ABSTRACT
During hemorrhagic shock and after resuscitation, the left ventricular pressure (LVP) and volume (LVV) vary over time. This study investigates and characterizes the LVP and LVV signals in the frequency and time domains in a hemorrhagic shock-resuscitation model. 40% of blood volume was withdrawn from anesthetized hamsters to induce moderate hemorrhagic shock conditions. A single volume infusion of the plasma expander (Hextend: hydroxyethyl starch) was administered after 30 min of the beginning of hemorrhagic shock. LVP and LVV were measured using a miniaturized pressure-volume conductance catheter. The fast Fourier transform and trajectory plot of both signals were performed for frequency and time domain analysis, respectively. Preliminary results show that, during shock stage, the amplitudes of the LVP spectrum at the 2nd and 4th harmonics were significantly higher compared with baseline and 30 min after resuscitation (p<0.01). We also found that the trajectory plot of LVP showed a markedly difference between normal conditions at baseline and the shock condition. However, there was no significant information in the LVV signal either in frequency or time domain during hemorrhagic shock-resuscitation. These findings demonstrated the applicability of frequency and time domains analysis of LVP signal for use as an alternative diagnostic tool.

KEY WORDS
signal analysis, left ventricular pressure, left ventricular volume, hemorrhagic shock.

1. Introduction
Blood loss during accidental injury or physical trauma causing multi-organ failure is a critical issue in the emergency care unit. Fluid resuscitation is required to manage blood loss. Hemorrhage caused by massive blood loss affects the pumping function of the heart, especially to pressure and volume features. During hemorrhagic shock and resuscitation, left ventricular pressure and volume change over time due to the compensatory mechanisms and volume replacement. Using nonlinear analysis in the frequency and time domains has revealed interesting characteristics in blood pressure in particular pathological conditions [1-3] suggesting that signals of left ventricular pressure and volume might contain useful information about hemorrhagic shock-resuscitation. The objective of this study was to investigate and characterize the left ventricular pressure and volume waveforms in frequency and time domains in an anesthetized animal during hemorrhagic shock-resuscitation. We used a miniaturized conductance catheter to measure variation of left ventricular pressure and volume. In this study, we apply the fast Fourier transform (FFT) and a trajectory plot, a nonlinear analysis, to characterize the signals in frequency and time domains, respectively.

2. Materials and Methods
2.1 Animal preparation
Studies were performed in anesthetized male Golden Syrian hamsters (Charles River Laboratories, Boston, MA) weighing 60-70g. Animal handling and care followed the NIH Guide for Care and Use of Laboratory Animals. The experimental protocol was approved by the local animal care committee. Surgery was performed with the animals anesthetized with sodium pentobarbital (50 mg/kg, i.p.). The left jugular vein and left femoral artery were catheterized for fluid infusion, blood pressure monitoring and blood withdrawal. Tracheotomy was performed and cannulated with a polyethylene-90 tube to facilitate spontaneous breathing. Animals were put in the supine position on the heating pad to maintain body temperature. A small bolus of sodium pentobarbital (10-15 mg/kg, i.p.) was given during the experiments if the animals responded to a toe pinch.

2.2 Inclusion criteria
Animals under anesthesia were suitable for the experiments if animals had no surgical bleeding and systemic parameters were within the normal range, namely, mean arterial blood pressure (MAP) above 80
mmHg, heart rate (HR) above 320 beats/minute and systemic hematocrit (Hct) above 45%.

2.3 Hemorrhagic shock-resuscitation protocol

Anesthetized animals were withdrawn 40% of estimated blood volume (BV) via the femoral artery catheter within 15 minutes to induce a moderate hemorrhage. The total BV was estimated as 7% of body weight. The shock condition was maintained for 30 minutes and at this time the animal was resuscitated with the plasma expander, Hextend (Hospira, IL), delivered through a jugular vein catheter in a volume equal to 50% of withdrawn blood volume, within 10 minutes. The animals were monitored for 60 minutes after resuscitation. This protocol is schematically shown in Figure 1.

2.4 Left ventricular pressure and volume

Figure 2 shows the experimental setup to acquire left ventricular pressure and volume signals. The closed chest method was performed to measure left ventricular pressure and volume.[4] The right common carotid artery was exposed allowing a 1.4F pressure-volume conductance catheter (PV catheter; SPR-839, Millar Instruments, TX) to be inserted. The PV catheter was advanced passing through the aortic valve into the left ventricle. The pressure and volume signals were instantaneously digitized and acquired (MPVS300, Millar Instruments, TX and PowerLab 8/30, ADInstruments, CO).

2.5 Signal analysis

The FFT was performed for both left ventricular pressure and volume waveforms using a commercial software built-in algorithm (DADiSP and Matlab). A trajectory plot or a return map, plotting between data at i and i+n where i is initial time point and n is preferred subsequent time, was applied to analyze time-series data of left ventricular pressure and volume.

