Detecting Change in Left Ventricular Ejection Time During Head-Up Tilt-Induced Progressive Central Hypovolemia Using a Finger Photoplethysmographic Pulse Oximetry Wave Form

Gregory S.H. Chan, Paul M. Middleton, Branko G. Celler, PhD, Lu Wang, and Nigel H. Lovell, PhD

**Background:** Change in cardiac preload caused by mild hypovolemia can alter left ventricular ejection time (LVET) without noticeable change in blood pressure (BP). Previously our group has explored a novel method of LVET monitoring using a noninvasive finger photoplethysmographic pulse oximetry wave form. The current study investigated the ability of photoplethysmographic pulse oximetry wave form-derived LVET (LVET_p) to identify progressive central hypovolemia induced by head-up tilt and evaluate the potential use of LVET_p as an early noninvasive indicator of blood loss.

**Methods:** Thirteen healthy subjects underwent graded head-up tilt from 0 degrees to 80 degrees. The response of LVET_p to tilt was compared with that of interbeat interval (RR) and BP. Least-squares linear regression analysis was performed on an intrasubject basis between various physiologic variables and sine of the tilt angle (which is associated with the decrease in central blood volume).

**Results:** During graded tilt, LVET_p had a very strong negative linear correlation with sine of the tilt angle, with correlation coefficients (r) ranging from −0.961 to −0.985. At a very mild hypovolemic state (10 degrees), there was a significant decrease in LVET_p compared with baseline (0 degrees) but without a significant change in RR and BP. Gradient analysis showed that LVET_p was sensitive to central volume loss at all volume states (0 degrees–80 degrees), whereas RR was only responsive at mild-to-moderate and moderate hypovolemic states (20 degrees–80 degrees) but not mild hypovolemic state (0 degrees–20 degrees).

**Conclusions:** LVET_p has a strong association with the change in central blood volume and may be a sensitive early marker of nonhypotensive progressive central hypovolemia. Joint interpretation of LVET_p and RR trends may help to characterize the extent of blood volume loss.

**Key Words:** Left ventricular ejection time (LVET), Photoplethysmogram (PPG), Pulse oximetry, Head-up tilt, Hypovolemia.

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limitations on any wider application of arterial pressure-based LVET monitoring techniques.

Our group has previously explored an alternative technique to monitor LVET variation by using the finger photoplethysmographic pulse oximetry wave form (PPG-POW). Since its introduction to clinical care, pulse oximetry has been a routine patient monitoring technique for the measurement of arterial blood oxygen saturation (\( \text{SpO}_2 \)). Despite its common use for \( \text{SpO}_2 \) estimation, clinicians noticed that the peripheral pulse wave form recorded by the pulse oximeter also carried significant information, which was yet to be fully utilized. There is a clear advantage of using pulse oximetry for continuous beat-to-beat monitoring of LVET variation—it is totally noninvasive and causes minimal discomfort to the patients. A recent study by our group verified that the PPG-POW-derived LVET is a clear advantage of using pulse oximetry for continuous monitoring techniques.

In the current study, the change in LVETp at different levels of central blood volume induced by graded tilt was examined along with corresponding responses in interbeat heart interval (RR) and BP. Intrasubject regression analysis was performed between the different physiologic variables and sin \( \theta \) 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 any 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.

**PATIENTS AND METHODS**

**Subject**

Thirteen healthy subjects (12 men and 1 woman, aged 18–44 years, mean age 30 years) were studied. Before 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 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). Electrocardiogram (ECG) was acquired from the lead I configuration and amplified with a bioamplifier (ADInstruments). The signals were recorded and digitized at a sampling rate of 1,000 Hz using the Powerlab data acquisition system (ADInstruments). BP measurements, including systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and pulse pressure (PP), were obtained using a clinically approved oscillometric BP device (Colin Co., Japan) from a cuff placed around the left arm over the brachial artery.

