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Pulse pressure and stroke volume variations during severe haemorrhage in ventilated dogs

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Background. Similarly to systolic pressure variation (SPV), pulse pressure variation (PPV) and stroke volume variation (SVV) derived from arterial pulse contour analysis have been shown to reflect fluid responsiveness in ventilated patients. However, unlike the SPV, both PPV and SVV have not been validated during extreme hypovolaemia. The aim of the present study was to examine whether these newly introduced variables respond to gradual hypovolaemia like the SPV by increasing gradually with each step of the haemorrhage even during extreme hypovolaemia.

Methods. SPV, SVV and PPV were measured in 8 dogs following initial volume loading (10% of the estimated blood volume administered as colloid solution), 5 steps of graded haemorrhage, each consisting of 10% of the estimated blood volume, followed by retransfusion of the shed blood.

Results. The correlations of the SVV, SPV and PPV to the stroke volume (SV) throughout the study were −0.89, −0.91 and −0.91, respectively. Correlations of the CVP and the global end-diastolic volume (GEDV) of the heart chambers to the SV were 0.79 and 0.95, respectively. The SPV correlated significantly with both the PPV and the SVV (r=0.97 and 0.93 respectively). However, the PPV increased by more than 400% at 50% haemorrhage compared with increases of 200% and 120% for the SVV and %SPV, respectively.

Conclusion. This study demonstrates that the present algorithm used for the calculation of the SVV and the formula used to calculate the PPV, perform well over a wide range of preload states including severe hypovolaemia. However, the PPV changes more than the SPV and SVV. This may be due to the changing relation of the SV to the pulse pressure when the filling of the aorta is greatly decreased.

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Systolic pressure variation (SPV), which is the difference between the maximum and minimum systolic blood pressure during one mechanical breath, has been demonstrated to reflect the degree of blood loss and the associated decrease in cardiac output (CO) during graded haemorrhage,[1–3] and to predict fluid responsiveness to volume loading.[4 5] Following the experimental and clinical validation of SPV, pulse pressure variation (PPV) and stroke volume variation (SVV) have also been introduced into clinical practice. PPV, which is the difference between the maximum and minimum values of the arterial pulse pressure (PP) during one mechanical breath divided by the mean of the two values, has been shown to be an accurate predictor of fluid responsiveness in critically ill patients.[6 7] SVV, which is the difference between the maximum and minimum SV during one mechanical breath relative to the mean SV, as provided by the PiCCO monitoring system (Pulsion, Germany), has also been found to be a good predictor of fluid responsiveness in neurosurgical patients[8] and patients undergoing cardiac surgery.[9 10]

However, unlike SPV, neither PPV nor SVV have been validated during conditions of extreme hypovolaemia, where these parameters may become less accurate. Specifically, the way that PPV is calculated, with the mean of the maximum and minimum PP values in the denominator, may cause this parameter to increase artificially as hypovolaemia progresses. This is because during hypovolaemia, when SV decreases significantly during each mechanical breath, the mean of the maximum and minimum PP values will always

†*Declaration of interest*. AP is a member of the medical advisory board of Pulsion Medical Systems, Munich, Germany.

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be smaller than the baseline PP (i.e. the PP during apnoea). Interestingly, in a recent study assessing PPV under open-chest conditions the apnoea PP was used in the denominator for PPV calculation.[11]

As to the SVV, concerns have been raised over the ability of the pulse contour technique to track accurately SV changes that occur over a short period of time,[12 13] and a recent study failed to demonstrate a correlation between the SVV and the response of the CO to volume loading.[14] In addition, there is only limited information about the relationship between the SVV, PPV and SPV during changes in volume status.[15]

Since specific threshold values of the PPV and SVV have already been suggested for the clinical assessment of fluid responsiveness, it is important to examine their reliability in varying volume states. Therefore the aim of the present study was to examine whether the newly introduced SVV and PPV respond to gradual hypovolaemia in the same way as SPV, i.e. they keep increasing with each step of haemorrhage up to extreme hypovolaemia.

