

Respiratory Variations in Pulse Oximetry Plethysmographic Waveform Amplitude to Predict Fluid Responsiveness in the Operating Room

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Background: **Respiratory variations in pulse oximetry plethysmographic waveform amplitude (ΔPOP) are related to respiratory variations in pulse pressure (ΔPP) and are sensitive to changes in preload. The authors hypothesized that ΔPOP can predict fluid responsiveness in mechanically ventilated patients during general anesthesia.**

Methods: **Twenty-five patients referred for cardiac surgery were studied after induction of general anesthesia. Hemodynamic data (cardiac index, central venous pressure, pulmonary capillary wedge pressure, ΔPP, and ΔPOP) were recorded before and after volume expansion (500 ml hetastarch, 6%). Fluid responsiveness was defined as an increase in cardiac index of 15% or greater.**

Results: **Volume expansion induced changes in cardiac index (2.0 ± 0.4 to 2.3 ± 0.5 mmHg; $P < 0.05$), ΔPP (11 ± 7 to 6 ± 5%; $P < 0.05$), and ΔPOP (12 ± 9 to 7 ± 5%; $P < 0.05$). ΔPOP and ΔPP were higher in responders than in nonresponders (17 ± 8 *vs.* 6 ± 4 and 14 ± 7 *vs.* 6 ± 4%, respectively; $P < 0.05$ for both). A ΔPOP greater than 13% before volume expansion allowed discrimination between responders and nonresponders with 80% sensitivity and 90% specificity. There was a significant relation between ΔPOP before volume expansion and percent change in cardiac index after volume expansion ($r = 0.62$; $P < 0.05$).**

Conclusions: **ΔPOP can predict fluid responsiveness noninvasively in mechanically ventilated patients during general anesthesia. This index has potential clinical applications.**

RECENTLY published studies have shown that intraoperative optimization of cardiac output using volume expansion decreases postoperative morbidity and hospital stay.[1] On the other hand, if inappropriate, volume expansion may have deleterious effects. Therefore, preload dependence and fluid responsiveness assessments are of major importance during surgery. Static indicators of fluid responsiveness such as central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), or left ventricular end diastolic area index are invasive or not easily available and have been shown to be poor predictors of fluid responsiveness.[2–9] Dynamic indicators, relying on the respiratory variations in stroke volume or its surrogates in mechanically ventilated patients, have been shown to be superior to static indicators for prediction of fluid responsiveness.[2–5,7,9–12] However, they are either invasive (respiratory variations in arterial pulse pressure (ΔPP),[2] stroke volume variations[5,12]) with their associated complications,[13,14] technically challenging (respiratory variations in pulse Doppler aortic flow velocity,[3] inferior vena cava diameter[11]), or not widely available (esophageal Doppler[15]).

Respiratory variations in the pulse oximetry plethysmographic waveform amplitude (ΔPOP) have now been extensively studied in mechanically ventilated patients.[16,17] They are strongly related to the respiratory variations in arterial pulse pressure (ΔPP)[18–20] and are sensitive to changes in ventricular preload.[21] Recently published studies have shown promising results regarding the ability of ΔPOP to predict fluid responsiveness in the intensive care unit[22] and in the operating room.[20] However, the POP waveform must be recorded and analyzed in specific conditions to be interpretable for fluid responsiveness prediction.

The hypotheses tested in the current study were that ΔPOP can predict fluid responsiveness in mechanically ventilated patients during general anesthesia in the operating room and that ΔPOP is as sensitive and specific as ΔPP to predict fluid responsiveness.

Materials and 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.

This group consisted of 18 men and 7 women aged between 56 and 85 yr (mean age, 69 ± 7 yr). Eighteen patients received β-blockers preoperatively. Induction of anesthesia was performed with propofol (3–5 mg/kg) and sufentanil (0.5–1.0 μg/kg), and orotracheal intubation was facilitated with pancuronium (0.1–0.15 mg/kg). After induction of anesthesia, a 8-cm, 5-French tipped catheter (Arrow International Inc., Reading, PA) was

This article is accompanied by an Editorial View. Please see: Pinsky MR: At the threshold of noninvasive functional hemodynamic monitoring. ANESTHESIOLOGY 2007; 106:1084–5.

