

# Systolic Blood Pressure Variation is a Sensitive Indicator of Hypovolemia in Ventilated Dogs Subjected to Graded Hemorrhage

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Systolic pressure variation (SPV) is defined as the difference between the maximum and minimum values of systolic blood pressure following a single positive pressure breath. An increase in the SPV is known to occur clinically during hypovolemia. This study aims to quantify SPV during graded hemorrhage in ventilated dogs, and to compare its reliability relative to other hemodynamic indicators of hypovolemia. Ten anesthetized dogs were mechanically ventilated with a fixed tidal volume. A continuously inflated vest was applied around the chest to maintain the ratio of lung to chest wall compliance similar to that of humans ( $0.83 \pm 0.12$ ). SPV was further divided into  $\Delta$  up and  $\Delta$  down components relative to apneic (5 s) systolic blood pressure. Dogs were bled 5, 10, 20, and 30% of their estimated blood volume. The measured parameters best correlated to the amount of bleeding were SPV ( $\bar{r}_s = 0.993$ ),  $\Delta$  down ( $\bar{r}_s = 0.981$ ), and cardiac output ( $\bar{r}_s = 0.976$ ). The SPV and its  $\Delta$  down component correlated to the degree of hemorrhage as well as the CO and the pulmonary capillary wedge pressure, and significantly better than the central venous pressure and the mean systemic blood pressure. Thus, SPV and its  $\Delta$  down component are accurate indicators of hypovolemia in ventilated dogs subjected to hemorrhage. (Key words: Blood pressure; hypovolemia; ventilation. Blood, volume; hemorrhage. Lung: compliance. Ventilation: artificial; controlled.)

THE FLUCTUATION OF THE arterial pressure waveform due to intermittent positive pressure ventilation is well known. Following a single positive pressure breath, arterial pressure increases and then decreases corresponding to the respective increase and decrease in left ventricular stroke output.<sup>1,2</sup> The decrease in systolic blood pressure (SBP) following a mechanical breath is believed to be due to a decrease in the venous return as the intrathoracic pressure rises during inspiration.<sup>3,4</sup> Clinically, it is well recognized that the decrease in SBP is more pronounced during hypovolemia.<sup>5</sup> This phenomenon was also identified during spontaneous ventilation with hypovolemia,<sup>6</sup> while Massumi *et al.*<sup>7</sup> described it in other clinical conditions and termed it "reversed pulsus paradoxus." Coyle *et al.*<sup>8</sup> have used the

difference between the maximum and minimum values of SBP during one mechanical breath, termed by them the "positive pressure paradox," as a parameter that reflects a state of hypovolemia and decreases following the administration of fluids to hypovolemic patients. They used the SBP at end-expiration (*i.e.*, when the airway pressure is constant) as a reference pressure to further divide the difference between the maximum and minimum SBP into  $\Delta$  up and  $\Delta$  down components. The  $\Delta$  up was defined as being the difference between the maximum SBP and the end-expiratory SBP, and the  $\Delta$  down as the difference between the end-expiratory SBP and the minimal SBP (fig. 1). They found that, during hypovolemia, the  $\Delta$  down was the major component of the difference between maximum and minimum SBP.<sup>8</sup>

To further quantify this parameter, we measured it during graded hemorrhage, correlated its change to the amount of hemorrhage, and compared it to other accepted hemodynamic parameters. We prefer the term Systolic Pressure Variation (SPV) rather than Positive Pressure Paradox or Reversed Pulsus Paradoxus, because it is a non-paradoxical physiological phenomenon that occurs almost invariably to one degree or another.

