Pleth variability index to monitor the respiratory variations in the pulse oximeter plethysmographic waveform amplitude and predict fluid responsiveness in the operating theatre

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Background. Respiratory variations in pulse oximetry plethysmographic waveform amplitude (ΔPOP) can predict fluid responsiveness in mechanically ventilated patients but cannot be easily assessed at the bedside. Pleth variability index (PVI) is a new algorithm allowing for automated and continuous monitoring of ΔPOP. We hypothesized that PVI can predict fluid responsiveness in mechanically ventilated patients under general anaesthesia.

Methods. Twenty-five patients were studied after induction of general anaesthesia. Haemodynamic data [cardiac index (CI), respiratory variations in arterial pulse pressure (ΔPP), ΔPOP, and PVI] were recorded before and after volume expansion (500 ml of hetastarch 6%). Fluid responsiveness was defined as an increase in CI \( \geq 15\% \).

Results. Volume expansion induced changes in CI \( [2.0 (\text{sd} 0.9) \text{ to } 2.5 (1.2) \text{ litre min}^{-1} \text{ m}^{-2}; P<0.01] \), ΔPOP \( [15 (7\%) \text{ to } 8 (3\%); P<0.01] \), and PVI \( [14 (7\%) \text{ to } 9 (3\%); P<0.01] \). ΔPOP and PVI were higher in responders than in non-responders \( [19 (9\%) \text{ vs } 9 (4\%) \text{ and } 18 (6\%) \text{ vs } 8 (4\%), \text{ respectively}; P<0.01 \text{ for both}] \). A PVI >14% before volume expansion discriminated between responders and non-responders with 81% sensitivity and 100% specificity. There was a significant relationship between PVI before volume expansion and change in CI after volume expansion \( (r=0.67; P<0.01) \).

Conclusions. PVI, an automatic and continuous monitor of ΔPOP, can predict fluid responsiveness non-invasively in mechanically ventilated patients during general anaesthesia. This index has potential clinical applications.

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Goal-directed intraoperative fluid administration has been shown to reduce the length of hospital stay,1–4 critical care admissions,5 and mortality6 after major surgery in various settings. In most of these studies, the haemodynamic endpoint was cardiac output (CO) or stroke volume (SV) assessed using oesophageal Doppler, thus requiring specific device and training.7 More recently, it has been shown that monitoring and minimizing the respiratory variations in arterial pulse pressure (ΔPP) by volume loading has potential to decrease the duration of hospital stay and mechanical ventilation, and postoperative morbidity in patients undergoing high-risk surgery.8 Dynamic indicators of fluid responsiveness relying on cardiopulmonary interactions in mechanically ventilated patients, such as ΔPP, have consistently been shown to be good predictors of fluid responsiveness.9 However, they are either invasive (ΔPP10 and SV variations)11 12 with their associated complications13 14 or technically

†Declaration of interest. M.C. is a member of Masimo Corp. scientific advisory board.
challenging (respiratory variations in pulse Doppler aortic flow velocity and inferior vena cava diameter). Recently, respiratory variations in the pulse oximeter plethysmographic waveform amplitude have been shown to be able to predict fluid responsiveness in the operating theatres and in the intensive care units. However, this cannot be easily measured at the bedside, cannot be continuously monitored, and therefore, cannot be optimized.

Pleth variability index (PVI) (Masimo Corp., Irvine, CA, USA) is a novel algorithm allowing for automated and continuous calculation of the respiratory variations in the pulse oximeter waveform amplitude. However, the ability of this algorithm to predict fluid responsiveness has never been tested.

The aim of this study was to test the ability of PVI to predict fluid responsiveness in mechanically ventilated patients in the operating theatre and to compare it with other dynamic indicators in this setting.

Methods

The protocol was approved by the institutional review board for human subjects of our institution (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale Lyon B). All patients gave informed and written consent. We studied 25 consecutive patients undergoing coronary artery bypass grafting. Patients with cardiac arrhythmias and intracardiac shunt were excluded.

