Poor Agreement between Respiratory Variations in Pulse Oximetry Photoplethysmographic Waveform Amplitude and Pulse Pressure in Intensive Care Unit Patients

Svein Aslak Landsverk, M.D.,* Lars O. Hoiseth, M.D.,† Per Kvandal, M.D.,‡ Jonny Hisdal, Ph.D.,§ Oivind Skare, Ph.D.,¶ Knut A. Kirkeboen, M.D., Ph.D.#

Background: To identify fluid responsiveness, a correlation between respiratory variations in pulse pressure (ΔPP) and respiratory variations in pulse oximetry photoplethysmographic waveform amplitude (ΔPOP) in mechanically ventilated patients has been demonstrated. To evaluate the agreement between the two methods, knowledge about the repeatability of the methods is imperative. However, no such data exist. Based on knowledge of slow oscillation in skin blood flow, the authors hypothesized that the variability of ΔPOP would be larger than that of ΔPP when calculations were performed continuously over a long recording period.

Methods: Respiration, continuous invasive blood pressure, pulse oximetry, and skin microcirculation were recorded in 14 mechanically ventilated intensive care unit patients. No intravenous fluid challenges were given, and no other interventions were performed during the measurements. Seventy consecutive comparisons between ΔPP and ΔPOP were calculated for each of the 14 patients.

Results: For all patients, ΔPOP was 13.7 ± 5.8% and ΔPP was 5.8 ± 2.6% (P < 0.001). There was a larger intraindividual (8.94 vs. 1.29; P < 0.001) and interindividual (26.01 vs. 5.57; P < 0.001) variance of ΔPOP than of ΔPP. In six patients, there was no significant correlation between ΔPP and ΔPOP. A Bland-Altman plot showed poor agreement between the two methods.

Conclusion: A large variability of ΔPOP and a poor agreement between ΔPP and ΔPOP limits ΔPOP as a tool for evaluation of fluid responsiveness in intensive care unit patients. This is in contrast to ΔPP, which shows a small variability.

RESPIRATORY variations in pulse pressure (ΔPP) are better able to predict fluid responsiveness in mechanically ventilated patients compared with static parameters, such as central venous pressure and pulmonary artery occlusion pressure.1 As a noninvasive method, monitoring respiratory variations in pulse oximetry photoplethysmographic waveform amplitude (ΔPOP) has been proposed as an alternative. Several studies have demonstrated correlations between ΔPP and ΔPOP.2–4 However, there is an ongoing debate about whether ΔPOP can be used to identify fluid responsiveness. The controversies relate to the site of measurement; the different technologies used in commercial pulse oximeters; the extent to which these respiratory variations are influenced by other mechanisms, such as sympathetic vasoconstriction; and the threshold value that indicates fluid responsiveness.2–4 Another issue, seldom addressed in method comparison studies, is the repeatability of each method. Larger variability in one of the methods will make the agreement between them poor. Therefore, if ΔPOP is to be applied in a clinical setting, the agreement of ΔPP and ΔPOP must also include within-subject, or intraindividual variability, as well as interindividual variability. To our knowledge, the variability of ΔPOP compared with ΔPP, in a time frame that could be comparable to a bedside evaluation of fluid responsiveness, has not been reported in intensive care unit (ICU) patients. The aim of the current study was, therefore, to explore the variability of ΔPP and ΔPOP in a registration period of approximately 15 min in ICU patients.

Based on our knowledge of oscillation in skin microcirculation, we hypothesized that slow oscillations in acral skin blood flow should induce a larger variability in ΔPOP than in ΔPP.6 To improve the detection of these oscillations, we measured finger skin blood flow with laser Doppler flowmetry (LDF). We also examined the relation between acral skin microcirculation in fingertips and variability in ΔPOP.

Materials and Methods

Subjects

The study was performed in an ICU at Ulleval University Hospital, Oslo, Norway, and approved by the local ethics committee. Written, informed consent was obtained from the patient’s next of kin. A heterogeneous group of 14 deeply sedated ICU patients on controlled mechanical ventilation were included in the study (Motor Activity Assessment Scale: 0–1). Exclusion criteria were cardiac arrhythmias. All patients included had ΔPP values below a threshold limit of 13%,2 indicating that they would not respond to fluid. The characteristics of the patients are given in table 1.

