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Predictor of fluid responsiveness in the 'grey zone': augmented pulse pressure variation through a temporary increase in tidal volume

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Abstract

Background: Pulse pressure variation (PPV) is widely used as a predictor of fluid responsiveness. However, a previous study has suggested a 'grey zone' between 9 and 13% in which PPV would be inconclusive to predict fluid responsiveness. Considering PPV is based on cardiopulmonary interactions, we evaluated whether an augmented PPV using a temporary increase in tidal volume (V_T) from 8 to 12 ml kg^{-1} has the predictability for fluid responsiveness in patients within the grey zone.

Methods: Adult patients requiring general anaesthesia were enrolled. During the period when PPV was within the range of 9–13%, haemodynamic variables such as stroke volume index (SVI) and PPV with an 8 ml kg^{-1} tidal volume ventilation (PPV8) were obtained before and after volume expansion (6 ml kg^{-1}) under mechanical ventilation. Augmented PPV induced by 2-min ventilation with a V_T of 12 ml kg^{-1} (PPV12) was also recorded immediately before volume loading. The patients whose SVI increased ≥10% after volume expansion were considered responders.

Results: In 38 enrolled patients, 20 were responders. Receiver operating characteristic curve analysis showed PPV12 had an excellent predictability for fluid responsiveness {area under the curve [AUC]=0.935 [95% confidence interval (CI) 0.805–0.989]; sensitivity 95%; specificity 72%; $P<0.0001$}. The optimal threshold for PPV12 was >17%. However, PPV8 failed to show significant predictability [AUC=0.668 (95% CI 0.497–0.812); sensitivity 65%; specificity 61%; $P=0.06$].

Conclusion: In mechanically ventilated patients, our augmented PPV successfully predicted fluid responsiveness in the previously suggested grey zone.

Clinical trial registration: ClinicalTrials.gov, NCT02653469.

Key words: cardiovascular system; effects; fluid therapy; heart; cardiac output; monitoring; intraoperative

In mechanically ventilated patients, pulse pressure variation (PPV) is generally accepted as the most accurate predictor for fluid responsiveness.[1–3] The accuracy and optimal threshold of PPV for discriminating fluid responsiveness have been proven in many studies using receiver operating characteristic (ROC) curve analysis. However, the ROC approach has unavoidable limitations since it artificially dichotomizes a continuous variable into a binary statistical index and this binary approach is not always an adequate representation of the clinical reality.[4–6]

To address this binary constraint in the ROC curve approach, recent studies have posed the possible existence of an inconclusive zone (grey zone) where the accuracy of PPV is not precise

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Editor's key points

- Pulse pressure variation (PPV) is used as a predictor of fluid responsiveness, but a PPV between 9 and 13% might not be useful.
- The authors studied whether an augmented PPV using a temporary increase in tidal volume (V_T) from 8 to 12 ml kg^{-1} has predictability for fluid responsiveness.
- Augmentation of PPV by an increase in V_T might be useful in predicting fluid responsiveness.

enough to predict fluid responsiveness.[5 7–10] A multicentre study demonstrated that PPV between 9 and 13% was uncertain for predicting fluid responsiveness during general anaesthesia in one-quarter of patients.[7] In addition, a recent study reported a broader range of the grey zone (4–17%) in 62% of ventilated patients in an intensive care unit (ICU).[8] Although the real range of the grey zone for PPV remains to be evaluated,[9] precise assessment of fluid responsiveness in patients within this uncertain area is essential. However, to our knowledge, there is no specific strategy to increase the predictability of PPV for fluid responsiveness in patients within the grey zone.

Because PPV is calculated from the heart–lung interaction, various factors that affect lung mechanics, including tidal volume (V_T), thoracic wall compliance, and intrathoracic or intra-abdominal pressure, could also influence PPV values.[11–15] Among these factors, the effect of V_T has been widely studied in various studies in which the PPV value was increased and its predictability for fluid responsiveness was improved when applying higher V_T ventilation.[11 12 16 17] Therefore, we hypothesized that a temporary increase in V_T from 8 to 12 ml kg^{-1} would improve the predictability of PPV for fluid responsiveness in this inconclusive zone. The aim of our study was to investigate whether augmented PPV using a temporary increase in V_T can predict fluid responsiveness in patients within the previously suggested grey zone.[7]

