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Early Detection of Spontaneous Blood Loss using Amplitude Modulation of Photoplethysmogram

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Abstract—**The present study was designed to investigate can the amplitude modulation (AM) of Photoplethysmogram (PPG) be used as an indicator of blood loss and if so what is the best PPG probe site. PPG from ear, finger and forehead probe sites, standard ECG, and Finapres blood pressure waveforms were continuously recorded from 8 healthy volunteers during baseline, blood withdrawal of 900 ml followed by the blood reinfusion. The instantaneous amplitude modulations present in heart rate (AM_{HR}) and breathing rate (AM_{BR}) band frequencies of PPG were extracted from high-resolution time-frequency spectrum. HR and pulse pressure showed no significant changes during the protocol. The AM_{HR} significantly ($P<0.05$) decreased at 100 ml through 900 ml blood loss from ear and finger probe sites. The mean percent decrease in AM_{HR} at 900 ml blood loss compared to baseline value was 45.2%, 42.0%, and 42.3% for ear, finger and forehead PPG signals, respectively. In addition, significant increases in AM_{BR} were found due to blood loss in ear and finger PPG signals. Even without baseline AM_{HR} values, 900 ml blood loss detection was shown possible with specificity and sensitivity both 87.5% from ear PPG signals. The present technique has great potential to serve as a valuable tool in the intraoperative and trauma settings to detect hemorrhage.**

Index Terms—**Photoplethysmography, time-frequency analysis, amplitude modulation, blood donation, hypovolemia**

I. Introduction

Accurate detection of early blood volume loss is an important component of intraoperative and trauma care. Although there is a significant amount of research on this topic, a useful, easily implementable, and effective method for early detection has yet to be identified [1]. A clinical blood withdrawal model is often used for modeling acute blood loss whereby a withdrawal amount of 400 to 900 ml corresponds to 10-20% blood volume loss. Changes in heart rate (HR) and blood pressure (BP) are typically minimal for moderate blood loss that depends on the percentage and time period of loss, sympathetic activation may also act to prevent a further decline in vital signs [2].

Signal processing approaches involving time-domain, frequency-domain, and joint time-frequency analysis have been previously studied to identify possible indicators of blood volume loss and have shown promising results in studies of respiratory influence on the Photoplethysmogram (PPG) [3-5]. However, the respiratory variations of the PPG waveforms have been shown inaccurate in predicting hemodynamic changes induced by lower body negative pressure (LBNP) [6]. Development of new quantitative methods that can account for time-varying dynamics with sufficient time and frequency resolution can overcome the inconsistencies of the present computational methods.

A novel method for analysis of time-frequency series, termed variable frequency complex demodulation (VFCDM), was recently shown to provide one of the highest time-frequency resolution and superior accuracy for measurement of respiratory rate from PPG [7]. Using this approach, we continuously extracted the amplitude modulation series associated with the HR (AM_{HR}) and breathing rate (AM_{BR}) band frequencies of the PPG. We found significant decreases in AM_{HR} values starting as early as 20% of the LBNP tolerance in spontaneously breathing healthy subjects [8]. In the present study, we demonstrate the efficacy of VFCDM approach for recognizing changes in blood volume after two-units of blood withdrawal followed by reinfusion. Specifically, we hypothesize that the AM_{HR} and AM_{BR} extracted from VFCDM will significantly decrease and increase, respectively, during progressive blood volume loss of 900 ml before significant changes are observed in HR and BP. This study also has an additional aim of identifying the optimal site for detecting blood volume loss by analyzing simultaneously collected PPG measurements of the ear, finger and forehead.

