CHANGE IN PULSE TRANSIT TIME AND PRE-EJECTION PERIOD DURING HEAD-UP TILT-INDUCED PROGRESSIVE CENTRAL HYPOVOLEMA

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ABSTRACT. Objective. Traditional vital signs such as heart rate (HR) and blood pressure (BP) are often regarded as insensitive markers of mild to moderate blood loss. The present study investigated the feasibility of using pulse transit time (PTT) to track variations in pre-ejection period (PEP) during progressive central hypovolaemia induced by head-up tilt and evaluated the potential of PTT as an early non-invasive indicator of blood loss. Methods. About 11 healthy subjects underwent graded head-up tilt from 0 to 80°. PTT and PEP were computed from the simultaneous measurement of electrocardiogram (ECG), finger photoplethysmographic pulse oximetry waveform (PPG-POW) and thoracic impedance plethysmogram (IPG). The response of PTT and PEP to tilt was compared with that of interbeat heart interval (RR) and BP. Least-squares linear regression analysis was carried out on an intra-subject basis between PTT and PEP and between various physiological variables and sine of the tilt angle (which is associated with the decrease in central blood volume) and the correlation coefficients (r) were computed. Results. During graded tilt, PEP and PTT were strongly correlated in 10 out of 11 subjects (median r = 0.964) and had strong positive linear correlations with sine of the tilt angle (median r = 0.966 and 0.938 respectively). At a mild hypovolaemic state (20–30°), there was a significant increase in PTT and PEP compared with baseline (0°) but without a significant change in RR and BP. Gradient analysis showed that PTT was more responsive to central volume loss than RR during mild hypovolaemia (0–20°) but not moderate hypovolaemia (50–80°). Conclusion. PTT may reflect variation in PEP and central blood volume, and is potentially useful for early detection of non-hypotensive progressive central hypovolaemia. Joint interpretation of PTT and RR trends or responses may help to characterize the extent of blood volume loss in critical care patients.

KEY WORDS. pulse transit time (PTT), pulse transmission time, pre-ejection period, head-up tilt, hypovolaemia, blood loss.

INTRODUCTION

Early detection of internal bleeding has often been a difficult task for clinicians. Vital sign monitors that are currently in use in emergency department (ED) or in emergency transport vehicles measure a range of physiological variables including heart rate (HR) and blood pressure (BP) but these variables are often regarded as insensitive markers of mild to moderate blood loss [1, 2]. The decrease in central blood volume during early stage of blood loss typically triggers a baroreflex response that acts to maintain a perfusing BP despite a decline in stroke volume. BP may not decrease considerably until about
30% of total blood volume has been lost, by which time patients are at high risk of cardiovascular collapse as a result of haemorrhagic shock [1, 3–6]. Delayed control of haemorrhage has been recognized as a major contributor to preventable trauma deaths and has often been related to delays in the assessment or diagnosis of haemorrhage [7, 8]. There are potentially large benefits to the critical care clinician if small volume losses could be diagnosed early, accurately and reproducibly simply by the assessment of a physiological variable that can be conveniently derived from existing patient monitoring equipment.

Recently, a significant amount of research effort has been devoted to the pulse transit time or the pulse transmission time (PTT) [9, 10]. PTT is typically measured as the time interval from the R-wave of the electrocardiogram (ECG) to a reference point on the systolic upstroke of a subsequent peripheral pulse wave. It consists of two components: the pre-ejection period (PEP), which corresponds to the timing from the onset of ventricular depolarisation to the onset of ventricular ejection, and the vascular transit time (VTT), which defines the period for the arterial pulse wave to travel from the aortic valve to the peripheral arteries. In particular, the PEP component of PTT is known to vary with cardiac preload [11–13]. Recent studies have shown that respiratory variation in PTT/PEP could predict fluid responsiveness in patients [14, 15]. From the perspective of clinical monitoring, PTT has the potential to become widely applied in patient care since its derivation only requires ECG and a peripheral pulse waveform, such as the finger photoplethysmographic pulse oximetry waveform (PPG-POW) which has been commonly used for the monitoring of arterial oxygen saturation (SpO2). Both ECG and PPG-POW are routinely measured by existing vital sign monitors, and their measurement is totally noninvasive and causes minimal discomfort to the patients. By monitoring PTT in a continuous beat-by-beat manner, it may be possible to identify subtle change in the patient’s cardiovascular status caused by small amounts of progressive blood loss over time.

Previous studies have identified the potential value of PTT in the detection of hypotension caused by central hypovolaemia [16, 17]. Ahlstrom et al. showed that PTT could track changes in systolic BP during simulated hypovolaemia with lower body negative pressure (LBNP) [16]. A study of actual haemorrhage in dogs by Ochiai et al. demonstrated that hypotension caused by acute blood loss could be potentially identified as a prolongation in PTT [17]. However, these studies involved a high degree of central hypovolaemia which subsequently led to hypotension. It is not clear whether PTT is also useful for detecting mild hypovolaemia in the absence of significant BP reduction.

