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Abstract

During the acute phase of hemorrhage, heart rate and peripheral resistance increases to maintain proper oxygen delivery to vital organs. This response is mediated by the autonomic nervous system. Heart rate variability (HRV) has become a widely utilized measure to determine the autonomic nervous system control over the heart. Recently, pulse rate variability (PRV) has been suggested to serve as a surrogate for HRV. This study evaluates the ability of PRV obtained from peripheral arterial pressure waveforms as a method for detecting hemorrhage. Time domain and frequency domain metrics were evaluated for 5-minute and 15-minute arterial pressure waveform signals prior to hemorrhage, during acute hemorrhage, and after the commencement of hemorrhage in four porcine subjects. PRV analysis demonstrates an increase in time domain and frequency domain metrics at the onset of hemorrhage, followed by an opposing decrease at the commencement of hemorrhage. The frequency domain metrics associated with sympathetic input increased at the onset of hemorrhage and decreased once hemorrhage ended. These results suggest that PRV metrics obtained from arterial pressure waveforms have the potential to serve as a diagnostic method for acute hemorrhage.

Abstract Word Count: 184 words

Introduction

Traumatic injury is the leading cause of death among young individuals, and approximately 20% to 40% of deaths following traumatic injury occurs after hospital admissions and are potentially preventable with rapid hemorrhage control [1, 2]. Therefore, early detection and accurate diagnosis of hemorrhage is essential to decreasing mortality rates among trauma patients. Currently, detection and diagnosis of hemorrhage relies on physical examination and traditional vital signs such as heart rate, arterial oxygen saturation, and blood pressure which lack the sensitivity to detect acute changes in blood volume and could remain normal until approximately 1 to 1.5 L of blood loss [3-5].

The compensatory response to hemorrhage occurs in two stages: the first stage is initiated by a progressive increase in sympathetic vasoconstriction, peripheral resistance, and heart rate to maintain arterial blood pressure at approximately normal levels, then, when approximately 20-30% of blood volume is lost, the second stage is initiated by reducing the sympathetic input, which results in a decrease in peripheral resistance and blood pressure [5, 6]. Since

this compensatory response is controlled by the autonomic nervous system, a method of measuring the autonomic nervous system activity may offer the ability to detect acute hemorrhage.

Heart rate variability (HRV) is a signal composed of the beat-to-beat intervals of the heart, which has been identified as a tool for assessing autonomic nervous system activity [7]. Traditionally, HRV is applied to long-term electrocardiogram (ECG) signals. Since the peripheral arterial and venous signals are affected by the change in peripheral resistance and the change in heart rate, peripheral pressure waveforms may provide greater sensitivity to detecting changes in blood volume. Recently, studies have shown that pulse rate variability (PRV) metrics can be acquired from the venous waveform and may serve as a surrogate for HRV [8].

There is growing evidence that the venous pressure waveform has the ability to detect acute changes in blood volume; however, the arterial vasculature is more susceptible to vasoconstriction and vasodilation, therefore, this study has chosen to focus analysis on the peripheral arterial signal [9]. The purpose of this study is to evaluate the utility of the PRV metrics derived from the peripheral arterial pressure waveform as a method for detecting acute hemorrhage.

Methods

Study Population

In a controlled animal study, arterial pressure waveforms were obtained from four female porcine subjects. The average weight of the subjects was 72.8 ± 1.6 kg, and the average age was 16.8 weeks old with all four subjects having an age between 16 and 17 weeks.

Instrumentation and Signal Acquisition

Each subject was anesthetized under isoflurane at a 1.5% minimum alveolar concentration and propofol at a concentration of 0.05 mg/kg/min prior to instrumentation. The femoral arterial pressure signal was collected by an MLT0670 disposable blood pressure transducer (ADInstruments). The pressure transducer was connected by MLAC11 Grass adapter cables (ADInstruments) to an FE221 bridge amplifier (ADInstruments). The output from the amplifier was then connected to a USB-6009 data acquisition system (National Instruments) by BNC-to-BNC cables. This data acquisition device, then interfaced with LabVIEW (National Instruments) to record the pressure waveform with a sampling frequency of 1000 Hz.

After instrumentation, a baseline 15-minute recording was collected prior to hemorrhage. Continuous 15-minute recordings were taken as each subject was exsanguinated at a rate of 0.4 cc/s from the arterial sensor.

