Original Research Article

Plethysmographic variability index as a tool to assess fluid responsiveness in critically ill patients: a correlation study with inferior vena cava distensibility index

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ABSTRACT

Background: In critically ill patients in the intensive care unit (ICU), early aggressive fluid replacement is the cornerstone of resuscitation. Traditionally employed static measures of fluid responsiveness have a poor predictive value. It is therefore imperative to employ dynamic measures of fluid responsiveness that take into account the heart lung interactions in the mechanically ventilated patients. The main objective of this study was to evaluate the reliability of one such non-invasive dynamic index: Plethysmographic variability index (PVI) compared to the widely employed Inferior vena cava distensibility index (dIVC).

Methods: Seventy-six adult patients admitted at a tertiary care mixed ICU, who developed hypotension (MAP<65 mmHg), were included in the study. PVI was recorded using the MASIMO-7 monitor and dIVC measurements done using Terson ultrasound. Based on the dIVC measurement threshold of 18%, the patients were classified into volume responders and non-responders. The hemodynamic, PVI and dIVC measurements were recorded at pre specified time points following a fluid challenge of 20 ml/kg crystalloid infusion.

Results: Baseline PVI values were significantly higher in the responders (22.3±8.2) compared to non-responders (10.1±2.9) (p<0.001) and showed a declining trend at all time points in the responders. Similar declining trend was observed in the dIVC measurements. Overall, the Pearson correlation graph showed strong correlation between dIVC and PVI values at all time points (r=0.678, p=0.001). The ROC curve between the dIVC and PVI values revealed that Baseline PVI (Pre PVI) >15.5% discriminated between responders and non-responders with a 90.2% sensitivity and 75% specificity with an AUC of 0.84 (0.72-0.96) (p<0.001).

Conclusions: There is good correlation between PVI values and measured dIVC values at baseline and following a fluid challenge. Thus, PVI may be an acceptable, real time, continuous, surrogate measure of fluid responsiveness in critically ill patients.

Keywords: Arterial pulse pressure variation, Cardiac index, Fluid responsiveness, IVC distensibility index, Plethysmographic variability index, Systolic pressure variation

INTRODUCTION

Fluid replacement is considered the cornerstone of resuscitation in critically ill patients in the intensive care unit. Studies have demonstrated that about a half of hemodynamically unstable patients in the ICU and Operating Room (OR) respond to a fluid challenge.¹ Despite aggressive resuscitation and supportive care, the course of critically ill patients progresses to the multitude of organ dysfunction, tissue dyoxia and death.² It is
speculated that early aggressive fluid resuscitation may limit and/or reverse this dyoxia and consequently stall the progression to organ failure and mortality.3,4

The resuscitation, therefore, needs to be tailored to balance the potential benefit of intravascular volume optimization and enhanced tissue delivery against the risk of ARDS and tissue edema.5 Traditional static measures of preload responsiveness including the central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) are poor predictors of preload responsiveness.6 Over the last three decades, the focus has shifted towards dynamic indices, that challenge the patients’ Frank-Starling curve (fluid challenge or a passive leg raising) and detect the corresponding change in stroke volume.7 A wide array of technologies are available to measure this stroke volume change in real-time by minimally invasive or non-invasive methods, including Doppler methods, pulse contour analysis, bioreactance, Systolic Pressure Variation (SPV) and arterial pulse pressure variation (PPV).7,8

A popular technique in the ICU is the echocardiographic assessment of the cyclic changes in Inferior Vena Cava diameter to predict fluid responsiveness. Of these parameters, the diastensibility index of the IVC (dIVC), which reflects the increase in the IVC diameter on inspiration in mechanically ventilated patients is advocated as a predictor of fluid responsiveness with a sensitivity of 90% and a specificity of 90%. 9 Despite its non-invasive nature, it has limitations, including the difficult subcostal window in obese patients, following laparotomy, poor reliability in patients with raised intra-abdominal pressure, technical expertise with a long learning curve and a non-continuous nature of the generated data.10