The purpose of the present study was to identify the change in PTT associated with the decline in central blood volume, similar to that which occurs during mild to moderate blood loss. Graded head-up tilt was used as a model to simulate progressive central hypovolaemia [3–5, 18, 19]. The sine of the tilt angle (sinθ) is proportional to the hydrostatic effect of head-up tilting [20, 21], and a linear relationship has been found between sinθ and the decrease in thoracic fluid content [22]. Although graded head-up tilt is not truly equivalent to actual blood loss since the blood volume is merely re-distributed to the lower body under gravitational influence rather than actually lost from the circulatory system, it may at least simulate most of the cardiovascular responses to a progressive decline in central blood volume similar to that occurring during haemorrhage.

In the current study, the change in PTT and PEP at different levels of central blood volume induced by graded tilt was examined along with corresponding responses in interbeat heart interval (RR) and BP. Intra-subject regression analysis was carried out (1) between PTT and PEP to determine how much PEP contributed to the PTT variations associated with change in central blood volume, and (2) between the different physiological variables and sinθ to determine the association of the variables with central blood volume. Moreover, the gradient of the variables with respect to tilt angle increment was computed to provide a measure of the directional change in the variable in response to a further decrease in central blood volume at a given volume status represented by the tilt angle. A positive/negative gradient would indicate an increasing/decreasing trend in the variable as volume loss progressed.

METHODS AND MATERIALS

Subject

About 11 healthy subjects (10 males and 1 female, aged 18–44 years, mean age 30 years) were studied. Prior to the experiment, subjects were requested to provide information about their physical condition and none reported any history of cardiovascular or respiratory disease. Written informed consent was obtained from all participants, and the study was approved by the Human Research Ethics Advisory (HREA) Panel of the University of New South Wales.

Measurement devices and systems

PPG-POW was measured from the tip of the right index finger using a reflection mode infrared finger probe...
(ADInstruments, Sydney, Australia). ECG was acquired from the lead I configuration and amplified with a bioamplifier (ADInstruments, Sydney, Australia). The thoracic impedance plethysmogram (IPG) was acquired using the Tetrapolar High-Resolution Impedance Monitor, also known as the THRIM (UFI, Morro Bay, USA). The two Ag/AgCl electrodes for the measurement of thoracic IPG were positioned over the sternum: one at the top of the sternum and another superior to the xiphoid process. From the anatomical perspective, this electrode arrangement should produce a thoracic IPG which reflects the change in blood volume predominantly in the aorta and in the thoracic vessels [23]. The signals were recorded and digitised at a sampling rate of 1000 Hz using the Powerlab data acquisition system (ADInstruments, Sydney, Australia). BP measurements, including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and pulse pressure (PP), were obtained using a Tetrapolar High-Resolution Impedance Monitor, also known as a cuff placed around the left arm over the brachial artery.

Measurement protocol

The subjects were advised not to eat for at least 2 h prior to the study, with any meal to be free of alcohol and caffeine beverages. The subjects were also asked not to undertake any intensive exercise within 12 h before the study. All measurements were made in a quiet dimly lit room at an ambient temperature of approximately 24°C. The subject initially rested in a supine position on the tilt table for a period of 20 minutes. The subject’s feet were supported by a footboard, and straps were applied at the levels of waist and knees to stabilize the body during head-up tilting. Measurements were made at each of the following tilt angles in incremental order: 0, 10, 20, 30, 40, 50, 60 and 80°. At each tilt angle, PPG-POW, ECG and thoracic IPG were simultaneously recorded for a period of 15 s, followed by a measurement of BP. A 15 s measurement period is considered sufficient to encompass at least one respiratory cycle, allowing the influence of respiratory phase on the measurements to be minimized by averaging. Once measurements at the current tilt angle were completed, the subject was tilted to the next angle. After each tilt, and before the next phase of measurement commenced, a 1.5 min adaptation period allowed the measured cardiovascular variables to settle to a stable level, which generally takes up to 30 s [24]. Measurements were made with the subject breathing spontaneously. BP measurements and finger PPG-POW signals were acquired with the subject’s forearms supported by armrests maintained at close to the heart level.

Signal processing and parameter extraction

All signal processing and feature extraction were implemented in Matlab (the MathWorks Inc., Natick, USA). The R-wave peaks were detected from the ECG signal using a set of automatic programming routines involving lowpass filtering, differentiation, and threshold peak detection. The processing of the PPG-POW and the AC component of the thoracic IPG involved four main stages: (1) Lowpass filtering—An 8th order Butterworth lowpass filter with a 3-dB point at 18 Hz was designed to remove high frequency noise. Zero-phase filtering was implemented, which involved filtering the signal in both forward and backward directions, to eliminate phase distortion. (2) Baseline removal—The baseline of the two signals was approximated by moving averaging. For the PPG-POW, a 2 s window (3-dB point at 0.23 Hz) was used, whereas for the thoracic IPG, a 1.5 s window (3-dB point at 0.3 Hz) was used. The baseline component was subsequently subtracted from the respective signals. (3) Differentiation—A 5-point digital differentiator was designed to differentiate the two signals to obtain the first derivative (d1), the second derivative (d2), and the third derivative (d3), namely d1PPG-POW, d2PPG-POW and d3PPG-POW for PPG-POW, and dZ/dt, d2Z/dt^2 and d3Z/dt^3 for thoracic IPG. The high order derivatives were generally noisy and therefore were smoothed by moving averaging with a 31.3 ms window (3-dB point at 14 Hz). (4) Pulse detection—A threshold detection algorithm was implemented for detecting the systolic peaks from the derivatives of the two signals. All the data traces were free of artefact and therefore artefact rejection was not necessary.

