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ORIGINAL ARTICLE

Stroke volume variation obtained with Vigileo/FloTrac™ system during bleeding and fluid overload in dogs

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Abstract
Purpose Stroke volume variation (SVV) is a parameter for estimating fluid responsiveness. Recently, the Vigileo™ and the Flo-Trac™ sensor (Edwards Lifesciences, Irvine, CA, USA) were made available for clinical use to estimate SVV. The aim of this study was to investigate the relationship between the circulating blood volume and SVV, measured by the Vigileo-FloTrac™ system (SVV-FloTrac) or by central venous pressure (CVP), during a dynamic change in circulating blood transfusion volume, using a continuous constant bleeding and fluid-overload model in dogs.
Methods Ten anesthetized and mechanically ventilated beagles were used. SVV-FloTrac and CVP were measured during a bleeding period (2 ml/kg/min, 15 min), a stabilization period (15 min), a blood transfusion period (2 ml/kg/min, 15 min), and a 6% hydroxyethyl starch solution overload period (2 ml/kg/min, 15 min).
Results SVV-FloTrac changed significantly when more than 8 ml/kg blood was withdrawn or when more than 8 ml/kg blood was transfused. The change in SVV-FloTrac directly reflected the circulating blood volume change during continuous bleeding and blood transfusion. CVP decreased significantly when more than 4 ml/kg blood was withdrawn or when more than 10 ml/kg was infused, and this indicated that the CVP change did not directly reflect the level of the circulating blood volume change. During the stable circulating blood volume period after blood withdrawal, SVV-FloTrac changed significantly but CVP remained constant. During the fluid overload period, CVP, but not SVV-FloTrac, changed significantly.
Conclusion SVV-FloTrac is a sensitive indicator of the dynamic circulating blood volume change during both bleeding and transfusion, but not during either the stable circulating blood volume period after blood withdrawal or the fluid-overload period, in mechanically ventilated dogs.

Keywords Stroke volume · Central venous pressure · Circulating blood volume

Introduction

During massive bleeding, accurate prediction of the cardiac preload and/or the circulating blood volume is crucial for fluid resuscitation. Although central venous pressure (CVP) has been used to assess the cardiac preload, many studies have suggested that cardiac filling pressures, such as CVP, are static indicators and the optimal cardiac preload for a given patient in a particular clinical setting cannot be assessed by CVP [1–3].

During positive-pressure ventilation, cardiac preload varies between the inspiratory phase and the expiratory phase. During the inspiratory phase, pleural pressure increases and this increase of pleural pressure decreases both right ventricular preload and right ventricular stroke volume (SV). This decrease of right ventricular SV during inspiration is proportional to the degree of left ventricular preload and is transmitted through the pulmonary vasculature and to the left heart after the long pulmonary blood transit time (approximately 2 s) [2]. This variation in left ventricular SV between the inspiratory phase and the expiratory phase during positive-pressure ventilation, the so-called stroke volume variation (SVV), is thought to be a

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good indicator of fluid responsiveness [1, 2, 4–6]. Although SVV is a good predictor of fluid responsiveness, the relationship between SVV and the circulating blood volume during bleeding, blood transfusion, and over-transfusion has not been fully examined. The relationship between SVV and the circulating blood volume level has been reported in graded (static) hypovolemia and hypervolemia models [7, 8], but not in a continuous (dynamic) bleeding and transfusion model. During surgery, the circulation volume changes dynamically. It is important to predict the circulation volume status while dynamic circulating volume changes occur.

Recently, new pulse contour methods [Vigileo^{TM} and the Flo-Trac^{TM} sensor (Edwards Lifesciences, Irvine, CA, USA)] have been introduced for the measurement of cardiac output. Unlike other SVV measuring systems, such as the PiCCO^{TM} monitoring system (PULSION Medical System, Germany), which require femoral or brachial arterial cannulation to estimate SVV, the Vigileo-FloTrac^{TM} system is able to estimate SVV using only a peripheral arterial pressure waveform without any other invasive monitoring. SVV measured by the Vigileo-FloTrac^{TM} system (SVV-FloTrac) has been reported to have acceptable sensitivity and specificity for the prediction of fluid responsiveness [6, 9, 10]. In the present study, we examined the relationship between the dynamic change of circulating blood level and the output of the FloTrac^{TM} sensor using a continuous constant bleeding, transfusion, and fluid-overload canine model. We also examined which parameter was more sensitive to the dynamic changes of circulating blood volume, SVV-FloTrac or CVP.