II. Materials And Methods

A. Experimental protocol

The protocol was approved by the Yale-New Haven Hospital IRB Committee and written informed consent was

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obtained from all subjects. Eight healthy volunteers (n=8, range 25-32 years) with no known cardiovascular or systemic disease were recruited for this study. The subjects were placed in a semi-recumbent position on a reclining chair at a room temperature of ~21°C. The subjects had a 16 gauge intravenous catheter inserted into an antecubital vein after a local anesthetic was applied to the skin. The catheter was attached to a CPDA-1 bag for subsequent blood withdrawal. A hematocrit of at least 36 was confirmed before blood withdrawal was started. After a venous tourniquet was applied to the arm, two units of blood (i.e, 900 ml) were allowed to drain by gravity over a period of 27.5 ± 6.3 min (mean ± SE). Later, the reinfusion of the same two units of blood was accomplished linearly over a period of 20 minutes. The study endpoints included changes in HR or BP that exceeded 15% of baseline and/or the development of any signs or symptoms of hypovolemia.

B. Data acquisition

Three infrared PPG-probes (Modified Model 520A, Oxypleth®, Novametrix/Respironics, Wallingford, CT) were placed at the finger, forehead and ear. The auto-gain function and other filtering algorithms were disabled during PPG recording. The standard ECG and continuous noninvasive arterial BP (Finapres, Ohmeda, Boulder, CO) were also simultaneously measured. All data were recorded at 200 Hz using a microprocessor-based data acquisition system (PowerLab 16, ADInstruments, Colorado Springs, CO). The recorded PPG data were analyzed offline using Matlab®.

The time events of the experimental protocol including baseline, amounts of blood withdrawn and reinfusion were marked in the LabChart® 7 (ADInstruments) file during the data acquisition process. Using the markers of time events, PPG data of 2 min were extracted for our data analysis by the end of each level of the experimental protocol: baseline, blood withdrawal of 100ml, 200ml, 300ml, 450ml, 550ml, 650ml, 750ml, and 900ml, post withdrawal of 900ml blood, reinfusion of 450ml and 900ml blood, and post reinfusion of 900ml blood. From each PPG data block of 2 min, a one minute window was shifted in 10 second intervals, and thus 7 PPG segments were obtained for our analysis. The PPG segments were down sampled to 20 Hz, zero-meaned, linearly detrended, normalized to unit variance and applied to the VFCDM algorithm.

C. VFCDM Time-Frequency Analysis

Development of the VFCDM algorithm has been previously reported in detail [7, 9]. A sample ear-PPG segment and its high resolution time-frequency spectra (TFS) via VFCDM method are shown in Fig. 1a-b, respectively. There are two dominant frequencies that can be observed at two distinct bands of the TFS: a HR ridge, representing the high frequency component in the PPG signal related to the cardiac pulse, and the BR ridge, corresponding to the low frequency component. Both ridges are outlined in the TFS (Fig. 1b). The collection of the largest instantaneous amplitude at each time sample within the desired frequency band of the TFS constitutes the

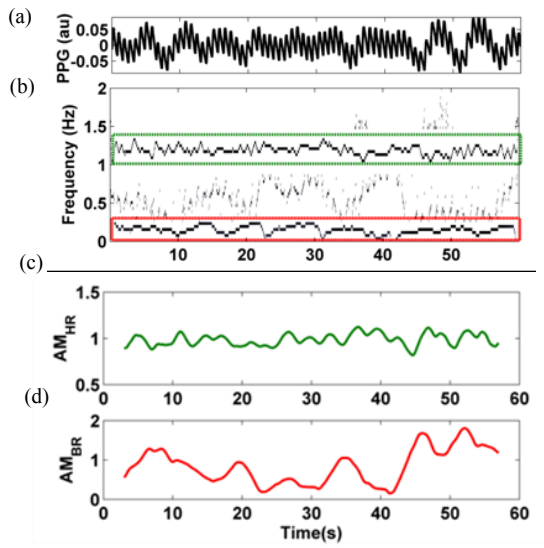

Fig. 1. (a) A sample ear PPG signal and its (b) time-frequency spectra (TFS) using VFCDM analysis. The prominent frequency oscillations were seen near heart rate (1 Hz) and respiratory rate (0.2 Hz) highlighted as boxes in TFS. The extracted amplitude modulation of heart rate band (i.e., AM_{HR}) and breathing rate band (i.e., AM_{BR}) are shown in (c) and (d), respectively.