**Measurement Protocol**

The subjects were advised not to eat for at least 2 hours before 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 hours 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 degrees, 10 degrees, 20 degrees, 30 degrees, 40 degrees, 50 degrees, 60 degrees, and 80 degrees. At each tilt angle, PPG-POW and ECG were simultaneously recorded for a period of 15 seconds, followed by a measurement of BP. A 15-second 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 minute adaptation period allowed the measured cardiovascular variables to settle to a stable level, which generally takes up to 30 seconds. 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). 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. RR was computed as the time interval between successive R-wave peaks. The processing of the PPG-POW signal and the estimation of LVET\(_p\) have been described in detail in a previous publication.\(^{10}\)

**Data Analysis**

The RR and LVET\(_p\) of a subject at a given tilt angle were averaged during the 15-second 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 sin \(\theta\). The range, coefficient of variation, and mean percentage change from baseline (0 degree) of LVET was computed. Moreover, the gradient of the variable was calculated as the difference in the variable divided by the difference in sin \(\theta\) 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 degrees to 20 degrees (mild hypovolemia), (2) 20 degrees to 50 degrees (mild-to-moderate hypovolemia), (3) 50 degrees to 80 degrees (moderate hypovolemia). Nonparametric Friedman’s analysis of variance 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’s rank sum test was performed post hoc with Bonferroni correction 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 performed between each variable and sin \(\theta\). 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 \((p < 0.001)\), LVET\(_p\) \((p < 0.001)\), DBP \((p < 0.01)\), MAP \((p < 0.01)\), and PP \((p < 0.01)\) during tilting but no significant change in SBP \((p > 0.05)\). Table 1 shows the values of RR, LVET\(_p\), SBP, DBP, MAP, and PP at different tilt angles and any significant change from baseline (0 degrees). There was no significant change in RR from baseline at 10 degrees to 30 degrees but there was significant decrease at 40 degrees and above. LVET\(_p\) was significantly below baseline at all tilt angles from 10 degrees to 80 degrees. The range, coefficient of variation, and mean percentage change from baseline of LVET\(_p\) was shown in Table 2. No significant change from baseline was identified in the BP variables. In Figures 1 and 2, the mean ± SE of each variable is plotted against sin \(\theta\). As sin \(\theta\) increased, RR decreased with the rate of decrease tending to be greater at higher tilt angles. LVET\(_p\) on the other hand, decreased linearly with sin \(\theta\). The BP variables did not appear to change with sin \(\theta\) 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 3 shows the gradients of RR, LVET\(_p\), SBP, DBP, MAP, and PP at the three stages (0 degrees–20 degrees, 20 degrees–50 degrees, and 50 degrees–80 degrees) and any significantly positive gradient (rising trend) or negative gradient (falling trend). A significantly negative gradient was identified in RR at 20 degrees to 50 degrees and 50 degrees to 80 degrees, in LVET\(_p\) at all three stages, and in PP at 20 degrees to 50 degrees. A significantly positive gradient was identified in MAP at 50 degrees to 80 degrees. Overall, there was a significant change in gradient in RR \((p < 0.005)\), DBP \((p < 0.005)\), and MAP \((p < 0.05)\) but not in other variables. A significant decrease in gradient compared with 0 degrees to 20 degrees was identified.