Several timing parameters were derived from ECG, PPG-POW, and thoracic IPG, including RR, PTT, PEP and VTT. RR was computed as the time interval between successive R-wave peaks. PTT was computed as the time interval between the R–wave peak and the arrival of the subsequent pulse in finger d1PPG-POW (see Figure 1). In the present study, d1PPG-POW was taken as the reference pulse signal for PTT measurement due to its close association with arterial inflow [25]. The reference point chosen for PTT computation was the onset or foot of d1PPG-POW, which could be reliably detected from the systolic peaks in d3PPG-POW based on the second derivative method [26].

PEP was computed as the time interval between R–wave peak and the onset of ventricular ejection detected from the subsequent thoracic dZ/dt pulse (see Figure 1).
R-wave peak was used as the reference point to represent ventricular depolarisation due to the reliability of its detection [16, 17]. The onset of ventricular ejection was identified from thoracic dZ/dt by locating the so-called B-point, which appeared as an incisura at the base of the rising edge of the large systolic wave in dZ/dt [27] and was detected using the derivatives [28].

**Data analysis**

The RR, PTT, PEP and VTT of a subject at a given tilt angle were averaged over the 15 s recording period. The mean and standard error (SE) of all subject measurements at each tilt angle were calculated, and the mean ± SE was plotted against sinθ. The range and coefficient of variation of PTT and PEP were computed for 0 and 80°. Moreover, the gradient of the variable was calculated as the difference in the variable divided by the difference in sinθ between successive tilt angles, to measure the directional change of the variable in response to a unit decrement in central blood volume. The average gradients of the variable in three stages were computed: (1) 0–20° (mild hypovolaemia), (2) 20–50° (mild-to-moderate hypovolaemia), (3) 50–80° (moderate hypovolaemia). Nonparametric Friedman’s ANOVA test for repeated measures was used to determine whether any significant change occurred in the variable and its gradient during sequential tilting, and when significant change was detected, Wilcoxon signed rank test was performed post hoc with Bonferroni correction to test whether there was significant increase/decrease in the variable and its gradient between the three stages. Wilcoxon signed rank test with Bonferroni correction was also used to test whether there was a significant positive/negative gradient in each stage. For all statistical tests, p < 0.05 was considered significant. Least-squares linear regression analysis was carried out between PTT and PEP, and between each variable and sinθ. The correlation coefficient (r) was computed. The regression relationship was considered significant if p < 0.05.

**RESULTS**

The results are expressed as mean ± SE. Overall, there was significant change in RR (p < 0.001), PTT (p < 0.001), PEP (p < 0.001), VTT (p < 0.001), DBP (p < 0.001), MAP (p < 0.05) and PP (p < 0.01) during tilting but no significant change in SBP (p > 0.05). Table 1 shows the values of RR, PTT, PEP, VTT, SBP, DBP, MAP and PP at different tilt angles.

**Table 1. Physiological variables at different tilt angles**

<table>
<thead>
<tr>
<th>θ (°)</th>
<th>RR (ms)</th>
<th>PTT (ms)</th>
<th>PEP (ms)</th>
<th>VTT (ms)</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>MAP (mmHg)</th>
<th>PP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1031 ± 17</td>
<td>190 ± 6</td>
<td>109 ± 5</td>
<td>81 ± 3</td>
<td>104 ± 3</td>
<td>60 ± 1</td>
<td>75 ± 2</td>
<td>44 ± 2</td>
</tr>
<tr>
<td>10</td>
<td>1031 ± 30</td>
<td>195 ± 6</td>
<td>117 ± 6*</td>
<td>78 ± 3</td>
<td>107 ± 2</td>
<td>60 ± 1</td>
<td>76 ± 2</td>
<td>47 ± 2</td>
</tr>
<tr>
<td>20</td>
<td>998 ± 25</td>
<td>202 ± 7*</td>
<td>122 ± 7*</td>
<td>80 ± 3</td>
<td>106 ± 3</td>
<td>58 ± 2</td>
<td>75 ± 3</td>
<td>47 ± 2</td>
</tr>
<tr>
<td>30</td>
<td>966 ± 32</td>
<td>204 ± 7*</td>
<td>126 ± 6*</td>
<td>78 ± 3</td>
<td>107 ± 3</td>
<td>59 ± 2</td>
<td>75 ± 2</td>
<td>48 ± 3</td>
</tr>
<tr>
<td>40</td>
<td>929 ± 36*</td>
<td>208 ± 7*</td>
<td>132 ± 7*</td>
<td>77 ± 3</td>
<td>106 ± 3</td>
<td>58 ± 2</td>
<td>75 ± 2</td>
<td>47 ± 2</td>
</tr>
<tr>
<td>50</td>
<td>881 ± 45*</td>
<td>212 ± 7*</td>
<td>137 ± 6**</td>
<td>75 ± 3</td>
<td>105 ± 3</td>
<td>61 ± 2</td>
<td>76 ± 3</td>
<td>44 ± 2</td>
</tr>
<tr>
<td>60</td>
<td>847 ± 40**</td>
<td>215 ± 7*</td>
<td>139 ± 7**</td>
<td>72 ± 3**</td>
<td>105 ± 3</td>
<td>61 ± 2</td>
<td>78 ± 2</td>
<td>43 ± 2</td>
</tr>
<tr>
<td>80</td>
<td>797 ± 45**</td>
<td>215 ± 7*</td>
<td>143 ± 7**</td>
<td>72 ± 3</td>
<td>105 ± 3</td>
<td>63 ± 2</td>
<td>79 ± 2</td>
<td>42 ± 2</td>
</tr>
</tbody>
</table>

