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# Photoplethysmographic Variability Analysis in Critical Care – Current Progress and Future Challenges

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***Abstract*—The concept of early goal-directed therapy emphasizes the need for early diagnosis and intervention to achieve better therapeutic outcomes in critical care. There has been rapidly growing interest in the use of the photoplethysmogram (PPG), also known as the "pulse oximetry waveform", as a noninvasive diagnostic tool in this clinical setting. The peripheral PPG exhibits beat-to-beat variability driven by physiological mechanisms such as respiration and sympathetic vascular activity. This paper provides an overview of the current progress towards the application of PPG waveform variability (PPGV) in emergency and intensive care. Studies to date have demonstrated the potential value of PPGV for assessing a range of pathophysiological conditions including blood loss, sepsis and low systemic vascular resistance. Translation of research findings into clinical practice poses several future challenges, including the need for large scale validation studies with appropriate measurement systems, more robust solutions to signal quality issues (such as motion artifacts), and better physiological understanding of the information-rich PPGV.**

## I. Introduction

In the critical care sector, including the emergency department (ED) and the intensive care unit (ICU), clinicians are required to make timely decisions (both diagnostic and therapeutic) that are critical to the survival of patients. The concept of early goal-directed therapy has emerged, which emphasizes the benefits of early recognition and intervention in critical pathophysiological conditions, such as sepsis and trauma [1]. The first period of disease following onset is seen as the "golden hour", given the significant improvement of outcome with treatment provided within this time window. To take advantage of the therapeutic benefits of this critical time frame, diagnostic tools that facilitate timely and accurate assessment of patients' conditions are therefore of great importance.

Assessment of cardiovascular conditions in critical care has been predominantly based on information available from vital sign monitors, with the basic metrics including heart rate (HR), blood pressure (BP) and arterial oxygen saturation ($SaO_2$). These metrics, however, often do not provide sufficient information for the early detection of critical conditions; one example is the detection of blood volume loss due to internal bleeding. Physiological regulatory mechanisms such as the baroreflex are effective in maintaining BP at a stable level in the presence of mild blood loss, whereas HR changes during blood loss are complex and stage dependent [2]. Hypotension (low BP) is a late sign which signifies blood volume loss by 30% or more, by which time patients are at high risk of cardiovascular collapse and death as a result of severe hemorrhagic shock.

The photoplethysmogram (PPG) is well recognized for its use in pulse oximetry for the estimation of $SaO_2$ (based on the differential absorption of red/infrared light by hemoglobins). The application of the PPG waveform, also known as the "pulse oximetry waveform", in cardiovascular monitoring has also attracted substantial interest from critical care clinicians in recent years [3, 4], given that measurement can be obtained noninvasively and continuously in a comfortable manner, either via the pulse oximeter module of vital sign monitors or using low cost portable sensors. The PPG utilizes the absorption or reflection of light by blood to measure blood volume change at a peripheral site, typically the finger, ear or forehead. The waveform may be seen as a result of the interaction between cardiac pulsation, arterial/venous pressure and peripheral vascular tone, leading to the intriguing possibility of characterizing subtle changes in both central and peripheral circulation, that may not be apparent based on metrics provided by existing vital sign monitors.

In this review, we focus on the clinical information derived from the beat-to-beat fluctuation in peripheral blood volume measured by PPG (Fig. 1), termed the PPG waveform variability (PPGV). Similar to the more well-known cardiovascular variability signals such as heart rate variability (HRV) and blood pressure variability (BPV), PPGV also consists of slow fluctuations generated by respiration and various regulatory mechanisms. It has been hypothesized that changes in the fluctuation patterns reflect physiological regulatory responses, which in turn may be helpful for diagnosis of critical illness. Previous work by our group and others towards the utilization of PPGV in critical care is presented in this review.

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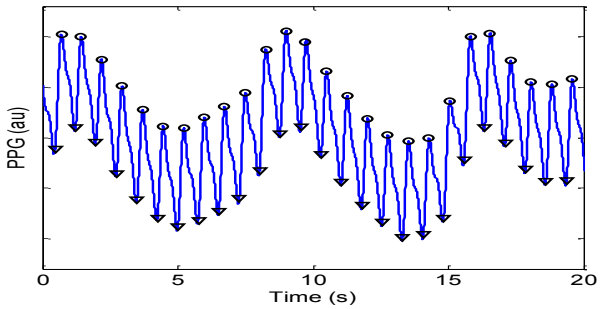

Fig. 1. Finger PPG waveform trace showing beat-to-beat fluctuations in peaks (circles) and troughs (triangles) that constitute PPGV.

