Assessment of Fluid Responsiveness After Tidal Volume Challenge During Pressure-Controlled Ventilation Volume Guaranteed: An observational study

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Research article

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Abstract

Background: The reliability of pulse pressure variation (PPV) and stroke volume variation (SVV) to predict fluid responsiveness have not previously been established when using pressure-controlled ventilation-volume guaranteed (PCV-VG) mode. We hypothesized that with a transient increase in tidal volume from 6 to 8 mL/kg of predicted body weight (PBW), which we reference as the “tidal volume challenge (TVC)”, the changes to PPV and SVV will be an indicator of fluid responsiveness.

Methods: The patients were first ventilated with a tidal volume of (V_t) 6 mL/kg of predicted body weight (PBW) using PCV-VG. Following intravenous anesthesia induction, PPV_6 and SVV_6 were recorded, then the TVC was performed, which increased V_t from 6 mL/kg to 8 mL/kg PBW for 1 minute and PPV_8 and SVV_8 were recorded again. The changes in value of PPV and SVV (ΔPPV_{6-8} and ΔSVV_{6-8}) were calculated after TVC. Following the minute of TVC, the tidal volume was returned to 6 ml/kg PBW for the fluid challenge (FC), a colloid infusion of 6ml/kg PBW for 20 minutes. Patients were classified as responders if there was an increase in cardiac index (CI) of more than 15% after FC, otherwise the patients were identified as non-responders. Eligible patients were divided into groups of responders or non-responders.

Results: 37 patients were classified as responders and 44 were non-responders. PPV_6 and SVV_6 could not predict the fluid responsiveness, while PPV_8 and SVV_8 could predict the fluid responsiveness when using PCV-VG mode. The changes in value of PPV and SVV after TVC (ΔPPV_{6-8} and ΔSVV_{6-8}) identified true fluid responders with the highest sensitivity and specificity in the above variables, which predicted fluid responsiveness with the area under the receiver operating characteristic curves (AUCs) (95% CIs) being 0.96 (0.93-1.00) and 0.98 (0.96-1.00), respectively. No significant difference was found when comparing the AUCs of ΔPPV_{6-8} and ΔSVV_{6-8} ($P > 0.05$). Linear correlation was represented between the change value of CI after FC and the change value of SVV or PPV after TVC (r = 0.68; $P < 0.0001$ and r = 0.77; $P < 0.0001$, respectively).

Conclusions: A transient increase in tidal volume, which we reference as the “tidal volume challenge (TVC)” could enhance the predictive value of PPV and SVV for the evaluation of fluid responsiveness in patients under ventilation with PCV-VG.

Trial registration: Chinese Clinical Trial Registry (ChiCTR2000028995). Prospectively registered on 11 January 2020. http://www.medresman.org.

1. Background

Fluid therapy is cornerstone of the hemodynamic management of patients undergoing major surgery. Goal-directed fluid therapy (GDFT) attempts to avoid the occurrence of excessive fluid load and hypovolemia, shorten the length of hospital stays, reduce mortality and minimize the complications caused by fluid imbalance during surgery [1, 2].To better implement GDFT, we need to find appropriate indicators that can accurately predict fluid responsiveness.

Studies have shown that dynamic indicators, such as pulse pressure variability (PPV) and stroke volume variability (SVV), are superior to static indices to predict fluid responsiveness [2–4]. However, accuracy and thresholds are affected by many factors, such as changes in the mode of ventilation or tidal volume [5, 6]. In surgeries involving general anesthesia, the application of volume-controlled ventilation (VCV) when attempting to

ensure adequate respiration often leads to excessive airway pressure. Pressure-controlled ventilation (PCV) often fails to provide adequate ventilation volume under the condition of ensuring proper airway pressure [7, 8]. Recently, a new type of intelligent ventilation mode, PCV-VG, has emerged, it combines the advantages of both VCV and PCV which utilizes a decelerating flow and constant pressure to offer the pre-set V_t without increasing airway pressures [9]. In addition, application of PCV-VG combined with low tide volume (V_t) (6–8 ml/kg PBW) had been advocated as a lung protective ventilation strategy, which can effectively reduce airway pressure, avoid the occurrence of pulmonary barotrauma, stabilize hemodynamics and reduce pulmonary complications [10, 11]. When the gas was delivered with decelerating flow rate in the ventilation with PCV-VG, the variability of intrathoracic pressure may decrease, which affects the accuracy of the prediction produced for fluid responsiveness [8, 12]. Additionally, previous studies reported that ventilation with the V_t below 8 ml/kg PBW is not enough to cause significant changes in intrathoracic pressure, and this may blunt the accuracy of PPV and SVV to predict the fluid responsiveness [13, 14]. Therefore, it is not clear whether PPV and SVV could accurately predict patients' fluid responsiveness during ventilation with PCV-VG combined with a lung protective ventilation strategy achieved by low V_t (6–8 ml/kg PBW).

We have failed to identify any previous studies exploring fluid responsiveness during ventilation with PCV-VG. This study was conducted to assess the reliability of PPV and SVV in predicting fluid responsiveness of patients ventilated using PCV-VG with low V_t (6–8 ml/kg PBW) and also to determine whether the TVC could enhance the predictive value of PPV and SVV in this lung protective ventilation strategy.

2. Methods

2.1 General information

This prospective study was conducted between January 2020 and March 2020 in accordance with the Declaration of Helsinki principles. The study was registered in the Chinese Clinical Trial Registry (ChiCTR2000028995) and was approved by the Ethics Committee for Clinical Trials of the Second Hospital of Anhui Medical University, Hefei, China [approval no: PJ-YX2019-037]. Written informed consent was obtained from the participants or guardians before surgery. Included in this study were eighty-one patients with American Society of Anesthesiologists (ASA) physical status of I-II, aged 18 to 65 years, scheduled for laparoscopy-assisted radical gastrectomy under general anesthesia. Patients were excluded according to the following criteria: kidney dysfunction; cardiac arrhythmias and valvular heart disease; chronic obstructive pulmonary disease; right ventricular failure; intracranial hypertension; severe obesity difficulty (BMI > 30 kg/m^2); airway asthma or a long history of smoking. FC was performed to identify fluid responders if there was an increase in CI ≥ 15%, otherwise the patients were identified as non-responders. The patients were separated into two groups, responder and non-responder.