Methods

After approval from the Institutional Animal Ethics Committee, eight healthy mongrel dogs (15–18 kg) were included in the study. Premedication consisted of oral midazolam 0.5 mg kg^{-1}. Anaesthesia was induced with ketamine 10 mg kg^{-1} and fentanyl 2 $\mu g\ kg^{-1}$ i.v., and maintained with halothane 0.5% and fentanyl infusion at 2 $\mu g\ kg^{-1}\ h^{-1}$. Pancuronium bromide was used for muscle relaxation. Following endotracheal intubation, the dogs were mechanically ventilated using a Servo 900 C Ventilator (Siemens, Sweden). Ventilator parameters were set to an inspired oxygen fraction of 1.0, an inspiratory pressure of 15 cm H_2O, a ventilatory frequency of 20 bpm and an inspiratory–expiratory time ratio of 1:2. Further adjustments of the respiratory rate were performed to maintain the end-tidal carbon dioxide concentration at 32–35 mm Hg, a level that was verified by arterial blood gas examination. An inflatable vest was wrapped around each dog's chest to simulate the human chest wall–lung compliance ratio.[1] Before each step of the study, vest inflation pressure was adjusted so that the pleural pressure (measured using a catheter inserted into the pleural space) was 50% of the airway pressure 3 s after an inspiratory hold.[16]

A 4F thermistor-tipped catheter for thermodilution and pulse contour analysis (PV 2014L, Pulsion, Munich, Germany) was inserted percutaneously into the femoral artery and connected to a PiCCO monitoring system (Pulsion, Munich, Germany). A 17-gauge catheter was inserted into the contralateral femoral artery for blood removal, and a central venous (CV) catheter was inserted through the right external jugular vein. Cardiac output (CO) and global end-diastolic volume (GEDV) were measured in triplicate by injecting physiological saline 0.9% (0.2 ml kg^{-1}) at a temperature of 2–5°C through the CV catheter.

GEDV is the sum of all end-diastolic volumes of the four heart chambers, and is calculated by the PiCCO monitoring system as the difference between the intrathoracic thermal volume (ITTV), which is the product of the CO and the mean transit time of the cold indicator, and the pulmonary thermal volume (PTV), which is the product of the CO and the downslope time of the thermodilution curve. Arterial pressure, heart rate (HR), central venous pressure (CVP), SV and SVV were continuously measured throughout the experiment.

Arterial and airway pressure waveforms were recorded for offline analysis. SPV was measured as the difference between the maximum and minimum values of the systolic blood pressure (SBP) during one mechanical breath. dDown was measured as the difference between the SBP value during 10 s of apnoea and the minimum SBP value during the respiratory cycle immediately following the apnoea. Both SPV and dDown were expressed as percentages of the SBP value during the apnoea period (%SPV and %dDown). Pulse pressure was calculated as the difference between the SBP and the diastolic blood pressure (DBP) of the previous beat. PPV was calculated as

$$100\times(\mathrm{PPmax}-\mathrm{PPmin})/[(\mathrm{PPmax}+\mathrm{PPmin})/2]$$

where PPmax and PPmin are the maximum and minimum PP values, respectively, during one respiratory cycle.[6 7] In addition, we measured the PP during apnoea (PPapnoea), and used this value to calculate the PPVapnoea as 100×(PPmax–PPmin)/(PPapnoea). The mean values of all the parameters during three consecutive breaths were used for further analysis. Two blinded investigators performed all measurements independent of each other and the mean of their results was used for the final analysis of the data.

Baseline measurements were obtained after 15 min of stable haemodynamic conditions. An artificial colloid solution (Poligeline 3.5%, Haemaccel, Behring), in a volume equivalent to 10% of the estimated blood volume (7% of body weight), was infused over 10 min, and a second set of measurements was obtained 5 min later. A graded haemorrhage of 10% of the total blood volume over 10 min was then performed and repeated five times, with haemodynamic measurements taken 5 min after each step. In the last phase of the study, the shed blood was retransfused over a 10-min period, followed by a final set of measurements. The whole experimental procedure lasted for 120 min.

Changes in haemodynamic parameters over time were analysed by analysis of variance corrected for repeated measures. The coefficient of linear correlation (r) between SVV and %SPV and PPV, and between PPV and PPVapnoea, was calculated for each animal and mean r values were obtained using inverse Fisher transformation. The linear correlation between SV and PPV, PPVapnoea, %SPV, %dDown, SVV, GEDV and CVP was calculated similarly.

