Dynamics of Arterial Pressure Components in a Sheep Model of Hemorrhage

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Abstract

There is a need for accurate monitors that can track blood loss and report a patient's current physiological response. We explored phase coherence between components of the arterial blood pressure waveform for this purpose.

Adult conscious sheep underwent 25 mL/kg$_{Body\text{-}Weight}$ hemorrhages over 15 minutes (14 total hemorrhage experiments) while continuous arterial blood pressure measurements were made. Phase coherence from a single arterial pressure monitor was assessed between all combinations of the pulse-pulse interval, systolic blood pressure, and pulse pressure sequences as a measure of the synchronization between the component dynamics. Phase coherence measures were compared during baseline, the peak compensatory response and a decompensation phase.

Phase coherence in the range of 0.06 – 0.15 Hz between the pulse-pulse interval and systolic blood pressure sequences as well as the systolic blood pressure and pulse pressure sequences was elevated during the peak compensation period. Analytical techniques to assess the relationship between signals recorded during hemorrhage can be explored for their potential predictive capabilities.

1. Introduction

Acute hemorrhage remains one of the primary causes of trauma mortality (1). Monitoring strategies that better inform medical responders of the amount of blood loss, need for interventions, and risk of shock are needed to improve patient outcomes (2). A number of techniques have been explored for this purpose including the assessment of heart rate and blood pressure variability (3, 4). As blood loss occurs, physiological compensation feedback mechanisms are triggered that can generate an oscillatory pattern in the heart rate and blood pressure dynamics (5). It is not clear if these dynamics are from a common source or represent independent physiological systems during the progression of hemorrhage. This knowledge could have implications for the development of new prognostic indicators of hemorrhage. If the oscillations are independent of each other, the variability assessed from each may represent specific systems. If the oscillations are common, then a more robust measure may be developed that can utilize values obtained from either if one is not available due to noise. To assess if heart rate and blood pressure oscillations are common, we can assess the phase synchronization between them. Phase coherence quantifies the consistency of the phase relationship over time in oscillatory dynamics between signals and is used for assessing synchronization between electroencephalographic (EEG) signals (6).

In this study, we explored the phase coherence between arterial blood pressure components (pulse-pulse interval, systolic pressure and pulse pressure) to determine their relationships during the various stages of hemorrhage and as a potential marker of impending hemodynamic decompensation.

2. Methods

2.1. Description of experiments

Data were obtained from a previously reported experiment approved by the Institutional Animal Care and Use Committee of the University of Texas Medical Branch (7). Adult sheep (N=7) were surgically prepared while under anesthesia with femoral arterial and venous catheters for bleeding and pressure monitoring and allowed one week to recover before initiating the experiments. For each sheep, hemorrhage experiments were performed one, two, or three times with at least 7 days recovery time between each experiment. Fourteen total conscious hemorrhage experiments were performed over the 7 animals.

The hemorrhage experiment consisted of physiological monitoring during a baseline period of at least 5 minutes followed by a hemorrhage of 25 mL/kg$_{Body\text{-}Weight}$ occurring over 15 minutes. After completion of the hemorrhage, monitoring continued during for at least 5

minutes. During each experiment femoral arterial pressure was continuously recorded at a sampling rate of 1,000 Hz (PowerLab, AD Instruments, Castle Hill, Australia).

2.2. Phase coherence analysis

Data analysis was performed by custom code written in MATLAB R2013A (The Mathworks, Inc., Natick, MA). Femoral arterial pressure data was first low-pass filtered with a cut-off frequency of 10 Hz and down-sampled to 20 Hz. A derivative-based pulse detector was used to identify the onset times of each pulse from the arterial pressure waveform to determine the pulse-pulse interval, systolic blood pressure and pulse pressure sequences. Beat-to-beat sequences were then linearly interpolated to 20 Hz.

