Combining Functional Hemodynamic Measures to Increase Precision in Defining Volume Responsiveness*

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Fluid resuscitation to restore an adequate cardiac output and organ perfusion pressure in critically ill patients is the cornerstone of resuscitation management (1). Unfortunately, many critically ill patients are not volume responsive (2), and those who are volume responsive may not need further fluids because they are already at their baseline, and further fluid infusion will only promote volume overload. Within this concept, we pioneered the concept of using functional hemodynamic monitoring parameters to identify those patients who were volume response and those who were not, thus avoiding excess fluid resuscitation in the roughly 50% of patients in circulatory shock who would not benefit from fluid infusions (3). The two most popular bedside maneuvers used today to create functional hemodynamic parameters are ventilatory maneuvers (4) and passive leg raising (5). Dynamic changes in left ventricular stroke volume variation (SVV) and its pressure counterpart, arterial pulse pressure variation (PPV), have been shown to accurately predict volume responsiveness in critically ill ventilated patients.

Two primary caveats limit the universal application of SVV- and PPV-driven resuscitation across patient groups. First, the patient must be adapted to the ventilator with minimal spontaneous breathing (6). Although not a limiting factor in intraoperative volume management and potentially also not an issue early on in the resuscitation of the profoundly shocked recently intubated patient, this issue becomes relevant after the initial "rescue" phase has been completed (1). Both small-volume fluid challenges and passive leg raising approaches should be used in those conditions. However, another major limiting factor in the use of SVV and PPV thresholds to define volume responders and nonresponders is the need to create enough of a dynamic change in intrathoracic pressure to induce the obligatory variation in venous return, upon which these parameters hinge (7). The most common cause of inadequate variations in intrathoracic pressure is the use of low-tidal volume ventilation. In the original studies, we used 8 mL/kg tidal volumes to derive threshold SVV and PPV values of 10% and 13%, respectively (8). Such "larger" tidal volumes, if sustained, may cause ventilator-induced lung injury. Large tidal volume ventilation increases mortality in both patients with acute respiratory distress syndrome (9) and those with normal lungs ventilated for only short periods of time (9). Thus, the negative predictive value of SVV and PPV degrades as tidal volumes are constrained to 6 mL/kg or less (10).

In this issue of *Critical Care Medicine*, Myatra et al (11) examined the predictive value of SVV and PPV changes from 6 mL/kg to a 1-minute 8 mL/kg "tidal volume challenge" in 20 critically ill patients already adapted to the ventilator. They also measured the end-expiratory occlusion change in systolic arterial pressure (end-expiratory occlusion test [EEOT]) as well as the raw SVV and PPV values observed at both 6 and 8 mL/kg breathing. They then gave a fluid bolus and noted which patients were true volume responders, defined as an increase in a cardiac output of greater than 15%, and which were not. Although SVV and PPV predicted volume responsiveness well at 8 mL/kg, both SVV and PPV and the EEOT performed poorly at 6 mL/kg. The threshold values in the change in SVV and PPV changes when ventilation was transiently increased from 6 to 8 mL/kg (ΔSVV_{6-8} and ΔPPV_{6-8}, respectively) that predict well volume responders and volume nonresponders were 2.5% and 3.5%, respectively. Importantly, these predictive values were better than the 8 mL/kg SVV and PPV threshold values and those were the initial conditions used to define volume responsiveness 15 years ago (2).

The study does have some limitations, which need to be remembered. Like all ventilation-associated volume responsive parameters, this measure required the patient to not be breathing spontaneously. Similarly, other limitations of SVV and PPV, like intra-abdominal hypertension (12) and severe cor pulmonale (13), were not addressed but probably limitations in this approach as well. And finally, the ΔSVV_{6-8} and ΔPPP_{6-8} calculations require very fine discrimination of maxima and minima stroke volumes and pulse pressures, which have not been fully vetted in the general clinical environment, where in arrhythmias may make their measures limited. Finally, although PPV is a readily available bedside parameter today, these tidal volume challenge measures are not and may not be routinely available going forward.

Still, these data are exciting for several reasons. First, they add the tidal volume challenge to the growing number of functional hemodynamic monitoring parameter tools available in the arsenal for the bedside clinician. Second, by combining SVV or PPV at two tidal volumes, this approach takes two dynamic processes instead of one to derive a functional measure of increased sensitivity and specificity. This is conceptually similar to the recently reported joining of PPV and

*See also p. 415.

Key Words: functional hemodynamic monitoring; protective lung ventilation; stroke volume variation

Dr. Pinsky has disclosed that he does not have any potential conflicts of interest.

DOI: 10.1097/CCM.0000000000002242

internal jugular vein diameter change indices into a fused metric, thereby greatly improving both measures utility to define volume responsiveness or its absence (14). This linkage of two dynamic functional tests into a single metric might also be applied across other functional parameters whose solitary discriminative value is poor, like inferior vena caval collapse or descending aortic flow variation.

