Prediction of fluid responsiveness in acute respiratory distress syndrome patients ventilated with low tidal volume and high positive end-expiratory pressure*

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Objective: **Dynamic preload indicators with pulse pressure variation and stroke volume variation are superior to static indicators for predicting fluid responsiveness in mechanically ventilated patients. However, they are influenced by tidal volume and the level of positive end-expiratory pressure. The present study was designed to evaluate the clinical applicability of pulse pressure variation and stroke volume variation in predicting fluid responsiveness on acute respiratory distress syndrome patients ventilated with protective strategy (low tidal volume and high positive end-expiratory pressure).**

Design: **Prospective, observational study.**

Setting: **A 20-bed medical intensive care unit of a tertiary medical center.**

Patients: **Twenty-two sedated and paralyzed early acute respiratory distress syndrome patients.**

Interventions: **After being enrolled, central venous pressure, pulmonary capillary wedge pressure, and cardiac output index were obtained from a pulmonary artery catheter (OptiQ SvO_2/CCO catheter), and intrathoracic blood volume, global end-diastolic volume, stroke volume variation, and pulse pressure variation were recorded from a PiCCOplus monitor. The whole set of hemodynamic measurements was performed before and after volume expansion with 500 mL hydroxyethyl starch (10% pentastarch 200/0.5).**

Measurements and Main Results: **Cardiac output index, central venous pressure, pulmonary capillary wedge pressure, global end-diastolic volume, and intrathoracic blood volume significantly increased, and pulse pressure variation and stroke volume variation significantly decreased after volume expansion. Baseline pulse pressure variation significantly correlated with volume expansion-induced absolute changes ($r = .62$), or percent changes in cardiac output index ($r = .75$) after volume expansion. The area under the receiver operating characteristic curve was the highest for pulse pressure variation (area under the receiver operating characteristic curve = 0.768) than other indicators. The threshold value for baseline pulse pressure variation greater than 11.8% predicted a significant positive response to volume expansion with a sensitivity of 68% and a specificity of 100%.**

Conclusions: **Baseline pulse pressure variation accurately predicted the fluid responsiveness in early acute respiratory distress syndrome patients. Roughly, a baseline pulse pressure variation greater than the threshold value of 12% is associated with a significant increase in cardiac output index after the end of volume expansion. (Crit Care Med 2008; 36:2810–2816)**

KEY WORDS: acute respiratory distress syndrome; fluid responsiveness; intrathoracic blood volume; global end-diastolic volume; pulse pressure variation; stroke volume variation

Fluid responsiveness refers to the ability of the heart to increase its stroke volume in response to volume expansion (VE). Accurately predicting fluid responsiveness obviates unnecessary fluid loading, and helps to detect patients who may benefit from a VE. Assessment of the traditionally used static hemodynamic monitoring indicators (pressure preload indicators with central venous pressure [CVP] and pulmonary capillary wedge pressure [PCWP] and volume preload indicators with intrathoracic blood volume index [ITBVI] or global end-diastolic volume index [GEDVI]) are of limited value in predicting fluid responsiveness in critically ill patients (1–3), especially in patients with a decreased left ventricular compliance (3–6), or with external or intrinsic positive end-expiratory pressure (PEEP) (3, 5, 6). By inducing cyclic changes in pleural and transpulmonary pressures, mechanical ventilation results in cyclic changes in the preload and afterload of both ventricles. The systolic, pulse pressure and stroke volume variation (SPV, PPV, and SVV) (3, 6–20), which are dynamic indicators from heart-lung interaction, have been found to be better than static indicators in assessing fluid responsiveness. However, the magnitude of dynamic preload indicators is affected by the tidal volume (V_T), the level of PEEP, cardiac rhythm, and ventricular failure (1, 3, 6).

