Pulse pressure variability during hemorrhage and reinfusion in piglets: effects of age and tidal volume

Variabilité de la tension différentielle due à l'hémorragie et au remplissage chez des porcelets: effets de l'âge et du volume courant

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Abstract

Purpose The dynamic change in arterial pulse pressure during mechanical ventilation (PPV) predicts fluid responsiveness in adults but may not be applicable to pediatric patients. We compared PPV during hemorrhage and reinfusion in immature vs mature piglets at two clinically relevant tidal volumes (V_T).

Methods Following Institutional Animal Care Committee approval, we measured hemodynamics and PPV in two groups of piglets, 10–15 kg (immature, $n = 9$) and 25–30 kg (mature, $n = 10$), under stable intravenous anesthesia at $V_T = 8$ and 10 mL·kg⁻¹. Measurements were taken at baseline, with blood withdrawal in 5 mL·kg⁻¹ steps up to 30 mL·kg⁻¹, and during stepwise reinfusion. For each age group and V_T , we constructed receiver

operating characteristic (ROC) curves to determine the threshold value that was predictive of fluid responsiveness.

Results Pulse pressure variability was significantly lower in immature vs mature pigs and at $V_T 8$ vs $V_T 10$ at every measurement period. The difference in PPV induced by changing V_T was less in immature animals. Significant areas under the ROC curve were obtained in immature pigs at both V_T s but in mature animals at $V_T 10$ alone. A PPV threshold was calculated to be 8.2% at $V_T 8$ and 10.9% at $V_T 10$ in immature animals vs 15.9% at $V_T 10$ in mature animals, but sensitivity and specificity were only 0.7.

Conclusion Pulse pressure variability values are lower and less sensitive to V_T in immature vs mature pigs. Adult PPV thresholds do not apply to pediatric patients, and a single PPV value representing fluid responsiveness should not be assumed.

Presentation: This study was presented as a poster at the Canadian Anesthesiologists Society Meeting in Quebec City, June 2012.

Author contributions M. Ruth Graham supervised the conception and design of the study and wrote the manuscript. M. Ruth Graham, Kristin McCrea, and Linda G. Girling participated in the conduct of the experiments and contributed to the data collection and analysis. Kristin McCrea, the co-investigator, contributed to the study design, helped with manuscript preparation, and presented the study in poster form at the Canadian Anesthesiologists' Society meeting. All authors contributed to the final manuscript.

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Résumé

Objectif La variation dynamique de la tension différentielle due à la ventilation mécanique (PPV) prédit la réponse aux fluides chez les adultes, mais pourrait ne pas être applicable aux patients pédiatriques. Nous avons comparé la PPV au cours d'une hémorragie et du remplissage chez des porcelets immatures et des porcelets matures pour deux volumes courants (V_T) cliniquement pertinents.

Méthodes Après l'accord du Comité institutionnel de protection des animaux (CIPA), nous avons mesuré les données hémodynamiques et la PPV dans deux groupes de porcelets, immatures ($n = 9$, 10–15 kg) et matures ($n = 10$, 25–30 kg), sous anesthésie intraveineuse stable avec un $V_T = 8$ et un $V_T = 10$ mL·kg⁻¹. Les mesures ont été effectuées à la ligne de base, après prélèvement sanguin par incréments de 5 mL·kg⁻¹ jusqu'à 30 mL·kg⁻¹, et au cours du remplissage par incréments équivalents.

Pour chaque groupe d'âge et de V_T , nous avons construit des courbes ROC (caractéristiques de la performance de test) pour déterminer la valeur seuil prédictive de la réactivité fluidique.

Résultats La tension différentielle sous ventilation a été significativement plus basse chez les porcelets immatures que chez les porcelets matures et à V_T 8 par rapport à V_T 10 pour chaque période de mesure. La différence de PPV induite par le changement de V_T a été moindre chez les animaux immatures. Des aires significatives sous la courbe ROC ont été obtenues chez les porcelets immatures pour les deux V_T , mais seulement à V_T 10 chez les animaux matures. Les calculs ont fourni un seuil de PPV de 8,2 % à V_T 8 et de 10,9 % à V_T 10 chez les animaux immatures contre 15,9 % à V_T 10 chez les animaux matures, mais la sensibilité et la spécificité n'ont été de que 0,7.

Conclusion Les valeurs de la tension différentielle sous ventilation ont été plus faibles et moins sensibles à la V_T chez les porcelets immatures que chez les porcelets matures. Les seuils de PPV chez l'adulte ne s'appliquent pas aux patients pédiatriques, et on ne doit pas supposer qu'une valeur unique de PPV représente la réactivité fluidique.

Determination of the status of intravascular volume and the need for fluid replacement is integral to anesthesia and intensive care, but traditional static filling pressures - central venous pressure (CVP) or pulmonary artery occlusion pressure (PCWP) - and cardiac output (CO) measurements require invasive monitoring and are insensitive and/or unavailable in pediatric patients.¹ More recently, dynamic indices, such as the pulse pressure variability (PPV) during mechanical ventilation, have been introduced as reliable indicators of fluid responsiveness in adults.^{2,3} However, these indices have not been extensively studied or fully validated in pediatric patients.⁴ Pulse pressure variability during mechanical ventilation, calculated simply from an arterial pressure trace as the maximal pulse pressure minus the minimal pulse pressure divided by the average pulse pressure over a single breath,² reflects the dynamic change in cardiac preload that occurs during controlled mechanical ventilation. During a positive pressure breath, the increase in pleural pressure decreases the gradient for venous return to the right ventricle and increases right ventricular afterload, resulting in a transient decrease in right ventricular stroke volume (RVSV).² This inspiratory reduction in RVSV leads to a decrease in left ventricular filling, left ventricular SV, and ultimately aortic pulse pressure, which itself is dependent on the left ventricular SV and aortic compliance. In contrast with SV variation (SVV), PPV is an indirect index of