amplitude modulation (AM) series. The AM series extracted from the HR band (HR±0.2 Hz) and BR band (0.05-0.35 Hz) were identified as AM_{HR} and AM_{BR}, respectively (as shown in Fig. 1c-d). Note that these AM_{HR} and AM_{BR} terms represent the time varying amplitude modulation. The initial and final 5s of the TFS were not considered for the extraction of AM_{HR} and AM_{BR} because of the edge effect [7]. The median values of AM_{HR} and AM_{BR} series were evaluated for each of the 7 PPG segments (due to 1 min window shifted by 10 seconds for 2 min data) which were then averaged. The percent changes in AM_{HR} and AM_{BR} values were calculated for each stage of analysis with respect to the individual's baseline responses for the three PPG signals. Receiver operating characteristic (ROC) curve analysis was also 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 AM_{HR} values to the baseline condition.

Further to assess the autonomic effects on AM_{HR} due to blood loss, power spectrum density (PSD) analysis using the Welch periodogram method of AM_{HR} series was carried out in which the LF power (0.05-0.15 Hz), HF power (0.15-0.35 Hz), and total power (0.05-0.7 Hz) were calculated. The LF and HF power of AM_{HR} were normalized with respect to the total power of AM_{HR} series.

In addition to the above PPG measurements, HR was evaluated at each level of the blood withdrawal protocol using beat-to-beat R wave detection in ECG recordings. From the Finapres recordings, the beat-to-beat values of systolic BP (SBP), diastolic BP (DBP), pulse pressure (PP), and mean arterial pressure (MAP) were obtained and averaged for each level of blood withdrawal protocol.

D. Statistical analysis

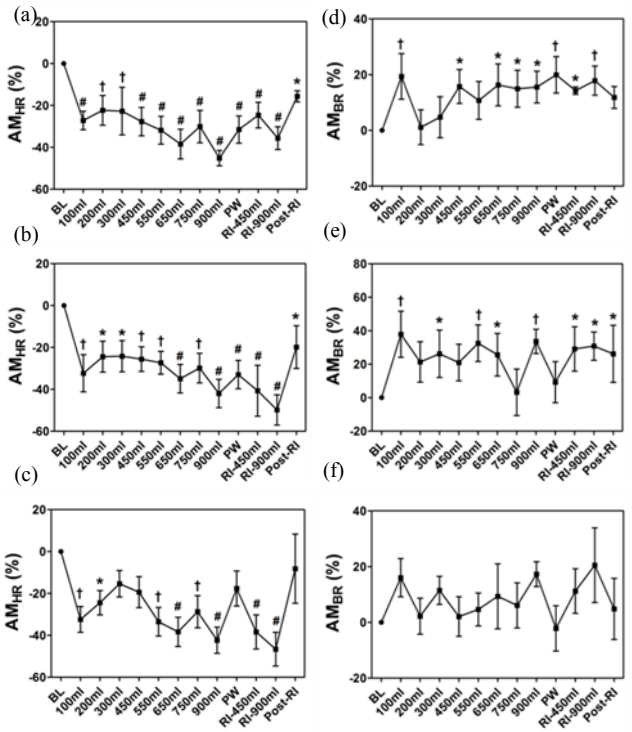

Fig. 2. The percent changes in AM_{HR} (Left column) and AM_{BR} measures (right column) obtained from ear (1st row), finger (2nd row) and forehead (3rd row) PPG signals during various stages of the blood donation protocol are given in mean ± SE. The significance levels are given with respect to BL, baseline. *P<0.05; †P<0.01; #P<0.001. PW, post-withdrawal of 900ml blood; RI, reinfusion.

Normality of each measure was assessed using D'Agostino & Pearson Omnibus normality test. Either parametric repeated measures ANOVA or repeated measures nonparametric Friedman test were used to assess the significance level among various conditions of blood donation protocol when appropriate. If statistical significance was found, either Bonferroni post test or Dunn's post test were performed appropriately to determine the statistical significance between every possible pair of conditions. The statistical significance was set at P<0.05. The data were given in mean ± SE.

