defined as the quotient of the higher systolic blood pressure (SBP) of the two ankle arteries (either the anterior or posterior tibial artery) and the average BP of the right and left brachial arteries BP [8]. A conventional indirect approach for ABI measurement is to assess the ratio of systolic BP (SBP) at the level of the ankle to that at the arm level using a sphygmomanometer. As the underlying measuring principle is primarily to fully occlude the artery measured, this may cause discomfort, leading to less cooperation from patients such as younger children when multiple prolonged monitoring is required [6].

Recently, a simple and non-occluding technique termed the pulse transit time ratio (PTTR) has been identified as a potential marker for ABI, as shown in Figure 1 [2, 4, 7]. It can be defined as the ratio of the transit time acquired for the lower limb to that for the upper limb. The principle of PTTR is based on the inverse correlation between pulse transit time (PTT) and BP that was established previously [14, 16]. PTT is generally measured as the time delay between the R-wave of the electrocardiogram (ECG) and the corresponding upstroke of the photoplethysmography (PPG) obtained from a selected peripheral site. However, one of the principal limitations of the PPG method occurs during events of poor periphery perfusion. As the vasculature in peripheries contains an abundance of α-adrenergic receptors, pulsatile flow during these events is most vulnerable when diversion of blood flow to more vital organs occurs, as in a cold environment [11]. Furthermore, it has been suggested that a lower surface temperature of the skin can produce localized vasoconstriction and subsequent vasodilatation, which can significantly decrease skin microcirculation [9].

Induced vasoconstriction and increased peripheral resistance due to cold peripheries are expected to change the vascular wall properties and pulse wave reflection may be altered. In view of this, optical-based PPG signals can be considered to be highly temperature-sensitive [5]. Since PTT computation is dependent on the PPG waveform, it can then be indirectly affected and thus the derived PTTR parameter is also affected. As the PTTR technique has potential as an ABI surrogate [2, 14, 16], it is essential to investigate the effect of cold peripheries on transit time-related measurements. Hence, the objectives of the present study were: (1) to understand the normal PTTR range acquired from healthy subjects with poorly perfused peripheries; (2) to examine possible PTTR differences in healthy subjects with normally perfused peripheries; and (3) to assess PTTR variances between the two study populations.

This study included two groups of subjects, one comprising subjects with normally perfused peripheries and the other comprising subjects with cold peripheries on both upper and lower limbs. The former group consisted of 23 healthy adults (13 male) with mean age 26.0 ± 3.8 years, weight 58.5 ± 9.7 kg and height 167.1 ± 5.7 cm. Their SBP was 111.8 ± 8.7 mm Hg, diastolic BP (DBP) was 64.1 ± 7.6 mm Hg and heart rate

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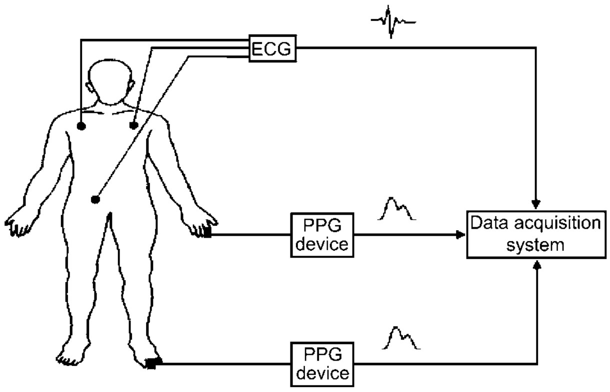

Figure 1 Experimental set-up and protocol of the study.
The subject first adopted a supine posture on the bed provided and rested for 5 min prior to any test activity to allow for cardiovascular stabilization. A photoplethysmography (PPG) probe was applied simultaneously to the index fingers and second toes of the subject. All PPG signals were recorded in conjunction with electrocardiogram (ECG) signals. The limbs measured were kept as parallel to the body as possible to maintain a consistent hydrostatic pressure acting on blood pressure for all limbs measured [15]. The subject was then requested to breathe normally whilst all parameters were recorded for another 5 min. Data from the first minute were discarded to ensure that ample time was given for the subject to accustom to the measuring apparatus. Then 50 consecutive readings free from any artifact were simultaneously selected for all five physiological parameters for further analysis. This procedure was standardized for both groups of subjects.