ventilation-induced changes in left ventricular SV based on complex underlying cardiopulmonary interactions. Factors independent of intravascular volume known to influence PPV include alterations in aortic and chest wall compliance,⁵⁻⁷ sympathetic stimulation,⁸⁻¹⁰ and mechanical ventilation parameters - tidal volume (V_T),¹¹⁻¹³ respiratory rate,¹⁴ and positive end-expiratory pressure (PEEP).¹⁵ Despite the complex interplay of factors underlying the measurement, a threshold of 11-13% PPV in the setting of a tidal volume (V_T) $\geq$ 8 mL·kg⁻¹ has been consistently reported to be predictive of fluid responsiveness in adults under a variety of conditions.³ Children have higher aortic and chest wall compliance which may dampen the transmission of ventilation-induced changes in pleural pressure.¹⁶⁻¹⁹ This could be predicted to produce lower PPV values with less impact from changes in tidal volume such that adult threshold levels may not apply. To date, studies are lacking that compare PPV in mature vs immature subjects after controlled alterations in intravascular volume to permit direct comparison by age. We determined PPV in two groups of pigs, 10-15 kg (approximately one month old - pediatric equivalent - immature) vs 25-30 kg (two to three months old - young adult equivalent - mature), under stable intravenous propofol/ketamine anesthesia, ventilated at two V_{Ts} (8 vs 10 mL·kg⁻¹) to determine baseline values. The measurements were repeated with stepwise blood withdrawal to 30 mL·kg⁻¹ and then during stepwise blood re-administration. We hypothesized that PPV values at equivalent intravascular volumes and the threshold PPV that predicts fluid responsiveness would be less in immature vs mature animals and that changes in tidal volume would have a smaller effect in the immature animals.

Methods

Twenty animals were studied, ten per weight category. One immature animal was withdrawn due to an inability to maintain normothermia. All animals were treated according to University of Manitoba Central Animal Care Standards (Central Animal Care Committee approval received November 2010). After fasting overnight with allowance for free access to water, the piglets were sedated with intramuscular atropine (0.02 mg·kg⁻¹), ketamine (6 mg·kg⁻¹), and midazolam (0.6 mg·kg⁻¹). Anesthesia was induced by facemask with isoflurane (4%). Tracheal intubation was carried out on the animals; their lungs were ventilated with a volume-controlled ventilator (F_iO_2 = 0.50, baseline V_T of 8 mL·kg⁻¹ and PEEP = 5 cm H₂O), and their respiratory rate was titrated to maintain PaCO₂ within a normal range. A 22G cannula was placed in a

marginal ear vein for fluid and drug administration. Lactated Ringer's solution $20 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ was given during surgical preparation to simulate a standardized fluid bolus prior to an anticipated blood loss surgery. The solution was then decreased to keep the vein open for the remainder of the experiment. Cutdowns were performed in the neck and groin, and bupivacaine 0.25% ($2 \text{ mg} \cdot \text{kg}^{-1}$ in total) was infiltrated into the wound edges. A 5 or 7-F pulmonary artery catheter was advanced into the pulmonary artery for measurement of CVP, PCWP, and CO by thermodilution (Cardiomax III®, Columbus Instruments, Columbus, OH, USA). Stroke volume was calculated from the CO divided by the heart rate (HR). Cannulae were placed in a femoral artery and vein. The femoral venous cannula was used to withdraw and replace blood. The arterial cannula was connected to a pressure transducer for continuous measurement of arterial pressure and PPV determination. All data were continuously monitored on a computerized data acquisition system (Advanced Cudas®, Dataq Instruments, Akron, OH, USA) and intermittently recorded. Pulse pressure variability was determined *post hoc* from recorded traces according to the formula:

$$\text{PPV} = 100 \times (\text{PPmax} - \text{PPmin}) / ([\text{PPmax} + \text{PPmin}] / 2),$$

where PP = pulse pressure, and max and min refer to maximum and minimum pulse pressure, respectively, determined over a single mechanical breath and averaged over two to three minutes.

Effect of tidal volume on baseline PPV during euvoemia

After surgical preparation, the animals were switched to intravenous propofol/ketamine anesthesia which was titrated until a stable anesthetic depth was achieved. This was manifested by an unchanged HR and arterial blood pressure for 15 min along with lack of spontaneous movement. The animals were then paralyzed with rocuronium to ensure absence of spontaneous ventilatory efforts. Total intravenous anesthesia was required to allow use of more precise ventilation and PEEP using an Esprit® ventilator (Respironics; Carlsbad, CA, USA). Anesthetic requirements to achieve the same endpoint differed between groups: immature (propofol 30/ketamine 7.5/rocuronium $2.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$) vs mature (propofol 20/ketamine 5/rocuronium $2.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$), and they were unaltered in each group for the duration of study. Cardiac output was then determined in duplicate by thermodilution with 5-mL aliquots of normal saline, and PPV was averaged over a three-minute period at $V_T = 8 \text{ mL} \cdot \text{kg}^{-1}$ and $\text{PEEP} = 5 \text{ cm H}_2\text{O}$. Tidal volume was then increased to $10 \text{ mL} \cdot \text{kg}^{-1}$; rate was adjusted to

maintain minute ventilation, and measurements were repeated after a five-minute stabilization period. We chose these V_T s to determine if even small clinically relevant changes in ventilator settings were significant. An inspiratory hold was performed at each tidal volume setting, and total respiratory system compliance was calculated by $V_T / (\text{plateau pressure obtained during the inspiratory hold} - \text{PEEP})$ in triplicate.