Going forward, the number of measures during mechanical ventilation or created by transient passive leg raising that can precisely define volume responsiveness at the bedside is growing and readily available at the bedside. Now we need to use these signposts to correctly chart personalized resuscitation pathways for our critically ill patients.

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Exploring the Dark Side of the Moon: Pulmonary Vascular Dysfunction in Acute Respiratory Distress Syndrome*

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Although it may seem obvious that patients with acute respiratory distress syndrome (ARDS) will have impaired gas exchange and decreased lung compliance, albeit heterogeneous in distribution, it is less clear to the practicing clinician that the pulmonary vasculature is equally affected and is often the primary cause of mortality in severe ARDS. Indeed, Zapol and Snider (1), almost 40 years ago, described a linear relation between calculated pulmonary vascular resistance (PVR) increases and mortality in their ARDS patients. Presumably, parenchymal damage associated with acute lung injury causes pulmonary vascular injury. The recent resurgence in interest in right ventricular (RV) function in the setting of ARDS has awakened renewed study of the interactions between RV function and lung disease as a primary determinant of survival (2, 3). Within this context, the study by Metkus et al (4) reported in this issue of *Critical Care Medicine* underscores the complex and important role that deranged pulmonary vascular physiology plays in the outcome from ARDS (3). These workers reported on a retrospective analysis of 363 subjects with ARDS who had 65 complete baseline right heart catheterization data from the Fluid and Catheter Treatment Trial (5). They tested the hypothesis that pulmonary artery compliance (CPA) at admission (baseline) and over the course of treatment predicted mortality. CPA was calculated as the ratio of mean stroke volume to pulmonary arterial pulse pressure. Stroke volume was calculated, in turn, as the ratio of mean cardiac output, estimated by three or more thermodilution measures, to heart rate, while pulmonary arterial pulse pressure as diastolic to systolic pressure, presumably measured at end expiration. They found, like Zapol and Snider (1) 40 years ago, that even today with smaller tidal volume ventilation, PVR

*See also p. 422.

Key Words: acute respiratory distress syndrome; outcomes; pulmonary vascular resistance; right ventricle

Dr. Pinsky has disclosed that he does not have any potential conflicts of interest.

DOI: 10.1097/CCM.0000000000002238

The Changes in Pulse Pressure Variation or Stroke Volume Variation After a "Tidal Volume Challenge" Reliably Predict Fluid Responsiveness During Low Tidal Volume Ventilation*

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Objectives: Stroke volume variation and pulse pressure variation do not reliably predict fluid responsiveness during low tidal volume ventilation. We hypothesized that with transient increase in tidal volume from 6 to 8 mL/kg predicted body weight, that is, "tidal volume challenge," the changes in pulse pressure variation and stroke volume variation will predict fluid responsiveness.

Design: Prospective, single-arm study.

Setting: Medical-surgical ICU in a university hospital.

Patients: Adult patients with acute circulatory failure, having continuous cardiac output monitoring, and receiving controlled low tidal volume ventilation.

Interventions: The pulse pressure variation, stroke volume variation, and cardiac index were recorded at tidal volume 6 mL/kg predicted body weight and 1 minute after the "tidal volume challenge." The tidal volume was reduced back to 6 mL/kg predicted body weight, and a fluid bolus was given to identify fluid responders (increase in cardiac index > 15%). The end-expiratory occlusion test was performed at tidal volumes 6 and 8 mL/kg predicted body weight and after reducing tidal volume back to 6 mL/kg predicted body weight.

Results: Thirty measurements were obtained in 20 patients. The absolute change in pulse pressure variation and stroke volume variation after increasing tidal volume from 6 to 8 mL/kg predicted body weight predicted fluid responsiveness with areas under the receiver operating characteristic curves (with 95% CIs) being 0.99 (0.98–1.00) and 0.97 (0.92–1.00), respectively. The best cutoff values of the absolute change in pulse pressure variation and stroke volume variation after increasing tidal volume from 6 to 8 mL/kg predicted body weight were 3.5% and 2.5%, respectively. The pulse pressure variation, stroke volume variation, central venous pressure, and end-expiratory occlusion test obtained during tidal volume 6 mL/kg predicted body weight did not predict fluid responsiveness.

Conclusions: The changes in pulse pressure variation or stroke volume variation obtained by transiently increasing tidal volume (tidal volume challenge) are superior to pulse pressure variation and stroke volume variation in predicting fluid responsiveness during low tidal volume ventilation. (*Crit Care Med* 2017; 45:415–421)

Key Words: end-expiratory occlusion test; fluid responsiveness; low tidal volume; pulse pressure variation; stoke volume variation; tidal volume challenge

***See also p. 558.**

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Existing hospital infrastructure for research was utilized.

