Changes in left ventricular ejection time and pulse transit
time derived from finger photoplethysmogram and
electrocardiogram during moderate haemorrhage

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Summary
Objectives: Early identification of haemorrhage is difficult when a bleeding site is not apparent. This study explored the potential use of the finger photoplethysmographic (PPG) waveform derived left ventricular ejection time (LVETp) and pulse transit time (PTT) for detecting blood loss, by using blood donation as a model of controlled mild to moderate haemorrhage.

Methods: This was a prospective, observational study carried out in a convenience sample of blood donors. LVETp, PTT and R-R interval (RRi) were computed from simultaneous measurement of the electrocardiogram (ECG) and the finger infrared photoplethysmogram obtained from 43 healthy volunteers during blood donation. The blood donation process was divided into four stages: (i) Pre-donation (PRE), (ii) first half of donation (FIRST), (iii) second half of donation (SECOND), (iv) post-donation (POST).

Results and conclusions: Shortening of LVETp from 303+/−2 to 293+/−3 ms (mean+/−SEM; P<0.01) and prolongation of PTT from 177+/−3 to 186+/−4 ms (P<0.01) were observed in 81% and 91% of subjects respectively when comparing PRE and POST. During blood donation, progressive blood loss produced falling trends in LVETp (P<0.01) and rising trends in PTT (P<0.01) in FIRST and SECOND, but a falling trend in RRi (P<0.01) was only observed in SECOND. Monitoring trends in timing variables derived from non-invasive ECG and finger PPG signals may facilitate detection of blood loss in the early phase.

Introduction
Delayed control of haemorrhage has been recognized as a major contributor to preventable trauma deaths (Gruen et al., 2006; Kauvar et al., 2006). Haemorrhagic shock, as defined by a systolic blood pressure (SBP) less than or equal to 90 mmHg in the pre-hospital setting or emergency department, is associated with high rates of organ failure (24%) and infection (39%) (Kauvar et al., 2006). Successful surgical treatment of the causes of haemorrhage and decreased levels of later complications are both associated with intervention early in the shock process, demonstrating the importance of recognizing bleeding as early as possible. However, it can be a difficult task to detect blood loss at an early stage when the bleeding site is not apparent, for example in the case of covert haemorrhage. Physiological regulatory mechanisms are effective in maintaining BP at a stable level with mild blood loss (up to about 15% of the central blood volume), whereas HR changes during blood loss are complex and dependent on the stage of hypovolaemia (Secher et al., 1992; Evans et al., 2001). Hypotension is a late sign of hypovolaemia which signifies blood volume loss by 30% or more (Secher et al., 1992; American College of Surgeons, 1993; Evans et al., 2001). The unreliability of BP and HR as markers of volume status has highlighted the need for alternative techniques for early diagnosis of haemorrhage.

The primary events that follow blood loss are reductions in venous return, central blood volume, ventricular end diastolic volume (or preload) and subsequently stroke volume, whereas changes in HR and BP are secondary events under the influence of the reflex response to hypovolaemia (Secher et al., 1992; Evans et al., 2001). Detecting change in central blood volume, preload or stroke volume is therefore the most direct way to
identify blood loss. Blood donation may be used as a model of mild to moderate blood loss, and for demonstrating the potential utility of stroke volume or preload related measures in early haemorrhage detection (Rea et al., 1991; Girard et al., 1992; Triedman et al., 1993; Hanson et al., 1998; Kosowsky et al., 2002; Haberthur et al., 2003; Leonetti et al., 2004; Lyon et al., 2005). The amount of blood lost during donation is usually around 500 ml, similar to class 1 haemorrhage (up to 750 ml or 15% of the circulating blood volume) (American College of Surgeons, 1993).