(HR) was 69.1±4.8 beats per minute (bpm). The latter group comprised 10 healthy adults (7 male) with mean age 27.2±4.6 years, weight 62.3±13.9 kg and height 170.2±8.3 cm. Their SBP was 117.3±6.7 mm Hg, DBP was 62.3±7.0 mm Hg and HR was 69.5±7.8 bpm. Only subjects who had cold peripheries of 22°C or less on both upper and lower limbs were recruited. The general inclusion criteria for both groups were individuals with no clinically apparent arterial disease or physical abnormality. They were also not observably obese, were not on any medication or stimulant (such as caffeine, alcohol and nicotine), and had not undertaken strenuous exercise in the previous 24 h. A specific exclusion criterion for the latter group was individuals with known Raynaud's disease. All measurements were performed in a typical tranquil environment at a controlled ambient temperature of 20°C. Informed consent and institutional ethics approval were obtained for the study.

ECG signals were acquired using a commercial monitor (S&W Medico Teknik, Denmark). Since most commercial pulse oximeters are known to be equipped with signal-processing capability and/or auto-gain features, they were not used. Therefore, PPG signals were derived using customized dual-channel devices as previously described [3]. The customized PPG device was tested for its compliance in introducing less than 90°-phase lag per period measured from 0 to 2 Hz. It had no signal-processing capability and had a signal bandwidth from 0 to 17.3 Hz. The PPG probe housed only a red light emitting diode with a nominal wavelength of 660 nm and a photo-detector. The ECG and both PPG signals were fed into a 16-channel analogue-to-digital converter system (PowerLab/16SP; AD Instruments Corporation, Sydney, Australia) and were recorded using its proprietary software (Chart version 5.2) for further analysis. The recorded signals were sampled at a rate of 1000 Hz and then imported into Matlab Release 14 (The MathWorks Inc., Natick, MA, USA), in which all transit time-related calculations were implemented. It has been suggested that the amplitude of the PPG signals obtained from cold peripheries is generally low, as shown in Figure 2. Thus, a recently proposed computational algorithm was used for detection of PPG signals with a minimal induced phase shift or variability [5]. Consistency in the timing accuracy of these PPG waveforms was compared to that

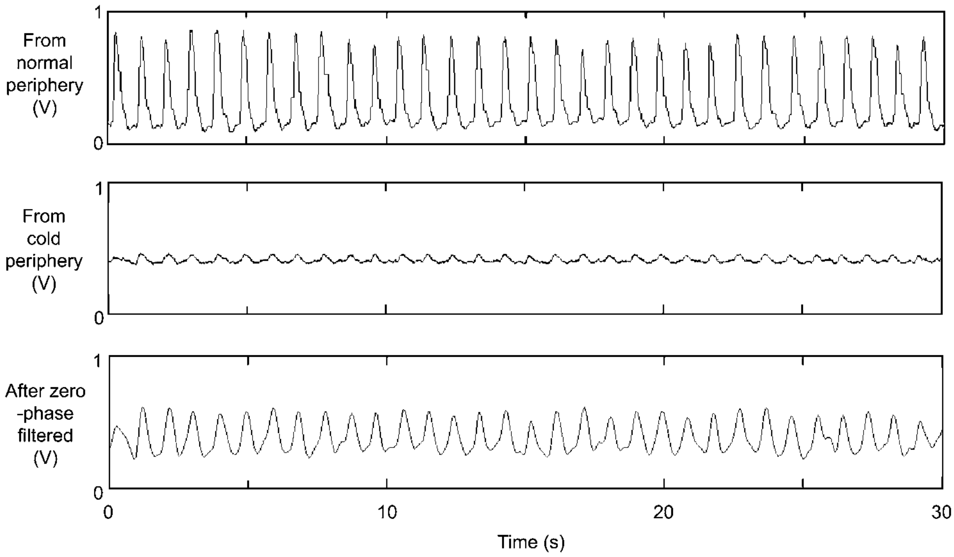

Figure 2 Signal optimization of the PPG waveforms acquired from a cold periphery.
The diagram illustrates the differences in PPG signal amplitude obtained from a normally perfused periphery (top plot) and a poorly perfused periphery (middle plot). The bottom plot shows the effect on PPG signals of zero-phase filtration with minimal phase shifts or induced variability. Statistical analyses reveal that the timing characteristics are highly significantly correlated with those acquired from the ECG signals. This process is necessary as location of the PPG waveform peak obtained from a cold periphery is rather difficult.

for the corresponding ECG signals in terms of their derived beat-to-beat HR.