This study was performed at Tata Memorial Hospital, Mumbai, India.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Drs. Monnet and Teboul are members of the Medical Advisory Board of Pulsion Medical Systems. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0000000000002183

Fluid administration is the first line of treatment in patients with acute circulatory failure. Although hypovolemia affects tissue oxygenation leading to organ dysfunction and death (1), excessive fluid loading is associated with increased complications, mortality, and length of ICU stay (2, 3). Only half the patients with circulatory failure respond positively to fluid administration (4). Hence, it is necessary to detect fluid responders.

Dynamic indices like stroke volume variation (SVV) and pulse pressure variation (PPV) are superior to static indices to predict fluid responsiveness (4–9). However, these dynamic indices are unreliable during low tidal volume (V_t) ventilation, that is, V_t less than or equal to 6 mL/kg predicted body weight (PBW) (10, 11). Low V_t ventilation is commonly used

in patients with sepsis and acute respiratory distress syndrome (ARDS) (12, 13). It is hypothesized that a low V_t might be insufficient to produce a significant change in the intrathoracic pressure; thus, these indices may indicate a nonresponsive status even in responders (14, 15). This may preclude the use of PPV and SVV during low V_t ventilation. To overcome these limitations, tests like passive leg raising test (PLRT) and end-expiratory occlusion test (EEOT) (16–18) have been proposed. However, studies that tested EEOT used mean V_t greater than or equal to 6.7 mL/kg PBW (17–19). PLRT requires continuous cardiac output monitoring (20) and cannot be used in patients with neurotrauma or those requiring immobilization (20, 21).

We hypothesized that the absolute changes in PPV and SVV (ΔPPV_{6-8} and ΔSVV_{6-8}) and the percentage changes in PPV and SVV ($\%\Delta PPV_{6-8}$ and $\%\Delta SVV_{6-8}$) after a "tidal volume challenge" predict fluid responsiveness during low V_t ventilation. We conducted a prospective study to test the predictive value of the "tidal volume challenge" to help unmask responders.

We also wanted to determine the reliability of EEOT to predict fluid responsiveness during low V_t ventilation.

PATIENTS AND METHODS

This study was conducted in a 14-bed medical-surgical ICU in a university hospital. It was approved by the institutional review board. Written informed consent was taken from the patients' surrogates.

Patients

We included patients 18 years old or older with acute circulatory failure (defined in the **supplemental material**, Supplemental Digital Content 1, http://links.lww.com/CCM/C254) receiving low V_t ventilation using volume-assist control ventilation, without any spontaneous breathing activity and having continuous cardiac output monitoring in whom the treating physician planned to give a fluid bolus. Patients having cardiac arrhythmias, valvular heart disease, right ventricular dysfunction, intracardiac shunt, air leakage through chest drains, abdominal compartment syndrome, and pregnancy or urgently requiring a fluid bolus were excluded.

Methods

Philips Intellivue MP70 monitors (Philips Medical Systems, Amsterdam, The Netherlands) were used for monitoring vital variables and measuring PPV from the arterial pressure waveform. Patients had a central venous catheter and a thermistor-tipped arterial catheter in the femoral artery with a transpulmonary thermodilution device: PiCCO (Pulsion Medical Systems SE, Feldkirchen, Germany) or VolumeView (Edwards Lifesciences Corporation, Irvine, CA) from which transpulmonary thermodilution variables, pulse contour cardiac index, and SVV were obtained.

All patients were sedated, and some also received neuromuscular blocking agents. The heart rate (HR), systolic blood pressure, diastolic blood pressure, mean arterial pressure, cardiac index, PPV, SVV, central venous pressure (CVP), ratio of the HR and respiratory rate (HR/RR), plateau pressure (P_{plat}), driving pressure (P_{plat} – positive end-expiratory pressure [PEEP]), and compliance of the respiratory system (C_{rs}) were recorded at baseline and at specific intervals (**Fig. 1**). Patients were ventilated using V_t 6 mL/kg PBW (12), and transpulmonary thermodilution variables, PPV (PPV_6), and SVV (SVV_6) were recorded. EEOT was performed ($EEOT_6$) (17). The "tidal volume challenge" was performed by increasing V_t to 8 mL/kg PBW, and pulse contour cardiac index, PPV (PPV_8), and SVV (SVV_8) were recorded after 1 minute. Following this, EEOT was performed again ($EEOT_8$). The V_t was reduced back to 6 mL/kg PBW, and EEOT was repeated. Thereafter, a fluid bolus was given over 10 minutes, and measurements were repeated. Details of the protocol are given in Figure 1 and in the supplemental material (Supplemental Digital Content 2, http://links.lww.com/CCM/C255). Patients were classified as responders if there was an increase in cardiac index more than 15% after giving a fluid bolus at V_t 6 mL/kg PBW. No more than two tidal volume challenges could be performed in any patient, and an interval of at least 24 hours was required between challenges. Doses of vasoactive medications and PEEP were kept constant. The change in SVV and PPV after giving the fluid bolus (ΔPPV_{fb} and ΔSVV_{fb}) was calculated.