Acute respiratory distress syndrome (ARDS) patients, because of the increased permeability (21), are most vulnerable to the deleterious effects of fluid overloading. Accurately predicting fluid responsiveness is of extreme importance for ARDS patients. With the protective ventilatory strategy, an ARDS Network study suggests decreasing the V_T to as low as 6 mL/kg (22). The cyclic perturbations to cardiac filling may not be great enough to induce cyclic variations in LV filling needed to identify

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fluid responsiveness (23). On the contrary, the high PEEP needed in ARDS (24) decreases cardiac output and exaggerates the undulation of systemic blood pressure, and increases PPV by increasing pleural and transpulmonary pressure (8). Up to now, neither PPV nor SVV has been validated on the assessment of fluid responsiveness in ARDS patients, where these parameters may become less accurate. The clinical value of PPV and SVV in ARDS, just as Teboul and Vieillard-Baron (25) said in an editorial, is still an unresolved issue.

The aim of this study was to evaluate the predictive values of PPV and SVV for fluid responsiveness, using pulse contour analysis from a PiCCOplus monitor (Pulsion Medical System, Munich, Germany), in ARDS patients ventilated with a protective strategy (low VT and high PEEP).

MATERIALS AND METHODS

Patients. This study was approved by the Institutional Review Board for Human Research of Chang Gung Memorial Hospital (Taoyuan, Taiwan), and informed written consent for clinical procedure was obtained from the nearest relative. A total of 22 early ARDS patients conforming to the American-European Consensus Conference criteria (26) and with an Acute Lung Injury score greater than 2.5 (27), who were admitted to the medical intensive care unit were enrolled. All the cases were studied early in the course of ARDS. The mean duration from diagnosis of ARDS to the time of study was 1.7 ± 0.7 days (range, 1–3 days). Patients' hemodynamics were judged to be clinically stable at the time of study, although vasoactive drugs (norepinephine and/or dopamine, or dobutamine) were still needed in 15 of the 22 patients.

Measurement of Cardiac Output and Hemodynamics. Heart rate and blood pressures, including systolic, mean systemic and pulmonary arterial pressures, CVP and PCWP, were recorded from a pulmonary artery catheter (OptiQ SvO_2/CCO catheter, Hospira, Lake Forest, IL) and an on-line HP Component Monitoring System (Model 56S, M 1165A, Hewlett-Packard, Boblingen, Germany). The cardiac output computer (Q_2 continuous cardiac output/SvO_2 computer, Abbott Laboratories, North Chicago, IL) used in this study could monitor cardiac output automatically and continuously using thermodilution principles from the pulmonary artery catheter.

Measurement of ITBVI, GEDVI, and Extravascular Lung Water, and Calculation of SVV and PPV. A 4F thermistor-tipped arterial catheter (Pulsiocath, Pulsion Medical Systems) was inserted into the femoral artery and connected to a bedside hemodynamic PiCCOplus monitor (version 5.2.2; Pulsion Medical Systems AG, Munchen, Germany). ITBVI, GEDVI, and EVLWI were determined via transpulmonary thermodilution measurements, which were performed by 3–5 injections of 15-mL iced saline into the central venous port of the pulmonary artery catheter randomly throughout the respiratory cycle (28). Continuous pulse-contour cardiac output and pulse-contour stroke volume can be measured using heart rate and the area under the arterial flow curve. SVV and PPV are presented as the changes in stroke volume and in pulse pressure (in percent) calculated by the mean difference between the highest and lowest stroke volume and pulse pressure, divided by a calculated mean stroke volume and pulse pressure over the previous 30 secs. SVV and PPV are calculated according to the following equation: SVV = (SVmax − SVmin)/SVmean; PPV = (PPmax − PPmin)/PPmean. SVmax and PPmax; SVmin and PPmin indicate mean value of four maximum or minimum stroke volumes and pulse pressures of the previous 30 secs, respectively. SVmean and PPmean indicate mean value of stroke volume and pulse pressure over the previous 30 secs (28).

Measurement of Pulmonary Mechanics and Compliance. The GALILEO ventilator automatically measures pulmonary compliance (static compliance, volume/pressure) breath by breath using a statistical technique called the least squares fit method. This method is applied on a breath-by-breath basis, without the need for special inspiratory flow patterns and occlusion maneuvers, provided that the patient is relaxed (29). The ventilatory settings, including VTs, peak and mean airway pressures, compliance, and PEEP level, were downloaded from the ventilator to a personal computer in a spreadsheet form for later analysis.

