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Hemodynamic Parameters in the Assessment of Fluid Status In a Porcine Hemorrhage and Resuscitation Model

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Abstract

Background—Measuring fluid status during intraoperative hemorrhage is challenging, but detection and quantification of fluid overload is far more difficult. Using a porcine model of hemorrhage and over-resuscitation, it is hypothesized that centrally obtained hemodynamic parameters will predict volume status more accurately than peripherally obtained vital signs.

Methods—Eight anesthetized female pigs were hemorrhaged at 30 mL/min to a blood loss of 400 mL. After each 100 mL of hemorrhage, vital signs (heart rate, systolic blood pressure [SBP], mean arterial pressure [MAP], diastolic blood pressure [DBP], pulse pressure, pulse pressure variation) and centrally obtained hemodynamic parameters (mean pulmonary artery pressure [MPAP], pulmonary capillary wedge pressure [PCWP], central venous pressure [CVP] and cardiac output [CO]) were obtained. Blood volume was restored, and the pigs were over-resuscitated with 2,500 mL of crystalloid, collecting parameters after each 500 mL bolus. Hemorrhage and resuscitation phases were analyzed separately to determine differences among parameters over the range of volume. Conformity of parameters during hemorrhage or over-resuscitation was assessed.

Results—Over the course of hemorrhage, changes from baseline euolemia were observed in vital signs SBP, DBP, MAP after 100 mL of blood loss. Central hemodynamic parameters MPAP and PCWP were changed after 200 mL blood loss, and CVP, after 300 mL of blood loss. Over the

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Conflicts of Interest: Dr. Wise, Dr. Polcz, Dr. Beilman, Dr. Sobey, Dr. Leisy and Dr. Kiberenge declare no competing interests, or potential conflicts of interest. Kyle Hocking, PhD, is founder, CEO and president of VoluMetrix and is an inventor of intellectual property in the field of venous waveform analysis assigned to Vanderbilt and licensed to VoluMetrix. Colleen Brophy, MD, is founder and CMO of VoluMetrix and an inventor of intellectual property in the field of venous waveform analysis assigned to Vanderbilt and licensed to VoluMetrix. Bret Alvis, MD, owns stock in VoluMetrix and is an inventor of intellectual property in the field of venous waveform analysis assigned to Vanderbilt and licensed to VoluMetrix and is married to the COO of VoluMetrix. None of the technology or intellectual property developed by VoluMetrix was considered or utilized at any point in this investigation.

course of resuscitative volume overload, changes were observed from baseline euvolemia in MPAP and CVP after 500 mL resuscitation, in PCWP after 1,000 mL resuscitation and CO after 2,500 mL resuscitation. In contrast to hemorrhage, vital sign parameters did not change during over-resuscitation. The strongest linear correlation was observed with PCWP in both hemorrhage ($r^2=0.99$) and volume overload ($r^2=0.98$).

Conclusions—Pulmonary capillary wedge pressure is the most accurate parameter to track both hemorrhage and over-resuscitation, demonstrating the unmet clinical need for a less-invasive PCWP equivalent.

Introduction:

Fluid management is the most common therapeutic intervention during anesthesia and can dramatically influence surgical outcomes.^{1,2} Maintaining accurate fluid replacement (“Goal Directed Fluid Therapy;” GDFT) is associated with decreased 30-day postoperative morbidity and mortality.^{3,4} Inadequate resuscitation can lead to systemic hypoperfusion and its sequelae. Conversely, excessive resuscitation, particularly in patients with diminished cardiopulmonary reserve, can result in pulmonary and peripheral edema, increased ventilator requirements and mortality.⁵

Clinical signs of hypovolemia such as decreased urine output, altered mentation and decreased skin turgor lack precision and represent delayed manifestations of intravascular volume loss.^{6,7} Vital signs including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) are routinely monitored for all surgical procedures and used as indicators of volume status. Central venous catheters can be used to determine the central venous pressure (CVP), a surrogate for preload, whose usefulness is confounded by variability in intrathoracic pressure, peripheral vascular tone and cardiac function.⁸ A pulmonary arterial catheter (PAC) can provide more accurate measures of volume status using central measures of cardiac filling, including mean pulmonary arterial pressure (MPAP), cardiac output (CO), and pulmonary capillary wedge pressure (PCWP), though imperfect, often considered the gold-standard for intravascular volume status.⁹ However, PACs are difficult to use accurately and have been associated with potentially severe complications such as pneumothorax and pulmonary artery rupture.⁹