Anaesthesia was induced with propofol (3–5 mg kg$^{-1}$) and sufentanil (0.5–1.0 μg kg$^{-1}$), and orotracheal intubation was facilitated with pancuronium (0.1–0.15 mg kg$^{-1}$). After induction of anaesthesia, an 8 cm 5 Fr tipped catheter (Arrow International Inc., Reading, PA, USA) was inserted in the left or right radial artery, a triple lumen 16 cm 8.5 Fr central venous catheter (Arrow International Inc.), and a pulmonary artery catheter (PAC, Swan-Ganz catheter, 7.5 Fr; Baxter Edwards, Lifescience, LLC, Irvine, CA, USA) were inserted in the right internal jugular vein. Pressure transducers (Medex Medical Ltd, Rossendale, UK) were placed on the midaxillary line and fixed to keep the transducer at atrial level throughout the study. Correct positioning of the PAC in West’s zone 3 was assessed. CO was measured by thermodilution, using the average of five successive measurements obtained by injection of 10 ml of dextrose at room temperature randomly during respiratory cycle. Cardiac index (CI) and SV index (SVI) were calculated using the same formula: CI=cardiac output/body surface area. Anaesthesia was maintained with continuous infusions of propofol (5–8 mg kg$^{-1}$ h$^{-1}$) and sufentanil (0.7–1.0 μg kg$^{-1}$ h$^{-1}$) in order to keep the bispectral index (BIS, Aspect 1000, Aspect Medical Systems Inc., Natick, MA, USA) between 40 and 50. All patients’ lungs were ventilated in volume-controlled mode with a tidal volume of 8–10 ml kg$^{-1}$ body weight at a frequency of 12–15 cycles min$^{-1}$. Positive end-expiratory pressure was set between 0 and 2 cm H$_2$O by the attending anaesthetist.

Data recording and analysis

Manual assessment of respiratory variations in pulse pressure

Arterial pressure waveforms were recorded from a bedside monitor (Intellivue MP70, Philips Medical Systems, Suresnes, France) to a personal computer using data acquisition software (TrendfaceSolo 1.1, Ixellence GmbH, Wildau, Germany) and were analysed by an observer blinded to the other haemodynamic data. Pulse pressure (PP) was manually defined as the difference between systolic and diastolic pressure. Maximal (PPmax) and minimal (PPmin) values were determined manually over the same respiratory cycle. $\Delta PP$ was then calculated as described:

$$\Delta PP = (PP_{max} - PP_{min}) / (PP_{max} + PP_{min}) / 2.$$ 

The measurements were repeated on three consecutive respiratory cycles and averaged for statistical analysis.

Automated calculation of respiratory variations in arterial pulse pressure

The algorithm used in this study is commercially available and has been previously described. The algorithm (pulse pressure variation (PPV)) is displayed online and in real time by Philips Intellivue MP70 monitors. Briefly, it allows for automatic $\Delta PP$ determination from the arterial pressure waveform alone with no need for the airway pressure acquisition. This method is based on automatic detection algorithms, kernel smoothing, and rank-order filters. PPV was calculated and averaged over four cycles of 8 s. We recorded both manual and automatic calculations for $\Delta PP$ to present similar methodology for respiratory variations in arterial pulse pressure and pulse oximeter waveform amplitude (i.e. $\Delta PP$ and PPV vs $\Delta POP$ and PVI).

Manual assessment of the respiratory variations in POP waveform amplitude analysis

A pulse oximeter probe (LNOP$^\circledR$ Adt, Masimo Corp., Irvine, CA, USA) was placed on the index finger of one hand and wrapped to prevent outside light from interfering with the signal and connected to a Masimo Radical 7 monitor with PVI software (version 7.0.3.3). Another pulse oximeter probe (Oxymax, Tyco Healthcare Group LP, Pleasanton, CA, USA) was attached similar to the third finger of the right hand. POP waveforms from this pulse oximeter were recorded from the Intellivue MP70 monitor to a personal computer using data acquisition software and were analysed by an observer blinded to the other haemodynamic data.

Pulse oximeter plethysmographic waveforms were recorded from the Radical 7 monitor to a personal computer using PhysioLog software (PhysioLog V1.0.1.1,
vascular resistance index (SVRI).

Haemodynamic measure-

lowed by i.v. volume expansion using 500 ml of hetastarch

Haemodynamic measurements was then performed and fol-

toned that may have affected PVI values. A baseline set of

Experimental protocol

All patients were studied immediately after induction of

anaesthesia and after a 5 min period of haemodynamic sta-

bility with no changes in anaesthesia and no volume

expansion. We avoided any stimulation of the patients for

1 min before data recording to limit changes in vasomotor
tone that may have affected PVI values. A baseline set of

haemodynamic measurements was then performed and fol-

lowed by i.v. volume expansion using 500 ml of hetastarch

6%, given more than 10 min. Haemodynamic measure-

ments were performed within 3 min after volume expan-

sion after 1 min of no stimulation.

