Hypovolemic Volunteers

In Awake, Spontaneously Breathing, Hypovolemic Volunteers

Susan P. McGrath, PhD,* Kathy L. Ryan, PhD,† Suzanne M. Wendelken, MS,* Caroline A. Rickards, PhD,† and Victor A. Convertino, PhD†

BACKGROUND: The primary objective of this study was to determine whether alterations in the pulse oximeter waveform characteristics would track progressive reductions in central blood volume. We also assessed whether changes in the pulse oximeter waveform provide an indication of blood loss in the hemorrhaging patient before changes in standard vital signs.

METHODS: Pulse oximeter data from finger, forehead, and ear pulse oximeter sensors were collected from 18 healthy subjects undergoing progressive reduction in central blood volume induced by lower body negative pressure (LBNP). Stroke volume measurements were simultaneously recorded using impedance cardiography. The study was conducted in a research laboratory setting where no interventions were performed. Pulse amplitude, width, and area under the curve (AUC) features were calculated from each pulse waveform recording. Amaigamated correlation coefficients were calculated to determine the relationship between the changes in pulse oximeter waveform features and changes in stroke volume with LBNP.

RESULTS: For pulse oximeter sensors on the ear and forehead, reductions in pulse amplitude, width, and area were strongly correlated with progressive reductions in stroke volume during LBNP ($R^2 > 0.59$ for all features). Changes in pulse oximeter waveform features were observed before profound decreases in arterial blood pressure. The best correlations between pulse waveform and stroke volume were obtained from the forehead sensor area ($R^2 = 0.97$). Pulse oximeter waveform features returned to baseline levels when central blood volume was restored.

CONCLUSIONS: These results support the use of pulse oximeter waveform analysis as a potential diagnostic tool to detect clinically significant hypovolemia before the onset of cardiovascular decompensation in spontaneously breathing patients. (Anesth Analg 2011;112:368–74)

Hemorrhage is a leading cause of death in both civilian and military trauma.1,2 Consequently, it is of paramount importance that the hypovolemia associated with hemorrhage and its severity be detected early to enable treatment to begin as soon as possible in both prehospital and hospital settings; this is underscored by reports that early intervention before the development of hemorrhagic shock is associated with a lower mortality rate.3 Unfortunately, compensatory mechanisms that act to defend arterial blood pressure during hemorrhage can mask the progressive loss of blood until seconds before cardiovascular collapse when rapid deterioration of blood pressure and loss of consciousness occur.4 Thus, the use of blood pressure as an indicator of blood loss can often prove to be too late and does not allow for early intervention.

Traditionally, pulse oximeters have only been utilized for the indirect assessment of arterial oxygen saturation ($SpO_2$) and heart rate in the clinical setting. However, previous studies have shown that the photoplethysmogram (PPG), frequently obtained from pulse oximeters, may provide a reliable indication of hemodynamic changes, including hypovolemia.5–9 For the most part, these investigations involved analysis of respiration-induced oscillations of the PPG in either anesthetized surgical patients undergoing positive pressure ventilation or healthy patients who underwent only moderate blood loss (e.g., 450 mL). The question of whether features of the PPG may provide diagnostic insight into the progression of central hypovolemia in spontaneously breathing trauma patients during the prehospital emergency phase of care has not been studied. To address this gap, an assessment is needed in awake, nonventilated patients to identify the relationship, if any, between changes in the PPG and reductions in central blood volume that mimic hemorrhage. In this study, we had the unique opportunity to investigate the pulse waveform features of the PPG obtained from finger, forehead, and ear sensors during an experimental model of central hypovolemia and to determine which features best serve as early indicators of reduction in central blood volume and impending cardiovascular collapse. The hemodynamic challenge was created using lower body negative pressure (LBNP), which safely and progressively reduces central blood volume by sequestering blood in the lower extremities through application of negative pressure around the legs and abdomen. LBNP has been shown to be an effective model of the early phases of hemorrhage in conscious humans,10 and allowed us to test the hypothesis that reduced pulse amplitude, width, and/or area under the
**Pulse oximeter plethysmographic waveform changes in awake, spontaneously breathing, hypovolemic volunteers**

**United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX**

Approved for public release, distribution unlimited

Security classification: unclassified

Abstract: Unavailable

Number of pages: 7
curve (AUC) calculated from recordings of the PPG pulse wave would be associated with progressive reductions in central blood volume and precede changes in standard vital signs. Our approach is unique in that experiments were conducted in awake, healthy subjects undergoing extreme hemodynamic challenge in a controlled laboratory setting and in the absence of the complicating effects of positive pressure ventilation or drugs.