Less invasive methods such as transthoracic or transesophageal echocardiography can provide critical information about preload and cardiac function, though these techniques requires user expertise and can be cumbersome.¹⁰ Additional non-invasive surrogates such as noninvasive cardiac output monitoring (NICOM; Baxter, Deerfield, IL) use principles of thoracic bioimpedance or bioactance to estimate CO, though are prone to motion artifact, require absence of dysrhythmia and are not validated in heart failure and cardiogenic shock.^{11,12} Vital signs and central hemodynamic parameters are measurements reflecting a single given time point, and are termed *static* measurements. Cardiovascular parameters reflective of real-time changes in preload indices over a given respiratory cycle are referred to a *dynamic* measurements, and include pulse pressure variation (PPV), stroke volume variation (SVV) and systolic pressure variation.¹³ These parameters are more accurate than vital signs in predicting fluid responsiveness, the ability to generate an increase in stroke volume

proportional to the administered volume.¹⁴ However, they require high tidal volumes during mechanical ventilation, regular HR, and heavy sedation for accuracy.¹⁵ Thus, to improve intraoperative monitoring of volume shifts, it is imperative to understand how vital signs and central hemodynamic parameters change throughout the entire spectrum of volume changes during anesthetic management, from hypovolemia to euvoemia to hypervolemia.

In this investigation, a porcine model of controlled hemorrhage followed by resuscitation and subsequent over-resuscitation was used to analyze static and dynamic peripherally and centrally obtained hemodynamic measurements. The hypothesis was that centrally obtained hemodynamic parameters would be most accurate in assessing volume status over the course of moderate hemorrhage and over-resuscitation, as alternative and less invasive parameters commonly used clinically have limitations that may restrict the ability to sustain accurate fluid management during anesthesia.

Materials and Methods:

The protocol was approved by the Vanderbilt University Institutional Animal Care and Use Committee (protocol M1800176-00), and National Institute of Health Guidelines for the care and use of laboratory animals were strictly followed. This experiment utilized a series of eight sequential 40-45 kg female Yorkshire pigs (Oak Hill Genetics, Ewing, IL) of approximately 12 weeks of age, used in the order received. The gender was chosen to facilitate easier urinary catheterization. Sample size was determined based on analogous experiments from our research group, considering the principle of reduction of animal specimens though sufficiently powering the study to mitigate the need for further animal use.^{16,17} No formal statistical power calculation was conducted. Experiments were performed in the Vanderbilt University Animal Operating Room (OR) facility, starting in the early morning. No randomization or blinding was employed.

General anesthesia was induced using a standard, widely utilized induction combination of ketamine (2.2 mg/kg)/xylazine (2.2 mg/kg)/telazol (4.4 mg/kg) administered through an intravenous catheter placed in an ear vein, and maintained with 1% isoflurane (Primal, Boston, MA).^{18,19} Pigs were intubated and maintained on volume-control ventilation at a tidal volume of 8 mL/kg, with respiratory rate titrated to an end-tidal CO₂ of 35-40 mmHg, and a positive end-expiratory pressure of 5 cm H₂O.²⁰ Intravenous unfractionated heparin was administered as a 10,000 international unit bolus initially, with 5,000 additional units every two hours.

Surgical exposure of bilateral internal jugular veins allowed for placement of a PAC (Edwards Lifesciences, Irvine, CA) and an 8.5 French catheter for blood removal. An arterial line was placed in the internal carotid artery and used to record continuous measurements of HR, SBP, DBP and MAP. Pulse pressure (PP) was taken as the difference between SBP and DBP, and PPV was calculated as the difference between peak pulse pressure at inspiration and expiration during the respiratory cycle.²¹ Using Lab Chart 8 (ADInstruments, Colorado Springs, CO), one-hundred pulse cycles were selected and input into the blood pressure module. The offline analysis was selected with the arterial pressure signal having a minimum peak height of 5 mmHg, and a minimum height of 5% of the peak

height was used. From this analysis, the following parameters were obtained from the signal: HR, SBP, DBP, MAP, PP, and PPV. The PAC was used to transduce MPAP and CVP. Cardiac output was obtained through the PAC using thermodilution. PCWP was obtained at end-expiration after inflation of the PAC balloon with 1.5 mL air and confirmation of restricted right to left blood flow through appropriate change in the pulmonary artery pressure waveform.