The continuous wavelet transform was applied to generate a time-frequency spectral representation, W(t,s) for each of the pulse-pulse interval, systolic blood pressure and pulse pressure sequences as

$$W(t,s) = \frac{1}{\sqrt{s}} \int_{-\infty}^{\infty} x(\tau)\Psi^*\left(\frac{\tau - t}{s}\right) d\tau \quad (1)$$

where x(τ) is the measured time sequence, *s* represents the wavelet scale and Ψ^* the complex conjugate of the wavelet function. The Morlet wavelet function was used with a center frequency ω_o of 6,

$$\psi(t) = \pi^{-1/4} e^{i\omega_o t} e^{-t^2/2}. \quad (2)$$

Phase coherence was assessed between all combinations of the pulse-pulse interval, systolic blood pressure, and pulse pressure in high frequency (0.15 – 1 Hz), low frequency (0.06 – 0.15 Hz), and very low frequency (0.02 – 0.06 Hz) regions. These regions were modified from traditional heart rate variability high and low frequency regions to account for the wide range in respiratory rates observed during the baseline period in the conscious sheep and strong oscillations occurring in the very low frequency region after the hemorrhage. For each frequency region, the maximum amplitude from the wavelet spectrum at every sample was determined to identify the dominant frequency across time. The phase at each sample, $\varphi(t)$, was then extracted from the wavelet phase spectrum.

Mean phase coherence was computed as the absolute value of the mean exponential difference between the continuous phases (φ_1 and φ_2) of two signals (6),

$$\text{Phase Coherence} = \left| \frac{1}{N} \sum_{k=1}^{N} e^{i(\varphi_1(k) - \varphi_2(k))} \right|. \quad (3)$$

Phase coherence was assessed over 5 minute periods between the baseline, peak compensation and a decompensation phase. The peak compensation period was defined as the 5 minutes preceding the peak heart rate. The decompensation period was defined as the 5 minute period beginning 2 minutes after the peak heart rate. The decompensation period from one experiment was excluded from analysis due to periods of significant motion artifacts in the arterial pressure waveform that did not enable the phase of oscillations to be assessed.

Phase coherence values between the baseline, peak compensation, and decompensation periods were compared with a linear mixed effects model that included the effect of the hemorrhage number (whether the experiment was the animal's first, second or third hemorrhage) using SAS 9.3 (SAS Institute Inc., Cary, NC). The three time-periods were compared as a repeated effect with the Tukey-Kramer correction. All data are reported as mean ± standard deviation.

3. Results

Femoral arterial blood pressure waveforms were broken down into their pulse-pulse interval, systolic blood pressure, and pulse pressure sequences, Figure 1.

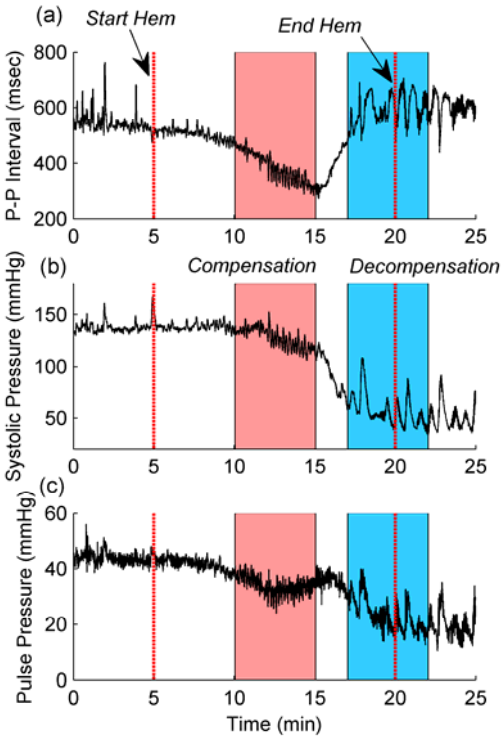

Figure 1. Continuous (a) pulse-pulse interval, (b) systolic blood pressure, and (c) pulse pressure during a single hemorrhage experiment. Dashed red lines indicate the start and stop times of hemorrhage and the red and blue rectangles indicate the peak compensation and decompensation periods used for analysis, respectively.

During hemorrhage, the pulse-pulse interval decreases till reaching a minimum value and then rising. While the

pulse-pulse interval is dropping the systolic blood pressure is relatively stable, but after the minimum pulse-pulse interval is reached the systolic blood pressure drops dramatically. This demonstrates how the rise in heart rate compensates for the loss of blood, but eventually the heart rate no longer rises and a period of decompensation begins.

A fast rhythm is observed to develop in each component prior to the minimum pulse-pulse interval (maximum heart rate) during the peak compensation period. A slower rhythm is observable during the decompensation period after the systolic blood pressure has dropped in each of the signals.