Effect of hemorrhage and fluid resuscitation

Blood was withdrawn in $5 \text{ mL} \cdot \text{kg}^{-1}$ aliquots into a sterile blood collection bag until a total of $30 \text{ mL} \cdot \text{kg}^{-1}$ was removed. At every stepwise decrease in blood volume and after stabilization of hemodynamics for three minutes, CO by thermodilution and PPV were determined at both $V_T = 8 \text{ mL} \cdot \text{kg}^{-1}$ and $V_T = 10 \text{ mL} \cdot \text{kg}^{-1}$ with identical minute ventilation.

When $30 \text{ mL} \cdot \text{kg}^{-1}$ blood had been withdrawn, blood was returned to the animal in $5 \text{ mL} \cdot \text{kg}^{-1}$ aliquots up to $25 \text{ mL} \cdot \text{kg}^{-1}$, followed by a $10 \text{ mL} \cdot \text{kg}^{-1}$ aliquot (total $35 \text{ mL} \cdot \text{kg}^{-1}$). We were able to return a total of $35 \text{ mL} \cdot \text{kg}^{-1}$ of blood despite removing only $30 \text{ mL} \cdot \text{kg}^{-1}$ as heparinized normal saline flushes were required to prevent clotting in the withdrawal line and contributed additional fluid to the blood collection bag. Pulse pressure variability and CO were determined at every step at both tidal volumes.

At the end of the experiment, the animals were euthanized with euthanol $100 \text{ mg} \cdot \text{kg}^{-1}$.

Statistical analysis

The data were analyzed by mixed effects analysis of variance and least-squares means matrices. Bonferroni's correction for repeated measures was applied, and all reported *P* values were two-sided. Significance was accepted at the $P < 0.05$ level. Using the PPV and SV changes obtained during stepwise reinfusion of the shed blood, we constructed receiver operating characteristic (ROC) curves for PPV from values obtained during reinfusion to determine the threshold PPV that was predictive of fluid responsiveness for each age group and V_T . A positive response was defined as $\geq 15\%$ increase in SV with a $5 \text{ mL} \cdot \text{kg}^{-1}$ bolus.

Results

Hemodynamics

Tidal volume had no effect on baseline hemodynamics in either age group. Hemodynamic data for both groups at

Table 1 Hemodynamics ($V_T 10$)

Parameter	Baseline		Out 20 mL·kg ⁻¹		Out 30 mL·kg ⁻¹		In 20 mL·kg ⁻¹		In 35 mL·kg ⁻¹	
	Mature	Immature	Mature	Immature	Mature	Immature	Mature	Immature	Mature	Immature
HR (beats·min ⁻¹)	128 (26)	133 (13)	152 (42)**	175 (35)**†	167 (36)**	203 (34)**†	117 (37)**	150 (36)**†	104 (17)**	133 (30)†
MAP (mmHg)	104.7 (12.4)	105.0 (17.5)	82.8 (15.7)**	96.6 (15.3)**†	73.8 (19.5)**	88.2 (16.9)**†	89.1 (19.7)**	106.3 (12.0)†	103 (14)	106.7 (12.4)†
CI (L·min ⁻¹ ·m ⁻²)	6.1 (1.1)	5.9 (0.8)	4.5 (1.2)**	5.2 (1.0)	4.0 (0.8)**	4.8 (0.7)**	5.1 (1.6)	5.5 (0.9)	6.3 (0.8)*	5.9 (1.0)†
SVI (mL·m ⁻²)	52 (7.5)	44.3 (3.5)†	30.2 (6.8)**	30.1 (3.5)**	23.7 (5.7)**	24.0 (4.6)**	44.4 (8.6)**	37.6 (3.9)**†	61.5 (7.4)**	44.7 (3.5)†
PAP (mmHg)	19.1 (2.1)	16.3 (1.8)†	17.9 (1.8)**	15.2 (1.7)†	17.5 (2.3)**	15.3 (1.9)†	19.6 (1.1)	17.2 (2.5)†	21.1 (1.6)	18.6 (3.6)†
PCWP (mmHg)	8.4 (1.0)	7.0 (1.6)†	6.6 (1.4)**	4.7 (0.9)**†	6.2 (1.2)**	3.8 (0.6)**†	8.5 (2.1)	6.3 (0.2)†	9.5 (1.1)	6.6 (1.0)†
CVP (mmHg)	7.9 (0.8)	5.4 (1.1)†	6.5 (0.8)**	4.1 (0.9)**†	6.4 (0.9)**	4.1 (1.0)**†	7.4 (0.9)	4.8 (1.0)*†	9.5 (1.6)	5.6 (1.3)†

Average (SD) hemodynamics for mature and immature groups during tidal volume (V_T) = 10 mL·kg⁻¹ at selected volumes of blood withdrawal and reinfusion. * $P < 0.05$ vs baseline within group; ** $P < 0.01$ vs baseline within group; † $P < 0.01$ between group comparison

CI = cardiac index (CO/ body surface area [m²]); CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; PAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; SVI = stroke volume index (SV/body surface area [m²])

$V_T = 10 \text{ mL} \cdot \text{kg}^{-1}$ are shown in Table 1. Baseline hemodynamics differed significantly between mature vs immature animals as recorded. Static filling pressures (CVP and PCWP) decreased significantly with maximal blood withdrawal in both groups, but the changes were small and may not be clinically important. At maximal blood withdrawal, the mean (SD) decrease in the cardiac index was 35.9 (10.3)% in mature animals vs only 19.0 (9.7)% in immature animals. The SV index (SVI) decreased by a more comparable degree: 56.4 (8.1)% in mature vs 46.1 (12.5)% in immature animals. The difference in cardiac index could be accounted for by a greater increase in HR with maximal hemorrhage in immature animals.

