Original Article

Predicting Fluid Responsiveness Using Change in Pulse Pressure Variation and Stroke Volume Variation after Tidal Volume Challenge in Postoperative Patients Receiving Lung Protective Ventilation

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Background: Lung protective ventilation with low tidal volume (VT) is beneficial in patients with intermediate to high risk of post-operative pulmonary complications. However, during low VT ventilation, pulse pressure variation (PPV) and stroke volume variation (SVV) do not predict fluid responsiveness.

Objective: To determine whether changes in PPV and SVV after transient increases in VT could predict fluid responsiveness.

Materials and Methods: The authors recorded 20 measurements from 15 patients experiencing post-operative acute circulatory failure. The authors performed a VT challenge by transient increasing VT from 6 to 8 mL/kg (VT_{6-8}), 8 to 10 mL/kg (VT_{8-10}), and 6 to 10 mL/kg (VT_{6-10}) of patients' predicted body weight. The change in PPV (ΔPPV) at VT_{6-8} (ΔPPV_{6-8}), VT_{8-10} (ΔPPV_{8-10}), VT_{6-10} (ΔPPV_{6-10}), and the change in SVV (ΔSVV) at VT_{6-8} (ΔSVV_{6-8}), VT_{8-10} (ΔSVV_{8-10}), and VT_{6-10} (ΔSVV_{6-10}) were recorded. Patients were classified as fluid responders if there was an increase in stroke volume of more than 10% after a fluid bolus.

Results: Following the VT challenge, ΔPPV and ΔSVV failed to predict fluid responsiveness, with areas under the receiver operating characteristic curves (with 95% confidence intervals) of 0.49 (0.23 to 0.74), 0.54 (0.29 to 0.79), 0.52 (0.28 to 0.77) for ΔPPV_{6-8}, ΔPPV_{8-10}, and ΔPPV_{6-10}, and 0.55 (0.30 to 0.80), 0.55 (0.31 to 0.80), and 0.59 (0.34 to 0.84) for ΔSVV_{6-8}, ΔSVV_{8-10}, and ΔSVV_{6-10}, respectively.

Conclusion: Changes in PPV and SVV after the VT challenge did not predict fluid responsiveness in post-operative patients with low VT ventilation.

Trial registration: Thai Clinical Trials Registry, TCTR 20190808003

Keywords: Pulse pressure variation, Stroke volume variation, Fluid responsiveness, Tidal volume challenge

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Patients with intermediate to high risk post-operative pulmonary complications (PPCs) should be ventilated with low tidal volume[1,2]. Evidence shows that conventional mechanical ventilation with a tidal volume of 10 to 12 mL/kg is associated with higher inflammatory mediators[3,4]. Therefore, the authors encouraged a low tidal volume ventilation of 6 to 8 mL/kg of predicted body weight in patients with intermediate to high risk of PPCs.

Pulse pressure variation (PPV) and stroke volume variation (SVV) have been widely used to assess fluid responsiveness based on heart-lung interactions. When using these parameters, the tidal volume must

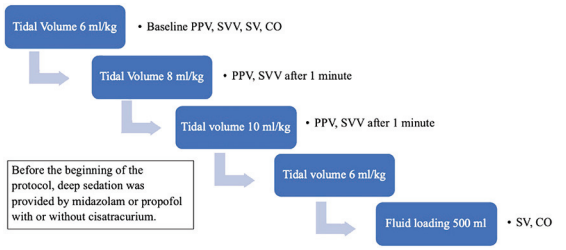

Figure 1. Protocol flow chart.

be at least 8 mL/kg to result in cyclic changes in stroke volume during respiration[5,6]. When patients are ventilated with a low tidal volume of 6 mL/kg, the effect of intrathoracic pressure is insufficiently high to see variations in PPV and SVV, even when patients are fluid-responsive[7]. Therefore, several studies have been performed to assess fluid responsive in this group of patients. One technique in these studies is called the "tidal volume challenge", which is a maneuver that increases tidal volume from 6 to 8 mL/kg of predicted body weight and assesses the increase in PPV and SVV. Previous studies found that the tidal volume challenge predicted fluid responsiveness[8,9]. In the present study, the authors analyzed the ability of the change in PPV (ΔPPV) and SVV (ΔSVV) after tidal volume challenge to assess fluid responsiveness in patients receiving low tidal volume ventilation after surgery. The authors also increased changing the tidal volume to 10 mL/kg of predicted body weight, which differed from previous studies.