Results are presented as mean ± SE. **p < 0.01, * p < 0.05: significant increase/decrease from 0° (with Bonferroni correction made). Abbreviations: θ = tilt angle.
different tilt angles and any significant changes from baseline. There was no significant change in RR from baseline at 10–30° but there was significant decrease at 40° and above. PTT was significantly higher than baseline at 20° and above whereas PEP was significantly higher than baseline at 10° and above. At 0°, PTT ranged from 152 to 228 ms with CV of 11%, whereas PEP ranged from 75 to 134 ms with CV of 16%. At 80°, PTT ranged from 160 to 255 ms with CV of 11%, whereas PEP ranged from 98 to 174 ms with CV of 16%. The percentage change in mean PTT and PEP between 0 and 80° were 13 and 31% respectively. There was no significant change in VTT from baseline except for a significant decrease at 60°. No significant change from baseline was observed in SBP, DBP, MAP and PP. In Figures 2–4, the mean ± SE of each variable is plotted against sinθ. As sinθ increased, RR decreased with the rate of decrease tending to be greater at higher tilt angles. PTT and PEP, on the other hand, increased linearly with sinθ, while VTT decreased slightly. The BP variables did not appear to change with sinθ at low tilt angles, although there was a tendency for MAP and DBP to increase and for PP to decrease at high tilt angles.

Table 2 shows the gradients of RR, PTT, PEP, VTT, SBP, DBP, MAP and PP at the three stages (0–20°, 20–50° and 50–80°) and any significantly positive gradient (rising trend) or negative gradient (falling trend). A significantly negative gradient was identified in RR at 20–50° and 50–80° and in PP at 20–50°. A significantly positive gradient was identified in PTT at 0–20° and 20–50°, in PEP at all three stages and in MAP at 50–80°. Overall, there was a significant change in gradient in RR (p < 0.05) and DBP (p < 0.05) but not in other variables. A significant decrease in gradient compared with 0–20° was identified in RR at both 20–50° and 50–80°.

The results of intra-subject regression analysis of PEP against PTT, and RR, PTT, PEP, VTT, SBP, DBP, MAP and PP against sinθ are shown in Table 3. The correlation between PEP and PTT was generally strong (median r = 0.964, range of r from 0.626 to 0.988), and 10 out of 11 subjects had positive and significant regression relationships (p < 0.05). The regression slope of PEP against PTT was significantly positive (1.18 ± 0.13). PEP had the strongest correlation with sinθ (median r = 0.966), and the regression relationships were positive.
and significant in 10 out of 11 subjects. The subject who had poor correlation between PEP and sinθ (r = 0.417, p > 0.05) also had poor correlation between PEP and PTT (r = 0.626, p > 0.05). The regression slope of PEP against sinθ was significantly positive (33.9 ± 4.4 ms). PTT showed a strong correlation with sinθ (median r = 0.938), and the regression relationships were positive and significant in 8 out of 11 subjects. The regression slope of PTT against sinθ was significantly positive (25.0 ± 3.0 ms). RR also showed a strong correlation with sinθ (median r = 0.938), and the regression relationships were negative and significant in 9 out of 11 subjects. The regression slope of RR against sinθ was significantly negative (−8.8 ± 2.7 ms). The regression relationships between the BP variables and sinθ varied considerably between subjects and did not reach statistical significance for most subjects, and the regression slopes were not significant.

