

Comparison of the Efficacy of Different Arterial Waveform-derived Variables (Pulse Pressure Variation, Stroke Volume Variation, Systolic Pressure Variation) for Fluid Responsiveness in Hemodynamically Unstable Mechanically Ventilated Critically Ill Patients

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ABSTRACT

Introduction: This study was conducted to assess fluid responsiveness in critically ill patients to avoid various complications of fluid overload.

Material and methods: This study was done in an ICU of a tertiary care hospital after approval from the institute ethical committee over 18 months. A total of 54 consenting adult patients were included in the study. Patients were hemodynamically unstable requiring mechanical ventilation, had acute circulatory failure, or those with at least one clinical sign of inadequate tissue perfusion. All patients were ventilated using tidal volume of 6–8 mL/kg, RR—12–15/minutes, positive end expiratory pressure (PEEP)—5 cm of water, and plateau pressure was kept below 30 cm water. They were sedated throughout the study. The arterial line and the central venous catheter were placed and connected to Vigileo-FloTrac transducer (Edward Lifesciences). Patients were classified into responder and nonresponder groups on the basis of the cardiac index (CI) after fluid challenge of 10 mL/kg of normal saline over 30 minutes. Pulse pressure variation (PPV), stroke volume variation (SVV), and systolic pressure variation (SPV) were assessed and compared at baseline, 30 minutes, and 60 minutes.

Results: In our study we found that PPV and SVV were significantly lower among responders than nonresponders at 30 minutes and insignificant at 60 minutes. Stroke volume variation was 10.28 ± 1.76 in the responder compared to 12.28 ± 4.42 ($p = 0.02$) at 30 minutes and PPV was 15.28 ± 6.94 in responders while it was 20.03 ± 4.35 in nonresponders ($p = 0.01$). We found SPV was insignificant at all time periods among both groups.

Conclusion: We can conclude that initial assessment for fluid responsiveness in critically ill mechanically ventilated patients should be based on PPV and SVV to prevent complications of fluid overload and their consequences.

Keywords: Cardiac index, Positive end expiratory pressure, Pulse pressure variation, Stroke volume variation, Systolic pressure variation.

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INTRODUCTION

Hemodynamic instability is quite common in critically ill patients.¹ This hemodynamic instability could be due to various reasons like volume insufficiency, septic myocardopathy, etc. This circulatory insufficiency leads to low cardiac output (CO), which fails to sustain tissue perfusion and oxygenation² leading to anaerobic metabolism, lactic acidosis, organ dysfunction, organ failure, and finally leading to rapid deterioration and death. Administering fluid to these patients may seem to be an easy option, but several studies had demonstrated that only about half of the critically ill hemodynamically unstable patients benefit from fluid loading.³ This follows that the other half of the patients might potentially or actually be harmed by any fluid administration.^{4–6} A patient may benefit from fluid administration only if there is some preload reserve left. But, often these patients have already been resuscitated partially, so the presence of preload reserve is not guaranteed and further fluid infusion, among other deleterious effects, may promote pulmonary edema, particularly in cases of increased pulmonary permeability. Also, positive cumulative fluid balance had been shown to be an independent risk of death.⁷

It is true that in patients with a high suspicion of severe sepsis or septic shock, several studies emphasized the importance of volume resuscitation in the first hours of management.^{8,9} But, in tertiary

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care centers, patients are often referred from smaller centers where they have been already somewhat resuscitated. Further volume administration, in sustained hypotension, represents a therapeutic dilemma. In patients with acute lung injury, a restrictive fluid strategy was demonstrated to be better than a liberal fluid strategy

in terms of ventilator-free and ICU-free days.¹⁰ Thus, decision to load a patient with fluid requires an accurate assessment of patients' intravascular volume status.

Previously, static hemodynamic parameters like central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and right ventricular end-diastolic volume (RVEDV) were used to assess fluid status. Several studies have highlighted that they suffer several fallacies and are insensitive markers of volume status and could be misleading. As a result of these shortcomings, the dynamic parameters of fluid responsiveness have been proposed, which use heart–lung interactions, i.e., respiration-induced changes in preload and afterload, to predict fluid responsiveness. These parameters include stroke volume variation (SVV), pulse pressure variation (PPV), and systolic pressure variation (SPV).^{11,12}

In spite of numerous studies, accurate prediction of fluid responsiveness remains one of the most difficult tasks at the bedside and to assess whether the volume expansion will increase patients' CO or not so that hypovolemia as well as hypervolemia can be avoided. So, we planned to do this study to assess and compare the efficacy of different arterial waveform-derived variables (PPV, SVV, SPV) for fluid responsiveness in hemodynamically unstable mechanically ventilated critically ill patients in Indian scenario.