### Table 1 Physiologic Variables at Different Tilt Angles

<table>
<thead>
<tr>
<th>(\theta) (degree)</th>
<th>RR (ms)</th>
<th>LVET(_p) (ms)</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>PP (mm Hg)</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>1043 ± 16</td>
<td>312 ± 3</td>
<td>106 ± 3</td>
<td>60 ± 1</td>
<td>76 ± 2</td>
<td>45 ± 3</td>
</tr>
<tr>
<td>10</td>
<td>1038 ± 26</td>
<td>299 ± 3*</td>
<td>108 ± 2</td>
<td>60 ± 1</td>
<td>76 ± 2</td>
<td>48 ± 2</td>
</tr>
<tr>
<td>20</td>
<td>1007 ± 22</td>
<td>290 ± 4*</td>
<td>107 ± 3</td>
<td>58 ± 1</td>
<td>75 ± 2</td>
<td>48 ± 2</td>
</tr>
<tr>
<td>30</td>
<td>983 ± 29</td>
<td>278 ± 4*</td>
<td>108 ± 3</td>
<td>59 ± 1</td>
<td>75 ± 1</td>
<td>48 ± 2</td>
</tr>
<tr>
<td>40</td>
<td>947 ± 33 †</td>
<td>265 ± 5*</td>
<td>107 ± 3</td>
<td>59 ± 2</td>
<td>75 ± 2</td>
<td>49 ± 2</td>
</tr>
<tr>
<td>50</td>
<td>893 ± 39*</td>
<td>253 ± 6*</td>
<td>106 ± 3</td>
<td>61 ± 2</td>
<td>77 ± 2</td>
<td>45 ± 2</td>
</tr>
<tr>
<td>60</td>
<td>856 ± 35 *</td>
<td>245 ± 6*</td>
<td>107 ± 2</td>
<td>62 ± 2</td>
<td>78 ± 2</td>
<td>45 ± 2</td>
</tr>
<tr>
<td>80</td>
<td>810 ± 39*</td>
<td>238 ± 6*</td>
<td>108 ± 4</td>
<td>65 ± 2</td>
<td>81 ± 2</td>
<td>43 ± 2</td>
</tr>
</tbody>
</table>

Results are presented as mean ± SE.

* \(p < 0.01\), significant increase or decrease from 0 degrees.
† \(p < 0.05\), significant increase or decrease from 0 degrees.
\(\theta\) indicates tilt angle.
Different Tilt Angles
Percentage Change From Baseline of LVETp at LVETp minimum; LVETp CV, coefficient of variation of LVETp; LVETp

<table>
<thead>
<tr>
<th>θ (degrees)</th>
<th>LVETp max (ms)</th>
<th>LVETp min (ms)</th>
<th>LVETp CV (%)</th>
<th>LVETp Change (%)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>330</td>
<td>296</td>
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<td>10</td>
<td>325</td>
<td>285</td>
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<td>322</td>
<td>271</td>
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</tr>
<tr>
<td>80</td>
<td>274</td>
<td>205</td>
<td>9</td>
<td>-24</td>
</tr>
</tbody>
</table>

θ indicates tilt angle; LVETp max, LVETp maximum; LVETp min, LVETp minimum; LVETp CV, coefficient of variation of LVETp; LVETp change, mean percentage change in LVETp from baseline.

Fig. 1. RR and LVETp against sin θ. As sin θ increased, RR decreased and the rate of decrease tended to be greater at higher tilt angles. LVETp decreased linearly with sin θ.

Fig. 2. SBP, MAP, DBP, and PP against sin θ. The BP variables did not appear to change with sin θ at low tilt angles although there was a tendency for MAP and DBP to increase and for PP to decrease at high tilt angles.

in RR at both 20 degrees to 50 degrees and 50 degrees to 80 degrees. A significant increase in gradient compared with 0 degrees to 20 degrees was identified in DBP at both 20 degrees to 50 degrees and 50 degrees to 80 degrees and in MAP at 50 degrees to 80 degrees.

The results of intrasubject regression analysis of RR, LVETp, SBP, DBP, MAP, and PP against sin θ are shown in Table 4. LVETp had a very strong correlation with sin θ (median r = -0.985, range of r from -0.961 to -0.997), and the regression relationships were negative and significant in all 13 subjects. RR also showed a strong correlation with sin θ (median r = -0.927), and the regression relationships were negative and significant in 11 of 13 subjects. However, the correlation coefficients for LVETp were higher (in absolute terms) compared with those of RR in all 13 subjects. The regression slopes of LVETp and RR against sin θ were both significantly negative (−76.8 ± 6.5 milliseconds and −242 ± 40 milliseconds, respectively). The regression relationships between the BP variables and sin θ varied considerably between subjects and did not reach statistical significance for most subjects, although the regression slopes were significantly positive for MAP against sin θ (4.26 mm Hg ± 1.68 mm Hg) and significantly negative for PP against sin θ (−3.01 mm Hg ± 1.11 mm Hg).