A novel dynamic predictor of fluid responsiveness obtained from the pulse oxymetry plethysmograph is Plethysmographic Variability Index (PVI). It is non-invasive and automatically calculated and continuously displayed on the screen of the Pulse Oximetry Monitor.11 The pulse oximeter as a guide to the volume status was first proposed by Partridge in 1987.12 Masimo developed a measurement (Plethysmographic Variability Index) to indicate cyclic changes in the Plethysmographic waveform due to cardiopulmonary alterations in physiology utilizing the Perfusion Index (PI).13 Perfusion index is a measurement displayed on many pulse oximeters, calculated by indexing the infra-red (IR) pulsatile signal against the non-pulsatile IR signal and expressed as a percentage of AC to DC.14 PVI is a measure of the dynamic changes in the PI, measuring changes in PI over an epoch when one or more complete respiratory cycles have occurred. Simplistically, lesser the variability in the PI over a respiratory cycle, lower is the PVI; denoting euvolections. Vice versa rising PVI values may be a marker of hypovolemia. PVI provides useful information about the heart-lung interactions between the intra-thoracic airway pressure and intravascular volume.

However, the reliability of PVI to determine fluid responsiveness in the critically ill is still a grey area. We therefore undertook this study in our tertiary care mixed population ICU to assess the validity of PVI as a means of titrating fluid resuscitation in critically ill patients and correlating it with more widely employed Inferior Vena cava distensibility index.

METHODS

The study was conducted as a prospective observational study over a two year period (Oct 2015- Sep 2017) in a tertiary care hospital with mixed ICU population, to evaluate the reliability of Plethysmographic Variability Index as a predictor of fluid responsiveness and evaluate the correlation coefficient of Plethysmographic Variability Index and Inferior Vena Cava distensibility Index as a marker for fluid responsiveness in mechanically ventilated hypotensive ICU patients. We enrolled consecutive surgical and non-surgical patients admitted to Intensive Care Unit (ICU) who were mechanically ventilated and experienced a hypotensive episode as defined. A total of 130 patients were enrolled of which 76 were finally included in the study. Demographic data included patient age, gender and body mass index. Institute ethical committee clearance was sought and obtained before the study commenced. Informed written consent was obtained from all the study participants / next of kin before including them in the study after explaining the implication of the study.

Inclusion criteria

Adult critically ill patients (>18 years) who were mechanically ventilated in the ICU and experienced a hypotensive episode (defined as the first hypotensive episode with an absolute value of Systolic Blood Pressure (SBP) <90 mmHg or Mean Arterial Pressure (MAP) < 65 mmHg without inotropes or a fall of >20 mmHg from the baseline with or without inotropes, lasting 5 min).

Exclusion criteria

Patients aged less than 18 years and more than 65 years, with underlying poor LV function (LVEF< 40 %), Chronic Kidney disease, decompenated liver failure and pregnant patients were excluded from the study.

Sample size was calculated keeping in view at the most 5% risk, with minimum 80% power and 5% significance level (significant at 95% confidence level). If the true relative risk of failure for experimental subjects is 0.20, it was estimated that at least 62 (rounded 70) subjects would be required to reject the null hypothesis that this relative risk equals 1 with probability (power) of 0.8. The Type I error associated with testing this null hypothesis was 0.05.
All enrolled patients were maintained on Volume-Controlled Ventilation with administration of muscle relaxants (0.5mg/Kg Atracurium) and Ventilator parameters adjusted to deliver tidal volume 8 to 10 mL/kg ideal body weight and PEEP of existing value or a value of 5 cm H2O whichever is higher. The radial artery was cannulated if not done earlier. The dynamic indices of PVI and dIVC were recorded using Masimo Radical-7 Pulse Co-Oximeter (Radical-7, Masimo Corp., Irvine, CA, USA) and Terason Smart 3200T Portable Ultrasound Machine (uSmart 3200T, Boston, MA, USA) respectively.

