Predicting Fluid Responsiveness in Septic Shock Patients by Using 3 Dynamic Indices: Is It All Equally Effective?

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Objective: To evaluate the effectiveness and accuracy of three dynamic indices, currently available in intensive care monitoring devices, which are pulse pressure variation (PPV), stroke volume variation (SVV) and pulse oximetry plethysmographic waveform variation (POPV) in septic patients.

Material and Method: This prospective clinical trial was conducted in 20 deeply sedated septic patients 18 years of age and older who had invasive blood pressure monitoring with an intraarterial cannula. PPV, SVV and POPV (%) were calculated using five consecutive snapshots from every patient's monitor. Statistical analysis compared using linear regression, paired t-test or student t-test, and receiver operating characteristic (ROC) curve analysis.

Results: The authors found that, strong correlation existed of PPV for the detection of percent cardiac index change (r² = 0.794, p < 0.001). A respiratory variation in POPV exceeding 14% (sensitivity of 72%, specificity of 90%), SVV exceeding 11% (sensitivity 90%, specificity 92%) allowed detection of PPV exceeding 12% (sensitivity 84%, specificity 96%).

Conclusion: Comparing of PPV, SVV and POPV, PPV is the most correlate with percent change in cardiac index and the most effective dynamic index for predict fluid responsiveness in adult septic critically ill patients who are on controlled mechanical ventilator, followed by SVV and POPV.

Keywords: Fluid responsiveness, Pulse pressure variation, Stroke volume variation, Pulse oximetry plethysmographic waveform variation

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Fluid responsiveness refers to the aptitude of the heart to regulate stroke volume in response to volume change. Because the slope of the Frank-Starling curve depends on ventricular contractility, static preload measurements are unable to predict fluid responsiveness(1,2). It has been accepted that dynamic parameters (relying on the heart-lung interaction in patients with positive pressure ventilation) are better predictors of fluid responsiveness than static indices(3). Absence of cardiac arrhythmia, intracardiac shunt and low tidal volume ventilation, pulse pressure variation (PPV) is now considered the most specific and sensitive tool than other parameters in mechanically ventilated patients(1). Recently, stroke volume variation (SVV) and pulse oximetry plethysmographic waveform variation (POPV) are also used more frequently at bedside and were validated in various patient conditions which have been shown strongly related to PPV and are sensitive to change in ventricular preload(4-8). Unfortunately, the power to predicting fluid responsiveness of these three dynamic parameters including PPV, SVV and POPV have never been compared in the same clinical setting in septic shock patients who need the best parameter to minimize the risk of fluid overload which result in pulmonary and interstitial edema. The present study is the first to evaluate and compare the effectiveness of three dynamic parameters which are more commonly used in the intensive care unit to define fluid responsiveness condition in septic shock patients. The authors also evaluated the correlation of these three dynamic parameters with the percent change of cardiac index to predict fluid responsiveness in septic mechanically ventilated patient. The authors defined the term “effectiveness” of the dynamic indices by probability to discriminate between fluid responder and nonresponder group, acquiring area under receiver operating characteristic (ROC) curves.
Material and Method

Ethical considerations

The present study protocol was approved by the Ethical Committee, The Royal Thai Army Medical Department, and informed consent was obtained from the patients or their relatives.

