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Comparison of Noninvasive Dynamic Indices of Fluid Responsiveness Among Different Ventilation Modes in Dogs Recovering from Experimental Cardiac Surgery

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Fluid resuscitation is a cornerstone of minimizing morbidity and mortality in critically ill patients, but the techniques for predicting fluid responsiveness is still a matter of debate. In this study, we aimed to evaluate the utility of noninvasive stroke volume variation (SVV), pulse pressure variation (PPV), and systolic pressure variation (SPV) as a dynamic predictor for assessing fluid responsiveness during different ventilation modes in anaesthetized, intubated dogs recovering from cardiac surgery.

Material/Methods: Thirty-six adult Beagle dogs undergoing experimental surgery for isolated right ventricular failure were monitored for SVV, PPV, and SPV simultaneously using electrical velocimetry device. The relationships between each indicator and SVI before and after volume loading were compared in 3 ventilatory modes: assist control (A/C), synchronized intermittent mandatory ventilation (SIMV), and continuous positive airway pressure (CPAP). Responders were defined as those whose stroke volume index increased by ≥10%.

Results: In all of the indices, the baseline values were greater in responders than in nonresponders ($P<0.01$) under A/C and SIMV. Receiver operating curve analysis confirmed the best predictive value during A/C [area under the curve (AUC): SVV, 0.90; PPV, 0.88; SPV, 0.85; $P<0.05$] followed by SIMV (AUC: SVV, 0.86; PPV, 0.83; CPAP, 0.80; $P<0.05$), with their sensitivities and specificities of ≥7 5%. By contrast, no statistically significance detected in any parameter during CPAP (AUC: SVV, 0.71; PPV, 0.66; CPAP, 0.65; $P>0.05$).

Conclusions: SVV, PPV, and SVV are all useful to predict cardiac response to fluid loading in dogs during A/C and SIMV, while their reliabilities during CPAP are poor.

MeSH Keywords: **Blood Pressure • Dogs • Monitoring, Intraoperative • Respiration, Artificial • Stroke Volume • Fluid Therapy**

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Background

Assessment of intravascular volume status in high-risk surgical patients is challenging. Cardiac filling pressures such as central venous pressure and pulmonary capillary wedge pressure have been traditionally used in clinical practice to estimate the circulating blood volume for guiding fluid therapy, but studies have shown that these static indices cannot reliably estimate preload [1–3]. On the other hand, volumetric variable global end-diastolic or intrathoracic blood volume obtained by transpulmonary thermodilution have been shown to reliably predict the response of the heart due to a volume challenge in different patient populations [2–4]. In addition, several studies suggest that dynamic variables of fluid responsiveness based on arterial pressure waveform analysis, such as stroke volume variation (SVV), pulse pressure variation (PPV), and systolic pressure variation (SPV), may also be suitable preload indicators in patients under mechanical ventilation [5–9]. More recently, noninvasive hemodynamic monitoring system using the electrical velocimetry (EV) method enables continuous measurements of SVV, stroke volume (SV), and cardiac output (CO), without the need for calibration and arterial line [10–13], while standard anesthesia monitors integrated with workstations for arterial pressure analyses are usually required for determination of PPV and SPV [14].

For perioperative management of cardiothoracic anesthesia, assessment of fluid responsiveness can be included at any point during surgery even during the course of weaning from mechanical ventilation. However, the reliability of functional dynamic indices in different ventilation modes has yet to be compared. Thus, the aim of this study was to compare the utility of noninvasive SVV, PPV, and SPV as a dynamic predictor for assessing fluid responsiveness among different ventilation modes in anesthetized, intubated dogs recovering from cardiac surgery.

Material and Methods

Animals

A total of 36 purpose-bred, adult male Beagle dogs with a median weight of 13.3 kg were studied. Dogs were determined to be healthy based on a physical examination, complete blood cell count, and serum biochemistry profile. All animals were fasted for 12 hours prior to each experiment, with free access to water. This study was approved by and conducted in accordance with the guidelines set forth by the Institutional Animal Care and Use Committee.