Statistical Analysis

Statstodo computer program was used to calculate the sample size requirement for comparing two receiver-operating characteristic (ROC) curves with expected areas under the curves of 0.65 (PPV_6) and 0.90 (ΔPPV_{6-8}), assuming an α error of 0.05 and power of 80%. Demographic variables are presented as frequency (percentage) and mean (SD) or median (interquartile range) as appropriate. Changes in continuous variables from 6 to 8 mL/kg PBW were compared using paired *t* test or Wilcoxon signed rank sum test, and group comparisons were made using independent *t* test or Mann-Whitney *U* test, as appropriate. Categorical variables were analyzed using chi-square test or Fisher exact test. ROC curves were used to determine the ability of indices to discriminate between responders and nonresponders. Comparison between the area under the ROC curves was made using the Delong method (22). The statistical analysis was performed

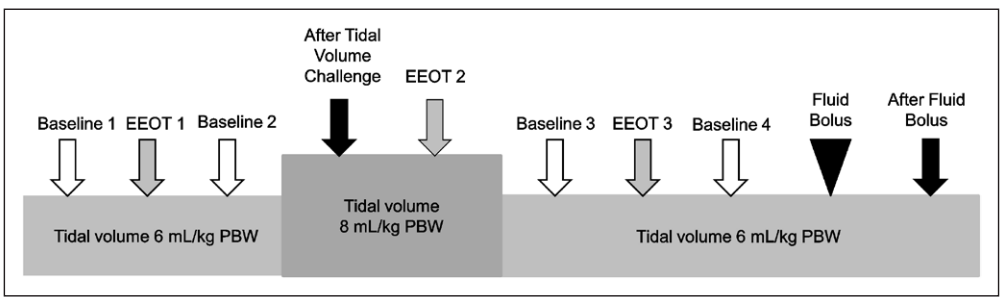

Figure 1. Study protocol. *Arrows* indicate time points at which measurements were made. EEOT = end-expiratory occlusion test, PBW = predicted body weight.

using SPSS software version 20 for Windows (IBM, Armonk, NY). A p value less than 0.05 was considered statistically significant.

RESULTS

Study Population

Twenty-two patients were screened. Two were excluded because of atrial fibrillation and right ventricular dysfunction. Fifty percent of patients were men. The age of the patients was 53 ± 14 years. The Acute Physiology and Chronic Health Evaluation II score was 24 ± 9. All patients had a diagnosis of septic shock (13). Ten patients had pneumonia, two had ARDS, seven had intra-abdominal sepsis, and one had a wound infection. The driving pressures were 12 (10–16) versus 15 (14–17) cm H_2O, and C_{rs} was 25 (23–33) versus 32 (24–40) mL/cm H_2O, during ventilation at 6 and 8 mL/kg PBW, respectively.

Thirty sets of measurements were recorded in 20 patients. It was not possible to do a second set of measurements in 10 patients because the treating physician did not feel the need to give another fluid bolus ($n = 7$), the patient was breathing spontaneously ($n = 2$), or the continuous cardiac output monitoring was discontinued ($n = 1$). On 16 occasions, patients were responders, whereas on 14 occasions, they were nonresponders. The baseline hemodynamic and respiratory characteristics are given in **Table 1**.

The evolution of hemodynamic variables is shown in **Table 2**. Following the "tidal volume challenge," there was a significant increase in PPV and SVV only in responders. Following volume expansion, there was a significant decrease in PPV and SVV only in responders.

Prediction of Fluid Responsiveness

The ability of ΔPPV_{6-8}, $\%\Delta PPV_{6-8}$, PPV_8, ΔSVV_{6-8}, $\%\Delta SVV_{6-8}$, SVV_8, and $EEOT_8$ to predict fluid responsiveness, along with their best cutoff values and respective sensitivities and specificities, is detailed in **Table 3**. There was no significant difference when the area under the ROC curves of the above variables were compared (**Fig. 2**). When ΔPPV_{6-8}, $\%\Delta PPV_{6-8}$, ΔSVV_{6-8}, and $\%\Delta SVV_{6-8}$ were compared among responders and nonresponders using box and whisker plots, there was a significant ($p < 0.05$) difference (**Supplemental Fig. 1**, Supplemental Digital Content 3, http://links.lww.com/CCM/C256; legend, Supplemental Digital Content 4, http://links.lww.com/CCM/C257). The PPV_6, SVV_6, CVP, and $EEOT_6$ could not predict fluid responsiveness (Table 3).