Statistical analysis

All data are presented as mean (sd). Changes in

haemodynamic measures induced by volume expansion

were assessed using a non-parametric Mann–Whitney

U-test or Wilcoxon rank sum test when appropriate.

Patients were allocated to two groups according to the per-

centage increase in CI after volume expansion: responders

were defined as ≥15% increase in CI and non-

responders as <15% increase in CI. Receiver operating

characteristic (ROC) curves were generated for CI, CVP,

PCWP, PI, ΔPP, ΔPOP, and PVI varying the discriminat-

ing threshold of each and area under the ROC curves was

calculated and compared (MedCalc 8.0.2.0, MedCalc

Software, Mariakerke, Belgium). From an earlier study, power analysis showed that 25 patients were necessary to
detect a difference of 0.15 between ΔPOP and PVI areas

under the ROC curves (5% type I error rate, 80% power,
two-tailed test). Spearman rank method was used to test
correlation. A P-value of <0.05 was considered as statisti-
cally significant. All statistic analysis was performed using

SPSS 13.0 for Windows (SPSS, Chicago, IL, USA).

Results

The patients studied included 16 males and nine females

of mean age 65 (range 48–82) yr. Seventeen patients

received beta-blockers before operation. No patients

received vasoactive drugs before operation. The pulse ox-

imeter plethysmography waveform was analysable in all

patients. PI at baseline ranged from 0.71% to 9.67%. PVI

was displayed for all PI values as was PPmax and

POPmax during inspiration in all patients. There was a
good correlation between ΔPOP and PVI over the 50

measurements (r=0.92; P<0.01). We also observed sig-
nificant relationships between ΔPOP and PVI before

(r=0.97; P<0.01) and after volume expansion (r=0.65;

P<0.01).

Changes in haemodynamic measurements after

volume expansion

As expected, volume expansion induced significant

increase in CI, MAP, CVP, and PCWP (Table 1). At the

same time, we observed significant decreases in both ΔPP,

ΔPOP, PPV, and PVI. We observed no change in PI.

PVI prediction of fluid responsiveness

Sixteen patients responded and nine patients did not

to respond to volume expansion (Table 2). ΔPP, ΔPOP, PPV,

and PVI before volume expansion were significantly

higher in responders than in non-responders [18 (5%) vs 7

(4%), 19 (9%) vs 9 (4%), 18 (7%) vs 7 (4%), 18 (6%) vs 8

(4%), respectively; P<0.01] (Fig. 1). There was no signifi-
cant difference in CVP [10 (4) vs 13 (6) mm Hg, P=0.18], in

PCWP [13 (5) vs 17 (6) mm Hg, P=0.16], in
**Discussion**

This study shows the ability of PVI to predict fluid responsiveness in mechanically ventilated patients in the operating theatre. Fluid responsiveness assessment has been studied for many years, and it is now established that dynamic measurements relying on cardiopulmonary interactions in mechanically ventilated patients are the best predictors of fluid responsiveness. More recently, fluid optimization based on minimizing ΔPP has been shown to be able to decrease morbidity and cost of surgery in patients undergoing high-risk surgery. Consequently, there is a need for automated and continuous calculation of these dynamic measures.

Respiratory variation in the pulse oximeter waveform amplitude (ΔPOP) has been widely studied in mechanically ventilated patients. They have been shown to relate to ΔPP to be sensitive to changes in ventricular preload and to predict fluid responsiveness in various clinical settings. However, this technique is not yet available in clinical practice as plethysmographic waveform processing and filtering requires specific tools and software that are not yet widely available. Visual analysis of the respiratory variations in this waveform from the monitor screen cannot be done as the amplitude of the displayed curve is processed in most available devices.

As described above, pulse oximeter waveform relies on the two components of light absorption. The PI is defined as the ratio between constant absorption (AC) and pulsatile absorption component. However, we can postulate that the vasomotor tone is constant during a single respiratory cycle. PI is then automatically and continuously calculated as (PImax−Pimin)/PImax, reflecting respiratory variations in PI. This algorithm allows for continuous monitoring of the respiratory variations in the pulse oximeter waveform amplitude.