2.6 Statistical analysis

Data between interesting time points and frequencies were analyzed using two-way ANOVA and followed by Bonferroni post test. All statistics were calculated using GraphPad Prism 4.01 (GraphPad Software, San Diego, CA). Results were considered statistically significant if \( p<0.05 \).

In this study, all animals survived from hemorrhagic shock (n=6; weight 62.5±2.0 g; baseline HR 453±18 bpm). Figure 3 presents left ventricular pressure signal in the time domain and the frequency-domain magnitude spectrum at baseline and 30 min after hemorrhage. The frequency-domain magnitude spectrum of left ventricular pressure showed a highest peak at the fundamental frequency (1x) which is the heart beat frequency in both baseline and shock conditions. There were other peaks at the higher harmonics such as 2x, 3x and 4x.

Figure 4 shows the relative amplitude of left ventricular pressure from frequency-domain magnitude spectra at baseline, during hemorrhagic shock and after resuscitation. The amplitudes of left ventricular pressure spectrum at the second harmonic (2x) and the fourth harmonic (4x) were significantly enhanced (p<0.01), suggesting that these might be the characteristics of hemorrhagic shock in the frequency domain.
The trajectory plots of left ventricular pressure waveforms normalized to their maximum value at different time points are presented in Figure 5. From these plots, we can distinguish the difference between a normal condition at baseline and a hemorrhagic shock condition as marked on the top-right corner in the Figure 5.

Figure 5. Representative trajectory plots of left ventricular pressure signal normalized to maximum value at baseline, 30 min hemorrhagic shock and 60 min after resuscitation.

Figure 6. Representative left ventricular volume signals and FFT spectrums at 30 min after hemorrhage.

There was no significant peak at higher harmonics for the frequency-domain magnitude spectrums of left ventricular volume at baseline and during hemorrhagic shock (Figure 6). Therefore, no statistical analysis was performed for the frequency-domain magnitude spectrums of left ventricular volume signals.

Figure 7 shows trajectory plots of left ventricular volume signal normalized to maximum value at different time points. There was a high variability in the trajectory plot of left ventricular volume signal at each time point.
4. Discussion

Our preliminary results indicate that left ventricular pressure waveform analyzed with FFT and trajectory plot show distinguishable characteristics between baseline, hemorrhagic shock and after resuscitation. Conversely, although the same analysis performed on left ventricular volume waveform showed differences between baseline and hemorrhagic shock-resuscitation, there was no specific feature that clearly differentiated these signals.

Several studies applied spectral and nonlinear analysis to blood pressure or other hemodynamic signals to detect and predict pathological conditions or abnormal condition after treatment.[2, 5, 6] As observed in the cardiac cycles, left ventricular pressure and volume periodically change over time. Acute massive blood loss, in case of hemorrhagic shock, significantly decreases blood volume and preload as well as blood pressure. Therefore, left ventricular pressure and volume are markedly affected during blood loss. Our results indicate that the higher amplitude of left ventricular pressure spectrum at harmonic 2x and 4x (as shown in figure 4) and the complex top-right corner of the trajectory plot (as marked with red squares in figure 5) are the characteristics of hemorrhagic shock. After resuscitation, we found that the amplitudes of left ventricular pressure spectrum at harmonic 2x and 4x were reduced to the baseline level as a result of the volume expansion effect of Hextend. This volume expansion effect was also clearly noticed in a trajectory plot of left ventricular pressure which returned to a shape of the trajectory plot similar to that at baseline. However, in some animals, after resuscitation, a trajectory plot of left ventricular pressure deviated from the baseline, implying that the effect of volume expansion was attenuated (as occurred in animal # 5 shown in Figure 5).

As blood volume decreases during hemorrhage, autoregulation pulls interstitial fluid from tissues into blood vessels in response to compensatory mechanisms. Therefore, preload is affected during this form of autoregulation as well as after fluid resuscitation. In this study, there were no significant distinguishable peaks in the frequency-domain magnitude spectrum of left ventricular volume between baseline, during hemorrhagic shock and after resuscitation. Furthermore, the trajectory plots of left ventricular volume highly varied between each time point of interest, unlike the trajectory plots of left ventricular pressure. This variation might suggest the complexity or no stability of the left ventricular volume measurement.

Similar information contained in left ventricular pressure and volume signals, as we found in this animal study, could be found when applying the frequency and time domains analysis to the human left ventricular pressure and volume signals during hemorrhagic shock and resuscitation. However, this diagnostic technique requires a catheter to measure pressure and volume inside the left ventricle which is an invasive technique. Therefore, at this stage, this is a critical limitation in applying this methodology to bedside monitoring.

5. Conclusion

This preliminary study suggests that left ventricular pressure waveform can provide specific information about hemorrhagic shock-resuscitation conditions in both frequency and time domains much clearer than left ventricular volume waveform.

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References