Methods

The following investigations were performed under a protocol approved by the Institutional Animal Care Committee, Kumamoto University (approval number A19-168). We studied 10 female beagles [body weight (mean ± SD): 11 ± 1 kg]. The animals had free access to food and water before the experiment. The trachea was intubated after the induction of anesthesia with thiamylal (25 mg/kg). Anesthesia was maintained with 1.5% isoflurane and 50% nitrous oxide in oxygen. The one minimum alveolar concentration (1 MAC) of isoflurane for dogs has been reported to be 1.28% [11]. Thus, 1.5% isoflurane and 50% nitrous oxide produced enough depth of anesthesia to perform this experiment. A ventilator was adjusted to maintain the $PaCO_2$ at 35–45 mmHg. The peak airway pressure during mechanical ventilation was maintained between 15 and 18 cmH_2O throughout the experiment. The right internal jugular vein was cannulated with a catheter (6 Fr) for fluid infusion, blood drainage, and blood transfusion. The left femoral artery was cannulated for the measurement of arterial blood pressure. Lactate Ringer's solution was infused at a rate of 5 ml/kg/h throughout the experiment, via a peripheral vein cannula that was inserted in the right foreleg. The animals were paralyzed with vecuronium (2 μg/kg/min) to avoid artifacts in the measurement of SVV-FloTrac secondary to muscle movement. The esophageal temperature was maintained at 37.0°C with a warming blanket.

The FloTrac^{TM} sensor kit was connected to the femoral arterial line and coupled to the Vigileo^{TM} monitor (software version 1.04; Edwards Lifesciences) to evaluate SVV-FloTrac. A central venous catheter was inserted from the external jugular vein for the measurement of CVP.

After all catheters had been placed, hemodynamics were stabilized for 30 min. If the level of SVV-FloTrac was more than 10%, the dogs received 6% hydroxyethyl starch solution (HES) until the SVV-FloTrac level was under 10%. Heparin (200 U/kg) was given intravenously just before blood removal. Blood was withdrawn at a speed of 2 ml/kg/min for 15 min (30 ml/kg blood loss), using a roller pump (BP-102; Terumo, Tokyo, Japan). The blood that was withdrawn was reserved in a bag that contained 2000 U heparin , to transfuse to the same dog. After the termination of blood withdrawal, the same circulating blood volume level was maintained in the animals for 15 min. The blood that was reserved in the bag was then transfused at a speed of 2 ml/kg/min for 15 min, using the roller pump (BP-102). After completion of the reserved blood transfusion, HES was infused at a speed of 2 ml/kg/min for 15 min in five of the ten dogs. SVV-FloTrac and CVP were measured every minute.

In addition, blood catecholamine (epinephrine and norepinephrine) levels were measured at the following time points: just before the start of blood withdrawal (pre-bleeding), just after the end of blood withdrawal (post-bleeding), just before the start of blood transfusion (pre-transfusion), and just after the end of blood transfusion (post-transfusion). For the norepinephrine and epinephrine assays, a 3-ml sample of blood was obtained via the external jugular vein. The samples were immediately spun in a refrigerated centrifuge and frozen (−70°C) for later batch analysis. Thawed plasma samples were assayed for epinephrine and norepinephrine (high-performance liquid chromatography; Tosho, Tokyo, Japan). The limit of measurement for both norepinephrine and epinephrine was 5 pg/ml or less. If the plasma concentration of norepinephrine or epinephrine was under the limit of measurement (5 pg/ml or less), 5 pg/mg was assigned as the plasma concentration. We also measured the hematocrit level at the time points of pre-bleeding, post-bleeding, pre-transfusion, and post-transfusion.

