ANESTHESIOLOGY

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

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- When implementing a goal-directed fluid therapy protocol, it is currently unknown what peripherally assessed signs (heart rate, blood pressure, pulse pressure, pulse pressure variation) and centrally measured (pulmonary artery pressure, pulmonary capillary wedge pressure, central venous pressure, cardiac output) hemodynamic parameters best reflect volume status during hemorrhage and resuscitation

What This Article Tells Us That Is New

- In anesthetized pigs who underwent incremental hemorrhage, resuscitation and over-resuscitation with crystalloid, blood pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, and central venous pressure decreased with hemorrhage, but only central hemodynamic parameters increased with resuscitation and over-resuscitation
- Pulmonary capillary wedge pressure had the closest correlation with the volume of crystalloid resuscitation administered

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, mean arterial pressure, diastolic blood pressure, pulse pressure, pulse pressure variation) and centrally obtained hemodynamic parameters (mean pulmonary artery pressure, pulmonary capillary wedge pressure, central venous pressure, cardiac output) 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: During the course of hemorrhage, changes from baseline euvolemia were observed in vital signs (systolic blood pressure, diastolic blood pressure, and mean arterial pressure) after 100 ml of blood loss. Central hemodynamic parameters (mean pulmonary artery pressure and pulmonary capillary wedge pressure) were changed after 200 ml of blood loss, and central venous pressure after 300 ml of blood loss. During the course of resuscitative volume overload, changes were observed from baseline euvolemia in mean pulmonary artery pressure and central venous pressure after 500-ml resuscitation, in pulmonary capillary wedge pressure after 1,000-ml resuscitation, and cardiac output 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 pulmonary capillary wedge pressure 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 pulmonary capillary wedge pressure equivalent.

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Fluid management is the most common therapeutic intervention during anesthesia and can dramatically influence surgical outcomes.[1,2] Maintaining accurate fluid replacement (*i.e.*, goal-directed fluid therapy) 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

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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 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), and although imperfect, is often considered the definitive standard for intravascular volume status.[9] However, pulmonary arterial catheters 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, although these techniques require user expertise and can be cumbersome.[10] Additional noninvasive surrogates such as noninvasive cardiac output monitoring (NICOM; Baxter, USA) use principles of thoracic bioimpedance or bioreactance to estimate CO, although 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 referred to as static measurements. Cardiovascular parameters reflective of real-time changes in preload indices during a given respiratory cycle are referred to as dynamic measurements, and include pulse pressure variation, stroke volume variation, 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 euvolemia 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 during the course of moderate hemorrhage and over-resuscitation, as alternative and less invasive parameters that are 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 (Nashville, Tennessee; protocol M1800176-00), and National Institutes of Health (Bethesda, Maryland) guidelines for the care and use of laboratory animals were strictly followed. This experiment utilized a series of eight sequential 40- to 45-kg female Yorkshire pigs (Oak Hill Genetics, USA) of approximately 12 weeks of age, used in the order received. Females were chosen to facilitate easier urinary catheterization. Sample size was determined based on analogous experiments from our research group and consideration of the principle of reduction of animal specimens, while 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 Medical Center 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, USA).[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 carbon dioxide of 35 to 40 mmHg and a positive end-expiratory pressure of 5 cm H_2O.[20] Intravenous unfractionated heparin was administered as a 10,000–international unit bolus initially, with 5,000 additional units every 2 hr.

Surgical exposure of bilateral internal jugular veins allowed for placement of a pulmonary arterial catheter (Edwards Lifesciences, USA) 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 was taken as the difference between SBP and DBP, and pulse pressure variation was calculated as the difference between peak pulse pressure at inspiration and expiration during the respiratory cycle.[21] Using Lab Chart 8 (ADInstruments, USA), 100 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, pulse pressure, and pulse pressure variation. The pulmonary arterial catheter was used to transduce MPAP and CVP. CO was obtained through the pulmonary arterial catheter using thermodilution. PCWP was obtained at end-expiration after inflation of the pulmonary arterial catheter balloon with 1.5 ml of air and confirmation of restricted right-to-left blood flow through appropriate changes in the pulmonary artery pressure waveform.