Study Design. Before enrollment, all patients had been sedated with a continuous infusion of midazolam (F. Hoffmann-La Roche, Basel, Switzerland) and/or propofol (ICI Pharmaceuticals, Cheshire, England), and/or paralyzed with atracurium (F. H. Faulding, Victoria, Australia) to facilitate synchronization of mechanical ventilation and to decrease oxygen consumption. They were ventilated with pressure-control mode with a mean peak inspiratory pressure 34.2 ± 4.9 cm H_2O to deliver a mean VT of 6.4 ± 0.7 mL/kg (range, 5.3–8.3 mL/kg) via a GALILEO GOLD ventilator (Hamilton Medical AG, Via Nova, Switzerland). The PEEP levels were set at least 2 cm H_2O above the lower inflection point derived from the P-V tool maneuvers of the GALILEO GOLD ventilator with the mean set PEEP level of 14 ± 1.4 cm H_2O (range, 12–17 cm H_2O), and the mean respiratory rate 24 ± 3 breaths/min (range, 20–30 breaths/min). After baseline measurements, VE was started by the infusion of HES (10% pentastarch, HAES-steril 200/0.5, Fresenius Kabi, B. Braun, Melsungen, Germany) at a rate of 10 mL/kg/hr for a total of 500 mL. The whole set of parameters was repeated at the end of infusion. According to the results of Stetz et al. (30), patients were classified to be VE responders or nonresponders according to whether the VE-induced cardiac output index (CI) increase at the end of HES infusion was ≥15% or <15% of baseline CI. The rates of intravenous fluid and vasopressor infusion and the settings of mechanical ventilation were kept fixed during the study periods.

Statistical Analysis. All variables were indexed to body surface area and expressed as mean ± SD. The significance of changes after VE in various hemodynamic data, preload indicators, oxygenation, and related variables when compared with baseline values were analyzed by Wilcoxon signed rank test. The difference between various baseline values of responders and nonresponders was evaluated by Mann-Whitney *U* test. Spearman's rank correlation was used to analyze the relationships between baseline measurements of static and dynamic preload indicators and changes in CI (ΔCI) after VE. The ability of the studied preload indicators to predict positive fluid responsiveness after VE was tested by the receiver operating characteristic curve. The area under each curve was calculated with a value of <0.5, meaning that the predictive performance of that indicator is no better than chance. The threshold value is the data that has maximal Youden's index (J = sensitivity + specificity − 1) (31). A p value <0.05 was considered statistically significant.

RESULTS

The main characteristics of the 22 ARDS patients (mean age 54 ± 17 yrs; range, 22–88 yrs; 16 men, 6 women) studied are summarized in Table 1. The mean Acute Physiology and Chronic Health Evaluation II score at the time of diagnosis of ARDS was 21.8 ± 5.5 (range, 12–33). Of the 22 patients recruited, the baseline PPV and SVV data were missing in two patients (one in the responder group and one in the nonresponder group) and 20 complete data sets were available for statistical analysis regarding the two parameters. The severity of ARDS expressed as a lung injury score was 3.1 ± 0.4 (range, 2.5–3.75). The Pa_{O_2}/F_{IO_2} and PCWP values at the time of diagnosis of ARDS were 95.8 ± 40.3 mm Hg (range, 33–183 mm Hg) and 12.9 ± 2.9 mm Hg (range, 7–17 mm Hg), respectively.

VE resulted in a significant elevation in systolic and mean pulmonary artery pressure (PAPs, PAPm), CI, stoke volume index, CVP, PCWP, GEDVI, ITBVI, and a significant decrease in heart rate, PPV, and SVV (Table 2). VE with HES increased Pa_{O_2} without exacerbating the Pa_{O_2}/F_{IO_2}, pulmonary edema (no change in extravascular lung water index) and lung compliance (Table 2). There were no significant difference between the volume responders and nonresponders in the mean VT (6.4 ± 0.7 mL/kg vs. 6.5 ± 0.8 mL/kg) and PEEP level (14.4 ± 1.4 cm H_2O vs. 13.2 ± 1.2 cm H_2O). The baseline