MATERIALS AND METHODS

This single-centered, interventional, comparative, prospective study was performed after getting approval from the Institutional Ethics Committee (IEC No.: 14/16). Patients who fulfilled the inclusion criteria were enrolled after obtaining an informed consent from the patient's legal guardian. The patient was able to withdraw from the study at any time, without giving any reason and without impact on treatment. The study was conducted in hemodynamically unstable critically ill nonsurgical patients, admitted in ICU. A total of 54 patients were included in the study. The data collection for the study spanned over a period of 1½ years starting from February 2017 to August 2018.

Inclusion Criteria

- Hemodynamically unstable patients requiring mechanical ventilation.
- Age >18 years of age
- Acute circulatory failure patient for which the decision was taken to administer fluids.
- Presence of at least one clinical sign of inadequate tissue perfusion defined as:
 - Systolic blood pressure (SBP) <90 mm Hg or mean arterial pressure (MAP) <65 mm Hg
 - The need of vasopressor drugs
 - Urine output <0.5 mL/kg/hour for at least 2 hours
 - Tachycardia (heart rate >100/minute)
 - Serum lactate (>2 mmol/L)
 - ScVO₂ (central venous oxygen saturation) <70%

Exclusion Criteria

Patients with irregular cardiac rhythm: Patient with atrial fibrillation (AF) or having frequent ectopics

- Patient with acute respiratory distress syndrome (ARDS)
- Valvular heart disease: Significant aortic or mitral valve lesions
- Spontaneously breathing patients
- Renal patient with oliguria and volume overload.

The sample size was calculated based on previous study¹³ using the following formula:¹⁴

$$n = Z_{1-\alpha/2}^2 \times SD^2 / d^2$$

$Z_{1-\alpha/2}$ = Power of the study

SD: Assumed standard deviation

d : Absolute error (difference in means)

Assuming 80% power, 5% significance level with 95% confidence interval, and assumed standard deviation being 2, the total sample size calculated was 41. We decided to include 50 patients.

Vigileo-FloTrac

Vigileo-FloTrac (Edwards Life Science, Irvine, CA, United States) allows for automated and continuous monitoring of CO based on pulse contour analysis and also monitoring of the respiratory variations in stroke volume (SVV). The Vigileo-FloTrac device analyzes the arterial waveform to determine stroke volume (SV). The FloTrac system (Edwards) is a specific pressure transducer attached to an arterial line catheter and connected to a specific monitor (Vigileo). The arterial waveform is assessed at 100 Hz. The standard deviation (SD) of the pulse pressure (PP) is determined over a 20-second period. To calculate CO, the software uses an algorithm based on the relationship between arterial PP and SV and considers vessel compliance and peripheral resistance. Vessel compliance is estimated from nomograms based on age, gender, height, and weight, and peripheral resistance is determined from arterial waveform characteristics. Vigileo-FloTrac devices allow for the determination of the SVV. This index is displayed continuously on the monitor.

Pulse pressure is defined as the difference between systolic and diastolic arterial blood pressure. Maximal (PP_{max}) and minimal (PP_{min}) were determined over the same respiratory cycle.

$$PPV = (PP_{max} - PP_{min}) / [(PP_{max} + PP_{min}) / 2] \times 100.$$

Stroke volume variation—It is the percent of change in SV during inspiration and expiration during the most recent 20 seconds. Stroke volume variation is also defined as the variation of beat-to-beat SV from the mean value during the most recent 20 seconds. It was calculated using the following formula:

$$SVV = (SV_{max} - SV_{min}) / SV_{mean} \times 100.$$

The mean value of three consecutive SVV determinations will be used for statistical analysis (>1 minute).

