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Original Article

Critical Information from High Fidelity Arterial and Venous Pressure Waveforms During Anesthesia and Hemorrhage

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Abstract
Purpose—Peripheral venous pressure (PVP) waveform analysis is a novel, minimally invasive, and inexpensive method of measuring intravascular volume changes. A porcine cohort was studied to determine how venous and arterial pressure waveforms change due to inhaled and infused anesthetics and acute hemorrhage.
Methods—Venous and arterial pressure waveforms were continuously collected, while each pig was under general anesthesia, by inserting Millar catheters into a neighboring peripheral artery and vein. The anesthetic was varied from inhaled to infused, then the pig underwent a controlled hemorrhage. Pearson correlation coefficients between the power of the venous and arterial pressure waveforms at each pig's heart rate frequency were calculated for each variation in the anesthetic, as well as before and after hemorrhage. An analysis of variance (ANOVA) test was computed to determine the significance in changes of the venous pressure waveform means caused by each variation.
Results—The Pearson correlation coefficients between venous and arterial waveforms decreased as anesthetic dosage increased. In an opposing fashion, the correlation coefficients increased as hemorrhage occurred.
Conclusion—Anesthetics and hemorrhage alter venous pressure waveforms in distinctly different ways, making it critical for researchers and clinicians to consider these confounding variables when utilizing pressure waveforms. Further work needs to be done to determine how best to integrate PVP waveforms into clinical decision-making.

Keywords—Peripheral venous pressure, Inhaled anesthetic, Hemorrhage, Cross-talk between venous and arterial circulations.

INTRODUCTION

Hemorrhage is the second leading cause of death for Americans between the ages of one to forty-six, despite approximately 20–40% of deaths involving massive hemorrhage being potentially preventable with rapid hemorrhage control.[10,14] The current standard for evaluating intravascular volume status and dehydration, however, relies on clinicians' interpretation of vital signs, physical exam signs, and urine output—all of which lack sensitivity to early blood loss.[17,20] This lack of sensitivity limits the ability to diagnose dehydration and detect early hemorrhage.[17,20]

Analysis of the minimally invasive peripheral venous pressure (PVP) waveforms have shown a greater sensitivity to acute changes in blood volume than traditional vital signs.[2–7,13,16] This is because the venous system is highly sensitive to changes in blood volume due to the large proportion of blood circulating within the venous tree and its high compliance.[12,24] Recent studies have proven that PVP waveform analysis in the frequency-domain can significantly detect acute blood loss as compared to traditional vital signs.[3,8] Specifi-

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cally, researchers have utilized the power spectral density (PSD) of the PVP signal.[1–8,13,16] The PSD is the visualization of a signal's power content across a range of frequencies, and in PVP research, peak power is often seen at the heart rate and respiratory rate frequencies.[25] Through the use of a PSD, correlations can be found in the PVP waveform between the power contributions at the heart rate frequency and changes in blood volume.[2,3,6,7,13] One recent use of PSD analysis occurred when Alian et al. discovered that heart rate frequencies were significantly reduced during mild hypovolemia.[2] It was proposed that this change in the venous pressure waveform at the heart rate frequency was due to the right atrium pulse pressure not being transmitted from the central venous pressure back (against flow direction) to the peripheral venous pressure in states of low venous blood volume.[2] Other recent studies have utilized PVP PSDs to determine strong correlations between the arterial and venous pressure waveforms at the heart rate frequency.[1,7]

Despite a growing understanding of the venous pressure waveform, the arterial pressure waveform has been more widely used than the venous signal.[11,22] Traditionally, the arterial pressure waveform has been easier to interpret because it is stronger than the venous signal, but, with the recent development of amplifying technologies, small changes in the venous pressure waveform may be detected. Given that the majority of current clinically available hemodynamic monitors focus on the arterial waveform and with the growing body of research supporting the potential for the venous pressure signal to detect acute changes in blood volume, it is vital to understand the relationship between the venous and arterial signals.[22] We believe that understanding this relationship could improve the sensitivity of current clinical technologies or lead to developing novel clinical monitors. In this study, we will evaluate the relationship between venous and arterial pressure waveforms throughout varying levels of anesthetic and hemorrhage.

The ability for the PVP waveform to detect acute hemorrhage combined with the arterial vasoconstriction associated with blood loss makes hemorrhage an ideal model for evaluating vasoconstricting effects on the relationship between the arterial and venous pressure waveforms.[23] While studies have evaluated the effects of vasoconstricting agents on the peripheral venous waveform in a controlled animal study, studies that evaluate the effects of vasodilating agents were found in a clinical setting.[1,6] Therefore, there remains the need to validate the effects of vasodilating agents in a controlled animal study. General anesthetics such as propofol and isoflurane, which are known vasodilators, are routinely used within trauma surgeries, where changes in intravascular volume are common. As vasodilators, anesthetics increase the proximity of neighboring arteries and veins.[15,19] Bonasso et al. proposed an additional hydromechanical interaction that states that the close physical proximity of veins and arteries allows for arterial pulse pressure to cross over into the venous system.[7] This hydromechanical interaction differs from the mechanism proposed by Alian et al. because it relies on the pulse pressure waveform that travels through the arterial tree from the aorta.[1] Bonasso proposes that as arteries dilate, they will become physically closer, which increases the "cross-talk," or the transfer of pulse pressure from the arterial system into the venous system.[1,7] Bonasso's hydromechanical interaction is illustrated in Fig. 1 to illustrate the hypothesis of an arteries effect on its neighboring vein under varying hemodynamic conditions.

While PVP waveforms continue to be studied to assess intravascular volume, it is critical to understand the effect of anesthesia on the waveform in a controlled hemorrhage experimental setting and the corresponding relationship between the artery and vein. This study aims to determine the effects of anesthetic vasodilation and hemorrhagic vasoconstriction on PVP waveforms and the relationship between venous and arterial pressure waveforms in a controlled setting. We hypothesize anesthetics and hemorrhage will produce contrasting effects on both the PVP waveform and the relationship between the arterial and venous pressure waveforms.

METHODS

Porcine Demographics

Four female pigs with an average weight of 72.8 ± 1.6 kg were entered into the study. The average age was 16.8 weeks.