2.2 Perioperative management

Intravenous and arterial access were established for monitoring of continuous invasive blood pressure and central venous pressure (CVP) after arrival to the operating room and before the induction of anesthesia. Drager monitor (model: A7, Hefei unity medical co.) was used for monitoring the non-invasive blood pressure, invasive radial arterial blood pressure, pulse oximetry, heart rate (HR), ratio of the HR and respiratory rate (HR/RR), electrocardiogram, peak airway pressure, plateau pressure (P_{pl}), driving pressure (P_{pl}-positive end-expiratory

pressure [PEEP]) and partial pressure of carbon dioxide in end expiratory gas ($P_{ET}CO2$). The vital variables, such as pulse pressure variability (PPV); stroke volume variability (SVV) and cardiac index (CI) were recorded by a continuous non-invasive arterial pressure monitor (CNAP) (model: CANP™ Monitor 500, Guangzhou Xinju Science and Trade Co.). All patients received fluid of Ringer's solution at a rate of 5 ~ 7 ml/kg/h. And bispectral index (BIS) (the America, Covidien IIc Co.) and the arterial blood gas analysisis of patients were monitored perioperatively.

General anesthesia was induced by intravenous (i.v.) midazolam (0.03 mg/kg), sufentanil (0.5 μg/kg), rocuronium (0.6 mg/kg) and etomidate (0.2 mg/kg) after mask oxygen inhalation for two minutes. Tracheal intubation was performed after reaching BIS between 40 and 60 and appropriate muscle relaxation was achieved, the Mindray anesthesia machine (model: A5, Shenzhen Mindray biomedical electronics co LTD) was connected for mechanical ventilation with PCV-VG mode and followed the setting: V_t of 6 ml/kg PBW; $P_{ET}CO_2$ remained in the 35–45 mmHg range with an inspired oxygen fraction 0.5 and a fresh gas flow 2 L/min of oxygen and air; PEEP was kept between 3–5 cmH_2O and SpO_2 was maintained at more than 95%. Maintenance of anesthesia was conducted by propofol (4 ~ 8 mg/kg/h), remifentanil (0.1 ~ 0.3 μg/kg/min), cisatracurium (0.1 ~ 0.2 mg/kg/h) and sevoflurane (1%~2%). Anesthetic depth was maintained at a BIS of 40–60 throughout the surgical procedure by adjusting the end-tidal concentration of sevoflurane. Simultaneously, the appropriate application of vasoactive drugs (atropine and noradrenaline) was for the maintenance of HR and mean arterial pressure (MAP) at around 20% of the base value.

2.3. Hemodynamic and Respiratory monitoring and Study Protocol

The PPV, SVV, MAP, HR, CVP, peak airway pressure, P_{pl}, driving pressure, central venous oxygen saturation, oxygenation index and compliance of the respiratory system (C_{rs}) were recorded after intravenous anesthesia induction. The depth of the anesthesia was ensured by the monitoring of BIS. Before the start of the surgery and administration of any vasopressor, with the patient supine, the study protocol (Fig. 1) was started as follows: (1) Patients were ventilated by PCV-VG with V_t 6 mL/kg PBW, maximum airway pressure of 30 mmH_2O, and PEEP 3 ~ 5 cmH_2O for 1 minute, baseline measurements including the PPV (PPV_6) and SVV (SVV_6) were recorded (T_0). (2) The TVC was performed by a transiently increasing Vt (from 6 up to 8 mL/kg PBW for 1 minute), and another set of measurements including the PPV (PPV_8) and SVV (SVV_8) was recorded after 1 minute (T_1). Additionally, the changes in value of PPV and SVV ($\Delta PPV_{6-8} = PPV_8 - PPV_6$ and $\Delta SVV_{6-8} = SVV_8 - SVV_6$) were calculated. (3) The V_t was reduced back to 6 ml/kg PBW with the completion of TVC. Measurements including the CI (CI_{T2}), PPV (PPV_{T2}) and SVV (SVV_{T2}) were recorded after an additional 1 minute (T_2). (4) The FC was achieved by infusion of 6 ml/kg PBW of hydroxyethyl starch over 20 minutes, simultaneously, a set of measurement including the CI (CI_{T2}), PPV (PPV_{T3}) and SVV (SVV_{T3}) were also recorded at the end of FC (T_3), and the change in PPV, SVV and CI after FC ($\Delta PPV_{fc} = PPV_{T3} - PPV_{T2}$, $\Delta SVV_{fc} = SVV_{T3} - SVV_{T2}$ and $\Delta CI = CI_{T3} - CI_{T2}$) were also calculated.

2.4. Sample size and statistical analyses

TVC has not previously been studied in patients ventilated with the ventilation of PCV-VG mode, the expected areas under the curves of PPV_6 and ΔPPV_{6-8} were respectively 0.65 and 0.90, which was used to calculate the sample size requirement for comparing two ROC curves by statstodo, a statistical analytics tool. A sample size of

60 patients, was sufficient to detect a significant difference (α = 5%) with a statistical power (β-value) of 90%, however it was increased to 81 patients for considering a 15% failure rate.

The continuous variables were presented as mean (standard deviation) or median (interquartile range) depending on the normal distribution tested by the D'Agostino-Pearson. Categorical variables presented as proportions (percentage), such as ASA physical status and gender, were analyzed using the χ^2 test. Continuous variables normally distributed were analyzed using independent-sample t-test while Mann-Whitney U or Wilcoxon signed-rank tests was used to compare abnormal distributions between two groups (responders and non-responders). A one-way analysis of variance (ANOVA) for repeated measurements has been performed for analysis of the hemodynamic values from T_0 to T_3. The Tukey test was used for post hoc pairwise multiple comparisons analysis. Moreover, the predictive value of SVV, PPV, TVC and FC were evaluated by receiver operating characteristic (ROC) curve (95% confidence interval). The DeLong test was used to compare the statistically significant ROC curves [15]. Statistical analyses and graphics were conducted using GraphPad PRISM V7 (GraphPad Software Inc, San Diego, CA). We considered a *P* values less than 0.05 to be significant for all comparisons.