## Materials and Methods

Ten dogs weighing 14.5–22 kg were anesthetized with intravenous pentobarbital (30 mg/kg). Following tracheal intubation, the dogs were paralyzed with a continuous intravenous infusion of succinylcholine ( $0.01 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ), and they were ventilated by a constant-volume ventilator (Harvard pump, Dover, MA) with a tidal volume of 12 ml/kg, at a rate of 12–14 breaths/min, so that mean  $\text{Pa}_{\text{CO}_2}$  was  $41.6 \pm 4.4$  mmHg. Inspired gas included 30% oxygen, 69% room air, and 1% halothane. Mean baseline  $\text{Pa}_{\text{O}_2}$  was  $139 \pm 26$  mmHg. Occasional metabolic acidosis was corrected with sodium bicarbonate. Throughout the study, each dog received a total of 5 ml/kg of Hemaccel (3.5% colloidal gelatin solution)<sup>§</sup> to preclude inadvertent hypovolemia.

A 16-gauge Teflon catheter was inserted into the femoral artery and a balloon-tipped catheter (7F, Instrumentation Laboratories, Lexington, MA) was in-

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serted into the pulmonary artery *via* the external jugular vein. An 8F catheter with additional side holes was inserted into the pleural space through the fifth intercostal space at the right midaxillary line. Airway pressure was measured through an opening in the endotracheal tube situated close to its tip. The airway and pleural pressure catheters were filled with normal saline and connected to Statham P23AA transducers, while systemic and pulmonary artery catheters were connected to Gould Statham P23Db transducers. All pressure traces were continuously recorded on a 4-channel Grass Polygraph (Grass Instruments, Quincy, MA).

Cardiac output was measured in triplicate by the injection of 5 ml iced saline using the IL cardiac output computer (model 701, Instrumentation Laboratories, Lexington, MA). All injections occurred at the same time during early expiration. Systemic and pulmonary vascular resistances, as well as intrapulmonary right-to-left shunt ( $Q_s/Q_T$ ), were calculated using standard formulae.

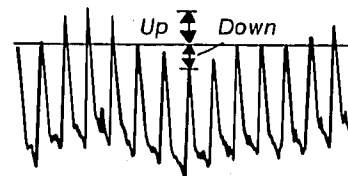
The SPV was measured as the mean difference between the maximum and minimum SBP during five consecutive breaths. The  $\Delta$  up and  $\Delta$  down components of the SPV were measured relative to the SBP during 5 s of apnea (SBP<sub>apn</sub>) (fig. 2). We have also calculated the ratio between the SPV itself and the maximum SBP, and termed it % SPV.

Lung (Cl) and chest-wall (C<sub>cw</sub>) compliances were measured by slow inflation of 300 ml of air with a pre-calibrated syringe, after which airway (P<sub>aw</sub>) and pleural (P<sub>pl</sub>) pressures were measured during a 2-s inspiratory hold. C<sub>cw</sub> and Cl were calculated as  $TV/\Delta P_{pl}$  and  $TV/(\Delta P_{aw} - \Delta P_{pl})$ , respectively. Because compliance of chest wall relative to lung compliance in dogs is greater than that of humans,<sup>9</sup> we used an inflatable vest situated around the dog's chest. The vest was inflated so that the Cl/C<sub>cw</sub> ratio increased to 0.75–1.0, which is the characteristic value for humans.<sup>10</sup> All hemodynamic parameters were measured before and after inflation of the vest, which was then kept inflated at the same level throughout the experiment. We then induced hypovolemia in the dogs by stepwise cumulative withdrawal of 5, 10, 20, and 30% of their estimated blood volume (presumed to be 7% of the body weight) from the arterial catheter. The interval between each step was 15 min, after which a new set of measurements was made. The shed blood was collected in plastic bags containing CPDA-1, and was retransfused 15 min after the last bleeding step. All parameters were measured 15 min after the completion of the retransfusion.