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Received from Hospices Civils de Lyon, Department of Anesthesiology and Intensive Care and Department of Cardiac Surgery, Louis Pradel Hospital, Claude Bernard Lyon 1 University, EA 1896, Lyon, France. Submitted for publication December 7, 2006. Accepted for publication February 5, 2007. Support was provided solely from institutional and/or departmental sources.

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inserted in the left or right radial artery, and a triple-lumen, 16-cm, 8.5-French central venous catheter (Arrow International Inc.) and a 7.5-French pulmonary artery catheter (Swan-Ganz catheter; Baxter Edwards, Lifescience, LLC, Irvine, CA) were inserted in the right internal jugular vein. Pressure transducers (Medex Medical Ltd., Rossendale, Lancashire, United Kingdom) were placed on the midaxillary line and fixed to the operation table to keep the transducer at the atrial level all along the study protocol. All transducers were zeroed to atmospheric pressure. Correct position of the pulmonary artery catheter in West zone 3 was assessed using the method of Teboul *et al.*[23] Cardiac output was measured by thermodilution, using the average of five successive measurements obtained by injection of 10 ml dextrose at room temperature randomly during respiratory cycle. Cardiac index and stroke volume index were calculated using the same formula: cardiac index = cardiac output/body surface area. A pulse oximeter probe (Oxymax; Tyco Healthcare Group LP, Pleasanton, CA) was attached to the index of either right or left hand and was wrapped to prevent outside light from interfering with the signal. Anesthesia was maintained with continuous infusions of propofol (5–8 $mg \cdot kg^{-1} \cdot h^{-1}$) and sufentanil (0.7–1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) to keep a Bispectral Index (Aspect 1000; Aspect Medical Systems Inc., Natick, MA) between 40 and 50. All patients were ventilated in a volume-controlled mode with a tidal volume of 8–10 ml/kg body weight at a frequency of 12–15 cycles/min. Positive end-expiratory pressure was set between 0 and 2 cm H_2O according to the attending physician.

Data Recording and Analysis

Arterial pressure and POP 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 analyzed by an observer blinded to the other hemodynamic data.

Respiratory Variations in Pulse Pressure Analysis. Pulse pressure (PP) was defined as the difference between systolic and diastolic pressure. Maximal (PPmax) and minimal (PPmin) values were determined over the same respiratory cycle. ΔPP was then calculated as described by its authors[2]: ΔPP = (PPmax − PPmin)/[(PPmax + PPmin)/2]. The measurements were repeated on three consecutive respiratory cycles and averaged for statistical analysis.

Respiratory Variations in POP Waveform Amplitude Analysis. The plethysmographic gain factor was held constant during POP waveform recording so that the POP waveform amplitude did not depend on automatic gain adjustment. The signal quality was considered as optimal when the perfusion index displayed by the monitor was greater than 1.0, as recommended by the manufacturer. POP waveform amplitude was measured on a beat-to-beat basis as the vertical distance between peak and preceding valley trough in the waveform and was expressed as pixels. Maximal POP (POPmax) and minimal POP (POPmin) were determined over the same respiratory cycle (fig. 1). ΔPOP was then calculated as previously described[18,21]: ΔPOP = (POPmax − POPmin)/[(POPmax + POPmin)/2]. The measurements were repeated on three consecutive respiratory cycles and averaged for statistical analysis.

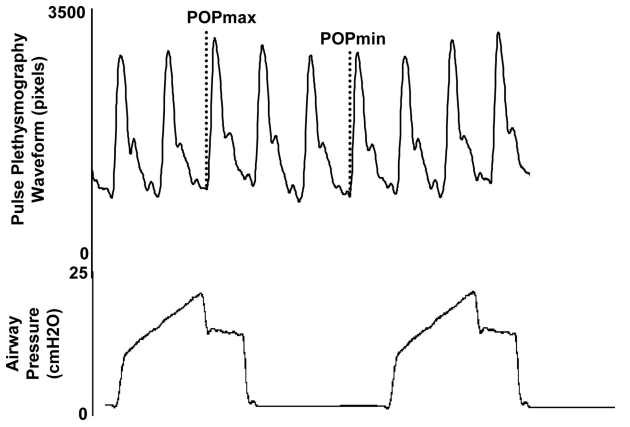

Fig. 1. Pulse oximetry plethysmographic waveform and airway pressure recordings in an illustrative patient. POPmax and POPmin were defined as maximum and minimum pulse oximetry plethysmographic waveform amplitudes, respectively, over a single respiratory cycle. Respiratory variations in pulse oximetry plethysmographic waveform amplitude (ΔPOP) was then calculated as (POPmax – POPmin)/[(POPmax + POPmin)/2].