Relationships in phase coherence vary between the three frequency regions and the different combinations of the pulse-pulse interval sequence, systolic blood pressure and pulse pressure, Figure 2. There are no significant changes in phase coherence in the high frequency region between baseline, compensation, and decompensation for any of the signal pairs. However, there is a trend towards higher phase coherence in this region between the systolic and pulse pressure sequences going from baseline to compensation to decompensation.

During the peak compensation period, phase coherence is significantly higher in the low frequency region between the pulse-pulse interval sequence and

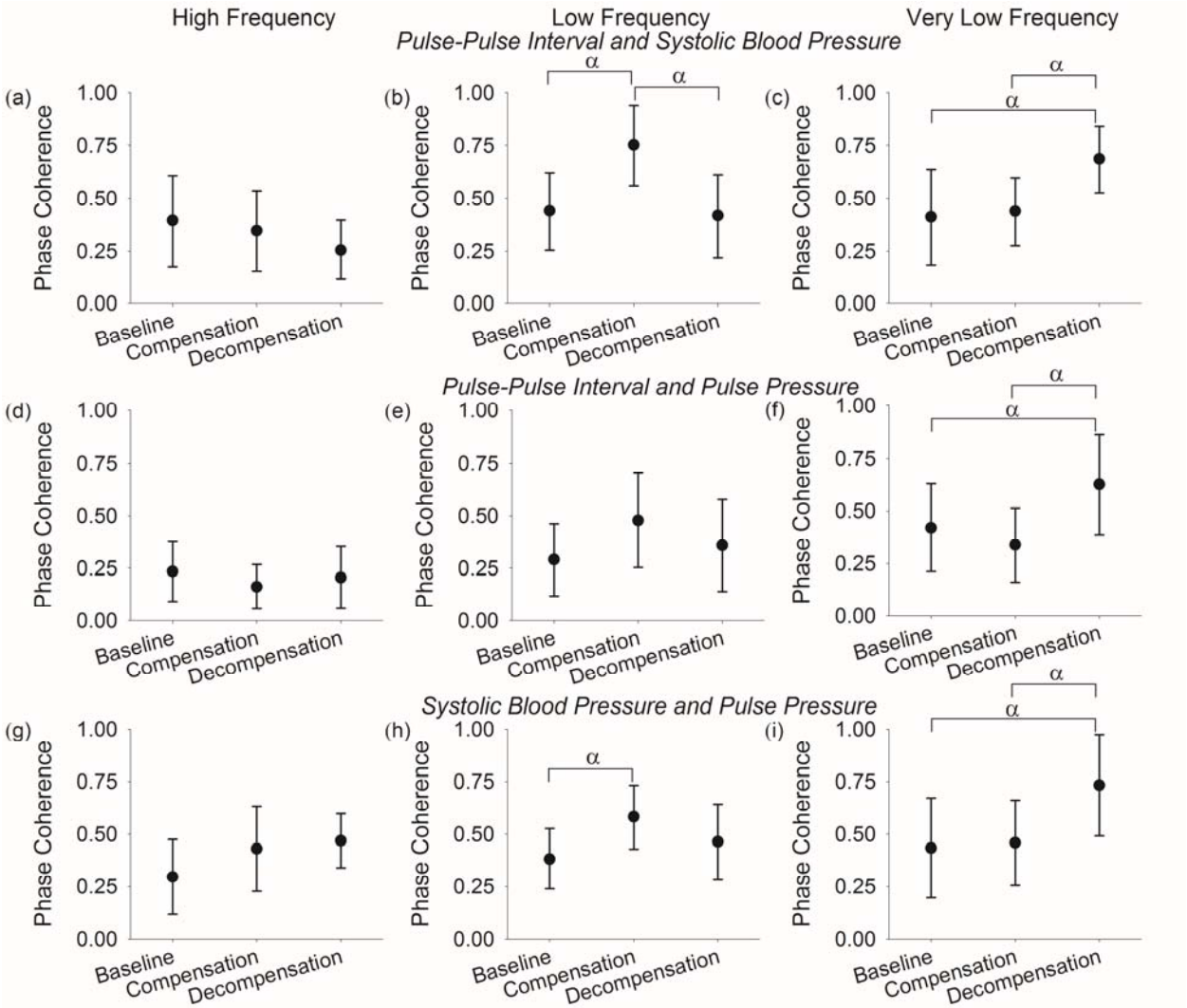

Figure 2. Phase coherence for the high (1st column), low (2nd column) and very low (3rd column) frequency regions during the baseline, peak compensation and decompensation periods. Results are shown for the phase coherence between the pulse-pulse interval and systolic blood pressure (top row), pulse-pulse interval and pulse pressure (middle row), and systolic blood pressure and pulse pressure (bottom row). Filled circles indicate mean phase coherence and bars indicate standard deviation. α represents significance with $p<0.05$ between the noted time points.

systolic blood pressure (0.44 ± 0.18 to 0.75 ± 0.19, p = 0.036) as well as systolic blood pressure and pulse pressure (0.38 ± 0.14 to 0.58 ± 0.15, P = 0.036). There is a rise in phase coherence during the decompensation period in the very low frequency region between all signal pairs from both baseline and peak compensation levels.