Table 1 Haemodynamic parameters (mean [SD]) during initial volume loading, steps of haemorrhage and retransfusion. *$P<0.05$ compared with baseline; †$P<0.05$ compared with post-initial fluid loading values

	Baseline	Initial volume loading	Haemorrhage (% of estimated blood volume)					Retransfusion
			10%	20%	30%	40%	50%	
SBP (mm Hg)	126 (16)	131 (18)	127 (20)	122 (19)	118 (18)†	97 (27)†	76 (23)†	123 (11)
HR (beats min^{-1})	100 (16)	97 (18)	101 (20)	114 (27)	133 (27)†	148 (23)†	169 (25)†	123 (24)*
SV (ml)	23 (5)	34 (5)*	28 (4)†	21 (6)†	15 (5)†	10 (4)†	6 (2)†	28 (4)*
CVP (mm Hg)	4.4 (2)	4.7 (2.2)	3.5 (1.3)†	2.4 (1.5)†	2.2 (1.5)†	2.1 (1.5)†	1.7 (0.9)†	4.4 (1.7)
GEDV (ml)	496 (128)	589 (200)*	526 (176)†	461 (160)†	381 (159)†	308 (145)†	256 (119)†	531 (140)
%SPV	5.2 (3.3)	3.9 (2.6)*	5.5 (2.6)†	6.7 (3.6)†	7.7 (4.1)†	9.5 (3.2)†	11.5 (2.6)†	3.9 (1.4)
%dDown	3.5 (0.4)	1.7 (1.2)*	3.4 (2.2)†	4.9 (3.4)†	5.9 (3)†	7.8 (2.8)†	10 (2.7)†	2.8 (1.4)*
PPV (%)	6.8 (3.9)	4.1 (2.3)*	9.2 (4.7)†	11.8 (5.5)†	15.6 (6.0)†	19.3 (6.6)†	25.7 (5.0)†	6.5 (3.4)
PPVapnoea (%)	6.7 (3.8)	4.1 (2.6)*	8.9 (4.5)†	11.3 (5)†	14.4 (5.1)†	17.9 (5.8)†	23.2 (4.2)†	6.5 (3.3)
SVV (%)	13 (6)	10 (3)	14 (6)†	15 (7)†	18 (7)†	22 (7)†	26 (7)†	7 (2)

Results

All haemodynamic parameters recorded during the study (mean [SD]) are presented in Table 1.

Initial fluid loading

Initial fluid loading induced a significant change in SV, PPV, PPVapnoea, %SPV, %dDown and GEDV, but not in SBP, HR and CVP. The mean SVV decreased but the change was not statistically significant.

Graded haemorrhage

Graded haemorrhage induced significant changes in all measured parameters from the initial 10% blood loss; however, the changes in SBP and HR only became significant after 30% haemorrhage.

Correlation between SV and other parameters

At 50% haemorrhage SV decreased to a mean of 6 ml compared with a mean of 34 ml before bleeding started (Table 1). SV correlated well with SVV ($r=-0.88$), PPV ($r=-0.91$), %SPV ($r=-0.91$) and %dDown ($r=-0.91$). The correlation coefficients of SV with CVP and GEDV were 0.79 and 0.95, respectively.

SPV, PPV and SVV

The changes in %SPV, PPV and SVV during the study are shown in Figure 1A. Although all these parameters increased gradually and significantly with every step in the haemorrhage, the rate of change was highest for PPV, which increased by more than 400% at 50% haemorrhage relative to baseline values, compared with increases of 200% and 120% for SVV and %SPV, respectively. The correlation coefficients for SVV and %SPV, PPV and %SPV, and SVV and PPV were 0.93, −0.97 and −0.93, respectively (Fig. 1B).

PPV and PPV apnoea

There was a significant difference between PPV, as calculated by the original formula, and PPVapnoea ($P<0.01$), with the difference increasing as the haemorrhage progressed (Fig. 2). The mean difference between PPV and PPVapnoea at 50% haemorrhage was 2.3(3.1)% (range 0–8%).

Discussion

The respiratory-induced variations in arterial pressure and its derivatives have been gaining increasing interest as useful dynamic predictors of fluid responsiveness in ventilated patients.[17 18] The first of these parameters to be studied experimentally and clinically was SPV, which was shown to be a sensitive predictor of fluid responsiveness in ventilated patients.[4 5] Later, PPV was shown to give an accurate prediction of the response of the CO to fluid loading, with PPV values of ⩾13% allowing discrimination between responders and non-responders.[6] PPV was suggested to be better than SPV since the pulse pressure correlates directly with the stroke volume, and since the arterial systolic pressure may be affected to some extent by transmission of airway pressure.[7] Although the ability of PPV and SPV to predict fluid responsiveness has been tested in a number of studies,[1–6] both parameters are only surrogates of the changes in left ventricular stroke volume (LVSV) during positive-pressure ventilation. The respiratory changes in the LVSV itself, measured echocardiographically as changes in the velocity–time integral of aortic blood flow, have also been shown to be highly predictive of fluid responsiveness.[19 20]

