A Novel Approach Using Time–Frequency Analysis of Pulse-Oximeter Data to Detect Progressive Hypovolemia in Spontaneously Breathing Healthy Subjects

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***Abstract*—Accurate and early detection of blood volume loss would greatly improve intraoperative and trauma care. This study has attempted to determine early diagnostic and quantitative markers for blood volume loss by analyzing photoplethysmogram (PPG) data from ear, finger, and forehead sites with our high-resolution time–frequency spectral (TFS) technique in spontaneously breathing healthy subjects ($n = 11$) subjected to lower body negative pressure (LBNP). The instantaneous amplitude modulations (AM) present in heart rate (AM_{HR}) and breathing rate (AM_{BR}) band frequencies of PPG signals were calculated from the high-resolution TFS. Results suggested that the changes ($P < 0.05$) in AM_{BR} and especially in AM_{HR} values can be used to detect the blood volume loss at an early stage of 20% LBNP tolerance when compared to the baseline values. The mean percent decrease in AM_{HR} values at 100% LBNP tolerance was 78.3%, 72.5%, and 33.9% for ear, finger, and forehead PPG signals, respectively. The mean percent increase in AM_{BR} values at 100% LBNP tolerance was 99.4% and 19.6% for ear and finger sites, respectively; AM_{BR} values were not attainable for forehead PPG signal. Even without baseline AM_{HR} values, our results suggest that hypovolemia detection is possible with specificity and sensitivity greater than 90% for the ear and forehead locations when LBNP tolerance is 100%. Therefore, the TFS analysis of noninvasive PPG waveforms is promising for early diagnosis and quantification of hypovolemia at levels not identified by vital signs in spontaneously breathing subjects.**

***Index Terms*—Blood loss, hypovolemia, lower body negative pressure (LBNP), photoplethysmogram (PPG), pulse oximeter, time–frequency analysis, trauma care.**

I. Introduction

ACCURATE and early detection of blood loss using noninvasive methods would greatly improve intraoperative and trauma care since a sensitive and specific approach to early recognition of blood loss has been elusive. Standard vital signs such as heart rate (HR) and blood pressure (BP) do not alert clinicians in advance of rapid blood loss and cardiovascular collapse [1], [2]. Thus, readily available and reliable detection of blood loss would be of great benefit in acute hospital settings, reducing morbidity and mortality as well as the ever-increasing cost of healthcare.

Toward this goal, the application of photoplethysmogram (PPG) for blood loss detection has gained more impetus recently because it is an already ubiquitous diagnostic tool that is easy to operate, inexpensive, and nonintrusive. For example, McGrath *et al.* [2] have recently reported significant reductions in time-domain PPG pulse features in response to progressive increase in hypovolemia induced by lower body negative pressure (LBNP). Significant increase in the respiration-related spectral power of the PPG waveform has also been shown in spontaneously breathing healthy subjects subjected to blood withdrawal [3], [4] and LBNP [5]. However, the respiratory variations of the PPG waveforms have been shown to be inaccurate in predicting hemodynamic changes induced by LBNP [6] and passive leg elevation in spontaneously breathing volunteers [7]. We believe that the previously mentioned inconsistent results are primarily due to the computational methods used to date that have largely relied on linear, time-domain, and time-invariant signal analyses, whose success has been limited to nearly motion-free environments.

To overcome the aforementioned limitations, time-varying power spectral density (PSD) [8] and continuous wavelet transform (CWT) [9] approaches have been utilized. Although these approaches partially solve the time-varying issue, they do not address the nonlinearity of the respiratory variations in the PPG amplitude due to baroreceptor feedback. Further, since the time–frequency resolution of the CWT is suboptimal, it is not the most effective approach for early blood loss detection. Thus, a major

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technological gap preventing accurate blood loss detection is due both to the lack of quantitative methods that can account for time-varying dynamics with sufficient time and frequency resolution, and to an insensitivity to motion and noise artifacts at the respiratory and HR frequencies. Hence, it is not surprising that a real-time, automatic, quantifiable detection of blood loss from PPG signals has not been realized to date. Therefore, our overriding goal is to develop an accurate computational method using PPG signals to detect hypovolemia.

Our innovative technical solutions overcome the aforementioned limitations by recognizing that the respiration rate modulates both the amplitude and frequency of the PPG signal [10]. This is similar to the way in which respiratory sinus arrhythmia modulates the HR signal, a modulation known to be a nonlinear phenomenon [11]. Variable frequency complex demodulation (VFCDM) is a novel time–frequency spectral (TFS) method that provides one of the highest time–frequency resolutions and accurate amplitude estimates [10], [12]. The amplitude modulations (AM) associated with the HR and BR band frequencies of the PPG can be continuously extracted from the TFS of the VFCDM as the $\mathrm{AM_{HR}}$ and $\mathrm{AM_{BR}}$ components of the PPG, respectively. Specifically, the $\mathrm{AM_{HR}}$ and $\mathrm{AM_{BR}}$ components of the PPG are related to the changes in arterial and venous pulsations, respectively.

To test the fidelity of our approach for the early detection of blood loss, we used the application of LBNP since it has been recognized as an effective model for varying the level of simulated blood loss, including severe hemorrhage, in conscious humans [2], [13]. We hypothesized that a significant decrease in the $\mathrm{AM_{HR}}$ component of the PPG would reflect the simulated progressive blood loss induced by LBNP in spontaneously breathing subjects. Our additional objective of this study was to identify the optimal site for detecting blood volume loss induced via LBNP by analyzing simultaneously collected PPG signals from common pulse oximeter probe sites such as the ear, finger, and forehead.