PI depends on vasomotor tone which may affect the pulsatile absorption component. However, we can postulate that the vasomotor tone is constant during a single respiratory cycle and that it does not alter the analysis of the relative changes in PI induced by mechanical ventilation. However, it is important to study patients under stable conditions as stimulation, such as nociceptive input, can lead to changes in PI that may affect the results.

**Table 1** Haemodynamic data at baseline and after volume expansion. Data are mean (sd). HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; SVI, stroke volume index; SVRI, systemic vascular resistance index; ΔPP, respiratory variations in arterial pulse pressure; ΔPOP, respiratory variations in plethysmographic waveform amplitude; PPV, automated pulse pressure variations; PVI, pleth variability index; PI, perfusion index.

<table>
<thead>
<tr>
<th>Before volume expansion</th>
<th>After volume expansion</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats min⁻¹)</td>
<td>61 (12)</td>
<td>59 (13)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>64 (9)</td>
<td>74 (9)</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>11 (5)</td>
<td>14 (5)</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>19 (5)</td>
<td>20 (6)</td>
</tr>
<tr>
<td>CI (litre min⁻¹ m⁻²)</td>
<td>2.0 (0.9)</td>
<td>2.5 (1.2)</td>
</tr>
<tr>
<td>SVI (ml m⁻²)</td>
<td>33 (12)</td>
<td>43 (16)</td>
</tr>
<tr>
<td>SVRI (dyn s⁻¹ cm⁻³)</td>
<td>2460 (1279)</td>
<td>2425 (1717)</td>
</tr>
<tr>
<td>ΔPP (%)</td>
<td>14 (7)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>ΔPOP (%)</td>
<td>15 (7)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>14 (7)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>PVI (%)</td>
<td>14 (7)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>PI (%)</td>
<td>4.3 (2.7)</td>
<td>3.8 (2.1)</td>
</tr>
</tbody>
</table>

**Table 2** Haemodynamic data at baseline in responders and non-responders to volume expansion. Data are mean (sd). HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; SVI, stroke volume index; SVRI, systemic vascular resistance index; ΔPP, respiratory variations in arterial pulse pressure; ΔPOP, respiratory variations in plethysmographic waveform amplitude; PPV, automated pulse pressure variations; PVI, pleth variability index; PI, perfusion index.

<table>
<thead>
<tr>
<th>Responders to volume expansion (n=17)</th>
<th>Non-responders to volume expansion (n=9)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats min⁻¹)</td>
<td>63 (13)</td>
<td>57 (10)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>64 (10)</td>
<td>63 (7)</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>10 (4)</td>
<td>13 (6)</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>13 (5)</td>
<td>17 (6)</td>
</tr>
<tr>
<td>CI (litre min⁻¹ m⁻²)</td>
<td>2.14 (1.02)</td>
<td>1.86 (0.57)</td>
</tr>
<tr>
<td>SVI (ml m⁻²)</td>
<td>33 (12)</td>
<td>34 (11)</td>
</tr>
<tr>
<td>SVRI (dyn s⁻¹ cm⁻³)</td>
<td>2424 (1225)</td>
<td>2524 (1443)</td>
</tr>
<tr>
<td>ΔPP (%)</td>
<td>18 (5)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>ΔPOP (%)</td>
<td>19 (9)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>18 (7)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>PVI (%)</td>
<td>18 (6)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>PI (%)</td>
<td>4.1 (2.4)</td>
<td>4.8 (3.2)</td>
</tr>
</tbody>
</table>

PI [4.1 (2.4)% vs 4.8 (3.2%), P=0.54], or CI [2.14 (1.02) vs 1.86 (0.57) ml min⁻¹ m⁻², P=0.44] in responders and non-responders, respectively. The areas under the ROC curves (SE) for ΔPP, ΔPOP, PPV, PVI, PI, CVP, PCWP, and CI are shown in Table 3.