Ventilatory parameters

Table 2 presents the ventilatory parameters obtained in the two groups of animals at each V_T . Peak inspiratory pressures were marginally greater and respiratory rate (RR) significantly less in the mature group compared with the immature group at either V_T . Minute ventilation (VE) was maintained constant at either V_T , but greater VE per kg was required in the immature group to maintain normal arterial blood gases. Total respiratory system compliance was higher in the younger animals at both $V_T 8$ and $V_T 10$ (difference by age at $V_T 8 = -0.2 \text{ mL} \cdot \text{cm H}_2\text{O}^{-1} \cdot \text{kg}^{-1}$; 95% CI: -0.35 to -0.06 ; $P < 0.01$ and difference by age at $V_T 10 = -0.15 \text{ mL} \cdot \text{cm H}_2\text{O}^{-1} \cdot \text{kg}^{-1}$; 95% CI = -0.3 to -0.09 ; $P < 0.05$). In the mature group, increasing V_T from 8 to 10 mL·kg⁻¹ had no effect on measured compliance. In the immature group, increasing V_T was associated with a significant decrease in total respiratory system compliance (difference = $-0.06 \text{ mL} \cdot \text{cm H}_2\text{O}^{-1} \cdot \text{kg}^{-1}$; 95% CI 0.1 to -0.02 ; $P < 0.01$).

Blood gases

Table 3 presents blood gases and temperatures for both groups of animals. Although minute ventilation was unchanged in either group with changing V_T , CO₂ values decreased from the higher to lower range of normal in the mature group alone at $V_T 10$, suggesting that the dead space to tidal volume ratio was preferentially improved in the older animals at higher V_T , but unlikely to be of clinical significance.

Figure 1 shows box and whiskers plots for PPV vs blood withdrawal and re-administration in both age groups and V_T . Both V_T and age were significant factors for PPV at every measurement point. Baseline mean (SD) PPV was lower in the immature group [6.4(0.7)% at $V_T 8$ and 7.9 (1.3)% at $V_T 10$] vs the mature group [10.5 (1.3)% at $V_T 8$

Table 2 Ventilation parameters

Parameter	V _T 8		V _T 10	
	Mature	Immature	Mature	Immature
PIP (cm H ₂ O)	18.6 (1.9)	17.2 (1.3)	20.5 (1.2)	19.1 (1.2)
V _T (mL·kg ⁻¹)	8.5 (0.7)	8.5 (1.0)	10.5 (0.6)	10.2 (1.3)
RR (breaths·min ⁻¹)	30 (0.5)	38 (2) [†]	25 (0.4)*	32 (1)* [†]
VE (mL·kg ⁻¹ ·min ⁻¹)	270 (10)	310 (50) [†]	270 (10)	320 (50) [†]
C _{RS} (mL·cm H ₂ O ⁻¹ ·kg ⁻¹)	0.97 (0.1)	1.2 (0.3) [†]	0.95 (0.1)	1.12 (0.2)* [†]

Average (SD) ventilation parameters at tidal volume (V_T) 8 and V_T 10 for both groups

C_{RS} = total respiratory system compliance; PIP = peak airway pressure, RR = respiratory rate; VE = minute ventilation

**P* < 0.05 within group comparison; [†]*P* < 0.05 between group comparison

and 12.9 (2.0)% at V_T 10]. The difference by age was 4.3% at V_T 8 (95% CI 2.1 to 6.4; *P* < 0.01) and 5.3% at V_T 10 (95% CI 2.8 to 7.8; *P* < 0.01). At 30 mL·kg⁻¹ hemorrhage, PPV increased to only 10.0 (2.5)% at V_T 8 and 12.3 (3.4)% at V_T 10 in the immature group vs 17.0 (6.0)% at V_T 8 and 20.1(5.7)% at V_T 10 in the mature group. The difference by age was 8.8% at V_T 8 (95% CI 6.5 to 11.0; *P* < 0.01) and 10.0% at V_T 10 (95% CI 7.4 to 12.7; *P* < 0.01). In both age groups, 20 mL·kg⁻¹ of blood withdrawal was required before PPV differed significantly from baseline. With 20 mL·kg⁻¹ reinfusion, PPV returned to values not significantly different from baseline in both groups.

Overall, increasing V_T from 8 to 10 mL·kg⁻¹ was associated with a greater increase in PPV in the mature group than in the immature group [3.2 (1.8)% vs 1.9 (1.1)%, respectively]. The overall difference by age was 1.27% (95% CI 0.74 to 1.8; *P* < 0.01).

Pulse pressure ventilation ROC curves were constructed for each age group and V_T and are shown in Fig. 2. Accounting for multiple measurements in each animal, statistically significant areas under the ROC curve (AUC) were obtained in immature pigs at both V_T 8 (AUC = 0.73; 95% CI 0.53 to 0.89; *n* = 43; *P* < 0.01) and V_T 10 (AUC = 0.73; 95% CI 0.58 to 0.88; *n* = 43; *P* < 0.001) but in mature animals at V_T 10 alone (AUC = 0.73; 95% CI 0.56 to 0.9; *n* = 39; *P* < 0.01). From the ROC curves generated, a PPV threshold could be determined to be 8.2% at V_T 8 and 10.9% at V_T 10, with sensitivity and specificity as well as positive and negative predictive values of 0.7 in the immature group. In the mature group, a higher threshold of 15.9% was obtained at V_T 10, with sensitivity, specificity, and positive and negative predictive values of 0.8.