Acquiring the High Fidelity Pressure Data

Porcine data was collected during a controlled animal study at the Arkansas Children's Hospital Research Institute. Venous and arterial pressure waveforms were measured with SPR-350S Millar Mikro-Tip Pressure Catheters *(Millar, Inc.)* in the first two porcine subjects and SPR-320 Millar Mikro-Tip Pressure Catheters in the second two porcine subjects. The SPR-320 Catheters were used in the last two trials because they were more easily guided through the narrow vasculature. The catheters were inserted in the extremity such that the catheter tips were anatomically within 4cm to each other, allowing a more accurate detection of mechanical crossover between the artery

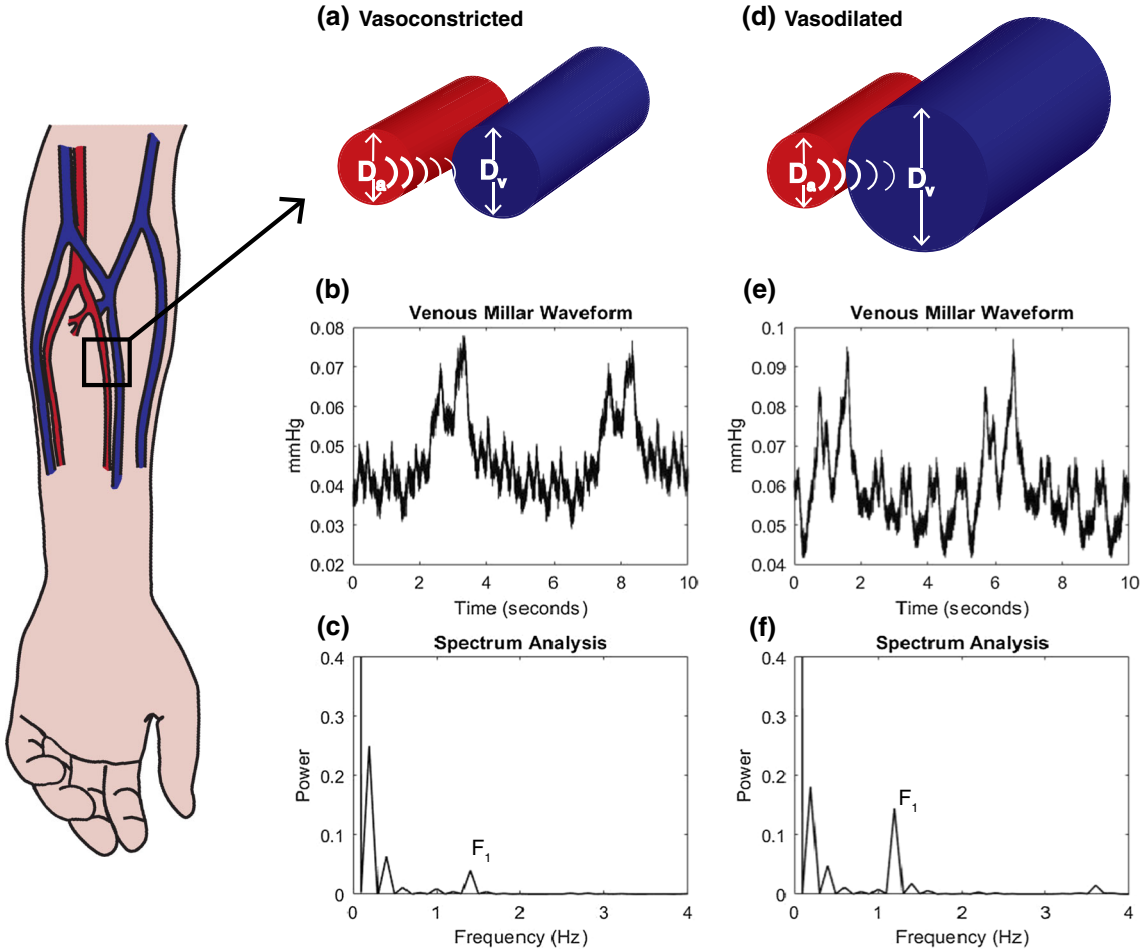

FIGURE 1. Illustration of the hydromechanical interaction, or cross-talk, proposed in Bonasso et al. (a) Under vasoconstriction, there is a lack of physical proximity between veins and arteries. (b) The venous pressure waveform on a 10-second interval for a vasoconstricted subject is used to generate the (c) power spectral density characterized by a peak at F_1, the heart rate frequency. (d) In a vasodilated state, there is a physical proximity between veins and arteries that allows for the pulse pressure to move from the artery to the neighboring vein. (e) The venous pressure waveform on a 10 second interval gives the corresponding (f) power spectral density characterized by an increase in F_1 in a vasodilated state.

and vein. In the first experiment the catheters were placed directly into the internal jugular vein and carotid artery and threaded downward to the extremity vessels. In all other samples, the catheters were placed in the radial artery and vein and passed centrally to a similar final location as in the first subject. The venous catheter was advanced in all cases to the inferior aspect of the superior vena cava (ultrasound placed) and the arterial catheter advanced to match. As shown in Fig. 2, the Millar Catheter tip locations were confirmed using a BK5000 Ultrasound system *(BK Medical)*, showing the transducer tips were approximately 2cm apart in the axial direction and less than 1cm apart in the radial direction. The axial direction was also controlled by using markers on the catheters, which ensured that the length of catheter inserted was approximately the same, within 5mm. Post-operative dissection confirmed that the axial/radial distances between the tip of the catheters were consistently less than 40mm/10mm.

The Venous and Arterial Millar Catheters were attached to a Millar PCU-2000 Pressure Control Unit *(Millar, Inc.)* via a pair of PED-10D cables. The Millar PCU-2000 then sent analog voltage signals for each catheter to a NI USB-6009 *(National Instruments)* data acquisition system via 1/4 inch phono-to-BNC cables. The NI USB-6009 interfaced with LabVIEW *(National Instruments)* with a USB to record the waveforms. The data acquisition setup is illustrated in Fig. 3. The venous and arterial pressure waveforms were sampled at a frequency of 1000 Hz. Each pig underwent varying levels of inhaled and infused anesthetics and was then subjected to a controlled hemorrhage until the estimated intravascular volume decreased by 20%. This is shown in Fig. 3 and details are stated in the following paragraph.