Approximately 20% blood volume was removed from each subject during the 15-minute signal during hemorrhage. After the hemorrhage commenced, a 15-minute recording was collected during the recovery phase.

Signal Analysis and Post Processing

Each 15-minute signal was maintained for post processing and then divided into three smaller 5-minute signals for short term PRV analysis. The collected femoral arterial pressure waveforms were passed through a low-pass filter with a normalized frequency of 15 Hz to exclude noise from other instruments in the room. Then, a beat-detection algorithm was utilized to determine the location of each pulse in the filtered 15-minute signals. The time difference between each pulse, or the R-R interval, was extracted for each signal. An adaptive filter was implemented to detect and remove abnormal beats and noise disturbances. This filter was applied to the R-R intervals to create a normalized N-N interval time series that excluded any R-R intervals less than 20 milliseconds or that were greater than three standard deviations away from the moving average.

PRV Analysis

From the time domain, three PRV indices were calculated in accordance with the standards of measurement guidelines from the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [7]. The time domain HRV indices that were utilized in this study are as follows:

- Mean: the mean N-N interval in milliseconds.
- STD: the standard deviation of N-N intervals for the entire signal in milliseconds.
- RMS: the root mean squared difference between successive N-N intervals

The power spectra of the linearly interpolated, equally spaced tachograms were taken to determine four PRV indices in the frequency domain. The frequency domain PRV indices that were utilized in this study are as follows:

- LF: the power of the low frequency band from 0.04-0.15 Hz measured in ms^2
- HF: the power of the high frequency band from 0.15-0.4 Hz measure in
- P: the total power of the power spectra measure in
- LF/HF: the ratio between LF and HF

Statistical Analysis

Across each porcine subject the percent change from before hemorrhage to during hemorrhage and during hemorrhage to after hemorrhage was assessed for each PRV metric obtained from the 15-minute signal. For each PRV metric, a one-way analysis of variance (ANOVA) was conducted to determine if a statistical difference was present between the average of the four subjects across each 5-minute signal. In the one-way ANOVA groups 5, 10, and 15 corresponding to the 5-minute intervals prior to hemorrhage, groups 20, 25, and 30 corresponding to the 5-minute intervals during hemorrhage, and groups 35, 40, and 45 corresponding to the 5-minute intervals after hemorrhage.

Results

15-Minute Analysis

The percent change in mean, STD, RMS, LF, HF, P, and LF/HF between the 15-minute recordings are reported in Table 1 and 2. Table 1 reports the percent change from before hemorrhage to during hemorrhage across all four porcine subjects, and Table 2 reports the percent change from during hemorrhage to after hemorrhage across all four porcine subjects.

Table 1- The percent change in PRV metrics from before hemorrhage to during hemorrhage for the 15-minute signals.

Time Domain	**Pig 1**	**Pig 2**	**Pig 3**	**Pig 4**
Mean	2.0%	-10.8%	3.5%	24.5%
STD	1343.8%	1129.5%	399.3%	701.8%
RMS	1493.6%	1416.1%	1036.0%	964.5%
Frequency Domain	**Pig 1**	**Pig 2**	**Pig 3**	**Pig 4**
LF	644706.9	243108.3%	101639.2%	25292.8%
HF	39783.8%	12663.8%	12533.6%	12047.073%
P	27744.2%	13359.0%	2223.8%	6542.2%
LF/HF	492.4%	1820.8%	706.9%	111.4%

Table 2- The percent change in PRV metrics from during hemorrhage to after hemorrhage for the 15-minute signals.

Time Domain	**Pig 1**	**Pig 2**	**Pig 3**	**Pig 4**
Mean	39.9%	-9.0%	32.1%	4.2%
STD	4.9%	-92.7%	22.7%	-32.6%
RMS	10.1%	-94.1%	51.6%	-18.3%
Frequency Domain	**Pig 1**	**Pig 2**	**Pig 3**	**Pig 4**
LF	-64.5%	-100.0%	-58.4%	-60.6%
HF	-44.4%	-99.5%	91.3%	-13.4%
P	-57.0%	-99.4%	-4.2%	-58.2%
LF/HF	-36.2%	-95.8%	-78.3%	-55.2%

From before hemorrhage to during hemorrhage, there was a large, positive percent change across all four porcine subjects for the STD, RMS, LF, HF, P, and LF/HF. The percent change in mean N-N intervals increased across three pigs and decreased for one pig from the 15-minutes before hemorrhage to the 15-minutes during hemorrhage.