**DISCUSSION**

The present study highlights the potential value of PTT as a sensitive early non-invasive marker of falling central blood volume. Graded head-up tilt from 0 to 80° has been used as a model to simulate the transition from mild to moderate central hypovolaemia, similar to that occurs in progressive blood loss. An important new finding of the present study is that PTT can signal a drop in central blood volume relative to the normovolaemic state (0°) at a

**Table 2. Gradients of physiological variables at the three stages**

<table>
<thead>
<tr>
<th>θ (°)</th>
<th>RR (ms)</th>
<th>PTT (ms)</th>
<th>PEP (ms)</th>
<th>VTT (ms)</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>MAP (mmHg)</th>
<th>PP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–20</td>
<td>−98 + 49</td>
<td>35 + 8**</td>
<td>38 + 9**</td>
<td>−3 + 6</td>
<td>5 + 5</td>
<td>−5 + 4</td>
<td>−2 + 5</td>
<td>10 + 6</td>
</tr>
<tr>
<td>20–50</td>
<td>−285 + 77** #</td>
<td>23 + 6**</td>
<td>35 + 4**</td>
<td>−11 + 5</td>
<td>−2 + 4</td>
<td>6 + 3</td>
<td>2 + 3</td>
<td>−8 + 2*</td>
</tr>
<tr>
<td>50–80</td>
<td>−380 + 69** #</td>
<td>14 + 13</td>
<td>28 + 9*</td>
<td>−14 + 12</td>
<td>1 + 8</td>
<td>10 + 4</td>
<td>16 + 6*</td>
<td>−9 + 6</td>
</tr>
</tbody>
</table>

Results are presented as mean ± SE. **p < 0.01, *p < 0.05: significantly positive/negative gradient (with Bonferroni correction made). #p < 0.01, # p < 0.05: significant increase/decrease from 0–20° (with Bonferroni correction made). Abbreviations: θ = tilt angle.

**Table 3. Correlation coefficients from intra-subject regression analysis**

<table>
<thead>
<tr>
<th>Subject</th>
<th>PEP-PTT</th>
<th>RR-θ</th>
<th>PTT-θ</th>
<th>PEP-θ</th>
<th>VTT-θ</th>
<th>SBP-θ</th>
<th>DBP-θ</th>
<th>MAP-θ</th>
<th>PP-θ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.969*</td>
<td>−0.952*</td>
<td>0.829*</td>
<td>0.922*</td>
<td>−0.937*</td>
<td>0.186</td>
<td>−0.181</td>
<td>0.306</td>
<td>0.275</td>
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<tr>
<td>2</td>
<td>0.964*</td>
<td>−0.514</td>
<td>0.982*</td>
<td>0.978*</td>
<td>−0.584</td>
<td>−0.015</td>
<td>−0.249</td>
<td>−0.176</td>
<td>0.155</td>
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<tr>
<td>3</td>
<td>0.931*</td>
<td>−0.618</td>
<td>0.957*</td>
<td>0.966*</td>
<td>−0.790*</td>
<td>0.521</td>
<td>0.912*</td>
<td>0.741*</td>
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<td>−0.941*</td>
<td>0.980*</td>
<td>0.966*</td>
<td>−0.612</td>
<td>−0.819*</td>
<td>−0.716*</td>
<td>−0.682*</td>
<td>−0.244</td>
</tr>
<tr>
<td>5</td>
<td>0.982*</td>
<td>−0.960*</td>
<td>0.996*</td>
<td>0.978*</td>
<td>−0.753*</td>
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<tr>
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<td>−0.855*</td>
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<td>0.559</td>
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<td>−0.927*</td>
<td>0.938*</td>
<td>0.987*</td>
<td>0.065</td>
<td>−0.263</td>
<td>0.201</td>
<td>0.308</td>
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<tr>
<td>8</td>
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<td>−0.988*</td>
<td>0.988*</td>
<td>0.990*</td>
<td>−0.958*</td>
<td>−0.051</td>
<td>0.846*</td>
<td>0.703</td>
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</tr>
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<td>9</td>
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<td>0.627</td>
<td>0.843*</td>
<td>−0.804*</td>
<td>−0.708*</td>
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<tr>
<td>10</td>
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<td>0.515</td>
<td>0.417</td>
<td>0.473</td>
<td>−0.213</td>
<td>−0.273</td>
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<td>11</td>
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<td>−0.774*</td>
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<td>0.899*</td>
<td>−0.665</td>
<td>0.730*</td>
<td>0.947*</td>
<td>0.622</td>
<td>−0.898*</td>
</tr>
<tr>
<td>Med r</td>
<td>0.964</td>
<td>−0.927</td>
<td>0.938</td>
<td>0.966</td>
<td>−0.665</td>
<td>−0.030</td>
<td>0.201</td>
<td>0.308</td>
<td>−0.161</td>
</tr>
<tr>
<td>Max r</td>
<td>0.988</td>
<td>−0.514</td>
<td>0.996</td>
<td>0.990</td>
<td>0.473</td>
<td>0.730</td>
<td>0.947</td>
<td>0.741</td>
<td>0.275</td>
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<tr>
<td>Min r</td>
<td>0.626</td>
<td>−0.988</td>
<td>0.515</td>
<td>0.417</td>
<td>−0.958</td>
<td>−0.819</td>
<td>−0.716</td>
<td>−0.682</td>
<td>−0.898</td>
</tr>
<tr>
<td>Mean m</td>
<td>1.18*</td>
<td>−245*</td>
<td>25.0*</td>
<td>33.9*</td>
<td>−8.8*</td>
<td>−0.16</td>
<td>2.49</td>
<td>2.92</td>
<td>−2.65</td>
</tr>
<tr>
<td>±SE m</td>
<td>±0.13</td>
<td>±47</td>
<td>±3.5</td>
<td>±4.4</td>
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<td>±2.32</td>
<td>±1.66</td>
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* p < 0.05: significant. Abbreviations: PEP-PTT = PEP against PTT, RR-θ = RR against sine of the tilt angle etc. The table displays the correlation coefficients of the intra-subject regressions, with the last five rows corresponding to the median, maximum and minimum of the subjects’ correlation coefficients, and the mean and standard error of the regression slopes.
much early stage than RR and BP. A significant rise in PTT occurred at 20° tilt whereas a significant fall in RR only occurred at 40° tilt and above, while BP did not show any significant change from baseline at all tilt angles.