Protocol

Recordings were made with subjects in a supine position in the ICU. All patients were ventilated with tidal volumes of approximately 8 ml/kg. Either volume-
pressure-controlled ventilation was used. The patients were sedated with fentanyl, midazolam, and/or propofol. All patients were monitored using standard equipment (Marquette Solar 8000i; GE Healthcare, Bucks, United Kingdom), including electrocardiogram, invasive blood pressure from the radial artery, and pulse oximetry (OxiMax 451N5; Nellcor, Boulder, CO). The pulse oximetry probe was attached to the index finger. Repeat (OxiMax 451N5; Nellcor, Boulder, CO). The pulse oximetry photoplethysmographic waveform; ScvO2 was measured from the thumb. No skin temperature was measured. To detect the impact of oscillations in acral skin blood flow on ΔPOP, LDF was measured on the pulp of the thumb bilaterally. Measurements were recorded once for 15 min in each patient. No intravenous fluid challenges were given, and no other interventions were performed during the measurements. No other clinical alterations were recognized in any of the patients in this period.

Laser Doppler Flowmetry
Laser Doppler flowmetry gives a semiquantitative measurement of microvascular blood perfusion, expressed in arbitrary units. LDF measurements from the skin reflect perfusion in capillaries, arterioles, venules, and the dermal vascular plexus. A major part of the signal reflects thermoregulatory perfusion. The LDF measurements were obtained with a two-channel flowmeter (MoorLAB server/satellite; Moor Instruments, Axminster, Devon, United Kingdom). A sampling frequency of 40 Hz and a time constant of 0.1 s were used. In addition to detect changes in perfusion, an average value of LDF for the whole recording was calculated in each patient (table 1).

Data Acquisitions and Analyses
Data were transferred from the analog output of the Marquette monitor and the Moorlab server to an analog-to-digital converter (NI-DAQPad-6015; National Instruments, Austin, TX) and then to a laptop personal computer using data acquisition software (VI logger; National Instruments). Calculations of ΔPP and ΔPOP were performed in a custom-made program in LAB VIEW version 8.2 (National Instruments). A respiratory cycle was chosen manually, and the program would then display the corresponding blood pressure, pulse oximetry photoplethysmographic waveform, and LDF curve. ΔPP was calculated as described by Michard et al.9: ΔPP (%) = 100 × ([PPmax − PPmin]/[(PPmax + PPmin)/2]). Pulse pressure (PP) was defined as the difference between systolic and diastolic arterial pressures. Maximal PP (PPmax) and minimal PP (PPmin) values were determined over the same respiratory cycle.

Pulse oximetry photoplethysmographic (POP) waveform amplitude, expressed in millimeters, was measured from beat to beat as the vertical distance between peak and preceding valley through the waveform. Maximal POP (POPmax) and minimal POP (POPmin) were determined over the same respiratory cycle. ΔPOP was calculated using a formula similar to that for ΔPP: ΔPOP (%) = 100 × ([POPmax − POPmin]/[(POPmax + POPmin)/2]). ΔPP and ΔPOP were calculated automatically for each respiratory cycle and then average over three consecutive respiratory cycles, giving the final values. From the start of each of the 14 recordings, calculations of ΔPP and ΔPOP were performed continuously and time-syn-

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Table 1. Characteristics of All Patients Included in the Study