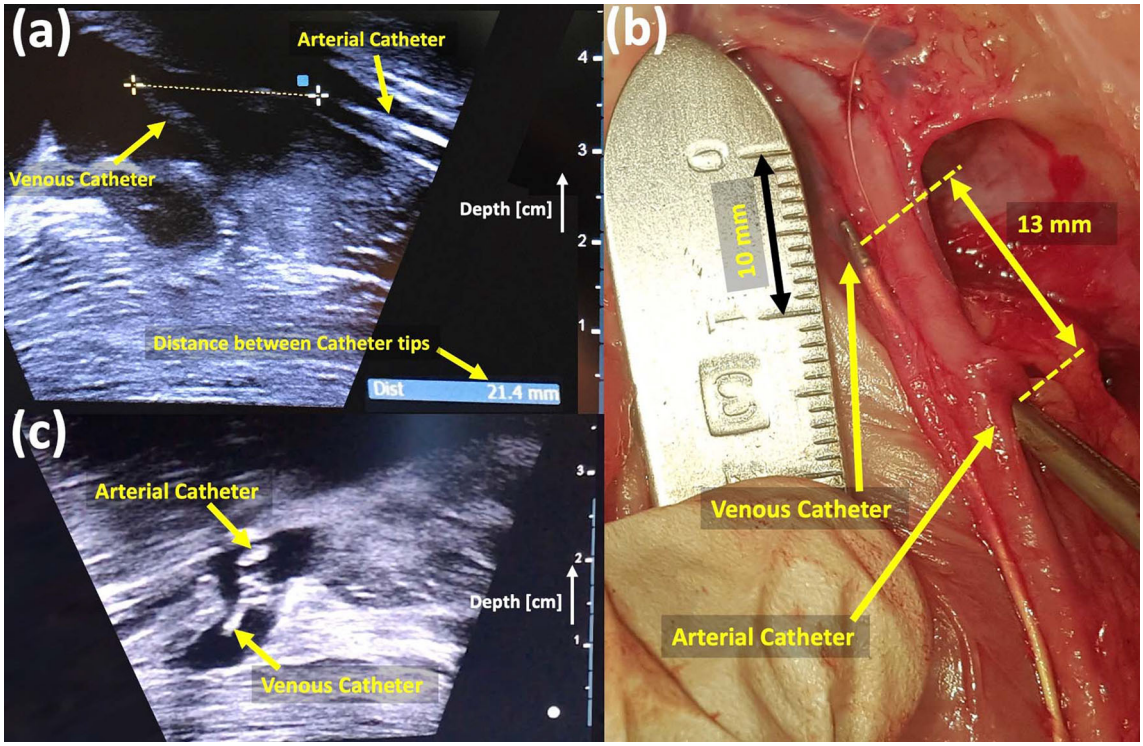

FIGURE 2. Indications of Millar pressure catheter tip distance proximity: (a) The axial distance was targeted at less than 4cm, which was confirmed during the experiments by ultrasound examination before measurements as well as (b) during post-op dissection. (c) The radial proximity near the tip of the catheters was also confirmed during the experiments with ultrasound before measurements.

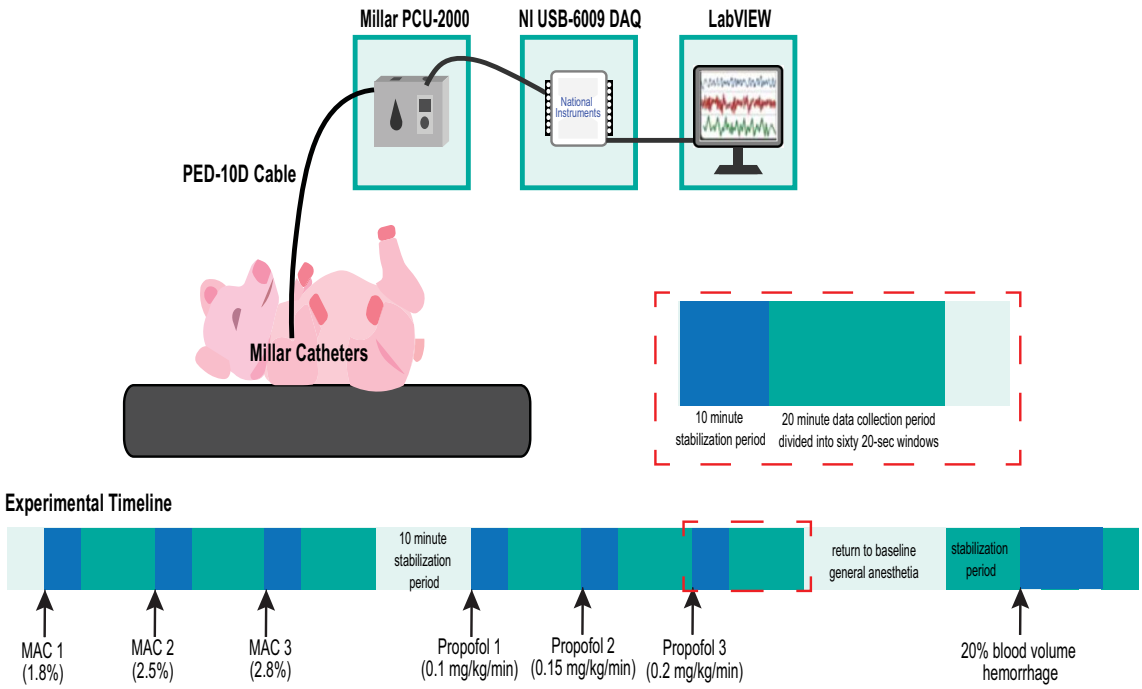

FIGURE 3. Illustration of the Arterial and Venous Millar Waveform data acquisition setup consisting of Millar Mikro-Tip Pressure Catheters *(Millar, Inc.)*, PED-10D cables, Millar PCU-200 *(Millar, Inc.)*, NI USB-6009 DAQ *(National Instruments)*, and LabVIEW *(National Instruments)*. Waveforms were viewed and data was saved on LabVIEW before being transferred for analysis in MATLAB (*MathWorks Inc.*).

Each animal was induced under general anesthesia with a fixed respiratory rate, instrumented, and left for a 10-minute stabilization period. Inhaled isoflurane anesthetics were increased to three varying levels of minimum alveolar concentration (MAC): MAC 1 (1.8%), MAC 2 (2.5%), and MAC 3 (2.8%). Anesthetic concentrations were chosen to represent a single general anesthetic level and to create a broad range of vascular system stress to optimize observable hemodynamic trends from varying anesthetic dosage. After inhaled isoflurane changes, the subjects were switched to infused propofol as the anesthetic. A stabilization period was present between the inhaled and infused anesthetics, The subjects were gradually taken off isoflurane to 1.5% before switched to 0.1 mg/kg/min propofol, and there was additional 10-minute stabilization period for propofol before data collection was performed. However, due to the inability of waking the subject in the experiment, it is unknown if the effects of the isoflurane were fully out of the subject's system. Infused anesthetics were increased to the three varying levels, Propofol 1 (0.1 mg/kg/min), Propofol 2 (0.15 mg/kg/min), and Propofol 3 (0.2 mg/kg/min). When the inhaled or infused anesthetic level was increased for each respective section, each subject underwent a 10-minute stabilization period, followed by a 15-minute data collection window. After the anesthetic returned to baseline, a 20-minute stabilization period occurred for euvolemic baseline data collection and then the porcine subject was subjected to hemorrhage of twenty percent of its blood volume over a 15-minute data collection period. Exsanguination was performed *via* central venous catheter into empty blood donation bags that were continuously weighed against a calculated total circulating blood volume. Another 20-minute stabilization period followed to collect the hypovolemic baseline.