After induction and preparation, baseline hemodynamic parameters were obtained (baseline PCWP, 9 ± 2 mmHg [mean ± SD]) after 30 min of equilibration to mitigate any potential sympathomimetic tachycardia or hypertensive effects of ketamine. Using a mechanical roller-pump, blood was removed at 30 ml/min, a flow rate chosen to approximate human hemorrhage.[16] A total of 400 ml of blood was drawn, representing 10 to 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/min until posthemorrhagic euvolemia 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 to a total of 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 mean ± SD. 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 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 *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 in a given course of volume changes were deemed best suited for use as a surrogate for intravascular volume status, as 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 euvolemic baseline after blood return after hemorrhage. Therefore, values of all vital signs and central hemodynamic parameters were also compared at their prehemorrhagic and resuscitated euvolemic (0 ml) states. Comparisons between all parameters at states of both prehemorrhagic and resuscitated euvolemia were performed, using the paired Student's *t* test to characterize whether these parameters differed between the two euvolemic states.

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

Results

Hemorrhage

There were no missing or excluded data; all animals (n = 8 pigs) survived and were included in the analysis. There was no observed change in HR throughout hemorrhage ($P = 0.665$). SBP ($P < 0.001$), 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 to 4% of the total blood volume).[22] Pulse pressure ($P = 0.145$) and pulse pressure variation ($P = 0.160$) were not significantly different during the course of hemorrhage. The central hemodynamic parameters MPAP ($P < 0.0001$), PCWP ($P < 0.0001$), and CVP ($P = 0.004$) significantly decreased during 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 during 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). HR had little correlation ($r^2 = 0.22$) with bleed volume, while SBP, DBP, MAP, pulse pressure, and pulse pressure variation all demonstrated linear conformity with $r^2 > 0.80$. All central hemodynamic parameters demonstrated $r^2 \geq 0.98$.

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 pulse pressure ($P = 0.421$) throughout resuscitation and volume overload. Pulse pressure variation too was not significant during the course of resuscitation and volume overload ($P = 0.055$). The central hemodynamic parameters MPAP, PCWP, CVP, and CO significantly

Table 1. Measured Parameters by Fluid Status: Hemorrhage Phase

Fluid Status	0 ml	–100 ml	–200 ml	–300 ml	–400 ml	*P* Value
Vital sign parameters						
Heart rate, beats/min	95 ± 11	95 ± 12	95 ± 14	95 ± 15	96 ± 15	0.665
Systolic blood pressure, mmHg	100 ± 12	95 ± 12*	88 ± 12‡	82 ± 13†	78 ± 13*	<0.001
Diastolic blood pressure, mmHg	68 ± 12	63 ± 13*	58 ± 15*	53 ± 16†	49 ± 15†	<0.001
Mean arterial pressure, 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
Central hemodynamic parameters						
Mean pulmonary arterial pressure, mmHg)	16 ± 3	15 ± 4	14 ± 4*	13 ± 3§	12 ± 4§	< 0.0001
Pulmonary capillary wedge pressure, mmHg	9 ± 2	7 ± 3	6. ± 3*	5 ± 3†	4 ± 3‡	< 0.0001
Central venous pressure, mmHg	7 ± 4	6 ± 4	5 ± 4	4 ± 4*	4 ± 4*	0.004
Cardiac output, 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 SDs. *P* values reflect one-way ANOVA analysis. Relative to 0 milliliters (ml):
*P<0.05, †$P \le 0.01$, ‡$P \le 0.001$, §$P \le 0.0001$.

increased during the course of resuscitation and volume overload ($P < 0.0001$ for all). Both MPAP and CVP were significantly greater than their euvolemic 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, pulse pressure, and pulse pressure variation) 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 definitive 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 figures 1 to 3, respectively.

