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A Comparison of Changes in Cardiac Preload Variables During Graded Hypovolemia and Hypervolemia in Mechanically Ventilated Dogs

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We developed an online monitoring system to measure systolic blood pressure variation (SPV) and its down (dDown) and up components, along with pulse pressure variation (dPP). Using the system, we compared different cardiac preload indicators—such as stroke volume variation (SVV) and corrected flow time (FTc)—along with central venous pressure and pulmonary artery occlusion pressure in mechanically-ventilated dogs during normovolemia, graded hypovolemia (−200 and −350 mL), and hypervolemia (+200 and +350 mL). We simultaneously measured these preload indicators along with global hemodynamic variables and investigated their validity and limitations to access preload changes. SPV increased from 4.8 ± 1.4 mm Hg at baseline to 11.2 ± 1.8 mm Hg during hypovolemia (−350 mL), but it did not change significantly during hypervolemia. Similar changes were observed with dDown, dPP, and SVV. FTc, conversely, increased during hypervolemia but remained unchanged during hypovolemia. The results of this study indicate that SPV, dDown, dPP, and SVV are useful indicators of hypovolemia, but not of hypervolemia. Conversely, hypovolemia could not be detected reliably by FTc, but it does reflect blood volume changes during hypervolemia. Although SPV, dDown, and dPP measurements require no additional invasion and cost beyond arterial cannulation, their limits must be kept in mind for the monitoring of blood volume status in mechanically-ventilated patients.

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Systolic blood pressure variation (SPV) was first demonstrated as a sensitive indicator of hypovolemia by using mechanical ventilation (1). A variety of studies have shown that it is also a better predictor of any increase in cardiac output (CO) by volume loading than other conventional indexes, such as central venous pressure (CVP) or pulmonary arterial occlusion pressure (PAOP), in experimental and clinical settings (2,3). We developed an automated system to measure SPV and its down and up components, (dDown and dUp, respectively), along with pulse pressure variation (dPP), online minute by minute and to display SPV as a graph during a respiratory cycle (4). SPV monitoring has advantages over other monitoring techniques because it is simple and not associated with additional costs or complications beyond arterial cannulation.

New variables—stroke volume variation (SVV) derived by the arterial pulse contour analysis technique and corrected flow time (FTc) derived by esophageal Doppler monitoring—have been introduced to assess blood volume status and to optimize it in patients under general anesthesia (5,6). Randomized controlled studies have also shown that intraoperative volume loading guided with FTc results in a significantly reduced hospital stay in patients with proximal femoral fractures (5) and moderate- to high-risk surgery (7). Both SVV and SPV have also proven helpful in predicting the response to preload loading in patients after cardiac surgery (6). However, their value for assessing intravascular blood volume status has not been fully quantified, especially in regard to their limits in severe hypovolemia and hypervolemia.

We simultaneously measured SPV, dDown, dUp, dPP, SVV, FTc, and the conventional variables, i.e., CVP and PAOP, and evaluated these variables as preload indicators in a canine model of graded hypovolemia and hypervolemia by using mechanical ventilation.

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Methods

The study protocol was reviewed and approved by the institutional animal research committee (02-101). We studied 8 mongrel dogs (body weight, 10.0 ± 1.0 kg; age, 18 mo). The animals had free access to water before the experiment. Anesthesia was induced with IV thiopental 100 mg after premedication with IM ketamine 100 mg. The trachea was intubated, and the lungs were ventilated with 1% halothane/oxygen/nitrous oxide (fraction of inspired oxygen was 0.5 with a ventilator [Servo B; Siemens Elema, Solna, Sweden]) throughout the experiment. The respiratory rate was set to 15 breaths/min, with 25% of inspiratory phase and 75% of expiratory phase. Tidal volume was adjusted to obtain normocapnia ($Paco_2$ = 35–40 mm Hg). The ventilator settings were not changed during the study. To eliminate spontaneous respiratory effort, vecuronium 2 mg was administered every 30 min.