Owing to possible inter-subject differences in arterial distensibility, absolute values for PTT measurements cannot be compared [14, 16]. However, since the PTTR parameter is a ratio-based parameter, similar to ABI, the effect of inter-subject arterial distensibility differences on PTTR normality should be minimal. In the present study, PTTR was defined as the quotient of the higher PTT value of the two obtained for the lower limbs to the average PTT for the right and left upper limbs. Two-way analysis of variance or a paired Student's t-test assuming equal variances was used to test for significant differences between the two groups of subjects. The same statistical treatment was used to assess the level of significance between the derived HR obtained from the ECG and all PPG sources. Pearson's correlation was also used to assess HR correlations between PPG signals and the ECG. A two-sample for variances or F-test was used to test the PTTR variance differences between the two groups. A p-value of 0.05 or less indicated statistically significant correlation at the 95% confidence level. All statistical calculations were performed using Excel 2003 (Microsoft Corporation, Redmond, WA, USA) and Matlab Release 14.

Measurements required for PTT computation were successfully acquired from the chest and all limbs of the study subjects. Comparison of HR values between the ECG and PPG signals revealed that they were highly correlated for the upper ($R^2=0.872$, $p<0.05$) and lower limbs ($R^2=0.841$, $p<0.05$). This indicates successful acquisition of timing characteristics from the low-amplitude PPG waveforms observed for cold peripheries. This was mandatory before the two study groups could be compared. From the results obtained, the mean PTTR for the groups with normally perfused and cold peripheries were 1.290 ± 0.027 (range 1.252–1.335) and 1.287 ± 0.043 (range 1.222–1.347), respectively, as shown in Figure 3.

Statistical t-test analyses revealed no significant difference ($p=0.818$) between the two groups. Since PTTR is a ratio, it was expected that inter-subject differences in arterial distensibility would have a minimal effect on the inter-group comparisons. Thus, the normal PTTR range for a subject should not be affected when both the lower and upper limbs had poorly perfused peripheries. However, wider PTTR variances were observed among subjects with cold peripheries according to the boxplots in Figure 3. Results for the F-test of variance revealed a significant difference ($p=0.042$) between the two groups. It is worth noting that the beat-to-beat PTTR also exhibited greater intra-subject variation for the subjects with poorly perfused peripheries.

The popular use of the ABI method signifies its importance in clinical practice [1, 8, 18]. Owing to occlusion of the arteries measured, the procedure is less suitable for subjects such as younger children, especially when multiple prolonged monitoring is required. The PTT technique, which has demonstrated potential in cardiorespiratory [14, 16] and cardiovascular [17] studies, has recently been proposed as a promising surrogate for ABI [2, 4, 7]. Moreover, it has been suggested that PTT-related measurements may be sensitive to temperature [5].

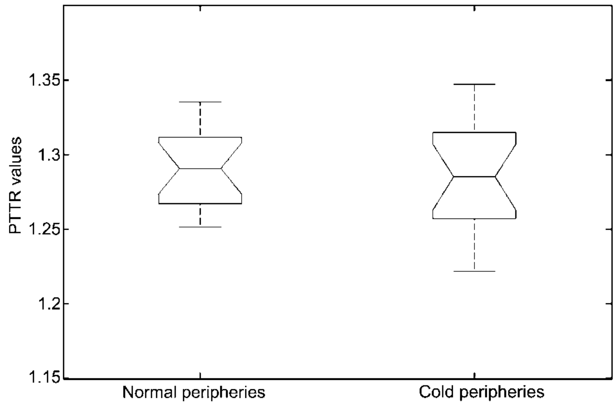

Figure 3 PTTR boxplots of the two recruited study populations.
The two boxplots show that no significant difference ($p>0.05$) in the mean pulse transit time ratio (PTTR) between subjects with poorly perfused peripheries and those with normally perfused peripheries. However, a notable difference ($p<0.05$) is evident in the PTTR variances. This suggests that a cold periphery affects the PPG waveforms and PTT measurements, but has a limited effect on the PTTR parameters. This is likely due to the similar methodology for PTTR and the ankle brachial index.