Materials and Methods

The present study was performed at the surgical intensive care unit (ICU) of the authors' institution, after obtaining written informed consents from all patients or their substitute decision makers. The protocol was approved by the Ramathibodi Institutional Review Board, number ID10-60-65.

Study population

The present study included adult surgical patients received lung protective ventilation with a low tidal volume of 6 mL/kg of predicted body weight because of a moderate to high risk of PPCs according to their Assess Respiratory Risk in Surgical Patients in Catalonia scores[10,11] between May and September 2018. All patients required a preload assessment because of shock defined by one of the following, mean arterial pressure of less than 65 mmHg, systolic blood pressure of less than 90 mmHg, a decrease in systolic blood pressure of more than 40 mmHg from baseline, arterial blood lactate of 4 mmol/L or more, or urine output of less than 0.5 mL/kg/hour for at least one hour. Patients with contraindications to the use of PPV or SVV were excluded, such as patients with arrhythmias, right heart failure, valvular heart disease, heart rate over respiratory rate ratio of less than 3.6, or abdominal compartment syndrome.

Outcomes

The primary outcome of the present study was the sensitivity and specificity of PPV and SVV to identify fluid responsiveness after tidal volume challenge. The secondary outcomes were the optimal cutoffs for ΔPPV and ΔSVV after the tidal volume challenge to detect fluid responsiveness.

Methods

All patients who met the inclusion criteria were deeply sedated to allow ventilator synchronization, with some patients receiving neuromuscular blocking agents. The authors measured stroke volume and SVV by pulse contour analysis (FloTrac/EV1000™; Edwards Lifesciences, Irvine, CA). PPV was measured using a Philips IntelliVue MX700 (Philips Medical Systems Boeblingen GmbH, Boeblingen, Germany). Stroke volume, cardiac output, PPV, and SVV were measured at baseline and after the tidal volume challenge. The tidal volume challenge was performed by increasing the tidal volume from 6 to 8 mL/kg and from 8 to 10 mL/kg of predicted body weight. If the plateau pressure was greater than 30 cmH_2O, the authors decreased the tidal volume to 6 mL/kg and excluded the patient from the study. Stroke volume, cardiac output, SVV, and PPV were measured one minute after each step. Finally, 500 mL of crystalloid fluids was infused over 30 minutes to classify a patient's fluid responsive status, which was defined as a 10% increase in stroke volume from baseline. Details of the procedures are shown in Figure 1.

Statistical analysis

The sample size was calculated by StasToDo, using the comparison between two receiver-operating characteristic (ROC) curves to detect fluid responsiveness from the previous study, which was 0.69 for PPV at tidal volume of 6 ml/kg and 0.99 for ΔPPV after tidal volume challenge, with power of 80% and alpha error of 0.05, the minimum requirement of the sample size was 16. The authors increased the sample size to 22 events of shock[8].