Anesthesia and instrumentation

This study measured hemodynamic variables anesthetized, intubated dogs following an experimental cardiac surgery that created a chronic model of isolated right ventricular failure [15]. The details of the apparatus and operating techniques have been fully described elsewhere [12,13]. At the conclusion of the previous experiment, dogs were randomly allocated to receive each of the 3 ventilator modes: A/C, synchronized intermittent mandatory ventilation (SIMV), and continuous positive airway pressure (CPAP) (Figure 1).

All instruments used for this study were established prior the surgical study. Lactated Ringer's solution was infused intravenously (IV) at 5 mL/kg/h. After induction of anesthesia with 5% sevoflurane delivered by facemask [16–19], the trachea was intubated and connected to a semi-closed rebreathing circle anesthesia system (GE Datex S/5; GE Datex-Ohmeda, Inc., Finland), which was calibrated at the start of each experiment using standard calibration gases supplied by the manufacturer. Anesthesia was then maintained with 2.0–3.5% sevoflurane delivered in 60% oxygen at a flow rate of 2 L/min and fentanyl administered an IV bolus (5 µg/kg) followed by constant rate infusion (CRI) of 10 µg/kg/h [20,21]. Mechanical ventilation was instituted immediately following the induction of anesthesia using an A/C mode [initial setting: volume-controlled ventilation with tidal volume (V_T) of 10 mL/kg, respiratory rate of 10–16 breaths/min, positive end-expiratory pressure (PEEP) of 2 cm H_2O, and inspired fraction of oxygen (F_IO_2) of 0.6] (PRO-NEXT +i/+s; ACOMA Medical Industry, Tokyo, Japan). End-tidal carbon dioxide partial pressure ($P_{ET}CO_2$) was adjusted to maintain between 30–42 mm Hg. Animals were paralyzed with rocuronium (0.5 mg/kg) administered IV as an initial loading dose and then a CRI of 0.2 mg/kg/h, adjusted to facilitate ventilation. Rectal temperature was maintained at 37–38°C using a forced-air patient warmer.

A noninvasive EV system (Aesculon; Osypka Medical, La Jolla, CA, USA) was established by placing four electrocardiographic electrodes for continuous measurements of heart rate, SV, CO, and SVV [12]. The values of CO and SV were indexed to body surface area and body weight (cardiac index and SVI, respectively). SVV was calculated as the ratio of the standard deviation of the SV to the arithmetic mean of SV over 30 cardiac cycles multiplied by 100 (%). A 20 G arterial pressure was placed in the right dorsal pedal artery for measurements of arterial blood pressure. The pressure transducer was horizontally placed at the level of the costochondral junction for the zero reference point. The measurement of SPV and PPV using simple tools on the Datex Ohmeda S/5 has been described by Gouvea and Gouvea [22]. PPV as percent of the mean pulse pressure PPV (%) and SPV (mm Hg) were calculated using the following formulas: SPV (%)=200×(SBPmax–SBPmin)/(SBPmax+SBPmin); SPV (mm Hg)=SBPmax–SBPmin; where SBPmax, SBPmin, PPmax, and PPmin are the maximal and minimal values within one respiratory cycle.