The change in PTT during mild to moderate central hypovolaemia has been shown to reflect predominantly the change in PEP, and this finding is in agreement with the study by Newlin which revealed considerable contribution of PEP to PTT variation [29]. A significantly positive linear correlation between PTT and PEP has been observed in 10 out of 11 subjects. The non-significant correlation observed in one subject was partly attributed to the lack of PEP response to tilting as indicated by the poor correlation between PEP and $\sin \theta$, but generally, the correlation coefficient between PTT and PEP was high (median $r = 0.964$), justifying the potential use of PTT to monitor PEP variations during mild change in volume status. Progressive prolongation of PEP/PTT during graded head-up tilt is believed to reflect a decline in stroke volume caused by the reduction of cardiac preload (or end diastolic volume) as a result of orthostatic volume shift from the central venous pool to the lower body [11]. During head-up tilt, the hydrostatic effect of tilting is proportional to $\sin \theta$ which reflects the body axis component of gravitational pull exerted on the blood volume inside the body [20, 21]. As demonstrated by the present study, PEP and PTT had strong positive correlation ($r > 0.8$) with $\sin \theta$ in most subjects and the overall regression slopes were significantly positive. These findings are consistent with the observed linear relationship between $\sin \theta$ and the decrease in thoracic fluid content during graded head-up tilt [22] and suggest that PEP and PTT may reflect proportional change in central blood volume or preload.

A new way of studying the haemodynamic effect of progressive hypovolaemia using gradient/trend analysis of PTT and RR has been presented in this study that may permit better characterization of the different stages of blood loss. From the perspective of clinical application, we propose that the changing trends in PTT and RR may be more useful than their absolute values for identifying and distinguishing between different phases of progressive blood loss. It is well recognized that trends in physiological variables, both with evolving pathology and with resuscitative measures, are very useful diagnostically and prognostically in acute illness. Although PTT may be augmented in hypovolaemia compared with normovolaemia, in a real life situation critical care clinicians often need to diagnose blood loss without prior knowledge of the patients’ pre-haemorrhage physiological variables. It seems not possible to use absolute values of PTT to identify patients with low central blood volume because of the high degree of inter-subject variability, as demonstrated by the considerable overlap in the ranges of PTT comparing the normovolaemic state (0°) with the most hypovolaemic state (80°) and the high inter-subject CV (11%) relative to the percentage difference (13%) between the two states. Alternatively, the trend or gradient of PTT may be useful for identifying patients who are progressively losing blood, since dynamic volume decrease may result in a rising trend in PTT over time. In the current study, three different stages of physiological response to central volume loss have been identified:

Stage 1 (0–20°): This stage simulated mild central hypovolaemia. A rising trend was observed in PTT/PEP as preload decreased. No significant falling trend was observed in RR, probably because small decrement in central blood volume at a mild hypovolaemic state was not sufficient to trigger noticeable baroreflex response.

Stage 2 (20–50°): This stage simulated mild-to-moderate central hypovolaemia. PTT/PEP continued to show a rising trend as preload decreased. A falling trend was also observed in RR, which could be attributed mostly to vagal withdrawal and also to sympathetic activation. The more negative RR gradient in this stage compared with stage 1 might result from augmented baroreflex responsiveness as central blood volume decreased [30].

Stage 3 (50–80°): This stage simulated moderate central hypovolaemia. A significant rising trend was not observed in PTT even though PEP was increasing with preload reduction, and this suggested that the decline in VTT might have offset the rise in PEP. The decline in VTT indicated an increase in pulse wave velocity (PWV) induced by sympathetic activation, which might result from a rise in MAP/DBP causing a passive increase in arterial stiffness or from an increase in myocardial contractility [31, 32]. PEP, despite continuing to increase, showed a weaker rising trend in this stage, possibly because the shortening effect of preload reduction was opposed by the shortening effect of sympathetic activation [12, 13]. A falling trend in RR continued in this stage as a result of the combined influence of vagal withdrawal and sympathetic activation with further reduction in central blood volume.