After induction and preparation, baseline hemodynamic parameters were obtained (baseline PCWP was 9 ± 2 mmHg [mean \pm standard deviation]) after thirty minutes of equilibration to mitigate any potential sympathomimetic tachycardia or hypertensive effect of ketamine. Using a mechanical roller-pump, blood was removed at 30 mL per minute, a flow rate chosen to approximate human hemorrhage.¹⁶ A total of 400 mL of blood was drawn, representing 10-15% of total blood volume.²² All vital signs and central hemodynamic measurements were obtained after each 100 mL of blood volume was removed, up to 400 mL. The entire hemorrhaged blood volume was returned at a rate of 100 mL per minute until post-hemorrhagic euvoemia was restored. Next, PlasmaLyte (37°C; Baxter) was infused at a rate of 100 mL/min via the same mechanical roller-pump, stopping after each 500 mL bolus for hemodynamic measurements. PlasmaLyte was infused up through 2,500 mL of fluid. Upon completion of the experiment, the pigs were euthanized with sodium pentobarbital (125 mg/kg). No randomization or blinding was used as all the pigs were subjected to the same intervention.

Statistical Analysis

Vital signs and central hemodynamic parameters at each measured volume were reported as means \pm standard deviations. The primary outcome measures were strength of linear correlation during both hemorrhage and over-resuscitation phases, as defined by the square of the linear regression correlation coefficient (r^2). The r^2 , representing the variance between the group means accounted for by the linear correlation, was used as the primary measure of goodness of fit.²³ The r^2 values ranged from 0.00 (no correlation) to 1.00 (perfect linear correlation). All statistical tests compare hemodynamic values among different volume statuses, with pigs (n=8) as the unit of analysis. Baseline (0 mL) values for all parameters were all found to be normally distributed among the eight pigs via the Shapiro-Wilk test; as such, parametric statistical comparison tests were used for analysis and outliers were not considered.

Hemorrhage and resuscitation phases were analyzed separately using one-way Analysis of Variance (ANOVA) with each of the eight pigs representing a repeated measure, to determine whether there were differences among these parameters over the range of volume. Tukey's *post-hoc* test of multiple comparisons was used to determine at which volume point a change represented a significant difference from baseline. Volume-based changes in hemodynamic parameters were characterized by simple linear regression analysis, to measure correlation of measured parameters to volume status (volume status was taken as the independent variable and the measured parameter as the dependent variable).²⁴ Parameters that conformed best to a linear trend line over a given course of volume changes were deemed best suited for use as a surrogate for intravascular volume status in that

linearity provides optimal predictability of the degree of change expected by a specific volume perturbation.²⁵

It could not be assumed that all parameters would return to their initial euvoletic baseline following blood return after hemorrhage. Therefore, values of all vital signs and central hemodynamic parameters were also compared at their pre-hemorrhagic and resuscitated euvoletic (0 mL) states. Comparisons between all parameters at states of both pre-hemorrhagic and resuscitated euvoletic states were performed, using the paired Student's *t* test to characterize whether these parameters differed between the two euvoletic states.

A two-tailed *P* value < 0.05 represented the standard for statistical significance in all analyses. Statistical analysis was conducted using GraphPad Prism 13 (GraphPad Software, San Diego, CA).

Results:

Hemorrhage

There were no missing or excluded data and all animals (n=8 pigs) survived, and were included in the analysis. There was no observed change in HR throughout hemorrhage (*P*=0.665). Systolic blood pressure (*P*<0.001), DBP (*P*<0.001) and MAP (*P*<0.001) significantly decreased with increasing volume of hemorrhage; changes in SBP, DBP, and MAP were all significant after the first 100 mL of blood removal (representing approximately 3-4% of the total blood volume).²² Pulse pressure (*P*=0.145) and PPV (*P*=0.160) were not significantly different over the course of hemorrhage. The central hemodynamic parameters MPAP (*P*<0.0001), PCWP (*P*<0.0001) and CVP (*P*=0.004) significantly decreased over the course of hemorrhage. Significant changes in these three measurements were first realized at hemorrhage volumes of 200 mL, 200 mL, and 300 mL, respectively. In contrast, CO did not significantly decrease over the course of hemorrhage (*P*=0.092). Mean values of all parameters during hemorrhage are summarized in Table 1. Simple linear correlations of the means of values from all eight pigs at each of the five-volume states achieved during hemorrhage were determined (Table 2). Heart rate had little correlation (*r*²=0.22) with bled volume, while SBP, DBP, MAP, PP and PPV all demonstrated linear conformity with an *r*²>0.80. All central hemodynamic parameters demonstrated an *r*² 0.98.