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

Table 2. Linear Correlation of All Parameters with Fluid Status

Hemodynamic Parameter	Hemorrhage r^2	Resuscitation r^2
Heart rate, beats/min	0.22	0.15
Systolic blood pressure, mmHg	0.99	0.40
Diastolic blood pressure, mmHg	0.99	0.72
Mean arterial pressure, mmHg	0.99	0.79
Pulse pressure, mmHg	0.91	0.41
Pulse pressure variation	0.84	0.74
Mean pulmonary arterial pressure, mmHg	0.99	0.89
Pulmonary capillary wedge pressure, mmHg	0.99	0.98
Central venous pressure, mmHg	0.99	0.93
Cardiac output, l/min	0.98	0.95

Hemorrhage r^2 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. Resuscitation r^2 similarly assessed the linear correlation between the hemodynamic parameter and the amount of excess fluid infused during the course of overload resuscitation from 0 ml to 2,500 ml.

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 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 goal-directed fluid therapy is among the few key evidence-based tenets of successful enhanced recovery after surgery protocols primarily influenced by the anesthesiology team.[26]

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* Value
Vital sign parameters							
Heart rate, beats/min	99 ± 16	96 ± 14	95 ± 13	95 ± 13	99 ± 9	101 ± 9	0.183
Systolic blood pressure, mmHg	89 ± 9	89 ± 13	89 ± 15	89 ± 15	91 ± 13	91 ± 12	0.750
Diastolic blood pressure, mmHg	58 ± 11	57 ± 14	57 ± 15	57 ± 14	59 ± 12	59 ± 12	0.700
Mean arterial pressure, 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
Central hemodynamic parameters							
Mean pulmonary arterial pressure, mmHg)	17 ± 4	20 ± 5*	22 ± 5‡	23 ± 5§	23 ± 4§	24 ± 4‡	< 0.0001
Pulmonary capillary wedge pressure, mmHg	8 ± 3	10 ± 3	12 ± 4*	15 ± 3§	16 ± 3‡	17 ± 3§	< 0.0001
Central venous pressure, mmHg	6 ± 4	9 ± 4*	11 ± 4‡	13 ± 4§	13 ± 4§	14 ± 4§	< 0.0001
Cardiac output, 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 SDs. *P* values reflect one-way ANOVA analysis. Relative to 0 ml:
*P<0.05, †$P \le 0.01$, ‡$P \le 0.001$, §$P \le 0.0001$.

The importance of goal-directed fluid therapy 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 goal-directed fluid therapy during anesthetic management.

During hemorrhage, minimal change was observed with HR, consistent with class 1 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 approximately 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 prehemorrhagic euvolemia values after reinfusion 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 setting.[35] Heart rate and blood pressure are even less useful in detecting volume overload,

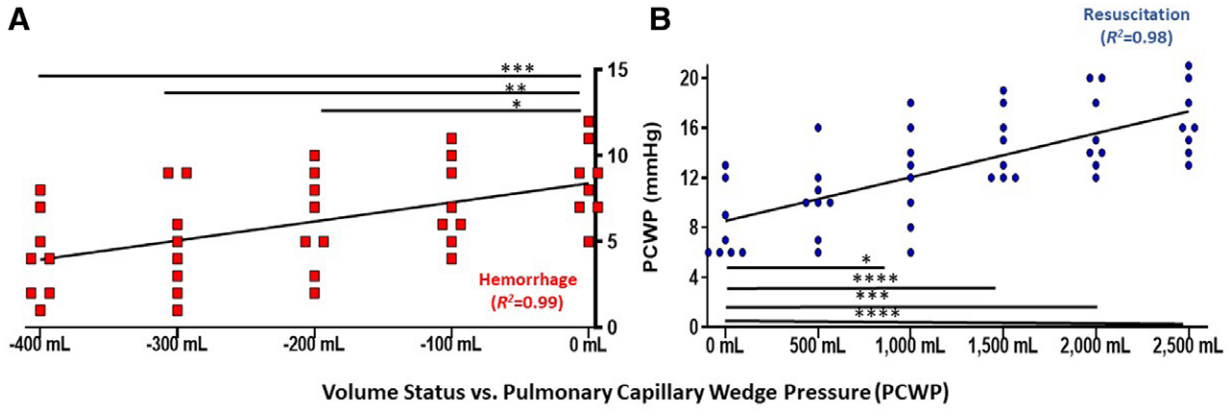

Fig. 1. Graphical depiction of pulmonary capillary wedge pressure (PCWP) during (*A*) whole blood hemorrhage and (*B*) crystalloid resuscitation. Trend line reflects linear regression of means; points reflect each replicate measurement (n = 8). Relative to 0 ml: *$P < 0.05$; **$P \le 0.01$, ***$P \le 0.001$; ****$P \le 0.0001$.

