Effect of Positive end-expiratory pressure on stroke volume variation: an experimental study in dogs

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Abstract

Background : Stroke volume variation (SVV) is reportedly affected by ventilation settings. However, it is unclear whether positive end-expiratory pressure (PEEP) affects SVV independent of the effect of driving pressure. We aimed to investigate the effect of driving pressure and PEEP on SVV under various preload conditions using beagle dogs as the model animal. **Methods :** Mild and moderate hemorrhage models were created in 9 anesthetized, mechanically ventilated beagle dogs by sequentially removing 10 mL/kg, and then an additional 10 mL/kg of blood, respectively. In all animals, driving pressure was incrementally increased by 4 cmH₂O, from 5 cmH₂O to 17 cmH₂O, under PEEP values of 4, 8, and 12 cmH₂O. Stroke volume (SV) was measured using the pulse-counter method and the thermodilution method. **Results :** The driving pressure did not significantly decrease SV under each preload condition and PEEP; however, increased SVV significantly. In contrast, the increased PEEP decreased SV and increased SVV under each preload condition and driving pressure, but these association were not statistically significant. According to multiple regression analysis, an increase in PEEP and decrease in preload significantly decreased SV ($P<0.01$). In addition, PEEP did not affect SVV, but the increased driving pressure and decreased preload significantly increased SVV. **Conclusion:** The SV decreased with an increase in PEEP; however, the SVV was not significantly affected by PEEP. Driving pressure had more influence than PEEP on SVV.

Background

Stroke volume variation (SVV) is a hemodynamic parameter that reflects fluid responsiveness.^{1,2} SVV is derived from an arterial pulse contour analysis that reflects the respiratory changes in stroke volume (SV) under positive pressure ventilation. Several papers have reported that an increased SVV could be used as a sensitive indicator of fluid responsiveness.¹⁻⁴ However, past studies have reported that the following factors influenced SVV: tidal volume, compliance of thoracic wall, and positive-end expiratory pressure (PEEP). Moreover, various respiratory settings are currently used in the care of critically ill patients; thus, we should understand the mechanism on how SVV changes under various respiratory settings and preloads.⁵⁻⁹

Previously, we reported that driving pressure significantly influenced SVV, and the association was enhanced by a decreased preload.¹⁰ However, it is still controversial whether PEEP increases SVV or not. Past studies have reported that SVV increases according to the increase in PEEP because the SV is reduced.^{11,12} However, these studies could not confirm the influence of PEEP on SVV, because PEEP and driving pressure changed simultaneously in these studies, with a fixed tidal volume under mechanical ventilation.¹³

Thus, we aimed to investigate the effect of PEEP on SVV by adjusting various preload conditions and driving pressure to differentiate the influence of PEEP and driving pressure.

Methods

This study is an animal experiment using beagle dogs and was performed following the Science Council of Japan guidelines for animal experimentation. We obtained approval from the ethics committee for Animal Experimentation of Osaka Prefecture University, Japan.

Five healthy beagle dogs, two spayed female dogs and three sexually intact male dogs, weighing approximately 10–12 kg, were evaluated and experimented in the operating room of same facility. Three of five dogs were used for repeated experiments, for a total of nine experiments. The dogs used twice received with a minimum 21-days period between experiments. The beagle dogs were purchased from Oriental Yeast Co., Ltd. in Tokyo, Japan, and bred in Osaka Prefecture University. They were housed in separate cages, in which the temperature was maintained at $23\pm 1^{\circ}\text{C}$ and the light/dark cycle of time was 12 hours. Feeding was once a day and water was available freely. All dogs were judged to be in good to excellent health based upon a physical examination, blood examination and chest radiography before each experiment by veterinarians. Food was withheld for at least 12hr before drug administration, but the dogs were allowed free access to water prior to each experiment.

Firstly, anesthesia was induced to the beagle dogs. We inserted a cannula into the peripheral vein and administered butorphanol tartrate continuously at a rate of 0.1 mg/kg/h. Subsequently, we administered the subcutaneous injection of 0.025 mg/kg atropine and intravenous injection of 0.5 mg/kg of diazepam during preoxygenation. While starting administration of propofol continuously at a rate of 8–16 mg/kg/h, we intubated the dogs with a cuffed endotracheal tube, with an internal diameter of 6.0–7.0 mm, after introducing anesthesia. After administration of neuromuscular blockade agents (1.0-mg/kg bolus of rocuronium bromide) with train-of-four monitoring, they were mechanically ventilated using a pressure-controlled mode with 50% oxygen, peak inspiratory pressure of 5–7 cm H₂O, inspiration to expiration ratio of 1:2, PEEP of 0 cmH₂O, and respiratory rate of 20 breaths/min (Evita 4, Dräger Medical, Lübeck, Germany). Before measurement, we adjusted the respiratory rate to maintain end-tidal CO₂ within 35–45 mmHg.