Critical care units and emergency transport vehicles are typically equipped with pulse oximeters for the non-invasive monitoring of arterial haemoglobin oxygen saturation (SpO₂). The derivation of SpO₂ is based on optical measurement of a peripheral volume pulse waveform, termed the photoplethysmographic (PPG) pulse oximetry waveform, but its clinical significance has not been appreciated (Murray & Foster, 1996; Middleton & Henry, 2000). Chan et al. have demonstrated the possibility of monitoring variation in central blood volume using the finger photoplethysmogram and electrocardiogram (ECG) (Chan et al., 2007a,b, 2008). Two timing variables have been identified as potential markers of central hypovolaemia, namely the PPG waveform derived left ventricular ejection time (LVETₚ) and pulse transit time (PTT).

Left ventricular ejection time was found to be correlated with the left ventricular ejection time (LVET) measured from Doppler aortic flow (Chan et al., 2007a), which confirms that LVETₚ can reflect changes in LVET (Quarry-Pigott et al., 1973; Geeraerts et al., 2004). The time interval between ventricular electrical activity and the arrival of a peripheral pulse wave is commonly referred to as PTT (Obrist et al., 1979; Newlin, 1981; Contrada et al., 1995; Foo & Lim, 2006). PTT is a sum of the ventricular pre-ejection period (PEP), which corresponds to the timing from the onset of ventricular depolarization 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. The variation in PTT tended to follow closely the variation in PEP (Newlin, 1981; Chan et al., 2007b). LVET and PEP are collectively known as systolic time intervals (STI), and progressive reduction in central blood volume induced by graded head-up tilting is known to cause linear changes in LVETₚ and PTT similar to those occurring in central LVET and PEP (Stafford et al., 1970; Chan et al., 2007b, 2008). Since both ECG and pulse oximetry measurements are routinely performed by existing vital sign monitors, it would be of clinical value to make use of the information embedded in these signals for early diagnosis of critical pathological conditions such as haemorrhage.

The purpose of the current study was to investigate the changes in LVETₚ and PTT together with R-R interval (RRI) by using blood donation as a model of controlled haemorrhage, and to evaluate these variables as early non-invasive markers of blood loss. We hypothesized that shortening of LVETₚ and prolongation of PTT would occur subsequent to blood donation, while during blood withdrawal, progressive reduction in central blood volume would be characterized by a falling trend in LVETₚ and a rising trend in PTT.

Methods

This was a prospective, observational study carried out in a convenience sample of healthy volunteer blood donors. The study was reviewed and approved by the Human Research Ethics Committees of the Australian Red Cross Blood Service (ARCBS) and the Prince of Wales Hospital, and written informed consent was obtained from all participants.

Study setting and population

A group of 48 healthy blood donors were recruited from the ARCBS Sydney city blood donation centre, which comprised 26 men and 22 women. None of the subjects were first time donors. The exclusion criteria for blood donation in Australia ensure that no subject who has suffered from uncontrolled hypertension, ischemic heart disease, or other cardiovascular disorders is eligible to be a blood donor.

Analysis was performed on data sets from 43 of 48 subjects, comprising 23 men and 20 women, with a mean age of 48 years (SD 13 years), a mean height of 174 cm (SD 11 cm) and a mean weight of 85 kg (SD 20 kg). The data sets from 5 subjects were rejected because of severe artefacts in the ECG signal (1 subject), severe artefacts in the PPG signal possibly due to movement or dislocation of the finger pulse sensor (3 subjects) and a noisy PPG signal with very weak and barely recognizable cardiac pulses (1 subject).

Study protocol and measurements

Data recording was performed with the subject placed comfortably in a semi-recumbent position on a reclining seat. Before the acquisition of PPG and ECG signals began, BP measurement was performed using a manual sphygmomanometer. PPG waveform was measured from the tip of the index finger using a reflection mode infrared finger probe utilizing light at 940 nm (MLT1020FC, ADInstruments, Sydney, Australia), on the hand opposite to that chosen for cannulation. ECG was acquired in a lead II configuration and amplified with a bioamplifier (ST4400, ADInstruments). The signals were recorded and digitized at 1000 Hz using the Powerlab data acquisition system (ST4400, ADInstruments). No highpass filtering was applied to the PPG waveform prior to sampling.