From the 15-minute signal during hemorrhage to the 15-minute signal after hemorrhage, there was a negative percent change in LF, P, and LF/HF across all four porcine subjects. HF had a positive percent change for one subject and a negative percent change for three subjects. The time domain metrics revealed a positive percent change in STD and for two subjects with a negative percent change for the remaining two subjects. The percent change in mean N-N intervals increased across three pigs and decreased for one pig from the 15-minutes during hemorrhage to the 15-minutes after hemorrhage.

5-Minute Analysis

Post-hoc analysis of the one-way ANOVA results comparing the mean N-N intervals revealed no significant difference between any groups. The box-plot comparison of the mean N-N intervals across the nine 5-minute signals is depicted in Figure 1.

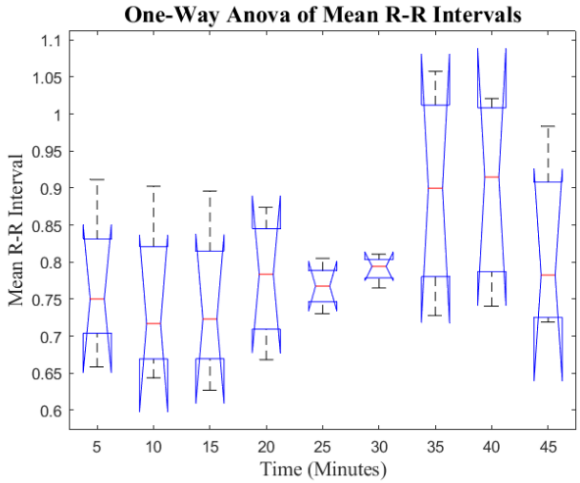

Figure 1- Boxplot comparison of the mean N-N intervals across nine 5-minute PRV signals.

The STD of N-N intervals obtained from the 5-minute PRV signals showed a substantial increase at the onset of hemorrhage, followed by two progressively smaller increases as hemorrhage continued. Additionally, there was a decrease in standard deviation from the last 5-minutes. Post-hoc analysis determined that groups 25 and 30 were significantly different than the three baseline recordings (groups 5, 10, and 15). Boxplot comparison of our samples average STD values across all nine 5-minute PRV signals is presented in Figure 2.

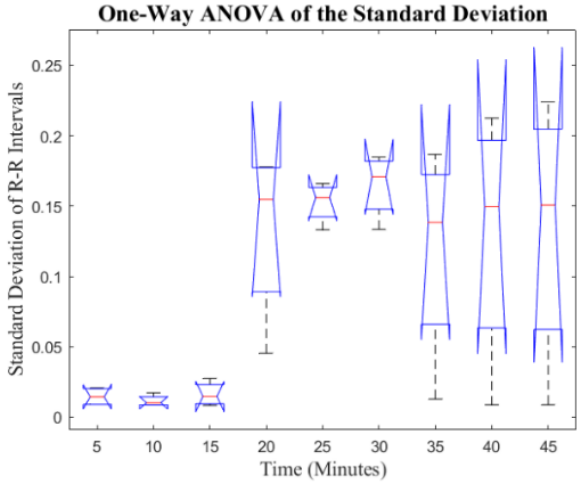

Figure 2- Boxplot comparison of the standard deviation of the N-N intervals across nine 5-minute PRV signals.

The one-way ANOVA comparing the average RMS value across all nine 5-minute PRV signals revealed an increase at the onset of hemorrhage and a sustained increase as hemorrhage progressed. At the end of hemorrhage, a drop in RMS values was seen. The boxplot representation of this comparison is depicted in Figure 3. Post-hoc analysis revealed a significant difference in the RMS values obtained in group 30 as compared to the recordings from baseline (groups 5, 10, and 15).