Segments of PPG-POW and d1PPG-POW obtained from two subjects at tilt angles of 0 degrees, 40 degrees, and 80 degrees are shown in Figures 3 and 4. The d1PPG-POW has demonstrated consistent morphology at different tilt angles, which allowed repeated measurements of LVETp to be made. Note the occurrence of transient vasoconstriction in the first subject at 80 degrees, which led to a decrease in pulse amplitude, but that did not affect the detection of feature points for LVETp measurement.

**DISCUSSION**

The current study shows that LVETp can be a highly sensitive early marker of falling central blood volume. Graded head-up tilt from 0 degrees to 80 degrees has been used as a model to simulate the transition from mild-to-moderate central hypovolemia, similar to that which occurs in progressive blood loss. An important new finding of the present study is that LVETp can signal a drop in central blood volume relative to the normovolemic state (0 degrees) at a much early stage than RR and BP. A significant drop in LVETp occurred at 10 degrees tilt whereas a significant fall in RR only occurred at 40 degrees tilt and above, whereas BP did not show significant change from baseline at any tilt angle. LVET is known to be positively correlated with stroke volume in normal individuals.21 Progressive shortening of LVET during graded head-up tilt is thought 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.22 During head-up tilt, the hydrostatic effect of tilting is proportional to sin θ, which corresponds to the body axis component of gravitational pull exerted on the blood volume inside the body.14,17,18 The current study has demonstrated a very strong negative correlation between LVETp and sin θ, with r ranging from -0.927 to -0.961 for most subjects, although the regression slopes varied considerably between subjects and did not reach statistical significance for most subjects, although the regression slopes were significantly positive for MAP against sin θ (4.26 mm Hg ± 1.68 mm Hg) and significantly negative for PP against sin θ (−3.01 mm Hg ± 1.11 mm Hg).
from -0.961 to -0.985 in a group of healthy subjects. This finding is consistent with the observed linear relationship between sin $\theta$ and the decrease in thoracic fluid content during graded head-up tilt\(^1\) and provides strong evidence that LVET\(_p\) may reflect proportional change in central blood volume or preload. Although the change in afterload (represented by DBP/MAP) as a result of peripheral vasoconstriction might also affect LVET\(_p\), it is unlikely to be the major cause of the tilt-induced change in LVET\(_p\) as MAP did not have any significant linear relationship with sin $\theta$ in most subjects.

Another major contribution of the current study is the introduction of a novel way to study the hemodynamic effect of progressive hypovolemia using gradient/trend analysis of LVET\(_p\) and RR, to better characterize different stages of blood loss. Even though LVET\(_p\) may be lower in hypovolemia compared with normovolemia, in a real-life situation critical care clinicians often need to diagnose blood loss without prior knowledge of the patients’ prehemorrhage physiologic variables. In this respect, the trend or gradient of LVET\(_p\) may be useful for identifying patients who are progressively losing blood, because dynamic volume decrease may result in a falling trend in LVET\(_p\) over time. In the current study, the physiologic responses to central volume loss in three different volume statuses are summarized as the following:

**Stage 1 (0 degrees–20 degrees)**

This stage simulated mild central hypovolemia. A falling trend was observed in LVET\(_p\) as preload decreased. No significant falling trend was observed in RR, probably because small decrement in central blood volume at a mild hypovolemic state was not sufficient to trigger noticeable baroreflex response.

**Stage 2 (20 degrees–50 degrees)**

This stage simulated mild-to-moderate central hypovolemia. LVET\(_p\) continued to show a falling trend as preload decreased, and a significant falling trend was also observed in RR, which may be attributed mostly to vagal withdrawal but also to sympathetic activation. The more negative RR gradient in stage 2, compared with stage 1, may result from augmented baroreflex responsiveness as central blood volume decreases.\(^{25}\)
Stage 3 (50 degrees–80 degrees)

This stage simulated moderate central hypovolemia, and the responses of RR and LVET\textsubscript{p} in this stage were similar to those in stage 2. The RR gradient became more negative, whereas the LVET\textsubscript{p} gradient became less negative compared with stage 2, although the changes were not statistically significant. A rising trend in MAP was probably caused by sympathetic-mediated peripheral vasoconstriction and a HR increase.