We inserted a cannula into the tarsal artery and continuously measured the arterial pressure and SVV using the Vigileo-FloTrac™ system (Edwards Lifesciences, Irvine, CA, USA). SVV was calculated based on an arterial pulse contour analysis, converting the animals' age to human terms and adjusting the body surface area according to the conversion table by Nelson et al.¹⁴ A thermodilution catheter (132F5, Edwards Lifesciences, Irvine, CA, USA) was inserted through an introducer (RR-A60G10S, TERUMO, Tokyo, Japan) into the right internal jugular vein. We measured continuously the central venous pressure (CVP) and intermittently cardiac output derived by the thermodilution method (COtd), injecting 5 mL of saline solution at a temperature of $<8^{\circ}\text{C}$ through a thermodilution catheter. SV derived from a thermodilution method (SVtd) was calculated using the formula: $\text{SVtd} = \text{COtd} / \text{HR} \times 1,000 \text{ (mL)}$. After induction of anesthesia, we administered 10 mL/kg of hydroxyethyl starch to maintain the mean arterial pressure (MAP) at $>60 \text{ mmHg}$ and pulse rate within 100 beats/min to stabilize hemodynamics and prevent hypotension during the experiment.

We prepared the following three preload conditions: baseline model, mild hemorrhage model, and moderate hemorrhage model. First, we removed 10 ml/kg of blood via an introducer catheter (mild hemorrhage model), then subsequently removed an additional 10 ml/kg of blood (moderate hemorrhage model).

We measured each parameter under varying ventilation settings and preloads. First, under the baseline model, driving pressure was incrementally increased by 4 cm H₂O, from 5 to 17 cmH₂O, under PEEP of 4, 8, and 12 cm H₂O. The higher limit of peak airway pressure was set to 21 cmH₂O to avoid injury to the dogs'

lung. We observed for at least 2 min between steps to stabilize the hemodynamics (Figure 1). We recorded SVV, CVP, MAP, COtd, heart rate (HR), and tidal volume (Vt) as baseline parameters under each ventilation setting. The CVP, MAP, and HR were obtained from the patient monitor (BP-608 Evolution II, Omron Colin, Tokyo, Japan). The COtd measurements were performed using the thermodilution method three times at driving pressure of 5, 13, and 17 cm H₂O, to avoid fluid loading. Under the mild and moderate hemorrhage models, we repeated the measurements in the same manner mentioned above. At the end of the experiment, the beagle dogs were carefully re-infused with removed blood, which was temporarily stored in a blood bag during measurement. The beagle dogs were followed up for a minimum 21-days period between experiments. All dogs were not euthanized, because a blood transfusion of 20 ml/kg at intervals more than 21-days is acceptable in the veterinary clinically.¹⁵

All data were presented as the mean±standard deviation (SD) or median (with interquartile range). We analyzed all data using the JMP Pro 12 software program for Windows (SAS Institute Inc., Cary, NC, USA). Correlations between more than two variables were analyzed using a linear regression model based on the least-squares method. The univariate analysis was used to analyze the effect of the relationship between PEEP and hemorrhage, driving pressure, and hemorrhage on SVV. We entered hemorrhage, PEEP, and driving pressure as covariates and performed a multivariate regression analysis to understand the factor affecting SV and SVV. Differences were considered significant for *p* values <0.05.

Results

Dog body weights ranged from 10.3 kg to 12.7 kg. All hemodynamic data recorded during the study are presented in Table 1. Under each preload condition, CO was significantly decreased according to the increase in PEEP; however, calculated SV and SVV were not decreased according to the increase in PEEP (Table 1).

Figure 2 shows that SVV decreases with increasing PEEP. The regression coefficients between SVV and PEEP were -0.16 (standard error [SE]; 0.12, *p*=0.18), -0.39 (SE; 0.20, *p*=0.05), and -0.68 (SE; 0.25, *p*<0.01) at baseline, with mild hemorrhage, and with moderate hemorrhage, respectively.

On the other hand, driving pressure significantly increased SVV under each preload condition (Figure 3). The regression coefficients between SVV and driving pressure were 0.59 (SE; 0.07, *p*<0.01), 0.91 (SE; 0.12, *p*<0.01), and 1.37 (SE; 0.14, *p*<0.01) at baseline, with mild hemorrhage, and with moderate hemorrhage, respectively.