Methods

Study design and patient population

After approval from our institutional review board (SMC 2015-06-015) and obtaining written informed consents, adult patients undergoing elective open laparotomy surgery were enrolled from September 2015 to February 2016. We also registered this prospective and observational study at ClinicalTrials.gov (NCT02653469). Exclusion criteria were patients with preoperative cardiac arrhythmia, moderate to severe valvular heart disease, preoperative left ventricular ejection fraction <40%, right ventricular dysfunction, intracardiac shunts, moderate to severe chronic obstructive pulmonary disease, preoperative need of inotropics, moderate to severe renal or liver disease, acute lung injury, coexisting open thorax condition, severe bradycardia, and spontaneous breathing.

Anaesthesia

After arriving at the operating theatre, our routine monitoring devices, including pulse oximetry, non-invasive arterial pressure, and three-lead ECG, were applied to the patients. Anaesthesia was induced with propofol 4–5 μg ml^{-1} and remifentanil 2–5 ng ml^{-1} at the effect site, using target-controlled infusion pumps. Rocuronium (0.6–0.8 mg kg^{-1}) was used to achieve neuromuscular block. Following endotracheal intubation, mechanical ventilation with a V_T of 8 ml kg^{-1} of the ideal body weight,[18] a fraction of inspired oxygen ($F_{I_{O_2}}$) of 0.5, and an *I:E* ratio of 1:2 with or without minimal PEEP (≤5 cm H_2O) was initiated. Respiratory rate (RR) was adjusted to maintain the value of end-tidal carbon dioxide between 35 and 40 mm Hg. To target the bispectral index score between 40 and 60, anaesthesia was maintained with continuous infusion of propofol and remifentanil. During surgery, intermittent bolus doses of rocuronium (10 mg or 0.15 mg/kg i.v. bolus) were injected to maintain a train-of-four count of less than two for adequate muscle relaxation.

Haemodynamic monitoring

A radial arterial catheter was placed and a pressure transducer was zeroed to an ambient pressure at the mid-axillary level. After connecting the arterial catheter to the FloTrac device (Edwards Lifesciences, Irvine, CA, USA), arterial pressure waveforms were simultaneously sent to the IntelliVue MP70 monitor (Philips Medical Systems, Böblingen, Germany) and the EV1000 monitor (Edwards Lifesciences). Through continuous beat detection and analysis, the EV1000 monitor showed stroke volume (SV), stroke volume index (SVI), and stroke volume variation (SVV) continuously without calibration. The IntelliVue MP70 monitor also displayed the automatically calculated PPV in real time using previously described algorithms.[19 20]

Study protocol

Fluid infusion was adjusted to maintain a PPV between 9 and 13%. When the patient's PPV was in the grey zone (between 9 and 13%), baseline haemodynamic and respiratory variables including cardiac index, SV, SVI, heart rate (HR), mean arterial pressure (MAP), SVV, RR, peak airway pressure, plateau airway pressure, PEEP level, and PPV with an 8 ml kg^{-1} tidal volume ventilation (PPV8) were recorded. After baseline measurement, V_T was increased from 8 ml kg^{-1} to 12 ml kg^{-1} of ideal body weight for 2 min and RR was adjusted to maintain constant minute ventilation. During the last minute of high V_T ventilation, the above-mentioned haemodynamic variables, including PPV with a 12 ml kg^{-1} tidal volume ventilation (PPV12), were recorded. After these two baseline haemodynamic measurements, volume expansion was performed for 10 min using an infusion of balanced crystalloid solution (6 ml kg^{-1} of ideal body weight). The same haemodynamic parameters were measured under ventilation with a V_T of 8 ml kg^{-1} 5 min after volume loading. All parameters were recorded in a stable haemodynamic state without using inotropes or vasopressors. To determine PPV and SVV values, at least three consecutive measures were averaged. The patients were excluded from analysis if their PPV failed to enter the grey zone (9–13%) in spite of adequate fluid management or if haemodynamic instability requiring immediate treatment developed.

Statistical analysis

Statistical analysis was performed using MedCalc 15.6.1 (MedCalc Software, Ostend, Belgium) and SPSS 22.0 (IBM, Armonk, NY, USA). Data are presented as mean (SD), median [interquartile range (IQR)], or number of patients (%). Student's *t*-test or Mann-Whitney *U*-test for continuous variables and the chi-square test or Fisher's exact test for categorical data were

used to compare patient characteristics between responders and non-responders. Haemodynamic parameters before and after fluid loading were analysed by paired *t*-test or Wilcoxon signed-rank test.