METHODS

Experimental procedures and protocols were reviewed and approved by the IRB for the use of human subjects at the Brooke Army Medical Center at Fort Sam Houston, Texas. Each subject gave written informed voluntary consent to participate in the experiments.

Study Design

LBNP was used in the present investigation as an experimental tool to simulate loss of central blood volume (e.g., hemorrhage) in conscious, healthy humans.10 With the use of a neoprene skirt designed to form an airtight seal between the subject and the chamber, the application of negative pressure to the lower body with the subject in a supine position results in a redistribution of blood away from the upper body (head and heart) to the lower extremities and abdomen. Thus, this model provides a unique method of investigating conditions of controlled, progressive, experimentally induced hypovolemic hypotension.

Each subject underwent exposure to an LBNP protocol designed to test his or her tolerance to experimentally induced hypotensive hypovolemia. The LBNP protocol consisted of a 5-minute baseline period (0 mm Hg) followed by 5 minutes of chamber decompression to −15, −30, −45, and −60 mm Hg and additional increments of −10 mm Hg every 5 minutes until the onset of cardiovascular collapse or the completion of 5 minutes at −100 mm Hg. Cardiovascular collapse was identified in real time by the attending investigator by a precipitous decrease in systolic blood pressure (SBP) >15 mm Hg concurrent with the onset of presyncopal symptoms such as bradycardia, gray out (loss of color vision), tunnel vision, sweating, nausea, or dizziness.

Selection of Participants

Eighteen healthy nonsmoking subjects (8 men, 10 women) with mean ± sd age of 23 ± 4 years, body weight of 69 ± 11 kg, and height of 171 ± 10 cm were recruited to participate in the study. Female subjects underwent an initial urine test before experimentation to ensure that they were not pregnant. Subjects maintained their normal sleep and dietary patterns, refrained from exercise, and abstained from caffeine and other autonomic stimulants such as prescription or nonprescription drugs for at least 24 hours before each experimental protocol. All subjects received a verbal briefing and a written description of all procedures and risks associated with the experiments and were familiarized with the laboratory, the protocol, and procedures.

Methods of Measurement

All subjects were instrumented with 3 Nonin® pulse oximeter sensors (Nonin Medical, Plymouth, MN; OEM III module, 16-bit data format) placed on the forehead, finger, and ear. The sensor on the forehead was securely taped to the skin, whereas the finger sensor was placed on the ring finger of the left hand. Unlike standard pulse oximeters that have autocalibration capability, the Nonin pulse oximeter did not alter the raw waveform signal with an autogain mechanism. In addition, an infrared finger PPG blood pressure monitor (Finometer® Blood Pressure Monitor, TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands) and an electrocardiogram were used to record beat-by-beat arterial pressures and heart rate. The Finometer blood pressure cuff was placed on the middle finger of the left hand, which in turn was held at heart level. Excellent estimates of directly measured intraarterial blood pressures during various physiologic maneuvers have been demonstrated with this device.11–14 Beat-to-beat stroke volume was measured noninvasively using thoracic electrical bioimpedance with an HIC-2000 Bio-Electric Impedance Cardiograph (Bio-Impedance Technology, Chapel Hill, NC). The thoracic electrical bioimpedance technique is based on the resistance changes in the thorax to a low-intensity (4-mA), high-frequency (70-kHz) alternating current applied to the thorax by 2 surface electrodes placed at the root of the neck and 2 surface electrodes placed at the xiphoid process at the midaxillary line. Ventricular stroke volume was calculated according to the technique described by Kubicek et al.15 Correlation coefficients of 0.70 to 0.93 have been reported in stroke volume measurements simultaneously made with thoracic electrical bioimpedance and thermodilution techniques.16 Despite this close association, stroke volume measurements made with noninvasive techniques are estimations of the actual stroke volume and are therefore presented as percentage change from baseline levels.