## II. PPG Variability in Critical Care

### A. Blood loss (hemorrhage)

The use of respiratory variability in pulse oximetry PPG peak, baseline and pulse amplitude to assess blood volume status has been extensively documented, with the prediction of fluid responsiveness (the ability of cardiac output to increase with fluid therapy) using pulse oximetry PPG being one of the most popular critical care research topics in recent years, as discussed in detail in previous reviews [3, 4]. It has been shown in mechanically ventilated patients that respiration-induced PPG fluctuation is augmented during reduction in central blood volume (hypovolemia), and that the magnitude of respiratory variation was indicative of how much cardiac output could be improved by fluid challenge. Respiratory PPGV was also found to be potentially useful for detecting hemorrhagic blood volume loss in spontaneously breathing subjects, based on studies of healthy blood donors [5] and trauma patients during prehospital transport [6], although conflicting results were seen in another study based on simulation of blood loss by lower body negative pressure (LBNP) [7].

An alternative approach of inferring blood loss from PPGV has been explored by our group [8, 9], based on analysis of the "slow waves" at the low frequency range (LF, 0.04-0.15 Hz) together with respiratory variation in the high frequency range (HF, 0.15-0.45 Hz). Information was obtained by frequency spectrum analysis of the beat-to-beat variation in the PPG peak/trough/pulse amplitude, performed on 2-5 min of continuous data. The underlying premise is that these LF waves reflect the modulation of peripheral vascular tone by sympathetic activity [10, 11], which is known to increase with blood volume reduction as a result of baroreflex activation. Previously we used blood donation as a model of moderate hemorrhage, and showed that the LF power of fingertip PPGV (expressed in mean-scaled units) increased in spontaneously breathing subjects during and after blood loss [9]. Similar increases were noted in a study of renal patients during removal of plasma volume in hemodialysis, with the increase correlating with the drop in relative blood volume [8]. Such responses were attributed to enhanced sympathetic drive to the peripheral vasculature during blood volume loss.

Two major limitations have been noted, however, with the use of PPGV spectral features in blood loss detection. Firstly, severe blood loss can result in poor perfusion and a high degree of vasoconstriction in peripheral vessels (particularly in the finger), leading to poor signal quality and unusable recordings. This may limit the application of PPGV to the detection of a mild to moderate degree of blood loss, given peripheral perfusion is still maintained. Secondly, the spectral powers of PPGV showed a considerable degree of inter-subject variability, limiting its use for distinguishing between hypovolemic and non-hypovolemic subjects based on a single measurement. Expression in normalized units (division by the sum of LF+HF power) would not be helpful in this context, given both LF and HF powers increase with blood loss. That being said, PPGV would still be useful for tracking the blood loss response of an individual over time, and provide an important indication of deterioration of physiological compensation related to critical conditions.

### B. Sepsis

Sepsis is one of the most lethal yet least understood syndromes in the critical care setting. It is generally defined as the presence (or presumed presence) of an infection accompanied by a systemic inflammatory response syndrome (SIRS), with symptoms such as either an abnormally high or low core body temperature, high HR (tachycardia), high respiratory rate and an abnormally high or low white blood cell count. At more severe stages of sepsis the mortality rate is high, exceeding 30% for severe sepsis (sepsis with organ dysfunction) and septic shock (sepsis with refractory hypotension) [1].

Peripheral circulatory dysfunction is common in sepsis patients, and has been identified as a main contributor to organ dysfunction and multiple organ failure in severe sepsis. Piepoli *et al.* were the first to propose PPGV as a marker of peripheral circulatory abnormalities in sepsis patients [12], and showed that the LF power in fingertip PPGV was suppressed in septic shock patients (attributed to a loss of normal sympathetic vasomotor function), with LF fluctuations subsequently restored as the patients recovered.