The change in PPV and SVV after a fluid bolus (ΔPPV_{fb} and ΔSVV_{fb}) discriminated responders from nonresponders (Table 3). However, ΔPPV_{fb} discriminated better than ΔSVV_{fb} when the areas under their ROC curves were compared ($p = 0.007$). The relationship between ΔPPV_{fb} and percentage change in cardiac index after a fluid bolus is shown in **Supplemental Figure 2** (Supplemental Digital Content 5, http://links.lww.com/CCM/C258; legend, Supplemental Digital Content 4, http://links.lww.com/CCM/C257). The results of the first set measurements in 20 patients are similar (**Supplemental Table 1**, Supplemental Digital Content 6, http://links.lww.com/CCM/C259; and **Supplemental Fig. 3**, Supplemental Digital Content 7, http://links.lww.com/CCM/C260; legend, Supplemental Digital Content 4, http://links.lww.com/CCM/C257).

TABLE 1. Baseline Hemodynamic and Respiratory Characteristics of Fluid Responders and Nonresponders

Characteristics	Fluid Responders ($n = 16$)	Fluid Nonresponders ($n = 14$)
Central venous oxygen saturation (%)	77 ± 8	75 ± 6
Lactate (mmol/L)	3.4 ± 0.9	2.9 ± 1.4
Tidal volume (mL/kg predicted body weight)	6.0 ± 0.2	6.0 ± 0.0
Total PEEP (cm H_2O)	8 ± 3	9 ± 3
P_{plat} (cm H_2O)	20 ± 6	22 ± 4
P_{plat} – PEEP (cm H_2O)	12 ± 4	14 ± 3
Compliance of the respiratory system (mL/cm H_2O)	29 ± 8	27 ± 6
Pao_2/Fio_2 (mm Hg)	231 ± 96	224 ± 92
Extravascular lung water index (mL/kg)	6 ± 2	9 ± 3[a]
Pulmonary vascular permeability index	2.5 ± 0.9	2.5 ± 1.0
Global end-diastolic volume index (mL/m^2)	541 ± 116	589 ± 109
No. of patients receiving norepinephrine (%)	16 (100)	14 (100)
Dose of norepinephrine (μg/kg/min)	0.9 ± 0.6	0.5 ± 0.4[a]

PEEP = positive end-expiratory pressure, P_{plat} = plateau pressure.
[a]$p < 0.05$, fluid responders vs fluid nonresponders.
Values are expressed as mean ± SD or frequency with percentage.

TABLE 2. Evolution of Hemodynamic Variables in Fluid Responders and Nonresponders

Variables	Baseline 1	EEOT 1	Baseline 2	After Tidal Volume Challenge	EEOT 2	Baseline 3	EEOT 3	Baseline 4	After Fluid Bolus
	V_t, 6 mL/kg	V_t, 6 mL/kg	V_t, 6 mL/kg	V_t, 8 mL/kg	V_t, 8 mL/kg	V_t, 6 mL/kg	V_t, 6 mL/kg	V_t, 6 mL/kg	V_t, 6 mL/kg
	PBW	PBW	PBW	PBW	PBW	PBW	PBW	PBW	PBW
HR (bpm)									
R ($n = 16$)	131 ± 22	132 ± 23	132 ± 23	132 ± 24	132 ± 24	132 ± 25	131 ± 24	132 ± 24	119 ± 30
NR ($n = 14$)	115 ± 26	112 ± 28	113 ± 27[a]	113 ± 29	111 ± 29 [a]	111 ± 28[a]	112 ± 28	112 ± 28[a]	119 ± 23
Systolic blood pressure (mm Hg)									
R ($n = 16$)	113 ± 18	113 ± 17	113 ± 17	111 ± 16	119 ± 16[b]	110 ± 15	111 ± 15	110 ± 16	121 ± 14[c]
NR ($n = 14$)	116 ± 18	115 ± 17	115 ± 17	113 ± 15	114 ± 16	113 ± 16	113 ± 17	114 ± 16	116 ± 17
Diastolic blood pressure (mm Hg)									
R ($n = 16$)	54 ± 7	56 ± 7	55 ± 8	55 ± 6	55 ± 7	53 ± 6	55 ± 6	54 ± 6	59 ± 7[c]
NR ($n = 14$)	55 ± 7	55 ± 6	56 ± 6	55 ± 7	56 ± 8	55 ± 7	55 ± 6	56 ± 6	55 ± 8
Mean arterial pressure (mm Hg)									
R ($n = 16$)	73 ± 8	74 ± 8	73 ± 8	72 ± 7	76 ± 6[b]	72 ± 6	73 ± 7	72 ± 7	79 ± 8[c]
NR ($n = 14$)	76 ± 8	74 ± 7	74 ± 6	74 ± 7	76 ± 8	74 ± 7	74 ± 8	74 ± 6	75 ± 8
Cardiac index (L/min/m^2)									
R ($n = 16$)	3.9 ± 0.9	3.9 ± 0.9	3.9 ± 0.9	3.8 ± 0.9[d]	4.3 ± 0.9[b]	3.8 ± 0.9	4.0 ± 0.9	3.8 ± 0.9	4.6 ± 0.9[c]
NR ($n = 14$)	3.8 ± 1.4	3.9 ± 1.4	3.8 ± 1.4	3.8 ± 1.4	3.8 ± 1.4	3.7 ± 1.4	3.9 ± 1.4	3.7 ± 1.4	3.6 ± 1.4[a]
HR/respiratory rate									
R ($n = 16$)	4.9 ± 0.8	–	4.9 ± 0.8	4.9 ± 0.8	–	4.9 ± 0.8	–	4.9 ± 0.8	4.6 ± 1.1
NR ($n = 14$)	4.8 ± 1.2	–	4.8 ± 1.2	4.9 ± 1.3	–	4.8 ± 1.2	–	4.8 ± 1.2	4.9 ± 0.9
Central venous pressure (mm Hg)									
R ($n = 16$)	8 ± 3	–	8 ± 3	9 ± 4[d]	–	9 ± 3	–	8 ± 4	12 ± 4[c]
NR ($n = 14$)	9 ± 4	–	9 ± 4	9 ± 4	–	9 ± 3	–	9 ± 4	11 ± 4
Pulse pressure variation (%)									
R ($n = 16$)	8 ± 3	–	8 ± 3	14 ± 3[d]	–	9 ± 2	–	8 ± 3	5 ± 1[c]
NR ($n = 14$)	7 ± 2	–	7 ± 2	8 ± 2[a]	–	8 ± 3	–	8 ± 2	7 ± 2
Stroke volume variation (%)									
R ($n = 16$)	7 ± 2	–	7 ± 2	12 ± 2[d]	–	8 ± 3	–	9 ± 2	5 ± 1[c]
NR ($n = 14$)	7 ± 2	–	7 ± 2	8 ± 2[a]	–	9 ± 4	–	7 ± 3	6 ± 2