3. Results

100 patients scheduled for laparoscopy - assisted radical gastrectomy under general anesthesia were screened and 90 considered eligible in the enrollment period. Totally 9 patients were excluded with following reasons: 8 patients were not accordant with the inclusion criteria and 1 suddenly decided to give up the operation before arrival to the operating room). 81 patients were eventually included, 37 were responders and 44 patients were non-responders, grouped based on the administration of FC. (Fig. 2)

3.1. Preoperative characteristics

As shown in Table 1, there was no statistically significant difference between the two groups in the baseline characteristics (gender, age, BMI, ASA, and preoperative complications), respiratory characteristics (peak airway pressure, driving pressure, oxygenation index, P_{pl} and C_{rs}) and hemodynamic characteristics (MAP, central venous oxygen saturation and the parameters of arterial blood gas analysis) ($P > 0.05$).

Table 1
Baseline Hemodynamic and Respiratory Characteristics

	R (n = 37)	NR (n = 44)	*P* Value
General characteristics			
ASA physical status (n)			
□	29 (78)	33 (75)	0.721
□	8 (22)	11 (25)	
Male (n)	19 (51)	24 (55)	0.774
Age (year)	53 (48–63)	58 (50–64)	0.159
BMI (kg/m^2)	22.4 (21.4–23.7)	23.3 (20.9–24.0)	0.663
MAP (cmH_2O)	81 (13)	80 (12)	0.854
Central venous oxygen saturation (%) AAssSsssaturation	74.9 (1.4)	75.4 (1.4)	0.123
PH	7.41 (0.04)	7.39 (0.03)	0.059
Lactate (mmol/L)	0.8 (0.7–1.1)	0.9 (0.8–1.2)	0.147
Chronic preoperative disease (n)			
Diabetes	8 (21.6)	11 (25.0)	0.721
Hypertension	8 (21.6)	10 (22.7)	0.905
Respiratory characteristics			
Ppeak (cmH_2O)	18.5 (2.2)	18.3 (1.8)	0.670
Pplat (cmH_2O)	11 (10–12)	11 (10–13)	0.627
Pplat-PEEP (cmH_2O)	8.0 (1.4)	8.5 (1.3)	0.084
C_{rs} (ml/cmH_2O)	60 (4)	59 (3)	0.215
PaO_2/FiO_2 (mmHg)	445 (27)	451 (26)	0.332

Values are reported as frequency (percentage), mean (standard deviation) and median (interquartile range), as appropriate. ASA, American Society of Anesthesiologists Classification; NR, non-responders; R, responders; MAP, mean arterial pressure; PEEP, Positive end-expiratory pressure; BMI, body mass index; Pplat, plateau pressure; Ppeak, peak airway pressure; PaO_2/FiO_2, arterial partial pressure of oxygen/fraction of inspired oxygen; C_{rs}, compliance of the respiratory system.

3.2. Effect of TVC and FC administration

The TVC significantly increased PPV (from 7.5–11.2%, $P < 0.001$) and SVV (from 8.6–13.4%, $P < 0.001$) in responders, but didn't affect PPV and SVV in non-responders (T_1 *vs* T_0). PPV and SVV in the responder's group were significantly higher than those in the non-responder's group at T_1 (Table 2).

Table 2
Hemodynamic Characteristics of Fluid Responders and Non-responders in Study Period

	T_0	T_1	T_2	T_3	*P* Value (T_0 *vs* T_1)	*P* Value (T_2 *vs* T_3)	*P* Value T_1 (R *vs* NR)	ANONA (*P*)
MAP (cmH_2O)								
R (n = 37)	78 (10)	79 (9)	80 (9)	78 (10)	0.940	0.913	0.245	0.857
NR (n = 44)	76 (9)	78 (11)	79 (10)	81 (12)	0.809	0.809		0.150
CVP (cmH_2O)								
R (n = 37)	5.2 (1.9)	5.6 (1.5)	5.9 (1.5)	10.6 (1.6)	0.710	<0.001	0.006	<0.001
NR (n = 44)	6.3 (1.8)	6.6 (1.7)	7.0 (1.3)	6.6 (1.2)	0.763	0.763		0.225
HR (beats/min)								
R (n = 37)	63 (10)	61 (9)	62 (9)	60 (8)	0.767	0.889	0.221	0.467
NR (n = 44)	61 (9)	59 (8)	60 (8)	59 (7)	0.497	0.906		0.483
CI ($L/min/m^2$)								
R (n = 37)	3.05 (0.14)	3.02 (0.11)	2.99 (0.11)	3.73 (0.17)	0.730	<0.001	0.003	<0.001
NR (n = 44)	3.12 (0.16)	3.11 (0.15)	3.11 (0.13)	3.15 (0.08)	0.962	0.671		0.577
PPV (%)								
R (n = 37)	7.5 (1.6)	11.2 (1.9)	12.0 (1.9)	5.5 (1.4)	<0.001	<0.001	<0.001	<0.001
NR (n = 44)	7.9 (2.1)	7.8 (2.2)	6.9 (1.3)	6.7 (1.4)	0.998	0.965		<0.001
SVV (%)								
R (n = 37)	8.6 (1.6)	13.4 (2.0)	14.3 (2.6)	6.5 (1.5)	<0.001	<0.001	<0.001	<0.001
NR (n = 44)	9.7 (2.7)	9.8 (2.6)	8.0 (1.3)	7.4 (1.4)	0.997	0.588		<0.001

Values are reported as mean (standard deviation); SVV, stroke volume variation; MAP, mean arterial pressure; R, responders; NR, non-responders; PPV, pulse pressure variation; CVP, central venous pressure; CI, cardiac index; HR, heart rate.