Table 1. Patient characteristics

Patient	Age	Gender	Time from Diagnosis of ARDS (days)	FIO_2 at Entry of Study	PaO_2/FIO_2 at Diagnosis of ARDS	PCWP (mm Hg)	ALIS	Tidal Volume (mL/kg)	PEEP	Respiratory Compliance (mL/cm H_2O)	Norepienphine, Dopamine, or Dobutamine	Serum Creatinine (mg/dL)	Diagnosis
1	52	M	2	0.8	81.7	16	2.75	6.4	14	31.9	Yes	5.1	Pneumonia
2	70	M	1	1	33	15	3.75	5.6	17	25.6	No	1.2	Pneumonia, NPC
3	47	M	2	1	53.9	13	3.25	5.3	15	23.4	Yes	1.5	Pneumonia, lymphoma, DM
4	78	M	2	1	84.7	17	2.75	6.2	12	33.0	No	0.6	Pneumonia, CVA, DM
5	46	M	2	0.6	110	12	2.5	5.8	14	32.9	Yes	0.8	Pneumonia, liver cirrhosis
6	56	F	2	1	119	11	3	6.3	15	15.0	Yes	0.9	Pneumonia, liver cirrhosis, DM
7	49	M	1	0.9	89	17	3	6.0	13	38.6	Yes	0.6	Pneumonia, alcoholism
8	22	M	1	1	81.4	11	2.75	6.2	14	25.6	No	1.1	Aspergillus, pneumonia, BMT
9	46	F	2	1	74	7	3.25	7.4	14	18.2	Yes	0.5	Pneumonia, NPC, septic shock
10	35	F	2	1	94	12	3.25	6.3	13	29.8	Yes	0.5	Pneumonia, DM
11	34	M	1	1	70	15	3.5	6.7	15	21.0	Yes	1.1	Pneumonia, alcoholism
12	79	M	1	0.8	83.7	13	3.25	6.2	15	31.3	Yes	0.8	Pneumonia
13	60	M	1	1	43	11	3.5	6.4	16	37.4	No	0.7	Pneumonia, DM
14	70	M	3	0.7	171	14	3.25	6.4	14	19.0	Yes	1.3	AIP
15	45	F	1	0.9	134	15	3	6.3	13	15.0	Yes	0.5	Alveolar hemorrhage, Bechet's disease
16	62	M	2	1	78	15	3	6.9	12	22.8	Yes	1	Pneumonia, NPC
17	71	F	1	0.8	172	8	2.75	8.3	12	26.1	Yes	1	Pneumonia, septic shock
18	57	M	3	1	125	15	2.75	5.6	14	36.5	No	1.3	Pulmonary hemorrhage
19	88	M	2	1	67	8	3	6.8	12	32.2	No	1.5	Pneumonia, CVA
20	39	F	2	0.85	81.7	15	3.75	7.6	15	12.0	Yes	1	Pulmonary hemorrhage
21	36	M	1	0.65	183	12	2.75	5.8	12	22.1	Yes	1.1	Pneumonia, lung cancer
22	44	M	3	0.95	78	11	3.5	7.4	14	25	No	0.6	AIP, lynphoma
Mean	54		1.7	0.91	95.8	12.9	3.1	6.4	13.9	26.1		1.12	
SD	17		0.7	0.13	40.3	2.9	0.4	0.7	1.4	7.6		0.94	

ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure; ALIS, Acute Lung Injury score; PCWP, pulmonary capillary wedge pressure; NPC, nasopharyngeal cancer; DM, diabetes mellitus; CML, chronic myeloid leukemia; BMT, bone marrow transplantation; AIP, acute interstitial pneumonitis; CVA, cerebral vascular accident.

values of hemodynamic data, preload indicators, oxygenation, and related variables for responders (n = 10) and nonresponders (n = 12) are presented in Table 3. Responder patients had lower baseline CI, stroke volume index, PCWP, and higher PPV than nonresponders. The SVV values were also higher in responder patients, but the difference did not reach a statistical significance. There were no differences in baseline arterial or mixed venous oxygenation, degree of pulmonary edema, mean airway pressure, or lung compliance between responders and nonresponders. Among the various baseline preload indicators, only baseline PPV showed a positive correlation with VE-induced absolute changes in CI (Fig. 1).