Systolic pressure variation is defined as the difference between the maximal and minimal values of systolic arterial pressure recorded over a respiratory cycle.

$$SPV = \Delta Up + \Delta Down \text{ normal value}$$

Sometimes calculated as a fraction by the equation:

$$SPV = SBP_{max} - SBP_{min} / (SBP_{max} + SBP_{min} / 2)$$

$$\Delta Up = SBP_{max} - \text{Apneic baseline normal value}$$

$$\Delta Down = \text{Apneic baseline} - SBP_{min} \text{ normal value}$$

All the selected patients were mechanically ventilated using the volume control mode with tidal volume 6–8 mL/kg, respiratory

rate 12–15/minute, PEEP up to 5 cm H₂O, and plateau pressure was kept below 30 cm H₂O. Ventilatory settings and dosages of inotropic and vasopressor drugs were kept constant during the entire study period. The patients remained sedated during the study period using propofol (1–4 mg/kg iv f/b infusion of 1–2 mg/kg/hour) so that their spontaneous effort will be masked. An 22G cannula was placed in the radial artery and 7Fr three-lumen CVC was placed in the right internal jugular vein using the Seldinger's technique after taking all aseptic precautions. Both radial artery and CVC were connected to a transducer and later on a dedicated FloTrac transducer was connected to these lines to one end and to the Vigileo system on the other ends. The system enables the continuous monitoring of CO, cardiac index (CI), SV, and SVV by the pulse contour analysis. The PPV and SPV were calculated using a standard Multipara monitor. These monitors have the features of measuring PPV and SPV in response to fluid replacement therapy. This feature can be used with the standard arterial pressure contour analysis. During the study period, we froze a pressure waveform and identify the maximum and minimum PP and also maximum and minimum systolic pressures, which coincided with the respiration cycles and estimated PPV and SPV by using the standard formula. Both PPV and arterial SPVs values were considered as the average of three consecutive values at a 1-minute interval. Hemodynamic measurements were recorded in the supine position with the all transducers positioned at the level of fourth intercostal space in the mid-axillary line. Three sets of measurements were recorded: The first set was at the baseline (0 minute), second after fluid challenge, i.e., 30 minutes, and third at 60 minutes. All selected patients were given 10 mL/kg body weight of normal saline as a fluid challenge over 30 minutes. The following hemodynamic variables were recorded: heart rate (HR), CVP, mean arterial blood pressure (MAP), and CI, and with the help of the multiparametric monitor and using the Vigileo system SVV, PPV, and SPV were measured. Variables obtained with the Vigileo-FloTrac device were sampled every 20 seconds. The values were recorded at baseline (0 minute), after fluid challenge at 30 minutes and at 60 minutes, and this was used to classify patients as responders and nonresponders. Following the crystalloid bolus, patients with a CI increase of more than 10% were classified as responders and those with an increase of less than 10% were classified as nonresponders.¹⁵ The CVP, HR, MAP, CI, PPV, SVV, and SPV were simultaneously recorded at each time point. The primary objective was to measure PPV, SVV, and SPV before and after fluid challenge to the mechanically ventilated critically ill patients to classify patients as responders and nonresponders based on the percentage change in CI, and the secondary objectives were to compare and validate the accuracy and predictability of fluid responsiveness measured using PPV, SVV, and SPV.

The statistical analysis was carried out using IBM Corp. (2013) IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY).

Data were presented as mean ± SD. Categorized data were presented as frequency and/or percentage. The parametric data were compared among groups using the one-way analysis of variance and the unpaired *t*-test. Nonparametric data were compared using the Pearson's chi-square test.

RESULTS

A total of 54 patients were recruited. Of these, two patients had technical issue as their arterial line got blocked during study period, one patient started breathing spontaneously, and one patient develop sudden hypotension, so his vasopressor support was increased during the study period. Hence, only 50 patients met our criteria. Out of these 50 patients, 32 patients were responders and 18 were nonresponders.

Table 1 shows the comparison of demographic parameters, sedation score (Richmond Agitation Sedation), and need for vasopressor support between responders and nonresponders. All these parameters are comparable among the groups. This showed that there was no confounding effect of baseline characteristics.

Table 2 shows the comparison of hemodynamic variables between responders and nonresponders at baseline and 30 minutes and 60 minutes after administering fluid bolus. There was significant difference in CI and MAP at 30 and 60 minutes after bolus fluid challenge. Also the SVV and PPV were significantly lower in responders compared to nonresponders at 30 minutes after fluid bolus.

Table 3 shows the percentage increase in CI from baseline to 30 minutes and baseline to 60 minutes. It was significantly higher at both the time intervals in responders compared to nonresponders.

Table 4 shows the predictive values of different hemodynamic variables like CVP, SVV, PPV, and SPV. Among all these, SVV with a cutoff value of 14.5% has the highest sensitivity to predict fluid responsiveness following a fluid bolus in critically ill patients.

Figure 1 shows the sensitivity and specificity of SVV for responders and nonresponders. The predictive values of SVV for responders. SVV ≥14.5 predicted responders correctly in 48% patients with sensitivity and specificity of 75% (95% CI = 60.0–90.0) and 44.4% (95% CI = 21.5–67.4), respectively.