The PPG and ECG data were collected throughout the blood donation process. After a resting period of about 6 min, cannulation of the median cubital vein in the antecubital fossa was performed and withdrawal of blood was started. The amount of blood volume withdrawn was determined using the ARCBS standard weight-based method (typically around 500 ml), and the average donation time was 9 min (range 6–13 min). Data recording was completed at approximately 3 min after the cessation of blood withdrawal, and followed by...
a second BP measurement. The subjects were encouraged to keep their fingers still and their hand stationary on an armrest. Poor quality PPG or ECG recordings which prohibited reliable pulse detection (such as those with weak and barely recognizable cardiac pulses and severe motion artefacts) were excluded from the analysis.

All signal processing and feature extraction were implemented in Matlab (Natick, MA, USA). The processing of PPG and ECG signals and the estimation of RRi, LVETp and PTT have been described in detail previously (Chan et al. 2007a,b). Figure 1 illustrates how PTT and LVETp are obtained from ECG and the dPPG (PPG first derivative) waveform. Some modifications were made in the lowpass filter settings: for detecting the pulse onset of the dPPG waveform, the signal was filtered with a 10 Hz cutoff, whereas for identifying the end of systolic ejection, the signal was filtered with a 14 Hz cutoff. These filter settings were necessary for reliably detecting LVETp and PTT in a wide range of subjects, given the presence of high frequency noise in the signals of some subjects which confounded the true locations of the onset and the end of systolic ejection. The average waveforms of PPG derivatives, which were used for computing reference values of LVETp, were constructed from every 40 consecutive pulses. Beat-to-beat sequences of RRi, LVETp and PTT were obtained for the complete blood donation process.

Data analysis

The blood donation process was divided into four stages: pre-donation (PRE), first half of donation (FIRST), second half of donation (SECOND) and post-donation (POST). The durations of PRE and POST were capped so that they would not exceed half of the blood donation duration. The measurements of RRi, LVETp and PTT in each stage for a given subject were obtained by averaging beat-to-beat values in that stage. Least-squares linear regression analysis was carried out on the beat-to-beat values of each variable versus time in each stage, and the gradients of the regression lines for RRi, LVETp and PTT (denoted as mRRi, mLVETp and mPTT respectively) were computed as indicators of the trends.

A non-parametric Friedman’s ANOVA test for repeated measures was used for comparison of each physiological variable and its gradient across the four stages. When a significant change was detected, a post hoc Wilcoxon signed rank test was performed between each pair of the stages. Adjustments for multiple comparisons were made based on the Bonferroni correction technique. A Wilcoxon signed rank test was also used to test whether there were significant changes in HR (calculated from RRi), systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP) and pulse pressure (PP) between the PRE and POST stages and whether there was a significant positive/negative gradient (mRRi, mLVETp and mPTT) in each stage. For all statistical tests, P<0.05 was considered significant. The coefficient of variation (CV) was computed as 100% × standard deviation/mean for the PRE and POST stages. All results were expressed as mean ± SEM unless otherwise indicated.

Results

RRi, LVETp, PTT and their respective gradients mRRi, mLVETp, mPTT all demonstrated an overall change (P = 0.0044 for mRRi and P<0.0001 for others from the ANOVA test). The changes during the four stages are illustrated in Fig. 2. RRi increased in FIRST compared with PRE, then decreased in SECOND compared with FIRST, and finally increased in POST compared with SECOND and PRE. Negative mRRi was found in PRE and SECOND. LVETp decreased in SECOND and POST compared with PRE, while mLVETp was found to be negative in FIRST and SECOND and positive in POST. PTT increased progressively in the four stages, while mPTT was found to be negative in PRE and positive in FIRST and SECOND.

Table 1 compares vital sign measurements and the timing variables between PRE and POST. A decrease was observed in HR (P<0.001), SBP (P = 0.002), DBP (P = 0.033) and MAP (P = 0.001) but not in PP (P = 0.096). No subject experienced hypotension (defined as SBP/DBP < 90/60 mmHg) subsequent to blood donation. High percentages of the subjects demonstrated a decrease in LVETp (81%) and an increase in PTT (91%) between PRE and POST.