Discussion

This is a novel study comparing PPV in immature vs mature animals under comparable anesthetic regimes, tidal volumes, and intravascular volume status. The PPV response to blood withdrawal and reinfusion is both tidal volume and age dependent. Baseline values for PPV are significantly lower in immature vs mature animals and increase to a lesser extent with 30 mL·kg⁻¹ hemorrhage. Increasing V_T by even 2 mL·kg⁻¹ results in a significant increase in PPV at any level of fluid loading in both mature and immature animals, but the difference in PPV is less in the younger group. Although a threshold for fluid responsiveness could be determined using ROC analysis, the value obtained depends on both age and V_T. Therefore, adult thresholds cannot be applied to the pediatric population, and the notion of a single PPV threshold must be interpreted with caution.

Baseline PPV and V_T effect

This novel study systematically compares age-dependent differences in baseline PPV. Under the same anesthetic, intravascular volume, and V_T conditions, we report lower PPV values in immature vs mature piglets. In neurosurgical patients, Pereira de Souza Neto *et al.*²⁰ report baseline PPV = 13 (3)% in zero to six year-old patients vs 19 (4)% in six to 14 yr olds, confirming a similar age effect but with substantially higher values than the baseline values obtained here. In 6-kg piglets, Renner reports baseline PPV of 7, 8.9, and 13.7% at V_T 5, 10, and 15 mL·kg⁻¹, respectively, comparable with the immature group in the present study.¹² Although in an identical experimental preparation in which V_T was not stipulated, the same authors⁹ document a baseline PPV of 12.4%. Factors that may contribute to these substantial differences in baseline PPV values in immature piglets include initial intravascular volume status, species differences, ventilation strategy, and anesthetic technique. This suggests that any single PPV determination is uninformative, and interpretation of PPV requires evaluation in the context of multiple parameters that may have independent effects on the measurement.

Tidal volume influences on PPV as an index of fluid responsiveness have been well documented in both adult^{11,13} and pediatric studies;¹² however, this study compares PPV directly by age using smaller changes in V_T as may be applied clinically. In adult patients, De Backer *et al.* showed that PPV was a reliable indicator of fluid responsiveness only when V_T is > 8 mL·kg⁻¹,¹³ although more recent studies in patients with acute respiratory distress syndrome report reliable (albeit lower) thresholds with V_T as low as 6 mL·kg⁻¹.²¹

Table 3 Blood gases and temperature

Mature	Baseline		Out 30 mL·kg ⁻¹		In 35 mL·kg ⁻¹	
	V _T 8	V _T 10	V _T 8	V _T 10	V _T 8	V _T 10
pH	7.44 (0.05)	7.46 (0.04)	7.41 (0.03)	7.42 (0.03)	7.42 (0.03)	7.38 (0.15)
PaCO ₂	41.8 (4.4)	38.8 (3.1)	41.0 (4.2)	39.3 (3.5)	43.1 (3.9)	36.2 (13.2)
PaO ₂	228 (26.1)	232.4 (27.7)	240.2 (15.2)	239.8 (16.1)	239.6 (17.0)	210.8 (91.6)
HCO ₃	27.6 (1.7)	27.7 (1.6)	25.3 (1.6)	255.6 (1.7)	27 (1.5)	26.6 (1.2)
Temp °C	36.6 (0.6)	37.6 (0.9)	37.6 (0.9)	37.6 (0.9)	37.1 (1.0)	36.7 (1.0)
Immature	Baseline		Out 30 mL·kg ⁻¹		In 35 mL·kg ⁻¹	
	V _T 8	V _T 10	V _T 8	V _T 10	V _T 8	V _T 10
pH	7.45 (0.05)	7.46 (0.05)	7.41 (0.04)	7.42 (0.05)	7.44 (0.03)	7.46 (0.03)
PaCO ₂	42.5 (8.0)	40.8 (6.4)	43.9 (4.5)	42.7 (5.2)	40.5 (4.1)	39.6 (3.2)
PaO ₂	226.2 (14.3)	220.9 (10.5)	224.6 (11.0)	224.2 (10.8)	221.6 (12.3)	219.5 (15.7)
HCO ₃	28.6 (2.1)	28.6 (1.9)	27.2 (2.9)	27.3 (3.1)	27.3 (3.2)	28.0 (2.8)
Temp °C	36.5 (0.7)	36.7 (0.6)	37.1 (0.4)	37.2 (0.4)	36.9 (0.4)	36.9 (0.4)

Arterial blood gas and temperature values at selected volumes of blood withdrawal and reinfusion. Upper table: mature group. Lower table: immature group. Blood gas values are given in mmHg

Fig. 1 Box and whisker plots showing the pulse pressure ventilation (PPV) response to hemorrhage and blood re-administration for each age group and tidal volume. The time course axis corresponds with the blood volume withdrawn and reinfused as follows: 1 = baseline, 2 = out 10 mL·kg⁻¹, 3 = out 20 mL·kg⁻¹, 4 = out 30 mL·kg⁻¹,

5 = in 10 mL·kg⁻¹, 6 = in 20 mL·kg⁻¹, 7 = in 35 mL·kg⁻¹. Boxes represent the median interquartile range: 25-75%. Whiskers delineate 99% of the variation in the data. Crosses represent outliers in each group. Stars delineate significant difference from baseline ($P < 0.05$). See text for further discussion