Following FC administration, there were significant decrease in PPV (from 12.0–5.5%, $P < 0.001$) and SVV (from 14.3–6.5%, $P < 0.001$) only in responders. And FC also significantly increased CVP only in responders. However, the all recorded variables in non-responders, as shown in Table 2, haven't been changed by the administration of FC.

3.3. Prediction of Fluid Responsiveness

As shown in Table 3, the PPV_6 and SVV_6 did not correlate to fluid responsiveness while ΔPPV_{6-8}, ΔSVV_{6-8}, PPV_8 and SVV_8 could predict the fluid responsiveness. The best cutoff value of ΔSVV_{6-8} was 1.5% with a sensitivity of 95.2% and a specificity of 94.7%. Similarly, the best cutoff value of ΔPPV_{6-8} was also 1.5% showing a sensitivity of 89% and a specificity of 93%. The AUCs of the ΔPPV_{6-8} and ΔSVV_{6-8} were 0.96 (95% CI, 0.93-1.00) and 0.98 (95% CI, 0.96-1.00), respectively. ΔPPV_{fc} and ΔSVV_{fc}, the change value of PPV and SVV after FC, discriminated responders from non-responders, which similarly have very high predictive value with AUCs (with 95% CIs) being 0.99 (0.98–1.01) and 0.98 (0.96–1.01), respectively (Table 3). The AUCs of ΔPPV_{6-8} and ΔSVV_{6-8} were all significantly greater than the AUCs of PPV_8 and SVV_8. And the AUCs for ΔPPV_{6-8}, ΔSVV_{6-8}, ΔPPV_{fc} and ΔSVV_{fc} were not significantly different (Table 4).

Table 3
Diagnostic Ability of Various Variables in Predicting Fluid Responsivenes

Variables	Area Under the Receiver-Operaing Characteristic Curve (95% CI)	*P* Value	Youden Index	Best cutoff Value (%)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
PPV_6	0.54 (0.41–0.66)	0.589		-	-	-		
SVV_6	0.62 (0.50–0.74)	0.069		-	-	-		
PPV_8	0.87 (0.80–0.95)	< 0.001	0.63	8.5	97	66	71(61–78)	97(81–100)
SVV_8	0.85 (0.78–0.93)	< 0.001	0.53	10.5	89	64	67(58–76)	88(73–95)
ΔPPV_{6-8}	0.96 (0.93-1.00)	< 0.001	0.82	1.5	89	93	92(79–97)	91(80–96)
ΔSVV_{6-8}	0.98 (0.95–1.01)	< 0.001	0.88	1.5	95	93	92(80–97)	95(84–99)
ΔPPV_{fc}	0.99 (0.98–1.01)	< 0.001	0.97	2.5	97	100	100(89–100)	98(86–100)
ΔSVV_{fc}	0.98 (0.96–1.01)	< 0.001	0.90	3.5	92	98	97(83–100)	94(83–98)

PPV_6, PPV at V_t 6 mL/kg PBW; SVV_6, SVV at V_t 6 mL/kg PBW; PPV_8, PPV at V_t 8 mL/kg PBW; SVV_8, SVV at V_t 8 mL/kg PBW; ΔPPV_{6-8}, change value of PPV after TVC; ΔSVV_{6-8}, change value of SVV after TVC; ΔPPV_{fc}, change value of PPV after fluid challenge; ΔSVV_{fc}, change value of SVV after fluid challenge; SVV, stroke volume variation; PPV, pulse pressure variation; TVC, tidal volume challenge; PBW, predicted body weight; V_t, tidal volume; Dashes indicate variable was not measured.

Table 4
Comparisons of Area under Receiver Operating Characteristic Curves

Tests	*P* Value
AUC PPV_8 *vs* AUC ΔPPV_{6-8}	0.013
AUC SVV_8 *vs* AUC ΔSVV_{6-8}	0.002
AUC ΔPPV_{6-8} *vs* AUC ΔPPV_{fc}	0.094
AUC ΔSVV_{6-8} *vs* AUC ΔSVV_{fc}	0.886
AUC ΔPPV_{6-8} *vs* AUC ΔSVV_{6-8}	0.237
AUC ΔPPV_{fc} *vs* AUC ΔSVV_{fc}	0.165

De Long test was used for comparation of ROC curves. AUC, area under the receiver operating characteristic curve; PPV_8, PPV at V_t 8 mL/kg PBW; SVV_8, SVV at V_t 8 mL/kg PBW; ΔPPV_{6-8}, change value of PPV after TVC; ΔSVV_{6-8}, change value of SVV after TVC; ΔPPV_{fc}, change value of PPV after fluid challenge; ΔSVV_{fc}, change value of SVV after fluid challenge; TVC, tidal volume challenge; PBW, predicted body weight; V_t, tidal volume.

The box and whisker plots have been performed to compare these variables (ΔPPV_{6-8}, ΔSVV_{6-8}, ΔPPV_{fc} and ΔSVV_{fc}) among two groups (responders and non-responders) and there was a significant ($P < 0.05$) difference (Fig. 4). The ROC curves of above variables were shown in Fig. 3.

3.4. Linear Correlation

A linear correlation between ΔCI after FC administration and ΔPPV_{6-8} (r = 0.68; $P < 0.001$) and ΔSVV_{6-8} (r = 0.77; $P < 0.001$) was observed (Fig. 5).

4. Discussion

The accuracy of predicting fluid responsiveness in patients is the key to guiding perioperative fluid management [16]. Therefore, it is necessary to identify the most accurate measures of fluid responsiveness with the objective of minimizing incidents of fluid overload and hypovolemia. The PPV could show predictive value with a Vt at least 8 mL/kg PBW as shown in the study of De Backer D et al [14]. Several studies have indicated that the SVV and PPV may signify a nonresponsive status even in responders during low Vt ventilation. The reason is that the Vt might be insufficient to produce a significant change in the intrathoracic pressure [17–19]. Meanwhile, previous studies show that ventilation using PCV-VG combined with low Vt (6–8 ml/kg PBW) has been effective as a lung protective ventilation strategy [10, 11]. It is not clear whether PPV and SVV can accurately assess patients' fluid responsiveness during mechanical ventilation using PCV-VG combined with low Vt (6–8 ml/kg PBW). In recent years, the assessment of fluid responsiveness performed via dynamic evaluation of hemodynamic parameters in response to certain interventions, known as functional hemodynamic tests, such as mini fluid challenge test (MFT), tidal volume challenge (TVC) and end-expiratory occlusion test (EEOT), have been considered reliable and effective methods in guiding perioperative fluid management [20–22].