Data Preparation

Data acquired from LabVIEW was analyzed in MATLAB R2020a (*MathWorks Inc.*). Figure 4 shows representative examples of the time domain waveforms for the venous and arterial signals under two anesthetic levels, MAC 1 and MAC 3. The figure includes only 10 seconds of the waveforms to demonstrate the shape and overall periodic oscillation due to respiration. The venous and arterial waveforms appear to be in phase with similar peaks around times 2 and 7 seconds, due to the respiratory rate of the subject. Figure 4a shows a noisier pressure waveform than Fig. 4b as respiration is more prominently seen in the venous pressure waveform. Despite the presence of noise in the venous pressure waveform, Bonasso et al. (2018) determined that this shape of the waveform would still provide accurate waveform analysis.[6]

Spectrum Analysis: Determining General Trends Across the Spectrums for Different Anesthetic and Hemorrhage Levels

A Fast Fourier Transform (FFT) was applied to the entire length of the acquired signal for both the arterial and venous waveforms. The power spectral density was plotted for the whole signal to compare the overall trends between the venous and arterial signals. The PSD of both signals indicate peaks at the same frequencies, as shown in Fig. 5. The power at the heart rate frequency, F_1, was determined for all subjects over the varying MAC, propofol, and hemorrhage levels. Continuous recordings of the heart rate were not collected during this study, and instead the heart rate frequencies for each pig were determined from the PSD, as there is a distinct peak at the heart rate frequency as shown in Fig. 5.

Spectrum Analysis: Demonstrating the Relationship Between the Arterial and Venous Waveforms

The simultaneously collected arterial and venous waveforms spanned across 135 minutes, giving 15 minutes to each variation of anesthetic or hemorrhage as displayed in Fig. 3. However, because anesthetics affect individuals differently, it was necessary to focus on changes that happen within each individual pig rather than across the whole dataset. To achieve this, the 15-minute waveforms collected under each varied setting were divided into forty-five 20-second windows. Because the overall waveform is periodic in nature, there was not a concern in creating smaller windows out of the whole waveform.

A FFT was applied to each 20-second window and the resulting PSD was plotted using MATLAB to use for statistical analysis. The magnitude of the power at the heart rate frequency, F_1, was determined from the venous and arterial PSDs. Pearson's correlation coefficients were calculated (Eq. 1) between the waveforms at the F_1 frequencies for each pig. In Eq. 1, X is the magnitude of the power at F_1 from the venous pressure waveform, and Y is the magnitude of the power at F_1 for the arterial pressure waveform.

$$\rho_{X,Y} = \frac{\sum((X-\mu_X)(Y-\mu_Y))}{\sigma_X \sigma_Y} \tag{1}$$

Statistical Analysis

An Analysis of Variance (ANOVA) test was conducted to determine whether a statistical difference was present between the mean of the venous pressure waveforms in mmHg due to anesthetic levels and volume status within each pig. The MATLAB *anova1*

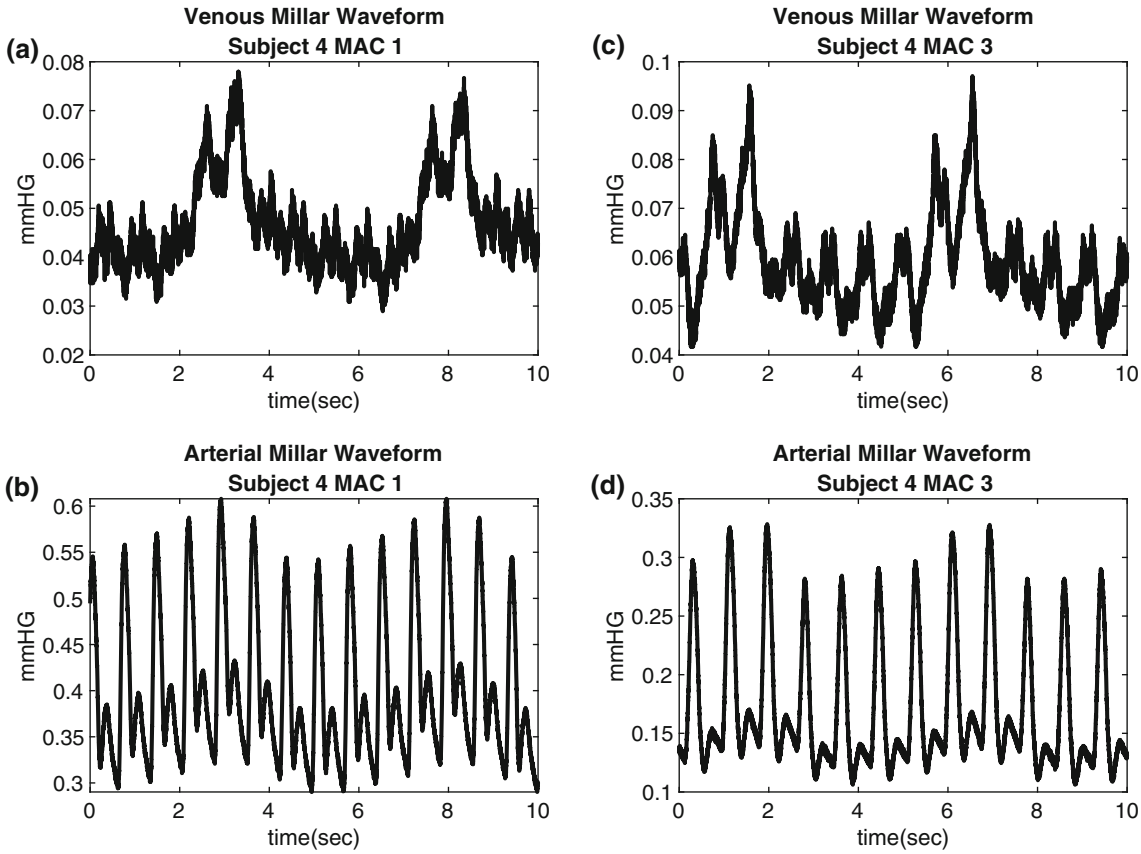

FIGURE 4. (a) Venous pressure waveform and (b) simultaneous 10-second arterial pressure waveform for porcine subject 4 while under MAC 1 inhaled anesthesia. (c) Venous pressure waveform and (d) simultaneous 10-second arterial pressure waveform for porcine subject 4 while under MAC 3.

function was used to determine the ANOVA results, and a 0.01 significance level was chosen.[18]

The venous pressure waveforms were collected for MAC 1, MAC 2, and MAC 3 for each porcine subject individually. ANOVA was conducted for each of the four subjects separately, with the dependent variable being the continuous venous waveform, and the MAC levels as the three categorical independent variables.

The venous pressure waveforms were also collected before, during, and after hemorrhage for each subject individually. The ANOVA test was conducted for each pig separately, not comparing across pigs, with the dependent variable being the continuous venous waveform, and the hemorrhage levels as three independent, categorical variables.