The PPG and SpO2 values from the Nonin pulse oximeter sensors were continuously and simultaneously recorded to a laptop PC using Java-based data collection software at a sample frequency of 75 Hz.

Analysis

Subjects reached cardiovascular collapse (i.e., maximal LBNP tolerance) at different absolute LBNP levels based on their individual physiologic responses. Because these responses are the same at cardiovascular collapse independent of the LBNP level at which an individual subject reaches this point,17 we chose to normalize each individual’s data by reapportioning their responses to equal fractions between 0% LBNP tolerance (baseline) and 100% LBNP tolerance, the level at which the LBNP protocol was terminated as a result of impending cardiovascular collapse (presyncope). This approach allowed us to consider the data from all subjects relative to their maximal capacity for LBNP tolerance.18–20

Pulse amplitude, width, and AUC for each cardiac cycle were automatically extracted from the PPG data using a feature extractor implemented in Matlab® (The MathWorks, Natick, MA). Figure 1 depicts these PPG features extracted by the analysis algorithms. Pulse amplitude was calculated as the difference between the PPG values of the cardiac peak and the preceding valley. Pulse width was calculated as the time width at half the cardiac peak amplitude. The AUC was calculated as a standard line...
integral minus the DC area. The amplitude, width, and area calculated from the PPG were normalized with respect to their baseline values to study the trends while accounting for individual physiologic variability. Baseline values were calculated by averaging each feature over the last 3 minutes of the pre-LBNP baseline period. Similarly, values for all variables were averaged over the last 3 minutes of each LBNP level and recovery and for 1 minute before presyncope. A 1-way (percentage LBNP level) randomized block (subjects) analysis of variance for repeated measures was used for comparison of outcome variables. If statistical differences were found, Bonferroni-corrected comparisons with baseline measurements were performed to determine the first percentage level of LBNP that could be distinguished statistically from baseline. Amalgamated correlation coefficients (i.e., coefficients generated by correlations between mean values of stroke volume changes and PPG pulse shape features at each LBNP tolerance level) were calculated to determine the relationship between the changes in PPG features and changes in stroke volume during LBNP and subsequent recovery. All data are presented as mean ± s, and exact P values are presented for all comparisons.

RESULTS
A representative tracing of the beat-to-beat pulse oximeter PPG waveform characteristics recorded from the ear sensor of 1 subject before, during, and after the progressive LBNP protocol is presented in Figure 2. PPG pulse amplitude, width, and area decreased with increasing LBNP in all pulse oximeter sensor sites. Immediately after the termination of LBNP with accompanying cardiovascular collapse, most subjects demonstrated a sudden rebound (increase) in pulse amplitude and area to levels greater than baseline, whereas the recovery of pulse width was more gradual.

Figure 3 illustrates group means for PPG pulse amplitude width and area, as well as alterations in hemodynamic variables during LBNP. LBNP induced a progressive reduction in central blood volume, indicated by changes in stroke volume (Fig. 3C) and a reduction in SBP at 60% of LBNP tolerance (Fig. 3A). $\text{SpO}_2$ did not change from baseline values (99.2% ± 0.2%) during the LBNP exposure (99.3% ± 0.3% at 100% of LBNP tolerance). LBNP caused a reduction in PPG pulse wave amplitude until the final point (100% of LBNP tolerance), at which it increased slightly (Fig. 3D). PPG pulse width did not change from baseline at early stages of LBNP but decreased at 80% and 100% of LBNP tolerance (Fig. 3E). These changes in pulse amplitude and width resulted in a progressive decrease in PPG area that became statistically significant ($P < 0.001$) at 60% of LBNP tolerance (Fig. 3F). Upon cessation of LBNP, all hemodynamic and PPG pulse features returned to pre-LBNP baseline values (Fig. 3).