A flow-directed pulmonary catheter was placed through the right jugular vein, and a thermistor-tipped catheter (PV 20L16; Pulsion Medical Systems AG, Munich, Germany) was placed in the right femoral artery. The arterial catheter was connected to a hemodynamic monitor (PiCCO 4.1; Pulsion Medical Systems AG) to measure mean aortic pressure and CO by the transcardiopulmonary thermodilution technique. The monitor computes beat-to-beat stroke volume changes with arterial pulse contour analysis and presents SVV from the means of 4 minimum and maximum stroke volumes every 30 s (3). A double-lumen catheter was inserted into the right femoral vein for blood withdrawal and infusion to achieve hypovolemia and hypervolemia, respectively.

A Doppler ultrasound probe was inserted orally into the esophagus and connected to the monitoring device (EDM-1000; Nihon Kohden, Tokyo, Japan) to display descending aortic blood flow velocity. The monitor calculates FTc by dividing systolic flow time by the square root of the cycle time (5).

The dPP is defined as the maximal pulse pressure minus the minimum pulse pressure divided by the average of these pressures over a respiratory cycle (8). SPV, dUp, and dDown are defined as the difference between the maximal and the minimal values of systolic blood pressure, the maximal increase from the reference point, and the maximal decrease from the reference point, respectively, where the reference point is regarded as the systolic blood pressure at end-expiration. They were computed in each respiratory cycle and averaged over 1 min by using a desktop computer (233-MHz Intel Pentium®) equipped with a 16-bit analog/digital converter board (PCI-3156; Interface Co., Hiroshima, Japan) and custom-made software (4). The validity of the system has been previously confirmed by comparison with manual calculation of dUp, dDown, and dPP (data not shown).

When all catheters and the esophageal Doppler probe were placed, hemodynamics were stabilized for 30 min under normocapnia. After baseline measurements (Step 1) were obtained, hypovolemia was induced by cumulative withdrawal of 200 mL at Step 2 and 350 mL at Step 3 into a preservative-containing blood bag. Then intravascular blood volume was restored by retransfusion of the shed blood after the same pattern (Steps 4 and 5). Hypervolemia was induced by cumulative infusion of 200 mL of 6% hydroxyethyl starch at Step 6 and 350 mL at Step 7. Blood was withdrawn after the same pattern at Steps 8 and 9 to the baseline level.

Blood withdrawal and infusions to change intravascular blood volume were performed over 4–5 min from the femoral venous catheter. Hemodynamics were measured after 15 min of stabilization at each step.

All data are presented as mean ± SD. The analysis of variance for repeated measurements was used to detect significant changes in hemodynamic variables. When a significant difference was detected, the least-significance test was performed to compare the differences from the baseline values (at Step 1). Agreement of SVV and dPP was evaluated by the method of Bland and Altman (8). The correlation between variables was also analyzed by linear regression analysis. The level of statistical significance was $P < 0.05$.

Results

Changes in hemodynamic variables during hypovolemic and hypervolemic states are summarized in Table 1. Heart rate (HR) increased from 96 ± 20 bpm at Step 1 during hypovolemia (116 ± 22 bpm, 151 ± 22 bpm, and 130 ± 28 bpm at Steps 2, 3, and 4, respectively). It remained increased during hypervolemia (175 ± 10 bpm, 190 ± 8 bpm, and 182 ± 11 bpm at Steps 6, 7, and 8, respectively). CO and mean aortic pressure did not decrease significantly during hypovolemia but increased during hypervolemia as compared with the baseline values. Systemic vascular resistance increased during hypovolemia and decreased during hypervolemia. Both CVP and PAOP paralleled changes in blood volume status across hypovolemia and hypervolemia.