In the multiple regression analysis, increasing PEEP and decreasing preload significantly decreased SV. The regression coefficients of PEEP and preload condition were -0.55 and -7.78, respectively (Table 2). In addition, in another multiple regression analysis, PEEP did not have an influence on SVV, but increasing driving pressure and decreasing preload significantly increased SVV. The regression coefficients of driving pressure and preload condition were 0.98 and 3.90, respectively (Table 3).

There were no important adverse events and death in each dogs.

Discussion

In this study, we demonstrated that PEEP decreased SV but did not increase SVV and driving pressure did not decrease SV but increased SVV under various preload conditions in experimental animals.

Previous studies have reported that SVV and systolic pressure variation (SPV), which can be derived from arterial pressure curve by pulse counter analyses, increase according to the increase in PEEP.^{11-13,16,17} Pizov et al. reported that SPV increases with increasing PEEP under mechanical ventilation with a fixed tidal volume of 15 ml/kg. They showed that driving pressure increases from 7.8 ± 2.6 cmH₂O to 15.5 ± 5.4 cmH₂O, and concomitantly PEEP increases from 0 cmH₂O to 20 cmH₂O.¹³ Similarly, Renner et al. reported that SVV increases with increasing PEEP under mechanical ventilation with a fixed tidal volume of 10 ml/kg.¹⁷ Given that their experiments were performed under volume-controlled ventilation, driving pressure was incrementally increased according to the increasing PEEP in healthy experimental animals. However, the major factor of elevating SVV should be driving pressure, not PEEP, because we reported that SVV correlates with driving pressure.¹⁰ Our experiment clarified that increasing driving pressure, rather than increasing PEEP, increases SVV.

On the other hand, Rose-Marieke et al. reported that SV decreased but SVV did not increase according to the increase in PEEP,¹⁸ with the driving pressure changing from 17 cmH₂O to 20 cmH₂O along with increasing PEEP. The discrepancy of these studies may be derived from unchanged driving pressure, while increasing PEEP. Why SVV did not increase with increasing PEEP is that driving pressure was not increase under the same volume condition, as previously described in our previous report.¹⁰

SVV is calculated from maximal SV (SVmax) and minimal SV (SVmin). SVmax is a measure of the inspiratory elevation of the left ventricle SV under mechanical ventilation.^{9,19,20} Additionally, the filling of the intrathoracic blood volume in the expiratory phase temporarily reduces LV preload and results in minimal SV (SVmin) at the beginning of expiration.

Driving pressure increase SVmax, and the difference between SVmax and SVmin increase. In fact, a previous study reported that a respiratory change of SV was low when a driving pressure was low.²¹

On the other hand, PEEP reduces the intrathoracic blood volume resulting in reduction of both SVmax and SVmin, but the difference between SVmax and SVmin was not increased by increasing the PEEP. Thus, our results that PEEP did not significantly affect SVV despite the reduction of SV were reasonable and understandable. Understanding the influence of PEEP and driving pressure on SV and SVV can lead to optimal fluid management.

The strength of our study is that we investigated the conditions under fixed driving pressure but not under fixed tidal volume. We recognize that, under fixed tidal volume, inspiratory pressure increased according to the increase in PEEP.⁵ Therefore, a study about the effect of PEEP on SVV with a fixed tidal volume may mislead our interpretation on the association between PEEP and SVV.

There are several limitations. First, we did not investigate the level of severe hemorrhage and high-PEEP model to avoid mortality in the studied animals. The conditions of severe hypovolemia and high-PEEP under mechanical ventilation may affect SVV. Second, ventilation settings used in healthy dogs cannot be

extrapolated for humans. Lung compliance, vascular responsiveness, and pulse counter changes during tachycardia may differ between sick humans and healthy dogs. The lung compliance of dogs is so high that their Vt can reach >40 mL/kg for a maximum peak inspiratory pressure of 21 cmH₂O.¹⁰

Conclusion

We found that PEEP reduced SV but did not increase SVV under various preload conditions in the experimental animals. Driving pressure had more influence than PEEP on SVV.

List Of Abbreviations

COTd: cardio output derived by the thermodilution method

CVP: central venous pressure

HR: heart rate

MAP: mean arterial pressure

PEEP: positive end- expiratory pressure

SV: stroke volume

SVV: stroke volume variation

SPV: systolic pressure variation

Vt: tidal volume

Declarations

Ethics approval and consent to participate

This study was performed following the Science Council of Japan guidelines for animal experimentation after obtaining approval from the ethics committee for Animal Experimentation of Osaka Prefecture University, Japan.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to institutional policy but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

TN, YK and TI designed the study; TI and YF anesthetized experimental dogs; SK, YK and KM drafted the manuscript; All authors have read and approved the final manuscript.