The percentage change in SVI according to volume loading was used as the principal indicator of fluid responsiveness. Responders or non-responders were determined when the increase in SVI was ≥10% or <10% after volume loading, respectively. To test the abilities of dynamic preload indices for predicting fluid responsiveness, areas under the receiver operating characteristics (ROC) curves of the responders were calculated and compared using the Hanley–McNeil test [area under the curve (AUC)=0.5, no better than chance, a useless test with no prediction possible; AUC=0.6–0.69, a test with a poor predictability; AUC=0.7–0.79, a fair test; AUC=0.8–0.89, a test with a good predictability; AUC=0.9–0.99, an excellent test; AUC=1.0, a perfect test with the best possible prediction].[21] A value of optimal threshold was determined for each variable to maximize the Youden index [sensitivity + (specificity – 1)].

For the sample size calculation, we considered augmented PPV (PPV12) to have good predictability for fluid responsiveness if the area under the ROC curve was >0.8. Therefore, considering that the null hypothesis was 0.5 (no discrimination), a minimum of 17 patients in each group were needed to detect an AUC difference of 0.3 with a two-sided type I error of 0.05 and a type II error of 0.1 when assuming the number of responders was similar to that of non-responders. Assuming a dropout rate of 10%, 19 patients needed to be enrolled in each group in the study.

Results

Of the 54 screened patients, 39 patients met the inclusion criteria and were enrolled in the protocol. One patient was excluded from the analysis because of unexpected severe bradycardia and hypotension that needed treatment after baseline measurements of haemodynamic variables (Fig. 1). Among 38 patients included in the final analysis, 20 patients were responders. Table 1 shows the baseline characteristics of the enrolled patients. No significant difference was found in patient characteristics between responders and non-responders except for body mass index, which was slightly higher in non-responders [median 24.74 (IQR 22.68–27.30)] than in responders [22.01 (20.68–23.19)] (Table 1).