The observed physiologic response to graded hypovolemia has demonstrated the superiority of LVET\textsubscript{p} over RR in detecting progressive central volume loss during mild hypovolemia. Furthermore, by joint interpretation of LVET\textsubscript{p} and RR trends, it may be possible to not only detect the presence, but also estimate the extent of blood loss. For example, a change in the patient’s status from falling LVET\textsubscript{p} and unchanged RR to both falling LVET\textsubscript{p} and RR may indicate the transition from mild hypovolemia to moderate hypovolemia.

Although a change in LVET\textsubscript{p} may signal a change in central blood volume, it is less clear whether the absolute value of LVET\textsubscript{p} is also useful for inferring volume status. As shown in this study, to some extent the absolute value of LVET\textsubscript{p} may be able to differentiate between normovolemia (0 degrees) and moderate hypovolemia (50 degrees–80 degrees) because the ranges of LVET\textsubscript{p} at 0 degrees and 50 degrees to 80 degrees did not overlap, and also because the intersubject CV seemed small relative to the percentage difference between the two states. However, the absolute value of LVET\textsubscript{p} is probably less useful for identifying mild and mild-to-moderate hypovolemia (10 degrees–40 degrees). Moreover, the current results were based on a group of healthy subjects aged approximately 20 to 40 years, so whether the ranges of LVET\textsubscript{p} would be significantly affected if elderly people or children were included would need to be addressed by further studies.

Head-Up Tilt as a Model of Progressive Hypovolemia

In this study, progressive central hypovolemia was induced in healthy awake subjects by incremental head-up tilt from 0 degrees to 80 degrees. The use of head-up tilt as a model to simulate the major hemodynamic response to hemorrhage in humans has been documented elsewhere.\textsuperscript{3–5,14–16} Although tilt-induced central hypovolemia is not identical to actual blood loss because the blood volume is merely redistributed to the lower body rather than actually lost from the circulatory system, the initial cardiovascular response to hemorrhage is essentially the same as that elicited by a reduction in central blood volume, for example by head-up tilt or by LBNP.\textsuperscript{3,5,6,14} Twenty-four degrees head-up tilt produces a similar cardiovascular response to 15 mm Hg LBNP,\textsuperscript{26} which approximates mild hemorrhage (loss of 400 mL–550 mL or \~10% of total blood volume),\textsuperscript{6} whereas 60 degrees head-up tilt produces a similar central cardiovascular response to 20 mm Hg to 40 mm Hg LBNP,\textsuperscript{27} which approximates moderate hemorrhage (loss of 550 mL–1,000 mL or \~10%–20% of total blood volume).\textsuperscript{6} However, a limitation of using head-up tilt as a model of blood loss is that regional blood volume changes and the associated vascular responses induced by gravitational fluid shift to the lower body may be different to that in actual hemorrhage.\textsuperscript{27,28} Nonetheless, head-up tilt may still be regarded as an acceptable model to simulate most of the cardiovascular response.
effect of the falling central blood volume that occurs in hemorrhage.

**Clinical Application of LVET**

The current findings regarding LVET have clear relevance to clinical care and critical illness monitoring, in particular, for those cases associated with covert hemorrhage into body cavities that are not easily recognizable in the early stages. Delayed control of abdominal, pelvic, or intrathoracic hemorrhage has been recognized as a major contributor of preventable trauma deaths and is often caused by delays in the assessment or diagnosis of hemorrhage. 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. Geeraerts et al. previously showed that a decrease in LVET measured from the peripheral BP wave form could indicate progressive central hypovolemia induced by LBNP. The current study extends this idea to the use of finger pulse oximetry wave form. There is clear benefit in using finger pulse oximetry wave form—it is totally noninvasive, causes minimal discomfort to patients, and may be monitored continuously for a long period of time. Continuous monitoring of arterial pressure generally requires the insertion of a radial artery catheter, which is an invasive procedure with its use limited to particular patient groups because of demands in terms of expertise and equipment, and associated with a significant risk of complications. For example, invasive BP monitoring is seldom achievable in the normal ambulance setting, except in the setting of medical retrieval where a doctor or paramedic team is sent to retrieve a critically ill patient back to ICU. Although noninvasive continuous BP devices (such as Finapres) are available, they have not been widely employed in clinical care, however. On the other hand, finger pulse oximetry has been a routine patient monitoring technique for some years. Its measurement is remarkably easy to perform, simply by attaching a sensor probe to the finger, without the need for skill or expertise. Moreover, it has been suggested that PPG-POW may be monitored continuously from a subject using wearable sensing devices and this application may have potentially large implications for remote prehospital assessment of hemorrhage.