Fig. 2 Receiver operating curves for fluid responsiveness as determined from pulse pressure ventilation (PPV) where a positive response was defined as $\geq 15\%$ change in SV with a $5 \text{ mL}\cdot\text{kg}^{-1}$ fluid bolus in both groups at tidal volumes (V_T) 8 and V_T 10. Mature curve at V_T 8: area under the curve (AUC) = 0.56; $P = 0.24$ (NS). Mature curve at V_T 10: AUC = 0.73; $P < 0.01$; threshold = 15.2. Immature V_T 8: AUC = 0.71; $P = 0.01$; threshold = 8.2. Immature V_T 10: AUC = 0.73; $P < 0.01$; threshold = 10.9

Wiklund *et al.* show that PPV is a reliable indicator of fluid responsiveness in pigs with normal lungs regardless of V_T .²² In a study involving adult post cardiac surgery patients, Reuter *et al.*¹¹ report baseline PPV values of 9.1 (0.9)% at V_T 5 and 14.4 (1.6)% at V_T 10 (a 6.3% difference in PPV), which persisted to a lesser degree (2.4%) after fluid loading. In 6-kg piglets, Renner *et al.*¹² report baseline PPV values of 7(1.8)% at V_T 5 and 8.9 (2.7)% at V_T 10, a 2% difference, smaller than that reported by Reuter in the adult population and unchanged after fluid loading. In the present study, we report a 1.5% baseline difference in PPV between V_T 8 and V_T 10 in the immature group compared with a 2.5% difference in the mature group. At maximal blood withdrawal, the difference in PPV due to V_T increased to 2.4% in the immature group and 4.8% in the mature group.

The age-related difference in both baseline PPV and the effect of V_T on PPV may be attributed to differences in aortic and/or lung/chest wall compliance, but the relative importance of each parameter to the determination of the measurement is unknown. In a recent review of pediatric studies, Chung and Cannesson⁴ propose that vascular compliance is of greater importance than lung or chest wall compliances to account for the finding that SVV was a more reliable measure of fluid responsiveness compared to PPV. Aortic compliance varies with both age and disease,⁶

but the mature animals we studied were healthy young adults and therefore unlikely to manifest significant changes in aortic stiffness related to hypertension, atherosclerosis, or the extremes of age. We can provide no further insight regarding the relative contribution of vascular vs respiratory compliance to the results obtained, as aortic compliance was not measured directly. Nevertheless, the significant age-related differences in total respiratory system compliance in our study suggest that the effects of lung/chest wall compliance cannot be discounted. Further studies with simultaneous vascular, lung, and chest wall measurements are warranted to determine the relative contribution of each to the age-related differences seen in PPV.

Effect of hemorrhage/reinfusion on PPV

Baseline PPV and the change in PPV with $30 \text{ mL}\cdot\text{kg}^{-1}$ blood withdrawal were less in younger animals and at lower V_T ; on the other hand, they were greater with older animals and at higher V_T . In the immature group, PPV increased from an average of 6.4% at baseline to 10.0% at maximal blood withdrawal at V_T 8 and increased from 8% to 12% at V_T 10. These are substantially lower values than those considered to be predictive of fluid responsiveness in adults. Pediatric PPV responses to hemorrhage and fluid loading have been infrequently studied. In a single group of two- to four-week-old pigs, Renner *et al.* document a baseline PPV of 12.4%, which increased to 27.2% with $25 \text{ mL}\cdot\text{kg}^{-1}$ blood withdrawal.⁹ In 11-kg adult dogs, Taguchi *et al.*²³ report SVV, an alternative dynamic index, of approximately 11% at baseline increasing to $> 40\%$ with hemorrhage of $30 \text{ mL}\cdot\text{kg}^{-1}$ under 1.5% isoflurane anesthesia. Tidal volume and PEEP were not reported. In a study comprising 15- to 18-kg dogs whose chests were strapped to mimic adult chest wall compliance, Berkenstadt *et al.*²⁴ report a baseline PPV of 6.7% that increased to 17.9% with hemorrhage, results more comparable to those obtained in the mature piglets. These responses are markedly greater than those obtained in the immature group in the present study. Differences may be due to variations in baseline fluid loading ($20 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ in the present study vs $10 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$),⁹ sympathetic tone, and potential differences in the ratio of HR to RR. Sympathetically-mediated increases in arterial tone should result in greater variations in pulse pressure for the same SV ejected.⁶ Nevertheless, both Renner *et al.*⁹ and Nouria *et al.*⁸ show that norepinephrine infusions mask the PPV response to hemorrhage and suggest that the predominant sympathetic effect is redistribution of blood from the peripheral unstressed compartment to the central compartment. Catecholamine levels were not measured in the present study, but we speculate that inherent sympathetic

stimulation with ketamine *vs* alternative anesthetic agents used in the previous studies may have afforded higher baseline sympathetic tone and a greater sympathetic response with hemorrhage to account for the relatively blunted PPV response obtained. Evidence supporting this view is the better maintained CO and greater HR response than in previous studies. With respect to HR effects, De Backer *et al.* have shown that PPV becomes negligible when the ratio of HR to RR is less than 3.6:1, as 3–4 heart beats·breath⁻¹ are required for pulmonary transfer of the decrease in right ventricular output that occurs during inspiration to reach the left ventricle and be manifest during expiration.¹⁴ This is unlikely to account for the results in the present study; however, as the ratio of HR to RR was consistently greater than 3.5:1 at all time periods in both groups of piglets.