Continuous variables were presented with mean

Table 1. Patients' characteristics

Variable	All patients (n=15) n (%)	All measurements (n=20); n (%)		p-value
		Responders (n=11)	Non-responders (n=9)	
Age (year)	60.5 (51.7 to 68.2)[a]	60.7±9.7[b]	62.0±11.0[b]	0.76
Sex: male	7 (58.3)	7 (63.3)	7 (63.6)	1.00
BMI (kg/m^2)	22.6 (19.1 to 26.0)[a]	20.0 (18.7 to 24.6)[a]	21.2 (18.7 to 22.7)[a]	1.00
APACHE II score	20.5 (14.5 to 27.0)[a]	20.0 (14.0 to 24.0)[a]	18.0 (14.0 to 28.0)[a]	0.94
ASA physical status ≥3	11 (91.6)	9 (81.8)	11 (100)	0.47
ARISCAT score for PPCs	39.5 (28.75 to 55.75)[a]	40 (26 to 59)[a]	39 (37 to 68)[a]	0.60
Comorbidities				
Hypertension	7 (58.30)	6 (54.5)	7 (63.6)	1.00
Diabetes mellitus	6 (50.00)	3 (27.2)	7 (63.6)	0.08
Stroke	3 (25.00)	4 (36.3)	2 (18.1)	0.63
COPD	3 (25.00)	2 (18.1)	4 (36.3)	0.63
Laboratory variables				
Lactate	11.0±3.4[b]	1.7 (0.5 to 7.0)[a]	3.80 (2.2 to 5.8)[a]	0.43
Surgery				
Gastrointestinal surgery	6 (50.0)	6 (54.5)	6 (54.5)	1.00
Neurosurgery	2 (16.6)	1 (9.0)	1 (9.0)	1.00
Vascular surgery	2 (16.6)	2 (18.1)	1 (9.0)	1.00
Gynecological surgery	1 (8.3)	0 (0.0)	3 (27.2)	0.21
Plastic surgery	1 (8.3)	2 (18.1)	0 (0.0)	0.47
Perioperative data				
Crystalloids (mL/hour)	794.7±439.3[b]	813.5±567.7[b]	770.5±245.1[b]	0.82
Urine output (mL/kg/hour)	0.6 (0.0 to 1.8)[a]	0.2 (0.2 to 4.6)[a]	0.2 (0.0 to 1.5)[a]	0.43

ASA=American Society of Anesthesiologists classification; BMI=body mass index; ARISCAT=Assess Respiratory Risk in Surgical Patients in Catalonia; COPD=chronic obstructive pulmonary disease; PPCs=postoperative pulmonary complications; APACHE=Acute Physiology and Chronic Health Evaluation II

[a] Median (25% to 75%), [b] Mean ± standard deviation

± standard deviation or median (interquartile range). Categorical variables were presented as number (percentage). The authors compared categorical variables using the chi-square test or Fisher's exact test. Normally-distributed quantitative variables were compared using the t-test, and other quantitative variables were compared using the Mann-Whitney U test. The areas under the ROC curves for fluid responsiveness were calculated. The optimal cutoff points for ΔPPV and ΔSVV were the values that maximized the weighted combination of sensitivity and specificity. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA).

Results

Fifteen patients were included in the present study. Two of the measurements were excluded during the tidal volume challenge because of life-threatening hypotension and the development of a new arrhythmia, leaving 20 measurements. The authors divided the 20 measurements into responders and non-responders with 11 responders and 9 non-responders.

Patients' characteristics did not differ significantly between responders and non-responders (Table 1). Baseline respiratory parameters also did not differ between responders and non-responders (Table 2). Plateau pressure was significantly higher from tidal volume 6 to 8 mL/kg and from 8 to 10 mL/kg in both responders and non-responders, but static respiratory compliance did not differ during the tidal volume challenge in either group (Table 3). Stroke volume before and after fluid loading were 59.1±22.0 and 70.0±27.3 mL for responders, and 50.9±17.0 and 51.9±16.7 mL for non-responders.

Table 2. Patients' baseline respiratory and hemodynamic parameters

Variable	All patients (n=15) Mean±SD	All measurements (n=20); mean±SD		p-value
		Responders (n=11)	Non-responders (n=9)	
PaO_2/FiO_2 ratio	310.5±187.2	400 (262 to 514)[a]	350 (157 to 360)[a]	0.24
Plateau pressure (cmH_2O)	17.1±5.0	15.7±2.6	17.4±5.9	0.39
Static respiratory compliance (mL/cmH_2O)	38.2±9.7	39.0±10.9	37.9±10.8	0.98
Mean arterial pressure (mmHg)	76.4±11.4	79.2±13.4	74.4±9.6	0.31
Heart rate (bpm)	98.8±19.8	93.7±22.0	96.9±18.5	0.71
Lactate	11.0±3.4	1.7 (0.5 to 7.0)[a]	3.8 (2.2 to 5.8)[a]	0.43
PPV	12.0±6.5	10.6±6.5	10.1±6.2	0.86
SVV	10.6±5.0	10.9±7.4	9.8±3.3	0.66
SV	52.5±18.9	57.3±19.8	51.6±17.8	0.48