This study initially explored the reliability of functional hemodynamic tests in predicting fluid responsiveness in patients ventilated using PCV-VG. The main finding showed that ΔPPV_{6-8} and ΔSVV_{6-8} are remarkable predictors of fluid responsiveness in patients undergoing laparoscopy-assisted radical gastrectomy with cutoff values of both 1.5%. The change in PPV and SVV after a fluid challenge (ΔPPV_{fc} and ΔSVV_{fc}) also accurately predicts fluid responsiveness with very high sensitivity and specificity. And yet, it requires a fluid bolus to discriminate responders from non-responders seen in the change of cardiac index and may increase the risk of fluid overload in the non-responder corhort. PVV and SVV at Vt 8 mL/kg PBW also identifies responders with the area under receiver-operating characteristic curve (AUC) (0.87 and 0.85, respectively), which are lower than those of ΔPPV_{6-8} and ΔSVV_{6-8} (Table 4). Therefore, TVC should be a good strategy to enhance the predictive value of PPV and SVV for the evaluation of fluid responsiveness in patients undergoing protective ventilation with small tidal volume.

Meanwhile, many studies have shown that using PCV-VG can reduce lung injury caused by mechanical ventilation as well as reduce expiratory pressure and improve arterial oxygenation. This is assumed to be a beneficial effect of the decelerating flow rate on the airway and the decelerating waveform on intrapulmonary distribution by PCV-VG [23–25]. Therefore, we suspected that the decelerating flow rate may influence the change of patients' intrathoracic pressure and the cardiopulmonary interactions weakly, thus affecting the accuracy of the dynamic indicators. The TVC (an increase of V_t from 6 to 8 mL/kg PBW) can reduce the influence of the decelerating flow rate on the change and conduction of intrathoracic pressure. As a result, ΔPPV_{6-8} and ΔSVV_{6-8} accurately predicted fluid responsiveness depending on the increased fluctuation of intrathoracic pressure, as well as greater dynamic compliance and cardiopulmonary interaction, during the implementation of TVC. This was confirmed in this study: In line with the findings of previous studies conducted in patients ventilated with the VCV mode, this study showed that the fluid responsiveness of patients predicted by the PPV_6 and SVV_6 under ventilation of PCV-VG mode were also not valuable. But the AUCs of PPV_6, SVV_6 in this study is lower than those in previous studies. Moreover, the AUCs of PPV_8 and SVV_8 are also lower than those in studies conducted in patients ventilated with the VCV mode. Nevertheless, it has been showed that the AUCs of ΔPPV_{6-8} and ΔSVV_{6-8} in this study were not significantly different with those in previous studies [26–28]. Simultaneously, the correlation between the ΔPPV_{6-8} and ΔSVV_{6-8} after the TVC application and ΔCI after FC administration (Fig. 5) suggests that the using PCV-VG with low tide volume in surgical subjects with normal respiratory compliance may not alter the interaction between volume status, the transmission of the intrathoracic pressure to the heart and the final effect on PPV and SVV, ensuring the application of TVC suitable for the setting of PCV-VG mode. The results shown above could support our hypothesis and confirm that the absolute changes in PPV and SVV (ΔPPV_{6-8} and ΔSVV_{6-8}) after TVC could also be a reliably functional hemodynamic test for predicting fluid responsiveness when using PCV-VG combined with low V_t (6–8 ml/kg PBW).

Our research showed that the TVC significantly increased PPV and SVV in responders but didn't affect PPV and SVV in non-responders, which is consistent with previous reports about TVC. The threshold of ΔPPV_{6-8} and ΔSVV_{6-8} were lower than those initially reported by Myatra *et al* [6]. This finding may be explained by two factors. On the one hand, compared with VCV mode used in Myatra's study, the decelerating flow rate of PCV-VG may weaken the transmission of intrathoracic pressure to pleural and atrial pressure and influence cardiopulmonary interaction and lead to a decrease of threshold of these variables. On the other hand, different from the patients with ASA physical status I-II and normal lung compliance we selected, the patients in Myatra's trail were critically ill patients with acute circulatory failure, 30% of whom were affected with a reduced chest wall compliance, which

may enhance the transmission of applied airway pressure to the pericardium and the vena cava [28, 29]. In other words, there were varying degrees of influence of TVC application in elective surgical and critically ill patients on account of the distinction of cardiopulmonary interactions [30].

Some limitations of this study should be discussed. First, the time frame takes place after the induction of anesthesia and before the intervention of surgery, because the aim was to evaluate whether the TVC could enhance the predictive value of PPV and SVV in patients under the ventilation of PCV-VG. Therefore, it is impossible to predict the influence of different surgical types and operations on the results, which still needs further study; Secondly, this study only explored the reliability of PPV and SVV in predicting fluid responsiveness under ventilation of PCV-VG, but the reliability of other functional hemodynamic tests, such as EEOT and MFT, are not clear and also need further study. Finally, the other limitations in application of PPV and SVV in ventilation of PCV-VG, such as cardiac arrhythmias, the presence of spontaneous breathing and right ventricular dysfunction, could not be avoidable.

5. Conclusions

A transient increase in tidal volume, which we reference as the “tidal volume challenge (TVC)” could enhance the predictive value of PPV and SVV for the evaluation of fluid responsiveness in patients under ventilation with PCV-VG.