Other Hemodynamic Measurements. At each step of the protocol, the following parameters were recorded: systolic arterial pressure, mean arterial pressure, diastolic arterial pressure, heart rate, end-expiratory CVP, end-expiratory PCWP, oxygen saturation measured by pulse oximeter, stroke volume index, cardiac index (CI), and systemic vascular resistance index.

Experimental Protocol

All patients were studied immediately after induction of anesthesia and after a 5-min period of hemodynamic stability with no changes in anesthetic protocol and no volume expansion. A baseline set of hemodynamic measurements was then performed and followed by an intravenous volume expansion consisting in 500 ml hetastarch, 6%, given over 10 min. Hemodynamic measurements were performed within 3 min after volume expansion.

Statistical Analysis

All data are presented as mean ± SD. Changes in hemodynamic parameters induced by volume expansion were assessed using a nonparametric Mann–Whitney U test or Wilcoxon rank sum test when appropriate. Patients were divided into two groups according to the percent increase in CI after volume expansion: Responders were defined as patients presenting an increase of

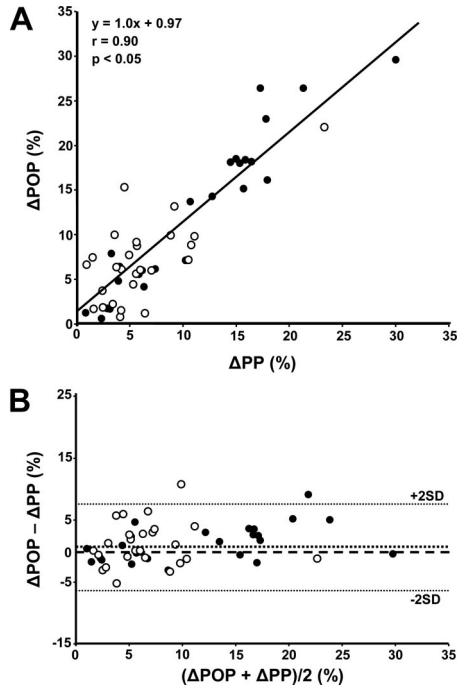

Fig. 2. Relation between respiratory variations in pulse oximetry plethysmographic waveform amplitude (ΔPOP) and respiratory variations in arterial pulse pressure (ΔPP) (*A*), and Bland-Altman analysis for the agreement between ΔPOP and ΔPP (*B*). ● = Before volume expansion; ○ = after volume expansion.

15% or more[2] in CI, and nonresponders were defined as patients presenting an increase of less than 15% in CI. Receiver operating characteristic curves were generated for CI, CVP, PCWP, ΔPP, and ΔPOP, varying the discriminating threshold of each parameter, and areas under the receiver operating characteristic curves were calculated and compared[24] (MedCalc 8.0.2.0; MedCalc Software, Mariakerke, Belgium). Considering previously published results,[2] power analysis showed that 25 patients were necessary to detect differences of 0.15 between ΔPOP and ΔPP areas under the receiver operating characteristic curves (5% type I error rate, 80% power, two-tailed test). The Spearman rank method was used to test correlation. A *P* value less than 0.05 was considered as statistically significant. All statistic analyses were performed using SPSS 13.0 for Windows (SPSS, Chicago, IL).

Results

No patients received vasoactive drugs. Pulse oximeter plethysmography waveform was analyzable in all patients. Perfusion index was always greater than 1.0, consistent with an optimal POP waveform signal. PPmax and POPmax appeared during inspiration in all patients. Correlation between ΔPP and ΔPOP over the 50 measurements was strong ($r = 0.90$; $P < 0.01$) (fig. 2). Agreement between ΔPP and ΔPOP (Bland-Altman analysis) was 1.1 ± 3.2% (fig. 2). We also observed significant relations between ΔPP and ΔPOP before volume expansion ($r = 0.95$; $P < 0.01$) and after volume expansion ($r = 0.73$; $P < 0.01$). Agreement between ΔPP and ΔPOP before volume expansion was 1.3 ± 2.8%. Agreement between ΔPP and ΔPOP after volume expansion was 1.1 ± 3.4%.