RESULTS

Spectrum Analysis

The full spectrum analysis allowed for interpretations based on major trends in the waveforms. The anesthetic and hemorrhage status had competing trends in the subject's heart rate frequency, F_1, and the arterial power at the same frequency. Due to the venous and arterial signals' simultaneous collection, the heart rate frequency, F_1, and consequential percent change are the same across both scenarios. A consistent decrease in the subject's heart rate frequency occurred as the inhaled anesthetic level increased, averaging an 8% decrease in heart rate frequency from MAC 1 to MAC 3. The infused anesthetic demonstrated a similar overall trend in the heart rate frequency decreasing from Propofol 1 to 3, but the results were not consistent for all four subjects like the inhaled anesthetic. As hemorrhage status changed, there was an average increase of 37% in the heart rate frequency.

The trends in the arterial power for inhaled anesthetic and hemorrhage were consistent with the trends in their heart rate frequency. However, the arterial power at F_1 increased for the infused propofol, which demonstrated a trend closer to hemorrhage rather than the isoflurane. The venous signal power trends at F_1 were not consistent for either anesthetic but was consistent for the hemorrhage model. The percent changes can be seen in Fig. 6.

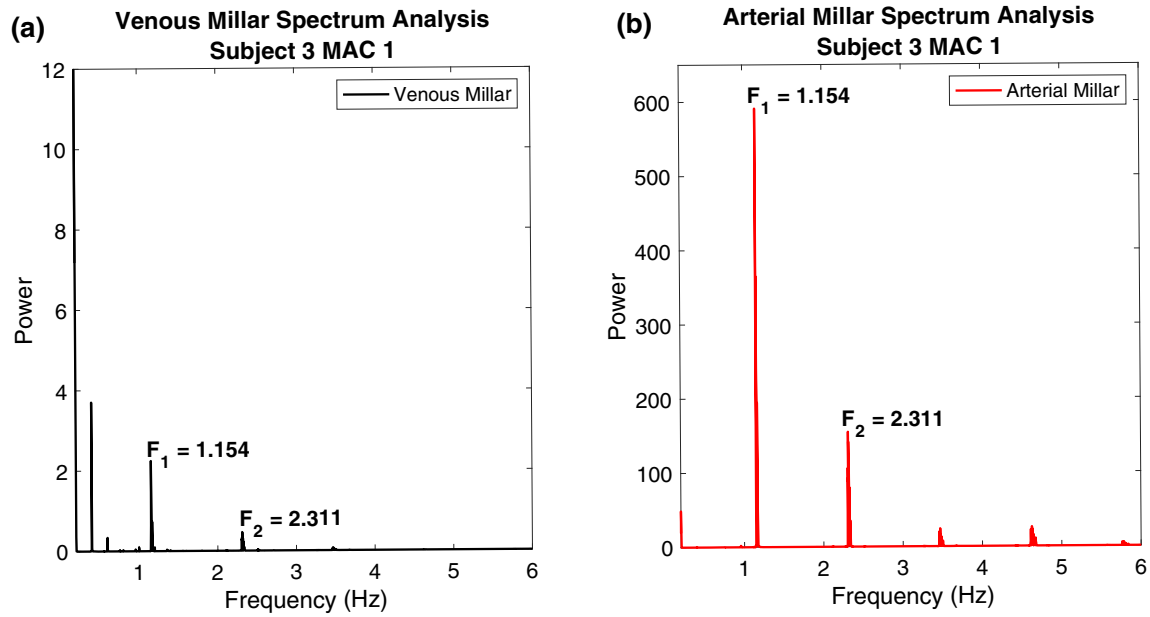

FIGURE 5. Power Spectral Density of the (a) venous pressure waveform and (b) arterial pressure waveform for porcine subject 3 while under MAC 1 inhaled anesthetic. The two plots display the pig's heart rate as F_1.

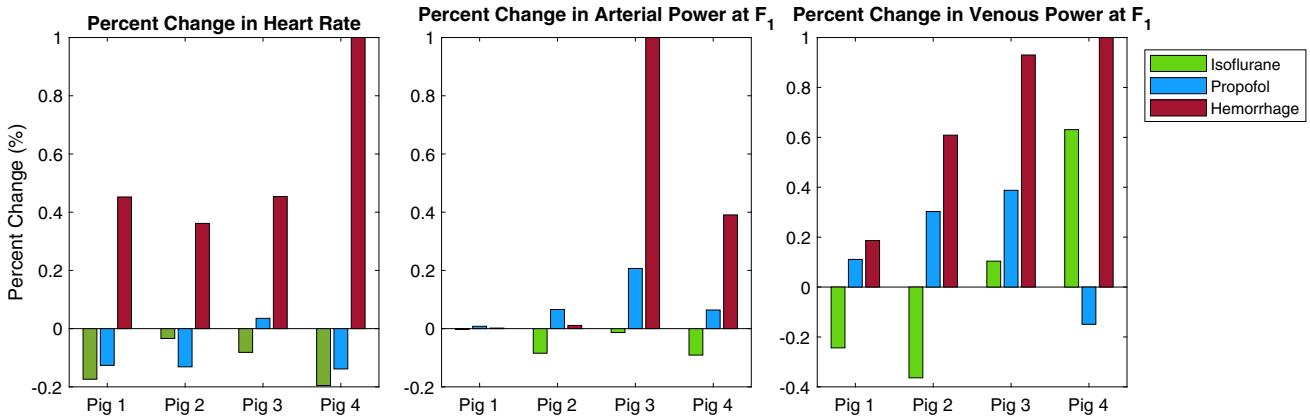

FIGURE 6. Percent changes in each pig's heart rate (left), arterial power at F_1 (middle), and venous power at F_1 (right) are shown after being influenced by isoflurane (green bars), propofol (blue bars), and hemorrhage (red bars). The percent change for each were calculated as follows: isoflurane was between MAC 1 and MAC 3, propofol was between Propofol 1 and 3, and hemorrhage was between before and after.

Relationship Between the Arterial and Venous Waveforms

The Pearson correlation coefficients between the power of the arterial and venous waveforms at the heart rate frequency under varying anesthetic and hemorrhage levels are reported in Table 1 for each pig.

There is a significant drop between the correlation at MAC 1 and MAC 3. This change in correlation can be visualized by the change in slope of the trendlines from MAC 1 to MAC 3 in Fig. 7, which shows the correlation coefficient plots for pig 1 and the two anesthetic levels. The correlation coefficient at the heart rate for infused propofol demonstrates the same drop in correlation from Propofol 1 to Propofol 3. Pig 1 does not follow this trend, but the overall trend for both inhaled and infused anesthetic shows as dosage increases, the correlation between arterial and venous circulation decreases. Since both anesthetics displayed the same trend, and inhaled isoflurane showed a more prominent drop in correlation only the plots of the isoflurane coefficients are shown in Fig. 7. The data

represented in Table 1 demonstrates no significant change between the correlations across hemorrhage levels. Figure 8 presents the correlation coefficient plots for all porcine subjects before and after hemorrhage and illustrates the stability of the correlation.