Abbreviations

PPV: Pulse pressure variation

SVV: Stroke volume variation

PCV-VG: Pressure-controlled ventilation-volume guaranteed

PBW: Predicted body weight

TVC: Tidal volume challenge

FC: Fluid challenge

CI: Cardiac index

ROC: The receiver operating characteristic curve

AUC: The area under the receiver operating characteristic curve

GDFT: Goal-directed fluid therapy

PCV: Pressure-controlled ventilation

VCV: Volume-controlled ventilation

V_t: Tide volume

ASA: American Society of Anesthesiologists

BMI: Body mass index

CVP: Central venous pressure

HR: Heart rate

P_{pl}: Plateau pressure

PEEP: Positive end-expiratory pressure

$P_{ET}CO2$: Partial pressure of carbon dioxide in end expiratory gas

BIS: Bispectral index

SpO_2: Oxygen saturation

MAP: Mean arterial pressure

C_{rs}: Compliance of the respiratory system

MFT: Mini fluid challenge test

EEOT: End-expiratory occlusion test

Declarations

Ethics approval and consent to participate

The study was registered in the Chinese Clinical Trial Registry (ChiCTR2000028995) and was approved by the Ethics Committee for Clinical Trials of the Second Hospital of Anhui Medical University, Hefei, China [approval no: PJ-YX2019-037].

Written informed consent was obtained from the all participants or guardians before surgery.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and / or analyzed during the current study will be available from the corresponding author on reasonable request.

Conflict of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Contributions

Y J and LL J is Co-First Author, participated in Conceptualization, Writing - Original Draft, Methodology, Formal analysis, Visualization, Investigation, Data curation and Project administration. J H did the statistical analysis and reviewed the manuscript Y Z participated in Conceptualization, Supervision, Methodology, Resources, Data curation, Validation, Writing - review & editing, Project administration and Funding acquisition. All authors read and approved the final manuscript.

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Figures

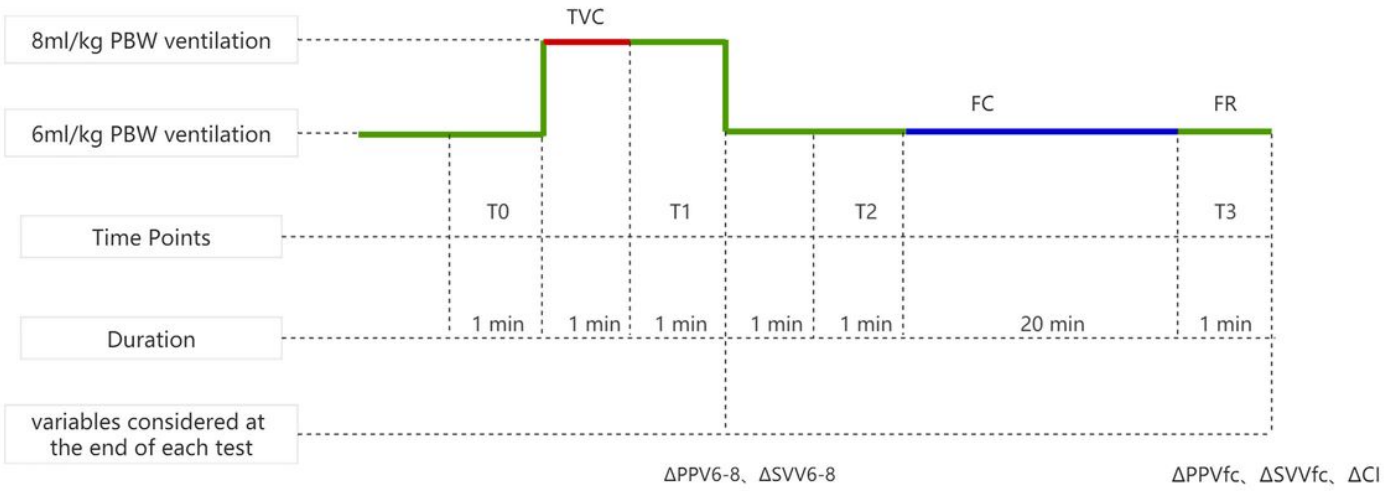

Figure 1

Study protocol . The TVC was applied by transiently increasing tidal volume (from 6 to 8 mL/kg PBW for 1 min) (red line) and the ΔPPV6-8 and ΔSVV6-8 were calculated. FR was evaluated 15 min after the administration of FC (blue line) and the change value of cardiac index, pulse pressure variations and stroke volume variations (ΔCI,

ΔPPVfc , ΔSVVfc) were calculated. ΔSVV6-8, change value of SVV after TVC; CI, cardiac index; ΔPPV6-8, change value of PPV after TVC; ΔPPVfc, change value of PPV after FC; ΔSVVfc, change value of SVV after FC; FC, fluid challenge; TVC, tidal volume challenge; FR, fluid responsiveness.