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Sex</th>
<th>Cause of Admittance</th>
<th>ScvO2, %</th>
<th>PEEP, cm H2O</th>
<th>MAP, mmHg</th>
<th>HR, beats/min</th>
<th>Temperature, °C</th>
<th>LDF, AU</th>
<th>Slow Oscill, µg · kg -1 · min -1</th>
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<tr>
<td>1</td>
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<td>M</td>
<td>Sickle cell crisis</td>
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<td>10</td>
<td>95</td>
<td>78</td>
<td>36.7</td>
<td>3.2</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>M</td>
<td>Trauma</td>
<td>80</td>
<td>8</td>
<td>87</td>
<td>58</td>
<td>38.1</td>
<td>3.3</td>
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<tr>
<td>3</td>
<td>19</td>
<td>M</td>
<td>Intoxication</td>
<td>78</td>
<td>16</td>
<td>92</td>
<td>99</td>
<td>37.6</td>
<td>2.9</td>
<td>+</td>
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<tr>
<td>4</td>
<td>20</td>
<td>F</td>
<td>Trauma</td>
<td>76</td>
<td>8</td>
<td>81</td>
<td>60</td>
<td>37.2</td>
<td>2.7</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>19</td>
<td>M</td>
<td>Trauma</td>
<td>78</td>
<td>5</td>
<td>95</td>
<td>60</td>
<td>36.4</td>
<td>2.7</td>
<td>+</td>
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<td>F</td>
<td>SAH</td>
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<td>7</td>
<td>84</td>
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<td>37.6</td>
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<tr>
<td>8</td>
<td>79</td>
<td>M</td>
<td>Trauma</td>
<td>81</td>
<td>10</td>
<td>85</td>
<td>63</td>
<td>37.8</td>
<td>5.7</td>
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<tr>
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<td>SAH</td>
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<td>Trauma</td>
<td>78</td>
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<td>63</td>
<td>81</td>
<td>36.4</td>
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<tr>
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<td>F</td>
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<td>76</td>
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<td>14</td>
<td>59</td>
<td>F</td>
<td>Trauma</td>
<td>85</td>
<td>7</td>
<td>72</td>
<td>66</td>
<td>37.7</td>
<td>1.6</td>
<td>+</td>
</tr>
</tbody>
</table>

Mean ± SD 39 ± 20 80 ± 4 8 ± 3.4 87 ± 12 78 ± 18 37.4 ± 0.7 3.6 ± 2.1

Data are mean ± SD.

AU = arbitrary units; D = dopamine; GTN = glyceryl nitrate; HR = heart rate; LDF = laser Doppler flowmetry; MAP = mean arterial pressure; NE = norepinephrine; PEEP = positive end-expiratory pressure; SAH = subarachnoid hemorrhage; Slow Oscill. = slow, large oscillations present in laser Doppler flowmetry and pulse oximetry photoplethysmographic waveform; ScvO2 = central venous oxygen saturation.
chronized until 70 pairs of comparisons between ΔPP and ΔPOP (based on 210 respiratory cycles) were obtained. This gave a total of 980 pairs of comparisons. The interobserver variability of the method for ΔPP and ΔPOP was evaluated independently by two of the authors in four patients. Threshold values of 13% for ΔPP and 15% for ΔPOP were chosen according to previous data.2

Statistics

Values are presented as mean ± SD unless otherwise stated. A correlation between ΔPP and ΔPOP for each patient was calculated using a Pearson correlation coefficient. A linear regressions analysis was performed between ΔPP and ΔPOP for each patient. Intraindividual and interindividual variances were calculated by a linear mixed model for repeated measures, using the lme function in R.10 Mixed models take into account the dependency in repeated measurements by adding variance components (random effects). Here, a variance component was added for individuals. The overall variance was then divided into two terms, intraindividual and interindividual.11 The comparison of the two methods is shown by a Bland–Altman plot.12 Two sets of lines, representing limits of agreement, are independent of the increase in average values. The other is regression based, representing situations where the difference between the methods changes with increasing average values.13 In both cases, the limits of agreement were adjusted for the mixture of between- and within-subjects values according to Bland-Altman.13 However, instead of analysis of variance, a linear mixed model for repeated measures, using the lme function, was used.14 For all statistical procedures, P ≤ 0.05 was considered significant. Statistical calculations were performed with SPSS 14.0 (SPSS Inc., Chicago, IL) and R version 2.5.1.**

Results

The causes of admittance for the 14 patients are given in table 1, together with mean arterial blood pressure, heart rate, temperature, and LDF. All patients with doses of norepinephrine higher than 0.1 μg·kg⁻¹·min⁻¹ had intracranial pressure monitoring because of injury or hemorrhage. The need for increased arterial blood pressure for these patients contributed to the high doses of norepinephrine. Before and during the recording period, the patients were hemodynamically stable, vasoactive drugs were not altered, and fluid expansion was not given.