II. Materials and Methods

A. Design of LBNP Experiment

The LBNP study was approved by the Yale University Human Investigation Committee and written informed consent was obtained from all the subjects. Healthy male volunteers ($n = 11$, range 23–39 years) with no known cardiovascular or systemic disease participated in this study. Subjects were instructed to refrain from caffeine, alcohol, or cigarettes within 12 hour of the protocol, but were otherwise allowed their normal amounts of food and fluid intake prior to enrollment.

The LBNP chamber was constructed of a sealed wood and acrylic box that is connected to a vacuum pump [14]. Each subject was placed in the LBNP chamber, which was sealed with a neoprene skirt just above the subject's pelvis. The LBNP protocol consisted of a baseline followed by the gradual exposure to -15, -30, -45, -60, -75, -90, and -100 mmHg or until the subject showed presyncopal symptoms such as lightheadedness, nausea or any concerns indicated by the subject. The time interval between each level of LBNP application varied from 20 s to 6 min among the subjects. At the onset of presyncopal symptoms, the negative pressure was stopped, but data were continuously recorded during the subsequent recovery stage. The maximal LBNP tolerance among the subjects was between -70 and -115 mmHg. One subject did not show any symptoms even after -110 mmHg of LBNP application. For this subject, the LBNP was terminated after his HR reached 140 beats/min. Although one subject showed presyncopal symptoms at -70 mmHg, the maximal LBNP tolerance in ten participants was at least -90 mmHg.

B. Data Acquisition and Preprocessing

Three identical reflective infrared PPG-probes (MLT1020; ADI Instruments, CO Springs, CO, USA) were placed at the finger, forehead, and ear. While the finger and ear PPG probes were attached with a clip, the forehead probe was securely covered by a clear dressing. The autogain function and other filtering algorithms were disabled during PPG recording. A respiratory belt transducer (MLT1132; ADInstruments, CO Springs, CO, USA) was placed around the chest for true respiratory recording. The standard ECG, and arterial BP data using a noninvasive Finapres monitor (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands) were also simultaneously measured. All data were recorded at 200 Hz with PowerLab/16SP with Quad Bridge Amp (ML795 and ML112; ADInstruments). The recorded PPG data were analyzed offline using MATLAB.

Each individual's PPG data were reapportioned into five stages between 0% LBNP tolerance (baseline) and 100% LBNP tolerance (the level at which the subjects showed presyncopal symptoms) based on the value of LBNP decompression and its duration [2]. This was necessitated by the fact that individual's maximal capacity of LBNP tolerance varied widely (e.g., -70 to -115 mmHg from our data). Thus, in some cases, our reapportioned PPG data at each level of LBNP tolerance may not accurately reflect the true LBNP decompression ratio, but either rounded up or down to the closest value of the five stages. Our analysis considered 2 min of PPG data from each level of LBNP tolerance. From each 2-min PPG data block, a 1-min window was shifted in 10 s intervals, and thus seven PPG segments were obtained for our analysis. When the available PPG data was less than a minute in few cases of early LBNP levels, the PPG data was considered as a single segment for VFCDM analysis. The PPG segments were downsampled to 20 Hz, preprocessed, zero meaned, linearly detrended, normalized to unit variance, and applied to the VFCDM algorithm to be described hereafter.

C. VFCDM Analysis

The development of the VFCDM algorithm has been previously reported in detail [10], [12]. Thus, the VFCDM algorithm will be briefly summarized here as follows.

Consider a sinusoidal signal $x(t)$ to be a narrow band oscillation with a center frequency f_o, instantaneous amplitude $A(t)$, phase $\phi(t)$, and the direct current component $\mathrm{dc}(t)$

$$x(t) = \mathrm{dc}(t) + A(t)\cos(2\pi f_o t + \phi(t)). \tag{1}$$

For a given center frequency, we can extract the instantaneous amplitude information $A(t)$ and phase information $\phi(t)$ by multiplying (1) by $e^{-j2\pi f_o t}$, which results in the following:

$$z(t) = x(t)e^{-j2\pi f_o t} = \mathrm{dc}(t)e^{-j2\pi f_o t} + \left(\frac{A(t)}{2}\right)e^{j\phi(t)} + \left(\frac{A(t)}{2}\right)e^{-j(4\pi f_o t+\phi(t))}. \quad (2)$$

A leftward shift by $e^{-j2\pi f_o t}$ results in moving the center frequency f_o to zero frequency in the spectrum of $z(t)$. If $z(t)$ in (2) is subjected to an ideal low-pass filter (LPF) with a cutoff frequency $f_c < f_o$, then the filtered signal $z_{lp}(t)$ will contain only the component of interest, and the following are obtained:

$$z_{lp}(t) = \frac{A(t)}{2}e^{j\phi(t)} \quad (3)$$

$$A(t) = 2|z_{lp}(t)| \quad (4)$$

$$\phi(t) = \tan^{-1}\frac{\mathrm{imag}(z_{lp}(t))}{\mathrm{real}(z_{lp}(t))}. \quad (5)$$