SPV and dDown increased from 4.8 ± 1.4 mm Hg and 2.0 ± 1.1 mm Hg, respectively, at Step 1 to 11.2 ± 1.8 mm Hg and 9.2 ± 1.3 mm Hg at Step 3 and then returned to 4.6 ± 1.6 mm Hg and 2.6 ± 1.4 mm Hg after complete retransfusion at Step 5 (Fig. 1, A and C). During hypervolemia, SPV and dDown were unchanged at Steps 6 and 7 but increased again at Steps 8 and 9 when hypervolemia was corrected by blood

Table 1. Hemodynamic Variables

Variable	Blood volume status (mL)					
	0	−200	−350	−250	0	+200
Step	1	2	3	4	5	6
HR (bpm)	96 ± 20	116 ± 22*	151 ± 22*	130 ± 28*	140 ± 12*	175 ± 10*
mAOP (mm Hg)	80 ± 8	80 ± 18	72 ± 16	92 ± 15	94 ± 12	100 ± 13
mPAP (mm Hg)	14 ± 2	11 ± 3*	11 ± 2*	13 ± 2	17 ± 2*	24 ± 2*
CVP (mm Hg)	7 ± 1	4 ± 1*	3 ± 2*	5 ± 2*	6 ± 1	10 ± 2*
PAOP (mm Hg)	7 ± 1	3 ± 3*	3 ± 2*	4 ± 2*	7 ± 2	11 ± 2*
CO (L/min)	1.1 ± 0.3	0.9 ± 0.2	0.8 ± 0.2	1.4 ± 0.3	2.4 ± 0.5*	3.6 ± 0.8*
SVR (dynes · s · cm^{-5})	5552 ± 888	6602 ± 1758*	7024 ± 1717*	4897 ± 577	3023 ± 716*	2047 ± 420*
SV (mL)	10.7 ± 1.5	8.5 ± 1.5	5.8 ± 1.5*	10.5 ± 1.5	15.0 ± 2.1*	17.7 ± 2.5*

Data are presented as means ± SD; $n = 8$.
HR = heart rate; mAOP = mean aortic pressure; mPAP = mean pulmonary artery pressure; CVP = central venous pressure; PAOP = pulmonary artery occlusion pressure; CO = cardiac output; SVR = systemic vascular resistance; SV = stroke volume.
* Significant compared with Step 1 ($P < 0.05$).

withdrawal to the baseline level. Although dUp changed significantly, these changes were small and could not be used to differentiate hypovolemia and hypervolemia (Fig. 1C). The changes in SPV were attributed mostly to changes in dDown.

SVV and dPP showed similar changes with dDown or SPV. They increased during hypovolemia and then returned to the baseline level with blood transfusion at Step 5 (Fig. 2, A and B). They decreased at Steps 6 and 7 during hypervolemia but increased again to 13.9% ± 4.6% and 11.8% ± 5.1%, respectively, at Step 9, when hypervolemia was corrected with blood withdrawal to the baseline level. Although FTc did not change during hypovolemia from 255 ± 29 ms at Step 1, it increased to 356 ± 117 ms at Step 5 when hypovolemia was corrected and to 434 ± 124 ms, 406 ± 109 ms, and 363 ± 75 ms at Steps 6, 7, and 8, respectively, during hypervolemia (Fig. 2C.

The mean difference between SVV and dPP was +1.9%, and the limits of agreements (mean ± 2SD) were +9.9 and −6.2% (Fig. 3). There was a significant correlation between SVV and dPP ($y = 0.64x + 5.4$; $r^2 = 0.67$; $P < 0.05$).

Discussion

The comparison of different variables of cardiac preload in this study demonstrated that SPV, dDown, dPP, and SVV are equally sensitive for detecting hypovolemia and for predicting fluid responsiveness during mechanical ventilation, but they do not correctly reflect blood volume status during hypervolemia. However, FTc did not change significantly during hypovolemia but increased significantly during hypervolemia, suggesting that it is more sensitive to blood volume changes during hypervolemia than during hypovolemia.

Attention should be paid to the fact that SPV, dDown, dPP, and SVV may still indicate hypovolemia when intravascular blood volume is corrected to the normovolemic level from severe hypervolemia. Increased venous capacitance due to preceding hypervolemia and, therefore, relative hypovolemia may explain this discrepancy. The increases in these variables should not be interpreted as indications of hypovolemia, but merely as a prediction of fluid responsiveness, when the blood volume state is acutely normalized from the hypervolemic state.