Resuscitation and volume overload

As with the hemorrhagic phase, there were no missing or excluded data and all animals (n=8) survived, and were included in the analysis. There was no observed change in HR (*P*=0.183), SBP (*P*=0.750), DBP (*P*=0.700), MAP (*P*=0.669) and PP (*P*=0.421) throughout resuscitation and volume overload. Pulse pressure variation too was not significant over the course of resuscitation and volume overload (*P*=0.055). The central hemodynamic parameters MPAP, PCWP, CVP and CO significantly increased over the course of resuscitation and volume overload (*P*<0.0001 for all). Both MPAP and CVP were significantly greater than their euvoletic values after administration of 500 mL PlasmaLyte, while PCWP and CO were significantly greater at PlasmaLyte volumes of 1,000 mL and

2,500 mL, respectively. Mean values of all parameters during resuscitation and volume overload are summarized in Table 3. Simple linear correlations of the means of values from all eight pigs at each of the six volume states during this phase were determined (Table 2). All vital signs (HR, SBP, DBP, MAP, PP and PPV) demonstrated a linear correlation with resuscitative volume status of $r^2 < 0.80$. The central hemodynamic parameters MPAP ($r^2=0.89$), PCWP ($r^2=0.98$), CVP ($r^2=0.93$) and CO ($r^2=0.95$) demonstrated strong linear correlations.

Pulse pressure variation, as the dynamic measurement assessed in this study, PCWP, as the gold-standard, and CO, a representative indicator of central filling assumed to be proportional to volume were examined graphically. The hemorrhage-resuscitation-overload sequences for these variables are depicted in Figure 1, Figure 2, and Figure 3, respectively.

The parameters SBP, DBP and MAP had still not returned to baseline upon blood volume reinfusion. All other parameters were not significantly different between both euvoletic states (Table 4).

Discussion:

This investigation provides a comprehensive analysis of vital signs and centrally derived hemodynamic parameters in relation to progressive perturbation of intravascular volume in a porcine model. The model included both hemorrhage for volume loss and resuscitation/ volume overload with crystalloid solution to simulate volume overload in a controlled resuscitation such as elective or urgent major surgery. While the assessed indices have previously been characterized in controlled hemorrhage models, there is a dearth of data in analogous models of volume overload. The principal finding is that blood pressure values and centrally obtained hemodynamic indices accurately and consistently change with progressive hemorrhage, while only centrally obtained parameters MPAP, PCWP, CVP and CO change with volume overload resuscitation.

Intraoperative fluid therapy is an element of the perioperative process in which there remains variability among anesthesiology teams. As Enhanced Recovery After Surgery (ERAS) protocols facilitate more cost-effective perioperative care, decreased complications, and shorter lengths of stay, there has been greater recognition of the importance of perioperative fluid management.²⁶ Along with avoidance of opioids and maintenance of normothermia, perioperative GDFT is among the few key evidence-based tenets of successful ERAS protocols primarily influenced by the anesthesiology team.²⁶

The importance of GDFT is perhaps most marked in cases requiring intentional fluid restriction such as major hepatic resection and thoracic surgery. Fluid restrictive approaches prevent acute lung injury and pneumonia after pulmonary resection, pneumonectomy and esophagectomy.^{27,28} However, intraoperative under-resuscitation poses the risk of systemic hypoperfusion. Incidence of acute kidney injury, the most common manifestation of perioperative fluid restriction, is estimated to be as high as 10% after thoracic surgery.²⁹ Excess fluid during these procedures promotes pulmonary endothelial disruption, fills dependent and residual portions of lung, and can overwhelm the ability of intrathoracic

lymphatics to effectively drain.^{27,30} Thus, both under- and over-resuscitation can have detrimental consequences, underscoring the significant clinical need for accurate monitoring of volume status to support GDFT during anesthetic management.