Wherever appropriate, data were expressed as mean ± SEM. Analysis of variance (ANOVA) for repeated

measurements was used to detect significant changes. Dunnett's multiple comparison test or Tukey's test was used for post-hoc analysis to determine the specificity of the changes at each time point. Linear regression analysis was used to detect the correlation between SVV-FloTrac and the circulating blood volume deficit. A $p < 0.05$ level of significance was considered statistically significant.

Results

Systolic blood pressures (mmHg; mean ± SEM) at the time points of pre-bleeding, post-bleeding, pre-transfusion, post-transfusion, and just after the HES overload period were 128 ± 7.3, 98.7 ± 10.2, 96.4 ± 10.1, 129 ± 5.4, and 137 ± 15.0, respectively. Heart rates (min^{-1}; mean ± SEM) at the time points of pre-bleeding, post-bleeding, pre-transfusion, post-transfusion, and post-overload were 118 ± 8.9, 140 ± 6.5, 131 ± 6.1, 118 ± 6.9, and 120 ± 12.0, respectively.

During blood withdrawal, the SVV-FloTrac increased significantly when the circulating blood volume deficit was more than 8 ml/kg; the SVV-FloTrac increased in a blood loss volume-dependent manner (Fig. 1, $p < 0.001$ by ANOVA). The CVP decreased significantly when the circulating blood volume deficit was more than 4 ml/kg; the CVP also decreased in a blood loss volume-dependent manner (Fig. 1, $p < 0.001$ by ANOVA).

During the 15-min stable circulating blood volume level period after 30 ml/kg blood withdrawal, SVV-FloTrac changed significantly (Fig. 2, $p < 0.001$ by ANOVA). On the other hand, CVP did not change during the 15-min stable circulating blood volume period (Fig. 2, $p = 0.448$ by ANOVA).

During blood transfusion, The SVV-FloTrac level decreased significantly when the blood transfusion volume was more than 8 ml/kg; the SVV-FloTrac decreased in a blood transfusion volume-dependent manner (Fig. 1, $p < 0.001$ by ANOVA). The CVP level increased significantly when the blood transfusion volume was more than 10 ml/kg; the CVP increased in a blood transfusion volume-dependent manner (Fig. 1, $p < 0.001$ by ANOVA).

Linear regression analysis revealed a significant correlation between SVV and the circulating blood volume deficit ($p < 0.0001$) during both bleeding and transfusion. The slope of the SVV regression line during bleeding was 1.03 (95% confidence interval 0.667–1.40) and that during transfusion was −0.727 (95% confidence interval −0.933 to −0.521). Linear regression analysis also showed a significant correlation between CVP and the circulating blood volume deficit during both bleeding ($p = 0.0003$) and transfusion ($p = 0.0006$). The slope of the CVP regression line was −0.0633 (95% confidence interval −0.0964 to −0.0302) and that during transfusion was 0.127 (95% confidence interval 0.0556–0.198).