Patients

A total of 20 mechanically ventilated patients with indwelling intraarterial and central venous catheter, who were diagnosed as acute circulatory failure related to sepsis were enrolled in the present study. All patients were admitted and provided care in the medical intensive care unit of Phramongkutklao Hospital, Bangkok, Thailand. Inclusion criteria consisted of (1) sepsis defined by the international criteria\(^9\); (2) acute circulatory failure defined by a systolic blood pressure less than 90 mmHg or the need of vasopressor drugs (dopamine more than 5 μg/kg/min or norepinephrine); (3) instrumentation with indwelling radial or femoral arterial catheters; (4) hemodynamic stability, defined by a variation in heart rate, blood pressure, and cardiac output of less than 10% over the 15 minutes period before starting the protocol. Exclusion criteria were as follows: (1) arrhythmia; (2) intracardiac shunt; (3) tidal volume ventilation less than 8 mL/kg or patient who had respiratory effort; (4) severe hypoxemia (arterial oxygen pressure to fraction of inspired oxygen (PaO\(_2\)/FiO\(_2\)) less than 100 mmHg). Sedation and analgesia were provided by continuous infusion of midazolam and fentanyl titrated for a Ramsay score of 6\(^{10}\). Patients were therapeutically paralysed with intravenous atracurium if the attending physician deemed this appropriate. All patients were ventilated with positive pressure ventilation with tidal volume, 8-10 mL/kg of body weight. The respiratory rate was set to obtain a PaCO\(_2\) of 35-45 mmHg and inspired fraction of oxygen was adjusted to obtain an arterial oxygen saturation more than 90%. Inspiratory to expiratory time ratio was approximately 1:2 in all patients.

Hemodynamic monitoring

All patients were monitored for mean arterial blood pressure (MAP), right atrial pressure (RAP), heart rate (HR), PPV and peripheral oxygen saturation using IntelliVue MP 70, Philips monitors with all pressure transducers were referenced to phlebostatic level. Stroke volume (SV), stroke volume index (SVI), cardiac output (CO), cardiac index (CI), SVV, systemic vascular resistance (SVR), systemic vascular resistance index (SVRI) were monitored by Flo-trac (Vigileo\(^\text{TM}\), Edwards Lifesciences) based on pulse contour analysis technique. M1191AL, Philips pulse oximetry probe was attached to the middle finger of either right or left hand. Pulse oximetry plethysmographic waveform variation (POPV) was then calculated as previously described\(^{11,12}\) and was shown in Fig. 1, in which \(\text{POPV} = [(\text{POPmax - POPmin})/\text{POPmax + POPmin}] \times 100\%\).

Study protocol

A complete set of continuous hemodynamic measurements (HR, MAP, RAP, PPV, SVV, SV, SVI, SVR, SVRI, CI, CO) were obtained at baseline and before each volume expansion (VE). VE consisted of 500 mL of synthetic colloid (Voluven\(^\text{®}\), hydroxyethylstarch 6%; Fresenius, Bad Homburg, Germany) infused over 30 minutes. The ventilatory settings and the rate of administration of vasoactive drugs were not changed throughout the present study. The VE was interrupted when the cardiac index or cardiac output did not increase further and RAP increased more than 5 mmHg\(^{13}\). At the end of VE, another complete set of hemodynamic measurements was obtained.

Statistical analysis

According to the percent increase in cardiac index in response to VE, patients were divided into two groups. Patients with a CI increase induced by VE more than 15% were classified as responders and less than 15% as nonresponders. Data was analyzed with STATA 11. After verifying normal distribution of the data, the parametric paired t-test was used to compare hemodynamic parameters at baseline and after VE. Student t-test was used to compare hemodynamic

\[\text{POPV} = [(\text{POPmax - POPmin})/\text{POPmax + POPmin}] \times 100\%\]

\[\text{Respiration curve} \quad \text{Arterial waveform} \quad \text{Plethysmograph}\]

Fig. 1 Pulse oximetry plethysmographic waveform recordings in an illustrative patient. POP\(_{\text{max}}\) and POP\(_{\text{min}}\) were defined.
parameters in responders and nonresponders groups. Receiver operating characteristics (ROC) curves were used to evaluate the predictive value of the various indices on fluid responsiveness. A p-value of less than 0.05 was considered significant.