The drawbacks of CVP and PAOP monitoring are 1) relatively large individual variances and 2) invasiveness associated with catheter placement. CVP and PAOP at single points are hence considered poor indicators for the intravascular blood volume state or for predicting the responsiveness to intravascular fluid administration (3). However, CVP and PAOP changed in parallel with the intravascular blood volume status in this study, indicating their value for following an acutely changing intravascular blood volume state across hypovolemia and hypervolemia, at least under conditions with normal cardiac function.

An automated system for the measurement of SPV was first invented by Schwid and Rooke in 2000 (9). With our system, both SPV and dPP are measured automatically. Such a system is appropriate for use in all mechanically-ventilated patients whose arterial blood pressure has been monitored via an arterial catheter, because it does not require additional invasion or cost. Whereas Perel et al. (1) and others (10,11) used systolic arterial blood pressure as a reference value after a 5- to 12-second apneic pause, the reference value with this system is calculated from the systolic blood pressures just before and after end-expiration (12). This method has the advantage of not requiring interruption of mechanical ventilation.

Table 1. *(Continued)*

+350	+200	0
7	8	9
190 ± 8*	182 ± 11*	154 ± 19*
102 ± 13*	108 ± 16*	100 ± 15*
26 ± 2*	18 ± 5*	13 ± 3
11 ± 3*	6 ± 2	4 ± 1*
13 ± 2*	6 ± 2	4 ± 2*
4.0 ± 0.8*	3.2 ± 0.6*	2.1 ± 0.5*
1875 ± 420*	2647 ± 703	3847 ± 827
18.0 ± 3.3*	16.0 ± 2.4*	12.6 ± 2.1*

Whatever the reference methods used, the respiratory setting should not be changed, and the absence of spontaneous respiration should be confirmed, because SPV is affected by the magnitude of tidal volume and respiratory effort (13).

SPV, dDown, dPP, and SVV are referred to as *dynamic variables* because they reflect respiration-induced cyclic changes in preload, whereas CVP and PAOP are called *static variables* (3). The exact mechanism of SPV is complex and is thought to be a combined reflection of pleural pressure changes and left ventricular stroke volume changes, whereas