The method can be easily extended to the variable frequency case as explained in [12], where the modulating frequency is expressed as $\int_o^t 2\pi f(\tau)d\tau$ and the negative exponential term used for demodulation is $e^{-j\int_o^t 2\pi f(\tau)d\tau}$. The instantaneous frequency can be obtained using the familiar differentiation of the phase information as follows:

$$f(t) = f_o + \frac{1}{2\pi}\frac{d\phi(t)}{d(t)}. \quad (6)$$

Thus, the VFCDM method involves a two-step procedure. First, the fixed frequency complex demodulation (FFCDM) technique identifies the signal's dominant frequencies, shifts each dominant frequency to a center frequency, and applies LPF to each of the center frequencies. The LPF, with a cutoff frequency less than that of the original center frequency, is applied to each dominant frequency. This process generates a series of band-limited signals. The instantaneous amplitude, phase, and frequency information are obtained for each band-limited signal using the Hilbert transform and are combined to generate a TFS. Later, the VFCDM method is applied to this spectral estimate wherein it selects only the dominant frequencies for refinement and produces a high-resolution TFS. The LPF filter length was set to 64, and the cutoff frequency was selected as 0.03 Hz for the FFCDM method and 0.015 Hz for the VFCDM method [10].

A representative ear PPG signal, recorded during baseline from a spontaneously breathing healthy subject, and its TFS are shown in Fig. 1(a) and (b), respectively. Two dominant oscillatory amplitudes can be observed at two separate frequency bands of the TFS: 1) a HR ridge, representing the high-frequency phenomenon, and; 2) the breathing rate (BR) ridge, corresponding to the low-frequency phenomenon. The HR and BR ridges are outlined in the TFS [see Fig. 1(b)]. The largest instantaneous amplitude at every time sample within the desired frequency band of the TFS constitutes the AM series. The AM series extracted from the HR band (HR $\pm$ 0.2 Hz) and BR band (0.05–0.35 Hz) were identified as $\mathrm{AM_{HR}}$ and $\mathrm{AM_{BR}}$, respectively [as shown in Fig. 1(c) and (d)]. Note that these $\mathrm{AM_{HR}}$ and $\mathrm{AM_{BR}}$ terms represent the time-varying AM. The initial and final 5 s of the TFS were not considered for the extraction of $\mathrm{AM_{HR}}$ and $\mathrm{AM_{BR}}$ because of the edge effect. The median values of the $\mathrm{AM_{HR}}$ and $\mathrm{AM_{BR}}$ components were evaluated for each of the seven PPG segments and were then averaged. The percent changes in $\mathrm{AM_{HR}}$ and $\mathrm{AM_{BR}}$ values were calculated for all LBNP stages with respect to the individual's baseline responses. Such measurements of $\mathrm{AM_{HR}}$ and $\mathrm{AM_{BR}}$ values were carried out in 11 subjects using ear and finger PPG signals at each level of the LBNP protocol. For forehead PPG, $\mathrm{AM_{HR}}$ values were obtained from ten subjects, because one subject's forehead PPG signals were intermittently undetectable. Further, the $\mathrm{AM_{BR}}$ measurements could not be obtained from forehead PPG signals in six out of the ten subjects at various stages of the protocol.

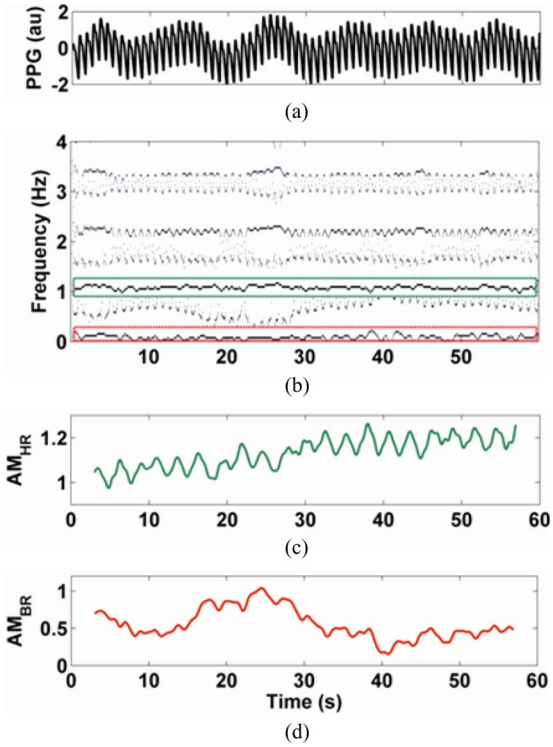

Fig. 1. (a) Representative ear PPG signal recorded during baseline from a spontaneously breathing healthy subject. (b) Estimated TFS using VFCDM with prominent frequency oscillations seen near hear rate (1 Hz) and BR (0.2 Hz) outlined as boxes in TFS. The extracted spectral power AM of HR band (i.e., $\mathrm{AM_{HR}}$) and BR band (i.e., $\mathrm{AM_{BR}}$) are shown in (c) and (d), respectively.

In addition to the relative changes in AM measures of PPG from baseline value for blood loss detection, receiver operating characteristic (ROC) curve analysis was performed to find the threshold value of absolute AM measures offering optimal specificity and sensitivity for the blood loss detection. The purpose of this was to examine if blood loss detection is possible without comparing its $\mathrm{AM_{HR}}$ values to the baseline condition.