Results

Twenty patients (mean age 60 ± 19 years) were included. Baseline characteristics of the patients including underlying disease, source of sepsis, APACHE II score, predicted death rate, initial ventilator setting and vasoactive drugs dosage are listed in Table 1. Mean tidal volume was 8.58 ± 0.5 mL/kg and plateau pressure less than 30 cm H2O in all patients. A total of 20 fluid challenges were analysed. 15 patients needed vasopressor support which were norepinephrine alone (0.47 ± 0.32 μg/kg/min) (n = 11), dobutamine (4.2 ± 1.04 μg/kg/min) combined with norepinephrine (1.1 ± 0.31 μg/kg/min) (n = 2) and dopamine (6.10 ± 1.03 μg/kg/min) alone (n = 2). Five remaining patients had severe hypotension (systolic blood pressure = 80 ± 8 mmHg) without vasoactive drug. Transthoracic echocardiography was performed in 8 patients, revealed systolic dysfunction in 4 patients and diastolic dysfunction in 7 patients. Fourteen patients survived. No patient experienced hypothermia at the time of the present study. Hemodynamic variables before and after volume infusion are shown in Table 2. Before VE, PPV, SVV and POPV ranged from 7 to 19%, from 6 to 17% and from 5 to 24%, respectively. VE produced an increase in cardiac index (CI) from 3.16 ± 0.8 to 3.63 ± 1.0 L/min/m² (p < 0.001). Ten patients were responders, the remaining ten were nonresponders. The correlation of PPV, SVV, POPV with VE induced changes in cardiac index show closed linear correlation, r² = 0.794, 0.667 and 0.633, respectively (Fig. 2A-C). In contrast with RAP which was not correlated with VE induced change in CI. After VE, significantly decrease all of PPV, SVV and POPV from 12.95 ± 5.98 to 6.35 ± 2.72%, from 12.15 ± 5.54 to 4.95 ± 1.82%, from 14.50 ± 9.36 to 6.30 ± 4.89%, respectively (p < 0.05 all). Comparing the effectiveness of discrimination between responders and nonresponders to volume expansion of PPV, SVV and POPV were shown in ROC curve (Fig. 3). The area under the ROC curves (± SE) were as follows: 0.965 ± 0.04 for PPV (p < 0.001), 0.92 ± 0.07 for SVV (p = 0.001) and 0.85 ± 0.09 for POPV (p = 0.008). The threshold PPV value 12% allowed discrimination between responder and nonresponder patients with a sensitivity of 84%, specificity of 96%, SVV 11% for sensitivity of 90%, specificity 92% and POPV 14% for sensitivity of 72%, specificity 90%.

Discussion

As inappropriate fluid administration to intensive care patients can result in pulmonary and interstitial edema, the rationale for guiding fluid therapy on cardiopulmonary interaction indices is that influence of changes in intrapulmonary pressure and lung volume during ventilatory cycle cause temporary changes in biventricular preload and afterload. This phenomenon then results in respiratory changes in stroke volume (SVV)4,14,15, arterial pulse pressure (PPV)5,16,17, systolic blood pressure (SBP)18,19 and pulse oximetry plethysmographic waveform (POPV) which signal resembles the peripheral arterial pressure waveform7,8,12,19,20. All these indices have also been shown to identify and distinguish between responders and nonresponders to fluid challenge in different patient populations.
In the term of SVV, the authors' study derived the SVV from pulse contour-base continuous cardiac output device which showed clinically acceptable assessment of cardiac output in the intensive care unit patients\(^{23}\). There are several trials on the predictiveness of SVV in the perioperative period including brain surgery\(^{4}\) and perioperative cardiac surgery\(^{5,14,15,24}\). The majority of these studies found a good predictive value of SVV. There are only two studies in patients with severe sepsis. First studied was conducted in severe septic patients who were controlled ventilation, resembling the presented populations, revealed that SVV correlated positively with the change in cardiac output after fluid challenge\(^{21}\). Comparable with the present result, the author found a good power to predict fluid responsiveness, however its specificity was lower than responsiveness of the dynamic indices\(^{6,8,21,22}\). And what if, the same the patient, the PPV predict the patient be a nonresponder but SVV or POPV predict patient may be a fluid responder. In septic patients, there is no published study comparing these 3 dynamic indices which become more available in the intensive care monitors. The authors’ results demonstrated that there are close relationships between PPV, SVV and POPV while RAP is poorly correlated with effect of VE. The authors’ cut-off point of PPV for sensitivity 84%, specificity 96% is 12% which closely with a recent study conducted in septic patients using 13% of PPV detected subsequent fluid responsiveness with 94% sensitivity and 96% specificity\(^{6}\).