Changes in Hemodynamic Parameters after Volume Expansion

Hemodynamic data at baseline and after volume expansion are shown in table 1. As expected, volume expansion induced significant increases in CI (from 2.0 ± 0.4 to 2.3 ± 0.5 $l \cdot min^{-1} \cdot m^{-2}$; $P < 0.001$), mean arterial pressure (from 60.0 ± 9.1 to 68.1 ± 10.2 mmHg; $P < 0.001$), CVP (from 9.8 ± 5.2 to 12.0 ± 3.2 mmHg; $P < 0.001$), and PCWP (from 12.2 ± 4.9 to 15.6 ± 4.4 mmHg; $P < 0.001$). At the same time, we observed significant decreases in both ΔPP (from 11.1 ± 7.3% to 6.2 ± 4.6%; $P < 0.01$) and ΔPOP (from 12.3 ± 8.7% to 7.2 ± 4.8%; $P < 0.01$).

ΔPOP to Predict Fluid Responsiveness

Fifteen patients were responders and 10 patients were nonresponders to volume expansion. Their hemodynamic data are shown in table 2. ΔPP and ΔPOP were significantly higher in responders than in nonresponders

Table 1. Hemodynamic Data at Baseline and after Volume Expansion

	Before Volume Expansion	After Volume Expansion	*P* Value
HR, beats/min	64.8 ± 13.9	62.6 ± 11.4	0.15
MAP, mmHg	60.0 ± 9.1	68.1 ± 10.2	<0.001
CVP, mmHg	9.8 ± 5.2	12.0 ± 3.2	0.02
PCWP, mmHg	12.2 ± 4.9	15.6 ± 4.4	<0.001
CI, $l \cdot min^{-1} \cdot m^{-2}$	2.0 ± 0.4	2.3 ± 0.5	<0.001
SVI, ml/m^2	31.4 ± 9.0	38.0 ± 9.1	<0.001
SVRI, $dyn \cdot s^{-1} \cdot cm^{-5} \cdot m^{-2}$	2,113 ± 537	2,001 ± 532	0.08
ΔPP, %	11.1 ± 7.3	6.2 ± 4.6	<0.001
ΔPOP, %	12.3 ± 8.7	7.2 ± 4.8	<0.001

Data are mean ± SD.

CI = cardiac index; CVP = central venous pressure; ΔPOP = respiratory variations in plethysmographic waveform amplitude; ΔPP = respiratory variations in arterial pulse pressure; HR = heart rate; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; SVI = stroke volume index; SVRI = systemic vascular resistance index.

Table 2. Hemodynamic Data at Baseline in Responders and Nonresponders to Volume Expansion

	Responders to Volume Expansion	Nonresponders to Volume Expansion	*P* Value
HR, beats/min	64.5 ± 16.5	65.4 ± 9.4	0.86
MAP, mmHg	58.5 ± 10.5	62.1 ± 6.3	0.30
CVP, mmHg	10.5 ± 5.9	8.5 ± 3.8	0.33
PCWP, mmHg	12.3 ± 4.3	12.1 ± 5.9	0.94
CI, $l \cdot min^{-1} \cdot m^{-2}$	1.98 ± 0.43	1.95 ± 0.29	0.84
SVI, ml/m^2	32.1 ± 10.8	30.3 ± 5.7	0.60
SVRI, $dyn \cdot s^{-1} \cdot cm^{-5} \cdot m^{-2}$	2,035 ± 624	2,230 ± 371	0.34
ΔPP, %	14.5 ± 6.9	5.8 ± 4.3	<0.001
ΔPOP, %	16.7 ± 8.2	5.8 ± 4.0	<0.001

Data are mean ± SD.

CI = cardiac index; CVP = central venous pressure; ΔPOP = respiratory variations in plethysmographic waveform amplitude; ΔPP = respiratory variations in arterial pulse pressure; HR = heart rate; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; SVI = stroke volume index; SVRI = systemic vascular resistance index.