Recently our group explored classification of sepsis severity by spectral analysis of PPGV measured at the earlobe [13, 14], with the most interesting finding that the normalized mid frequency power (MF, 0.09-0.15 Hz) of ear PPGV was much higher in patients with SIRS compared with the high lactate severe sepsis patients [14]. This was evident by the emergence of large magnitude slow waves in the SIRS patients (Fig. 2), which was absent in severe sepsis patients. This could not be explained by respiration, as the breathing rates in these patients were well above 0.15 Hz. HRV (derived from the electrocardiogram) was also analyzed in the study, but did not show such characteristic changes. The most likely source of these MF waves is believed to be a peripheral vascular mechanism associated with autonomic and metabolic abnormalities in the sepsis syndrome,

although further investigation is required for a more complete understanding. Nevertheless, preliminary results have clearly demonstrated the utility of PPGV for the diagnosis of sepsis, and also its potential application in the categorization of sepsis patients using a statistical classifier [13].

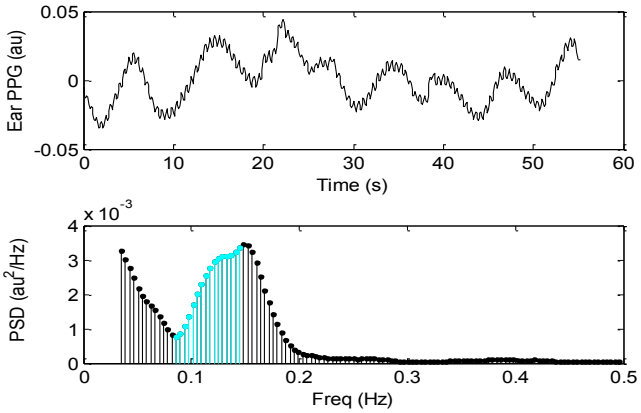


Fig. 2. Ear PPG waveform of an SIRS patient (top) characterized by large magnitude slow waves, with a power spectrum (bottom) showing the relative dominance of MF power (0.09-0.15 Hz, in lighter colour) in PPGV. Abbreviations: au, arbitrary units.

To gain further insight into the PPGV response during the progression of sepsis syndrome, we employed an experimental model of sepsis involving infusion of endotoxin or lipopolysaccharide (LPS) in anesthetized rabbits, with a dosage sufficiently large to induce endotoxic shock [15]. The most significant finding was the substantial but transient elevation of LF and MF powers in PPGV (measured at the rabbit toe), with augmented slow waves similar to those seen in Fig 2, which started before the onset of endotoxin-induced hypotension and peaked at the onset of hypotension. This sudden rise in spectral power coincided with a fall in toe pulse amplitude, suggesting a sudden surge in sympathetic vasoconstrictor drive prior to the onset of endotoxic shock. BPV was also measured in this study, but did not show such characteristic changes. Thus, the observed patterns of change in PPGV were most likely reflecting regional vasomotion in peripheral vasculature, mediated by the interaction of sympathetic and autoregulatory influences. The implication of these findings in human sepsis is not totally clear, given the potential difference in physiological responses between anesthetized animals and conscious humans. Nevertheless, these findings raised an interesting possibility of detecting abnormal vascular response prior to the occurrence of circulatory shock using PPGV, which further adds to the clinical value of this simple and noninvasive signal.

### C. *Systemic vascular resistance*

Systemic vascular resistance (SVR) represents the overall vascular tone of the systemic circulation, with important diagnostic value in a range of critical illnesses; for instance, low SVR may be observed in distributive shock states, particularly in vasodilatory sepsis or anaphylaxis patients. Persistently low SVR, regardless of etiology, can contribute to mortality, thus the identification of low SVR is of clinical importance. Conventional methods of determining SVR involve highly invasive procedures such as insertion of a pulmonary artery catheter to determine cardiac output, then using this to calculate resistance. However, given that PPGV reflects the sympathetic modulation of peripheral vasculature, it would be useful if it was also able to provide some indication of SVR in a completely noninvasive manner.

Early work by Larsen *et al.* showed that suppression of basal sympathetic tone by induction of anesthesia could cause a relative reduction in sympathetic-related LF fluctuations, and enhancement of respiratory HF fluctuations, in the fingertip PPGV [11]. We further explored the possibility of detection of sympathetic withdrawal with PPGV, by investigating the relationship between fingertip PPGV and SVR in post cardiac surgery ICU patients [16]. Moderate but significant positive correlations were obtained between the normalized LF powers ($LF_{nu}$) of PPGV and SVR in these patients, and more importantly, a low value of $LF_{nu}$ appeared to be a highly specific marker of low SVR. These results not only provided quantitative evidence to confirm the association between PPGV and sympathetic vascular control, but also justified its practical use in a realistic clinical setting as an indicator of systemic vascular tone. The discrimination of SVR using PPGV may be improved further by incorporating other PPG features as inputs to a statistical classifier [17]. The ability to classify SVR given the range of pathological conditions and medications used in these ICU patients seems encouraging, although future work is needed to precisely determine the specific influences of vasoactive drugs and anesthetics on the PPGV-SVR relationship.