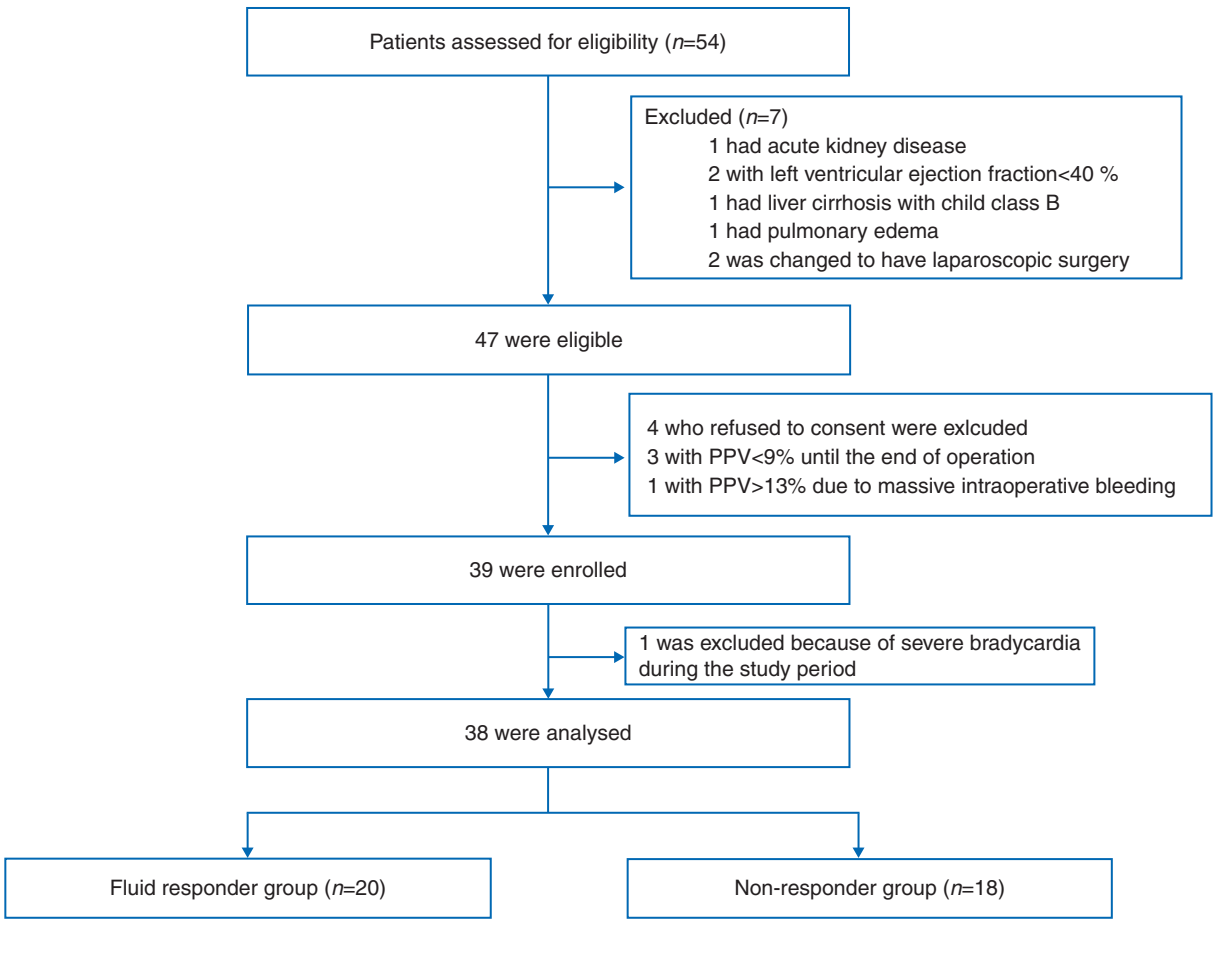

Fig 1 Study diagram.

Table 1 Patients' characteristics

	Overall (n=38)	Responders (n=20)	Non-responders (n=18)	P-value
Age, years (range)	55.50 (23–80)	53.50 (23–78)	57.72 (31–80)	0.341
Male, *n* (%)	7 (18.4)	2 (10)	5 (27.8)	0.222
Height, cm, mean (SD)	158.06 (7.35)	157.15 (5.66)	159.08 (8.93)	0.426
Ideal body weight, kg, median (IQR)	49.91 (46.04–53.60)	48.47 (46.58–52.21)	52.65 (42.80–62.24)	0.393
Body mass index, kg/m^2, median (IQR)	22.77 (21.44–25.81)	22.01 (20.68–23.19)	24.74 (22.68–27.30)	0.007
Smoker, *n* (%)	2 (5.3)	0	2 (11.1)	0.218
Ex-smoker, *n* (%)	3 (7.9)	1 (5)	2 (11.1)	0.595
Hypertension, *n* (%)	9 (23.7)	5 (25)	4 (22.2)	1
Diabetes mellitus, *n* (%)	3 (7.9)	1 (5)	2 (11.1)	0.595
Dyslipidaemia, *n* (%)	3 (7.9)	2 (10)	1 (5.6)	1
Previous stroke history, *n* (%)	1 (2.6)	1 (5)	0	1
Peripheral vascular disease, *n* (%)	1 (2.6)	1 (5)	0	1
Medication, *n* (%)				
Beta blocker	1 (2.7)	1 (5)	0	1
Calcium channel blocker	2 (5.4)	1 (5)	1 (5.9)	1
Oral hypoglycaemic agent	2 (5.4)	1 (5)	1 (5.9)	1
Angiotensin receptor blocker	3 (8.1)	2 (10)	1 (5.9)	1

Table 2 Haemodynamic and respiratory variables. Data are presented as mean (SD) or median (IQR). *P<0.05 *vs* baseline; †P<0.01 *vs* baseline; ‡P<0.01 *vs* non-responders. bpm, beats per minute; VE, volume expansion