**PVI response to volume expansion**

There was a statistically significant positive linear correlation between ΔPP at baseline and percentage change in CI induced by volume expansion (ΔCI) (r=0.67; P<0.01) and between PPV and ΔCI induced (r=0.61; P<0.01), indicating that the higher ΔPP and PPV at baseline, the higher ΔCI. Similarly, there was a statistically significant positive linear correlation between ΔPOP at baseline and per cent changes in CI induced by volume expansion (ΔCI) (r=0.69; P<0.01) and between PVI and ΔCI induced (r=0.67; P<0.01), indicating that the higher ΔPOP and PVI at baseline, the higher ΔCI. We observed no statistically significant relationship between CVP at baseline and ΔCI (r=−0.16; P=0.77) and between PCWP at baseline and ΔCI (r=−0.14; P=0.77).
induce changes in vasomotor tone. It appears that PVI is not yet able to distinguish between changes in PI induced by respiration from changes induced by any other phenomenon. Consequently, to be related to respiratory variations, PVI has to be studied in standardized conditions. However, in the present study, we found that PVI was more stable in mechanically ventilated patients under general anaesthesia than in spontaneously breathing volunteers. That may be related to a decrease in sympathetic tone related to general anaesthesia but further studies are required to answer this question.

Respiratory variations in the POP waveform are influenced by the site of measurements, in that the ear plethysmographic waveform is less affected by vasoconstriction than the finger plethysmographic waveform. In our study, we recorded PVI at the finger. We can postulate that signal would be steadier at the ear. However, most of the previously published studies focusing on ΔPOP have used the finger waveform. Whether the ear would provide equivalent data still has to be demonstrated.

Monitoring fluid responsiveness using a non-invasive device may help for fluid optimization in the operating theatre. Further studies are planned to assess the ability of PVI optimization in the operating theatre to decrease morbidity and cost of surgery.

The results from this study have to be interpreted with care. First, the patients were studied under very stable conditions. We used a 5 min period of stability before data acquisition. During this period and during volume expansion, any stimulation was avoided. Whether this index can be used for fluid optimization in patients undergoing surgery still has to be demonstrated and cannot be extrapolated from the present results. Further studies are then required to answer this question. Secondly, our patients were deeply sedated. PVI, as any other dynamic indicators, may not be reliable in spontaneously breathing patients. Thirdly, the threshold value of 14% for prediction of fluid responsiveness has to be interpreted with caution. As for ΔPP and for any other indices of fluid responsiveness, threshold value may vary between studies and settings.

<table>
<thead>
<tr>
<th>Area under the curve</th>
<th>Standard error</th>
<th>Asymptomatic 95% confidence interval</th>
<th>P-value</th>
<th>Cutoff</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔPP</td>
<td>0.938</td>
<td>0.046</td>
<td>&lt;0.001</td>
<td>12.5%</td>
<td>87</td>
<td>89</td>
</tr>
<tr>
<td>ΔPOP</td>
<td>0.944</td>
<td>0.042</td>
<td>&lt;0.001</td>
<td>12%</td>
<td>87</td>
<td>89</td>
</tr>
<tr>
<td>PPV</td>
<td>0.941</td>
<td>0.044</td>
<td>&lt;0.001</td>
<td>10.5%</td>
<td>87</td>
<td>89</td>
</tr>
<tr>
<td>PVI</td>
<td>0.927</td>
<td>0.051</td>
<td>&lt;0.001</td>
<td>14%</td>
<td>81</td>
<td>100</td>
</tr>
<tr>
<td>CVP</td>
<td>0.417</td>
<td>0.120</td>
<td>0.497</td>
<td>12.5 mm Hg</td>
<td>44</td>
<td>78</td>
</tr>
<tr>
<td>PCWP</td>
<td>0.396</td>
<td>0.120</td>
<td>0.396</td>
<td>14.5 mm Hg</td>
<td>50</td>
<td>67</td>
</tr>
<tr>
<td>CI</td>
<td>0.556</td>
<td>0.118</td>
<td>0.651</td>
<td>2.8 litre min^{-1} m^{-2}</td>
<td>44</td>
<td>89</td>
</tr>
<tr>
<td>PI</td>
<td>0.438</td>
<td>0.131</td>
<td>0.610</td>
<td>1.43%</td>
<td>94</td>
<td>22</td>
</tr>
</tbody>
</table>
It has been shown previously\textsuperscript{10} that ΔPP values ranging from 8% to 13% may constitute an inconclusive or "grey zone"\textsuperscript{37} with uncertain predictive value. Consequently, using this threshold value for fluid optimization cannot be recommended from our results. We did not perform Bland–Altman analysis to compare PVI and ΔPOP, as explained in the Methods section, the formulae for these two indices are slightly different and, consequently, their values are not expected to be the same.

In conclusion, PVI is a non-invasive, automatic, and continuous monitor of fluid responsiveness in mechanically ventilated patients under general anaesthesia. This index has potential clinical applications.

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