The baseline vital parameters including Mean arterial blood pressure (MAP), heart rate (HR), Oxygen Saturation (SPO2) and central venous pressure (CVP) were recorded. The Masimo pulse co-oximeter probe (MasimoSET® Rainbow R2-25r and R225a, Masimo Corp., Irvine, CA, USA) was placed on the index finger of the patients and wrapped with a gauge piece to eliminate any interference with ambient light, as per the manufacturer recommendations. PVI and PI variations were automatically measured and displayed on the Masimo monitor (Masimo Radical-7, Masimo Corp., Irvine, CA, USA) with PVI software.

Inferior vena cava diameter (D) at end-expiration (Dmin) and at end-inspiration (Dmax) were measured by echocardiography using a subcostal approach. Patient was positioned supine and sub-xiphoid view of the heart obtained. The ultrasound indicator was directed toward the patient’s left flank and the right atrium identified, ultrasound probe was rotated 90 degrees counterclockwise and IVC identified as it entered the right atrium. In the M-mode, the ultrasound was taken as the cursor crossed the IVC approximately 2 cm inferior to the junction with the right atrium. The distensibility index of the IVC (dIVC) was calculated as the ratio of Dmax minus Dmin to Dmin. This was expressed as percentage; dIVC of 18% was taken as threshold for “Volume responders” and “non-responders”. A fluid challenge of 20 mL/kg Ringer’s Lactate fluid was infused intravenously over 10 minutes. Time of fluid challenge was noted as the start of the study period (T0). Vital parameters (MAP, heart rate and SPO2) as well as CVP, dIVC and PVI were recorded at baseline (TPre), starting time (T0), 5 minutes (T5), 10 minutes(T10), 15 minutes(T15) and 30 min (T30) after the fluid challenge, which was assigned as the end of the study period.

Data analysis

SPSS (Statistical Package for Social Sciences) Software Version 17.0 was used for statistical analysis. Results were expressed as the mean, standard deviation (SD), numbers and percentages (%). The hemodynamic parameters pre and post fluid challenge were compared using the paired Student t test and responders and non-responders inter group analysis was done using the 2-sample Student t test for normally distributed variables and Mann–Whitney U test for nonparametric data.

The measure of the strength of the association between the two variables in order to determine the correlation coefficient was done by using Pearson’s correlation coefficient analysis and Bland Altman Analysis. P value < 0.05 was considered to be significant. Receiver Operator Characteristic (ROC) Curve and Area under the curve (AUC) was calculated for PVI values in comparison to dIVC values before fluid challenge and at all pre specified time points to find out the sensitivity and specificity of PVI.

RESULTS

The present study was a prospective observational study conducted on 76 patients, both surgical and non-surgical, admitted in the ICU of a tertiary care hospital over a two-year period. One hundred and thirty mechanically ventilated patients who experienced their first hypotensive episode were enrolled in the study. Of these 49 patients were excluded from the study for various reasons (did not fulfil the inclusion criteria, pre-existing cardiac / renal disorder which contraindicated fluid bolus). (Figure1) Another 13 patients had to be abandoned from the study because of cardiac arrest/ change of ventilator settings or unrecordable PVI due to poor signal strength.

![Figure 1: Consort diagram progress of patient through your study.](https://example.com/figure1)

Out of 76 patients 34 (44.7%) were admitted as Medical/ non-surgical cases and 42 (55.3%) were admitted as surgical cases. Forty patients were males (52.6%) and 36 were females (47.4%). The mean age of the patients was 46.6 years; majority of the patients in the medical and surgical ICU were middle aged (52.6%). The average duration of mechanical ventilation for entire study sample was 52.4 hours, with duration being more for the medical
group (85.3 hrs) compared to the surgical group (25.8 hrs).

Of the 76 patients studied, 58 patients were grouped as “Volume responders” (dIVC >18% before fluid challenge) and remaining 18 patients as “Non-responders”. The recorded hemodynamic parameters (HR, MAP, PVI, dIVC) were analysed as a comparison between the two subgroups at the prespecified time points TPre, T0, T5, T10, T15 and T30. (Table 1)

Table 1: Comparison of Hemodynamic parameter pre and post fluid challenge between the “responders” and “non-responders”.