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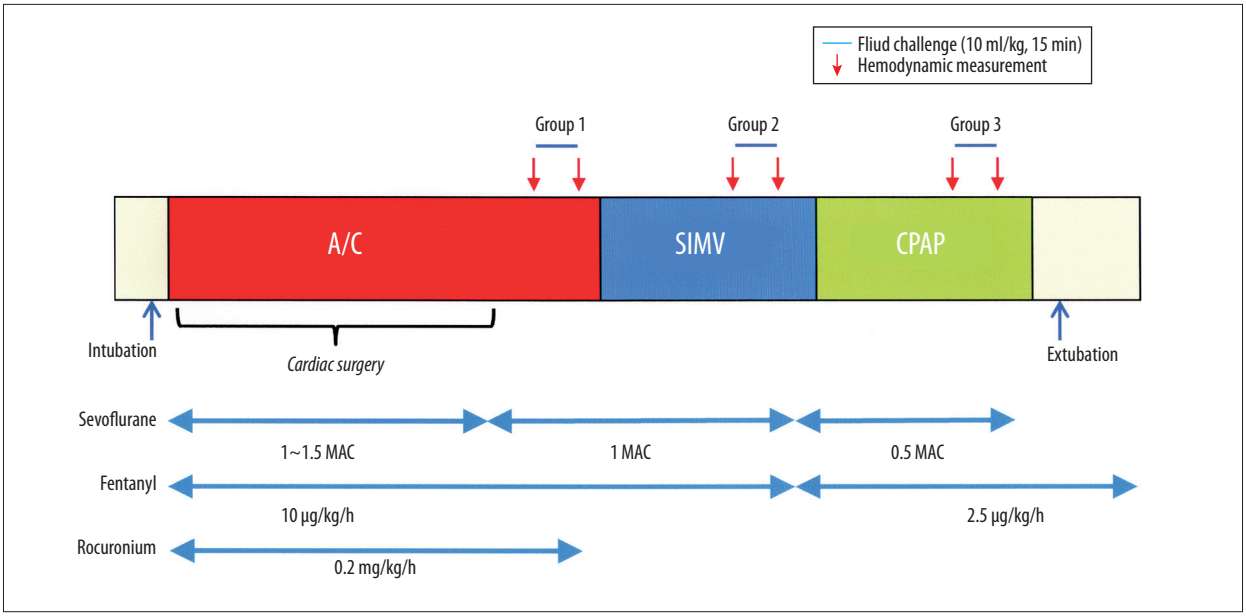

Figure 1. Schematic experimental design of fluid challenge in intubated anesthetized dogs after experimental cardiac surgery. EV-derived hemodynamic parameters were measured before and after the fluid loading (arrows) during one of the 3 ventilation modes: A/C (Group 1), SIMV (Group 2), or CPAP (Group 3) (n=12 per each group).

Experimental protocol

At the conclusion of the previous experiment, anesthesia was maintained at 2.36% (1 MAC) of end-tidal sevoflurane concentration (FE_{sevo}) for at least 15 minutes until a steady hemodynamic state was attained. After simultaneous recordings of the baseline data including the SVI, SVV, PPV, and PSV, lactated Ringer's solution was administered as an IV bolus of 10 mL/kg over 15 minutes to assess fluid responsiveness. Dogs were considered fluid responsive if SVI measured immediately after completion of the fluid challenge increased by 10% or more after volume loading [23,24].

In each animal, the protocol was performed in each of the 3 ventilator modes studied (A/C, SIMV, and CPAP) as part of the postoperative weaning strategy. SIMV was started 3–5 minutes after cessation of rocuronium infusion with the following settings: V_T: 10 mL/kg, mandatory respiratory rate (RR) of 8 breaths/min, PEEP of 2 cm H_2O, inspiratory pressure support (PS) above PEEP of 8 cm H_2O, I: E ratio of 1: 2, and F_IO_2 of 0.6. After subsequent reversal with sugammadex (8 mg/kg), dogs were allowed to breathe spontaneously. FE_{sevo} was then decreased to 0.5 MAC and CRI of fentanyl adjusted to 2.5 µg/kg/h, and the ventilator mode was changed to CPAP (PEEP of 2 cm H_2O, PS of 8 cm H_2O, and F_IO_2 of 0.6) (Figure 1).

All animals were then allowed to recover from anesthesia with appropriate postoperative analgesia and care according to the protocol of the separate study and euthanized with IV sodium pentobarbital (120 mg/kg) after a 2-week study period of monitoring of cardiac function by echocardiogram.