During hemorrhage, minimal change was observed with HR, consistent with class one hemorrhagic shock.³¹ Mitigation of early tachycardia can be explained by volume redistribution, hormonally activated compensatory vasoconstriction and parasympathetic reflexes.³² Excellent linear correlations for SBP, DBP and MAP were observed during hemorrhage, with clinically appreciable absolute changes of ~ 20 mmHg detected after 400 mL of hemorrhage. Blood pressure was preserved in early hemorrhage, though this is likely hemorrhage rate-dependent.^{33,34} Furthermore, SBP, DBP and MAP did not return to pre-hemorrhagic euolemia values after re-infusion of removed blood, in contrast to other assessed parameters. These findings suggest limitations in using vital signs for detecting and quantifying hemorrhage intraoperatively or in the intensive care unit (ICU) setting.³⁵ Heart rate and blood pressure are even less useful in detecting volume overload, though few studies have examined these changes in controlled experiments.^{1,36}

The two most common dynamic parameters for fluid status assessment supported by most GDFT protocols and ERAS pathways are SVV and PPV. Both have improved sensitivity and specificity in predicting of fluid responsiveness relative to static measures such as CVP.^{25,37} PPV predicts fluid responsiveness in ventilated patients better than SVV, particularly in patients with lung-protective *low* tidal volume ventilator strategies, and was thus chosen for assessment in this study.^{14,38} As illustrated in Figure 3, PPV correlated well with progressive induction of class one hemorrhage, commensurate with absolute blood pressure parameters (SBP, MAP and DBP). Its performance during over-resuscitation was superior to HR, SBP, PP and CVP; however, it was inferior to MPAP, PCWP and CO when examined using linear regression. These results were consistent with the findings of Graham and colleagues in an analogous model of fluid status prediction during hemorrhage and resuscitation in smaller pigs.³⁹ Graham and colleagues further concluded that PPV should not be used as a singular determinant for titration in GDFT, as it is influenced by multiple patient factors including autonomic tone, co-administered medications, and need for constant ventilator settings.³⁹ Additional commonplace factors compromising its use include intra-abdominal hypertension, spontaneous ventilation, poor lung compliance and dysrhythmias.²¹

Cardiac output demonstrated a strong linear trend with both blood removal as well as fluid overload (Figure 2). As summarized by Mehta and Arora, multiple monitors have been developed for less invasive estimation of CO including the PiCCO system (PiCCO; Genting, Germany), the Non-invasive Cardiac Monitor (NICO; Novamatrix Medical Systems, Wallingford, CT) system and the Endotracheal Cardiac Output Monitor (ECOM; Con-Med, Irving, CA).⁴⁰ These devices still require cumbersome or restrictive conditions, including arterial cannulation, regulated ventilation and high tidal volumes. In this experiment, CO correlated linearly with volume status over the volume range examined; deviation is expected at the extremes of hemorrhage and volume overload due to the Starling relationship, however, this did not manifest in the utilized volume range.¹⁶

For cardiologists, PCWP is critical in assessing the hemodynamic effect of mitral valve pathology, pulmonary hypertension and left ventricular dysfunction. PCWP is also used to diagnose patients with acute congestive heart failure and guide diuretic therapy, and is a critical determinant of suitability for left ventricular assist device placement.^{41,42} Despite limited intraoperative adaptation by anesthesiologists, PCWP demonstrated the strongest linear correlation in detecting changes in both hemorrhage as well as volume overload, as illustrated in Figure 1. Its use for intraoperative assessment of cardiac filling and fluid responsiveness is only hindered by both the complexity of PAC usage, and the additional risk conferred by advancement into a distal pulmonary artery. PAC-guided resuscitation may even confer a benefit in trauma patients presenting with advanced hemorrhagic shock, suggesting the effort to place a PAC or use adjuncts such as echocardiography may be warranted in extreme circumstances, rather than relying on more easily obtainable measures.⁴³ These data may perhaps not be surprising, as they confirm the relevance of PCWP as a gold-standard measure of fluid status.