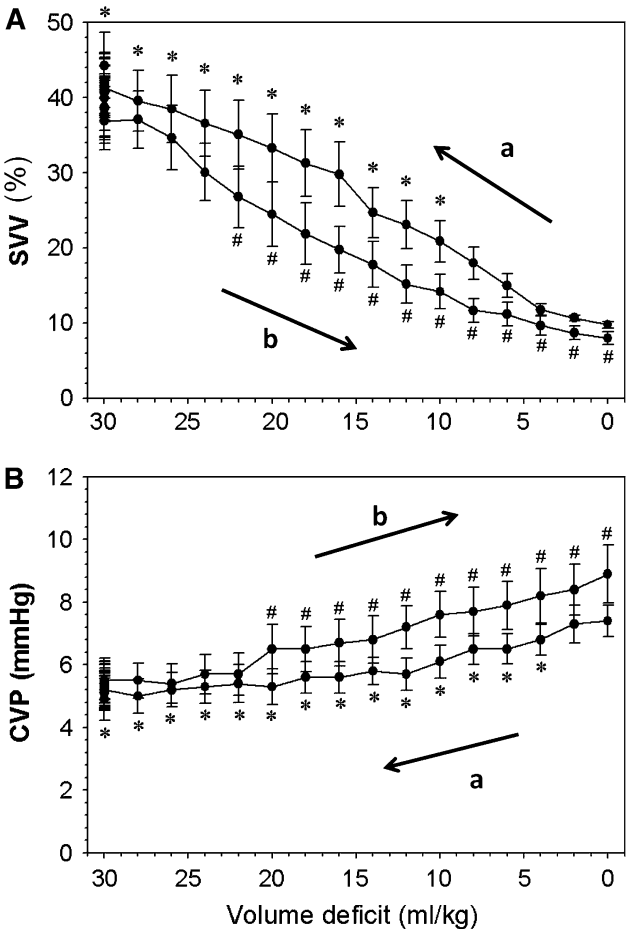

Fig. 1 Time course of change in stroke volume variation (SVV) measured by the Vigileo/FloTrac™ system (*SVV-FloTrac*) (**a**) and central venous pressure (*CVP*) change (**b**) during blood withdrawal (2 ml/kg/min) and blood transfusion (2 ml/kg/min). *Arrow a* indicates blood withdrawal and *arrow b* indicates blood transfusion. *Ordinate*: **a** SVV, **b** CVP. *Abscissa*: circulating blood volume deficit from pre-bleeding state (ml/kg). $^{*}p > 0.05$ as compared with the data at blood deficit level = 0. $^{\#}p > 0.05$ as compared with the data at blood deficit level = 30 ml/kg

HES overload (0–30 ml/kg) had no effect on SVV-FloTrac ($p = 0.121$ by ANOVA), but CVP increased when the volume of HES overload was more than 22 ml/kg ($p < 0.001$ by ANOVA) (Fig. 3).

The plasma norepinephrine level was significantly increased by 30 ml/kg blood withdrawal (Fig. 4). The pre-transfusion plasma epinephrine level was significantly increased as compared with the pre-bleeding level (Fig. 4). Transfusion, at 30 ml/kg, of the reserved blood significantly decreased both the plasma norepinephrine level and the plasma epinephrine level (Fig. 4). The hematocrit levels (%; mean ± SEM) at the time points of pre-bleeding, post-bleeding, pre-transfusion, and post-transfusion