Table 4. Comparison of Prehemorrhagic and Resuscitated (Posthemorrhagic) Euvolemia

Parameter	Prehemorrhagic Euvolemia	Resuscitated Euvolemia	*P* Value
Vital sign parameters			
Heart rate, beats/min	95 ± 11	99 ± 16	0.300
Systolic blood pressure, mmHg	100 ± 12	90 ± 9	0.008
Diastolic blood pressure, mmHg	68 ± 12	58 ± 11	0.005
Mean arterial pressure, 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
Central hemodynamic parameters			
Mean pulmonary arterial pressure, mmHg)	16 ± 3	17 ± 4	0.624
Pulmonary capillary wedge pressure, mmHg	9 ± 2	8 ± 3	0.584
Central venous pressure, mmHg	7 ± 4	6 ± 4	0.487
Cardiac output, l/min	3.9 ± 0.7	4.3 ± 1.3	0.283

Values are reported with their SDs.

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 goal-directed fluid therapy protocols and enhanced recovery after surgery pathways are stroke volume variation and pulse pressure variation. Both have improved sensitivity and specificity in predicting of fluid responsiveness relative to static measures such as CVP.[25,37] Pulse pressure variation predicts fluid responsiveness in ventilated patients better than stroke volume variation, 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, pulse pressure variation correlated well with progressive induction of class 1 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 *et al.* in an analogous model of fluid status prediction during hemorrhage and resuscitation in smaller pigs.[39] Graham *et al.* further concluded that pulse pressure variation should not be used as a singular determinant for titration in goal-directed fluid therapy, as it is influenced by multiple patient factors including autonomic tone, coadministered medications, and need for constant ventilator settings.[39] Additional commonplace factors compromising its use include intraabdominal hypertension, spontaneous ventilation, poor lung compliance, and dysrhythmias.[21]

CO demonstrated a strong linear trend with blood removal as well as fluid overload (fig. 2). As summarized by Mehta and Arora, multiple monitors have been developed for less invasive estimation of CO including the PiCCO (Pulse index Contour Continuous Cardiac Output) system (Gentinge, Germany), the NICO (Non-invasive Cardiac Monitor) system (Novametrix Medical Systems, USA), and the ECOM (Endotracheal Cardiac Output Monitor) system (ConMed, USA).[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 in 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 pulmonary arterial catheter usage, and the additional risk conferred by advancement into a distal pulmonary artery. Pulmonary arterial catheter–guided resuscitation may even confer a benefit in trauma patients presenting with advanced hemorrhagic shock, suggesting the effort to place a pulmonary arterial catheter 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 definitive 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 noninvasive surrogates for volume status as alluded to previously, some of which have gained widespread use in intensive care and operating room settings. Nonetheless, these data underscore the need for a noninvasive modality that is commensurate with PCWP to mitigate the need for a pulmonary arterial catheter while aiding in fluid titration. In contrast to direct measurements often used with invasive catheters (*e.g.*, PCWP, MPAP), peripherally obtained noninvasive intravascular fluid status is best obtained *via* interpretation of physiologic waveforms. Derived from photoplethysmogram waveform analysis, the 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 pulse pressure variation and various forms of pulse wave analysis, as recently