The area under the receiver operating characteristic curve (AUC) analysis for the various preload indicators to predict fluid responsiveness after VE was the highest for PPV (0.768) compared with other indicators (AUC for CVP: 0.429; PCWP: 0.187; GEDVI: 0.323; ITBVI: 0.323; SVV: 0.606, respectively). The threshold value for the baseline PPV greater than 11.8% predicted a significant positive response to subsequent VE by an increase of CI $\geq$15% with a sensitivity of 68% and a specificity of 100% (Fig. 2).

DISCUSSION

The major findings of our study are that PPV accurately predicts the response of cardiac output to VE, and remains a reliable predicator of fluid responsiveness for ARDS patients ventilated with low VT and high PEEP. VE significantly increased both the pressure and volume indicators of preload and significantly decreased PPV and SVV. Although the hemodynamics were stable (15 of 22 patients still receiving norepinephine and/or dopamine, or dobutamine infusion), VE with HES further increased cardiac output and PaO_2 without worsening PaO_2/FIO_2, pulmonary edema (no change in extravascular lung water index), or lung compliance. Responder patients had lower baseline CI, SVI, and PCWP and higher PPV than nonresponders.

Static pressure preload indicators (CVP and PCWP) have been used for standard hemodynamic monitoring for a long time. However, the poor predictive value

Table 2. Hemodynamic data, preload indicators, oxygenation, and related variables at baseline and after volume expansion

Variable	Baseline	End of HES Infusion
HR (beats/min)	120 ± 21	115 ± 18[a]
ABPs (mm Hg)	126 ± 20	134 ± 22
ABPm (mm Hg)	85 ± 12	88 ± 14
PAPs (mm Hg)	39 ± 10	47 ± 10[a]
PAPm (mm Hg)	29 ± 7	33 ± 6[a]
CI (L/min/m^2)	4.50 ± 1.82	5.07 ± 1.75[a]
SVI (mL/m^2)	37.1 ± 13.7	43.6 ± 12.6[a]
CVP (mm Hg)	12 ± 4	17 ± 5[a]
PCWP (mm Hg)	13 ± 3	18 ± 4[a]
GEDVI (mL/m^2)	910 ± 232	986 ± 222[a]
ITBVI (mL/m^2)	1137 ± 290	1234 ± 282[a]
PPV (%)	9.8 ± 4.5	6.7 ± 4.5[a]
SVV (%)	11.6 ± 4.4	7.4 ± 5.3[a]
Pao_2 (mm Hg)	90.6 ± 24.1	99.8 ± 30.6[a]
Svo_2 (%)	0.70 ± 0.09	0.69 ± 0.10
Pao_2/Fio_2 (mm Hg)	140 ± 51	147 ± 56
EVLWI (mL/kg)	21.8 ± 10.7	21.1 ± 9.1
Compliance (mL/cm H_2O)	26.2 ± 7.8	25.5 ± 7.4

Values are mean ± SD.

CI, cardiac output index; HR, heart rate; ABPs, systolic arterial pressure; ABPm, mean arterial pressure; PAPs, systolic pulmonary arterial pressure; PAPm, mean pulmonary arterial pressure; SVI, stroke volume index; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; GEDVI, global end-diastolic volume index; ITBVI, intrathoracic blood volume index; PPV, pulse pressure variation; SVV, stroke volume variation; Svo_2, mixed venous oxygen saturation; EVLWI, extravascular lung water index.

[a]Significantly different from its baseline value at 5% level.

Table 3. Baseline hemodynamic data, preload indicators, oxygenation, and related variables of responders and nonresponders