A beat-to-beat *R* wave detection in ECG recordings was used to calculate reference HR at each level of the LBNP protocol. From the Finapres recordings, the beat-to-beat values of systolic BP (SBP), diastolic BP (DBP), pulse pressure (PP), and mean

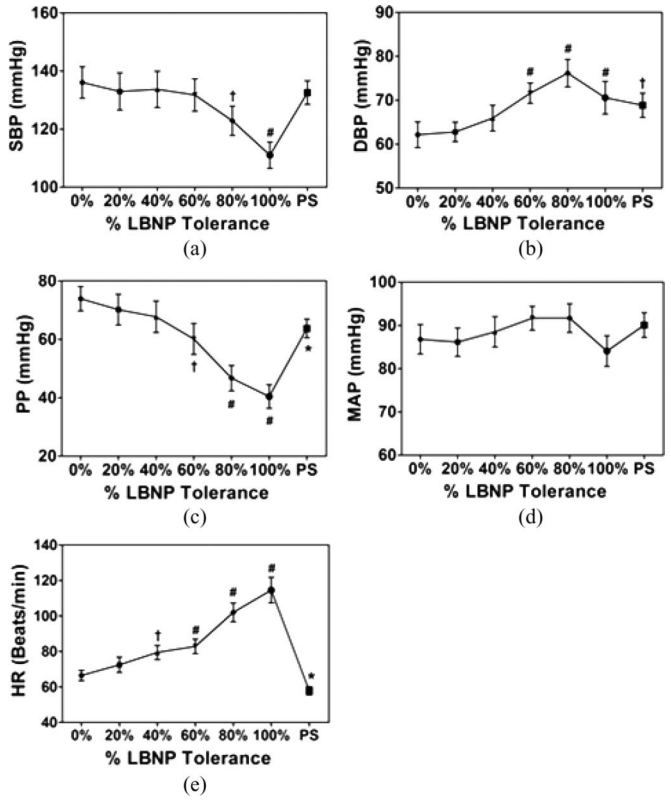

Fig. 2. Changes in (a) SBP-systolic BP, (b) DBP-diastolic BP, (c) PP-pulse pressure, (d) MAP-mean arterial pressure, and (e) HR-heart rate are given in mean ± SE for various stages of the LBNP protocol. The significance levels are found with respect to 0% LBNP tolerance (i.e., baseline). $^{*}P < 0.05$; $^{\dagger}P < 0.01$, $^{\#}P < 0.001$. PS denotes postsymptomatic.

arterial pressure (MAP) were obtained and averaged for each level of LBNP.

D. Statistical Analysis

Normality of each measure was assessed using D'Agostino and Pearson Omnibus normality test. The statistical significance among various levels of the LBNP protocol was assessed using either parametric repeated measures analysis of variance or repeated measures nonparametric Friedman test when appropriate. If statistical differences were found, either a Bonferroni post-test or Dunn's posttest was performed appropriately to determine the statistical significance between every possible pair of conditions. The statistical significance was set at $P < 0.05$.

III. Results

A. Measurements of Vital Signs During the LBNP Protocol

Fig. 2 shows the changes in SBP, DBP, MAP, PP, and HR obtained from 11 healthy volunteers during various levels of LBNP application. SBP and PP both decreased ($P < 0.01$) from 80% LBNP and 60% LBNP, respectively, through 100% LBNP tolerance level as compared to the baseline [see Fig. 2(a) and (c)]. During recovery, PP was still lower ($P < 0.05$) than the baseline. DBP increased ($P < 0.001$) at 60% to 100% LBNP tolerance and remained higher also at the recovery ($P < 0.01$) with respect to baseline [see Fig. 2(b)]. MAP showed no significant changes throughout the LBNP protocol [see Fig. 2d]. The HR was increased ($P < 0.01$) at 40% to 100% of LBNP tolerance. After the LBNP application was terminated, HR recovered but was still lower ($P < 0.05$) than the baseline value [see Fig. 2(e)]. Table I shows the statistical significances found among different stages of the LBNP protocol other than the baseline condition for these vital measures.

TABLE I
Statistical Significance Among Various Levels of the LBNP Protocol Found for the Vital Signs

SBP	DBP	PP	MAP	HR
20% vs. 100% #	20% vs 60 % †	20% vs 80 % #	None	20% vs. 60% *
40% vs. 100% #	20% vs. 80% #	20% vs. 100% #		20% vs. 80% #
60% vs. 100% †	20% vs. 100% #	40% vs. 80 % #		20% vs. 100% #
100% vs. PS #	20% vs. PS †	40% vs. 100% #		20% vs. PS #
	40% vs 80 % #	60% vs. 80 % †		40% vs. 80 % #
	40% vs. 100% *	60% vs. 100% #		40% vs. 100% #
	80% vs PS *	80% vs. PS †		40% vs. PS #
		100% vs. PS #		60% vs. 80 % #
				60% vs. 100% #
				60% vs. PS #
				80% vs. 100% †
				80% vs. PS #
				100% vs. PS #

$^{*}P<0.05$; $^{\dagger}P<0.01$; $^{\#}P<0.001$.

B. Detection and Quantification of Simulated Blood Loss Using Multisite PPG Signals

Fig. 3 shows the VFCDM analysis of representative ear PPG data obtained during the LBNP protocol. While the TFS of ear PPG data showed a marked increase in HR frequency as the application of LBNP increased, the instantaneous amplitude of HR oscillations were reduced [see Fig. 3(b)]. This observation corresponds with the AM_{HR} values of the PPG derived from the HR ridge of the TFS [see Fig. 3(c)]. The AM_{BR} values of the PPG derived from the BR band of the TFS showed constant oscillations throughout the LBNP protocol [see Fig. 3(d)].