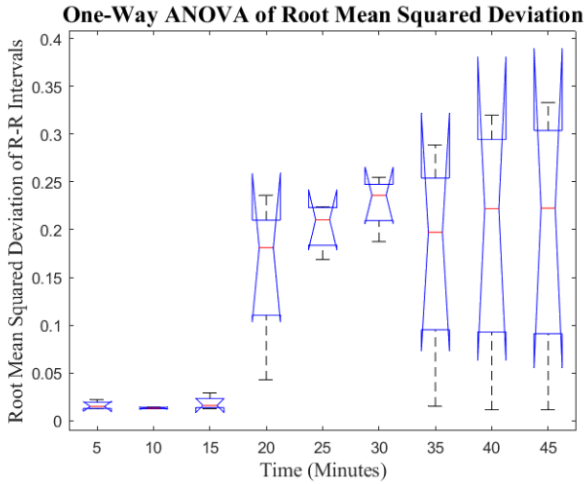

Figure 3- Boxplot comparison of the root mean standard deviations of the N-N intervals across nine 5-minute PRV signals.

At the onset of hemorrhage, there was an increase in HF, and, as hemorrhage continued, HF continually increased. Then, when hemorrhage ended, there was a decrease in the average HF value. Post-hoc analysis of the one-way ANOVA revealed no significant difference between any of the nine groups of 5-minute signals. The box plot comparison of the average HF values across all nine 5-minute signals is displayed in Figure 4.

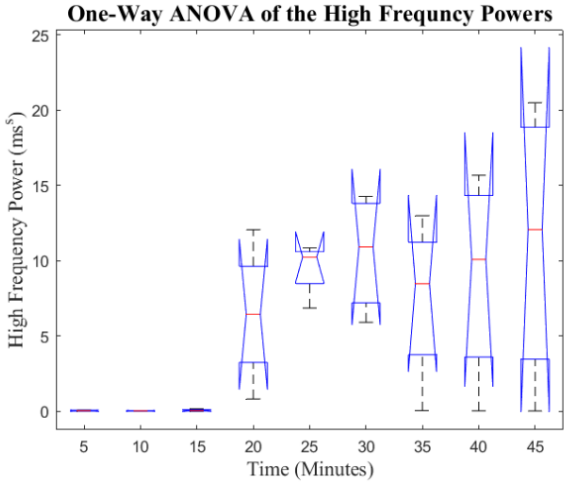

Figure 4- Boxplot comparison of the high frequency power across nine 5-minute PRV signals.

The boxplot comparison of the 5-minute analysis of LF, represented in Figure 5, demonstrates an increase in LF at the onset of hemorrhage and a decrease in LF as hemorrhage commenced. Post-hoc analysis of the results from the one-way ANOVA revealed that the LF values for the groups during hemorrhage (groups 20, 25, and 30) were significantly different than the groups during baseline recording (groups 5, 10, and 15). Additionally, it was found that final group during hemorrhage (group 30) was significantly different than the first group after hemorrhage ended (group 35).

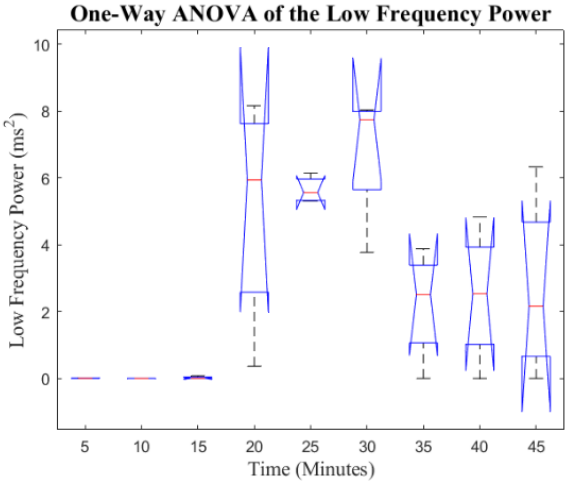

Figure 5- Boxplot comparison of the low frequency power across nine 5-minute PRV signals.

One-way ANOVA results comparing the total power across all nine 5-minute PRV signals demonstrated an increase in power throughout hemorrhage and decrease once hemorrhage was concluded. The post-hoc analysis revealed that the last 5-minute signal during hemorrhage (group 30) was significantly different than all 5-minute baseline recordings (groups 5, 10, and 15). The boxplot comparison of these results is portrayed in Figure 6.