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PPV, SVV more than 11% allowed sensitivity 90%, specificity 92%. In contrast to the second study of Perner et al which showed negative result of SVV to predict fluid responsiveness in septic patients. The reasons for these discrepancies are due to differences in ventilation which used pressure support mode in patients who still had trigger efforts and less degree of sedation. From the presented result, the authors used the threshold of SVV 11% detected changes in cardiac index more than 15%, comparing with studies in patients undergoing cardiac surgery and brain surgery with threshold of SVV 9.5% and 12.5% respectively for VE-induced changes in SVI more than 25%.

Invasive arterial blood pressure monitoring facilitate the measurement of PPV and SVV, but this invasive technique generally is a required skill and takes time to perform with the risk of mechanical complication or local infection. SVV also need more devices to achieve the data. Continuous monitoring of arterial blood saturation using pulse oximetry has become the standard of care in the intensive care unit. Recently, using respiratory variation in “pulse” wave of plethysmographic waveform (POPV) for the detection of PPV were validated in various settings with a good correlation and a new automatic calculating POPV device was developed recently, POPV was termed “PVI” (Pleth variability index), its accuracy was also validated.

The threshold of POPV is varied from 13% in cardiac surgery patients who received general anesthesia and the threshold of SVV is 11%.

### Table 2. Hemodynamic data at baseline and after volume expansion (VE)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>After VE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beat/min)</td>
<td>104.25 ± 18.72</td>
<td>104.55 ± 18.54</td>
<td>0.844</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>71.45 ± 11.60</td>
<td>80.65 ± 11.82</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>11.15 ± 5.22</td>
<td>16.40 ± 5.53</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>12.95 ± 5.98</td>
<td>6.35 ± 2.72</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SVV (%)</td>
<td>12.15 ± 5.54</td>
<td>4.95 ± 1.82</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>POPV (%)</td>
<td>14.50 ± 9.36</td>
<td>6.30 ± 4.89</td>
<td>0.002</td>
</tr>
<tr>
<td>CO. (L/min)</td>
<td>5.13 ± 1.54</td>
<td>5.82 ± 1.78</td>
<td>0.001</td>
</tr>
<tr>
<td>CI. (L/min/m²)</td>
<td>3.16 ± 0.80</td>
<td>3.63 ± 1.00</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>51.10 ± 14.60</td>
<td>54.70 ± 16.85</td>
<td>0.104</td>
</tr>
<tr>
<td>SVI (mL/m²)</td>
<td>31.90 ± 8.33</td>
<td>34.40 ± 9.97</td>
<td>0.07</td>
</tr>
<tr>
<td>SVR (dynes/s/cm²)</td>
<td>978.10 ± 356.17</td>
<td>954.60 ± 398.61</td>
<td>0.375</td>
</tr>
<tr>
<td>SVRI (dynes/s/cm²/m²)</td>
<td>1,548.75 ± 478.00</td>
<td>1,514.80 ± 543.27</td>
<td>0.383</td>
</tr>
</tbody>
</table>