Based on the observed physiological response to the three stages of simulated hypovolaemia, it is clear that rising trend in PTT can be a useful marker for progressive volume loss in stages 1 and 2 (mild and mild-to-moderate hypovolaemia), but not when the patient has entered stage 3 (moderate hypovolaemia). In stage 3, sympathetic activation is believed to cause variation in VTT which reduces the ability of PTT to follow changes in PEP. The shortcoming of PTT can be mitigated, however, by also considering RR, which tends to fall sharply as a result of an enhanced sympathetic tone. The present study has demonstrated that the joint interpretation of PTT and RR trends may offer promising...
possibility of not only detecting the presence, but also estimating the extent of progressive blood loss. For example, a change in the patient’s status from rising PTT and unchanged RR to unchanged/falling PTT and falling RR may indicate the transition from mild hypovolaemia to moderate hypovolaemia.

**PTT/PEP and BP**

Although an increase in afterload (represented by MAP/DBP) due to peripheral vasoconstriction may also lead to an increase in PEP [33], it was unlikely to be the major cause of the tilt-induced change in PEP and PTT because MAP/DBP did not have a significant linear relationship with sinθ. The lack of concomitant BP change with mild decrease in central blood volume induced by head-up tilt has been reported elsewhere [34–37], and this finding supports the concept of insensitivity of BP to small volume loss [1]. It is known that in phase I of haemorrhage (loss of up to ~750 ml or ~15% of total blood volume), sympathetic activation would help to maintain a stable BP despite a drop in stroke volume, and only until blood loss reaches a critical level (~30–40% of total blood volume), a decompensatory phase II commences during which BP and HR fall dramatically [3–5]. In contrast to previous studies which utilized PTT as a surrogate marker of BP change for detecting hypovolaemia-induced hypotension [16, 17], the present study demonstrates that PTT may in fact be a more robust indicator of mild volume loss than BP itself and may signal an early stage of hypovolaemia well before the phase II hypotension occurs. The theoretical basis for the use of PTT as a surrogate marker of BP was initially suggested to be the potential negative correlation between VTT/PWV and BP [38] but the relationship between PTT and BP can be significantly influenced by the variation in PEP which may oppose the change in VTT [17, 29, 39]. The results of this study have provided further evidence that PTT and PEP can change in a dissociated way from VTT and BP during mild to moderate central hypovolaemia.

**Head-up tilt as a model of progressive hypovolaemia**

In this study, progressive central hypovolaemia was induced in healthy awake subjects by incremental head-up tilt from 0 to 80°. The use of head-up tilt as a model to simulate the major haemodynamic response to haemorrhage in humans has been documented elsewhere [3–5, 18, 19]. Although tilt-induced central hypovolaemia is not identical to actual blood loss since the blood volume is merely re-distributed to the lower body rather than actually lost from the circulatory system, the initial cardiovascular response to haemorrhage is essentially the same as that elicited by a reduction in central blood volume, e.g. by head-up tilt or by lower body negative pressure (LBNP) [4–6, 19]. About 24° head-up tilt produces a similar cardiovascular response to 15 mmHg LBNP [36], which approximates mild haemorrhage (loss of 400–550 ml or ~10% of total blood volume) [6], while 60° head-up tilt produces a similar cardiovascular response to 20–40 mmHg LBNP [37], which approximates moderate haemorrhage (loss of 550–1000 ml or ~10–20% of total blood volume) [6]. However, a limitation of using head-up tilt as a model of blood loss is that the regional blood volume changes and the associated vascular responses induced by gravitational fluid shift to the lower body can be different from that in actual haemorrhage [37, 40]. Nonetheless, head-up tilt may still be regarded as an acceptable model to simulate most of the cardiovascular effect of falling central blood volume that occurs in blood loss.

**Comparison with actual haemorrhage in anaesthetized dogs**

Since the present findings are based on a simulated model of haemorrhage, whether the results are applicable to an actual blood loss situation remains to be investigated. Kubitz et al. studied variation in PEP and cardiac preload during acute haemorrhage in pigs, but concluded that PEP was not sensitive to the change in intravascular volume status [41]. Ochiai et al. showed that acute blood loss led to significant prolongation in VTT and PTT, yet with no significant change in PEP [17]. We suggest that one reason for the lack of PEP change in these haemorrhage studies may be due to the magnitude of blood loss being severe given the presence of hypotension. It was noted in the present study that PEP showed a weaker rising trend in stage 3 (50–80°) compared with stage 1 and 2 (0–50°), which suggests that PEP may be less sensitive to volume change as the degree of hypovolaemia becomes more severe, most likely due to the opposite effect of preload reduction and sympathetic activation. Another possible reason for the difference may be the effect of experimental procedure on the physiologic response of haemorrhaged animals, including the method of blood withdrawal and the induction of anaesthesia which may have confounding effects on the cardiovascular response to volume loss [42, 43]. For example, the use of isoflurane in the study by Ochiai et al. could lead to vasodilatation and might subsequently influence the PEP/PTT response to haemorrhage.