#### STATISTICAL ANALYSIS

Lung mechanics, blood gases, and hemodynamic parameters before and after vest inflation were compared

by the Wilcoxon matched-pairs test. For each dog, we have calculated the Spearman's rank correlation coefficient ( $r_s$ ) of each variable to the degree of hemorrhage. Mean  $r_s$  values ( $\bar{r}_s$ ) for all dogs were then calculated using the sine transformation<sup>11</sup> followed by Fisher's z transformation.<sup>12</sup> The mean correlation coefficients of SPV, %SPV, and  $\Delta$  down to the degree of hemorrhage were compared to those of cardiac output (CO), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), and mean systemic blood pressure (MBP) by a two-tailed Wilcoxon matched-pairs test. To maintain the experimentwise (type I) error rate  $\alpha$  below 0.05, use was made of Sidak's inequality:  $\alpha^1 = 1 - (1 - \alpha)^{1/k}$ , where k is the number of comparisons and  $\alpha^1$  is



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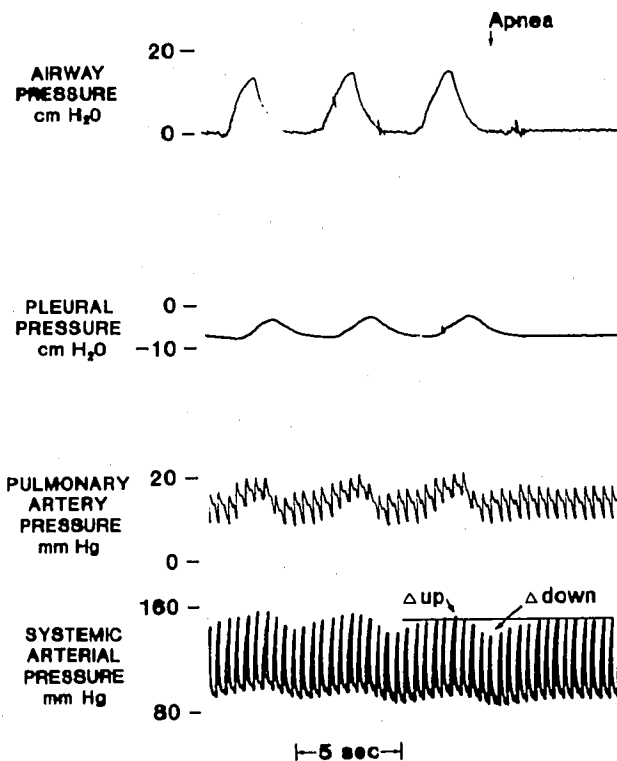


FIG. 2. Continuous record from a single mechanically ventilated dog with inflated thoracic vest after bleeding of 10% of estimated blood volume. The record shows airway, pleural, pulmonary arterial, and systemic pressures. The  $\Delta$  up and  $\Delta$  down components of SPV are indicated relative to systolic blood pressure during a 5-s period of apnea.

TABLE 1. Change in Cardiorespiratory Parameters Following Inflation of Perithoracic Vest (Mean  $\pm$  SD)