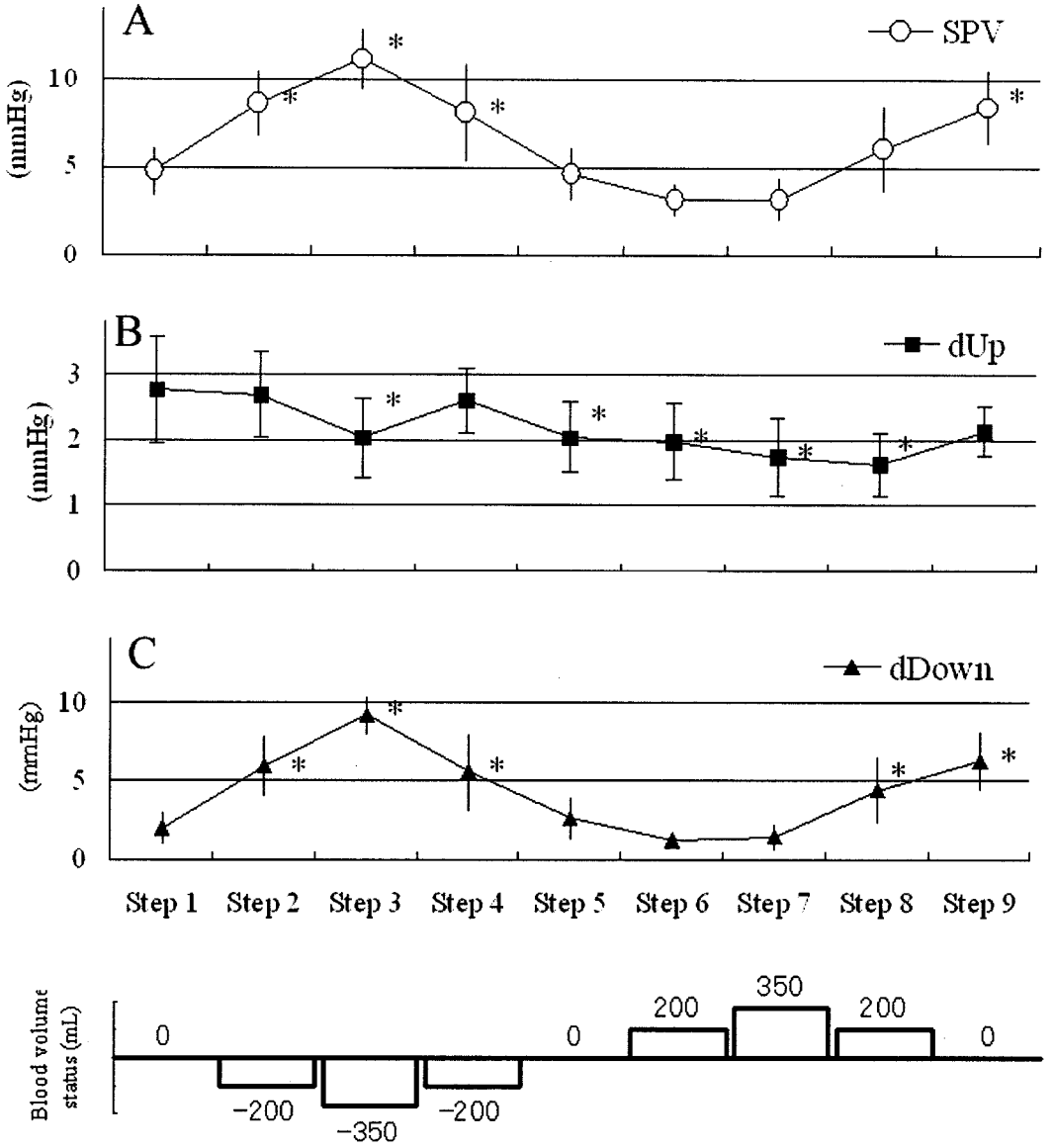

Figure 1. Changes in systolic blood pressure variation (SPV) (A), the up component of SPV (dUp; B), and the down component of SPV (dDown; C) during normovolemia (Steps 1, 5, and 9), hypovolemia (Steps 2, 3, and 4), and hypervolemia (Steps 6, 7, and 8). Hypovolemia and hypervolemia were induced by graded blood withdrawal and by infusion of 6% hydroxyethyl starch, respectively. SPV and dDown increased during hypovolemia but remained unchanged during hypervolemia. They increased again at Step 9, when intravascular blood volume was restored to normovolemia. Data are presented as means ± SD. **Significant compared with Step 1 ($P < 0.05$).