Statistical analysis

Normal probability plots revealed that all outcomes followed a normal distribution and data were summarized as the mean ± standard deviation, unless otherwise indicated. Categorical frequencies were compared using the χ^2 test. Changes in parametric data were analyzed using paired *t*-test (within each group) or one-way analysis of variance (ANOVA) with post hoc Bonferroni-Dunn correction (among the groups). The predictive ability of a variable for fluid responsiveness was assessed using a receiver operating characteristic (ROC) curve calculated with a 95% confidence interval. We assumed that the SVV would predict fluid responsiveness with an area under the curve (AUC) of >0.8 (implying a clinically reliable predictor). For each variable, a threshold value was determined to maximize both sensitivity and specificity. The difference in AUCs was compared between 2 ROC curves on the same subjects (paired design) [25]. A *P*-value of 0.05 was considered statistically significant. All analyses were performed using GraphPad Prism version 7.0 (GraphPad Software, Inc., La Jolla, CA, USA) and SigmaPlot version 13 (Systat Software, Inc., San Jose, CA, USA), and IBM Statistics SPSS version 24.0 (IBM SPSS Inc., Chicago, IL, USA).

Results

Table 1 shows the baseline characteristics of the overall study subjects. In this study, responders to fluid challenge for the different ventilator modes (defined as an increase in SVI ≥10%)

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Table 1. Baseline characteristics.

	Overall (n=36)
Age (months)	3.0 (2.8–3.2)
Body weight (kg)	13.3 (13.0–14.4)
Body surface area (m^2)	0.55 (0.55–0.59)
Anesthesa time (min)	153.5±11.8
Operation time (min)	53.1±9.8

Data are expressed as median (interquartile range) or mean ± standard deviation.

were 67% for A/C and SIMV (n=8/12, per each group) and 58% (n=7/12) for CPAP (*P*=0.89). Before fluid challenge, there were no significant differences in cardiopulmonary variables among the ventilation modes (*P*>0.05; data not shown), with the exception of higher RR (Δ4±1 breath/min; *P*<0.05) during CPAP compared with A/C.

During A/C and SIMV, all of the dynamic indices decreased significantly after fluid challenge as compatible with previous findings [12–14,26,27], the magnitude of which was greater in responders than in nonresponders (Figure 2). The ROC analysis confirmed the best predictive value during A/C

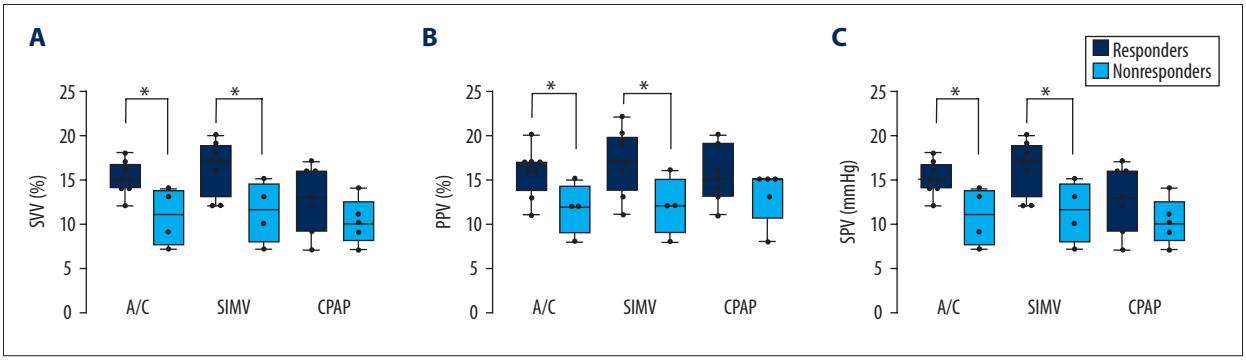

Figure 2. Box-and-whisker plots of SVV (**A**), PPV (**B**), and SPV (**C**) in dogs ventilated by A/C, SIMV, and CPAP before fluid challenge in responders and nonresponders (n=12 per each group). Data are expressed as median values and interquartile ranges with scatter plots.