The variations of the venous pressure waveform means across anesthetic levels and hemorrhage status are displayed in Figs. 9 and 10 to exemplify the results of the ANOVA. The plots show a significant relationship between the venous signal mean and the anesthetic and hemorrhage levels. For the infused propofol, while the means were significantly different, there was no consistent trend in the mean venous pressure displayed in a boxplot. The ANOVA results for hemorrhage show that as the subject loses blood volume the mean values of the venous waveform show no clear trends. This relationship is depicted in Fig. 10. Additionally, a pairwise ANOVA was conducted for anesthetics and hemorrhage for every possible pair for porcine subjects. The p-value was <0.01 for all pairwise groups, thus demonstrating statistical differences between all mean venous pressure waveforms.

An ANOVA test was computed for the arterial pressure as well. Under the influence of both inhaled and infused anesthetics, the mean pressure in the artery dropped as anesthetic increased. The ANOVA results for arterial pressure under the hemorrhagic condition did not show a clear trend in the effect on mean pressure. Some porcine subjects had a greater arterial pressure after bleeding, while other subjects were the opposite. All ANOVAs and additional post-hoc pairwise tests for arterial pressure had a p-value less than 0.01, displaying a statistical difference amongst the arterial pressures as well.

DISCUSSION

Our results demonstrate that the relationship between venous and arterial pressure waveforms are impacted by *both* anesthetics and hemorrhage. There was a decrease in the correlation coefficient between venous and arterial pressure as the inhaled and infused anesthetics dosage increased. Similarly, the correlation coefficient increased after hemorrhage occurred for three of the four porcine subjects. Furthermore, increasing levels of isoflurane was associated with an increase in the PVP mean value, and hemorrhage demonstrated a decrease in the PVP mean value. Overall, our study displayed the hypothesized competing trends for the anesthetics and hemorrhage.

As anesthetics are vasodilators, the increase in cross-sectional area of arteries due to an increase in anesthetic level causes a decrease in resistance across the arterioles. This decrease in arterial resistance creates a drop in mean arterial pressure, or the average arterial pressure per cardiac cycle.[9] Additionally, the weakening of the mean arterial pressure is proportional to a decrease in cardiac output, which can be achieved through a reduction in heart rate, which explains the change in heart rate from MAC 1 to MAC 3 in Fig. 2.[9] The decrease in the arterial power from the addition of anesthetics displays that the vasodilation is causing a drop in the average of the pressure waveform in mmHg. Our preliminary results show that as inhaled anesthetic is increased, the mean value of the venous pressure increases. Thus, as vasodilation occurs, there is a corresponding rise in the venous system's mean pressure. However, the infused anesthetic showed no trend in the mean venous pressure from the first dose of propofol to the last, which may be due to residual isoflurane from the beginning of the study.

TABLE 1. Correlation coefficients at the heart rate frequency for varying anesthetic (MAC and Propofol) and hemorrhage status.

	Porcine Subject 1				Porcine Subject 2		
	MAC	Propofol	Hemorrhage		MAC	Propofol	Hemorrhage
1	0.98	0.95	0.97	1	0.77	0.99	0.89
2	0.96	0.95	0.95	2	0.92	0.99	0.93
3	0.68	0.99	0.98	3	0.36	0.94	0.91
	Porcine Subject 3				Porcine Subject 4		
1	0.98	0.92	0.90	1	0.89	0.99	0.95
2	0.99	0.90	0.85	2	0.77	0.92	0.97
3	0.79	0.89	0.99	3	0.65	0.87	0.95

The correlations were determined between the power of the arterial waveform and the power of the venous waveform. 1 indicates the first dose and before hemorrhage, 2 indicates the second dose and during hemorrhage, and 3 indicates the third dose and after hemorrhage for anesthetics and hemorrhage respectively.

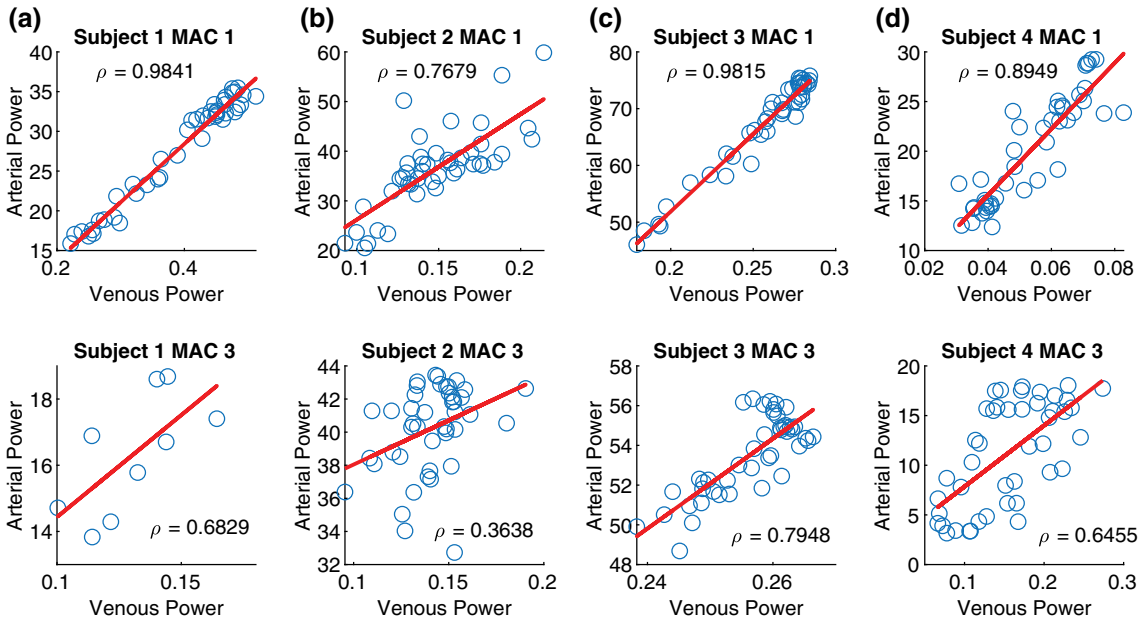

FIGURE 7. Correlation coefficient plots all four porcine subjects at heart rate frequency for MAC 1 and MAC 3 anesthetic level for (a) porcine subject 1, (b) porcine subject 2, (c) porcine subject 3, (d) porcine subject 4. The correlation coefficients for each scenario are displayed on its corresponding plot. Note: Subject 1 MAC 3 has significantly less data points due to a shorter data collection window, resultant from the subject becoming unstable at the high anesthetic dosage.

