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Effect of the respiratory rate on the pulse pressure variation induced by hemorrhage in anesthetized dogs

Dalhae Kim (ID), **Won-Gyun Son** (ID), **Donghwi Shin** (ID), **Jiyoung Kim** (ID), **Inhyung Lee** (ID) *

Department of Veterinary Clinical Science, College of Veterinary Medicine, Seoul National University, Seoul 08826, Korea

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*Corresponding author:
Inhyung Lee
Department of Veterinary Clinical Sciences,
College of Veterinary Medicine, Seoul National
University, 1 Gwanak-ro, Gwanak-gu, Seoul
08826, Korea.
Email: inhyunglee@snu.ac.kr
https://orcid.org/0000-0002-0712-7165

ABSTRACT

Background: Studies on anesthetized dogs regarding pulse pressure variation (PPV) are increasing. The influence of respiratory rate (RR) on PPV, in mechanically ventilated dogs, has not been clearly identified.

Objectives: This study evaluated the influence of RR on PPV in mechanically ventilated healthy dogs after hemorrhage.

Methods: Five healthy adult Beagle dogs were premedicated with intravenous (IV) acepromazine (0.01 mg/kg). Anesthesia was induced with alfaxalone (3 mg/kg IV) and maintained with isoflurane in 100% oxygen. The right dorsal pedal artery was cannulated with a 22-gauge catheter for blood removal, and the left dorsal pedal artery was cannulated and connected to a transducer system for arterial blood pressure monitoring. The PPV was automatically calculated using a multi-parameter monitor and recorded. Hemorrhage was induced by withdrawing 30% of blood (24 mL/kg) over 30 min. Mechanical ventilation was provided with a tidal volume of 10 mL/kg and a 1:2 inspiration-to-expiration ratio at an initial RR of 15 breaths/min (baseline). Thereafter, RR was changed to 20, 30, and 40 breaths/min according to the casting lots, and the PPV was recorded at each RR. After data collection, the blood was transfused at a rate of 10 mL/kg/h, and the PPV was recorded at the baseline ventilator setting.

Results: The data of PPV were analyzed using the Friedman test followed by the Wilcoxon signed-rank test ($p < 0.05$). Hemorrhage significantly increased PPV from 11% to 25% at 15 breaths/min. An increase in RR significantly decreased PPV from 25 (baseline) to 17%, 10%, and 10% at 20, 30, and 40 breaths/min, respectively (all $p < 0.05$).

Conclusions: The PPV is a dynamic parameter that can predict a dog's hemorrhagic condition, but PPV can be decreased in dogs under high RR. Therefore, careful interpretation may be required when using the PPV parameter particularly in the dogs with hyperventilation.

Keywords: Anesthesia; hemodynamic indices; hemorrhage; pulse pressure variation; respiratory rate

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ORCID iDs
Dalhae Kim
https://orcid.org/0000-0003-4333-2454
Won-Gyun Son
https://orcid.org/0000-0001-5431-3254
Donghwi Shin
https://orcid.org/0000-0002-5226-4855
Jiyoung Kim
https://orcid.org/0000-0001-6733-6009
Inhyung Lee
https://orcid.org/0000-0002-0712-7165

INTRODUCTION

Maintaining adequate circulatory blood volume is one of the major concerns during anesthesia, and volume expansion through fluid administration is a standard treatment for improving the hemodynamics [1, 2]. The hemodynamic function needs to be constantly checked; however, estimating it by monitoring changes in the cardiac output (CO) for fluid infusion is invasive, time-consuming, and often unavailable in a clinical setting [3]. Therefore, fluid management has usually been usually performed by monitoring traditional hemodynamic markers such as heart rate (HR), central venous pressure (CVP), and arterial blood pressure [4,5].