Variable	Responders (n = 10)	Nonresponders (n = 12)
HR (beats/min)	119 ± 26	121 ± 17
ABPs (mm Hg)	122 ± 19	130 ± 22
ABPm (mm Hg)	86 ± 13	84 ± 12
PAPs (mm Hg)	36 ± 9	41 ± 10
PAPm (mm Hg)	28 ± 7	30 ± 7
CI (L/min/m^2)	3.3 ± 0.8	5.5 ± 1.84[a]
SVI (mL/m^2)	28.2 ± 7.7	44.6 ± 13.2[a]
CVP (mm Hg)	12 ± 3	12 ± 4
PCWP (mm Hg)	11 ± 2	14 ± 3[a]
GEDVI (mL/m^2)	846 ± 276	63 ± 183
ITBVI (mL/m^2)	1057 ± 345	203 ± 229
PPV (%)	12.1 ± 5.4	7.9 ± 2.6[a]
SVV (%)	12.2 ± 4.6	11.0 ± 4.4
Pao_2 (mm Hg)	93 ± 32	88 ± 16
Svo_2 (%)	0.65 ± 0.11	0.73 ± 0.05
Pao_2/Fio_2 (mm Hg)	141 ± 68	128 ± 33
EVLWI (mL/kg)	25.1 ± 11.8	19.0 ± 9.3
Pmean (cm H_2O)	20.2 ± 2.5	19.8 ± 2.1
Compliance (mL/cm H_2O)	25.1 ± 7.2	26.9 ± 8.5

Values are mean ± SD.

CI, cardiac output index; HR, heart rate; ABPs, systolic arterial pressure; ABPm, mean arterial pressure; PAPs, systolic pulmonary arterial pressure; PAPm, mean pulmonary arterial pressure; SVI, stroke volume index; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; GEDVI, global end-diastolic volume index; ITBVI, intrathoracic blood volume index; PPV, pulse pressure variation; SVV, stroke volume variation; Svo_2, mixed venous oxygen saturation; EVLWI, extravascular lung water index; Pmean, mean airway pressure.

[a]Significantly different between baseline data of responders vs. nonresponders at 5% level.

of CVP and PCWP in estimating fluid responsiveness in mechanically ventilated patients has been addressed repeatedly in review articles (3, 6). Volumetric indicators (ITBVI, GEDVI) more accurately reflect the changes of cardiac preload (32, 33). Because the slope of the steep portion of the Frank-Starling curve depends on myocardial contractility, together with the curvilinear rather than linear relationship between preload and stroke volume, static preload measurements are not equal to preload responsiveness. Even accurately estimated ventricular preload does not always ensure accurate prediction of hemodynamic response to VE. The usefulness of static volume indicators, such as ITBVI and GEDVI by PiCCOplus monitor, to predict fluid responsiveness in mechanically ventilated patients reported in different studies is conflicting (3, 11, 14–19, 34). In our results, although the responders had lower baseline PCWP values, no correlations existed between the baseline CVP, PCWP, ITBVI, GEDVI, and the HES infusion-induced changes in CI. Moreover, the areas under the receiver operating characteristic curves for the four indicators (Fig. 2), all were smaller than 0.5, indicating that their abilities to assess the hemodynamic response were no better than chance. Similar to the previous studies (1–3, 11, 14–19, 34), both the static preload indicators (pressure and volume) in our study were not capable of predicting the fluid responsiveness in ARDS patients.

For the dynamic preload indicators to be effective in estimating the hemodynamic response, the respiration-induced pleural and transpulmonary pressure fluctuation must be great enough to induce significant cyclic changes in right ventricular (RV) and left ventricular preload. Among the pulmonary mechanics, V_T rather the airway pressures was found to be the main determinant of pleural and pericardial pressure, and RV afterload (35, 36). Increasing V_T induces a leftward shift on the Frank-Starling curve. As suggested by Reuter et al. (13) and de Backer et al. (20), instead of plateau pressure, it is the V_T that affects the magnitude of PPV and SVV. High V_T has been shown to be associated with a high SPV by Szold et al. (37) and high PPV and SVV by Reuter et al. (13) rather than low V_T. In addition, de Backer et al. (20) demonstrated that PPV is a reliable predictor of fluid responsiveness in mechanically ventilated patients only when V_T is at least 8 mL/kg. The other important ventilatory setting is PEEP. By increasing pleural pressure and transpulmonary pressure, PEEP decreases RV preload and increases RV afterload and results in greater respiratory variation in stroke volume and arterial pressure. Greater levels of PEEP are as-