III. Results

The Finapres arterial BP measurement was unobtainable intermittently in three subjects during various stages of the protocol. Hence, the measurements of SBP, DBP, MAP, and PP were obtained only from 5 subjects. The HR values were obtained from ECG recordings in all 8 participants. SBP increased (P<0.05) at 100 ml of blood donation (143.1±2.3 mmHg) and post-reinfusion of 900 ml blood (144.9±9.1 mmHg) as compared to baseline value (126.4±3.3 mmHg). The DBP and MAP also increased (P<0.05) at 100ml of blood withdrawal, reinfusion of 450ml blood, reinfusion of 900ml blood, and post reinfusion of 900ml blood stages with respect to baseline. No significant changes were found for the PP and HR throughout the experimental protocol.

The percent changes in AM_{HR} and AM_{BR} values obtained from 8 healthy subjects at each level of the blood withdrawal protocol are provided in Fig. 2 for ear, finger and forehead probe sites. A decrease (P<0.01) in AM_{HR} values were found at a very early stage of 100 ml blood loss in all three PPG probe sites (Fig. 2a-c). The AM_{HR} value was also shown to decrease (P<0.05) throughout the process of blood withdrawal in ear and finger PPG sites. For the forehead probe site, AM_{HR} values were significantly decreased during all stages of blood withdrawal except for the 300 ml and 450 ml measurement points. The mean percent decreases in AM_{HR} reached maximum values during 900 ml blood loss of 45.2±3.7 %, 42.0±6.8 %, and 42.3±6.2 % for ear, finger and forehead PPG signals, respectively. After two unit reinfusion, the AM_{HR} measure showed a recovery towards the baseline value. However, AM_{HR} values of ear and finger PPG sites at post reinfusion were significantly lower than the baseline. The AM_{HR} of forehead during post reinfusion showed no significant difference as compared to the baseline. The AM_{HR} of the ear PPG was found to be consistent as it showed significant changes among various phases of the experimental protocol (not shown). On the other hand, the percent changes in AM_{BR} value of the ear and finger PPG increased (P<0.05) during various stages of protocol as shown in Figs. 2d and 2e, respectively. During post-reinfusion stage, AM_{BR} measure of ear recovered to baseline, but AM_{BR} of finger remained higher (p<0.05). No significant changes were observed in AM_{BR} of the ear probe site during post reinfusion (Fig. 2f).

In addition to the analysis of relative percent changes in AM_{HR} values, the absolute values of AM_{HR} obtained from 8 subjects were compared between baseline and 900ml blood withdrawal conditions for ear, finger and forehead PPG as shown in Fig. 3. ROC analysis found the optimal threshold value for absolute AM_{HR} (in au) as 0.55 for ear and finger PPG signals, and 0.68 for forehead PPG signals. The specificity and sensitivity of AM_{HR} measure for blood loss detection were found to be 87.5% and 87.5% respectively for ear PPG signals, 100% and 75.0% for finger PPG signals, and 75.0% and 100% for forehead PPG signals. Therefore, ROC analysis revealed that the AM_{HR} measure from ear PPG signals had the best combination of specificity and sensitivity for the detection of blood volume loss. Neither LF_{nu} power nor HF_{nu} power showed significant changes for any of the three probe sites during the stages of the blood withdrawal protocol.

IV. Discussion

A computational method for noninvasive and early detection of blood loss using a pulse oximeter has not yet been accomplished in spontaneously breathing subjects despite significant efforts to date. Our VFCDM analysis of PPG signals has shown promise for more sensitive and far earlier detection of blood loss (i.e. 100 ml) than traditional vital signs. The decrease in AM_{HR} measure may be attributed to the decrease in end-diastolic and stroke volume during blood loss. The AM_{HR} measure of ear PPG was found to be the most accurate measure for the detection of 900 ml blood volume loss with both specificity and sensitivity of 87.5% (n=8). The present results agree with our previous LBNP study [8] where the detection of simulated blood loss was