The percent changes in AM_{HR} and AM_{BR} measures obtained from the three PPG probes sites at each level of the LBNP protocol ($n = 11$) are given in Fig. 4. The AM_{HR} measure decreased ($P < 0.05$) from 20% LBNP through 100% LBNP for ear and finger PPG signals [see Fig. 4(a) and (c)], whereas in forehead PPG, the significant decrease was found only from 80% LBNP [see Fig. 4(e)]. More importantly, a linearly degraded AM_{HR} response was observed with the progressive increase in LBNP decompression from ear PPG [see Fig. 4(a)]. After the termination of LBNP application, no significant changes in AM_{HR} were observed from finger and forehead PPG signals, but AM_{HR} of ear PPG increased ($P < 0.05$) from the baseline value. In contrast to AM_{HR} measure, the AM_{BR} measure increased ($P < 0.05$) from 20% LBNP through 100% LBNP for ear PPG, but also in finger PPG except 100% LBNP. No significant differences were noticed in AM_{BR} measure during the recovery stage from ear and finger probe sites.

Table II summarizes the statistically significant effects found among various stages of the LBNP protocol other than

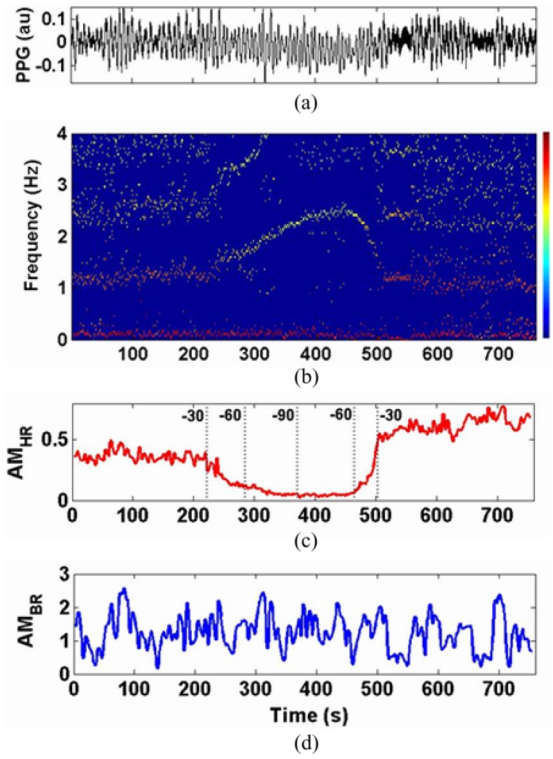

Fig. 3. (a) Representative ear-PPG data recorded during LBNP experiment. (b) TFS obtained from VFCDM analysis. The continuous changes in (c) AM_{HR}, and (d) AM_{BR} components of PPG signal extracted from TFS of VFCDM. The gradual decrease in AM_{HR} components of PPG reflect the progressive increase in simulated blood loss induced by LBNP. The time events of chamber decompression in mmHg are shown with dotted vertical lines.

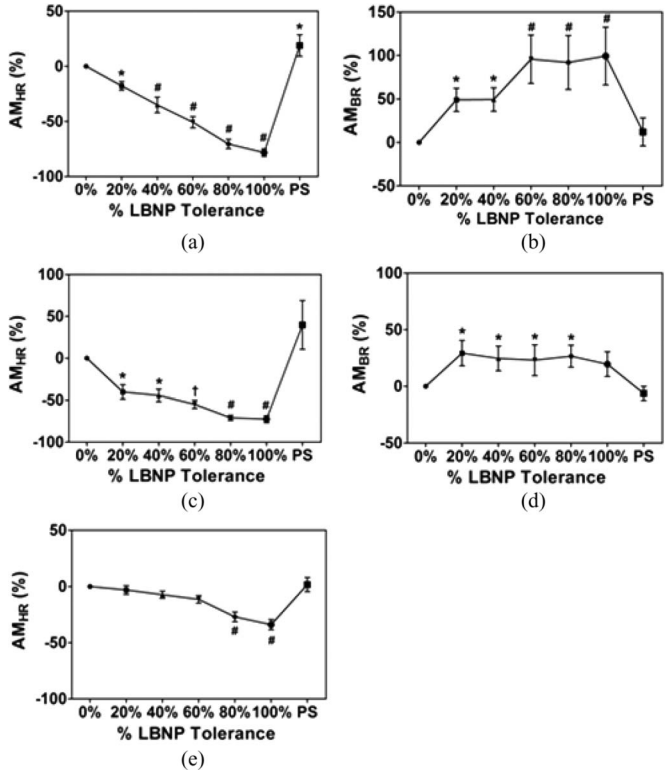

Fig. 4. Percent changes in AM_{HR} (left panels) and AM_{BR} (right panels) components are given in Mean $\pm$ SE for ear (first row), finger (second row), and forehead (third row) PPG signals. The significance levels are found with respect to 0% LBNP tolerance (i.e., baseline). $^{*}P < 0.05$; $^{\dagger}P < 0.01$, $^{\#}P < 0.001$. PS denotes postsymptomatic.

baseline condition. The AM_{HR} of the ear PPG was the most sensitive measure as it showed significant changes between every phase of the progressive blood volume loss caused by LBNP in spontaneously breathing subjects. The mean percent decrease in AM_{HR} values at 100% LBNP tolerance was 78.3%, 72.5%, and 33.9% for ear, finger, and forehead PPG signals, respectively. This observation suggests that the forehead site is not as sensitive as the ear and finger PPG sites. The mean percent increase in AM_{BR} values at 100% LBNP tolerance was 99.4% and 19.6% for ear and finger sites, respectively. This observation suggests that the increase in respiratory related AM_{BR} of the PPG signal was five times stronger in the ear compared to the finger site.