EEOT = end-expiratory occlusion test, HR = heart rate, NR= fluid nonresponders, PBW = predicted body weight, R = fluid responders, V_t = tidal volume.
[a]$p < 0.05$, fluid responders vs fluid nonresponders (comparison in columns).
[b]$p < 0.05$, tidal volume (V_t) 8 mL/kg predicted body weight (PBW) vs end-expiratory occlusion test 2 (comparison in rows).
[c]$p < 0.05$, baseline 4 vs after fluid bolus (comparison in rows).
[d]$p < 0.05$, baseline 2 (V_t, 6 mL/kg PBW) vs after tidal volume challenge (V_t, 8 mL/kg PBW) (comparison in rows).
Dashes indicate variable was not measured.
Values are expressed as mean ± SD.

DISCUSSION

The main finding of our study is that when V_t is increased from 6 to 8 mL/kg PBW (tidal volume challenge), the absolute change in PPV and SVV (ΔPPV_{6-8} and ΔSVV_{6-8}) reliably predicts fluid responsiveness with cutoff values of 3.5% and 2.5%, respectively, whereas PVV and SVV at V_t 6 mL/kg PBW do not. Although the percentage change in PPV and SVV ($\%\Delta PPV_{6-8}$ and $\%\Delta SVV_{6-8}$) is reliable in predicting fluid responsiveness, it requires additional

TABLE 3. Diagnostic Ability of Various Variables to Predict Fluid Responsiveness

Variables	Area Under the Receiver-Operating Characteristic Curve (95% CI)	*p*	Best Cutoff Value (%)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
PPV at V_t 6 mL/kg PBW	0.69 (0.49–0.89)	0.071	–	–	–	–	–
SVV at V_t 6 mL/kg PBW	0.56 (0.35–0.77)	0.575	–	–	–	–	–
PPV at V_t 8 mL/kg PBW	0.91 (0.81–1.00)	< 0.001	11.5	75	100	100 (76–100)	78 (55–91)
SVV at V_t 8 mL/kg PBW	0.92 (0.82–1.00)	< 0.001	10.5	75	93	92 (67–99)	76 (53–90)
Change in PPV from V_t 6 to 8 mL/kg PBW	0.99 (0.98–1.00)	< 0.001	3.5	94	100	100 (80–100)	93 (70–99)
Change in SVV from V_t 6 to 8 mL/kg PBW	0.97 (0.92–1.00)	< 0.001	2.5	88	100	100 (78–100)	88 (64–97)
Percentage change in PPV from V_t 6 to 8 mL/kg PBW	0.97 (0.92–1.00)	< 0.001	48	94	100	100 (80–100)	93 (70–99)
Percentage change in SVV from V_t 6 to 8 mL/kg PBW	0.96 (0.89–1.00)	< 0.001	43	88	93	93 (70–99)	87 (62–96)
Percentage change in cardiac index during EEOT performed at V_t 6 mL/kg PBW	0.44 (0.23–0.66)	0.590	–	–	–	–	–
Percentage change in cardiac index during EEOT performed at V_t 8 mL/kg PBW	0.95 (0.88–1.00)	< 0.001	4.1	88	93	93 (70–99)	78 (45–94)
Central venous pressure at V_t 6 mL/kg PBW	0.48 (0.27–0.69)	0.852	–	–	–	–	–
Change in PPV after fluid bolus	0.98 (0.95–1.00)	< 0.001	1.5	94	100	100 (80–100)	91 (62–98)
Change in SVV after fluid bolus	0.71 (0.52–0.92)	0.048	2.5	75	71	92 (67–99)	60 (31–83)