## III. Future Challenges

Whilst studies to date have revealed the very interesting clinical potential of PPGV, its actual value in the management of critical care patients is yet to be fully established. The use of respiratory PPGV as a measure of fluid responsiveness in the ICU setting has made significant progress towards gaining clinical acceptance, with a number of large-scale clinical validation studies being conducted in recent years [3, 4]. Evaluation of respiratory PPGV as a blood loss indicator in the prehospital transport setting has also been reported, based on study of a large cohort of trauma patients [6]. However, given that most clinical studies have been based on PPG signals obtained from commercially available pulse oximeters, whose baseline fluctuations (below the cardiac pulse frequency) have been removed by built-in filters, the clinical utility of the complete PPGV, which includes also the modulation of signal baseline at the LF and HF ranges, remains to be validated. Moreover, most clinical studies have been based on the fingertip waveform, while it has been shown on a number of occasions that

PPGV measured from an alternative site (e.g. the ear) might provide better diagnostic value [5, 13, 14]. Hence, the availability of unfiltered PPG signals and pulse oximetry sensors for alternative body sites seems crucial for the clinical validation of PPGV.

The greatest hurdle in the move to clinical application of PPGV (or the PPG waveform in general) will no doubt be the susceptibility of signal quality to motion artifact and poor peripheral perfusion. In the ICU setting, these concerns are minimized as patients are typically lying still on a bed, and may often be receiving sedative medications which cause peripheral vasodilatation, thus ensuring good perfusion. In the emergency care setting however, it is more difficult to obtain good quality PPG signals given the unavoidable presence of motion artifact and poor peripheral perfusion (e.g. in trauma patients), as a recent study based on data from prehospital transport has revealed [6]. It will be a great challenge from the perspectives of hardware and software designs to obtain reliable information from the PPGV under such conditions. The solution may involve development of artifact-resistant biosensor units, or smart computer algorithms for artifact rejection/recognition.

The mechanisms underpinning PPGV are still not fully understood particular those associated with the low frequency waves below the respiratory rate. Whilst studies have demonstrated a clear relevance of sympathetic vascular control in the LF band [8-11, 15, 16], the potential role of local mechanisms such as autoregulation cannot be neglected. The differential patterns exhibited in multi-site PPGV further highlight the complexity of regional circulatory control [14, 15], which warrants more extensive investigation. Future work should also consider the incorporation of very low frequency (VLF, < 0.04 Hz) PPGV in the analysis, which has previously been linked with sympathetic vasomotor activity [18] and may provide additional information to the LF and HF bands.

## IV. Conclusion

Research studies so far have demonstrated the potential value of PPGV in critical care for assessing a range of pathophysiological conditions, including blood loss, sepsis and other low systemic vascular resistance. Several challenges will need to be overcome to translate research findings into clinical practice, which will include conducting large scale validation studies, with appropriate measurement systems for the acquisition of raw signals. There is also a need for more robust hardware/software solutions to signal quality issues such as motion artifact, and a more complete understanding of the physiological mechanisms behind PPGV. It is hoped that continued research efforts will eventually establish PPGV as a noninvasive and convenient tool for clinical diagnosis, and ultimately contribute to reduction in mortality in the critical care setting via early recognition of life threatening pathophysiological conditions.

## References


[1] E.P. Rivers, L. McIntyre, D.C. Morro, and K.K. Rivers, "Early and innovative interventions for severe sepsis and septic shock: taking advantage of a window of opportunity," *CMAJ,* vol. 173, no. 9, pp. 1054-65, 2005.

[2] N.H. Secher, J. Jacobsen, D.B. Friedman, and S. Matzen, "Bradycardia during reversible hypovolaemic shock: associated neural reflex mechanisms and clinical implications," *Clin Exp Pharmacol Physiol,* vol. 19, no. 11, pp. 733-43, 1992.

[3] K. Bendjelid, "The pulse oximetry plethysmographic curve revisited," *Curr Opin Crit Care,* vol. 14, no. 3, pp. 348-53, Jun, 2008.