Dynamic hemodynamic markers (e.g., pulse pressure variation [PPV], stroke volume variation, systolic pressure variation, and plethysmography variability index) have been introduced to guide the initiation and termination of fluid therapy [4-6]. Dynamic indices indicate the interaction between the determinants of venous return and cardiac performance based on respiratory variation [4,6]. Dynamic indices use dynamic heart-lung interactions during mechanical ventilation [7-9]. Mechanical ventilation induces cyclic changes in the venous return and CO equilibrium by increasing intrathoracic pressure, resulting in variability in pulse pressure [4,6,10]. In hypovolemic conditions, mechanical ventilation significantly compromises venous return and increases variability [4].

A PPV is one of the dynamic parameters used to predict fluid responsiveness and is considered the most sensitive and specific parameter among the dynamic indices [11]. In human medicine, PPV > 13% is relatively hypovolemia and distinguishes responders to fluid therapy from non-responders with 94% sensitivity and 96% specificity [12]. In veterinary medicine, experimental studies in dogs have demonstrated that PPV is an early indicator of decreased CO during hemorrhagic shock, and when dogs lose 18%–20% of estimated blood volume, PPV values increase to more than 13% [4,13,14].

Although PPV effectively predicts fluid responsiveness, the clinical usefulness of PPV is limited owing to certain confounding factors, such as regular cardiac rhythms and controlled mechanical ventilation [11]. Some researchers have suggested that a low HR/respiratory rate (RR) ratio, either bradycardia or high RR, has resulted in false-negative results among humans, highlighting the uncertainty of PPV [15,16]. Some authors have reported that PPV occurs in hypovolemic conditions, with HR varying between 70 and 150 beats/min [17-20]; they have suggested that RR may be a major factor influencing the uncertainty in PPV rather than HR.

Studies on anesthetized dogs regarding PPV are increasing [2,5,13,21-23]. However, the influence of RR on dynamic indices, in mechanically ventilated dogs, has not been clearly identified. This study aimed to evaluate the influence of RR on PPV in mechanically ventilated healthy dogs after hemorrhage. A better understanding of the specific influence of RR will allow better interpretation of the PPV in dogs.

MATERIALS AND METHODS

Animals

This study was approved by the Institute Animal Care and Use Committee of Seoul National University (SNU-191012-3). Five castrated male beagle dogs, judged to be healthy based on

physical examination, thoracic radiographic imaging, and blood analysis (complete blood cell count and serum chemistries), were included in the study. These dogs were 3.0 ± 1.0 years old and weighed 12.0 ± 1.1 kg (mean ± standard deviation).

Anesthetic procedure

The dogs were kept without food for at least 12 h with free access to water, before anesthesia. The right or left cephalic veins were catheterized with an over-the-needle polyurethane 22-gauge catheter (IV Catheter; Sewoon Medical, Korea), and Hartmann's solution (HS Hartmann's solution; JW Pharmaceutical, Korea) was intravenously (IV) administered at a rate of 3 mL/kg/h during the anesthetic procedure. Five minutes after premedication with acepromazine (Acepromazine, 0.01 mg/kg IV; Samu Median, Korea), anesthesia was induced with alfaxalone (Alfaxalone, 3 mg/kg IV; Jurox Pty, Australia), intubated and maintained with isoflurane in 100% oxygen (2 L/min) at a target of 1.3% end-tidal isoflurane (Isoflurane; Hana Pharm, Korea) concentration using a rebreathing circuit system (Multiplus; Royal Medical, Korea). HR and rhythm with a lead II electrocardiogram, end-tidal carbon dioxide ($EtCO_2$), esophageal temperature, and oxygen saturation were monitored continuously with a multi-parameter monitor (CARESCAPE Monitor B650; GE Healthcare, Finland). Rocuronium (Rocuronium, 0.5 mg/kg IV; Hana Pharm) was administered and continuously maintained at a rate of 0.2 mg/kg/h to eliminate spontaneous breathing.

