INTRODUCTION

In humans, stroke volume variation (SVV) is a haemodynamic 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).\(^5\)\(^6\) 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.\(^7\)\(^9\)
Past studies reported that the changes in SVV directly reflected the fluid load in experimental dogs as well as humans.\textsuperscript{10,11} Thus, we previously reported that the peak inspiratory pressure (PIP) significantly influenced SVV, and the association was enhanced by a decreased preload in ventilated dogs, because we investigate the effect of PIP and preload on SVV.\textsuperscript{13} 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.\textsuperscript{13,14} 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.\textsuperscript{15}

Thus, we aimed to investigate the effect of PEEP on SVV by adjusting various preload conditions and driving pressure, which is PIP minus PEEP, to differentiate the influence of PEEP and driving pressure with pressure-controlled mode under mechanical ventilations in animal experiment.\textsuperscript{16}

2 | RESULTS

2.1 | Changes in the measured parameters in relation to PEEP and each preload

Dog body weights were 11.2 ± 1.0 kg. All haemodynamic data recorded during the study are presented in Table 1. Under each preload condition, cardiac output (CO) was significantly decreased according to the increase in PEEP; however, calculated SV and SVV were not significantly decreased according to the increase in PEEP under baseline and mild haemorrhage (Table 1). The changes of CO according to increasing PEEP under various preload are presented in Figure S1. CVP and PCWP were significantly increased according to the increase in PEEP under each preload.

Stroke volume (SV), SVV, CO, HR, MAP, CVP and PCWP were significantly changed according to blood withdrawal under each PEEP.

2.2 | The relationship between PEEP and SVV under each preload

Figure 1 shows that SVV decreases with increasing PEEP. The regression coefficients between SVV and PEEP were −0.16 (standard error [SE]: 0.12, \( P = .18 \)), −0.39 (SE: 0.20, \( P = .05 \)), and −0.68 (SE: 0.25, \( P < .01 \)) at baseline, with mild haemorrhage, and with moderate haemorrhage, respectively.

2.3 | The relationship between driving pressure and SVV under each preload

Driving pressure significantly increased SV under each preload condition (Figure 2). The regression coefficients between SVV and driving pressure were 0.59 (SE; 0.07, \( P < .01 \)), 0.91 (SE; 0.12, \( P < .01 \)), and 1.37 (SE; 0.14, \( P < .01 \)) at baseline, with mild haemorrhage, and with moderate haemorrhage, respectively.

2.4 | The relationship of driving pressure and PEEP and haemorrhage for SVV

In the 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 2). In addition, increasing PEEP and decreasing preload significantly decreased SV. The regression coefficients of PEEP and preload condition were −0.55 and −7.78, respectively (Table 3).

3 | DISCUSSION

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

The strength of our study is that we investigated the conditions under fixed driving pressure but not under fixed tidal volume. We recognized that, under fixed tidal volume, increasing in PEEP elevates inspiratory pressure which correlates with SVV.\textsuperscript{5,12} 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. Understanding the influence of PEEP and driving pressure on SV and SVV can lead to optimal fluid management.

Stroke volume variation 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.\textsuperscript{9,17,18} 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.\textsuperscript{19}

On the other hand, PEEP reduces the intrathoracic blood volume resulting in reduction of both SVmax and SVmin, and SVV: the difference between SVmax and SVmin is 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.

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.\textsuperscript{20,21} 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 cmH\textsubscript{2}O to 15.5 ± 5.4 cmH\textsubscript{2}O, and concomitantly PEEP increases from 0 cmH\textsubscript{2}O to 20 cmH\textsubscript{2}O.\textsuperscript{15} Similarly, Renner et al reported that SVV increases with increasing PEEP under mechanical ventilation with a
fixed tidal volume of 10 mL/kg. 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. In their experiments, SVV may have been strongly influenced by driving pressure because they experimented with a fixed tidal volume. 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, with the driving pressure not changing along with increasing PEEP. The discrepancy of these studies may be derived from unchanged driving pressure, while increasing PEEP.