(14.5 ± 6.9 *vs.* 5.8 ± 4.3 and 16.7 ± 8.2% *vs.* 5.8 ± 4.0%; $P < 0.01$ for both) (fig. 3), whereas differences in CVP (10.5 ± 5.9 mmHg in responders *vs.* 8.5 ± 3.8 mmHg in nonresponders; $P = 0.33$), PCWP (12.3 ± 4.3 mmHg in responders *vs.* 12.1 ± 5.9 mmHg in nonresponders; $P = 0.94$), and CI (1.98 ± 0.43 $ml \cdot min^{-1} \cdot m^{-2}$ in responders *vs.* 1.95 ± 0.29 $ml \cdot min^{-1} \cdot m^{-2}$ in nonresponders; $P = 0.84$) did not reach statistical significance between these two groups. The areas under the receiver operating characteristic curves (± SE) were as follows: 0.847 ± 0.084 for ΔPP, 0.847 ± 0.081 for ΔPOP, 0.570 ± 0.115 for CVP, 0.510 ± 0.122 for PCWP, and 0.520 ± 0.118 for CI (fig. 4). The area for ΔPOP was significantly higher than the area for CVP, PCWP, and mean arterial pressure ($P < 0.05$ for both). The difference in area under the curve between ΔPP and ΔPOP did not reach significance ($P = 0.91$). The threshold ΔPP value of 11% allowed discrimination between responders and nonresponders with a sensitivity of 80% and a specificity of 90%. The threshold ΔPOP value of 13% allowed discrimination between responders and nonresponders with a sensitivity of 93% and a specificity of 90%.

ΔPOP to Quantify Response to Volume Expansion

There was a statistically significant positive linear correlation between ΔPOP at baseline and percent changes in CI induced by volume expansion (ΔCI) ($r = 0.62$; $P < 0.01$) as well as between ΔPP and ΔCI ($r = 0.56$; $P < 0.01$) (fig. 5), indicating that the higher ΔPOP and ΔPP are at baseline, the higher ΔCI is. We observed no statistically significant relation between CVP at baseline and ΔCI ($r = -0.28$; $P = 0.17$) and between PCWP at baseline and ΔCI ($r = -0.06$; $P = 0.79$) (fig. 5).

Discussion

This study shows that ΔPOP can predict response to volume expansion and can quantify the effects of volume expansion on hemodynamic parameters in the operating room.

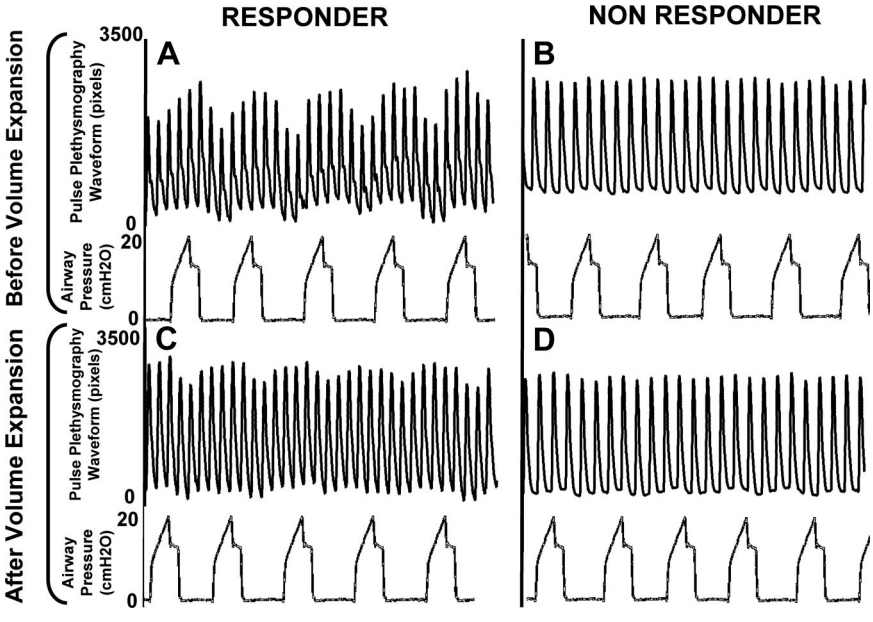

Fig. 3. Pulse oximetry plethysmographic waveform and airway pressure recordings in a patient responder to volume expansion and in a patient nonresponder to volume expansion before (*A* and *B*, respectively) and after volume expansion (*C* and *D*, respectively). Responder to volume expansion shows much higher respiratory variations in the pulse oximetry waveform amplitude. These respiratory variations decrease after volume expansion.