Repeatability has been considered a major concern for photoplethysmographic measurements. In this study, the measurement of PPG-POW was repeated at eight different tilt angles for each subject during a time period of about 1 hour. As shown in Figures 3 and 4, the d1PPG-POW signal, which is used to derive LVETp, has demonstrated consistent wave form morphology over all three tilt angles, and therefore allows repeatable LVETp measurements to be made. The ability to consistently obtain a strong negative correlation between the PPG-POW-derived LVET and sin θ in each of the subjects is further evidence to suggest that the LVETp measurements were repeatable and consistent during the 1 hour period. Further studies should be conducted to assess repeatability of the measurements during a longer time frame of at least an hour.

It was noted in Figure 3 that transient vasoconstriction may lead to a sudden decrease in amplitude of the finger PPG-POW signals. Fingertip vasculature has an abundance of adrenergic receptors and as a result the finger PPG-POW is sensitive to sympathetic influences on local vascular tone. Although a mild degree of transient vasoconstriction as shown in Figure 3 would not affect the ability to measure LVETp, stronger vasoconstriction causing low perfusion might lead to noisy PPG-POW signal and increase the difficulty in feature detection. Other problems that may be encountered during PPG-POW measurement include motion artifact arising from finger or arm movement and variation in contact force with the sensor. Degradation of signal quality caused by motion artifact or low peripheral vascular perfusion is not uncommon in pulse oximetry photoplethysmographic devices. In this study, each PPG-POW measurement was performed during a short period of time (15 seconds) during which the subject’s finger and arm remained still and the fingertip vessels were not under strong and sustained vasoconstriction, thus providing good signal quality. When PPG-POW is monitored continuously during a longer period of time, motion artifact becomes virtually unavoidable and may affect reliable continuous measurement of LVETp. To mitigate the motion artifact problem, robust automatic techniques may be required to differentiate between artifacts and true cardiac pulses; for example, some manufacturers of pulse oximeters use the R-wave of the patient’s ECG to synchronize PPG-POW measurements to improve the detection of noisy pulsatile signals. Studies should be performed in future to assess the feasibility of the PPG-POW-based technique during a long period of continuous monitoring with these artifact rejection techniques implemented.

Several other issues need to be addressed in future investigations; first, it is unclear what the optimal duration is for the reliable detection of a decreasing trend in LVETp and RR associated with blood loss. Certainly, the analysis period has to be sufficiently long, because LVET and RR exhibit respiratory fluctuations as well as other spontaneous low frequency oscillations that may confound the genuine trend related to physiologic perturbations. Second, there is a need to identify patient groups whose LVET may have limited responsiveness to a change in preload, such as those who suffer from heart failure or aortic valve disease. In addition, there may be difficulties in precisely identifying the onset and the end of systolic ejection from the peripheral pulse wave form in patients with aortic valve disease. Third, as discussed before, the physiologic mechanisms associated with graded head-up tilt is not exactly identical to that associated with genuine hemorrhagic shock, because it involves a gravitational shift in blood volume rather than an actual loss of blood volume. It would be best to further demonstrate the utility of the present technique for early hemorrhage detection by using...
a model of blood loss that involves withdrawal of blood from the body, such as blood donation from volunteers.

CONCLUSION

In conclusion, this study has shown that LVETp has a strong association with the change in central blood volume during graded head-up tilt and may be a sensitive early marker of nonhypotensive progressive central hypovolemia. Joint interpretation of LVETp and RR trends may help to characterize the extent of blood volume loss. Further investigation is necessary to evaluate the applicability of LVETp in the examination of critical care patients who may be suffering from hemorrhage.

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