Data presented in mean ± SD

### Table 3. Hemodynamic data at baseline in responders (R) and nonresponders (NR)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NR (n = 10)</th>
<th>R (n = 10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beat/min)</td>
<td>107.20 ± 16.99</td>
<td>101.30 ± 20.79</td>
<td>0.496</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>70.70 ± 8.87</td>
<td>72.20 ± 14.29</td>
<td>0.781</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>11.00 ± 5.21</td>
<td>11.30 ± 5.52</td>
<td>0.902</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>8.80 ± 2.39</td>
<td>17.10 ± 5.62</td>
<td>0.001</td>
</tr>
<tr>
<td>SVV (%)</td>
<td>8.10 ± 2.13</td>
<td>16.20 ± 4.87</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>POPV (%)</td>
<td>9.35 ± 5.06</td>
<td>19.65 ± 10.01</td>
<td>0.012</td>
</tr>
<tr>
<td>CO. (L/min)</td>
<td>5.76 ± 1.50</td>
<td>4.50 ± 1.37</td>
<td>0.066</td>
</tr>
<tr>
<td>CI. (L/min/m²)</td>
<td>3.47 ± 0.57</td>
<td>2.85 ± 0.91</td>
<td>0.084</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>55.10 ± 14.25</td>
<td>47.10 ± 14.54</td>
<td>0.230</td>
</tr>
<tr>
<td>SVI (mL/m²)</td>
<td>33.60 ± 7.12</td>
<td>30.20 ± 9.46</td>
<td>0.376</td>
</tr>
<tr>
<td>SVR (dynes/s/cm²)</td>
<td>855.40 ± 276.80</td>
<td>1,100.80 ± 397.16</td>
<td>0.126</td>
</tr>
<tr>
<td>SVRI (dynes/s/cm²/m²)</td>
<td>1,394.50 ± 322.12</td>
<td>1,703.00 ± 570.72</td>
<td>0.154</td>
</tr>
</tbody>
</table>

Data presented in mean ± SD
anesthesia(7) to 15% in patients who were on mechanical ventilator in the intensive care unit(11). In the septic patients, the present study found that POPV greater than 14% allowed sensitivity 72% and specificity 90%. Interestingly, the authors' threshold of both PPV and POPV resemble the threshold of a previous study by Feissel et al which studied the relationship between respiratory changes in the amplitude of the plethysmographic pulse wave (POPV) and respiratory changes in pulse pressure (PPV) in septic ventilated patients, they found that PPV of 12% and POPV 14% allowed discrimination between responders and nonresponders with sensitivity of 100% and 94% respectively and specificity of 70% and 80% respectively(8).

Despite dynamic indices become clearly superior than static indices in predicting fluid responsiveness from various studies(1-3,26), the current standard practice of sepsis management for guiding volume infusion still use the static index (i.e. RAP) to reassure the adequacy of LV preload(27). The explanation may be some limitations of dynamic indices which are requiring adequate tidal volume by positive pressure ventilation and absence of cardiac arrhythmia. However, the roles of SVV, PPV and POPV were recently mentioned as the tools for hemodynamic monitoring in early resuscitation of sepsis management(28,29). From the present study, the authors criticized that in the future, adapting the dynamic indices into the sepsis or septic shock guideline in the patients who need controlled mechanical ventilatory support may increase power of discriminate between responder and nonresponder group. And PPV should be a dynamic index of choice because of its highly sensitivity and specificity. In addition, unless PPV or SVV data can be achieved rapidly, a totally non-invasive monitoring technique that is almost available in every emergency or intensive care unit, POPV may be an optional tool to imply and still be a good dynamic index.

The limitations of the present study can be categorized into two parts. First, due to limitation of indices relying on the respiratory variations of LV stroke volume or its surrogate, these dynamic indices can not imply in patients with cardiac arrhythmia, intracardiac shunt, spontaneous breathing patient or controlled ventilation with tidal volume less than 8 mL/kg. Second is the limitation in the signaling process of pulse oximeter, POPV can not be assessed in the patient with poor finger perfusion (hypothermia or severe peripheral vasoconstriction), skin pigmentation, motion artifact of pulse oximeter, dyshemoglobins and automatically gained adjusted pulse oximeter device.

In conclusion, of these 3 dynamic indices including PPV, SVV and POPV, PPV is the most correlated indices with the percent change in cardiac index and the most effective dynamic index for predicting fluid responsiveness in adult septic critically ill patient who is on a controlled mechanical ventilator.