While invasive hemodynamic parameters are the most accurate measures of volume status from hypovolemia to hypervolemia, there has been progress in the development of non-invasive surrogates for volume status as alluded to previously, some of which have gained widespread use in ICU and OR settings. Nonetheless, these data underscore the need for a non-invasive modality *commensurate with PCWP* to mitigate the need for a PAC while aiding in fluid titration. In contrast to direct measurements as often used with invasive catheters (e.g. PCWP, MPAP), peripherally obtained non-invasive intravascular fluid status is best obtained via interpretation of physiologic waveforms. Derived from photoplethysmogram waveform analysis, compensatory reserve index represents a validated measure of blood volume, useful for highly sensitive detection of small-volume hemorrhage and earlier detection of impending hemodynamic collapse.⁴⁴ Approaches to arterial waveform interpretation include assessment of PPV, and various forms pulse wave analysis, recently and comprehensively summarized in *Anesthesiology*.^{40,45} Finally, though not yet applied clinically, venous waveform analysis has shown promise in detecting fluid status in both pigs and humans via a validated algorithm that considers harmonic amplitudes in fast Fourier transform spectra of peripherally and transcutaneously acquired venous waveforms to produce a “PCWP-equivalent.”¹⁶

There are multiple limitations to this study. Ostensibly, the introduction of human error inherent in data collection and interpretation influences the reliability of hemodynamic parameter measurements both within each pig, and among all pigs. The study used healthy female pigs and extrapolating to pathologic states and between genders would require additional studies with appropriate models.⁴⁶ Moreover, females may respond better to post-hemorrhagic resuscitation than males, potentially lessening external validity of these findings.⁴⁷ Furthermore, eight pigs were considered, a number thoughtfully chosen to minimize animal use but may be restrictive. This study aimed to critically assess parameters over the spectrum of volume status in a controlled series of clinically germane hemodynamic shifts. However, the sequences of rapid hemorrhage and initial blood resuscitation, and choice of *crystalloid* for over-resuscitation do not fully mirror an analogous clinical process such as elective surgery with intermittent blood loss, acute surgery with high volume blood loss, or trauma resuscitation. Next, while isoflurane anesthetic is regarded to have minimal

effect on vital signs, cardiac and autonomic function, data suggest a blunted sympathetic response to hemorrhage and volume overload that would otherwise manifest in a non-anesthetized human may have occurred.⁴⁸ Differential responses to hemorrhage and resuscitation among the pigs, as quantified by the standard deviations, were unavoidable and may be due to differences in lung compliance and cardiac function, among other factors.⁴⁹ Additionally, extrapolation of these results to hemorrhage or resuscitation at faster, slower, or variable rates is limited.⁵⁰ Finally, myocardial dysfunction may occur due to severe trauma and hemorrhage, a case in which superimposed cardiogenic shock physiology may hinder optimal performance of PCWP and other parameters. Conclusions on monitoring of severe shock, and gauging resuscitation in cases of potential myocardial compromise cannot be made.

This study suggests efficacy and utility of centrally obtained parameters in quantifying intraoperative fluid status throughout hemorrhage and volume overload resuscitation. Despite the recognized limitations, these results support PCWP as a useful measurement of volume status in hemorrhage, while novelly showing its relevancy in controlled volume overload. Given the significant limitations of PAC utilization, establishment of a peripherally obtained PCWP-equivalent for widespread use may be ideal and represents a critical unmet clinical need.

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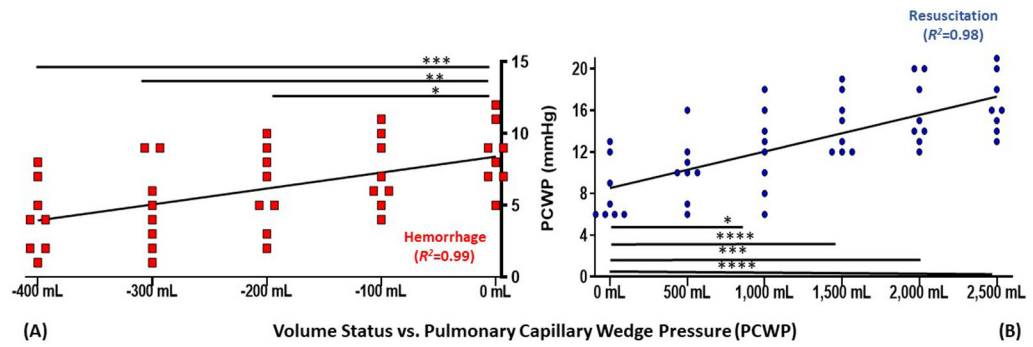