Direct measurement of SVV has become clinically available with the introduction of arterial pulse contour analysis into selected monitors for the measurement of real-time continuous CO. Indeed, SV values obtained by PiCCO pulse-contour analysis have been repeatedly shown to correlate extremely well with SV measured by pulmonary and transpulmonary dilution techniques.[21–23]

We have previously demonstrated that an SVV value of 9.5%, measured with the PiCCO monitor, has an acceptable sensitivity and an excellent specificity in predicting a 5% increase in SV, in response to a minimum 100 ml plasma expander load.[8] Others have also demonstrated the

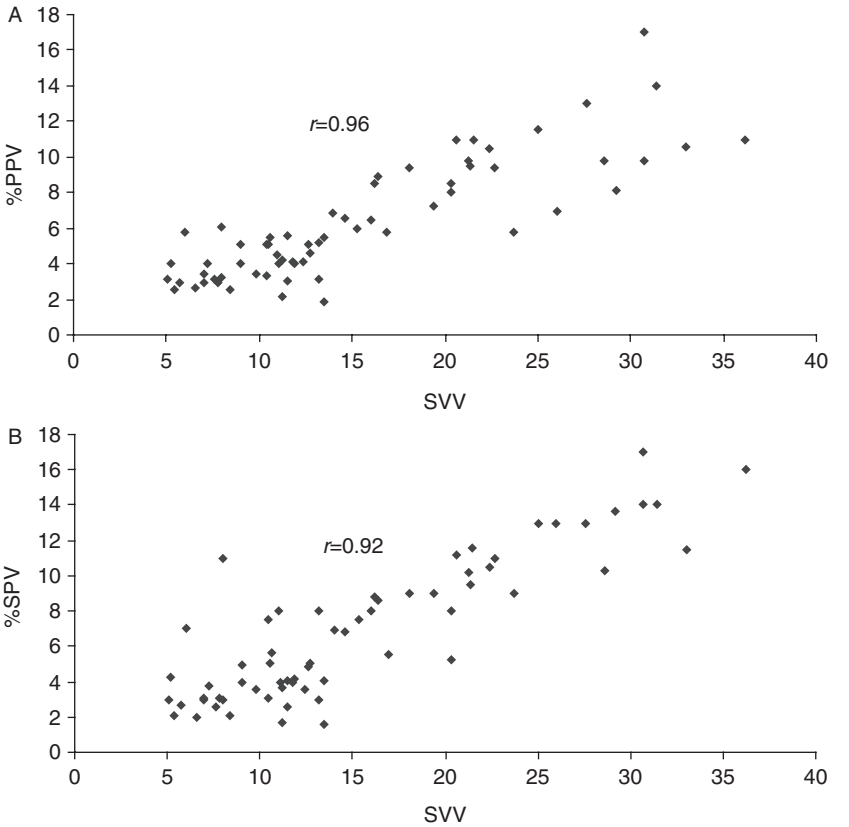

Fig 1 The correlation between (A) %PPV and SVV and (B) % SPV and SVV.

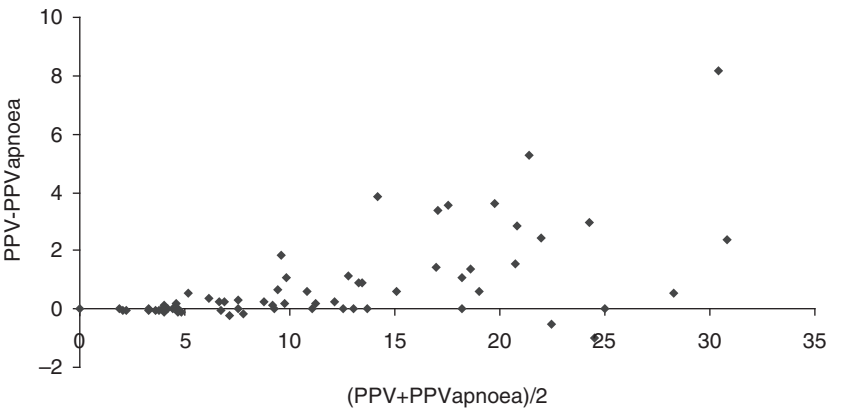

Fig 2 The difference between PPV and PPVapnoea against the mean of these parameters.

usefulness of the PiCCO-derived SVV in ventilated patients following cardiac surgery[9 10] and in critically ill patients.[22]

However, Wiesenack and colleagues[14] have found that SVV derived from PiCCO pulse contour analysis was unable to predict fluid responsiveness in ventilated patients after cardiac surgery, and Pinsky[12 13] raised concerns over the ability of the pulse contour algorithm to measure SVV accurately in two separate editorials where he correctly pointed out that the SVV has to be validated against the PPV as part of its clinical acceptance process.