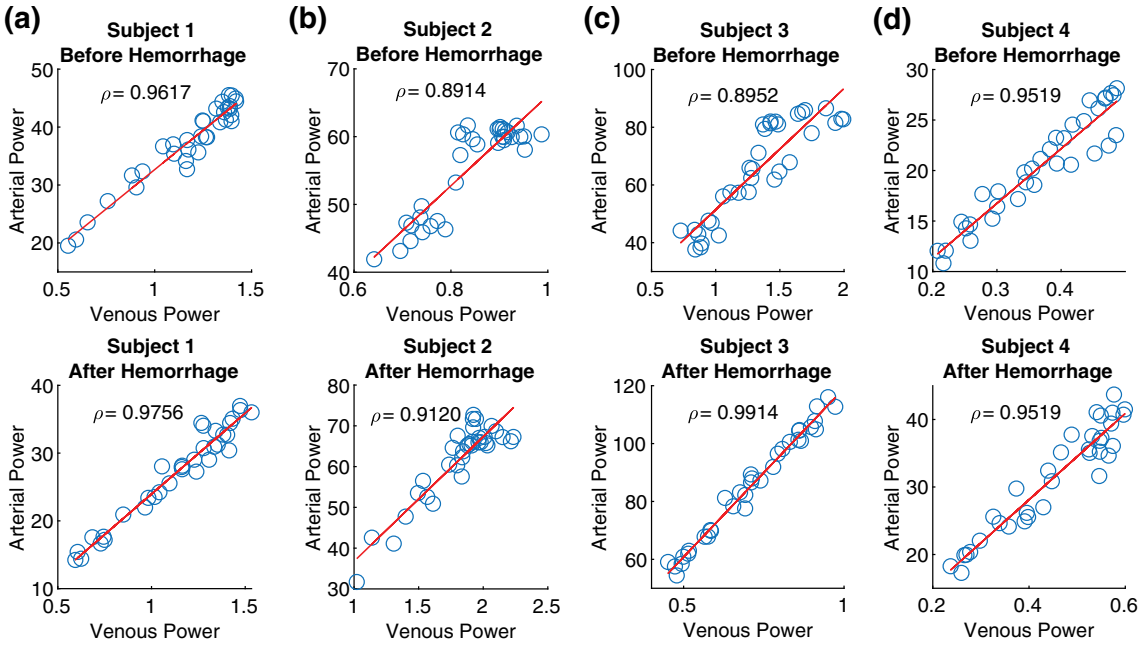

FIGURE 8. Correlation coefficient plots for all four porcine subjects at heart rate frequency before and after hemorrhage for (a) porcine subject 1, (b) porcine subject 2, (c) porcine subject 3, (d) porcine subject 4. The correlation coefficients for each scenario are displayed on its corresponding plot. ANOVA: The ANOVA p-values and F-statistics were computed and are shown in Tables 2 and 3. The tables show a significant relationship between the venous waveform and anesthetics and hemorrhage.

In contrast, the hemorrhage model shows a consistent increase in both heart rate and arterial power at the heart rate frequency. Since hemorrhage is a vasoconstricting model, it has opposing effects on arterial diameter, mean arterial pressure, and cardiac output than the vasodilating effects previously discussed.[9] Therefore, the decrease in arterial diameter corresponds to an increase in arterial power at the heart rate frequency as seen in Fig. 2. There is no clear evidence of the venous signal trends from the spectrum analysis.

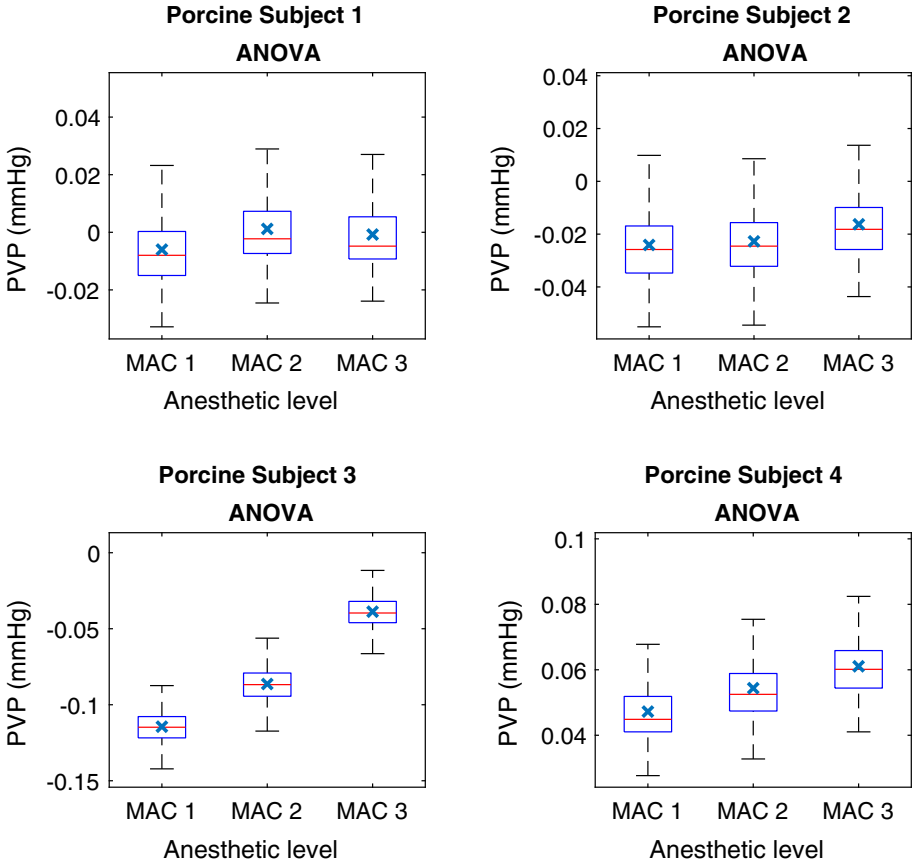

FIGURE 9. Boxplot Display of ANOVA for each Porcine Subject under varying Anesthetic levels. For each boxplot the values on the x-axis correspond to the same MAC level: 1 is MAC 1, 2 is MAC 2, and 3 is MAC 3. The mean for each scenario is notated with a blue X. Significant difference bars and asterisks have been omitted for clarity, due to all pair wise ANOVAs demonstrating statistical differences.

Thus, to understand this, more subjects would be needed to determine a stronger trend.