In addition to the previous analysis of the relative changes in AM measures to detect the hypovolemia, the absolute values of AM_{HR} measure were also compared between baseline, 60% LBNP, 80% LBNP, and 100% LBNP as shown in Fig. 5. We observed more overlapping in absolute values of AM_{HR} measure during early stages of LBNP (not shown), but with a very clear separation during later stages of LBNP with respect to baseline. From ROC analysis, the optimal threshold value of absolute AM_{HR} measure (in au) that may allow for hypovolemic detection at 100% LBNP tolerance was found to be 0.43, 0.3, and 1.1 for ear, finger, and forehead PPG signals, respectively. Using these threshold values, the specificity and sensitivity values of AM_{HR} measure for hypovolemic detection are given in Table III. The AM_{HR} measure of ear PPG offered the specificity of 90.9% and sensitivity of 90.9% for hypovolemic detection at 100% LBNP; for forehead PPG, the sensitivity and specificity values were 90% and 100%, respectively, at 100% LBNP.

TABLE II
STATISTICAL SIGNIFICANCE AMONG VARIOUS LEVELS OF THE LBNP PROTOCOL FOUND FOR AM_{HR}, AM_{RR} MEASURES OF THE PPG SIGNAL RECORDED AT EAR, FINGER, AND FOREHEAD SITES

Ear PPG		Finger PPG		Forehead PPG
AM_{HR}	AM_{RR}	AM_{HR}	AM_{RR}	AM_{HR}
20% vs. 40% *	20% vs. 60% *	20% vs. 100% †	20% vs. PS †	20% vs. 80 % #
20% vs. 60% #	20% vs. 80% *	20% vs. PS *	40% vs. PS †	20% vs. 100% #
20% vs. 80 % #	20% vs. 100% *	40% vs. 80% *	60% vs. PS †	40% vs. 80 % #
20% vs. 100% #	40% vs. PS †	40% vs. 100% †	80% vs. PS †	40% vs. 100% #
20% vs. PS #	60% vs. PS #	40% vs. PS *	100% vs. PS *	40% vs. PS *
40% vs. 60% *	80% vs. PS #	60% vs. 100% *		60% vs. 100% †
40% vs. 80 % #	100% vs. PS #	60% vs. PS *		60% vs. PS *
40% vs. 100% #		80% vs. PS #		80% vs. PS #
40% vs. PS #		100% vs. PS #		100% vs. PS #
60% vs. 80% *				
60% vs. 100 % #				
60% vs. PS #				
80% vs. PS #				
100% vs. PS #				

$^{*}P$ <0.05; $^{\dagger}P$ <0.01; $^{\#}P$ <0.001.

IV. DISCUSSION

Early detection of blood loss is essential so that an immediate clinical intervention can be made before a patient develops hemorrhagic shock. However, early blood loss detection has been a

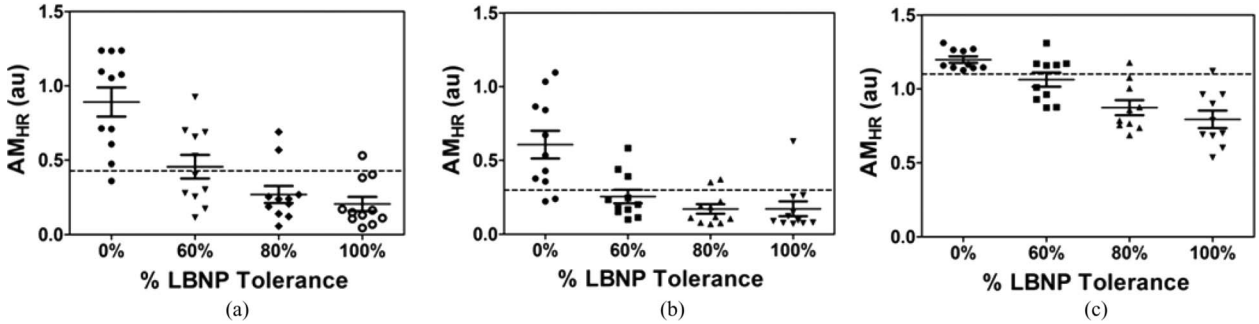

Fig. 5. Comparison of absolute AM_{HR} values between baseline (0%), 60%, 80%, and 100% LBNP tolerance conditions are given for (a) ear, (b) finger, and (c) forehead PPG sites. The bars are referred to mean $\pm$ SE. The optimal threshold values of absolute AM_{HR} measure of ear, finger, and forehead PPG were found to be 0.43, 0.3, and 1.1, respectively, as denoted by the dotted lines.