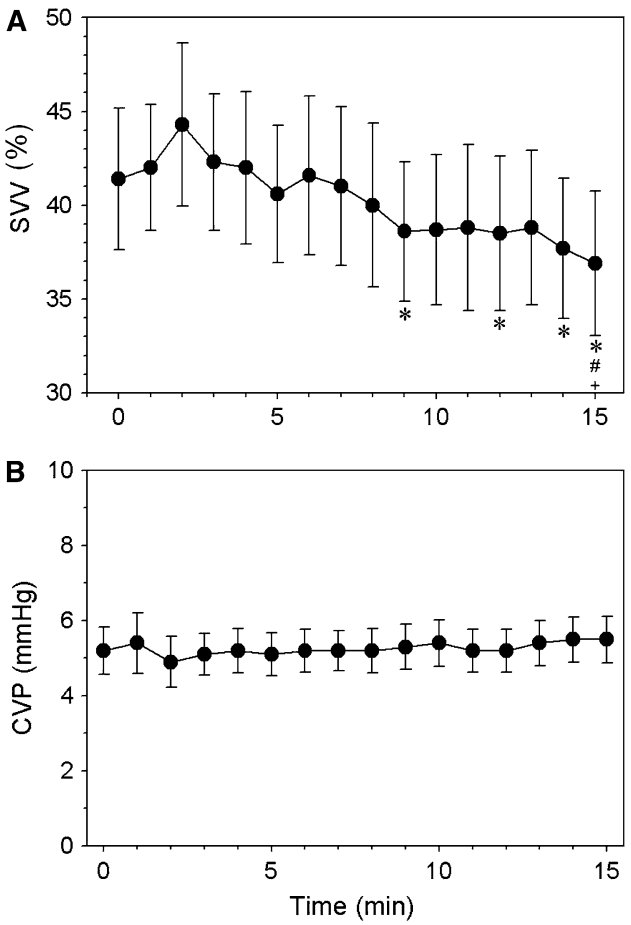

Fig. 2 Time course of SVV-FloTrac change (**a**) and CVP change (**b**) during 15-min stable circulating blood volume period after 30 ml/kg blood withdrawal. *Ordinate*: **a** SVV, **b** CVP. *Abscissa*: time after 30 ml/kg blood withdrawal (min). $^{*}p > 0.05$ as compared with the data at 3 min. $^{\#}p > 0.05$ as compared with the data at 4 min

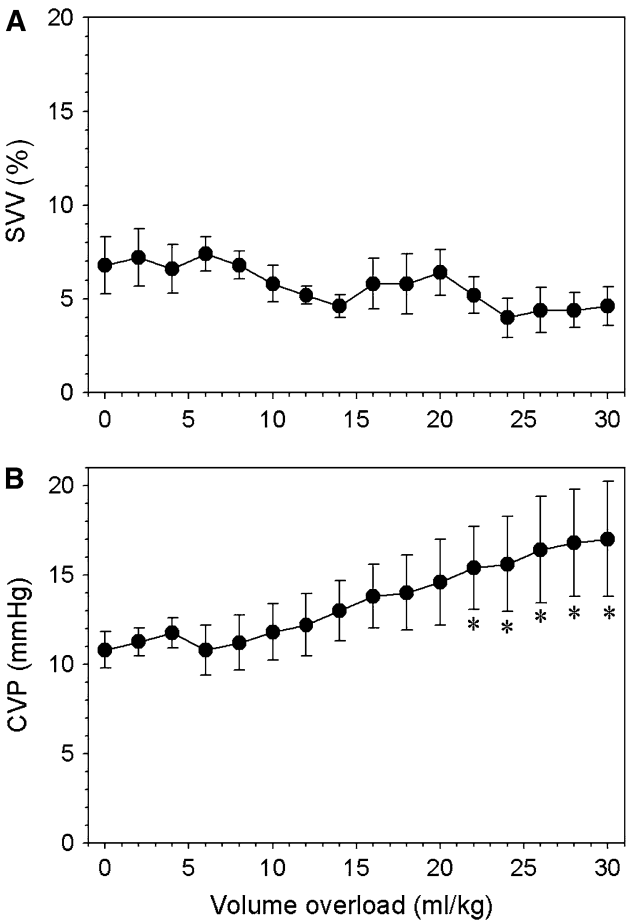

Fig. 3 Time course of SVV-FloTrac change (**a**) and CVP change (**b**) during hydroxyethyl starch solution (HES) overload period (2 ml/kg/min). *Ordinate*: **a** SVV, **b** CVP. *Abscissa*: time after the start of HES overload (min). $^{*}p > 0.05$ as compared with the data at time = 0

were 31.5 ± 0.9, 31.7 ± 0.7, 31.2 ± 0.9, and 29.7 ± 0.5, respectively. There was no statistically significant difference between pre-bleeding hematocrit and post-bleeding hematocrit ($p > 0.9$) or between post-bleeding hematocrit and pre-transfusion hematocrit ($p > 0.7$).

Discussion

In the present study, we demonstrated that, during the 15-min stable circulating blood volume level period after 30 ml/kg blood loss, SVV-FloTrac changed significantly. In previous graded ciculation volume change model (static model) study, SVV was obtained after the stabilization of hemodynamic parameters. Thus, the SVV obtained in the previous graded circulating blood volume change models (static-SVV) [7, 8] was different from that obtained in the present continuous circulating blood volume change model (dynamic-SVV). It is obvious that our present data are more relevant to the clinical surgical situation than the previous data that were obtained from static models.