[4] K.H. Shelley, "Photoplethysmography: beyond the calculation of arterial oxygen saturation and heart rate," *Anesth Analg,* vol. 105, no. 6 Suppl, pp. S31-6, 2007.

[5] M.J. Gesquiere, A.A. Awad, D.G. Silverman, R.G. Stout, D.H. Jablonka, T.J. Silverman *et al.*, "Impact of withdrawal of 450 ml of blood on respiration-induced oscillations of the ear plethysmographic waveform," *J Clin Monit Comput,* vol. 21, no. 5, pp. 277-82, 2007.

[6] L. Chen, A.T. Reisner, A. Gribok, and J. Reifman, "Is respiration-induced variation in the photoplethysmogram associated with major hypovolemia in patients with acute traumatic injuries?," *Shock,* vol. 34, no. 5, pp. 455-60, 2010.

[7] L. Nilsson, T. Goscinski, M. Lindenberger, T. Lanne, and A. Johansson, "Respiratory variations in the photoplethysmographic waveform: acute hypovolaemia during spontaneous breathing is not detected," *Physiol Meas,* vol. 31, no. 7, pp. 953-62, 2010.

[8] F. Javed, P.M. Middleton, P. Malouf, G.S. Chan, A.V. Savkin, N.H. Lovell *et al.*, "Frequency spectrum analysis of finger photoplethysmographic waveform variability during haemodialysis," *Physiol Meas,* vol. 31, no. 9, pp. 1203-16, 2010.

[9] P.M. Middleton, G.S. Chan, E. O'Lone, E. Steel, R. Carroll, B.G. Celler *et al.*, "Spectral analysis of finger photoplethysmographic waveform variability in a model of mild to moderate haemorrhage," *J Clin Monit Comput,* vol. 22, no. 5, pp. 343-53, 2008.

[10] L. Bernardi, A. Radaelli, P.L. Solda, A.J. Coats, M. Reeder, A. Calciati *et al.*, "Autonomic control of skin microvessels: assessment by power spectrum of photoplethysmographic waves," *Clin Sci (Lond),* vol. 90, no. 5, pp. 345-55, 1996.

[11] P.D. Larsen, M. Harty, M. Thiruchelvam, and D.C. Galletly, "Spectral analysis of AC and DC components of the pulse photoplethysmograph at rest and during induction of anaesthesia," *Int J Clin Monit Comput,* vol. 14, no. 2, pp. 89-95, 1997.

[12] M. Piepoli, C.S. Garrard, D.A. Kontoyannis, and L. Bernardi, "Autonomic control of the heart and peripheral vessels in human septic shock," *Intensive Care Med,* vol. 21, no. 2, pp. 112-9, 1995.

[13] C.H. Tang, P.M. Middleton, A.V. Savkin, G.S. Chan, S. Bishop, and N.H. Lovell, "Non-invasive classification of severe sepsis and systemic inflammatory response syndrome using a nonlinear support vector machine: a preliminary study," *Physiol Meas,* vol. 31, no. 6, pp. 775-93, 2010.

[14] P.M. Middleton, C.H. Tang, G.S. Chan, S. Bishop, A.V. Savkin, and N.H. Lovell, "Peripheral photoplethysmography variability analysis of sepsis patients," *Med Biol Eng Comput*, 2010.

[15] G.S. Chan, C.H. Tang, P.M. Middleton, G. Cave, M. Harvey, A.V. Savkin *et al.*, "Augmented photoplethysmographic low frequency waves at the onset of endotoxic shock in rabbits," *Physiol Meas,* vol. 31, no. 12, pp. 1605-21, 2010.

[16] P.M. Middleton, G.S. Chan, E. Steel, P. Malouf, C. Critoph, G. Flynn *et al.*, "Fingertip photoplethysmographic waveform variability and systemic vascular resistance in intensive care unit patients," *Med Biol Eng Comput (in press)*.

[17] Q.Y. Lee, G.S. Chan, S.J. Redmond, P.M. Middleton, E. Steel, P. Malouf *et al.*, "Classification of low systemic vascular resistance using photoplethysmogram and routine cardiovascular measurements," *Conf Proc IEEE Eng Med Biol Soc,* vol. 1, pp. 1930-3, 2010.

[18] M. Nitzan, A. Babchenko, D. Shemesh, and J. Alberton, "Influence of thoracic sympathectomy on cardiac induced oscillations in tissue blood volume," *Med Biol Eng Comput,* vol. 39, no. 5, pp. 579-83, 2001.