Threshold PPV predicting fluid responsiveness

In both immature and mature piglets, PPV did not differ significantly from baseline until 20 mL·kg⁻¹ blood withdrawal, and PPV returned to values not different from baseline with 20 mL·kg⁻¹ reinfusion. In immature animals, this volume out is associated with a PPV of 8.5 (1.6)% at V_T 8 and 10.7 (2.3)% at V_T 10, much lower than the corresponding values in mature animals, 13.1 (2.0)% at V_T 8 and 16.1(2.5)% at V_T 10. These mature values are similar to adult human threshold PPV values obtained using ROC analysis in clinical studies.⁵ We also constructed ROC curves using the PPV determined before each stepwise bolus reinfusion of blood and the resultant change obtained in SVI. The definition of fluid responsiveness is not standardized in the literature but includes fluid challenges of 250–1,000 mL (5–20 mL·kg⁻¹) with positive responses defined as 10–20% increases in either SV or CO. We chose a smaller fluid challenge, as 10 mL·kg⁻¹ fluid boluses resulted in a greater than 15% increase in SVI in virtually 100% of subjects and therefore were not discriminating. As each animal received up to five fluid challenges, we applied Bonferroni's correction to the resulting *P* values to control for multiple comparisons within groups. Although not typical of the usual methodology for determination of fluid responsiveness, in our view, the results are valid, as correction was included for multiple measurements and all subjects would be expected to be fluid responsive at the point of maximal hemorrhage and less so with increasing transfusion. Despite the limited range of PPV change seen in immature animals over the course of blood reinfusion, we were able to obtain a significant ROC curve at both V_Ts studied, but at V_T 10 only in the mature group. The threshold PPV for fluid responsiveness was significantly lower in the immature group (8.2% at V_T 8 and 10.9% at

V_T 10) than in the mature group (15.2% at V_T 10). Therefore, adult thresholds cannot be applied to the pediatric population, and even small changes in V_T must be taken into account when interpreting this value.

From the forgoing, we suggest that reliance on a single PPV value to predict fluid responsiveness or intravascular volume status in any individual patient is unlikely to be reliable. In mechanically ventilated anesthetized adults, Cannesson *et al.*²⁵ showed that PPV values from 9–13% were inconclusive with respect to fluid responsiveness in 25% of adult patients – clearly representing a “grey zone”. Although we were able to determine thresholds using the ROC analysis, sensitivity and specificity values were only 0.7–0.8, and examination of the entire range showed that PPV values up to 2% above or below the “threshold value” resulted in sensitivity/specificity values only marginally less than the maxima – a “grey zone” equivalent in the present study.

Limitations

We chose to report PPV, a surrogate of the variability in left ventricular SV, rather than other dynamic indices, such as SVV or total aortic flow, as it is the easiest of the available indices to use clinically, requiring only a peripheral arterial line. Controversy exists regarding which of these indices is the most reliable. Renner reports SVV to be a more reliable indicator of fluid responsiveness in an infant piglet model¹² but reports PPV to be more reliable in infants undergoing cardiac surgery.²⁶ Durand *et al.*²⁷ report a more accurate prediction of response to volume expansion using echocardiography to determine aortic flow velocity, likewise Pereira de Souza Neto *et al.*²⁰ with echocardiography-derived SVV *vs* PPV in children. In adult patients, however, a meta-analysis suggests that PPV is more predictive overall than SVV.³ Pulse contour SVV monitors, such as the Vigileo-Flotrac[®], calculate SVV from analysis of the arterial pulse contour using predetermined estimates of arterial compliance in adults and have not been properly validated in pediatric patients.²³ Single indicator thermodilution monitors, such as the PiCCO[®], which calculate CO, SV, and SVV from a calibrated signal, require a central venous cannula and a specialized thermistor-tipped arterial cannula,¹² not readily available in most pediatric centres. Significant training is required to interpret echocardiographic measurements of aortic flow, and echocardiography systems, which can be critically orientation sensitive, are not available over the long term in either the operating room or the intensive care unit. Given the lack of availability of invasive monitoring and either access to and/or training for devices such as the PiCCO monitor or intraoperative echocardiography in most pediatric centres, we suggest that it is even more important

to explore the possibility of tracking intravascular volume changes by a measurement as simple as PPV in this patient population.

The lack of direct system measures of aortic, lung, and chest wall compliance preclude further insight regarding the relative contributions of each to the age-related differences in PPV values obtained.

We were limited to measurements in piglets no smaller than 10 kg to permit reliable pulmonary artery catheter placement, thus excluding the neonatal age group from our study and limiting the age range over which these differences were documented. We predict that a wider age range would result in obtaining even greater differences in PPV values.

Total intravenous anesthesia was chosen to permit use of a ventilator capable of delivering accurate V_T and PEEP. Steady state infusion rates were set at baseline with no further adjustment; consequently, it would be expected that serum levels would differ during blood withdrawal and re-administration. Alterations in anesthetic depth may have affected the results, but these should have been similar between subjects. Follow-up studies using an inhalational technique with constant end-tidal concentrations may yield differing results.

Conclusions

Our results suggest that, under the same anesthetic regime and tidal volume, PPV values are lower in immature vs mature animals at equivalent levels of blood loss and replacement and vary with even small changes in V_T . Therefore, adult PPV thresholds cannot be applied to younger subjects. Arbitrarily choosing the commonly quoted adult PPV threshold of 11–13% could potentially place the pediatric patient at risk of not receiving fluid when it may be required. Moreover, our results corroborate the difficulty in defining a single PPV threshold to represent fluid responsiveness, as age, V_T , sympathetic stimulation, and anesthetic/sedative regime may alter the value obtained. As such, PPV may provide information regarding fluid status and response to fluid administration, but it should more accurately be considered a trend monitor in any given patient, to be used in conjunction with other available parameters and interpreted in the light of age, ventilation parameters, anesthetic/sedative administration, and sympathetic stimulation.