Table 2. Prediction of fluid responsiveness by ROC curves of noninvasive dynamic indices of fluid responsiveness measured using the EV device in dogs maintained under different ventilation modes after cardiothoracic surgery.

	Cut-off value	AUC (95%CI)	*p*	Specificity (%)	Sensitivity (%)
A/C (n=12)					
SVV	13.5%	0.90 (0.73–1.08)	0.01	75	88
PPV	14.0%	0.88 (0.67–1.08)	0.02	75	75
SPV	8.5 mmHg	0.85 (0.65–1.07)	0.02	75	75
SIMV (n=12)					
SVV	14.0%	0.84 (0.65–1.07)	0.03	75	75
PPV	14.5%	0.83 (0.64–1.07)	0.04	75	75
SPV	9.3 mmHg	0.80 (0.67–1.08)	0.04	75	50
CPAP (n=12)					
SVV	N/A	0.71 (0.41–1.02)	0.22	N/A	N/A
PPV	N/A	0.66 (0.34–0.98)	0.37	N/A	N/A
SPV	N/A	0.65 (0.33–0.97)	0.37	N/A	N/A

ROC – receiver operating characteristics; EV – electrical velocimetry; A/C – assist control; SIMV – synchronized intermittent mandatory ventilation; CPAP – continuous positive airway pressure; SVV – stroke volume variation; PPV – pulse pressure variation; SPV – systolic pressure variation; AUC – area under the ROC curve; SE – standard error; CI – confidence interval; N/A – not available.

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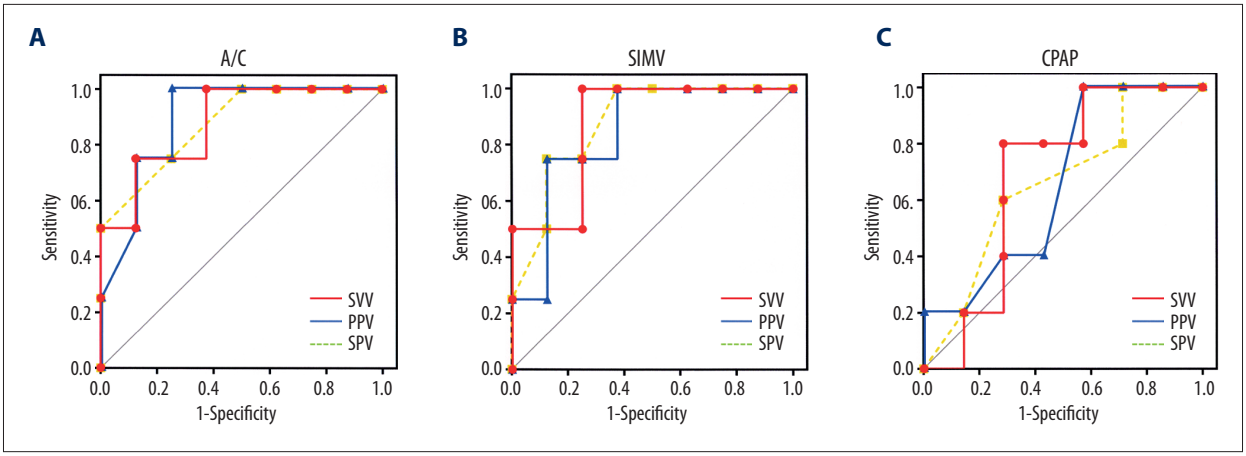

Figure 3. Prediction of fluid responsiveness (increase in SVI ≥10%) by receiver operating characteristic of SVV, pulse pressure variation (PVV), and systolic pressure variation (SPV) in dogs ventilated by A/C (**A**), SIMV (**B**), and CPAP (**C**) (n=12 per each group). The 45-degree diagonal line indicates the reference line of no-discrimination.