Figure 2 shows the sensitivity and specificity of PPV for responders and nonresponders. The predictive values of PPV for responders. PPV ≤21.5 predicted responders correctly in 38% patients with sensitivity and specificity of 59.4% (95% CI = 42.4–76.4) and 50% (95% CI = 26.9–73.1), respectively.

Figure 3 shows the sensitivity and specificity of SPV for responders and nonresponders. The predictive values of SPV for responders. SPV ≤14.5 predicted responders correctly in 38% patients with sensitivity and specificity of 59.4% (95% CI = 42.4–76.4) and 72.2% (95% CI = 51.5–92.9), respectively.

Table 1: Comparison of demographic parameters, sedation score, and need for vasopressor support between responders and nonresponders

Parameters	Responders	Nonresponders	<i>p</i> value
Age (years) (mean ± SD)	41.88 ± 17.74	50.17 ± 8.59	0.06*
Gender (percentage of males)	59.4	72.2	0.36**
Weight (kg) (mean ± SD)	57.34 ± 9.65	60.72 ± 6.7	0.19
Richmond Agitation Sedation Score (mean ± SD)	−3.91 ± 1.17	−3.67 ± 1.18	0.49
Percentage of patients needing vasopressor support	28.1	44.1	0.24**

Unpaired *t* test, **Chi-square test

Table 2: Comparison of hemodynamic variables between responder and nonresponders at baseline, and after 30 and 60 minutes of administering fluid bolus

Parameters	Time from bolus	Responder (mean ± SD)	Nonresponder (mean ± SD)	p value*
CI (L/minute/m ²)	Baseline	3.58 ± 0.69	3.41 ± 0.64	0.39
	30 minutes	4.24 ± 0.73	3.59 ± 0.69	0.004*
	60 minutes	4.62 ± 0.67	3.80 ± 0.69	0.0001*
MAP (mm Hg)	Baseline	63.56 ± 3.10	62.89 ± 2.99	0.45
	30 minutes	69.53 ± 2.19	66.06 ± 3.15	0.001*
	60 minutes	68.91 ± 5.38	64.72 ± 5.77	0.01*
HR (in minutes)	Baseline	121.91 ± 13.32	121.67 ± 12	0.95
	30 minutes	105.69 ± 13.4	113.06 ± 11.68	0.06
	60 minutes	111.66 ± 10.76	115.83 ± 10.77	0.18
CVP (cm of H ₂ O)	Baseline	6.97 ± 1.93	7.61 ± 1.29	0.21
	30 minutes	10.16 ± 1.76	9.28 ± 1.6	0.08
	60 minutes	9.03 ± 2.13	8.28 ± 1.49	0.19
SVV (%)	Baseline	16.09 ± 2.18	15.89 ± 7.47	0.88
	30 minutes	10.28 ± 1.76	12.28 ± 4.42	0.02*
	60 minutes	11.47 ± 2.30	12.00 ± 5.40	0.62
PPV (%)	Baseline	20.28 ± 7.37	23.09 ± 8.12	0.21
	30 minutes	15.28 ± 6.94	20.03 ± 4.35	0.01*
	60 minutes	16.99 ± 7.16	20.46 ± 7.26	0.10
SPV (%)	Baseline	13.66 ± 4.08	15.40 ± 3.05	0.12
	30 minutes	11.12 ± 3.83	12.21 ± 3.87	0.34
	60 minutes	10.66 ± 4.01	12.41 ± 3.20	0.12

*Significant

Table 3: Comparison of percent increase (%) in CI from baseline to 30 and 60 minutes between responders and nonresponders

Time periods	Responders	Nonresponders	p value ¹
Baseline to 30 minutes	15.86 ± 4.82	5.29 ± 1.74	0.0001*
Baseline to 60 minutes	23.08 ± 6.01	10.51 ± 3.82	0.0001*

¹Unpaired t-test, *significant

Table 4: Predictive values of different parameters

Parameter	Cutoff value	Predictive values % (95% CI)			
		Sensitivity	Specificity	PPV	NPV
CVP	7.5 mm Hg	62.5	50.0	69.0	42.9
SVV	14.5%	75	44.4	70.6	50.0
PPV	21.5%	59.4	50.0	67.9	40.9
SPV	14.5%	59.4	72.2	79.2	50.0

DISCUSSION

This study, to our knowledge, is first ever Indian study to undertake a head-to-head comparison of three arterial waveform-derived variables in their ability to predict responsiveness to fluid bolus in critically ill hemodynamically unstable patients. It is different from previous studies in that instead of administering an arbitrary volume of fluid, irrespective of weight, as boluses, ranging from 500 mL to 1000 mL,^{13,16-18} we calculated the volume of fluid given as challenge on the basis of body weight (10 mL/kg). Also, we collected data at 60 minutes, unlike previous studies, and so our study is better poised to evaluate the duration of effects of fluid challenge.