EEOT = end-expiratory occlusion test, PPV = pulse pressure variation, PBW = predicted body weight, SVV = systolic pressure variation, V_t = tidal volume. Dashes indicate variable was not measured.

calculations and is not practical for use at the bedside. The PPV_8 and SVV_8 also reliably discriminate responders from nonresponders; however, their sensitivity (75% for both) and negative predictive value (78% and 76%, respectively) are lower than those of ΔPPV_{6-8} and ΔSVV_{6-8} (Table 3) and will thus fail to identify one in four responders. Another study also found that PPV at 8 mL/kg PBW predicted fluid responsiveness at V_t 6 mL/kg PBW when PPV was measured 5 minutes after increasing V_t from 6 to 8 mL/kg PBW (23). However, this study also showed that PPV reliably predicted fluid responsiveness during low V_t ventilation, unlike our study and previous studies (10, 11). The ΔPPV_{fb} also reliably discriminated responders from nonresponders and hence could be used to confirm fluid responsiveness following a fluid bolus.

Fluid responsiveness is reliably predicted by the PPV provided that the V_t is at least 8 mL/kg PBW (8, 10). During low V_t ventilation, the PPV and SVV may indicate a nonresponsive status even in responders as the V_t might be insufficient to produce a significant change in the intrathoracic pressure (14, 15). We hypothesized that raising the V_t from 6 to 8 mL/kg PBW increases the intrathoracic pressure and the magnitude of the heart-lung interactions and can unmask fluid responsiveness during low V_t ventilation. This was confirmed in our study, which showed that changes in PPV and SVV after performing a "tidal volume challenge" identified true fluid responders with high sensitivities and specificities, whereas they could not be identified using PPV_6 and SVV_6. Thus, the "tidal volume challenge" helped unmask responders as the increase in PPV and SVV was significant only in responders. Our results are consistent with a study (24) that showed a significant increase in PPV and SVV at V_t 10 mL/kg compared with 5 mL/kg; however, their analysis included only fluid responders. Charron et al (25) showed that PPV increased in fluid responders but not in nonresponders when V_t was increased from 6 to 10 mL/kg.

Low lung compliance can result in reduction of airway pressure transmission. The cyclic changes in intrathoracic pressure may be attenuated even with marked changes in alveolar pressure (26), making PPV unreliable in patients with