PaO_2/FiO_2=arterial partial pressure of oxygen/fraction of inspired oxygen; bpm=beats per minute; PPV=pulse pressure variation; SVV=stroke volume variation; SV=stroke volume; SD=standard deviation

[a] Median (25% to 75%)

Table 3. Patients' respiratory and hemodynamic parameters during each step of the tidal volume challenge

Variables	Tidal volume 6 mL/kg Mean±SD	Tidal volume 8 mL/kg Mean±SD	Tidal volume 10 mL/kg Mean±SD
Plateau pressure			
Responders	15.7±2.6	19.0±6.7*	22.4±5.7**
Non-responders	17.4±5.9	20.6±6.7[Y]	23.0±6.7[X]
Static respiratory compliance			
Responders	39.0±10.9	37.0 (30.0 to 52.0)[a]	41.1±10.4
Non-responders	37.9±10.8	39.7±8.1	40.1±9.3
Heart rate			
Responders	93.7±22.0	93.9±22.2	90.9±20.1
Non-responders	96.9±18.5	97.0±19.5	94.9±17.4
Mean arterial pressure			
Responders	79.7±13.0	79.7±11.5	78.8±10.0
Non-responders	74.7±9.6	72.8±5.1	70.0±18.7
Stoke volume			
Responders	57.3±19.8	58.2±21.9	57.7±23.0
Non-responders	51.6±17.8	50.5±17.8	50.6±18.2

SD=standard deviation

* p<0.05 compared with VT 6 mL/kg between responders, ** p<0.05 compared with VT 8 mL/kg between responders, [Y] p<0.05 compared with VT 6 mL/kg between non-responders, [X] p<0.05 compared with VT 8 mL/kg between non-responders, [a] Median (25% to 75%)

Baseline PPV and SVV values at tidal volume 6 mL/kg were in grey zone, and other hemodynamic parameters did not differ between responders and non-responders (Table 2). After the tidal volume challenge, the authors saw no significant difference between ΔPPV and ΔSVV between responders and non-responders at each step of the tidal volume challenge (Table 4). The areas under the ROC curves (with 95% confidence intervals) were 0.4 (0.2 to 0.7), 0.5 (0.2 to 0.7), and 0.5 (0.2 to 0.7) for $\Delta PPV_{6\text{-}8}$, $\Delta PPV_{8\text{-}10}$, and $\Delta PPV_{6\text{-}10}$ (Figure 2A), and 0.5 (0.3 to 0.8), 0.5 (0.3 to 0.8), and 0.5 (0.3 to 0.8) for $\Delta SVV_{6\text{-}8}$, $\Delta SVV_{8\text{-}10}$, and $\Delta SVV_{6\text{-}10}$, respectively (Figure 2B). The results showed that the tidal volume challenge did not discriminate fluid responders from non-responders.

Table 4. Pulse pressure variation, stroke volume variation, and stroke volume after tidal volume challenge

Variables	VT from 6 to 8 mL/kg Mean±SD	VT from 8 to 10 mL/kg Mean±SD	VT from 6 to 10 mL/kg Mean±SD
ΔPPV			
Responders	2.8±3.5	4.4±3.3*	7.2±3.5**
Non-responders	3.1±2.8	3.9±3.8*	7.0±3.6**
ΔSVV			
Responders	2.5±2.9	4.3±3.6	6.9±4.3**
Non-responders	2.0±3.4	3.6±2.8	5.6±3.4
ΔSV			
Responders	0.9±3.8	−2.0 (−3.0 to 0)[a]	0.3±5.3
Non-responders	0 (−1.0 to 3.0)[a]	0±4.7	−1.0±4.3