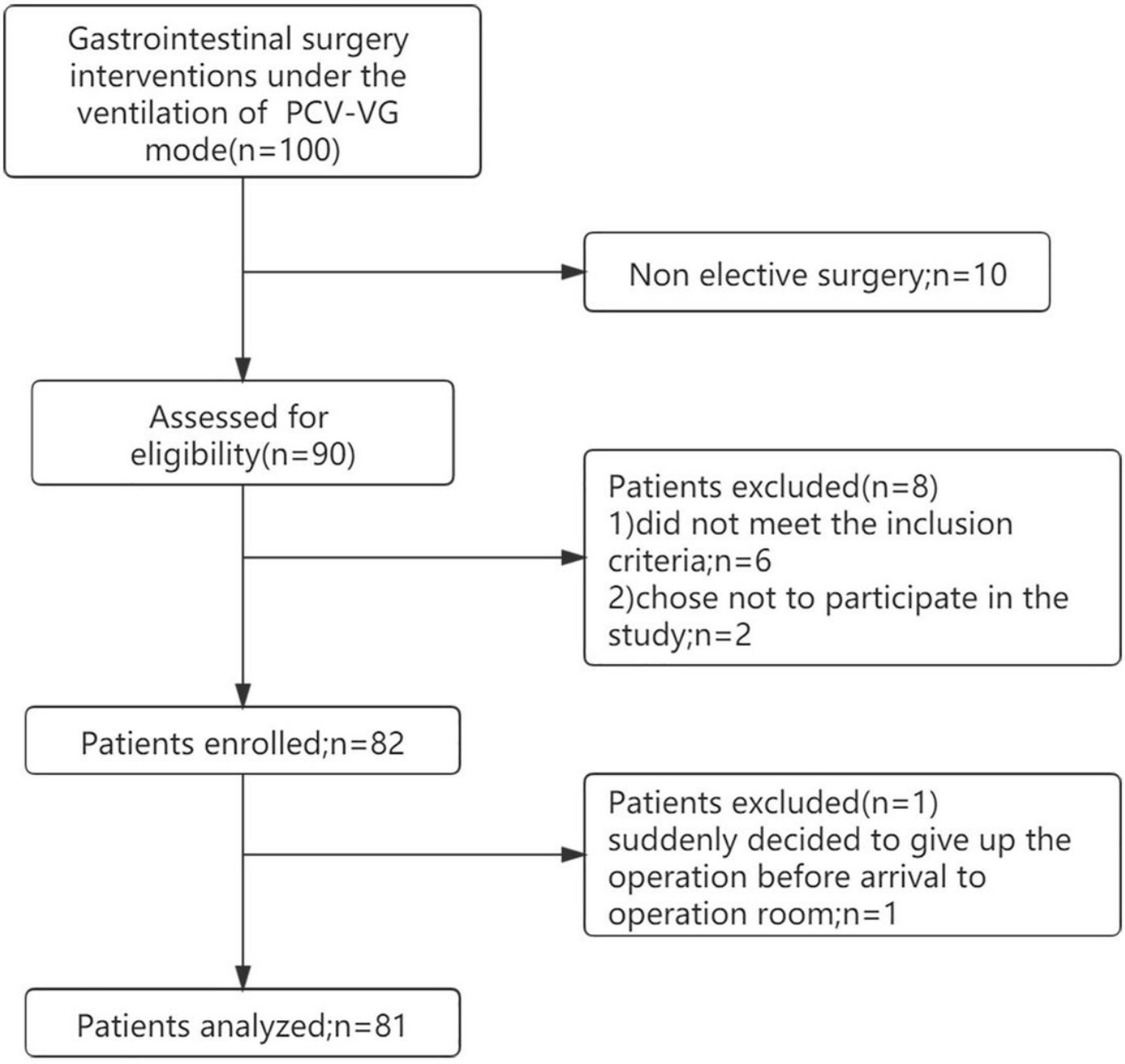

Figure 2

The flow diagram of study.

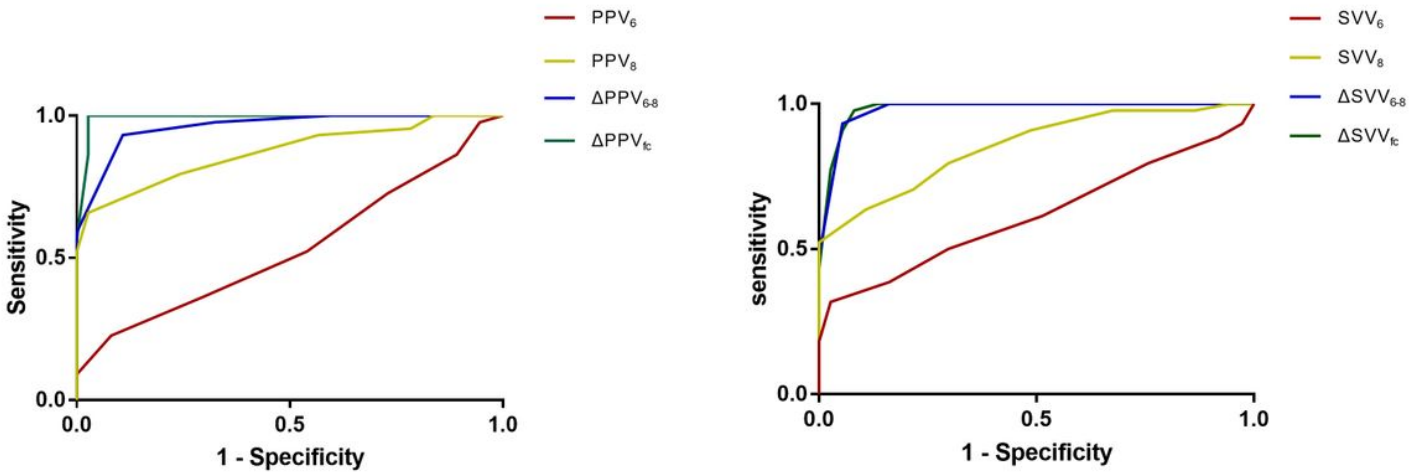

Figure 3

Receiver-operating characteristic curves of various variables ΔPPV6-8, change value of PPV after VTC; ΔSVV6-8, change value of SVV after TVC; ΔPPVfc , change value of PPV after fluid challenge; ΔSVVfc, change value of SVV after FC; SVV, stroke volume variation; PBW, predicted body weight; PPV, pulse pressure variation; PPV6, PPV at Vt 6 mL/kg PBW; PPV8, PPV at Vt 8 mL/kg PBW; SVV6, SVV at Vt 6 mL/kg PBW; SVV8, SVV at Vt 8 mL/kg PBW; Vt, tidal volume.