We found in our study that there was no significant difference in CI between responders and nonresponders at baseline. However,

CI was found to be significantly higher among responders than nonresponders at 30 minutes and 60 minutes (Table 2). Several studies had shown that rise in CI was the only predictor of fluid responsiveness.^{13,15}

We found in our study that there was no significant difference in CVP between responders and nonresponders at all the time periods (Table 2). In their systematic review that compared CVP with measured circulating volume, the authors demonstrated a very poor relationship between CVP and blood volume as well as the inability of CVP/ΔCVP to predict the hemodynamic response to a fluid challenge.¹⁵

In our study, we found that SVV was significantly lower among responders than nonresponders at 30 minutes. There was no significant difference in SVV between responders and

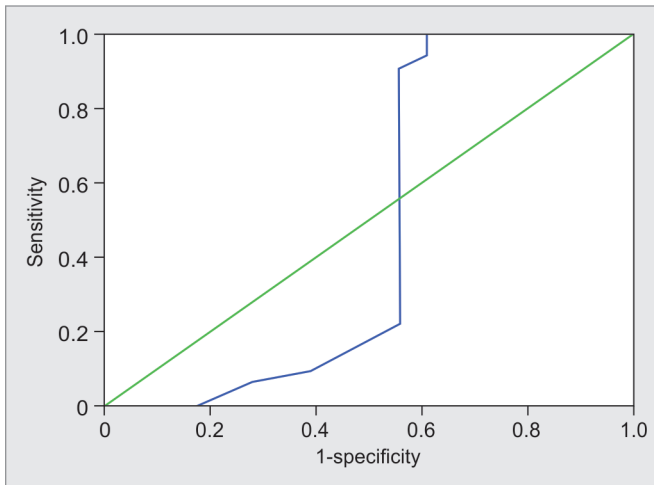


Fig. 1: Receiver operating characteristic curve showing sensitivity and specificity of stroke volume variation for responders

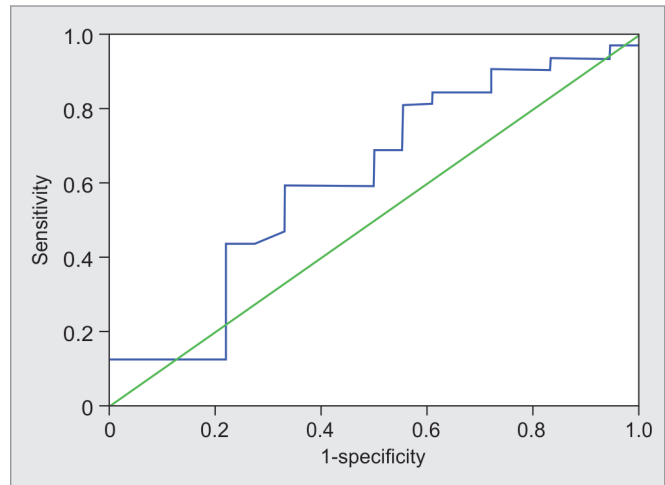


Fig. 2: Receiver operating characteristic curve showing sensitivity and specificity of pulse pressure variation for responders

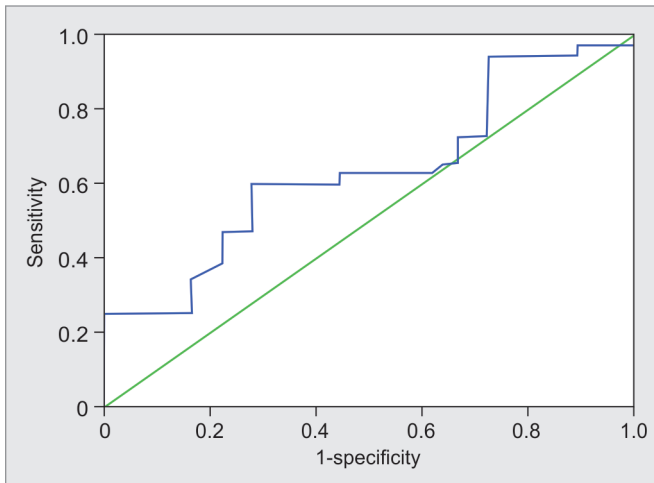


Fig. 3: Receiver operating characteristic curve showing sensitivity and specificity of systolic pressure variation for responders