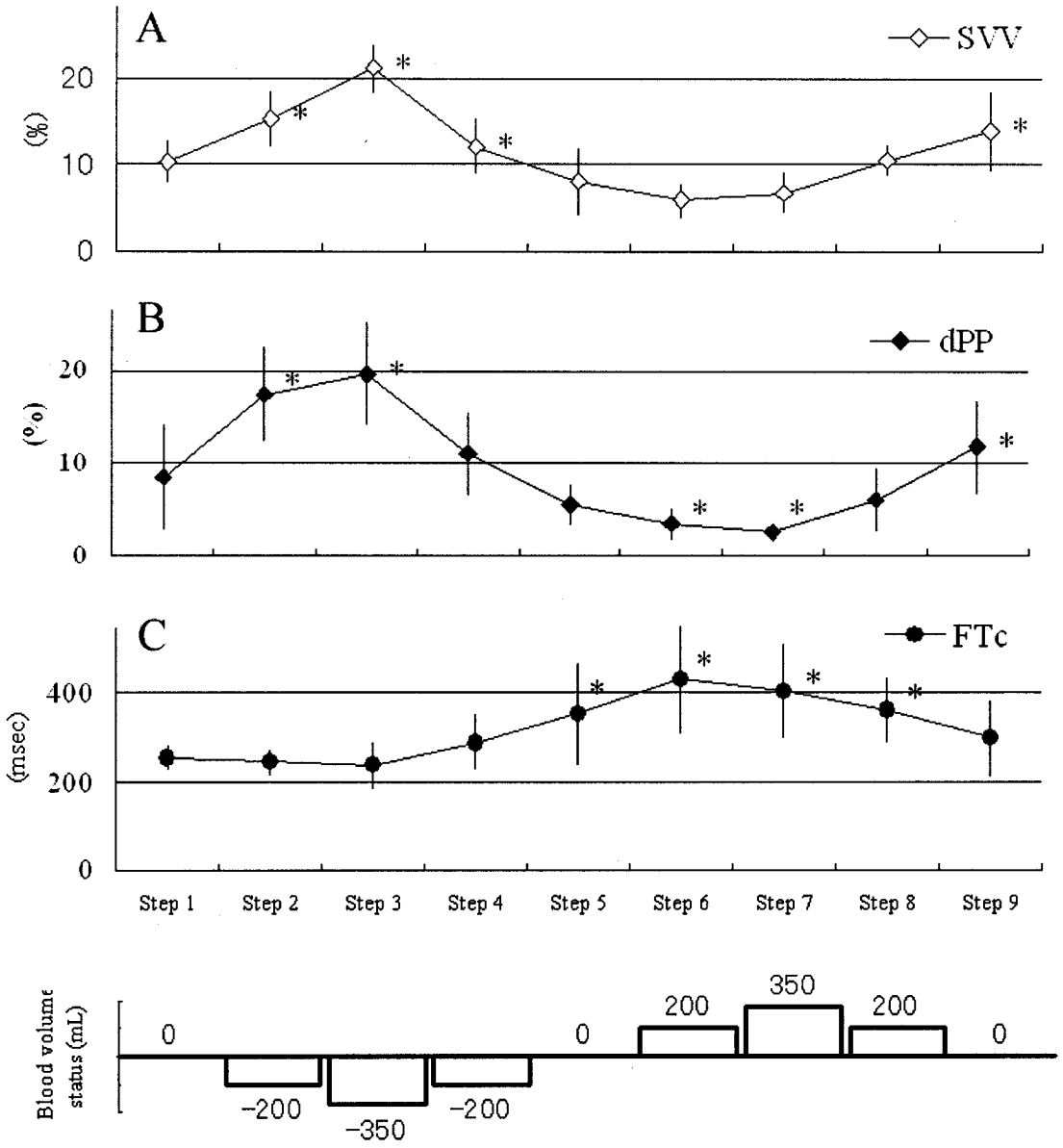

Figure 2. Changes in stroke volume variation (SVV) (A), pulse pressure variation (dPP; B), and esophageal Doppler-derived corrected flow time (FTc; C) during normovolemia (Steps 1, 5, and 9), hypovolemia (Steps 2, 3, and 4), and hypervolemia (Steps 6, 7, and 8). Hypovolemia and hypervolemia were induced by graded blood withdrawal and by infusion of 6% hydroxyethyl starch, respectively. SVV and dPP increased significantly during hypervolemia, and FTc increased during hypervolemia. SVV and dPP increased again when intravascular blood volume was restored to normovolemia after hypervolemia at Step 9. Data are presented as means ± SD. *Significant compared with Step 1 ($P < 0.05$).

dPP is thought to reflect changes in left ventricular stroke volume more directly (14). This study confirmed a close relation between SVV and dPP. A study by Reuter et al. (6) showed that SVV correlates well with the retrospective offline quantification of SPV. In line with their study, in this study SVV and SPV changed in parallel. On the basis of these results, it is thus considered that these dynamic variables are equally useful as indicators of hypovolemia in mechanically-ventilated patients.