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Tables

Table 1. Changes in the measured parameters in relation to PEEP and blood withdrawal

Baseline

PEEP (cmH ₂ O)	SVtd (ml)	SVV (%)	COtd ^{ab} (l/ml)	HR ^{ab} (beats/min)	mBP ^{ab} (mmHg)	CVP ^{ab} (cmH ₂ O)	PCWP ^{ab} (mmHg)	TV ^a (ml)
4	31	8	3.9	101	72	3	6	255
	(24 , 42)	(6 , 11)	(2.2 , 4.5)	(83 , 122)	(66 , 78)	(2 , 6)	(3 , 8)	(135 , 358)
8	28	7	2.7	85	82	4	8	200
	(20 , 39)	(6 , 11)	(1.5 , 3.3)	(69 , 100)	(79 , 86)	(3 , 6)	(5 , 10)	(120 , 265)
12	27	7	2.7	85	83	6	10	120
	(20 , 36)	(6 , 10)	(1.5 , 3.2)	(74 , 100)	(79 , 86)	(4 , 6)	(7 , 10)	(91 , 166)

Mild hemorrhage model

PEEP (cmH ₂ O)	SVtd (ml)	SVV (%)	COtd ^{ab} (l/ml)	HR (beats/min)	mBP ^{ab} (mmHg)	CVP ^{ab} (cmH ₂ O)	PCWP ^a (mmHg)	TV ^a (ml)
4	20	11	2.6	112	74	1	4	287
	(17 , 35)	(8 , 16)	(1.7 , 3.8)	(87 , 137)	(65 , 80)	(1 , 3)	(2 , 4)	(173 , 362)
8	19	11	2.4	86	81	3	5	200
	(16 , 32)	(9 , 13)	(1.3 , 3)	(79 , 117)	(73 , 86)	(1 , 4)	(4 , 7)	(115 , 258)
12	20	11	2.2	100	81	4	7	123
	(15 , 28)	(7 , 12)	(1.3 , 3)	(86 , 117)	(72 , 85)	(2 , 4)	(6 , 8)	(91 , 160)

Moderate hemorrhage model

PEEP (cmH ₂ O)	SVtd (ml)	SVV ^{ab} (%)	COtd ^{ab} (l/ml)	HR (beats/min)	mBP (mmHg)	CVP ^{ab} (cmH ₂ O)	PCWP ^{ab} (mmHg)	TV ^a (ml)
4	16	16	2.3	140	64	1	3	270
	(11 , 23)	(11 , 24)	(1.4 , 2.8)	(124 , 153)	(55 , 73)	(0 , 1)	(1 , 3)	(179 , 343)
8	14	14	2.2	131	77	2	5	185
	(10 , 21)	(11 , 20)	(1.1 , 2.5)	(119 , 145)	(61 , 81)	(0 , 3)	(4 , 5)	(110 , 259)
12	12	14	2	140	64	3	6	118
	(8 , 17)	(11 , 18)	(1.1 , 2.2)	(127 , 147)	(54 , 71)	(2 , 4)	(5 , 7)	(86 , 154)

Data are expressed as mean [95% confidence interval]. Vt/w, tidal volume per kg body weight; SVV, stroke volume variation; SVtd, stroke volume derived using a thermodilution method;

COTd, cardiac output derived using a thermodilution method; HR, heart rate; CVP, central venous pressure; MAP, mean arterial pressure.

a Significant correlation with positive end-expiratory pressure, $P < 0.05$

b Significant difference with the hemorrhage model, $P < 0.05$

The presented parameters were aggregated without separating each driving pressure.

Table 2. The relationship of driving pressure, PEEP, and hemorrhage for SV by multiple regression analysis

	Coefficient (SE)	p value
Driving pressure	-0.13 (0.16)	0.44
PEEP	-0.55 (0.21)	<0.05
Hemorrhage	-7.78 (0.76)	<0.05

SE: standard error

Table 3. The relationship of driving pressure and PEEP and hemorrhage for SVV by multiple regression analysis

	Coefficient (SE)	p value
Driving pressure	0.98 (0.07)	<0.05
PEEP	0.08 (0.09)	0.4
Hemorrhage	3.90 (0.33)	<0.05

SE: standard error

Figures

Figure 1

The changes of ventilation settings under various preload conditions. We observed for at least 2 min between each ventilation settings on baseline, mild hemorrhage model (removal of 10 mL/kg of blood) and moderate hemorrhage model (removal of an additional 10 mL/kg).

Figure 2

The relationship between PEEP and SVV under each preload. Univariate analysis was used to analyze the relationship between PEEP and SVV under each preload using a linear regression model based on the least-squares method.

Figure 3

The relationship between driving pressure and SVV under each preload. Univariate analysis was used to analyze the relationship between driving pressure and SVV under each preload using a linear regression model based on the least-squares method.

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