Potential conflicts of interest
Phramongkutklao Hospital’s Foundation under Her Royal Highness Princess Maha Chakri Sirindhorn’s Patronage.

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การทำนายภาวะสารน้ำในหลอดเลือดโดยใช้ดัชนีแบบพลวัต 3 ชนิด ในผู้ป่วยที่มีภาวะความดันโลหิตต่ำจากการติดเชื้อ: ประสิทธิภาพเท่ากันหรือไม่?

เพชร วัชรสินธุ์, อมรชัย เลิศรถ, อภิชาติ เวชสวัสดิ์

วัตถุประสงค์: เพื่อศึกษาและเปรียบเทียบประสิทธิภาพของการติดเชื้อ 3 ชนิด ได้แก่ pulse pressure variation (PPV), stroke volume variation (SVV) และ pulse-oximetry plethysmographic waveform variation (POPV) ในการทำนายภาวะสารน้ำในหลอดเลือดของผู้ป่วยที่มีความดันโลหิตต่ำจากการติดเชื้อ

วิสัยและวิธีการ: ทำการศึกษาในผู้ป่วยที่โรคเรื้อรังหายใจและมีความดันโลหิตต่ำจากการติดเชื้อจำนวน 20 คน ในห้องกักกันของโรงพยาบาลพระมงกุฎเกล้า โดยผู้ป่วยทุกคนจะได้รับการบันทึกค่าต่างๆ ทางระบบไหลเวียนโลหิต รวมทั้งค่าดัชนีแบบพลวัตทั้ง 3 ค่าที่ต้องการศึกษา หลังจากนั้นผู้ป่วยจะได้รับสารน้ำทางหลอดเลือด เป็นปริมาตร 500 มล. จากนั้นจะตรวจสอบว่าระหว่างระยะเวลาที่ได้รับสารน้ำครบแล้ว แนวทางดัชนีแบบพลวัตทั้ง 3 ค่ามีความสัมพันธ์กับอัตราการเปลี่ยนแปลงของค่า cardiac index และประเมินประสิทธิภาพ ของค่าทั้ง 3 โดยใช้กราฟ ROC

ผลการศึกษา: หลังจากที่ให้สารน้ำทางหลอดเลือดแก่ผู้ป่วยแล้วพบว่า PPV มีความสัมพันธ์กับอัตราการเปลี่ยนแปลงของค่า cardiac index มากที่สุด ($r^2 = 0.794, p < 0.001$) ในขณะที่ค่า SVV มีความสัมพันธ์กับอัตราการเปลี่ยนแปลงของค่า cardiac index รองลงมา ($r^2 = 0.667, p < 0.001$) และค่า POPV มีความสัมพันธ์กับอัตราการเปลี่ยนแปลงของค่า cardiac index น้อยที่สุด ($r^2 = 0.633, p < 0.001$) ค่าที่ใช้ในการทำนายภาวะสารน้ำในหลอดเลือดพบว่าหากใช้ PPV ที่มากกว่ารอยละ 12 จะมีความไว รอยละ 84 และความจำเพาะรอยละ 96 หากใช้ SAV ที่มากกว่ารอยละ 11 จะมีความไว รอยละ 90 และความจำเพาะรอยละ 92 และหากใช้ POPV ที่มากกว่า รอยละ 14 จะมีความไว รอยละ 72 และความจำเพาะรอยละ 90 ตามลำดับ

สรุป: เมื่อเปรียบเทียบประสิทธิภาพของดัชนีแบบพลวัตทั้ง 3 ชนิด ได้แก่ PPV, SVV และ POPV ดัชนีที่สามารถพยากรณ์ภาวะสารน้ำในหลอดเลือดในผู้ป่วยความดันโลหิตต่ำจากการติดเชื้อได้ดีที่สุดคือ PPV รองลงมาคือ SVV และ POPV ตามลำดับ