The results of our study demonstrate that SVV measured by the PiCCO monitor reflects the decreases in blood volume even when low SV values of 6 ml are reached. Furthermore, the good correlation found between SVV, PPV and %SPV, in addition to the correlation between SVV and SV itself over a wide range of preload states, support the use of SVV as a parameter that can reflect changes in fluid status. Our study also demonstrates that GEDV, which is a volumetric parameter of preload, correlates well with functional haemodynamic parameters in this model of haemorrhage,

which is in accordance with previous findings.[16] The low correlation found between CVP and SV is not surprising and supports existing data.[23]

In this study we also compared two methods of calculating the PPV. According to the traditional formula, PPV is calculated as the ratio of the difference between PPmax and PPmin to the mean of these two values.[6 7] Using the mean of PPmax and PPmin in the denominator may seem logical under normal conditions where the mechanical breath induces an early increase and a later decrease in the LVSV. However, during hypovolaemia, when the only significant variation in the LVSV is a decrease in the LVSV, it seems more logical to relate the respiratory change in the PP to the PP value during apnoea. Indeed, our results show that when hypovolaemia progresses, the PPV values calculated according to the original formula gradually overestimate the PPV that is calculated using the PP value during apnoea in the denominator. However, the range of this overestimation was found to be $\leqslant$10% of the measured PPV values, and in the range of high PPV values such an overestimation may be of little clinical value. It is important to note that all our measurements of PPV have been done manually and offline, and that we have not tested the real-time automated PPV measurement that has become available in later models of the PiCCO plus monitor.

Although %SPV, PPV and SVV changed in the same direction during the successive steps of the haemorrhage and following retransfusion, and were found to correlate very well, the relative change of these parameters during the haemorrhage was not the same. While %SPV and SVV changed by 120% and 200%, respectively, PPV changed by $\sim$400% at the peak of hypovolaemia. The overestimation of PPV during hypovolaemia because of the way it is calculated, as discussed above, cannot account for this magnitude of change compared with the other parameters. Thus, although %SPV, SVV and PPV are very often used interchangeably, these parameters may be affected differently with progressing hypovolaemia as a result of their different natures. During severe hypovolaemia the aorta is emptier and more compliant. Therefore the stroke volumes that enter the aorta during the respiratory-induced phase of decreasing LV outflow (dDown) are entering an aorta which becomes progressively emptier, so that each successive SV produces a lower pulse pressure. Some aspects of this phenomenon have recently been addressed by Magder.[17] Therefore it is possible that the changing relationship between SV and the pulse pressure during severe hypovolaemia accounts for the growing disparity between PPV and SVV under these conditions. Since SVV is a direct measure of the changes in SV, and the pulse-contour SV (and hence SVV) was calibrated by the measurement of thermodilution CO, we can hypothesize that SVV is more accurate than PPV under these conditions. Nevertheless, the practical implications of this theoretical difference may be relatively insignificant since SVV and PPV both point clearly to the presence of significant fluid responsiveness.

One limitation of the present study is that SVV, PPV, %SPV and %dDown were not compared regarding their ability actually to predict fluid responsiveness precluding any quantitative conclusion as to which is the better parameter: PPV, SVV or SPV. Neither have we validated the individual respiratory-induced changes in the SV, as determined by the PiCCO pulse contour algorithm, against another method that independently measures individual SV. Such a study is certainly needed for a final validation of the SVV algorithm. Another limitation of our study was that recalibration of the pulse contour CO measurement was automatically performed when thermodilution CO measurement was done at each stage of the study. Thus we were not able to test the accuracy of the non-calibrated pulse contour algorithm when significant changes in vascular volume and tone occurred. It is also important to note that our findings regarding the SVV are relevant only to this parameter as measured by the algorithm used in the PiCCO monitor, and cannot be extrapolated to SVV measured by other algorithms.

In conclusion, this study demonstrates that in an experimental model of haemorrhage and retransfusion, the SVV, as measured by the pulse contour algorithm of the PiCCO monitor, and the PPV, as calculated by the formula originally proposed, change gradually and consistently with decreasing blood volume, and reflect changes in stroke volume even during extreme hypovolaemia.

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