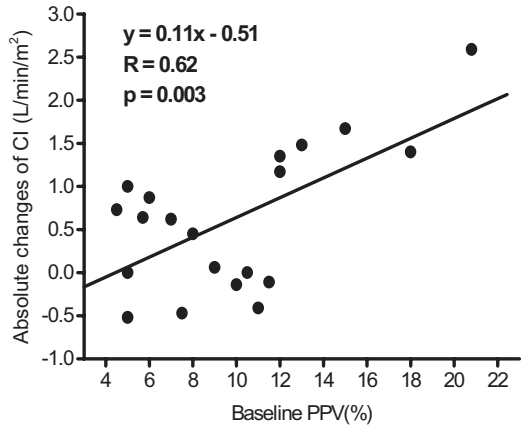

Figure 1. Linear correlation between baseline pulse pressure variation (*PPV*) and absolute changes in cardiac output index (*CI*) at end of volume expansion.

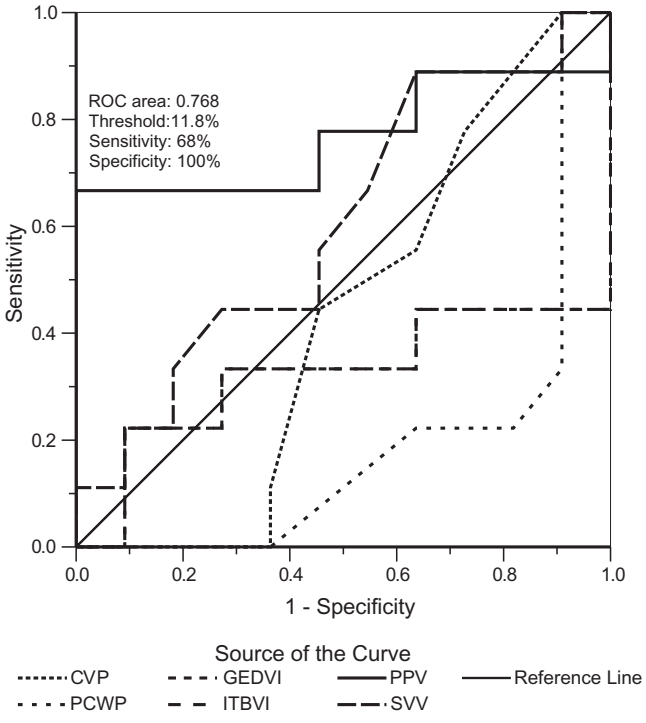

Figure 2. Receiver operating characteristic (*ROC*) curves comparing the ability of various preload indicators to discriminate responders and nonresponders to volume expansion at the end of infusion. The area under the ROC curve for pulse pressure variation (*PPV*) is greater than other preload indicators. *CVP*, central venous pressure; *GEDVI*, global end-diastolic volume index; *PCWP*, pulmonary capillary wedge pressure; *ITBVI*, intrathoracic blood volume index; *SVV*, stroke volume variation.

sociated with greater SPV, PPV, and SVV, respectively (8, 38, 39).

Dynamic or functional hemodynamic preload measurements (SVV and it's surrogate variables SPV and PPV) have been shown to be highly sensitive in predicting fluid responsiveness in various clinical settings, including brain or cardiac surgery (10–15, 17–18), acute circulatory failure or sepsis-induced hypotension (7, 9, 16), or animal studies (19, 37, 38). Only one study by Michard et al. (8) enrolled acute lung injury patients and half of the patients studied by de Backer et al. (20) were ARDS patients. Most of the aforementioned reports used V_T >8–10 mL/kg, larger than the low limit of 8 mL/kg proposed by de Backer et al (20). However, still valid predictions were also demonstrated in studies using lower V_T by Rex et al. (15) with a V_T of 7.5 ± 1.25 mL/kg, Wiesenack et al. (18) with a V_T of 7 mL/kg on coronary artery bypass grafting patients, and Marx et al. (16) with a V_T of 6–8 mL/kg on ventilated severe sepsis or septic shock patients.