<table>
<thead>
<tr>
<th>Time (in mins)</th>
<th>Responders (n=58)</th>
<th>Non-Responders (n=18)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate (beats/min) expressed as Mean±SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPre</td>
<td>110.7±26.5</td>
<td>95.6±23.9</td>
<td>0.03</td>
</tr>
<tr>
<td>T0</td>
<td>107.7±26.4</td>
<td>94.3±23.8</td>
<td>0.05</td>
</tr>
<tr>
<td>T5</td>
<td>106.7±26</td>
<td>93.9±22.9</td>
<td>0.05</td>
</tr>
<tr>
<td>T10</td>
<td>105.7±26.4</td>
<td>93.3±23.9</td>
<td>0.07</td>
</tr>
<tr>
<td>T15</td>
<td>105.3±26.4</td>
<td>92.4±23.4</td>
<td>0.05</td>
</tr>
<tr>
<td>T30</td>
<td>104.0±26.9</td>
<td>92.4±22.6</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Mean arterial pressure (MAP) mmHg expressed as Mean±SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPre</td>
<td>64.03±10.7</td>
<td>66.8±8.6</td>
<td>0.33</td>
</tr>
<tr>
<td>T0</td>
<td>67.5±10.5</td>
<td>67.1±8.4</td>
<td>0.87</td>
</tr>
<tr>
<td>T5</td>
<td>70.7±11.8</td>
<td>69.0±7.8</td>
<td>0.57</td>
</tr>
<tr>
<td>T10</td>
<td>70.5±12.9</td>
<td>69.4±8.6</td>
<td>0.75</td>
</tr>
<tr>
<td>T15</td>
<td>71.3±12.0</td>
<td>70.3±9.0</td>
<td>0.75</td>
</tr>
<tr>
<td>T30</td>
<td>72.8±12.1</td>
<td>72.4±7.8</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Pulse variability index (PVI in %) values expressed in Mean ±SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPre</td>
<td>22.3±8.2</td>
<td>10.1±2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T0</td>
<td>19.7±7.1</td>
<td>9.3±2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T5</td>
<td>17.4±6.7</td>
<td>9.4±3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T10</td>
<td>15.9±6.4</td>
<td>7.8±2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T15</td>
<td>14.5±6.5</td>
<td>7.0±2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T30</td>
<td>12.7±5.5</td>
<td>6.8±2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>IVC Distensibility Index (dIVC in %), values expressed in Mean ±SD Mean ± SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPre</td>
<td>33.7±16.4</td>
<td>12.0±2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T0</td>
<td>23.7±12.3</td>
<td>10.8±3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T5</td>
<td>17.8±8.7</td>
<td>9.5±4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T10</td>
<td>22.7±60.4</td>
<td>10.7±7.9</td>
<td>0.41</td>
</tr>
<tr>
<td>T15</td>
<td>28.2±90.3</td>
<td>10.7±7.4</td>
<td>0.43</td>
</tr>
<tr>
<td>T30</td>
<td>20.2±10.9</td>
<td>14.4±6.6</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*P value of < 0.05 is considered significant.

TPre: Pre fluid challenge; T0: Start of fluid challenge, T5: 5 minutes post fluid challenge; T10: 10 minutes post fluid challenge, T15: 15 minutes post fluid challenge and T30: 30 minutes post fluid challenge

Baseline HR in “responders” group was higher (109.3±22.8) vs. “non-responders” (96±24.3), which was statistically significant before fluid bolus and at T0, T5 and T15. At time points T10 and T30 difference was not statistically significant. Also, the decrease in heart rate following the fluid challenge was more pronounced for “responders” compared to “non-responders”. The Responder group had greater increase in MAP values post fluid challenge as compared to non-responder group, but the difference was not statistically significant. (Table 1). The pulse oximetry values were maintained above 95% in all groups throughout the study period.