Figure 1- Graphical depiction of pulmonary capillary wedge pressure (PCWP) during (A) whole blood hemorrhage and (B) crystalloid resuscitation

Trend line reflects linear regression of means; points reflect each replicate measurement (n=8)

Relative to 0 mL: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$

mL, milliliters

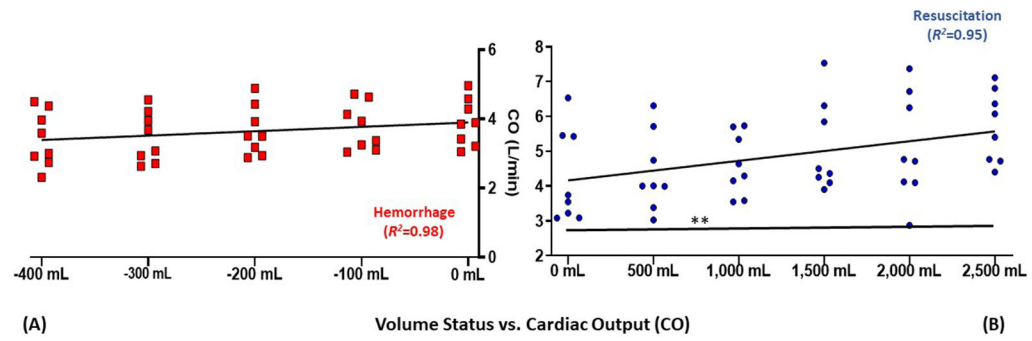


Figure 2- Graphical depiction of cardiac output (CO) during (A) whole blood hemorrhage and (B) crystalloid resuscitation

Trend line reflects linear regression of means; points reflect each replicate measurement (n=8)

Relative to 0 mL: ** P 0.01

mL, milliliters

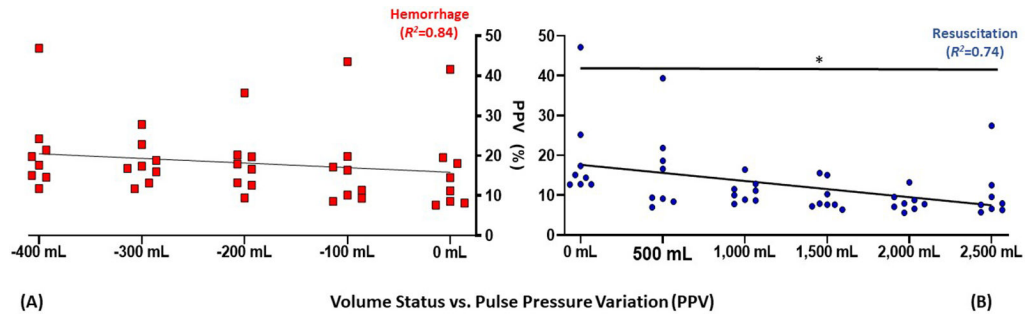


Figure 3- Graphical depiction of pulse pressure variation (PPV) during (A) whole blood hemorrhage and (B) crystalloid resuscitation

Trend line reflects linear regression of means; points reflect each replicate measurement

(n=8)

Relative to 0 mL: * $P < 0.05$

mL, milliliters

Table 1-

Measured parameters by fluid status: hemorrhage phase

Fluid Status:	0 mL	-100 mL	-200 mL	-300 mL	-400 mL	P
<i>Vital Sign Parameters</i>						
Heart Rate (beats per minute)	95±11	95±12	95±14	95±15	96±15	0.665
SBP (mmHg)	100±12	95±12 *	88±12 ***	82±13 **	78±13 *	<0.001
DBP (mmHg)	68±12	63±13 *	58±15 *	53±16 **	49±15 **	<0.001
MAP (mmHg)	83±12	77±13 *	71±14 **	64±15 **	60±15 **	<0.001
Pulse Pressure (mmHg)	32±6	32±6	30±8	29±7	29±6	0.145
Pulse Pressure Variation	16±11	17±12	18±8	18±5	21±11	0.160
<i>Central Hemodynamic Parameters</i>						
MPAP (mmHg)	16±3	15±4	14±4 *	13±3 ****	12±4 ****	<0.0001
PCWP (mmHg)	9±2	7±3	6±3 *	5±3 **	4±3 ***	<0.0001
CVP (mmHg)	7±4	6±4	5±4	4±4 *	4±4 *	0.004
CO (L/min)	3.9±0.7	3.8±0.7	3.7±0.7	3.5±0.7	3.4±0.8	0.092