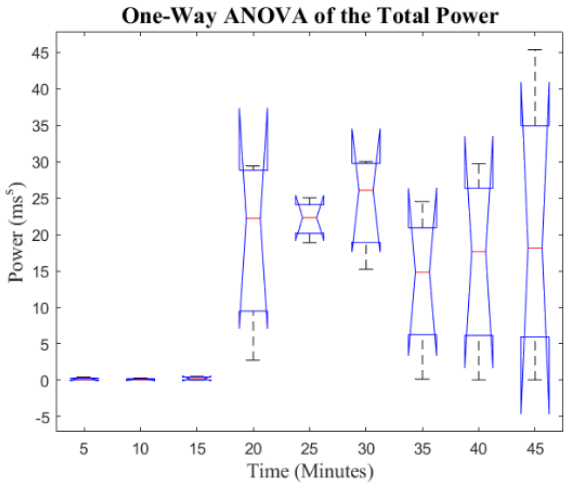

Figure 6- Boxplot comparison of the total power across nine 5-minute PRV signals.

The analysis of the change in LF/HF across the 5-minute signals revealed an increase in the LF/HF ratio at the onset of hemorrhage followed by a decrease in the LF/HF ratio once hemorrhage was completed. The boxplot comparison of the LF/HF ratio across all nine 5-minute signals is shown in Figure 7. Post-hoc analysis of the one-way ANOVA results displayed a significant difference between the groups during hemorrhage (groups 20, 25, and 30) and the baseline groups prior to hemorrhage (groups 5, 10, and 15). Additionally, it was found that the first group during hemorrhage (group 20) was significantly different than all the groups after hemorrhage (groups 35, 40, and 45) and the last group during hemorrhage (group 30) was significantly different than two groups after hemorrhage (group 35 and 45). The multi-comparison of the last group during hemorrhage (group 30), displayed in blue, compared to all other groups is portrayed in Figure 8.

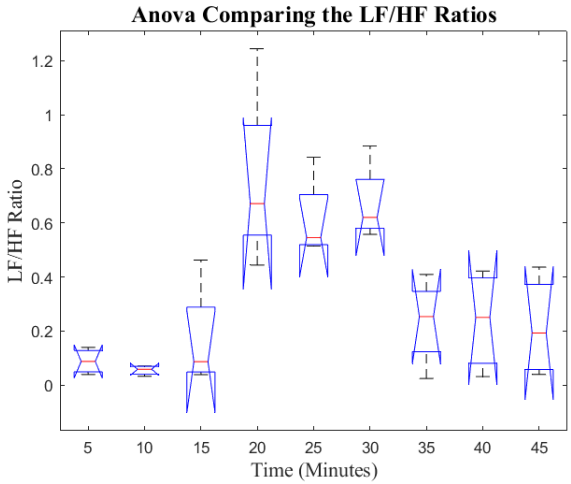

Figure 7- Boxplot comparison of the ratio of low frequency power to high frequency power across nine 5-minute PRV signals.

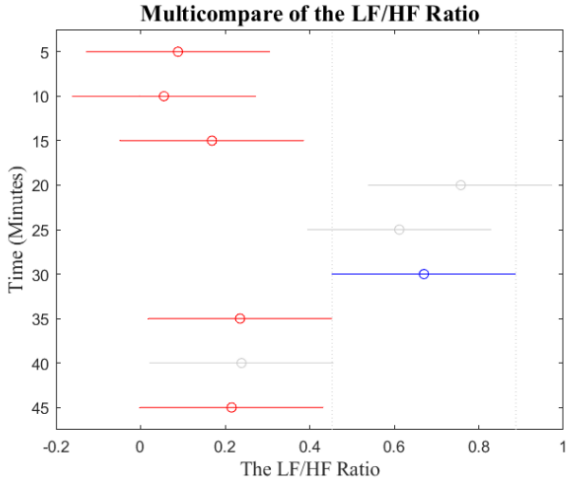

Figure 8- The comparison of the ratio of low frequency power to high frequency power in group 30 to the ratio of low frequency power to high frequency power across all 5-minute PRV signals. Group 30, corresponding to the last 5-minute signal during hemorrhage, is displayed in blue. All groups that are significantly different than group 30 are displayed in red.

Discussion

The physiological response to hemorrhage occurs in two distinct phases. The first phase is associated with an increase in heart rate and peripheral resistance in order to maintain a near normal blood pressure, which has been shown to fall by only a few mmHg after approximately 25% blood loss [6]. The second stage is associated with failure of baroreceptor mediated recovery and results in a dramatic drop in heart rate and peripheral resistance, which results in an accompanying drop in blood pressure [6, 10]. Once patients enter the secondary decompensatory phase of hemorrhage, there is insufficient oxygen delivery to organs resulting in hemorrhagic shock [5].