Figure 2: Trend of PVI values in the “Responders” and “Non-responders” over the prespecified time points (TPre: Pre fluid challenge; T0: Start of fluid challenge, T5: 5 minutes post fluid challenge; T10: 10 minutes post fluid challenge, T15: 15 minutes post fluid challenge and T30: 30 minutes post fluid challenge).

Figure 3: Trend of dIVC values in the “Responders” and “Non-responders” over the prespecified time points (TPre: Pre fluid challenge; T0: Start of fluid challenge, T5: 5 minutes post fluid challenge; T10: 10 minutes post fluid challenge, T15: 15 minutes post fluid challenge and T30: 30 minutes post fluid challenge).

There was a declining trend of PVI over the 30 minutes post fluid challenge for most of the patients across the groups signifying fluid optimisation. (Fig 2) There appeared to be no apparent difference in the trend of PVI between medical and surgical patients. Baseline PVI values were significantly higher in Responder group (22.3±8.2) vs. Non-Responders (10.1±2.9), (p < 0.001). This difference diminished over 30 minutes but was
statistically significant at all time intervals post fluid challenge. (Figure 2) There was a declining trend of dIVC values post fluid challenge and initial 5 minutes for most of the patients in all groups. (Table 1, Figure 3) Over next 10-15 minutes again there was a rising trend, signifying need for ongoing resuscitation as maintenance fluid in addition to initial fluid challenge.

Baseline dIVC values were intuitively higher in Responder group (33.8±16.4) vs. Non-Responders (12.0±2.7), (p<0.001). This difference diminished over time and remained significant only till 5 minutes after fluid challenge. This may be interpreted as decreased compressibility of IVC once normovolemia was achieved in the responder group after 10 minutes of fluid challenge as compared to non-responders who were already euvoletic.

**Baseline dIVC and PVI (TPre)**

The Bland Altman analysis of the correlation between dIVC and PVI at baseline prior to fluid bolus showed a mean difference of –9.20 with 2.6% of the values falling outside the limits of agreement (48.12 and-29.72). (Figure 4) This difference was clinically significant.

Baseline showed strong positive correlation between dIVC and PVI with \( r = 0.679 \) (\( p = 0.001 \)), which was statistically significant. (Figure 5) Responders had a stronger positive correlation (\( r= 0.520 \)) as compared to non-responders (\( r= 0.054 \)). (Figure 6)

**Post fluid challenge (T0) dIVC and PVI**

Bland Altman analysis of the correlation between dIVC and PVI post fluid challenge showed a mean difference of –3.43 with 1.3% of the values falling outside the limits of agreement (35.37 and -28.50). This difference was clinically significant. (Figure 7). As shown in Figure (8) the Pearson’s correlation graph post fluid challenge showed moderately strong positive correlation between dIVC and PVI with \( r = 0.481 \) and which was statistically significant (\( p < 0.001 \)). Also, non-responders had poor correlation as compared to responders’ group. (Figure 9)
Five minutes post fluid challenge (T5) dIVC and PVI

Bland Altman analysis of the correlation between dIVC and PVI, 05 minutes after the fluid challenge, showed a mean difference of 0.34 with 2.6% of the values falling outside the limits of agreement (25.95 and 25.28). (Figure 10) The Pearson’s correlation graph post 5 minutes after fluid challenge showed mildly strong positive correlation between dIVC and PVI with $r = 0.225$ and $p = 0.05$, which is statistically significant. (Figure 11) Also, non-responders had poor correlation as compared to responders’ group.

Ten minutes Post fluid challenge (T10) dIVC and PVI

The Bland Altman analysis of the correlation between dIVC and PVI, 10 minutes after the fluid challenge, showed a mean difference of 0.38 with 2.6% of the values falling outside the limits of agreement (34.67 and 33.91). The Pearson’s correlation graph at 10 minutes post fluid challenge also showed positive correlation between dIVC and PVI with $r = 0.516$ & $p <0.001$, which was statistically significant. Also, responders group showed negative correlation as compared to non-responders group having moderate positive correlation.