[AUC: SVV, 0.90 (*P*=0.01); PPV, 0.88 (*P*=0.02); SPV, 0.85 (*P*=0.02)] followed by SIMV [AUC: SVV, 0.86 (*P*=0.03); PPV, 0.83 (*P*=0.04); CPAP, 0.80 (*P*=0.04)], while no statistically significance detected during CPAP [AUC: SVV, 0.71 (*P*=0.19); PPV, 0.66 (*P*=0.51); CPAP, 0.65 (*P*=0.46)] (Table 2). There were no significant differences between the AUCs in each ventilation mode (*P*>0.05). The optimal cutoff values were 13.5% (75% specificity and 88% sensitivity) for SVV, 14.0% (75% specificity and 75% sensitivity) for PPV, and 8.5 mm Hg (75% specificity and 75% sensitivity) for SPV under A/C and 14.0% (75% specificity and 75% sensitivity) for PPV, and 8.5 mm Hg (75% specificity and 75% sensitivity) for SPV under SIMV, respectively (Figure 3).

Discussion

SVV, PPV, and SPV are dynamic physiologic parameters that depend on cyclic interaction between the heart and lung during mechanical ventilation [28]. Whereas PPV and SPV may be calculated simply and manually from an arterial trace line, estimation of SVV needs an advanced monitoring method (e.g., transpulmonary thermodilution, arterial pressure waveform analysis, bioreactance and EV) [6,12,13,29–32] which is capable of converting the waveform into continuous measurements of SV and CO simultaneously. The present data demonstrated that all of the dynamic indices showed comparable and reliable performance (AUC of >0.8) in predicting fluid responsiveness under A/C and SIMV in anesthetized, intubated dogs after experimental cardiac surgery.

It is reasonable that SVV in fully-controlled, mechanically ventilated dogs could be the best practical predictor of fluid responsiveness. Mechanical ventilation induces cyclic changes in fixed intrathoracic and transpulmonary pressures that transiently affect left ventricular filling (preload) status, resulting in respiratory-induced changes in SV in preload-dependent subjects. In fact, the fluid response predictability of $SVV_{A/C}$ was compatible with results of our previous study which used the EV device in mechanically ventilated dogs during thoracotomy, values which were more accurate than those predicted by central venous pressure or pulmonary capillary wedge pressure [13].

It is noteworthy that SVV_{SIMV} showed an acceptable predictive value of fluid responsiveness, close to $SVV_{A/C}$, the observation which is in agreement with our recent study evaluating in healthy dogs anesthetized with sevoflurane [10]. Considering the respiratory data seen during SIMV, our experimental setting, including the depth of anesthesia, appears to be enough to deliver appropriate V_T (>8 mL/kg) and regular spontaneous breathing to confirm appropriate fluid responsiveness [28].

Although neither dynamic compliance nor lung resistance was monitored during the CPAP mode, spontaneous breathing under light sevoflurane anesthesia may have hampered the efficacy of SVV in CPAP than occurring during controlled or synchronized ventilation [33]. Decreased reliability of SVV-guided fluid prediction has also been reported in human patients ventilated spontaneously with CPAP assisted by PS mode [34,35]; this may in part support our results.

This study has several limitations that warrant further investigation by its relatively small sample size. In addition, clinical fluid parameters such as fluid balance and urine output were not studied because of the mini-fluid challenge protocol. Nevertheless, the strengths of this study include its prospective nature under various ventilatory status. Future studies are needed to establish the utility of goal-directed therapy to ensure adequate tissue oxygenation and improved outcomes in more generalized critical illnesses beyond cardiac surgery.

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Conclusions

The present preclinical study suggests that functional dynamic indices SVV, PPV, and SVV are all useful to predict cardiac response to fluid loading in dogs ventilated in A/C and SIMV modes after cardiac surgery, while their reliabilities during CPAP are poor. Of particular, the entirely noninvasive technique for monitoring both SVV and CO using the current EV system would be valuable for estimating fluid responsiveness.

Conflicts of interest

None.

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