	Before Inflation	After Inflation	
Lung compliance (Cl) (ml/cmH <sub>2</sub> O)	65.5 $\pm$ 77.2	53.1 $\pm$ 44.1	NS
Chest wall compliance (C <sub>cw</sub> ) (ml/cmH <sub>2</sub> O)	100.2 $\pm$ 71.7	65.6 $\pm$ 51.8	*
Cl/C <sub>cw</sub>	0.55 $\pm$ 0.11	0.83 $\pm$ 0.12	*
Peak-inspiratory P <sub>pl</sub> (cmH <sub>2</sub> O)	2.8 $\pm$ 0.9	4.6 $\pm$ 1.4	*
CVP (mmHg)	4.6 $\pm$ 2.5	7.2 $\pm$ 4.1	*
PCWP (mmHg)	8.7 $\pm$ 3.4	10.8 $\pm$ 3.3	*
CO (l/min)	4.34 $\pm$ 1.10	4.76 $\pm$ 1.60	NS
MBP (mmHg)	109 $\pm$ 10	112 $\pm$ 20	NS
SPV (mmHg)	5.3 $\pm$ 1.8	8.1 $\pm$ 3.3	*
%SPV	3.4 $\pm$ 1.1	5.1 $\pm$ 1.2	*
$\Delta$ up (mmHg)	2.3 $\pm$ 2.2	3.1 $\pm$ 3.6	NS
$\Delta$ down (mmHg)	3.5 $\pm$ 2.5	5.3 $\pm$ 5.7	NS
Q <sub>s</sub> /Q <sub>T</sub> (%)	10.0 $\pm$ 4.2	14.8 $\pm$ 4.3	*
Pa <sub>O<sub>2</sub></sub> (mmHg)	146 $\pm$ 22	125 $\pm$ 24	*
Pa <sub>CO<sub>2</sub></sub> (mmHg)	42.3 $\pm$ 3.8	42.3 $\pm$ 4.0	NS
pH <sub>a</sub>	7.32 $\pm$ 0.04	7.32 $\pm$ 0.03	NS
PVR (dynes-sec/cm <sup>5</sup> )	167 $\pm$ 61	150 $\pm$ 69	NS
SVR (dynes-sec/cm <sup>5</sup> )	2017 $\pm$ 521	1918 $\pm$ 208	NS

\*  $P < 0.05$ .

the corresponding level of rejection for each individual comparison.<sup>13</sup> All values are shown as mean  $\pm$  SD.

### Results

Following inflation of the perithoracic vest, C<sub>cw</sub> decreased significantly, so that the Cl/C<sub>cw</sub> ratio increased (table 1). Vest inflation was also accompanied by expected increases in all intrathoracic pressures and an increase in SPV, while CO and BP did not change significantly. There was also a moderate, but significant, increase in Q<sub>s</sub>/Q<sub>T</sub> with a decrease in the Pa<sub>O<sub>2</sub></sub> following vest inflation (table 1).

The changes in the hemodynamic parameters during the gradual hemorrhage and the retransfusion are shown in figure 3, together with the mean correlation coefficients ( $\bar{r}_s$ ) of each variable to the degree of hemorrhage. The mean blood pressure and heart rate remained practically unchanged during the hemorrhage and retransfusion in most dogs. The SPV, %SPV and  $\Delta$  down showed an extremely significant correlation to the amount of bleeding (fig. 3), as did cardiac output, SVR, and PCWP. We have compared each of the mean correlation coefficients to the degree of hemorrhage of the SPV, %SPV, and  $\Delta$  down, to those of CO, PCWP, CVP, and MBP using the Wilcoxon matched-pairs test. Since each of the first three parameters was compared four times, the level of rejection ( $\alpha^1$ ) for each individual comparison was calculated to be 0.0127 according to Sidak's inequality (see Materials and Methods). Thus, the SPV, %SPV, and  $\Delta$  down correlated to the degree

of hemorrhage as well as did the CO and PCWP. The SPV and %SPV correlated to the degree of hemorrhage significantly ( $P < .01$ ) better than the CVP and MBP. The correlation coefficients of the SPV, %SPV, and  $\Delta$  down were not different from each other. Following retransfusion, all hemodynamic variables returned to their baseline values (fig. 3), except for the CO that stayed somewhat lower ( $3.97 \pm 1.74$  l/min after retransfusion, compared to  $5.21 \pm 2.1$  l/min at baseline,  $P < 0.054$ ).