15-minutes post fluid challenge (T15) dIVC and PVI

The Bland Altman plot of the correlation between values of dIVC and PVI at 15 minutes post initiation of fluid challenge showed a mean difference of 2.44 with 1.3% of the values falling outside the limits of agreement (34.80 and -29.92). The Pearson’s correlation graph at 15 minutes post fluid bolus showed mildly strong positive correlation between dIVC and PVI with $r = 0.374$ & $p <0.001$, which was statistically significant. Also, responders group showed weak negative correlation as compared to Non-Responders’ group which had a weak positive correlation.
30-minutes post fluid challenge (T30) dIVC and PVI

The Bland Altman plot of the correlation between values of dIVC and PVI at 30 minutes post initiation of fluid challenge. Bland Altman analysis of the correlation between dIVC and PVI 30 minutes after fluid challenge showed a mean difference of 7.56 with 2.6 % of the values falling outside the limits of agreement (38.85 and -23.73). (Figure 12) The Pearson Correlation coefficient between PVI and SPV at 30 minutes post fluid challenge. The Pearson’s correlation graph 30 minutes post fluid bolus showed moderately strong positive correlation between dIVC and PVI with r = 0.560 & p<0.001, which was statistically significant. (Figure 13) The Responder as well as non-responder group showed positive correlation at end of study period.

The Receiver Operator Characteristic Curve Between dIVC and PVI. A PVI >15.5% before volume expansion discriminated between responders and non-responders with 90.2% sensitivity and 75% specificity at 95% CI. (Fig 14) The area under the curve (AUC) between the PVI and dIVC at baseline was 0.84 (0.72-0.96) and was statistically significant. (p<0.001) (Table 2)

![Figure 12: Bland Altman plot of the correlation between values of dIVC and PVI at 30 minutes post initiation of fluid challenge.](image1)

![Figure 13: Pearson’s Correlation coefficient thirty minutes after the fluid challenge between values of dIVC and PVI.](image2)

![Figure 14: Receiver Operator Characteristic Curve Between dIVC and PVI at baseline (prior to fluid challenge).](image3)

DISCUSSION

The present study was a prospective observational study conducted on 76 hypotensive ICU patients to evaluate the correlation between PVI and widely used dynamic index of dIVC, as a marker of fluid responsiveness. With a threshold dIVC of 18 % to differentiate for fluid responders and non-responders we obtained a PVI value above15.5% before volume expansion discriminated between responders and non-responders with 90.2% sensitivity and 75% specificity. The finding was corroborated by an observed declining trend in dIVC and PVI values after the fluid bolus among all the patients over a period of 30 mins, irrespective of their gender and medical or surgical group.

A large body of evidence emphasizes the importance of an accurate assessment of volume status in critically ill patients and early goal directed fluid resuscitation to reverse tissue hypoxia, prevent organ damage and improve outcomes. In a landmark study, Rivers et al. demonstrated that early goal-directed therapy (EGDT) reduces organ failure and improves survival in sepsis patients with reduced in-hospital mortality in the EGDT group in comparison to the conventional therapy group (30.5% vs 46.5%; p = 0.009). Additionally, the mean APACHE II scores were significantly lower, indicating less severe organ dysfunction, in the patients in the EGDT group (p < 0.001). On the other hand, overzealous hydration is associated with increased complications and poor outcomes. The “Vasopressin in Septic Shock Trial” enrolled 778 ICU patients and
evaluated net fluid balance quartile correlation with 28-day mortality and clearly demonstrated that the highest adjusted mortality was observed in the quartile of patients with the largest fluid balance at 12 hours and at 4 days.\textsuperscript{16}

<table>
<thead>
<tr>
<th>Area under the curve</th>
<th>Test Result Variable(s)</th>
<th>Area</th>
<th>Std. Error#</th>
<th>Asymptotic Sig.¶</th>
<th>Asymptotic (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRE PVI</td>
<td>0.841</td>
<td>0.062</td>
<td>0</td>
<td>0.72–0.961</td>
</tr>
</tbody>
</table>

The test result variable(s): PRE PVI has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. # Under the nonparametric assumption, ¶ Null hypothesis: true area = 0.5.