	Responders (n=20)			Non-responders (n=18)		
	Baseline	Increased V_T (12 ml kg^{-1})	After VE	Baseline	Increased V_T (12 ml kg^{-1})	After VE
Heart rate, bpm	68 (60–74)	67 (58–74)	65 (57–71)*	68 (61–72)	67 (61–75)	64 (61–71)
Mean arterial pressure, mm Hg	80 (13)	76 (13)†	89 (79–98)*	82 (11)	79 (11)	85 (11)
Dynamic compliance	26.2 (23.3–37.2)	30.5 (26.2–36.1)*	29.8 (23.7–34.6)	27.6 (23.1–32.2)	30.3 (24.9–36.5)†	26.8 (22.9–31.3)
Static compliance	31.5 (28.7–46.2)	37.9 (32.5–51.2)*	36.3 (26.7–44.8)	30.7 (26.4–41.7)	35.7 (30.8–45.0)†	32.7 (27.7–38.7)
Driving pressure, cm H_2O	12 (10.3–13)	16 (13.3–18)†	12 (10–13.5)	13.5 (10.8–15.3)	17 (16–19)†	13 (11–15)
Cardiac index, litre min^{-1}	2.6 (0.5)	2.7 (0.9)	3.0 (0.8)*	2.5 (0.4)	2.5 (0.6)	2.6 (0.5)
Stroke volume index	38.6 (6.8)	37.3 (7.6)	44.7 (8.5)†,‡	37.1 (6.6)	37.2 (8.5)	37.7 (6.8)
PPV	12 (11–13)	20 (19–23)†,‡	7 (5–9)†	11 (10–12)	15 (13–18)†	8 (7–11)†
SVV	12 (11–14)	20 (18–23)†,‡	8 (6–9)†	11 (10–13)	16 (14–17)†	9 (6-12)†

With increased V_T from 8 to 12 ml kg^{-1}, both the HR:RR ratio and driving pressure (plateau pressure – PEEP) significantly increased [mean 7.9 (SD 1.5) *vs* 9.2 (2.4), P=0.001 and 12.6 (3.1) *vs* 16.1 (4.4), P<0.001, respectively]. Both static and dynamic lung compliances (C_{static} and C_{dyn}, respectively) also significantly increased when applying high V_T ventilation [C_{static}: 35.8 (SD 13.3) *vs* 39.8 (13.0), P=0.015 and C_{dyn}: 29.1 (SD 9.4) *vs* 31.5 (7.9), P<0.001, respectively].

The changes in haemodynamic and respiratory parameters related to volume expansion are presented in Table 2. In the responders, HR decreased and MAP, cardiac index, and SVI increased significantly after volume loading, whereas no significant changes were observed in non-responders. Baseline dynamic and static lung compliances were comparable between the two groups and were not changed after volume expansion in both groups. In both responders and non-responders, the values of PPV8 and SVV8 significantly decreased after fluid loading. Both PPV8 and SVV8 showed no significant differences between responders and non-responders; however, responders showed higher PPV12 [20 (IQR 19–23)] and SVV12 [20 (IQR 18–23)] than non-responders [15 (13–18) and 16 (14–17), respectively; both P<0.001].

In the ROC curve analysis, PPV12 and SVV12 showed excellent predictability for fluid responsiveness with AUCs of 0.935 (95% CI 0.805–0.989, P<0.0001) and 0.91 (95% CI 0.771–0.978, P<0.0001), respectively (Table 3 and Fig. 2). The optimal threshold values of PPV12 and SVV12 were 17% [sensitivity 95% (95% CI 75–99); specificity 72% (95% CI 47–90)] and 16% [sensitivity 85% (95% CI 62–97); specificity 78% (95% CI 52–94)], respectively (Table 3). However, both PPV8 and SVV8 did not predict fluid responsiveness. The AUCs for PPV12 and SVV12 were significantly larger than those for PPV8 (P=0.0005) and SVV8 (P=0.0002), respectively. No significant differences were found between AUCs for PPV8 and SVV8 (P=0.615) and between those for PPV12 and SVV12 (P=0.585).

Discussion

Our study showed that augmented PPV by a temporary increase in V_T from 8 ml kg^{-1} to 12 ml kg^{-1} can predict fluid

Table 3 Prediction of fluid responsiveness by the ROC curves of PPV and SVV measured before fluid loading

	Cut-off value, %	AUC (95% CI)	P-value	Sensitivity, % (95% CI)	Specificity, % (95% CI)
PPV8	>11	0.668 (0.497–0.812)	0.057	65 (41–85)	61 (36–83)
PPV12	>17	0.935 (0.805–0.989)	<0.0001	95 (75–99)	72 (47–90)
SVV8	>11	0.618 (0.446–0.770)	0.198	70 (46–88)	50 (26–74)
SVV12	>16	0.910 (0.771–0.978)	<0.0001	85 (62–97)	78 (52–94)