Hemorrhagic shock can directly lead to early fatality and has been identified as a predictor of poor outcomes in injured patients [11]. Additionally, one common therapeutic approach to mitigating adverse effects of hemorrhagic shock is the use of red blood cell transfusions, which has been associated with multiple organ failure, increased intensive care unit admissions, increased length of hospital stays, and mortality [11, 12]. Therefore, identification of hemorrhage prior to the decompensatory phase may decrease adverse effects of traumatic injury and may lead to a decrease in the mortality rates associated with hemorrhage.

Since the initial physiological response to hemorrhage is mediated by sympathetic input into baroreceptors, tools that can identify sympathetic activity, such as heart rate variability (HRV), may be able to detect acute hemorrhage with greater sensitivity than traditional vital signs. Recently, studies have found that pulse rate variability (PRV) obtained from piezoelectric recording of venous pressure waveforms can be used as a surrogate for HRV [8]. While the venous and arterial pressure waveforms are both affected by the change in heart rate, the arterial vasculature is more susceptible to the vasoconstriction that occurs during the acute phase of hemorrhage [9]. Therefore, PRV analysis obtained from the arterial pressure waveform may be able to detect the early sympathetic input associated with acute hemorrhage.

In this study, we evaluate the utility of peripheral arterial pressure waveforms for 15-minute and 5-minute short-term PRV signals. The initial reduction of blood volume, less than approximately 20%, results in the initial compensatory response, so we would expect to see an increase in heart rate and a decrease in the N-N intervals as hemorrhage begins and an opposing decrease in heart rate and increase in N-N intervals after hemorrhage stops. Additionally, previous studies have reported a decrease in mean N-N intervals obtained from HRV at the onset of hemorrhage [13]; however, in this study, we found that the mean N-N intervals during the 15-minute signals increased for three subjects and a decreased for one subject with a total range in percent change from –10.8% to 24.5% across

all four pigs. Additionally, after hemorrhage commenced, there was a continued increase in the mean N-N intervals across three subjects and a decrease for one subject. This large variability demonstrates that on an individual basis, the mean N-N interval from 15-minute short-term PRV may not be a reliable method for detecting acute hemorrhage.

Further analysis in the time domain of the 15-minute signals aligned with expectations and previously reported trends in HRV indices at the onset of hemorrhage. We saw that the standard deviation and root mean squared deviation of N-N intervals during the 15-minute signals provided cohesive results with all four porcine subjects seeing a positive percent change at the onset of hemorrhage. This suggests that standard deviation and root mean squared deviation of N-N intervals may provide the ability to detect the onset of acute hemorrhage. From during hemorrhage to after hemorrhage, there was a continued increase in standard deviation and root mean squared deviation for two subjects and a decrease for the remaining two subjects. These results demonstrate that the standard deviation and root mean squared deviation obtained from the 15-minute PRV signals may not be able to detect the end of hemorrhage.

Across all four porcine subjects, LF, HF, total power, and the LF/HF ratio was increased from before hemorrhage to during hemorrhage in the 15-minute PRV signals. Furthermore, opposing trends were observed in the 15-minute signals from during hemorrhage to after hemorrhage resulting in a decrease in LF, total power, and the LF/HF across all four porcine subjects. The HF values of the 15-minute signals from during hemorrhage to after hemorrhage demonstrated a negative percent change across three porcine subjects and a positive percent change in one porcine subject. These results demonstrate that the frequency domain metrics form the 15-minute signals may have a higher sensitivity to detect the onset and the commencement of hemorrhage than the time domain metrics. Among the frequency domain metrics, it was seen that the LF values and the LF/HF ratio provided a greater ability to detect the commencement of hemorrhage than the HF values.

LF values have been associated with sympathetic activity such as thermoregulation, peripheral vasomotor activity, and baroreflex function, therefore, we hypothesize that this increase in LF values at the onset of hemorrhage may be attributed to the increase in peripheral resistance that occurs during the acute phase of hemorrhage [7, 14]. The HF values have been associated with parasympathetic activations such as respiration, which may be attributed to a rise in respiration to maintain proper oxygen delivery to tissues during the acute phase of hemorrhage [7, 14].