Table 1 presents amalgamated correlation coefficients between the changes in stroke volume and changes in PPG waveform characteristics. We found correlation coefficients ($R^2$) ≈0.59 between stroke volume and PPG pulse amplitude, pulse width, and area during LBNP and recovery in the ear and forehead sensors, with extremely high correlation coefficients (0.91 from ear sensor and 0.97 from forehead sensor) between stroke volume and AUC. Correlations with stroke volume were not as strong for pulse amplitude and AUC in the finger sensor.

DISCUSSION
Strong correlations between the reduction in stroke volume and pulse amplitude, width, and area during LBNP support our hypothesis that PPG waveform characteristics obtained from a standard pulse oximeter may prove to be sensitive and specific as early indicators of blood loss in
trauma patients. Our data are consistent with previous studies that demonstrated that PPG pulse shape features change significantly and predictably during hypovolemia in anesthetized surgical patients. To our knowledge, however, this investigation is the first to demonstrate, in conscious, spontaneously breathing humans, the ability of PPG pulse wave features to provide early and continuous indications of central hypovolemia during preshock hemorrhage when standard vital signs such as arterial blood pressure and SpO₂ remain within clinically normal levels (Fig. 3).

Hemorrhagic shock remains the leading cause of death on the battlefield. Data from current military conflicts demonstrate that the mortality rate of combat casualties is dramatically increased when treatment commences after, rather than before, the onset of circulatory shock. It is clear from these data that early recognition of progressive blood loss and the need for immediate intervention before the development of shock could prove critical in the attempt to save lives. In this regard, the measurement of physiologic responses that are altered before changes in standard vital signs such as SBP could improve survival from hemorrhagic trauma. Results from the present investigation support the notion that the measurement of PPG pulse characteristics can represent a significant adjunct to current monitoring capabilities by providing information about the degree of blood volume reduction before any profound change in SBP. Although SBP changes statistically at 60% LBNP, it is still well above any clinical alert threshold (e.g., 110 mm Hg) until 100% LBNP. The decrease in SBP at this point indicates that, by Advanced Trauma Life Support definition, subjects were progressing into class III of shock, which is associated with loss of effective blood volume between 30% and 40%. Because pulse oximetry is ubiquitously used for monitoring patient status, it is likely that embedding new algorithms for measurement of PPG pulse characteristics into current oximeters would be logistically simple and readily accepted by the medical community.

The correlations between the PPG pulse features and stroke volume measurements were typically higher when measured from the ear and forehead sensors than the finger sensor, particularly for pulse amplitude and, consequently, pulse area. Progressive reduction in central blood volume is associated with both increased sympathetic nerve activity and concomitant peripheral vasoconstriction. The amplitude of finger PPG is reduced by increased sympathetic activation and vasoconstriction. In addition, blood flow to the forehead seems to be less influenced by sympathetically mediated reflex peripheral vasoconstriction, suggesting that PPG waveforms measured at the forehead may therefore more closely reflect alterations in central hemodynamics associated with blood loss (e.g., stroke volume) than those in the finger. Our results support this postulate and indicate that the forehead region may be a better location than a peripheral digit for predicting early blood volume loss using the PPG. Operationally, the use of a head sensor site is also preferred because the finger sensor is more prone to

**Figure 2.** Representative tracings of the ear photoplethysmogram (PPG) waveform, pulse amplitude, pulse width, and area from a single subject. Vertical lines denote pressure changes of the lower body negative pressure (LBNP) device. The final vertical line denotes the onset of presyncope.
motion artifact and extremity injury is very common, particularly on the battlefield, which would potentially eliminate any possibility of using the finger site.