Our results further indicate that the relationship between venous and arterial circulation is influenced by confounding effects. As anesthetics and hemorrhage have opposing effects on the venous system, they further have differing effects on the relationship between arterial and venous circulation. Increasing anesthetics causes a drop in the correlation between arterial and venous circulation. The porcine subjects demonstrated strong correlations between the arterial and venous waveform at the initial anesthetic dosage, MAC 1, and a drop in correlation coefficients when anesthetics reached MAC 3. The consistent drop across all porcine subjects shows a consistent decrease in the correlation as inhaled anesthetic value increases. Thus, as the venous system reacts to the increase in diameter and the pressure simultaneously increases, a less noticeable relationship occurs. Therefore, the physiological correlation between the arterial and venous pressure waveforms provides a potential future mechanism for inhaled anesthetic monitoring. The hemorrhage correlation coefficients demonstrated a consistently strong relationship between the arterial and venous circulation before and after acute hemorrhage. There was a slight increase in correlation for three porcine subjects from before to after hemorrhage, which could indicate the opposite of the relational effect seen in anesthetics. However, the overall consistency suggests that while hemorrhage occurs, a constant inhaled anesthetic overwhelms the hemorrhage effect. Thus, under general anesthesia, the relationship between arterial and venous pressure waveforms may not be reliable in drawing conclusions to better assess volume status.

Limitations

The small sample size of porcine subjects while creating important indications include some limitations in the broader generalization of the study's findings. For future analysis, more porcine subjects would be studied to draw more general conclusions on the relationship between the arterial and venous pressure waveforms. Additionally, in future studies we

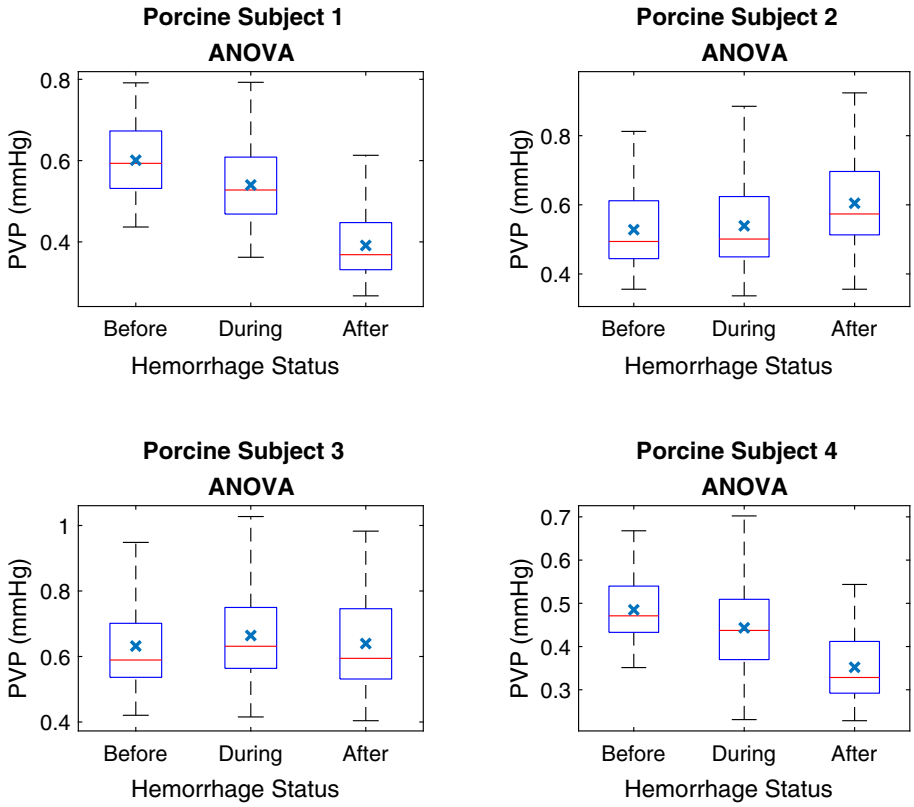

FIGURE 10. Boxplot Display of ANOVA for each Porcine Subject under varying hemorrhage levels. For each boxplot the values on the x-axis correspond to hemorrhage level: 1 is before hemorrhage, 2 is during hemorrhage, and 3 is after hemorrhage. The mean for each scenario is notated with a blue X. Significant difference bars and asterisks have been omitted for clarity, due to all pair wise ANOVAs demonstrating statistical differences.

TABLE 2. ANOVA results for anesthetic level.

Porcine Subject #	*df*	*df error*	*F*	p-value
Isoflurane				
1	2	599997	15084	<0.01
2	2	2699997	87072	<0.01
3	2	2699997	10384000	<0.01
4	2	2699997	516337	<0.01
Propofol				
1	2	1499997	449	<0.01
2	2	2699997	569	<0.01
3	2	2699997	77374100	<0.01
4	2	2699997	207214	<0.01

TABLE 3. ANOVA results for hemorrhage status.

Porcine Subject #	*df*	*df error*	*F*	p-value
1	2	2099997	138020	<0.01
2	2	2099997	29180	<0.01
3	2	2099997	632250	<0.01
4	2	2099997	69970	<0.01

would like to additionally record a 'true baseline' venous and arterial pressure waveform from the animal subjects prior to any anesthetic application. Overall, this study does not prove causation of the relationships between the venous and arterial circulations, as there could be more confounding factors affecting the determined relationships, such as the slight variations caused by different sizes of catheters. However, the study proves a noticeable relationship under both the influence of anesthetics and acute hemorrhage. There is also a clear distinction between the effects on the venous pressure's mean between competing vasodilation and vasoconstriction impacts. Thus, PVP waveform researchers are encouraged to take into account the affect anesthetics and acute hemorrhage have on the venous waveform and additionally consider the hydromechanical cross-talk between the arterial and venous circulation.

CONCLUSION

Isoflurane and propofol are known vasodilators, and acute hemorrhage results in vasoconstriction. Our results suggest that the opposing vascular resistance changes due to anesthetics and hemorrhage cause dis-

tinct differences in the venous waveforms under the two conditions. The results demonstrate a correlation between the venous and arterial pressure waveforms, which supports the theory that the heart rate pulse from the arterial waveform may influence findings on the venous side. The correlation between the venous and arterial signals found in this controlled setting demonstrates the reliability of similar findings in a clinical setting. The apparent strong correlation between venous and arterial waveforms throughout varying dosages of anesthetic and hemorrhage attests to a relationship between venous and arterial circulation that should be investigated further in future PVP research. The evident opposing effects of anesthetic and hemorrhage should also be considered in future research as the two have confounding effects on the venous pressure waveform.

SUPPLEMENTARY INFORMATION

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AUTHOR CONTRIBUTIONS

KWS, JAS, MOJ, AAV, SES, and LDC collected porcine subject data. LDC, GPB, and KRH developed and tested the methods and performed the statistical analyses under the guidance of HKJ, MOJ, and JW. LDC, GPB, and KRH wrote the first draft of the manuscript. MAH and JW supervised the signal analysis protocol. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL APPROVAL

The study was approved by the University of Arkansas for Medical Sciences Institutional Animal Care and Use Committee.

CONSENT TO PARTICIPATE

Not applicable.**Guarantor:** MOJ

HUMAN STUDIES

No human studies were carried out by the authors for this article.

ANIMAL STUDIES

All institutional and national guidelines for the care and use of laboratory animals were followed and approved by the appropriate institutional committees.

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