4. Discussion

Phase coherence between arterial pressure components varied during the response to hemorrhage. In the low and very low frequency regions, there was a similar response between the three signal pairs. In the high frequency region, systolic and pulse pressure had a trend towards increasing phase coherence. High frequency phase coherence between the pressure signals and the pulse-pulse interval sequence did not share this trend.

High phase coherence in the low frequency region during peak compensation between the pulse-pulse interval and systolic pressure indicate that the oscillations occurring have a consistent phase relationship. This suggests that the oscillations in the low frequency region during peak compensation are from a common physiological source. Similarly, the very low frequency oscillations observable in Figure 1 during the decompensation period also have high phase coherence.

Batchinsky et al. previously showed a reduction in high frequency heart rate variability during hemorrhage in anesthetized sheep (8). This may explain the trend of diminished high frequency phase coherence seen between the pulse-pulse interval and systolic blood pressure signals. As the effect of the respiratory sinus arrhythmia decreases in the heart rate signal there are no dominant respiratory oscillations to be synchronized with those in the blood pressure signal.

It has previously been shown that heart rate variability measures can distinguish groups of patients undergoing central hypovolemia from those that are not, but have limited predictive power for any individual patient due to significant inter-patient variability (4). Assessment of heart rate and blood pressure variability using advanced analytical techniques, such as phase coherence, may identify more specific biomarkers from the physiological signals. Advanced assessment of signals can also be affected by noise and use of signal quality assessment strategies including fusing information from multiple sources may help to overcome this aspect for a practical trauma monitor (9).

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References

[1] Dutton RP, Stansbury LG, Leone S, Kramer E, Hess JR, Scalea TM. Trauma mortality in mature trauma systems: are we doing better? An analysis of trauma mortality patterns, 1997-2008. The Journal of Trauma 2010;69:620-6.

[2] Shackelford SA, Colton K, Stansbury LG, Galvagno Jr SM, Anazodo AN, DuBose JJ, et al. Early identification of uncontrolled hemorrhage after trauma: Current status and future direction. Journal of Trauma and Acute Care Surgery 2014.

[3] Zollei E, Paprika D, Makra P, Gingl Z, Vezendi K, Rudas L. Human autonomic responses to blood donation. Auton Neurosci 2004;110:114-20.

[4] Ryan KL, Rickards CA, Ludwig DA, Convertino VA. Tracking central hypovolemia with ecg in humans: cautions for the use of heart period variability in patient monitoring. Shock (Augusta, Ga) 2010;33:583-9.

[5] Madwed JB, Cohen RJ. Heart rate response to hemorrhage-induced 0.05-Hz oscillations in arterial pressure in conscious dogs. The American Journal of Physiology 1991;260(4 Pt 2):H1248-53.

[6] Mormann F, Lehnertz K, David P, E. Elger C. Mean phase coherence as a measure for phase synchronization and its application to the EEG of epilepsy patients. Physica D: Nonlinear Phenomena 2000;144:358-69.

[7] Ying H, Bonnerup CA, Kirschner RA, Deyo DJ, Michell MW, Kramer GC, editors. Closed-loop fuzzy control of resuscitation of hemorrhagic shock in sheep. 24th Annual Conference and the Annual Fall Meeting of the Biomedical Engineering Society EMBS/BMES Conference; 2002.

[8] Batchinsky AI, Cooke WH, Kuusela T, Cancio LC. Loss of complexity characterizes the heart rate response to experimental hemorrhagic shock in swine. Critical Care Medicine 2007;35:519-25.

[9] Liu N, Cancio L, Salinas J, Batchinsky A. Reliable real-time calculation of heart-rate complexity in critically ill patients using multiple noisy waveform sources. J Clin Monit Comput 2013:1-9.

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