The LF/HF ratio is a PRV metric that has been suggested to reflect the balance between sympathetic and parasympathetic activation [7, 14]. Therefore, the increase in the LF/HF ratio at the onset of hemorrhage demonstrates that the power in the frequency domain dominates in the low frequency range, which has been associated with a high

sympathetic activity and low parasympathetic activity [7, 14]. Additionally, the decrease in the LF/HF ratio at the end of hemorrhage demonstrates that as hemorrhage commenced the power in the frequency domain begins to shift back into the high frequency range. These results align with our general understanding of the physiological response to hemorrhage. This suggests that the LF/HF ratio may provide a proper indication of the acute phase of hemorrhage.

Further analysis of the 5-minute short term PRV signals reveals that the frequency domain metrics provides greater sensitivity to acute hemorrhage than the time domain metrics. The mean N-N intervals had no significant difference across all hemorrhage statuses. This demonstrates that the mean N-N interval of 5-minute PRV signals may not be sensitive enough to detect hemorrhage. The standard deviation and the root mean squared deviation showed greater sensitivity than the mean N-N intervals by having one or two of the 5-minute signals during hemorrhage show significantly different values than the three baseline recordings; however, none of the signals during hemorrhage were significantly different than the three 5-minutre PRV signals after hemorrhage ended. This demonstrates that the time domain metrics may not have the sensitivity to detect the immediate onset of hemorrhage and do not have the ability to detect the commencement of hemorrhage; however, the standard deviation and root mean squared deviation do have the sensitivity to differentiate between PRV metrics in the acute phase of hemorrhage and baseline PRV metrics.

In the frequency domain, the HF values during the 5-minute PRV signals increased throughout hemorrhage and decreased at the end of hemorrhage; however, there was no significant difference across all hemorrhage statuses. This shows that 5-minute analysis of the high frequency power may not be a viable metric to indicate acute hemorrhage. The total power in the frequency domain showed similar increases throughout hemorrhage with the last 5-minute signal providing a significantly different power than the three baseline recordings prior to hemorrhage. This shows that the total power in the frequency domain of 5-minute HRV signals may not have the sensitivity to detect the early onset of hemorrhage, but it does have the ability to detect hemorrhage during the acute phase.

The LF values were shown to increase during hemorrhage and decrease at the commencement of hemorrhage. The 5-minute analysis revealed that all three 5-minute PRV signals during hemorrhage were significantly different than the three 5-minute PRV signals prior to hemorrhage. This demonstrates that the LF values of 5-minute PRV signals can detect the onset and continuation of hemorrhage. Additionally, it was found that the final group during hemorrhage was significantly different than the first 5-minute interval after hemorrhage. This suggests that the LF values have the ability to differentiate between the onset and commencement of hemorrhage.

The 5-minute analysis of the LF/HF ratio demonstrated the greatest ability to detect hemorrhage by showing significant differences between all groups during hemorrhage and all baseline recording groups prior to hemorrhage. Additionally, the first group during hemorrhage was found to be significantly different than every group after hemorrhage ended and the last 5-minute signal during hemorrhage had significantly different LF/HF ratios than the first and last 5-minute signal after hemorrhage. These results suggest that the LF/HF ratio has the sensitivity to detect the onset of hemorrhage, the continuation of hemorrhage, and the commencement of hemorrhage. Across all PRV metrics evaluated in this study, the LF/HF ratio of 5-minute PRV signals demonstrated the greatest ability to detect hemorrhage.

Conclusion

During the acute phase of hemorrhage, traditional vital signs are insufficient measures for detecting hemorrhage. This study shows that PRV obtained from a peripheral arterial pressure waveforms can serve as an indicator of hemorrhage status during the acute phase. Opposing trends in PRV metrics were found at the onset of hemorrhage and at the commencement of hemorrhage. The results suggests that the 5-minute signals provided a greater sensitivity to detecting changes in blood volume status than the 15-minute signals. Furthermore, it was found that the frequency domain metrics provided a greater sensitivity to the changes in blood volume than the time domain metrics. It was found that the frequency domain metrics from 5-minute PRV signals provided the greatest sensitivity to detecting changes in hemorrhage status, with the low frequency powers and the ratio of low frequency power compared to the high frequency power providing the greatest ability to determine the onset of hemorrhage and the commencement of hemorrhage.

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