Discussion

Early identification of covert haemorrhage has been a clinically challenging problem, and this study has demonstrated the possibility of using simple non-invasive signals such as ECG and PPG pulse oximetry waveforms to detect blood loss at an early phase. Although the amount of blood loss during blood
donation is relatively small, it is sufficient to cause a reduction in circulatory blood volume, as indicated by stroke volume or preload related measures (Hanson et al., 1998; Kosowsky et al., 2002; Leonetti et al., 2004; Lyon et al., 2005), and a subsequent compensatory rise in muscle sympathetic nerve activity (Rea et al., 1991) and plasma catecholamine levels (Haberthur et al., 2003). A key finding of this study was that a small amount of blood loss was sufficient to induce shortening of LVETp and prolongation of PTT in a majority of the subjects (81% and 91% respectively), which were attributed mainly to reduction of LVET and prolongation of PEP that occur concurrently with a decline in central blood volume (Stafford et al., 1970; Geeraerts et al., 2004; Chan et al., 2007a,b, 2008). This proportion of subjects was higher than that which experienced a drop in BP, either measured by systolic BP (57%), diastolic BP (45%), MAP (71%) or PP (57%). The current results have clearly indicated the superiority of timing variables derived from ECG and PPG waveforms over BP measurements in providing diagnostic information related to mild to moderate blood loss.

However, a main limitation of using LVETp and PTT as indicators of blood loss is their relatively large inter-subject variations in comparison with the changes induced by blood donation, which means that it is their intra-subject changes rather than their absolute values that are clinically useful, as with most other haemodynamic measurements. In the current study, the use of the absolute values of LVETp and PTT for indication of the lowered central blood volume does not appear to be possible, although the changes in LVETp and PTT over time may still be useful for detecting ongoing blood loss in the initial phase. Nevertheless, given the small volume donated, one may argue that the post-donation blood volume status may not be sufficiently low to be identifiable in an inter-subject manner.

Another important contribution of the present study is the characterization of dynamic changes during blood donation by regression trend analysis of beat-to-beat RRi, LVETp and PTT time series. The most noteworthy finding was the discovery of a significant falling trend in LVETp (negative mLVETp) and rising trend in PTT (positive mPTT) in both halves of blood donation. These trends agreed with previous observations of a declining trend in stroke volume computed from the finger arterial pressure waveform during blood withdrawal (Leonetti et al., 2004), and may be very useful for indicating progressive volume loss due to bleeding.

In the second half of donation, the rising trend in PTT was significantly weakened compared with the first half. This weakening may be attributed to a sympathetic-mediated increase in myocardial contractility, which has a shortening effect on PEP and PTT that opposes the prolongation effect of preload reduction (Bendjelid, 2007; Chan et al., 2007b). The falling trend in RRi in this stage was further evidence for the enhancement of cardiac sympathetic activity, along with the suppression of cardiac vagal activity due to central hypovolaemia (Triedman et al., 1993; Furlan et al., 2001). Interestingly, comparing with head-up tilt-induced central hypovolaemia, the change from falling LVETp, rising PTT and flat RRi in the first

Figure 2 Changes in R-R interval (RRi), photoplethysmographic waveform derived left ventricular ejection time (LVETp), pulse transit time (PTT) and their gradients (mRRi, mLVETp, mPTT) in the 4 stages of blood donation: 0) Pre-donation, 1) First half of donation, 2) Second half of donation, 3) Post-donation. * P<0.05, ** P<0.01: significant increase/decrease from 0). #P<0.05, ## P<0.01: significant increase/decrease from previous stage. & P<0.05, && P<0.01: significant positive/negative gradient.
interpretation of LVETp, PTT and RRi trends may be able to 2007b, 2008). This supports the previous belief that joint time (PTT) in pre-donation (PRE) and post-donation (POST).