Hemodynamic investigation

The left dorsal pedal artery was cannulated with a 22-gauge catheter after intubation, and the left arterial catheter was connected to a transducer system (TruWave; Edwards Lifesciences, Germany) filled with 2 IU/mL of heparinized physiological saline (0.9% NaCl; JW Pharmaceutical). The zero-level reference of this system was set at the level of the right atrium and periodically flushed to prevent clots and remove air bubbles. The accuracy of the arterial pressure waveform was verified using the fast flush test. The catheter was connected to a fluid-filled hemodynamic monitoring system with a multi-parameter monitor (CARESCAPE Monitor B650; GE Healthcare), and the systolic arterial pressure (SAP), mean arterial pressure (MAP), and diastolic arterial pressure (DAP) were monitored.

A wide area of the skin over the jugular vein was clipped and prepared with antiseptic solutions. A 6-F, 10-cm introducer (Percutaneous Sheath Introducer Set, SI-09600; Arrow International, USA) was used for percutaneous puncture into the left jugular vein with each dog assuming the right lateral recumbent position. A 5-F, 75-cm 4-lumen thermodilution Swan-Ganz catheter (93-132-5F; Edwards Lifesciences) for measuring CVP was then advanced through the introducer into the jugular vein. Correct catheter placement was verified using a waveform and C-arm (KMC-650TA, GEMSS Healthcare, Korea). The proximal end of the catheter was positioned at the right atrium and connected to a fluid-filled hemodynamic monitoring system with a multi-parameter monitor (CARESCAPE Monitor B650; GE Healthcare).

The CO (L/min) was measured by rapid injection of 5 mL of cold (1–2°C) 0.9% NaCl through the proximal port of the thermodilution catheter at the end of a breath. At each time point, 5 CO measurements were performed, outliers were discarded, and the remaining values were averaged. The cardiac index (CI, $mL/min/m^2$) was computed by dividing CO by the body surface area, and the body surface area was calculated according to the formula $(10.1 \times kg^{0.67})/100$. The PPV was automatically calculated using the multi-parameter monitor, from continuous and simultaneous recordings of the arterial blood pressure and respiratory cycles.

Table 1. The order in which respiratory rates were performed

Measurement number	First (breaths/min)	Second (breaths/min)	Third (breaths/min)
1	20	40	30
2	30	40	20
3	40	20	30
4	30	20	40
5	20	30	40

Experimental protocol

Blood withdrawal was performed on each dog. Hemorrhage was induced by withdrawing blood into collection bags containing sodium citrate, citric acid, dextrose, and adenine through the right dorsal pedal artery catheter. The circulating blood volume was estimated to be 80 mL/kg; hence, 8 mL/kg was considered a 10% hemorrhage. A total of 30% of blood (24 mL/kg) was withdrawn over 30 min using graduated syringes. Under volume-controlled ventilation (Vent V; Royal Medical), the tidal volume (10 mL/kg), inspiration-to-expiration ratio (1:2), inspired O_2 fraction (1.0), and RR (15 breaths/min) were set at the baseline, and the variables (HR, SAP, MAP, DAP, CVP, and PPV) were recorded. The RR was changed to 20, 30, and 40 breaths/min for 5 min each according to the casting lots (**Table 1**), and the hemodynamic variables were recorded at each RR. After data collection, the autologous blood was transfused at a rate of 10 mL/kg/h. After blood transfusion, all hemodynamic variables were recorded at the baseline ventilator setting. The CO was measured twice in total: the first time immediately after 30% of blood loss occurred and then immediately after completion of the transfusion at the baseline ventilator setting.

For the recovery, the vaporizer was turned off, rocuronium was discontinued, and a combination of neostigmine (Neostigmine, 0.08 mg/kg IV; Daihan Pharm, Korea) and glycopyrrolate (Glycopyrrolate, 0.01 mg/kg IV; Myungmoon Pharm, Korea) was administered to reverse the effect of rocuronium. Dogs were recovered from anesthesia uneventfully. The pulmonary artery catheter and arterial and venous catheters were removed. The dogs recovered from the anesthesia uneventfully.