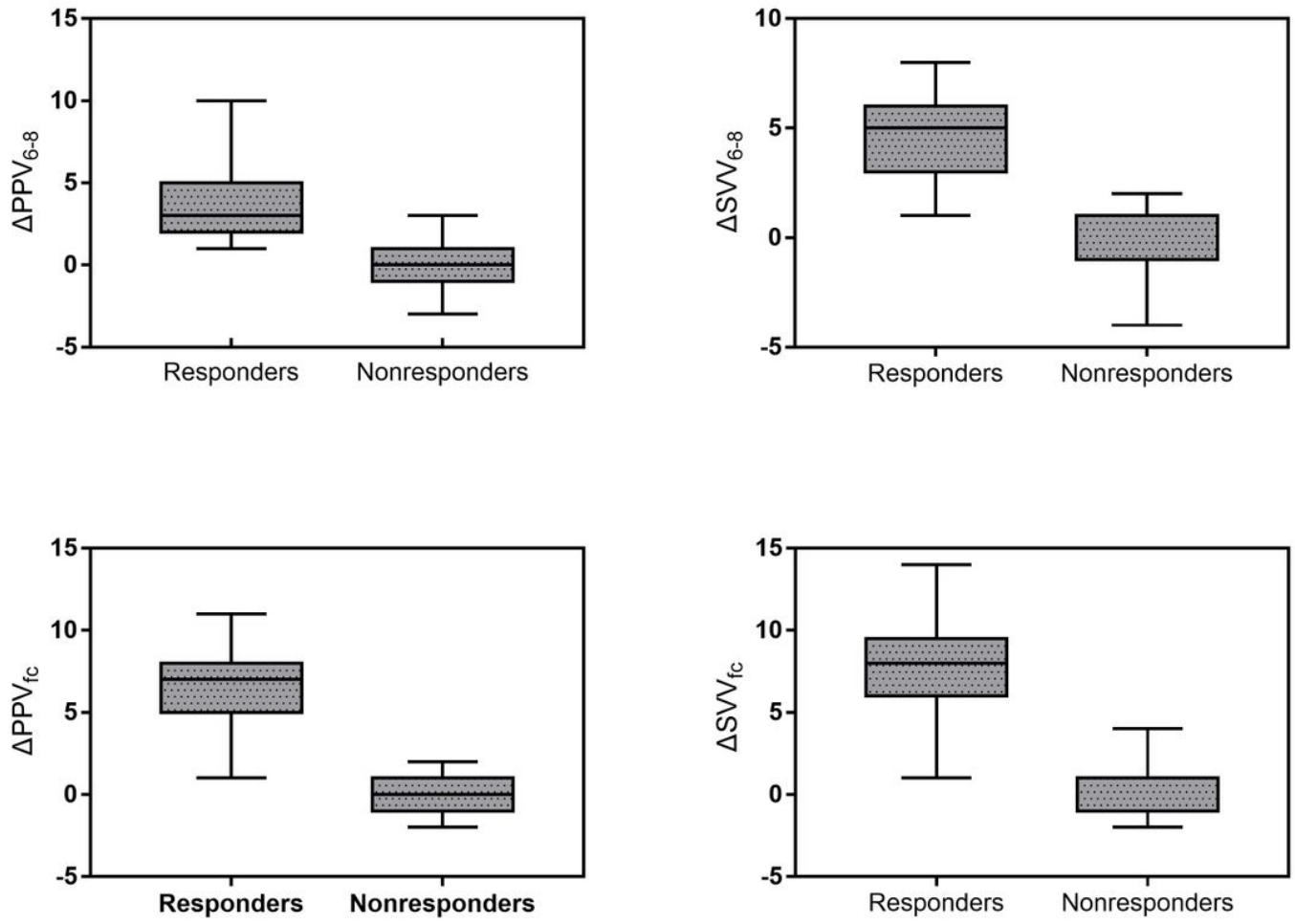

Figure 4

Box and Whisker plots comparing change in pulse pressure variation and stroke volume variation between responders and non-responders after administration of tidal volume challenge or fluid challenge. The upper and lower edges indicates the maximum and minimum values while the central box indicates the values from the lower to upper quartile (25% to 75%), respectively. The middle line represents the median. ΔPPV6-8, change value of PPV after TVC; ΔSVV6-8, change value of PPV after TVC; ΔPPVfc , change value of PPV after fluid challenge; ΔSVVfc, change value of SVV after fluid challenge.

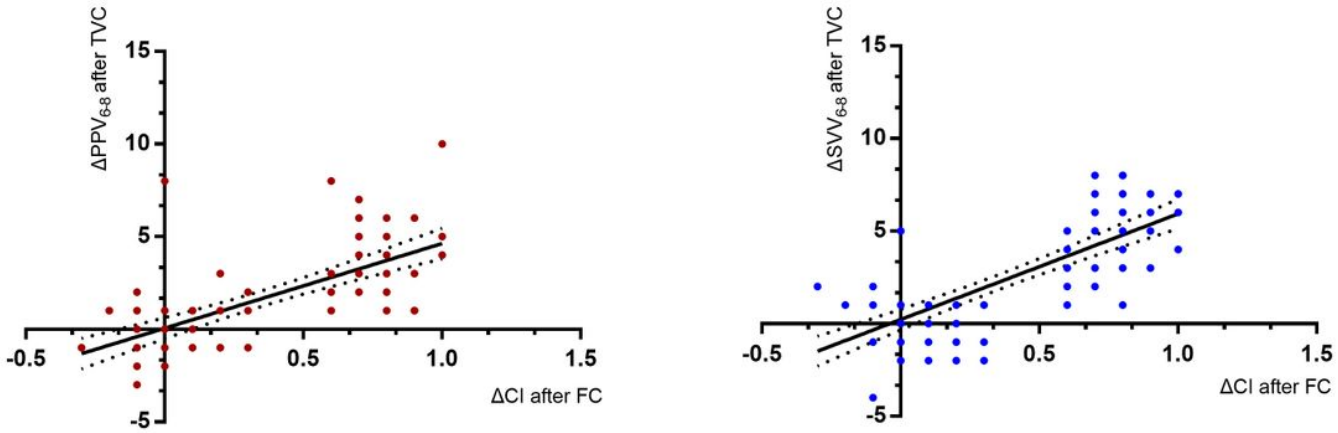

Figure 5

Correlation analysis between change value of pulse pressure variations (ΔPPV6-8) and stroke volume variations (ΔSVV6-8) after TVC and the change value of cardiac index (ΔCI) after FC. FC, fluid change; TVC, tidal volume challenge.

Supplementary Files

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