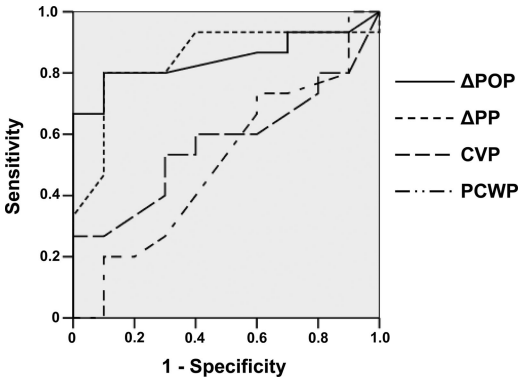

Fig. 4. Receiver operating characteristic curves comparing the ability of respiratory variations in pulse oximetry plethysmographic waveform amplitude (ΔPOP), respiratory variations in arterial pulse pressure (ΔPP), central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP) at baseline to discriminate between responders and nonresponders to volume expansion.

Over the past 10 years, fluid responsiveness assessment has been extensively studied in mechanically ventilated patients.[2–12,15] It is now well accepted that dynamic parameters (relying on the cardiopulmonary interactions in patients under positive pressure ventilation) are better predictors of response to volume expansion than static indicators. Respiratory variations in left ventricular stroke volume or its surrogates are predictive of response to volume expansion.[7] It has been demonstrated that the respiratory variations in arterial PP are better predictors of fluid responsiveness than the respiratory variations in systolic arterial pressure.

Several studies are now suggesting that the pulse oximeter waveform contains much other information that has been underexploited despite its potential useful clinical applications.[16–19,21,22,25,26] One of these informations is the respiratory variations component of the waveform. The respiratory variations in the POP waveform amplitude (ΔPOP) are closely related to the respiratory variations in the arterial pulse pressure (ΔPP)[18,19,27] and are sensitive to changes in ventricular preload.[21] Moreover, some recent studies suggest that ΔPOP may be an accurate predictor of fluid responsiveness.[20,22] Solus-Biguenet *et al.*[20] investigated the ability of various noninvasive indices to predict fluid responsiveness during major hepatic surgery. They found that ΔPOP was significantly higher in responders compared with nonresponders to volume expansion and that ΔPOP was able to predict fluid responsiveness. More recently, a promising study from Natalini *et al.*[22] demonstrated that ΔPOP is able to predict response to volume expansion in patients with circulatory failure related to sepsis in the intensive care setting. They found no difference between ΔPOP and ΔPP to compare fluid responsiveness in these patients. These two previously published studies are clearly encouraging, and our results are consistent with theirs. In the current study, we found better sensitivity and specificity regarding the ability of ΔPOP to predict fluid responsiveness. However, our protocol used slightly different techniques for plethysmographic waveform acquisition and analysis and was performed in a different surgical patient population.[28]

Pulse oximeters are part of the routine monitoring in patients under mechanical ventilation.[29] The signal displayed by the pulse oximeter is proportional to light absorption between the nail and the anterior face of the finger. During systole, the amount of hemoglobin