nonresponders at baseline and 60 minutes (Table 2). The mean threshold value was $11.6 \pm 1.9\%$ for the SVV in responders, which was similar to our findings,¹⁵ whereas it showed that baseline $SVV > 8.15\%$ predicted fluid responsiveness in mechanically ventilated patients with acute circulatory failure.¹³ In contrast, older studies failed to appreciate the ability of SVV to predict fluid responsiveness.^{19,20} This could probably be explained by the fact that they used the first software version (1.01) of Vigileo-FloTrac, which has a recalibration interval of 10 minutes. This time period is too long to detect accurately the respiratory variations in the arterial pressure curve.

On comparison of PPV between the groups, we found that there was no significant difference in PPV between responders and nonresponders at baseline and 60 minutes. However, PPV was significantly lower among responders than nonresponders at 30 minutes (Table 2). Previous meta-analyses had also shown that PPV had a high degree of diagnostic accuracy in detecting fluid responsiveness in hemodynamically unstable critically ill patients under controlled mechanical ventilation.^{21,22} In a systematic review of the literature of total of 649 spontaneously breathing patients assessed for fluid responsiveness, it was reported that PPV during

the Valsalva maneuver (ΔPPV) of 52% and passive leg raising-induced change in stroke volume ($\Delta SV-PLR$) $> 13\%$ showed the highest accuracy to predict fluid responsiveness in spontaneously breathing patients.²³ Thus, PPV may be used to assess fluid responsiveness in spontaneously breathing patients too.

In our study, we found that there was no significant difference in SPV between responders and nonresponders at all the time periods. Previous studies also failed to demonstrate any relation of SPV to intravascular volume status.^{24,25} Further, it was reported that SPV cannot be explained by only left ventricular volume changes and other factors such as intrathoracic and airway pressure changes affect SPV.²⁵

Table 4 shows the predictive values of SVV for responders. $SVV \geq 14.5\%$ predicted responders correctly in 48% patients with sensitivity and specificity of 75 and 44.4%, respectively. A previous prospective, interventional observer-blinded study also reported poor value of SVV in predicting fluid responsiveness with figures similar to that of our study.²⁶ They found that $SVV \geq 8.5\%$ predicted fluid responsiveness with sensitivity of 77%, specificity of 43%, positive predictive value of 84%, and negative predictive value of 33%. Another study reported that a threshold SVV value of 10% allowed discrimination of responders to volume expansion with a sensitivity of 82% and a specificity of 88% and they concluded that SVV predicts fluid responsiveness with an acceptable sensitivity and specificity.¹¹

We have shown in our study that $PPV \leq 21.5\%$ predicted responders correctly in 38% patients with sensitivity and specificity of 59.4 and 50%, respectively (Table 3). Our study suggested that $SPV \leq 14.5\%$ predicted responders correctly in 38% patients with sensitivity and specificity of 59.4 and 72.2%, respectively (Table 3).

We found that SVV and PPV are both significant at 30 minutes of fluid challenge and nonsignificant at 60 minutes (Table 2). This could be probably due to the $T_{1/2}$ for crystalloids, which is usually 20–40 minutes.²⁷

Our study suffers from certain important limitations like small sample size, use of crystalloids for fluid challenge, and use of homogeneous group of patients.

Assessment of SVV requires special monitors such as Vigileo monitors with FloTrac transducers, which is expensive and may not be widely available. The Vigileo-FloTrac system, which is based on analysis of arterial pulse contour, does not need external calibration,

dye dilution, or thermodilution. The system provides nearly beat-to-beat estimate of SV and SVV. The PPV is a derivative of the arterial pulse waveform integrated in monitors of most anesthesia workstations and so more widely available with less cost.²⁸

So, we suggest that in view of limitations of our study we need to have studies with bigger sample size and with the use of different type of fluid for challenge on heterogeneous group of patients (e.g., intraoperative, postoperative, septic shock, and pediatric).

So, to conclude, the initial assessment for fluid responsiveness in critically ill mechanically ventilated hemodynamically unstable patients should be based on SVV and PPV to prevent the complications of fluid overload and their consequences in critically ill patients.

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