### Discussion

Our model of gradual hemorrhage in dogs is unique because the ratio of lung to chest wall compliance was altered to resemble that of humans. We noticed, during pilot studies, that the SPV in hypovolemic dogs without the inflated perithoracic vest seemed to be less pronounced than that seen in human patients. This probably occurs because the high natural compliance of the chest wall in dogs<sup>9</sup> leads to decreased intrathoracic pressures and lower increases in pleural pressure<sup>14</sup> during mechanical inspiration. With smaller increases in pleural pressure, the impedance to venous return into the chest during mechanical inspiration is decreased, and cardiac output is thus less influenced by positive pressure ventilation, even during hypovolemia. By inflating the vest around the chest, we created mechanical conditions that are similar to the heart-lung interaction in humans. Although all intrathoracic pressures increased following vest inflation, the transmural pressures (*i.e.*, intravascular minus pleural pressures), CO and the MBP did not change significantly.

The hemorrhage induced in our model was both gradual and moderate, leaving ample time for circulatory compensation to occur in the lightly anesthetized dog. The hypovolemic state that was induced by gradual hemorrhage was not reflected by changes in blood pressure, heart rate, or CVP. Such a state of latent hypovolemia is very common in clinical practice, where the degree of hemorrhage cannot always be suspected from commonly monitored variables. Although we bled our dogs by 30% of their calculated blood volume, the actual effective intravascular volume probably had sufficient time to partially recover, due to both spleen contraction<sup>15</sup> and shift of fluids into the vascular space. Nevertheless, CO persistently decreased, and closely reflected each step of the hemorrhage. The analysis of the changes in the arterial waveform provided us with parameters, in addition to CO, to identify and quantify the stage of compensated hypovolemia.

Increased intrathoracic pressure was shown to contribute to decreased venous return as long as four decades ago.<sup>3,16</sup> The decreased venous return is ex-

pressed, after a delay due to the passage through the pulmonary circulation,<sup>17</sup> as a decrease in arterial pressure during the end of mechanical inspiration, reaching minimum values in the first part of expiration, and gradually increasing to a pre-inspiratory plateau if the ventilatory rate is slow enough. With a smaller effective blood volume, the output of the left ventricle will depend even more on preload. This is why SPV, %SPV, and  $\Delta$  down reflected the degree of hemorrhage as well as did CO itself. The %SPV was even more sensitive than the SPV, because it relates SPV to the absolute value of the systolic pressure at the time of measurement.

Cardiopulmonary mechanisms other than pure reduction in right and, subsequently, left ventricular preload may play a role in the changes of the arterial waveform following positive-pressure ventilation. Mechanical lung inflation increases pulmonary vascular resistance and, hence, may reduce right ventricular output by increasing its afterload. Acute dilatation of the right ventricle has been claimed to reduce left ventricular output by a leftward shift of the interventricular septum.<sup>18</sup> However, such shift has not been observed in later echocardiographic studies, either during positive-pressure ventilation<sup>2</sup> or during PEEP.<sup>19</sup> During mechanical inspiration, the afterload of the right ventricle is increased, but its preload is acutely decreased at the same time, so that, overall, its transmural filling pressure decreases.<sup>20</sup> At the same time, the preload of the left ventricle increases as blood is squeezed from the lungs during inflation. Thus, it is difficult to assume that a leftward shift of the interventricular septum occurs with each mechanical inspiration, and the eventual reduction in left ventricular stroke output seems to be a preload-dependent phenomenon only. The existence of reflexogenic mechanisms that may explain the ventilatory induced fluctuations in the arterial waveform has been intermittently mentioned over the years, but never proven. The slight but significant increase in heart rate that has been observed during lung inflation<sup>2</sup> cannot explain such fluctuations. Increased sympathetic or other autonomic discharges that increase during hypovolemia have not been shown to occur, and are difficult to imagine. It seems, therefore, that the main reason for the observed increases in SPV, %SPV, and  $\Delta$  down during hypovolemia is a significant reduction in preload due to the increased intrathoracic pressure.