(Obrist et al., 1995). The subsequent increase in RRi (decrease in HR) and part of the increase in PTT in the first half of donation might be a consequence of relaxation from stress. On the other hand, LVETp seemed to be relatively insensitive to psychological stress, as shown by its lack of change. *P<0.05, **P<0.01: significant increase/decrease from PRE.

The psychological stress of subjects prior to cannulation and the induced beta-sympathetic activation might explain the parallel falling trends in RRi and PTT in the pre-donation stage (Obrist et al., 1974; Contrada et al., 1995). The subsequent increase in RRi (decrease in HR) and part of the increase in PTT in the first half of donation might be a consequence of relaxation from stress. On the other hand, LVETp seemed to be relatively insensitive to psychological stress, as shown by its lack of significant trend during pre-donation, and this would make LVETp a more superior marker of blood volume status compared with PTT. The use of PTT as an indicator of blood loss would require joint interpretation with RRi, for example, rising PTT and unchanged or falling RRi may indicate progressive hypovolaemia and the associated reflex response, while parallel trends in PTT and RRi are more likely to reflect beta-sympathetic effect on contractility and heart rate.

The concomitant increase in RRi and PTT from the second half of donation to post-donation seemed to indicate a suppression of cardiac sympathetic tone, and most likely also an enhancement of vagal tone, as blood donation was completed. The major cause could be that once the withdrawal of blood was ceased, compensatory mechanisms which comprise both vasoconstriction and venoconstriction might have become effective in partially recovering the central blood volume by shifting blood from peripheral to central veins, and subsequently leading to restored cardiac autonomic tone.

The pattern of LVETp and PTT displayed during blood donation may reflect not only the change in ventricular preload but also the alteration in vascular properties. Reflex response to hypovolaemia involves peripheral sympathetic vasoconstriction, which causes an increase in vascular resistance in the systemic circulation. It has been shown that sympathetic vasoconstriction induced by alpha-adrenergic stimulation could lead to an increase in pulse wave velocity (PWV) correlated with a rise in DBP, possibly due to a pressure-dependent passive increase in arterial stiffness (Nunberg et al., 2003). In the current study, however, BP decreased rather than increased during blood loss. An acute haemorrhage study in pigs has shown that blood loss was associated with a later return of systolic reflected pressure waves from the trunk to the central aorta, as a consequence of lower MAP and intra-abdominal PWV (Dark et al., 2006). The drop in BP in our study might be partly responsible for the post-donation increase in PTT via an increase in its VTT component (or a decrease in PWV), but unfortunately, PWV was not measured in this study. Nevertheless, the contribution of PWV was likely to be small compared with that of preload reduction, since the percentage of subjects experiencing an increase in PTT was much higher than that showing a drop in BP. The decrease in LVETp, on the other hand, could not be explained on the basis of a decrease in PWV, which would lead to a late return of reflected waves. However, it remains a possibility that the diastolic reflected waves, which have a larger potential impact on LVETp, may not be regulated by the same mechanism as the systolic reflected waves (Ahlund et al., 2008), and may be less dependent on aortic PWV and more dependent on peripheral vascular change.

The use of blood donation as a model of mild to moderate blood loss has been suggested by a number of investigators (Rea et al., 1991; Girard et al., 1992; Triedman et al., 1993; Hanson et al., 1998; Kosowsky et al., 2002; Haberthur et al., 2003; Leonetti et al., 2004; Lyon et al., 2005). However, some limitations associated with this model were noted. Firstly, the rate of blood loss might not always be constant throughout the blood donation process, and this might influence the change in physiologic variables during blood donation, and in particular, the gradients of RRi, LVETp and PTT. Secondly, in order to avoid interruption to the operation of the blood donation centre, a short resting period was adopted prior to blood withdrawal, and as discussed before, cannulation took place at the end of the pre-donation period, which means that the baseline