There are several limitations. First, we did not investigate the level of severe haemorrhage and high-PEEP model to avoid mortality in the studied animals. The conditions of severe hypovolaemia 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 tidal volume (TV) can reach >40 mL/kg for a maximum peak inspiratory pressure of 21 cmH₂O. We must perform a similar experiment because we cannot apply this experiment to humans as it is. Third, the number of experimental dogs was small. The sample size may be markedly small, and the results may be affected by various factors, individual dogs, and haemodynamics. We obtained accurate results by avoiding the unstable hemodynamic state; this was achieved by observing the animals for at least 2 minutes between steps to stabilize their hemodynamics, and we measured the parameters at least four times for every ventilation setting. Fourth, we administered

### TABLE 1 Changes in the measured parameters in relation to PEEP and blood withdrawal

| PEEP (cmH₂O) | SVtd (mL) | SVV (%) | COtdᵃᵇ (l/mL) | HRᵃᵇ (beats/min) | MAPᵃᵇ (mm Hg) | CVPᵃᵇ (cmH₂O) | PCWPᵃᵇ (mm Hg) | TVᵃ | Baseline |
|-------------|-----------|---------|---------------|-----------------|-----------------|----------------|----------------|-----|-----------|
| 4           | 31 (24, 42) | 8 (6, 11) | 3.9 (2.2, 4.5) | 101 (83, 122)   | 72 (66, 78)     | 2 (3.2, 4)     | 6 (3.8, 8)     | 255 (135, 358) |
| 8           | 28 (20, 39) | 7 (6, 11) | 2.7 (1.5, 3.3) | 85 (69, 100)    | 82 (79, 86)     | 4 (3.6, 8)     | 8 (5.1, 10)    | 200 (120, 265) |
| 12          | 27 (20, 36) | 7 (6, 10) | 2.7 (1.5, 3.2) | 85 (74, 100)    | 83 (79, 86)     | 6 (4.6, 8)     | 10 (7.0, 12)   | 120 (91, 166)  |

Mild haemorrhage model

| PEEP (cmH₂O) | SVtd (mL) | SVV (%) | COtdᵃᵇ (l/mL) | HRᵃᵇ (beats/min) | MAPᵃᵇ (mm Hg) | CVPᵃᵇ (cmH₂O) | PCWPᵃᵇ (mm Hg) | TVᵃ |
|-------------|-----------|---------|---------------|-----------------|----------------|----------------|----------------|-----|
| 4           | 20 (17, 35) | 11 (8, 16) | 2.6 (1.7, 3.8) | 112 (87, 137)   | 74 (65, 80)    | 1 (1.3, 3)    | 4 (2.4, 8)     | 287 (173, 362) |
| 8           | 19 (16, 32) | 11 (9, 13) | 2.4 (1.3, 3)  | 86 (79, 117)    | 81 (73, 86)    | 3 (1.4, 4)    | 5 (4.7, 10)    | 200 (115, 258) |
| 12          | 20 (15, 28) | 11 (7, 12) | 2.2 (1.3, 3)  | 100 (86, 117)   | 81 (72, 85)    | 4 (2.4, 8)    | 7 (6, 8)       | 123 (91, 160)  |

Moderate haemorrhage model

| PEEP (cmH₂O) | SVtd (mL) | SVV (%) | COtdᵃᵇ (l/mL) | HRᵃᵇ (beats/min) | MAPᵃᵇ (mm Hg) | CVPᵃᵇ (cmH₂O) | PCWPᵃᵇ (mm Hg) | TVᵃ |
|-------------|-----------|---------|---------------|-----------------|----------------|----------------|----------------|-----|
| 4           | 16 (11, 23) | 16 (11, 24) | 2.3 (1.4, 2.8) | 140 (124, 153)  | 64 (55, 73)   | 1 (0, 1)       | 3 (1.3, 4)     | 270 (179, 343) |
| 8           | 14 (10, 21) | 14 (11, 20) | 2.2 (1.1, 2.5) | 131 (119, 145)  | 77 (61, 81)   | 2 (0.3, 5)    | 5 (4.5, 10)    | 185 (110, 259) |
| 12          | 12 (8, 17)  | 14 (11, 18) | 2 (1.1, 2.2)  | 140 (127, 147)  | 64 (54, 71)   | 3 (2.4, 7)    | 6 (5.5, 10)    | 118 (86, 154)  |

Note: Data are expressed as median (interquartile range).

Abbreviations: COtd, cardiac output derived using a thermodilution method; CVP, central venous pressure; HR, heart rate; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; PEEP, positive end-expiratory pressure; SVtd, stroke volume derived using a thermodilution method; SVV, stroke volume variation; TV, tidal volumes.

The presented parameters were aggregated without separating each driving pressure.

ᵃSignificant correlation with PEEP, \( P < .05 \)
ᵇSignificant difference with the haemorrhage model, \( P < .05 \)
atropine and some sedatives while inducing anaesthesia. These drugs often affect the haemodynamic parameters, which may have affected the results of this experiment. However, we administered starch to stabilize the haemodynamics before measuring the parameters; this experiment was not interrupted while increasing PEEP.

In 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.

4 | 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.