VT=tidal volume; ΔPPV=change in pulse pressure volume; ΔSVV=change in stroke volume variation; ΔSV=change in stroke volume
* p<0.05 compared with VT 6 to 10 mL/kg, ** p<0.05 compared with VT 6 to 8 mL/kg , [a] Median (25% to 75%)

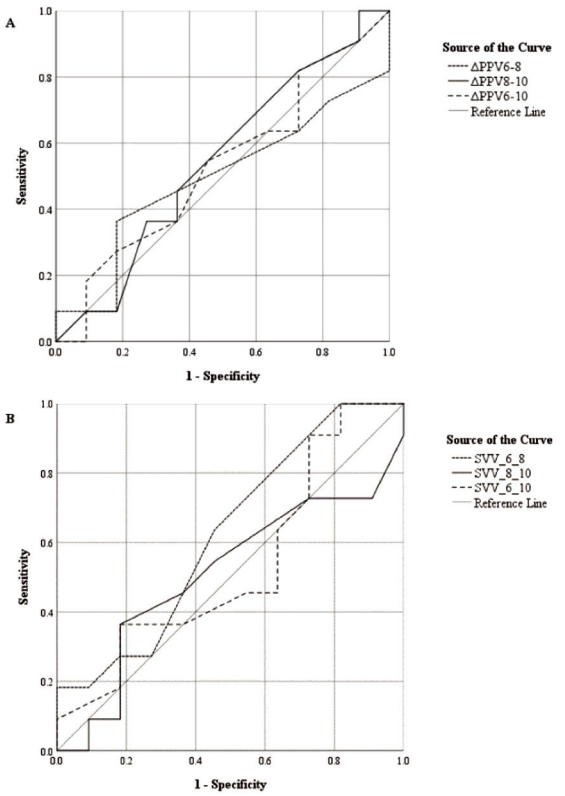

Figure 2. Receiver operating characteristic curves of pulse pressure variation (A) and stroke volume variation (B) after the tidal volume challenge.

Discussion

PPV and SVV have been widely used to predict fluid responsiveness based on heart-lung interaction. The principle of heart-lung interaction is that cyclic changes in intrathoracic pressure and transpulmonary pressure affect cardiac preload. Therefore, these effects can be seen when ventilating with a sufficient tidal volume of at least 8 mL/kg of predicted body weight[5]. During low tidal volume ventilation, PPV and SVV may be falsely low because the tidal volume may be insufficient to produce a significant change in intrathoracic pressure[5,12]. Therefore, it is recommended to use a tidal volume of at least 8 mL/kg with cutoff points for static SVV and PPV of 10% and 13%, respectively. In some situations, a tidal volume of 8 mL/kg might injure the lungs; therefore, the authors reduced tidal volume to 6 mL/kg, which resulted in the inability of SVV and PPV to predict fluid responsiveness. For example, patients with acute respiratory distress syndrome (ARDS) who received lung-protective ventilation have been excluded from studies using PPV and SVV to predict fluid responsiveness because of the decrease in transmission of intrathoracic pressure to the cardiovascular system[13]. However, Myatra et al[8] demonstrated that a tidal volume challenge from 6 to 8 mL/kg predicted fluid responders with larger areas under the ROC curves compared with using static PPV and SVV at a tidal volume of 8 mL/kg, the cutoff values of ΔPPV and ΔSVV were 3.5% and 2.5%, respectively. Jun et al also demonstrated the predictive ability of a tidal volume challenge from 6 to 8 mL/kg in robotic-assisted laparoscopic surgery in the Trendelenburg position, with cutoff values of 1% for ΔPPV and 2% for ΔSVV[9]. Messina et al performed a tidal volume challenge from 6 to 8 mL/kg in elective neurosurgery and found that tidal volume challenge predicted fluid responsiveness with ΔPPV of 13.3% and ΔSVV of 12.1%[14]. Additional previous