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Conflict of interest The authors declare no commercial or non-commercial affiliations or associations that may be or perceived to be a conflict of interest.

References

1. Kumar A, Anel R, Bunnell E, et al. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. *Crit Care Med* 2004; 32: 691–9.
2. Michard F. Changes in arterial pressure during mechanical ventilation. *Anesthesiology* 2005; 103: 419–28.
3. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med* 2009; 37: 2642–7.
4. Chung E, Cannesson M. Using non invasive dynamic parameters of fluid responsiveness in children: there is still much to learn. *J Clin Monit Comput* 2012; 26: 153–5.
5. Chemla D, Hebert JL, Coirault C, et al. Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. *Am J Physiol* 1998; 274: H500–5.
6. Magder S. Clinical usefulness of respiratory variations in arterial pressure. *Am J Respir Crit Care Med* 2004; 169: 151–5.
7. Renner J, Gruenewald M, Quaden R, et al. Influence of increased intra-abdominal pressure on fluid responsiveness predicted by pulse pressure variation and stroke volume variation in a porcine model. *Crit Care Med* 2009; 37: 650–8.
8. Nouira S, Elatrous S, Dimassi S, et al. Effects of norepinephrine on static and dynamic preload indicators in experimental hemorrhagic shock. *Crit Care Med* 2005; 33: 2339–43.
9. Renner J, Meybohm P, Hanss R, Gruenewald M, Scholz J, Bein B. Effects of norepinephrine on dynamic variables of fluid responsiveness during hemorrhage and after resuscitation in a pediatric porcine model. *Paediatr Anaesth* 2009; 19: 688–94.
10. Biais M, Cottenceau V, Petit L, Masson F, Cochard JF, Sztark F. Impact of norepinephrine on the relationship between pleth variability index and pulse pressure variations in ICU adult patients. *Crit Care* 2011; 15: R168.
11. Reuter DA, Bayerlein J, Goepfert MS, et al. Influence of tidal volume on left ventricular stroke volume variation measured by pulse contour analysis in mechanically ventilated patients. *Intensive Care Med* 2003; 29: 476–80.
12. Renner J, Cavus E, Meybohm P, et al. Pulse pressure variation and stroke volume variation during different loading conditions in a paediatric animal model. *Acta Anaesthesiol Scand* 2008; 52: 374–80.
13. De Backer D, Heenen S, Piagnerelli M, Koch M, Vincent JL. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med* 2005; 31: 517–23.
14. De Backer D, Taccone FS, Holsten R, Ibrahimi F, Vincent JL. Influence of respiratory rate on stroke volume variation in mechanically ventilated patients. *Anesthesiology* 2009; 110: 1092–7.
15. Renner J, Gruenewald M, Meybohm P, et al. Effect of elevated PEEP on dynamic variables of fluid responsiveness in a pediatric animal model. *Paediatr Anaesth* 2008; 18: 1170–7.
16. Papastamelos C, Panitch HB, England SE, Allen JL. Developmental changes in chest wall in infancy and early childhood. *J Appl Physiol* 1995; 78: 179–84.
17. De Robertis E, Liu JM, Blomquist S, Dahm PL, Thorne J, Jonson B. Elastic properties of the lung and the chest wall in young and adult healthy pigs. *Eur Respir J* 2001; 17: 703–11.
18. Fisher JT, Mortola JP. Statics of the respiratory system in newborn mammals. *Respir Physiol* 1980; 41: 155–72.
19. Senzaki H, Akagi M, Hishi T, et al. Age-associated changes in arterial elastic properties in children. *Eur J Pediatr* 2002; 161: 547–51.

20. *Pereira de Souza Neto E, Grousson S, Duflo F, et al.* Predicting fluid responsiveness in mechanically ventilated children under general anaesthesia using dynamic parameters and transthoracic echocardiography. *Br J Anaesth* 2011; 106: 856-64.
21. *Freitas FG, Bafi AT, Nascente AP, et al.* Predictive value of pulse pressure variation for fluid responsiveness in septic patients using lung-protective ventilation strategies. *Br J Anaesth* 2013; 110: 402-8.
22. *Wiklund CU, Morel DR, Orbring-Wiklund H, et al.* Influence of tidal volume on pulse pressure variations in hypovolemic ventilated pigs with acute respiratory distress-like syndrome. *Anesthesiology* 2010; 113: 630-8.
23. *Taguchi H, Ichinose K, Tanimoto H, Sugita M, Tashiro M, Yamamoto T.* Stroke volume variation obtained with Vigileo/FloTracTM system during bleeding and fluid overload in dogs. *J Anesth* 2011; 25: 563-8.
24. *Berkenstadt H, Friedman Z, Preisman S, Keidan I, Livingstone D, Perel A.* Pulse pressure and stroke volume variations during severe haemorrhage in ventilated dogs. *Br J Anaesth* 2005; 94: 721-6.
25. *Cannesson M, Le Manach Y, Hofer CK, et al.* Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a “gray zone” approach. *Anesthesiology* 2011; 115: 231-41.
26. *Renner J, Broch O, Duetschke P, et al.* Prediction of fluid responsiveness in infants and neonates undergoing congenital heart surgery. *Br J Anaesth* 2012; 108: 108-15.
27. *Durand P, Chevret L, Essouri S, Haas V, Devictor D.* Respiratory variations in aortic blood flow predict fluid responsiveness in ventilated children. *Intensive Care Med* 2008; 34: 888-94.