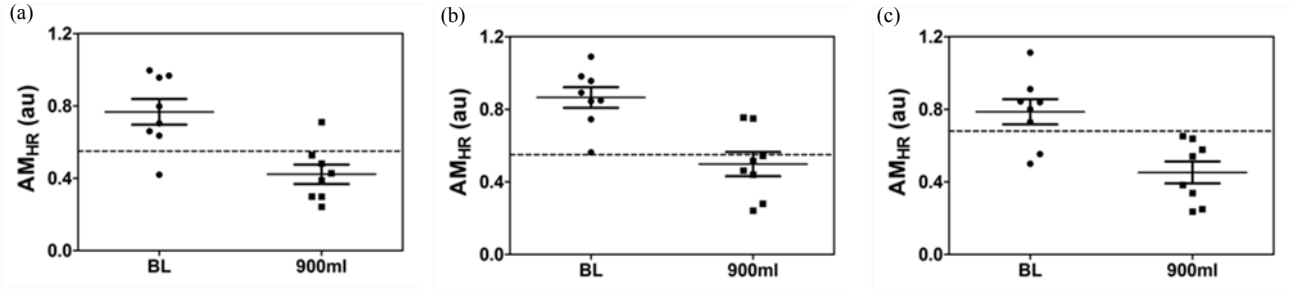

Fig. 3. The comparison of absolute AM_{HR} values between baseline and 900cc blood withdrawal conditions are given for (a) ear, (b) finger, and (c) forehead PPG sites. The bars are referred to mean ± SE. The optimal threshold values of absolute AM_{HR} measure (in au) were found to be 0.55 for ear and finger PPG, and 0.68 for forehead PPG as denoted as the dotted lines.

shown possible at the very early stage of 20% LBNP tolerance where there was a linear decrease in AM_{HR} values corresponding to the progressive increase in LBNP.

The present results showed that the standard vital sign measures such as HR and PP did not show any significance changes during the progressive blood loss of 900 ml. This is in agreement with previous studies [10-11] where no significant changes in HR and PP were found during blood donation of 450 ml under supine position. A normal BP typically is sustained despite a loss of up to 30% of blood volume [1]. Therefore, HR and BP are not sensitive markers to alert clinicians to prevent the patients from developing the cardiovascular collapse [1]. In response to the two units of blood withdrawal, the human body might mobilize the extracellular fluid into the intravascular space. The reinfusion of blood might have induced hypervolemia in these subjects, reflected as the significant increase in MBP during the reinfusion process as shown in our results.

Zollei et al [2] showed that there is an increase in sympathetic activity when 350-400 mL of blood is withdrawn rapidly over five minutes. But, the blood withdrawal in our study varied among subjects from 12–40 min for two units. The varying timeline of blood loss may affect the sympathetic influence. The PSD analysis of AM_{HR} series showed no significant differences in LF_{nu} and HF_{nu} band powers throughout the blood withdrawal protocol. Our PSD analysis of AM_{HR} series are in agreement with a previous study [4] which showed no significant changes in LF_{nu} power (0.04-0.145 Hz) of PPG amplitude variability during blood withdrawal of approximately 500 ml.

Our approach is less affected by artifacts, a common problem with PPG, because the extracted AM_{HR} time series itself is the dominant periodic signal in the narrow HR frequency band, which reduces the effect of other high and low frequency noise sources. Our algorithm can be implemented detection of blood volume loss in real-time since the computational time of our algorithm for 1 minute data is 717 ms in a 1.66 GHz Intel Core2 processor using Matlab®.

In conclusion, we have shown a promising non-invasive method for detecting blood loss at a very early stage during blood withdrawal in spontaneous breathing subjects. Further a clear separation of absolute AM_{HR} values between baseline and 900 ml blood loss indicated accurate blood loss detection even without baseline values. This finding is significant as the present technique has the potential to detect significant blood loss even if monitoring is initiated after blood loss has begun. We are unaware of any published reports that are able to provide such reliable and sensitive blood loss detection directly from a pulse oximeter. Thus, our novel computational technique may provide effective monitoring of blood volume in the intraoperative and trauma settings.

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