The fine line between under and over hydration needs to be towed cautiously to improve outcomes. Traditional measures of fluid responsiveness have time and again proven infructuous in guiding volume resuscitation in the critically ill patients. Marik et al, performed a systematic review to assess the value of the CVP in directing fluid management.\textsuperscript{6} The pooled correlation coefficient between the baseline CVP and change in stroke index/cardiac index was 0.18 (95% CI 0.08–0.28). The pooled area under the ROC curve was 0.56 (95% CI 0.51–0.61), indicating that CVP fails to predict fluid responsiveness.

The main essence of present study are the dynamic indices of fluid responsiveness which have become somewhat of a gold standard for guiding fluid therapy in the operating room and ICU. Though there are several studies that have demonstrated the utility of indices as SPV and PPV; both SPV and PPV are invasive methods with associated complications and are technically challenging.\textsuperscript{16,17} On the other hand, IVC distensibility index and PVI are both non-invasive techniques and have been validated to transesophageal echocardiographic (TEE) cardiac index(CI) measurement.

In this study we have considered IVC distensibility index to be the gold standard with which we are comparing another dynamic index: PVI. For this purpose, we undertook the widely employed dIVC percentage of 18% as a cut off between fluid responders and non-responders. Barbier and colleagues compared dIVC with esophageal doppler determined CI in 23 septic patients and found that dIVC cutoff of 18% was predictive of fluid responsiveness with a sensitivity of 90% and a specificity of 90%.\textsuperscript{9} Though IVC indices are appealing, nevertheless they are difficult to obtain in some ICU patient populations (post-laparotomy, morbidly obese), and require trained intensivist with added disadvantages of a lack of reproducibility and non-continuous nature of the data.\textsuperscript{17}

PVI on the other hand is automatically calculated and displayed on the screen of the Pulse Oximetry monitor with a special software. Of the various dynamic parameters based on the lung-heart interactions, PVI has demonstrated fair accuracy in the ICU patients.

Feissel and colleagues demonstrated in 23 septic patients that PVI of 14% discriminated volume responders and non-responders with a sensitivity of 84% and specificity of 80%.\textsuperscript{18} Lupec et al, conducted a study in forty mechanically ventilated patients in ICU with circulatory insufficiency in whom volume expansion was planned. PVI, PPV and TEE measured cardiac output were recorded before and after fluid challenge.\textsuperscript{19} Fluid responsiveness was defined as an increase in cardiac output of ≥15%. PVI threshold value of 17% allowed discrimination between responders and non-responders with a sensitivity of 95% (95% CI 0.74–1.0) and a specificity of 91% (95% CI 0.70–0.99). The PVI at baseline correlated (r =.72, p <.0001) with the percentage change in cardiac output induced by fluid challenge, suggesting that a higher PVI at baseline will correlate with a higher percentage change in cardiac output after volume expansion.

Though the reliability of PVI in controlled settings in the operating room has been supported by various studies, 20–22 its application in the ICU setting remains questionable with large intra- and inter-individual variations.\textsuperscript{23,24} Systematic reviews of various studies evaluating PVI in the OR and ICU environment have found PVI to be reasonable means of preload responsiveness with sensitivity higher in the OR population compared to the ICU patients.\textsuperscript{25} A recent meta-analysis evaluated the reliability of PVI in various settings as a tool for predicting fluid responsiveness and included twenty-five studies with about a thousand patients on mechanical ventilation. The ability of PVI to predict fluid responsiveness had a pooled sensitivity of 0.77 (95% CI 0.67–0.85) and specificity of 0.77 (95% CI 0.71–0.82). Subgroup analysis showed the reliability was sustained in the subgroup of medical ICU patients (AUC =.86, Youden index =.65) and the results of subgroup of patients in ICU (AUC =.89, Youden index =.67) were reliable. The authors concluded though the reliability of PVI is limited, it can nevertheless play a role as bedside continuous monitor of preload responsiveness in ICU patients.\textsuperscript{26}