Thus, the main objective of this study was to investigate the effect of cold temperature on the normality of the derived PTTR parameter. Subjects who had poorly perfused peripheries on all four limbs were recruited for this purpose. The PTTR results obtained for this group of subjects were compared to results for subjects with normally perfused peripheries.

The PTTR parameter is based on the established principle that there is an inverse correlation between PTT and arterial wall stiffness [14, 16]. Thus, transit time-related measurements are dependent on changes in BP and HR. To minimize complications due to these two physiological parameters on the reliability of the results obtained, additional criteria were implemented. In particular, only subjects with SBP <130 mm Hg and with no clinically apparent arterial disease or physical abnormality were recruited. Moreover, ample time was allowed for cardiovascular stabilization and familiarization with the test apparatus. Besides being sensitive to temperature, PTT normality can be affected by the beat-to-beat pre-ejection period of the subject [16]. For convenience of PTT measurement, an additional time delay is imposed on the pulse wave traveling from the aortic valve to the periphery. Using the R-wave of the ECG waveform as the starting point, the left-ventricular isometric contraction time or the time delay between the R-wave and opening of the aortic valve is added to the observed PTT value [6, 16]. Transit time-related measurements may be complex unless this time delay is accounted for in the computed PTT value. By using the ratio of the transit time between the upper and lower peripheral sites, the intrinsic time delay can be minimized, since this delay is included in the PTT acquisition for both limbs.

The results obtained revealed no significant difference ($p>0.05$) between subjects with cold peripheries and those who had normally perfused peripheries. This is probably because PTTR derivation is similar to that of ABI. Therefore, it is likely that the PTTR parameter is dependent only on local arterial distensibility changes observed in one of the peripheries measured. However, there was a significant difference ($p < 0.05$) in PTTR variance between the two study groups, whereby subjects with cold peripheries exhibited wider variance. This is expected, as the optical signals from the PPG probe sensor reflect tissue blood volume and pulsation strength within the periphery measured [11]. The wider PTTR variances may be due to redistribution of skin microcirculation (both local and reflex response) to the surrounding ambient temperature. The microcirculation in these peripheries is mainly regulated by small arteries and arterioles. A significant decrease in total blood volume and pulsation strength is expected despite a stable pulse pressure, since these vessels have a high proportion of smooth muscle in their walls and they constrict more in response to temperature [10]. Changes in PPG waveform features can also vary, depending on inter- and intra-subject sensitivity to the instantaneous responses of the peripheral vasculature to the surrounding temperature. Thus, to detect such poor-quality PPG signals, a computational algorithm [5] was successfully used. Highly correlated results for beat-to-beat HR comparison with the corresponding ECG signals verify its usefulness. The findings reported here suggest that cold exposure may affect PPG waveforms and PTT measurements, but the effect on the PTTR parameter is limited because of its similarity to ABI, and only abnormal local peripheral changes in one of the limbs measured can confound the normal PTTR range of a subject.

There are some limitations to the present study. First, comparison of time-related measurements acquired during the study could be better qualified using standard instruments such as Doppler ultrasound or applanation tonometry. However, it has been suggested that these methods are of low accuracy because of their associated noise levels, which can interfere with detection of the exact location of the pulse minimum [12]. In addition, previous studies have suggested that use of piezoelectric transducer is an alternative technique to obtain pulsations from the finger peripheral site [13]. However, it is known that distinct pulsations from either the anterior tibial artery or the posterior tibial artery can be acquired with reasonable complexity. Therefore, further work is required to understand the feasibility of the piezoelectric technique in this context. Finally, we did not recruit subjects with a cold periphery on only the upper or lower limbs because of the difficulty in locating such subjects who can maintain this physiological state for the duration of the study. Alternatively, induced cold peripheral tests could be conducted to accomplish the same physiological state. However, this would be unethical, as it requires a painful stimulus and should only be used to test sympathetic responses in essential pathological investigations [19].

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Received September 12, 2007; accepted January 19, 2008