TABLE III
RECEIVER OPERATING CHARACTERISTIC CURVE ANALYSIS OF AM_{HR} MEASURE FOR HYPOVOLEMIC DETECTION

AM_{HR} measure		Ear PPG	Finger PPG	Forehead PPG
Optimal threshold (au)		0.41	0.35	1.1
Specificity (%)		90.9	81.8	100
Sensitivity (%)	60% LBNP	54.5	72.7	50.0
	80% LBNP	81.8	81.8	90.0
	100% LBNP	90.9	90.9	90.0

challenging task in emergency/critical care medicine, surgery, and anesthesia because computational methods have not matured to the point of providing accurate, reliable, and real-time detection of blood loss. The routinely measured vital signs are not useful for such early detection, as they become sensitive only after blood losses have approached critical levels [1]. Indeed, our study also confirmed this observation. Ours are the first studies to demonstrate a new approach that allows more sensitive and far earlier detection of blood loss than given by vital signs measures. Specifically, the most important finding of this study is that our AM_{HR} parameter derived from TFS of the PPG signal offered significant relative changes at a very early stage (i.e., 20% LBNP tolerance). Further, a clear separation of AM_{HR} values between the baseline and LBNP tolerance levels especially at 80% and 100% indicate blood loss detection even without baseline values.

None of the vital signs produced such significant changes at very early stage of simulated blood loss. Among the vital signs measured, HR was the most sensitive as it significantly increased from 40% LBNP through 100% LBNP with respect to baseline value. However, the changes in mean HR between 80 and 120 beats/min are clinically considered as the normal HR levels [see Fig. 2(e)]. Hence, the HR may not be a good surrogate for blood loss detection. Clinicians have routinely recognized hypotension as SBP $\leq$ 90 mmHg. Eastridge *et al.* [15] have redefined the clinical alert threshold of SBP for hypotension as 110 mmHg. From our results, even though SBP significantly decreased from 80% LBNP, SBP was well above the clinical threshold of either 90 or 110 mmHg; hypotension was not reached until 100% LBNP tolerance [see Fig. 2(a)]. Similar to SBP, a significant decrease in PP occurred during the later stages of the LBNP protocol [see Fig. 2(c)]. The decrease in PP may reflect a reduction in stroke volume and an increase in vasomotor tone and peripheral resistance due to the elevated LBNP decompression.

The PSD of the PPG signal has been previously used to calculate the ratio of the respiratory peak power to the HR peak power as a measure of respiratory variation [5], [16]. While PSD is more resistant to motion artifacts than time-domain approaches and as blood loss detection is localized to either HR or BR frequency band, PSD does not account for time-varying dynamics of the HR and BR components of the PPG signal. Furthermore, determining the precise location of the respiratory frequency peak is problematic, since it is often one of the smallest peaks in the spectrum, and can be increasingly difficult to decipher with motion or noise artifacts. Therefore, the PSD and other time-invariant methods are not very successful for blood loss detection and they are also limited to motion-free conditions, which preclude their wide clinical usefulness.

Our approach using the time–frequency analysis of PPG signals indicates using the AM_{HR} values of ear as well as finger PPG signals that the detection of blood volume loss is possible at a very early stage of 20% LBNP. Further, the progressive linear decline in AM_{HR} values concomitant with the increased LBNP indicates that quantifying the progressive blood volume loss induced by LBNP is possible well before subjects reach hypotension and tachycardia. Our approach is more sensitive than any of the vital sign measures demonstrated in our study. McGrath *et al.* [2] have reported some success using a time-domain approach, but their work showed a statistically significant change in the PPG amplitude only at 60% LBNP tolerance. We believe that the decrease in AM_{HR} is related to the reduction in central blood volume, a reduction that subsequently results in the concomitant increase in sympathetic activity, vasomotor tone and peripheral vasoconstriction [17].

Physically, the AM_{HR} series represents the AM of the cardiac components of the PPG signal driven by the respiratory rate as the dominant spectral peak of the AM_{HR} series corresponds to the breathing frequency. This is similar to the respiratory sinus arrhythmia modulating the HR variability. Using our VFCDM approach, we have recently showed that accurate breathing rates

can be determined by computing spectral density of the AM_{HR} series [10], [18].

We have also examined whether the AM_{BR} values correlate with blood loss. The AM_{BR} series derived from the BR frequency band (0.05–0.35 Hz) reflects the respiratory-induced activity and the combined autonomic influence exerted by the sympathetic and parasympathetic activities on the PPG waveform. Note that the AM_{BR} series does not distinguish the autonomic activity from the respiratory induced activity on the PPG waveform. Unlike the decrease in AM_{HR}, we found significantly increased AM_{BR} values at a very early stage of 20% LBNP that reached a plateau at 60% LBNP for both ear and finger PPG signals. We believe that the increase in AM_{BR} values is largely attributable to the fact that relatively empty veins will collapse in response to negative intrathoracic pressure. Once the veins collapse, they will not empty further; hence, one does not see the pronounced further change in the AM_{BR} values during the later stages of LBNP. Thus, the AM_{BR} values are less sensitive than the AM_{HR} for detection of progressive hypovolemia during spontaneous ventilation.

Our observation of the increased AM_{BR} values with increased LBNP agrees with Wendelken *et al.* [5], who also showed increased respiratory power of PPG signals at later stages of LBNP. But this observation disagrees with Nilsson *et al.* [6], who found that the respiratory variation of PPG signals tends to be less prominent during spontaneous ventilation. These different findings and the fact that AM_{BR} values are not as sensitive as AM_{HR} further strengthen the importance of the AM_{HR} values as a marker for early detection of blood loss.