We observed an immediate restoration of PPG pulse wave amplitude, width, and area in all subjects upon termination of LBNP (Figs. 2 and 3). Recovery of the PPG pulse wave is not unexpected because the immediate restoration of central blood volume with the cessation of LBNP is related to the complete recovery of stroke volume, sympathetic nerve activity, and peripheral blood flow to baseline levels. These data support the notion that the continuous measurement of PPG pulse wave amplitude, width, and area could be used to monitor the effectiveness of interventions designed to resuscitate patients (e.g., fluid and blood transfusions) in addition to assessing the magnitude of blood loss before any intervention has commenced.

Table 1. Amalgamated Correlation Coefficients ($R^2$) Derived from Linear Regression Analysis of Changes in Photoplethysmogram (PPG) Pulse Shape Features with Changes in Stroke Volume Measurements

<table>
<thead>
<tr>
<th>PPG parameter</th>
<th>Ear</th>
<th>Finger</th>
<th>Forehead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse amplitude</td>
<td>0.69</td>
<td>0.36</td>
<td>0.95</td>
</tr>
<tr>
<td>Pulse width</td>
<td>0.59</td>
<td>0.90</td>
<td>0.71</td>
</tr>
<tr>
<td>AUC</td>
<td>0.91</td>
<td>0.44</td>
<td>0.97</td>
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AUC = area under the curve.

This study is not without limitations. Perhaps most importantly, although our laboratory model of progressive central hypovolemia provides an opportunity to collect physiologic data on healthy human subjects, we recognize that cardiovascular responses to experimentally induced hypovolemia may be different than responses to actual severe hemorrhage. Conversely, the use of LBNP to simulate the early phases of hemorrhage may also be seen as a benefit, inasmuch as we were able to determine PPG
characteristics during central hypovolemia without confounding factors such as tissue injury, painful stimuli, or the presence of anesthesia or other drugs. Hence, our results may be the first to strictly reflect the relationship between reduced central blood volume and PPG characteristics in humans.

PPG collection for this study was performed with a commercial pulse oximeter system. The sensors in such systems are not without limitations, and the output of these devices can be affected by a number of factors including sensor placement, skin pigmentation, and motion artifact. Consequently, an automated hemorrhage detection algorithm integrated into pulse oximetry devices must include reliability and safety mechanisms to account for variations in the population and sensor placement.

Changes in the PPG characteristics described in this study may also be affected by other physiologic states, including hypothermia and other stresses that produce sympathoexcitation; in this regard, however, compensatory responses to LBNP also include pronounced activation of the sympathetic nervous system as reflected in increases in muscle sympathetic nerve firing and plasma catecholamines. Regardless, such confounding issues must also be considered in the further development of algorithms for monitoring hemorrhagic shock.

Importantly, because the absolute initial values for the PPG characteristics will differ with different patients and at varying times during clinical application, there is no way to define absolute values that represent a given hemorrhagic state. Our study demonstrates that the PPG waveform may provide trending capabilities during bleeding. In this regard, the development of a monitor with a machine-learning algorithm capable of providing calculations of changes in PPG characteristics could provide a valuable clinical tool for real-time monitoring of bleeding patients.

In summary, significant reductions in the PPG pulse amplitude, width, and area were observed for all sensor locations in proportion to progressive reductions in stroke volume induced by exposure of subjects to LBNP. Often, these changes were observed as early as the first stage of LBNP. These results support the use of features derived from the pulse oximeter waveform in addition to standard vital signs to provide earlier identification of clinically significant hypovolemia in bleeding patients, before the onset of shock. Because the pulse oximeter is already used and accepted by both military and civilian medical care providers in the prehospital setting, the results of this study could be used to implement new algorithms within existing technology, thereby providing an inexpensive, portable, noninvasive blood volume status monitor.

STUDY FUNDING
Supported by funding from the United States Army Medical Research and Materiel Command Combat Casualty Care Research Program (US Army Contract W81XWH-06-1-0509) to Dartmouth College.

DISCLAIMER
The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

ACKNOWLEDGMENTS
The authors thank the subjects for their cheerful cooperation and Mr. Gary Muniz, Mr. Michael Clare, Mr. Josh Pyke, and Mr. Vincent Capuano for their excellent technical assistance.

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