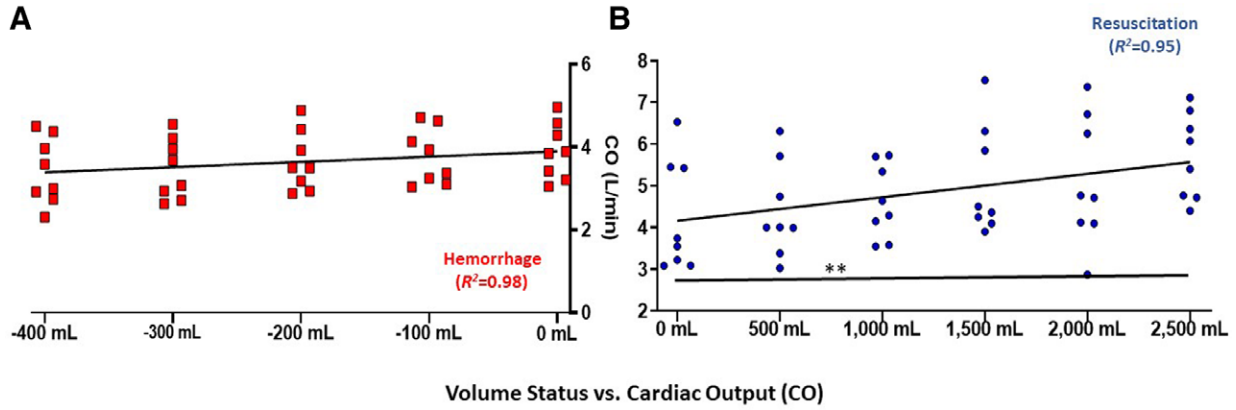

Fig. 2. Graphical depiction of cardiac output (CO) during (*A*) whole blood hemorrhage and (*B*) crystalloid resuscitation. Trend line reflects linear regression of means; points reflect each replicate measurement (n = 8). Relative to 0 ml: $^{**}P \leq 0.01$.

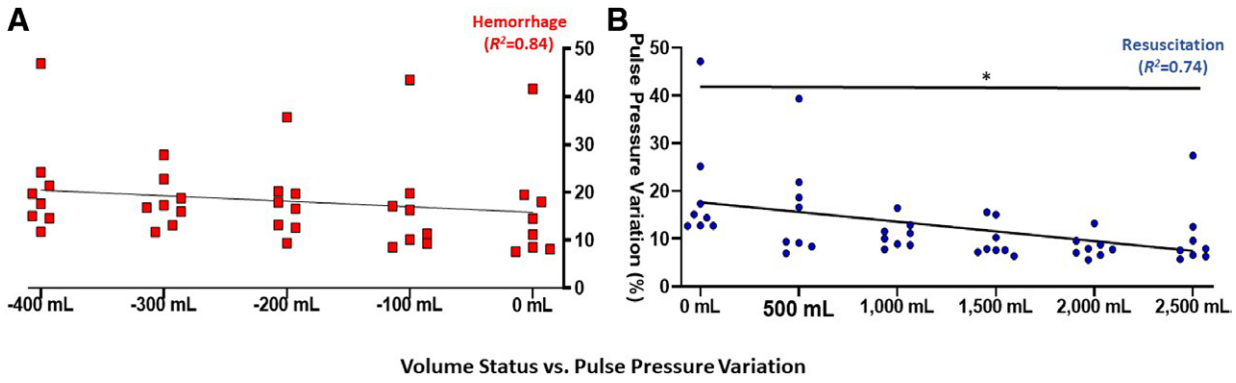

Fig. 3. Graphical depiction of pulse pressure variation during (*A*) whole blood hemorrhage and (*B*) crystalloid resuscitation. Trend line reflects linear regression of means; points reflect each replicate measurement (n = 8). Relative to 0 ml: $^{*}P \leq 0.05$.

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 the 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 sexes would require additional studies with appropriate models.[46] Moreover, female pigs may respond better to posthemorrhagic resuscitation than male pigs, potentially lessening external validity of these findings.[47] Furthermore, eight pigs were considered, a number thoughtfully chosen to minimize animal use but that also may be restrictive. This study aimed to critically assess parameters in the spectrum of volume statuses in a controlled series of clinically germane hemodynamic shifts. However, the sequences of rapid hemorrhage and initial blood resuscitation and the 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, as well as cardiac and autonomic function, data suggest a blunted sympathetic response to hemorrhage and volume overload that would otherwise manifest in a nonanesthetized human may have occurred.[48] Differential responses to hemorrhage and resuscitation among the pigs, as quantified by the SDs, 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, in which case a 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 pulmonary arterial catheter 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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Competing Interests

Dr. Hocking is founder, CEO, and president of VoluMetrix (Nashville, Tennessee) and is an inventor of intellectual property in the field of venous waveform analysis assigned to Vanderbilt and licensed to VoluMetrix. Dr. Brophy 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. Dr. Alvis is CSO of 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. The other authors declare no competing interests.

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