For the protective ventilatory strategy, two major ventilatory settings to prevent ventilator-associated lung injury are low V_T to avoid overstretching and volutrauma, and high PEEP to prevent shearing injury in an injured lung. The two settings induce an opposite shift on the Frank-Staring curve and are conflicting on the prediction of fluid responsiveness. The net shift by low V_T and high PEEP, toward the steep or flat portion of the Frank-Starling curve, was unknown in ARDS patients. In the ARDS Network study, the V_T was decreased to as low as 6 mL/kg predicted body weight to achieve the protective effect (22). Up until now, only our study has completely focused on the most severe early ARDS patients. The mean V_T we set was 6.4 ± 0.7 mL/kg (or 6.8 ± 0.9 mL/kg predicted body weight), and the mean PEEP level was set at 14 ± 1.4 cm H_2O, higher than any of the previous studies. With this small V_T, high PEEP level and disadvantageous pulmonary mechanics, we still found a significant correlation between baseline PPV and the VE-induced absolute change in CI (Fig. 1). Baseline PPV has the highest AUC (0.768, Fig. 2) compared with other indicators, and allows for an assessment of hemodynamic response to volume loading and prediction of fluid responsiveness after VE. Our study suggested that, even in the most severe ARDS patients ventilated with low V_T, PPV was still an accurate parameter of fluid responsiveness, because patients had a very low compliance probably inducing large fluctuations in transpulmonary pressure.

Among the aforementioned and cited reports, the study of de Backer et al. (20) enrolled more heterogeneous critically ill intensive care unit patients, and was more suitable for comparison with our results. In the entire population, interestingly, the threshold value of 11.8% was identical in both studies. Focusing on the subgroup patients with a V_T <8 mL/kg, nearly all were ARDS cases (32 of 33, 97%). Our patients had more severe lung injury with a lower mean Pa_{O_2}/F_{IO_2} value (96 vs. 132 mm Hg). The mean V_T was almost the same (6.4 mL/kg vs. 6.3 mL/kg), but the mean PEEP level was higher in our study (14 vs. 11 cm H_2O). With a higher mean PEEP level, the performance of PPV, at the same threshold value of 11.8%, in our results (AUC 0.768, sensitivity 68%, and specificity 100%) was better than the ARDS subgroup of de Backer et al.

(AUC 0.71, sensitivity 39%, and specificity 65%). Our data corroborate the findings of Pizov et al. (38), Michard et al. (8), and Kubitz et al. (39), and emphasizes that PEEP, by exaggerating the cyclic changes in pleural and transpulmonary pressures, offsets the disadvantageous effect of low VT in predicting fluid responsiveness.

Although accurate for defining preload responsiveness, PPV is still a surrogate of SVV, and is more influenced by vasomotor tone than SVV (40). Theoretically, measurements of SVV should be more accurate than PPV and SPV. However, neither SVV nor comparison between SVV and PPV has ever been validated on ventilated acute lung injury or ARDS patients. Arterial pulse contour analysis enables the use of arterial pressure waveforms to measure stroke volume and its change during ventilation. Simultaneous real time display of PPV and SVV based on pulse contour analysis is now available on a PiCCOplus monitor. In our data, only baseline PPV, but not SVV, correlated with absolute changes or percent changes of CI after VE (Fig. 1). Systolic and pulse pressures depend not only on stroke volume but also directly on arterial compliance. For a given stroke volume, low aortic compliance is associated with greater changes in pulse pressure (6, 41). In functionally hypovolemic patients, actual SVV may be less than PPV because arterial elastance will be increased (40). By decreasing venous return and inducing a functionally hypovolemic status, and by extramurally compressing the intrathoracic aorta, high PEEP during mechanical ventilation may decrease the aortic compliance and magnify the changes in pulse pressure. An accurate SVV signal may be less than expected for the same degree of PPV and partly explains why PPV is better than SVV as an indicator of fluid responsiveness in ARDS patients ventilated with low VT.

There is one limitation in our study. Because we only enrolled ARDS patients with adequate renal function, whether our results can be extrapolated to more critically ill ARDS patients with multisystem organ failure and renal failure requires further investigation. In conclusion, our findings indicate that PPV assessed by the PiCCOplus monitor accurately predicts the fluid responsiveness in early ARDS patients mechanically ventilated with low VT and high PEEP. Roughly, a baseline PPV greater than the threshold value 12% is associated with a significant increase in CI after the end of VE.

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