We found that SVV-FloTrac changed significantly when more than 8 ml/kg blood was withdrawn or when more than 8 ml/kg blood was transfused; the SVV-FloTrac changed in a circulating blood volume deficit level-dependent manner throughout the periods of both blood withdrawal and blood transfusion. A significant correlation between SVV-FloTrac and the circulating blood volume deficit was observed during both the bleeding period and the transfusion period. This clearly indicates that SVV-FloTrac reflects the dynamic changes of the circulating blood volume deficit level during both blood withdrawal and blood transfusion. These data also indicate that SVV-FloTrac has similar sensitivities to the circulating blood volume changes that occur during bleeding and those that occur during blood transfusion. Although CVP, which is thought to be a static indicator of cardiac preload, decreased as the circulating blood volume deficit increased,

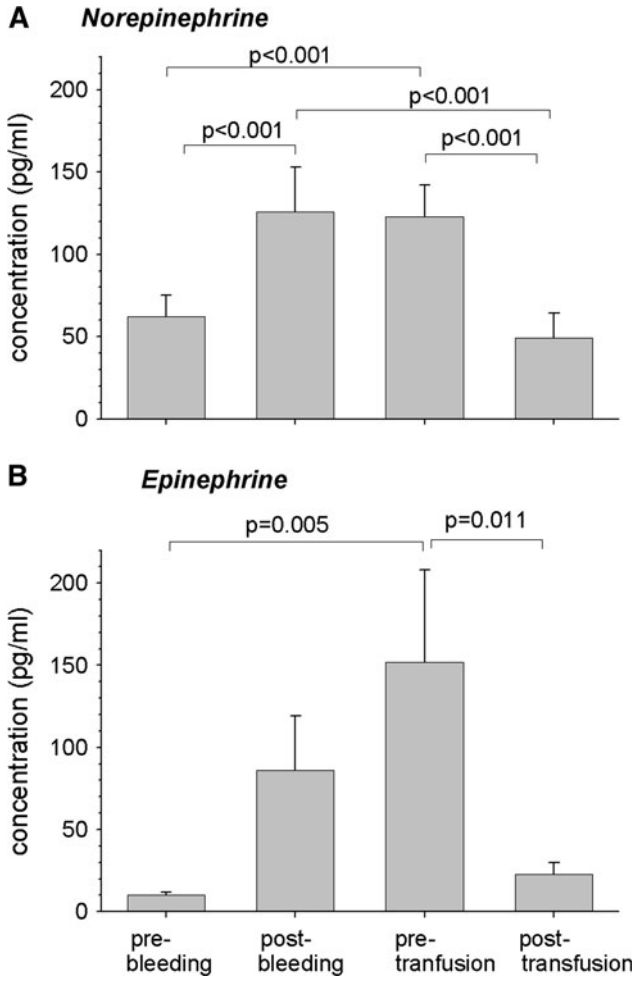

Fig. 4 Time course of plasma norepinephrine (**a**) and epinephrine (**b**) changes during blood withdrawal and blood transfusion. *Ordinate*: **a** plasma norepinephrine level (pg/ml), **b** plasma epinephrine level (pg/ml)

CVP changed significantly when more than 4 ml/kg blood was withdrawn or when more than 10 ml/kg was infused. Thus, CVP has different sensitivities to the circulating blood volume changes that occur during bleeding and those that occur during blood transfusion. Moreover, linear regression analysis revealed that the slopes of the SVV regression lines were significantly steeper than those of the CVP regression lines during both bleeding and transfusion. This also suggests that SVV is a much more sensitive indicator than CVP of the level of the dynamic circulating blood volume deficit during both bleeding and transfusion. During the overload phase, we found that SVV-FloTrac did not change as the overload volume level increased. This suggests that SVV-FloTrac is not a suitable indicator of circulating blood volume status during volume overload. On the other hand, CVP increased as the volume overload level increased. These findings are similar to those in a previous report which examined the relationship between the static change of circulation blood volume and SVV [7]. Our data strongly suggest that SVV-FloTrac is a more adequate indicator to assess the level of the circulating blood volume deficit during both bleeding and blood transfusion than CVP, and that CVP is a more adequate indicator than SVV-FloTrac during circulating blood volume overload . Thus, while SVV has been thought to be a good indicator of fluid responsiveness, our data indicate that SVV-FloTrac is also a good indicator of the circulating blood volume deficit level during bleeding and blood transfusion.