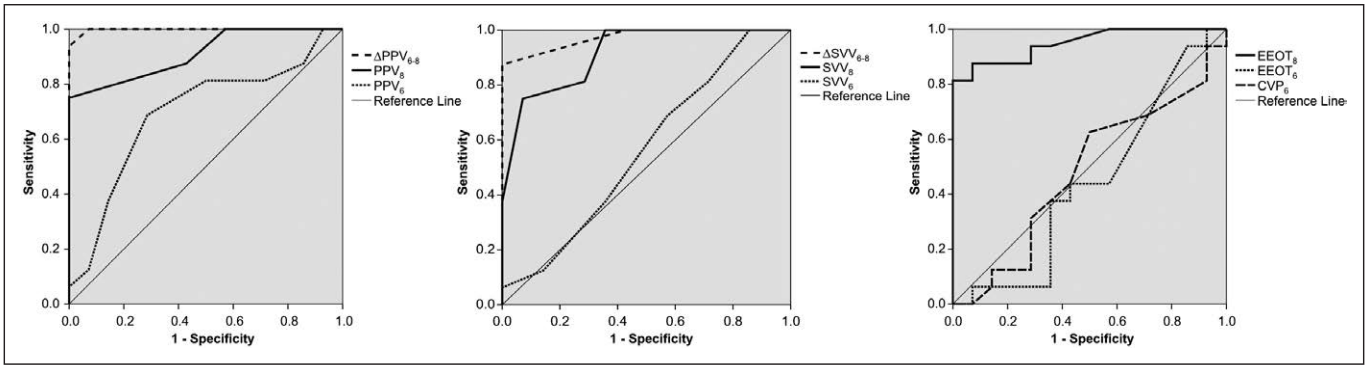

Figure 2. Receiver-operating characteristic curves comparing the ability of various variables to discriminate between fluid responders and nonresponders. ΔPPV_{6-8} = change in PPV after increasing V_t from 6 to 8 mL/kg PBW, ΔSVV_{6-8} = change in SVV after increasing V_t from 6 to 8 mL/kg PBW, $\%\Delta PPV_{6-8}$ = percentage change in PPV after increasing V_t from 6 to 8 mL/kg PBW, $\%\Delta SVV_{6-8}$ = percentage change in SVV after increasing V_t from 6 to 8 mL/kg PBW, CI = cardiac index, CVP = central venous pressure, CVP_6 = CVP at 6 mL/kg PBW, EEOT = end-expiratory occlusion test, $EEOT_6$ = percentage change in CI during EEOT performed at 6 mL/kg PBW, $EEOT_8$ = percentage change in CI during EEOT performed at 8 mL/kg PBW, PBW = predicted body weight, PPV = pulse pressure variation, PPV_6 = PPV at V_t 6 mL/kg PBW, PPV_8 = PPV at V_t 8 mL/kg PBW, SVV_6 = SVV at V_t 6 mL/kg PBW, SVV_8 = SVV at V_t 8 mL/kg PBW, V_t = tidal volume.

ARDS (18). PPV is less reliable in predicting fluid responsiveness when C_{rs} is less than 30 mL/cm H_2O than when C_{rs} is greater than or equal to 30 mL/cm H_2O (18). In our study, although the C_{rs} was less than 30 mL/cm H_2O during low V_t ventilation, it increased to greater than or equal to 30 mL/cm H_2O after the "tidal volume challenge." Thus, this test may help identify responders even when C_{rs} is low during low V_t ventilation.

EEOT did not predict fluid responsiveness during low V_t ventilation but did so following a "tidal volume challenge." This may be because the amplitude of change in airway pressure and presumably intrathoracic pressure during low V_t ventilation may be inadequate to increase the preload sufficiently. Another reason may be that the P_{plat} and driving pressures were lower in the patients with low V_t ventilation when compared with those ventilated at 8 mL/kg in our patients and in patients in previous studies testing EEOT (17–19) although the C_{rs} was similar.

Strengths of the Study

To the best of our knowledge, this is the first study that shows that the absolute change in PVV and SVV recorded one minute after a "tidal volume challenge" reliably predicts fluid responsiveness during low V_t ventilation, whereas PPV, SVV, and EEOT obtained during low V_t ventilation do not. The "tidal volume challenge" is a simple test that can be performed easily at the bedside. Importantly, observing the change in PPV (obtained from a simple bedside hemodynamic monitor) during this test does not require a cardiac output monitor, making this test especially applicable in resource-limited settings. Since ΔPPV_{fb} reliably confirms fluid responsiveness, a combination of ΔPPV_{6-8} with ΔPPV_{fb} can help predict and thereafter confirm fluid responsiveness after giving a fluid bolus, especially where continuous cardiac output monitoring is unavailable. The EEOT can be used reliably in patients ventilated with low V_t after performing the "tidal volume challenge"; however, this requires an additional maneuver.

During controlled mechanical ventilation, the use of low V_t ventilation is a common limitation for the use of PPV and SVV, and its indications are expanding in ICU (27) and in the operating room (28). Two multicentre studies (29, 30) that questioned the applicability of PPV in ICU showed that the presence of low V_t ventilation made PPV unsuitable for use in as many as 72% and 87% of the patients on controlled mechanical ventilation. The "tidal volume challenge" thus helps overcome a major limitation in patients receiving low V_t ventilation.

Unlike most studies, we ventilated all patients using the same V_t calculated using PBW. Varying V_ts may give different PPV and SVV values for a given volume status (as shown in the responders in our study), making the determination of a clinical cutoff using ROC curves inaccurate. Although the test was performed by increasing V_t to 8 mL/kg PBW, fluid responsiveness was assessed by giving a fluid bolus after returning the V_t to 6 mL/kg PBW, thus reliably identifying the true responders and nonresponders during low V_t ventilation.

Limitations of the Study

We did not specify a time window after development of shock for inclusion in the study nor did we document the volume of fluid given prior to inclusion. This was because our objective was purely to determine whether the "tidal volume challenge" could help predict fluid responsiveness and unmask true responders at any stage of shock. Unlike PPV, observing the changes in SVV requires the use of a continuous cardiac output device. The "tidal volume challenge" cannot overcome the other limitations with the use of PPV and SVV during low V_t ventilation, such as the presence of spontaneous breathing, cardiac arrhythmias, open chest, raised intra-abdominal pressure, HR/RR less than or equal to 3.6, and right ventricular dysfunction.

CONCLUSIONS

The changes in PPV or SVV obtained by transiently increasing tidal volume (tidal volume challenge) are superior to PPV

and SVV in predicting fluid responsiveness during low V_t ventilation.

ACKNOWLEDGMENTS

We acknowledge Mr. Rohit Dusane, Statistician in the Clinical Research Secretariat, Tata Memorial Hospital, Mumbai, India, for his help with the statistical analyses.

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