The EDM has been recognized as a less invasive technique for CO monitoring and preload assessment by means of FTc. FTc is the time required for the left ventricle to eject the stroke volume with correction for the HR. FTc is considered to be closely related to the left ventricular end-diastolic volume and thus can be used as an indicator of the preload. Actually, FTc has been shown to be useful in guiding optimal cardiac filling in patients undergoing surgery (5,7). The results of this study, however, indicated that FTc is not a

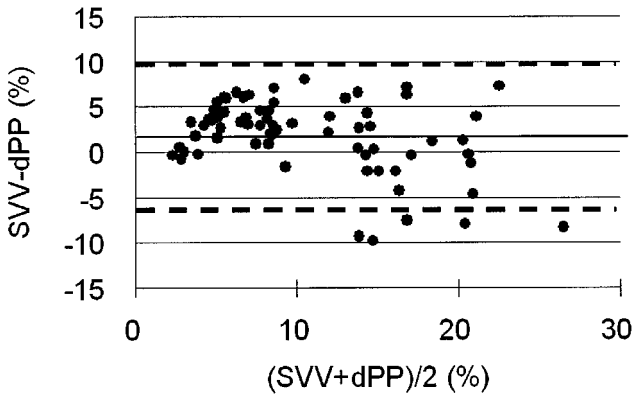

Figure 3. Differences between stroke volume variation (SVV) and pulse pressure variation (dPP) plotted against their means during normovolemia, hypovolemia, and hypervolemia in eight dogs. SVV was calculated by the arterial pulse contour technique, and dPP was measured by the automated system (see text for details). The horizontal solid line indicates the mean bias, and the dashed lines indicate the limits of agreement (mean ± 2SD).

reliable indicator of hypovolemia because it did not decrease during hypovolemia, as indicated by comparison with the value of normovolemia (Step 1). However, restoration of the blood volume after hypovolemia and the subsequent hypervolemic state resulted in a longer FTc, thus confirming the utility of this variable for assessing cardiac preload during a hypervolemic state. We defined the starting blood volume status as normovolemia, whereas optimal cardiac filling is usually achieved at the point of maximal stroke volume after intravascular fluid administration (7). The FTc (255 ± 29 ms) at baseline in our animals suggests suboptimal cardiac filling, because the normal range of FTc is 330–360 ms in humans (15). In other words, the baseline in this study was normovolemic in terms of the dynamic variables (i.e., SPV, dPP, and dDown) and, at the same time, suboptimal in terms of FTc. This discrepancy in the blood volume state at the baseline may explain the lower sensitivity of FTc during hypovolemia than during hypervolemia. In addition, the increases in vascular resistance during hypovolemia may have blunted a decrease in FTc, because FTc is dependent not only on cardiac preload, but also on vascular resistance (15).

There were some limitations in this experimental study. First, we evaluated the response of the newer variables during induced hypovolemia and hypervolemia. This study does not provide a comparison of these variables for predicting fluid responsiveness. Because the validity of arterial pulse contour-derived SVV as a predictor of fluid responsiveness was contradicted in a recently published article (16), further studies are required to confirm the validity of automatically measured SPV and dPP for predicting fluid responsiveness in different clinical settings. Second, the hypovolemia and hypervolemia induced in our experiment were regarded as moderate to severe, because 200 and 350 mL of blood or hydroxyethyl starch are estimated to be 25% and 43% of circulating blood volume, respectively, in dogs of 10 kg body weight. This is associated with increased sympathetic activity and a compensatory volume shift into and from the intravascular compartment.

In summary, findings in this study, which measured cardiac preload variables simultaneously in an animal model of graded hypovolemia and hypervolemia, indicated that SPV, dDown, dPP, and SVV are useful indicators of hypovolemia, but not of hypervolemia. Further, their values were found to be unreliable when blood volume was restored to normovolemia after severe hypervolemia. FTc is not appropriate for detecting hypovolemia, but it does reflect increases in blood volume during a hypervolemic state, and its usefulness to guide preload optimization is well accepted. Although online SPV and dPP measurements do not require any additional costs or invasion, beyond arterial cannulation, their limits must be considered for the monitoring of blood volume status in mechanically-ventilated patients.

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