**Technical aspects of PTT/PEP derivation**

The ability of PTT to monitor PEP variation may depend on which part of the peripheral pulse waveform is used as a reference point for PTT measurement. In the present study,
the first derivative of the finger PPG-POW (d1PPG-POW) was used as the reference pulse waveform since it is considered to be closely related to peripheral arterial flow [25]. The foot of d1PPG-POW was used as the reference point for pulse arrival, in order to eliminate the potential contribution of the rising time of systolic upstroke on PTT, so that the PTT measurement would more closely reflect the variation in PEP. In fact, it is possible that sympathetic activation during haemorrhage may induce a change in the systolic rising time that opposes the prolongation of PEP caused by preload reduction.

For PEP measurements, the present study used thoracic IPG to identify the onset of ventricular ejection. The thoracic dZ/dt pulse waveform has been regarded as a measure of intrathoracic blood volume change and experimental evidence tended to suggest a major role played by systolic blood volume expansion in the ascending aorta [23, 44], although the precise anatomic site of its onset (B-point) remains speculative. Nevertheless, it has been demonstrated that B-point occurred synchronously with the first heart sound which marks the onset of ventricular contraction [27] and the use of B-point to estimate PEP has been validated by comparison with the standard technique based on carotid pulse and phonocardiogram [45]. Comparing PEP measurements in our study with Stafford et al. [11], the differences between the mean PEP at equivalent tilt angles were actually quite small (the differences were 1 ms at 0°, 3 ms at 10°, −2 ms at 20 and 30°, and 5 ms at 60°), despite the difference in methodology used for PEP computation. The close agreement between the PEP measurements in our study and in Stafford et al. provides us with further reassurance that the thoracic IPG-based technique is reliable.

Clinical application of PTT

The ability of PTT to identify early stages of hypovolaemia has a potentially enormous benefit to clinical practice, in particular for those cases associated with covert haemorrhage into body cavities that are not easily recognizable at the beginning. Delayed control of abdominal, pelvic or intrathoracic haemorrhage has been recognized as a major contributor of preventable trauma deaths and is often caused by delays in the assessment or diagnosis of haemorrhage [7, 8]. Notably, it would be of great interest if such events could be detected as early as possible based on information that could be obtained from existing patient monitoring devices. Although PTT may not be as good as PEP for detecting preload variation due to the confounding effect of VTT, it can be easily computed from simultaneous measurements of ECG and finger pulse oximetry, both of which have been routine patient monitoring techniques for some years. The measurements of ECG and finger PPG-POW are totally noninvasive, cause minimal discomfort to the patients, and can be obtained continuously in a beat-to-beat manner which may permit the early detection of small physiological perturbations. It would certainly be advantageous to critical care clinicians if these two routine measurements can provide information relevant to the diagnosis of blood loss in addition to their conventional use for HR and SpO2 monitoring.

Apart from detecting progressive blood loss, the response pattern of PTT/PEP to graded tilt at different volume status may also have direct relevance towards the use of tilt test in the clinical assessment of hypovolaemia and fluid responsiveness. Due to a lack of response to volume challenge in some patients who are suspected to be hypovolaemic, the test for fluid responsiveness has often been considered an important initial therapeutic question [46]. In clinical practice, one method to test for fluid responsiveness is to measure the haemodynamic change by first tilting the patient to the reverse Trendelenburg position (30° head-up tilt) to induce relative depletion of central blood volume then to the Trendelenburg position (30° head-down tilt) to simulate volume expansion [47]. Ideally, the change in stroke volume or cardiac output during the manoeuvre would define fluid responsiveness, but in cases where stroke volume or cardiac output measurements are not available or not preferred due to their invasive nature, non-invasive indices such as PTT/PEP may be useful alternatives. Previous studies have demonstrated the potential value of respiratory fluctuation in PTT/PEP in predicting fluid responsiveness [14, 15]. The current study has further demonstrated the possibility of using PTT/PEP for assessing fluid responsiveness by studying their dynamic change during tilt manoeuvres, although more clinical studies are required to validate this.

For the PTT technique to be applied clinically, several issues need to be addressed in future investigations; firstly, it is unclear what the optimal duration is for the reliable detection of an increasing/decreasing trend of PTT/RR associated with blood loss. Certainly, the analysis period has to be sufficiently long since both PTT and RR exhibit respiratory fluctuations as well as other spontaneous low frequency oscillations [14, 39, 48] that may confound the genuine trend related to physiological perturbations. Secondly, there is a need to identify patient groups whose PEP/PTT may have limited responsiveness to a change in preload, such as those who suffer from heart failure [11]. Thirdly, the PTT measurement may be influenced by the contact force with the sensor [49], the peripheral temperature [50] and the limb position [51]. Whether these factors would affect the applicability of PTT in the monitoring of critical care patients remains to be investigated.
Conclusion

In conclusion, this study has shown that PTT may reflect variation in PEP and is potentially useful for early detection of non-hypotensive progressive central hypovolaemia. Joint interpretation of PTT and RR trends or responses may help to characterize the extent of blood volume loss. Further work is required to evaluate the applicability of PTT in the examination of critical care patients who may be suffering from haemorrhage.

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REFERENCES