Statistical analyses

Statistical analysis was performed using International Business Machines Statistical Package (SPSS, version 25; SPSS, USA). The data of hemodynamic variables at different RRs were analyzed using the Friedman test, followed by the Wilcoxon signed-rank test. Data are presented as median (percentile 25–75) and considered as statistically significant at $p < 0.05$. The achieved statistical power was evaluated using GPower (Version 3.1.3; Department of Psychology, University of Düsseldorf, Germany) software [24] and the group size was found to be adequate to detect significance with 95% power.

RESULTS

All the dogs recovered from anesthesia uneventfully, and the total anesthetic time was 100 ± 15 min (mean ± standard deviation). The dogs were observed for 14 days following anesthesia, and no complications were associated with hemorrhage.

As defined per method, tidal volume and inspiratory to expiratory ratio remained unchanged. The hemodynamic variables are presented in **Table 2**. All dogs recovered from anesthesia uneventfully, and the total anesthetic time was 100 ± 15 min. The dogs were observed for 14 days after anesthesia, and no complications were associated with hemorrhage.

Table 2. Evaluation of the hemodynamic variables (percentile 25–75) during changes in RR, BH, AH and after ABT

Variables	Condition					
RR (breaths/min)	15	15 (baseline)	20	30	40	15
BH/AH/ABT	BH	AH	AH	AH	AH	ABT
HR (beats/min)	101 (85–108)	101 (82–111)	92 (86–112)	95 (81–108)	90 (81–107)	98 (88–105)
HR/RR ratio	6.7 (5.7–7.2)	6.7 (5.5–7.4)	4.6 (4.3–5.6)	3.2 (2.7–3.6)	2.3 (2.0–2.7)	6.5 (5.9–7)
SAP (mmHg)	94 (88–108)*	64 (62–66)	68 (64–72)	66 (64–74)	64 (61–74)	96 (88–110)*
MAP (mmHg)	64 (60–66)*	44 (43–48)	49 (46–52)	45 (44–54)	45 (44–53)	66 (62–68)*
DAP (mmHg)	52 (48–55)*	37 (36–41)	41 (39–45)	38 (37–46)	39 (36–45)	54 (48–57)*
CVP (mmHg)	4 (3–5)	3 (2–5)	4 (2–6)	3 (3–6)	3 (3–5)	4 (3–5)
PPV (%)	11 (10–12)*	25 (22–34)	17 (14–24)*	10 (8–17)*	10 (4–11)*	10 (8–12)*
CI (mL/min/m²)		1.2 (0.9–1.3)				3.0 (1.8–4.0)

RR, respiratory rate; BH, before hemorrhage; AH, after hemorrhage; ABT, autologous blood transfusion; HR, heart rate; SAP, systolic arterial pressure; MAP, mean arterial pressure; DAP, diastolic arterial pressure; CVP, central venous pressure; PPV, pulse pressure variation; CI, cardiac index.
*Significant difference from RR 15 breaths/min AH ($p < 0.05$).

The CO was measured for the identification of fluid responsiveness. The CI immediately after 30% bleeding was 1.2 mL/min/m² (percentile 25–75, 0.9–1.3 mL/min/m²) and the CI immediately after completion of the transfusion was 3.0 mL/min/m² (percentile 25–75, 1.8–4.0 mL/min/m²) at the baseline ventilator setting. The present results showed increased PPV > 13% after hemorrhage and decreased PPV < 13% and increased CO after autologous blood transfusion, which demonstrated that PPV predicted the hemorrhagic condition and fluid responsiveness well in anesthetized dogs.

Hemorrhage significantly increased PPV from 11% to 25% at 15 breaths/min in **Table 1**. An increase in RR significantly decreased PPV from 25 at baseline to 17%, 10%, and 10% at 20, 30, and 40 breaths/min, respectively (all $p < 0.05$). In addition, as the RR increased, the PPV gradually decreased. HR, SAP, MAP, DAP, and CVP did not change significantly during changes in RR.