The results of our study are in congruence with the study by Piskin et al, that compared the performance of IVC
diameter and PVI to TEE measured CI in mechanically ventilated patients and deduced that PVI threshold of >14% predicted fluid responsiveness with 95% sensitivity and 81.2% specificity with an AUC of 0.939 (0.857-0.982; p<0.001) and that both PVI and dIVC can be useful bedside tools in the ICU to monitor volume expansion.\(^7\)

A major limitation in this study is that we compared PVI to dIVC which is not a gold standard for assessing the intravascular volume status. However, considering that dIVC has been widely validated dynamic index in comparison to the more objective thermodilution technique; we planned on utilizing dIVC as a surrogate measure. Another limitation is the observer bias; wherein both the parameters dIVC and PVI were recorded by the same physician. However, the physician doing the recording was not involved in the management of the patients. Further it is prudent to accept that PVI is largely dependent on perfusion index, in other words peripheral perfusion, which gets compromised when vasopressors are being used.\(^23\) In our study in 8 patients of severe hypoperfusion Plethysmographic signal could not be obtained and had to be excluded from the study. This emphasizes the need of non-perfusion-based markers like echocardiography/IVC distensibility Index or invasive dynamic indices to complement the information obtained from PVI data. A noteworthy criticism may be that almost half the patients in our study were post-operative surgical patients and the results may not be reproducible to non-surgical cohort of critically ill patients. However, subgroup analysis did not show any significant difference in the trend of dIVC and PVI values between the non-surgical and surgical group. Another limitation was the application of fluid challenge which would be more of a treatment rather than a test. In a study that subjected critically ill patients to a 500 ml normal saline bolus, the changes in pulse pressure variation poorly detected (sensitivity 65%; range 56-72%) concomitant changes in cardiac output, also there were significant false negatives (22%) noted.\(^28\) Further concerns regarding fluid overload, volume and technique of fluid challenge are intuitive and may influence the results.\(^29\)

A major strength of this study is that this proves feasibility and reliability of using PVI in the ICU as a non-invasive continuous reproducible measure of fluid responsiveness with dIVC complementing the information in the mixed population of ICU patients.

Despite the strengths and limitations, it is noteworthy that PVI shares the same limitations as other functional hemodynamic parameters, including reduced reliability during arrhythmias, right heart failure, spontaneous breathing activity, low tidal volume, abnormally large dicrotic notches or a photo-plethysmogram that is corrupted by patient movement.\(^30\) It is imperative that the information obtained from PVI be complemented with echocardiographic indices.

**CONCLUSION**

As the use of invasive hemodynamic monitoring is declining, there is a trend towards utilizing continuous non-invasive reproducible repeatable measures of fluid responsiveness in the hypotensive critically ill patients to guide optimal fluid resuscitation. Bedside-focused ultrasound and Plethysmography Variability Index are increasingly becoming valuable bed side tools to optimize resuscitation and vasopressor therapy in hypotensive patients. The study is one of its kind exploring the correlation between dIVC and PVI for fluid responsiveness in hypotensive mechanically ventilated ICU patients. With dIVC of 18 % as cut off for fluid responders and non-responders, PVI threshold of 15.5% using the ROC at baseline predicted fluid responsiveness with 90.2% sensitivity and 75% specificity. It is therefore recommended that use of PVI and echocardiography based IVC distensibility index be incorporated into the treatment algorithms of fluid resuscitation in mechanically ventilated ICU patients. Further large-scale tests of diagnostic accuracies may be required to explore the utility of PVI alone and dIVC with PVI together in predicting fluid responsiveness with comparison to the gold standard criteria of thermodilution technique.

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