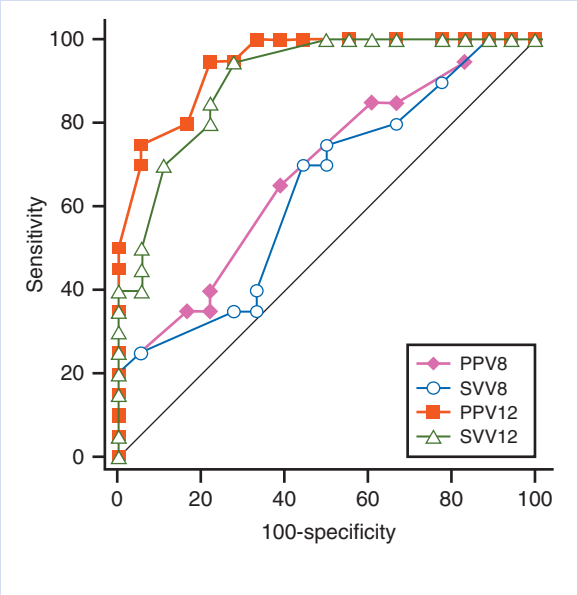

Fig 2 Prediction of fluid responsiveness by ROC curves of PPV8, SVV8, PPV12, and SVV12 in patients within the grey zone. The straight line is a reference line.

responsiveness in patients within the grey zone, whereas conventional PPV measured with V_T of 8 ml kg^{-1} was not predictive. The optimal threshold of augmented PPV was >17%.

A number of studies have suggested that PPV is a useful predictor of fluid responsiveness in patients receiving mechanical ventilation.[1–3 10 22 23] Therefore, in present-day clinical practice, it is well accepted that dynamic preload indices (i.e., PPV and SVV) are superior to predict fluid responsiveness compared with static preload indices[1 24 25] and therefore dynamic indices are widely used at the bedside to guide fluid therapy. A previous systematic review has suggested that the diagnostic threshold for those dynamic preload indices to predict fluid responsiveness is between 11 and 13%.[1]

However, all clinicians know that some patients increase SV sufficiently according to volume loading despite a baseline PPV of ~9%, whereas volume expansion fails to increase SV in other patients even though their baseline PPV is 15%.[10] In addition, most previous studies used ROC curve analysis to evaluate predictors of fluid responsiveness. However, when using this statistical approach, patients should be either responders or non-responders based on a threshold value without overlap. However, in real clinical practice, perfect discrimination is sometimes impossible.[6] Therefore, to avoid this binary constraint of responders or non-responders, recent studies have applied a grey zone approach and have proposed a possible range of uncertainty of PPV for predicting fluid responsiveness.[7 8]

To our knowledge, there have been two notable studies applying the grey zone approach to the predictability of dynamic preload indices for fluid responsiveness.[7 8] First, in their multicentre trial Cannesson and colleagues[7] suggested that PPV between 9 and 13% in the operating theatre did not accurately predict fluid responsiveness in one-quarter of patients undergoing general anaesthesia. Second, Biais and colleagues[8] reported a broader-range inconclusive zone of PPV between 4 and 17% to predict fluid responsiveness in 62% of ICU patients under mechanical ventilation. The grey zone of our study was defined as PPV values between 9 and 13% since the present study was performed in anesthetized patients receiving mechanical ventilation with a V_T of 8 ml kg^{-1}, which is similar to the study design of Cannesson and colleagues.[7]

A previous editorial suggested that the reported ranges of the grey zone might be exaggerated by various confounding factors such as mixed methods of cardiac output measurements.[9] Moreover, the problem of applying the range of grey zone for PPV directly to SVV has been also raised.[26] Our study showed that PPV8 is not accurate to predict fluid responsiveness in the previously reported grey zone range for PPV when applying a single method for SV measurement. Interestingly, SVV8 also did not show predictability for fluid responsiveness in the same grey zone range as for PPV. Moreover, the predictive power of both SVV and PPV for fluid responsiveness was increased by a temporary increase of V_T from 8 ml kg^{-1} to 12 ml kg^{-1}.