In our model of graded hemorrhage, the  $\Delta$  up remained practically unchanged. Several explanations were offered for this normally occurring transient early increase in arterial blood pressure. The increased inspiratory intrathoracic pressure squeezes blood out of the lungs and increases left ventricular preload.<sup>16</sup> At the same time, decrease in systolic wall stress and aortic

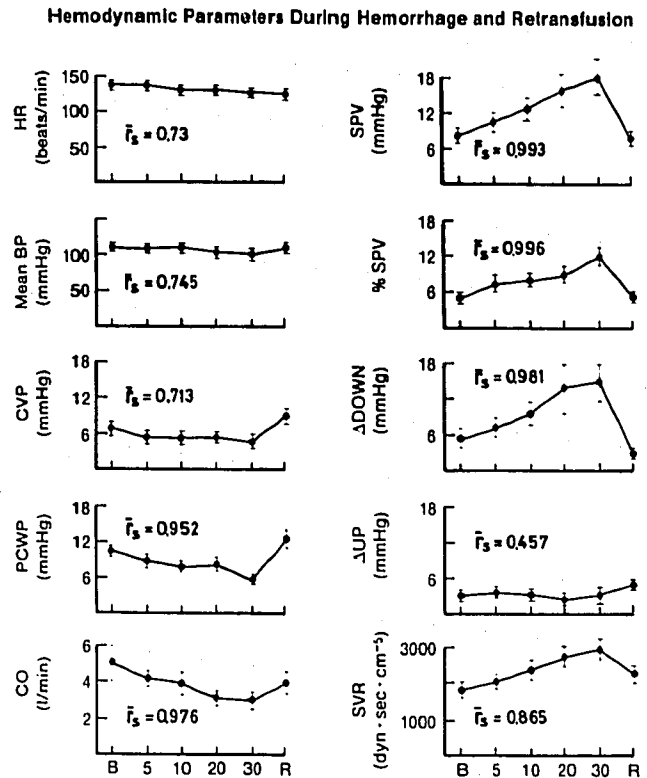


FIG. 3. The effect of the various stages of the experiment on: heart rate (HR), mean blood pressure (Mean BP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), systolic pressure variation (SPV), per cent SPV (% SPV),  $\Delta$  down component of SPV,  $\Delta$  up component of SPV, and systemic vascular resistance (SVR). On the abscissa are the stages of the experiment: B = baseline after vest inflation; 5, 10, 20, and 30 = the amount of blood removed as per cent of blood volume; R = retransfusion of shed blood. For each parameter, the mean Spearman's rank coefficient correlation ( $\bar{r}_s$ ) to hemorrhage is shown.

impedance are effectively equivalent to a decrease in left ventricular afterload.<sup>20-23</sup> Performance of the left ventricle may further be supported by the direct pressure of the expanding lungs on the heart,<sup>22,24</sup> and by improved left ventricular compliance due to a transient decrease in the volume of the right heart.<sup>18,25</sup> In pilot studies we have performed on dogs with congestive heart failure, the  $\Delta$  up component was the main component of the SPV, while the  $\Delta$  down component was insignificant. Presumably, this is because the transient decrease in venous return following a positive pressure breath affects CO less in congestive heart failure associated with high filling pressures.

Technically, SPV can be determined from good quality display of the arterial waveform. The introduction of a 5-s apnea period helps to determine the "true" systolic blood pressure, the %SPV, and the  $\Delta$  up and  $\Delta$  down components. It also serves to exclude continuous depression of the venous return and cardiac output due

to a combination of high ventilatory rate and low intravascular volume or air trapping. When a large  $\Delta$  down component is identified, excessively large tidal volume,<sup>4</sup> decreased chest wall compliance (e.g., such as during circular burn, external pressure, or muscle rigidity), and occasional arrhythmias<sup>7</sup> should be excluded before the diagnosis of hypovolemia is made.

Our experimental study suggests that the monitoring changes in the arterial pressure waveform during mechanical ventilation may constitute an additional parameter in the evaluation of effective hypovolemia in patients. This parameter is easily quantified once direct arterial pressure is monitored, and is more commonly available than CO measurement in both the operating room and intensive care environment.

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