Values are reported with their standard deviations

P values reflect one-way ANOVA analysis

Relative to 0 milliliters (mL):

* P<0.05

** P 0.01

*** P 0.001

**** P 0.0001

Table 2-

Linear correlation of all parameters with fluid status

Hemodynamic Parameter	r^2 (hemorrhage)	r^2 (resuscitation)
Heart Rate (beats per minute)	0.22	0.15
SBP (mmHg)	0.99	0.40
DBP (mmHg)	0.99	0.72
MAP (mmHg)	0.99	0.79
Pulse Pressure (mmHg)	0.91	0.41
Pulse Pressure Variation	0.84	0.74
MPAP (mmHg)	0.99	0.89
PCWP (mmHg)	0.99	0.98
CVP (mmHg)	0.99	0.93
CO (L/min)	0.98	0.95

r^2 (hemorrhage) refers to the square of the correlation coefficient (between 0 and 1) used to assess goodness-of-fit of the linear relationship between the hemodynamic parameter and the amount of blood hemorrhaged over the course of hemorrhage up to -400 mL. r^2 (resuscitation) similarly assessed the linear correlation between the hemodynamic parameter and the amount of excess fluid infused over the course of overload resuscitation, from 0 mL to 2,500 mL.

Table 3-

Measured parameters by fluid status: resuscitation and overload phase

Fluid Status:	0 mL	500 mL	1,000 mL	1,500 mL	2,000 mL	2,500 mL	P
<i>Vital Sign Parameters</i>							
Heart Rate (beats per minute)	99±16	96±14	95±13	95±13	99±9	101±9	0.183
SBP (mmHg)	89±9	89±13	89±15	89±15	91±13	91±12	0.750
DBP (mmHg)	58±11	57±14	57±15	57±14	59±12	59±12	0.700
MAP (mmHg)	72±10	71±14	72±16	72±15	73±13	74±12	0.669
Pulse Pressure (mmHg)	33±6	32±7	32±7	32±7	32±7	32±7	0.421
Pulse Pressure Variation	20±12	16±11	11±3	10±4	8±2	11±7*	0.055
<i>Central Hemodynamic Parameters</i>							
MPAP (mmHg)	17±4	20±5*	22±5***	23±5****	23±4****	24±4***	<0.0001
PCWP (mmHg)	8±3	10±3	12±4*	15±3****	16±3***	17±3****	<0.0001
CVP (mmHg)	6±4	9±4*	11±4***	13±4****	13±4****	14±4****	<0.0001
CO (L/min)	4.3±1.3	4.4±1.1	4.6±0.88	5.1±1.3	5.1±1.5	5.7±1.0**	<0.0001

Values are reported with their standard deviations

P values reflect one-way ANOVA analysis

Relative to 0 milliliters (mL):

* P<0.05

** P 0.01

*** P 0.001

**** P 0.0001

Table 4-

Comparison of pre-hemorrhagic and resuscitated (post-hemorrhagic) euvoemia

Parameter	<i>Pre-hemorrhagic Euvoemia</i>	<i>Resuscitated Euvoemia</i>	<i>P</i>
<i>Vital Sign Parameters</i>			
Heart Rate (beats per minute)	95±11	99±16	0.300
SBP (mmHg)	100±12	90±9	0.008
DBP (mmHg)	68±12	58±11	0.005
MAP (mmHg)	83±12	72±10	0.006
Pulse Pressure (mmHg)	32±6	33±6	0.849
Pulse Pressure Variation	16±11	20±12	0.217
<i>Central Hemodynamic Parameters</i>			
MPAP (mmHg)	16±3	17±4	0.624
PCWP (mmHg)	9±2	8±3	0.584
CVP (mmHg)	7±4	6±4	0.487
CO (L/min)	3.9±0.7	4.3±1.3	0.283

Values are reported with their standard deviations