Although the exact mechanisms are hard to clarify, an increased V_T would directly augment the values of these dynamic parameters and their predictive power for fluid responsiveness. Because dynamic preload indices are based on the heart–lung interaction, SVV and PPV have shown a significant correlation with the magnitude of V_T.[13 16 27] Moreover, several studies have demonstrated that an increase in V_T strengthened the predictability of dynamic indices for fluid responsiveness.[8 17 28] In these studies, PPV measured during augmented ventilation with forced inspiration or the Valsalva manoeuvre successfully overcame the limitation of low V_T and successfully predicted fluid responsiveness in spontaneously breathing patients.[17 28]

Even though several recent reports have raised concerns regarding the statistical limitations of previous fluid responsiveness studies, there have been no investigations demonstrating specific and practical strategies to improve the predictive power of PPV for fluid responsiveness in patients within the grey zone. Therefore, our study has clinical implications in that a simple temporary increase in V_T to 12 ml kg^{-1} improved the ability of augmented PPV to predict fluid responsiveness in patients within the grey zone from fair to excellent diagnostic ability. However, application of this methodology to patients with non–grey zone PPVs is not recommended since the usefulness of

non–grey zone PPVs for predicting fluid responsiveness is well established and there would be no additional benefit. When a patient's PPV is within the uncertain zone for fluid responsiveness, our simple method can provide additional information that should contribute to decision making regarding whether or not to give fluids to the patient. Moreover, this could expand the clinical usefulness of PPV for intraoperative fluid management.

There are several limitations in this observational study. First, as our study was conducted in the setting of the operating theatre with a fixed V_T of 8 ml kg^{-1} in patients without any respiratory problems, and considered the range of the grey zone to be a PPV between 9 and 13%, a range identified from data for anesthetized patients,[7] the applicability of our method to predict fluid responsiveness in the ICU setting cannot be clarified. However, the exact range of the grey zone of PPV in ICU ventilated patients may need further investigation with a uniform cardiac output measurement method in more controlled settings. Second, other factors that might improve the predictability of PPV for fluid responsiveness during high-V_T ventilation were not fully explored. Previously, an HR:RR ratio >3.6 and airway driving pressure >20 cm H_2O have been suggested to improve the predictability of PPV for fluid responsiveness.[8 29 30] Although both the HR:RR ratios and the mean driving pressures in our study significantly increased with high-V_T ventilation, the actual contribution of each factor to the improved predictive power of PPV is hard to discriminate because HR:RR was >3.6 and the driving pressure was <20 cm H_2O at any time point in our study. Third, while we employed a short-duration V_T increase, the possible clinical effects of temporary increases in V_T are unclear. Transient high V_T may reduce intraoperative atelectasis or could potentially be harmful due to alveolar stretch, especially in patients with severe pulmonary disease (i.e. acute respiratory distress syndrome). Therefore, our strategy for PPV augmentation should be applied carefully with consideration of the risks and benefits. Fourth, the use of PEEP in our study was inconsistent, ranging from 0 to 5 cm H_2O. Because the use of PEEP could affect the respiratory driving pressure, lung compliance, and subsequent PPV values, it would be ideal to apply a consistent level of PEEP in every patient for clear data interpretation. However, we only applied a low level of PEEP <5 cm H_2O without any change during the study period, and no significant differences were found in lung compliances between responders and non-responders. Moreover, a low level of PEEP ranging from 0 to 10 cm H_2O has been widely used in previous published studies.[7] Finally, because the present study was not designed to investigate the real range of the grey zone, it is impossible to suggest the range of the grey zone of PPV for predicting fluid responsiveness from this study. The exact range of the grey zone of PPV in different clinical situations remains to be evaluated.

In conclusion, in this study of anaesthetized patients in the inconclusive zone for fluid responsiveness (with PPV values between 9 and 13%), augmentation of PPV through a temporary increase in V_T from 8 ml kg^{-1} to 12 ml kg^{-1} led to excellent predictability of fluid responsiveness. When carefully used, our simple method can provide useful information regarding the clinical application of PPV and can contribute to decision making regarding whether to administer fluids in patients within the grey zone.

Authors' contributions

Study design, patient recruitment, data collection, data analysis, writing of the first draft and revision of the paper, and archiving of the study files: J.J.M.
Study design, data analysis, discussion of results, revision of the manuscript, and approval of final version: N.-S.K.
Study design, data analysis, discussion of results, revision of the manuscript, and approval of final version: J.-H.L.
Study design, data collection, data analysis, and approval of final version: D.K.R.
Study design, data collection, discussion of results, and approval of final version: W.K., C.S.K., S.M.L.

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Declaration of interest

None declared.

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