studies illustrated the ability of tidal volume challenge to predict fluid responsiveness, using variable cutoff values. The main factor explaining these different cutoff values may be differences in patients' chest wall compliance. Liu et al inserted esophageal balloons in patients with ARDS and found that pleural pressure change (ΔPpl) was the most important determinant of PPV among other respiratory variables (plateau pressure, change in airway pressure, tidal volume, respiratory elastance [ERS], ΔPpl, and chest wall elastance [Ecw]/ERS) in both responders and non-responders[15]. Moreover, the authors emphasized that ΔPpl was attenuated primarily by a low Ecw over ERS ratio and, to a lesser extent, by low tidal volume. Therefore, PPV and SVV in patients with low Ecw over ERS were less reliable than in patients with a high Ecw over ERS, with a proposed cutoff of 0.28, according to Liu et al's study[15], and tidal volume challenge in low Ecw might result in an insufficient increase in ΔPpl.

In the present study, the authors performed tidal volume challenge in patients with intermediate to high risk of PPCs receiving lung-protective ventilation using a tidal volume of 6 mL/kg of predicted body weight. To the authors' knowledge, this is the first study to evaluate increasing tidal volume from 6 to 8 mL/kg and then from 8 to 10 mL/kg, to maximize the efficacy of the tidal volume challenge. The authors found different results compared with previous studies and hypothesized that tidal volume challenges using increases from 6 to 8 mL/kg, 8 to 10 mL/kg, and 6 to 10 mL/kg did not cause adequate ΔPpl. Because the present study patient population constituted of post-operative patients with intermediate to high risk of PPCs (primarily atelectasis), the average respiratory compliance was 38.2±9.7 mL/cmH_2O, therefore, more than half of the patients had respiratory compliance values below the normal range. Atelectasis might have caused decreased lung compliance in the present study patients. The authors assumed that the patients had normal chest wall compliance according to results from previous studies evaluating low chest wall compliance, for example, the present study patients were not obese or septic, and the administered perioperative fluid volume was less than 3L[16]. The present study patients might have had normal or good chest wall compliance, but low respiratory compliance from increased lung stiffness secondary to atelectasis, therefore, the usefulness of the tidal volume challenge was limited in these patients. Differences in the cutoff values reported after tidal volume challenges in different studies may be explained by differences in patients' Ecw and ERS, which were not measured in the present study. Messina et al[14] reported much higher cutoff values after the tidal volume challenge compared with the studies of Myatra et al and Jun et al[8,9]. Patients from Messina et al's study[14] underwent cranial surgery and had an average respiratory compliance of 65 (58 to 73) mL/cmH_2O, suggesting that the sensitivity of the tidal volume challenge was lower in patients with good respiratory compliance. The authors concluded that a change of 2 or 4 mL/kg of tidal volume from baseline might not cause sufficient changes in pleural pressure to affect cardiac preload, especially in patients with good chest wall compliance and low total respiratory compliance.

The main limitation of the present study was that the authors did not measure ΔPpl, therefore, the conclusion regarding the inability of the tidal volume challenge to predict fluid responsiveness in the present study was based on knowledge from previous studies. Another limitation is that the authors intermittently administered sedative agents during the procedure, which might have induced cardiovascular effects, for instance, vasodilatation. As a result, the interval between the beginning of the study and the fluid loading to identify fluid responsiveness might be a confounder because of changes in fluid responsive status related to the sedative drugs. This limitation can be minimized by performing the tidal volume challenge under constant-level sedation or anesthesia.

Conclusion

Changes in PPV and SVV after the tidal volume challenge did not predict fluid responsiveness in post-operative patients with low tidal volume ventilation. Future studies including pleural pressure measurements after the tidal volume challenge in post-operative patients are needed to fully explain the present study findings.

What is already known on this topic?

Tidal volume challenge has been proposed as one of the alternative methods to detect fluid responsiveness, especially in patients with low tidal volume ventilation. However, the method needs more studies to support its accuracy.

What this study adds?

PPV and SVV changes after tidal volume challenge were unable to predict fluid responsiveness in patients ventilated with lung protective ventilation. The authors hypothesized that, with different lung mechanics, patients respond differently after tidal

volume challenge. The measurement of ΔPpl after tidal volume challenge should be added in future studies.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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