| Table 1 Heart rate (HR), blood pressure (BP), finger photoplethysmographic waveform derived left ventricular ejection time (LVETp) and pulse transit time (PTT) in pre-donation (PRE) and post-donation (POST). |
|-----------------|-----------------|--------------------|-----------------|-----------------|
|                | PRE             | POST              | Change          | % Change        | % Sub    |
| Mean ± SEM     | CV              | Mean ± SEM        | CV              | Change          | % Sub    |
| HR (bpm)       | 74 ± 1         | 13%               | 70 ± 1**        | 13%             | −3-2     | −4-2%    | 84%    |
| SBP (mmHg)     | 127 ± 2        | 11%               | 122 ± 2**       | 11%             | −6-8     | −4-3%    | 57%    |
| DBP (mmHg)     | 71 ± 1         | 13%               | 68 ± 1*         | 13%             | −2-5     | −3-1%    | 45%    |
| MAP (mmHg)     | 90 ± 1         | 10%               | 86 ± 1**        | 10%             | −3-6     | −3-8%    | 71%    |
| PP (mmHg)      | 57 ± 2         | 21%               | 53 ± 2          | 22%             | −3-3     | −3-5%    | 57%    |
| LVETp (ms)     | 303 ± 2        | 5%                | 293 ± 3**       | 6%              | −10-5    | −3-5%    | 81%    |
| PTT (ms)       | 177 ± 3        | 12%               | 186 ± 4**       | 13%             | +9-0     | +5-1%    | 91%    |

Abbreviations: SBP, systolic BP; DBP, diastolic BP; MAP, mean arterial pressure; PP, pulse pressure; Change = average absolute change between PRE and POST, % Change = average percentage change between PRE and POST, % Sub = percentage of subjects with same directional change as the average change. *P<0.05, **P<0.01: significant increase/decrease from PRE.
measurements of RRI and PTT may be affected by psychological stress. Thirdly, withdrawal of a set volume of blood in blood donation can only mimic the hemodynamic effect of a reduction in circulatory blood volume as expected to occur in hemorrhage, but cannot exactly reproduce the identical effects of ongoing uncontrolled hemorrhage in real life trauma (Lomas-Niera et al., 2005).

Since the current study was performed on healthy volunteers, there is a need to identify patients groups in which LVETp or PTT may have limited preload responsiveness, including those suffering from cardiovascular disorders such as heart failure or aortic valve disease and those under medications such as beta-blockers or other vasoactive agents (Weissler et al., 1961; Stafford et al., 1970; Lewis et al., 1977). The identification of the feature point corresponding to the end of ventricular ejection (e.g. the dicrotic notch) may also be difficult in some of these patients and in the elderly subjects, causing problems in estimating LVETp. Moreover, whilst the current results were obtained from conscious subjects, it is unclear whether similar responses of LVETp and PTT to blood loss can be obtained from anaesthetized humans with a loss of sympathetic tone. Previous studies have demonstrated that respiratory change in PTT/PEP could predict fluid responsiveness in deeply sedated patients (Bendjelid et al., 2004; Feissel et al., 2005), which raises the possibility that systolic timing measurements are preload responsive despite sympathetic withdrawal. The amount of blood loss in blood donation, however, is quite small, and there needs to be further investigations on the usefulness of LVETp and PTT in severe blood loss when the sympathetic tone is substantially elevated.

The PPG signal is known to be susceptible to various external or internal influences, including motion artifact, vascular tone and contacting force (Mendelson, 1992; Teng & Zhang, 2004, 2006). In the current study, the data from 4 of the 48 subjects were excluded from analysis because of poor PPG signal quality – three of them were affected by excessive motion and one of them was due to noisy signal with weak pulses possibly resulting from poor perfusion. In a clinical trauma setting, motion artifacts (e.g. due to shivering or agitation) and poor peripheral perfusion (e.g. due to strong and sustained vasoconstriction) seem to be unavoidable. These problems may affect the practicality of the finger PPG waveform for diagnostic purpose, and require future technological advancement to resolve.

In conclusion, monitoring trends in timing variables derived from non-invasive ECG and finger PPG signals, such as LVETp and PTT, may facilitate detection of blood loss in the early phase. However, given the limitations of the model, further studies are required to assess the reliability and diagnostic accuracy of the current techniques in the clinical setting.

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