### Experimental animals

Nine healthy beagle dogs, weighing 11.2 ± 1.0 kg, were used. The dogs used twice for the present study received with a minimum 21-days period between experiments. The beagle dogs were purchased from Oriental Yeast Co. and bred in Osaka Prefecture University. They were housed in separate cages, in which the temperature was maintained at 23 ± 1°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 12 hours before drug administration, but the dogs were allowed free access to water prior to each experiment.

### Anaesthetic management

First, we subcutaneously injected 0.025 mg/kg atropine. We inserted a cannula into the peripheral vein and intravenously administered 0.5 mg/kg of diazepam during preoxygenation. Anaesthesia was induced by continuous administration of butorphanol tartrate at a rate of 0.1 mg/kg/h and of propofol at a rate of 8 mg/kg/h. We performed bolus injection of 1 mg/kg propofol and continuously increased the concentration up to 16 mg/kg/h. We intubated the dogs using a cuffed endotracheal tube, with an internal diameter of 6.0-7.0 mm, after inducing anaesthesia. After administration neuromuscular blockade agents by a 1.0-mg/kg bolus of rocuronium bromide with train-of-four monitoring, they were mechanically ventilated with pressure-controlled mode with 50% oxygen, a PIP of 5-7 cmH₂O, an inspiration to expiration ratio of 1:2, a PEEP of 0 cmH₂O and a respiratory rate of 20 breaths/min (Evita 4; Dräger Medical, Lübeck, Germany). Before measurement, we adjusted respiratory rate to maintain end-tidal CO₂ within 35-45 mm Hg.

We inserted a cannula into the tarsal artery and continuously measured the arterial pressure and SVV using the Vigileo-FloTrac™ system (Edwards Lifesciences). SVV was calculated based on a linear regression model based on the least-squares method. Driving pressure is PIP minus PEEP with pressure-controlled mode. The regression coefficients between SVV and driving pressure were 0.59 (SE 0.07, P < .01), 0.91 (SE 0.12, P < .01), and 1.37 (SE 0.14, P < .01) at baseline, with mild haemorrhage, and with moderate haemorrhage, respectively. PEEP, positive end-expiratory pressure; PIP, plateau airway pressure; SVV, stroke volume variation; ( ), Baseline; ( ), Mild haemorrhage; ( ), moderate haemorrhage.
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°C through a thermodilution catheter. Moreover, we measured pulmonary capillary wedge pressure (PCWP) by injecting 5 mL of air and expanding the balloon. SV derived from a thermodilution method (SVtd) was calculated using the formula: SVtd = COtd/heart rate (HR) × 1000 (mL). After induction of anaesthesia, we administered 10 mL/kg of hydroxyethyl starch to maintain the mean arterial pressure (MAP) at >60 mm Hg and pulse rate within 100 beats/min to stabilize haemodynamics and prevent hypotension during the experiment.

4.3 Measurement of haemodynamic parameter under baseline model and haemorrhage models

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

We measured each parameter under varying ventilation settings and preloads. First, under the baseline model, initial ventilator setting was driving pressure of 5 cmH₂O under PEEP of 4 cmH₂O. PIP was incrementally increased by 4 cmH₂O, from 9 to 21 cmH₂O. Similarly, PIP was incrementally increased by 4 cmH₂O, from 13 to 21 cmH₂O under PEEP of 8 cmH₂O and from 17 to 21 cmH₂O under PEEP of 12 cmH₂O. The higher limit of PIP was set to 21 cmH₂O to avoid injury to the dogs' lung. We observed for at least 2 minutes between steps to stabilize the haemodynamics (Figure 3). We recorded SVV, CVP, MAP, COtd, HR, and TV as baseline parameters under each ventilation setting at least four times. The CVP, MAP, and HR were obtained from the patient monitor (BP-608 Evolution II; Omron Colin). The COtd measurements were performed using the thermodilution method three times at PIP of 9, 17, and 21 cmH₂O, to avoid fluid loading. Under the mild and moderate haemorrhage models, we repeated the measurements in the same manner mentioned above. At the end of the experiment, the dogs were carefully re-infused with removed blood, which was temporarily stored in a blood bag during measurement. The dogs were followed up for a minimum 21-days period between experiments. All dogs were not killed, because a blood transfusion of 20 mL/kg at intervals more than 21-days is acceptable in the veterinary clinical practice. There were no important adverse events or death in any dogs.

4.4 Statistical analysis

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, 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 haemorrhage, driving pressure, and haemorrhage on SVV. We entered haemorrhage, 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 <.05.
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CONFLICT OF INTERESTS

The authors declare that they have no competing interests and funding is nothing.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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