Our hemodynamic data indicated that continuous constant bleeding and fluid-overload procedures did not result in a state of shock, but resulted in a fairly stable hemodynamic state throughout the entire experiment. The hematocrit level did not change during the bleeding period or during the stable circulating blood volume period. This may suggest that blood withdrawal (30 ml/kg) itself did not induce water shift from the extracellular space to the intravascular space during the bleeding period or during the stable circulating blood volume period, and that the stable hemodynamic state resulted from the dynamic norepinephrine and epinephrine changes. During the 15-min stable circulating blood volume period after the 30 ml/kg blood loss, the epinephrine, but not the norepinephrine, level increased. Although this epinephrine increase was not statistically significant, we believe that this epinephrine increase may increase the preload of the left ventricle and decrease the SVV-FloTrac during the stable circulating blood volume period.

In the Vigileo-FloTrac^{TM} system, SVV is calculated by taking (maximum SV (SV_{max}) − minimum SV (SV_{min}))/ mean SV every 20 s. SV is reported to be proportional to the standard deviation of the pulse pressure and therefore SV can be calculated by using the following equation: $SV = \chi \times SD$ [12]. The Vigileo-FloTrac^{TM} system uses this equation to calculate SV. χ is a parameter that reflects the individual changes in aortic compliance and vascular resistance, and the value of χ changes from moment to moment. The Vigileo-FloTrac^{TM} system predicts an optimal χ value every 20 s according to the data obtained from an adult, but not a child. This indicates that SV measured by the Vigileo-FloTrac^{TM} system is reliable only when SV is measured in *an adult*, but not in *a child*. On the other hand, $SVV = \frac{SV_{max}-SV_{min}}{(SV_{max}+SV_{min})/2}$ can be replaced by $SVV = \frac{\chi\times SD_{max}-\chi\times SD_{min}}{(\chi\times SD_{max}+\chi\times SD_{min})/2}$. From this equation, we can cancel out the χ, $SVV = \frac{SD_{max}-SD_{min}}{(SD_{max}+SD_{min})/2}$. This equation is independent of χ. Therefore, SVV-FloTrac can be shown to be a measurement that is obtained by the standard deviation of the blood pressure waveform. This indicates that SVV-FloTrac, but not SV-FloTrac, measured by the Vigileo-FloTrac^{TM}

system, can be used universally. Thus, the SVV-FloTrac level obtained from dogs (body weight, 11 ± 1 kg) in the present study is reliable, and we did not use SV-FloTrac data in this study.

Variation in pulse pressure (PPV) was shown to be a useful predictor of fluid responsiveness [13]. PPV can be determined by the following equation: $PPV = (PP_{max} - PP_{min})/PP_{mean}$. Although PPV and SVV occur as a result of the same mechanism (cyclic changes of intrathoracic pressure induced by mechanical ventilation), PPV is based on the changes in pulse pressure and SVV is based on the changes in stroke volume. The Vigileo-FloTrac™ system can measure SV based on pulse wave-contour analysis and can estimate SVV. It has been suggested that alterations of vasomotor tone may influence PPV more than SVV [13]. Thus, we believe that SVV-FloTrac is a more valuable parameter than PPV for estimating the circulating blood volume level.

In conclusion, SVV-FloTrac was found to be a sensitive indicator of the level of the dynamic circulating blood volume deficit during both bleeding and transfusion in mechanically ventilated dogs. On the other hand, during the stable circulating blood volume period after blood withdrawal, SVV-FloTrac changed significantly. Moreover, during HES overload period, SVV did not change. The Vigileo-FloTrac™ system can estimate SVV using only a peripheral artery pressure waveform. We believe that SVV-FloTrac would be a useful indicator to assess the level of circulating blood volume in a mechanically ventilated patient during bleeding or blood transfusion.

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