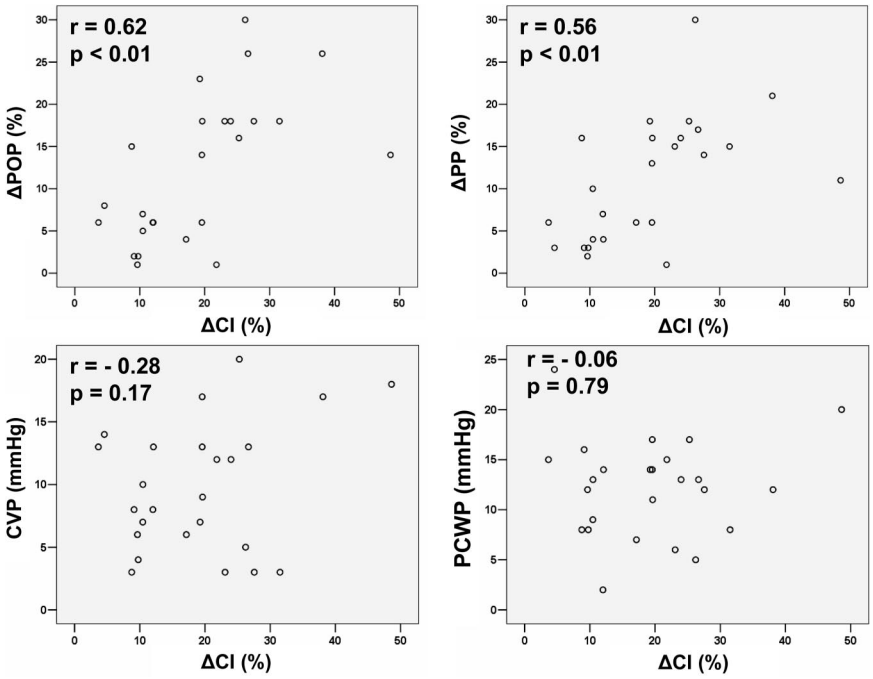

Fig. 5. Relation between respiratory variations in pulse oximetry plethysmographic waveform amplitude (ΔPOP), respiratory variations in arterial pulse pressure (ΔPP), central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP) before volume expansion and percent increase in cardiac index (ΔCI) after volume expansion.

present in the fingertip is increased and, consequently, light absorption is decreased. An inverse phenomenon is observed during diastole. Therefore, the POP waveform depends on the arterial pulse.[29] The pulse density signal is not really the pulse density change but a time-averaged mean-adjusted signal wherein the actual mean density is held constant but the changes in density reported for calibration purposes for the calculation of oxygen saturation. The raw plethysmographic signal is much more variable. Density will be a function of tissue (nonchanging signal) and blood (changing signal), and changing density will be a function of changing blood. Finally, the blood density change is determined by both perfusion pressure and vasomotor tone.[25] POP waveform also depends on outside light absorption. In our study, attention was paid to all of these parameters. The pulse oximeter was wrapped to prevent outside light from interfering with the signal, gain was maintained constant during POP waveform recording, and the perfusion index was always greater than 1.0. Moreover, one can postulate that vascular tone is constant throughout a single respiratory cycle and that it does not impact the minimal and maximal pulse oximeter waveform amplitudes during the same respiratory cycle. Another important point is that the POP waveform is unitless. However, because ΔPOP assesses relative changes in POP waveform amplitude, it can be used whatever the unit.[18–21]

We chose to record the POP waveform at the finger, and we consistently did it over the 25 studied patients. This is of major importance because it is now known that these variations depend on the site of measurements.[17] Shelley *et al.*[17] recently demonstrated that respiratory variations in POP waveform can be up to 10 times stronger in the region of the head when compared with the finger. Consequently, mixing the site of measurements may induce bias. Further studies evaluating the ear, forehead, and finger signal for fluid responsiveness prediction are required to answer this question.

We used a specific pulse oximeter model for this study. Whether our finding can be exported to other models cannot be answered. However, other authors using different models found similar results.[17,19,20,22] Further studies exploring this issue are warranted.

Finally, ΔPOP has to be calculated off-line because no monitor allows online estimation. Future studies are planned to elaborate and to test software for automated calculation of ΔPOP.

Study Limitations

As other indices relying on the respiratory variations of left ventricular stroke volume or its surrogate, ΔPOP cannot be calculated in patients with cardiac arrhythmia. Similarly, ΔPOP interpretation in patients with right ventricular failure must be cautious.

The threshold value of 13% 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 among studies and settings. To quote Solus-Biguenet *et al.*[20]: "ΔPP values ranging from 8 to 13% may constitute an inconclusive or 'gray zone'[30] where its predictive value is uncertain."

Finally, ΔPOP can only be performed in mechanically ventilated patients during general anesthesia. However, this situation reflects the most common situation encountered by the anesthesiologists in their daily practice.

In conclusion, ΔPOP seems to be a noninvasive and widely available index of fluid responsiveness in mechanically ventilated patients during general anesthesia. ΔPOP has potential clinical applications.

The authors thank all the physicians and nurse anesthetists from the Department of Anesthesiology (Louis Pradel Hospital, Hospices Civils de Lyon, Lyon, France) for their help and support during this study.

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