DISCUSSION

This study aimed to evaluate the influence of RR on PPV by assessing hemorrhagic conditions in mechanically ventilated healthy dogs and an increase in RR significantly decreased PPV. In addition, the decreased PPV showed false-negative results (< 13%) which could not predict actual hemorrhage when the RR was > 30 breaths/min in the hemorrhagic phase.

While the superiority of CVP, which has been used for a long time to monitor circulating blood volume, is being denied, the usefulness of the dynamic indices has been confirmed through many studies, especially in human medicine [1-14]. Among the dynamic indices, the usefulness of PPV has been widely reported in human medicine, and PPV is being studied as a clinically useful monitoring parameter in veterinary medicine [4,8,13,21-23]. To obtain a meaningful PPV, the importance of controlled mechanical ventilation (e.g., mechanical ventilation with no spontaneous respiration, tidal volume > 7 mL/kg, HR/RR ratio) has been proven through several studies in humans [15]. However, there are few studies on the effects of ventilation conditions on PPV in veterinary medicine.

The mechanism of the influence of RR on PPV may be explained by the increased left ventricular preload and decreased venous return to the right atrium of the heart. Positive pressure ventilation forces the blood contained in the lungs to the left side of the heart, increasing the left ventricular preload, resulting in a decrease in thoracic blood volume

and a decrease in afterload [25]. After a few heartbeats, the inspiratory decrease in the right ventricular stroke volume causes a decrease in left heart refilling and consequently a reduction in stroke volume and pulse pressure [26]. The increased RR makes the increased left ventricular preload merge with the decreased right ventricular output, so that respiratory variation in the left ventricular preload might be abolished. De Backer and colleagues [10] have studied the influence of RR on stroke volume variation in mechanically ventilated human patients and measured respiratory variation in pulmonary vein flow and mitral E wave, which illustrated the variation in left ventricular preload during mechanical ventilation. The parameters decreased at high RRs (30 and 40 breaths/min), supporting the merge of increased left ventricular preload and decreased right ventricular output.

Blood pressure, HR, and CVP are traditional markers to predict circulating blood volume. In this study, 30% bleeding reduced the arterial blood pressure of the dogs from 94 to 64 mmHg, 64 to 44 mmHg, and 52 to 37 mmHg for SAP, MAP, and DAP, respectively. These changes were statistically significant. However, not all hypotensive events are due to hemorrhage and should not serve as an automatic trigger for fluid administration [11]. Tachycardia is considered a classic sign of hypovolemia but was not identified in this study. HR cannot differentiate whether hypotension is caused by hypovolemia or anesthetic drugs and shows a slow change due to the cardiovascular compensation mechanism, except in extreme hypovolemia [11]. Moreover, HR is not a sensitive indicator of hypovolemia; only the degree of change in HR after fluid resuscitation can be used as an additional tool to determine the effectiveness of fluid therapy [11]. CVP did not change with hemorrhage in this study. CVP has been considered a good predictor of fluid responsiveness; however, the CVP may be unreliable because it does not reflect the compliance of the heart and venous tone [2,13]. Recently, the use of CVP as a predictor of fluid administration has not been recommended [11,13].

The present study has some limitations. First, there was an insufficient evaluation of the numerical value that can support the left ventricular preload merge. In this study, the reason for the false-negative result of PPV when the RR increased could be explained based on the human study, but there may be physiological differences between humans and dogs and therefore, further studies should be considered. Second, the CO was measured twice over the duration of the experiment because of concerns that the cold saline injection used to calculate CO could compensate for hemorrhagic conditions. The CO was also not compared for each RR, but this data was meaningful because it confirmed the relationship between CO and PPV when the bleeding situation was compensated for. Third, although the sample size was calculated using power calculation, these results are based on a relatively small number of dogs.

In conclusion, PPV is a good indicator of a dog's hemorrhagic condition and fluid responsiveness. However, the high RRs in PPV can indicate false-negative results. These false-negative results could lead to a misunderstanding that hemorrhage is not the cause of hypotension but further studies are needed to confirm these findings.

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