Data from the PPG probe sites at the ear followed by finger show significant changes in AM_{HR} values at a very early stage of LBNP. The importance of this finding is that given the available baseline AM_{HR} values, our method is able to detect blood loss even as early as 20% of LBNP. In certain instances, the baseline AM_{HR} may not be available to make diagnostic measure of blood loss using our approach. However, as shown in Fig. 5, the fact that there is a clear separation between the baseline and LBNP tolerance at 80% and 100% especially for ear location suggest a possible device approach to detection of blood loss even without the baseline AM_{HR} values. While the forehead location provided higher specificity than the ear at 100% LBNP tolerance level as shown in Table III and Fig. 5, it was not as sensitive when relative changes in AM_{HR} values during various LNBP tolerance levels are compared to the baseline. Further, it is our experience that motion and noise artifacts have more pronounced effect on the forehead than ear PPG signals.

While vital sign measures (see Fig. 2) do indicate significant changes relative to the baseline values at large LBNP tolerance levels, their capabilities become limited without baseline values as they are within the normal operating ranges. These findings are unique observations of this study. Further, our results show that the increase in AM_{BR} due to hypovolemia was five times stronger in ear PPG than the finger PPG, a finding which suggests that the former modality is more sensitive than the latter. This observation agrees with Shelley *et al.* [16]. The respiratory spectral content in the forehead-PPG signals (see Fig. 6) was found to be very weak, and consequently those extracted AM_{BR} values are negligible in some cases. This is the primary reason why using the estimation of AM_{RR} values from forehead-PPG signals was not possible for all the subjects. While ear and finger PPG signals showed significant decreases in AM_{HR} values at 20% LBNP, the forehead site showed significant decreases only at 80% LBNP. Our results agree with those of McGrath *et al.* [2], who found significant decreases in pulse amplitude of forehead PPG at 60% LBNP. Furthermore, in our recent work, we found that, when compared to either ear or finger PPG sensors, the forehead PPG sensor was the most prone to motion and noise artifacts [19]. These findings suggest that the forehead site is not as sensitive as the ear and finger PPG sites for the detection of progressive hypovolemia.

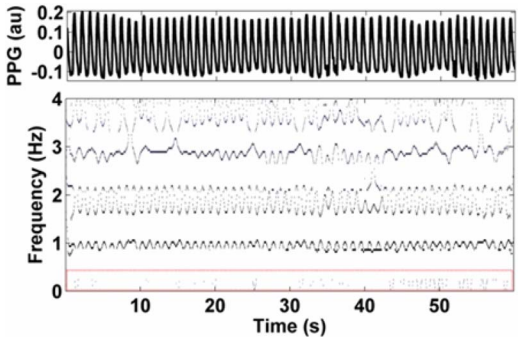

Fig. 6. Representative forehead-PPG signal recorded during baseline of LBNP experiment is shown with its TFS of VFCDM. While the HR spectral content is predominantly seen at 1 Hz, the respiratory spectral content was weak and found absent for most of the time as highlighted with the box. Therefore, the AM_{BR} values were not quantifiable in various stages of LBNP and in all the subjects. Meanwhile, the estimation of AM_{HR} values was possible in all the subjects as reported in the results section.

Our computational approach to quantitative and early detection of blood loss is fundamentally different from others reported in the literature to date. The success of our approach is predicated on addressing both the time-varying and nonlinear dynamics of cardiorespiratory system interplay during blood loss. The success of this approach to early blood loss detection is largely due to the use of a spectral analysis method with one of the highest resolutions in both the time and frequency domains [12], a method that allows extraction of the AM at the HR frequency. This approach differs from others, because we do not perform direct calculations on the PPG signal, but rather we extract the AM time series from which blood loss is quantified. Thus, our approach is less affected by noise and motion artifacts than other approaches because the extracted AM time series is the dominant periodic signal in the narrow HR frequency band, which reduces the effect of other high- and low-frequency noise sources. With our approach, if the motion and noise artifacts still remain in the extracted AM time series, they are often not persistent at all time points, and thus their magnitudes are negligible. The PPG segments corrupted with extreme motion artifacts certainly cannot be included in our VFCDM analysis for blood loss detection. Thus, an effective motion artifact detection and removal technique for real-time blood volume loss applications is essential. In our companion paper [19], we illustrate approaches for automatic and real-time

realizable detection of motion and noise artifacts. Finally, our computational approach for detecting of blood volume loss can be implemented in real time, since the MATLAB computational time is 717 ms in a 1.66 GHz Intel Core2 processor.

It should be noted that there are several physiological factors that may cause vasoconstriction, which subsequently affects our reliance on AM_{HR} value for blood loss detection. For example, cold exposure has been shown to significantly decrease the amplitude of the finger PPG signals [20]. However, the ear PPG amplitudes were shown to be immune to the vasoconstrictive effects with no significant changes [20]. Pain sensation during blood loss also has a vasoconstrictive effect. It should be noted that cold pressor test also elicits pain perception. Thus, the fact that ear PPG amplitude is immune to the vasoconstrictive effects and the ear being the most sensitive for blood loss in our study, all suggest that AM_{HR} value may have a diagnostic value in blood loss detection.

V. Conclusion

We presented an approach that suggests that a sensitive, early detection of blood loss is possible using an ear pulse oximeter sensor. Further, our study suggests such detection of blood loss even without baseline values that further enhances the novelty of the current study. We are unaware of any published reports that are able to provide such reliable and sensitive blood loss detection directly from a pulse oximeter. Finally, our algorithm is real-time realizable as the computation time is less than 1 s.

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Authors' photographs and biographies not available at the time of publication.