The two first columns of table 2 give mean ± SD for ΔPP and ΔPOP for the 14 patients. For the whole group, ΔPP was 5.8 ± 2.6% and ΔPOP was 13.7 ± 5.8% (P < 0.001). Intraindividual variance for ΔPOP was 8.94 versus 1.29 for ΔPP (P < 0.001), and interindividual variance for ΔPOP was 26.01 versus 5.57 for ΔPP (P < 0.01). The distribution of all values of ΔPP and ΔPOP (from all patients) is shown in a histogram (fig. 1), including two vertical lines representing threshold limits for fluid responsiveness.2 The proportion of the ΔPP and ΔPOP values related to established threshold limits could then be evaluated. The ΔPP values had 0.7% of the cases above the 13% threshold value, whereas 39% of the ΔPOP values were above the 15% threshold.

Figure 2 shows regression lines between ΔPP and ΔPOP in all of the 14 patients and illustrates the relation between the two variables. In figure 3, the two methods

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are compared in a Bland–Altman plot. The difference between the two methods increases with increasing average values. If the limits of agreement are calculated independently of this, the mean value is 7.9%, and the horizontal lines of agreement show a range of approximately 25%. When using regression-based limits of agreement to adjust for the increased average values, the interval of the limits was narrowed to approximately 19%.

In six patients, there was no significant correlation between ΔPP and ΔPOP, and for the total values of ΔPP and ΔPOP, there was no significant correlation. In eight patients, there were significant positive correlations between ΔPP and ΔPOP, and for the total values of ΔPP and ΔPOP, there was no significant correlation. In eight patients, there were significant positive correlations between ΔPP and ΔPOP, and six of these (patients 4, 6, 8, 10, 12, and 14) had average values below the threshold limit of 15% (table 2). There were no significant differences in these six patients’ characteristics compared with the whole group regarding LDF values (4.1 ± 2.7 vs. 3.2 ± 1.5; P = 0.43), temperature (37.5 ± 0.6 vs. 37.2 ± 3.7; P = 0.51), norepinephrine doses (0.14 ± 0.11 vs. 0.19 ± 0.18; P = 0.52), or central venous oxygen saturation values (82 ± 5% vs. 79 ± 4%; P = 0.29).

Laser Doppler flowmetry values from table 1 and mean values of ΔPOP from table 2 were also correlated, giving a Pearson correlation coefficient of −0.19 (P = 0.51).

Interobserver variability between two investigators was evaluated in four patients. This comparison showed no significant difference in mean ± SD for either ΔPP (4.8 ± 2.2 vs. 4.9 ± 2.2; P = 0.72) or ΔPOP (16.8 ± 7.4 vs. 17.1 ± 6.9; P = 0.79).

**Discussion**

The main finding in this observational study is the large intraindividual and interindividual variability in ΔPOP compared with ΔPP in a heterogeneous group of ICU patients. As many as 39% of the ΔPOP values were above...
the threshold limit of 15%, whereas only 0.7% of the ΔPP values were above the 13% threshold limit. Therefore, more than every third calculation of ΔPOP indicated that the patients would respond to fluid, when ΔPP indicated the opposite. Averaging ΔPOP over more than three respiratory cycles would not improve this method, because 6 of the 14 patients had total average ΔPOP values above 15%. Increasing the threshold limit for ΔPOP would not improve this method either, because the correlation between ΔPP and ΔPOP was weak or non-existent in 6 of the 14 patients. The relation between the two methods is illustrated in the Bland–Altman plot (fig. 3) where the difference between the two methods increases with increasing mean values. The limits of agreement are unacceptably wide for ΔPOP measurements to be applied in a clinical setting, regardless of which model was used to estimate them.

Our results contrast with the findings in three previous studies,2,14,15 where there was a significant correlation between ΔPP and ΔPOP. These studies were performed in deeply sedated ICU patients or postoperative patients. In the study by Cannesson et al.2 and Wyffels et al.,15 there was no detailed information on how the values of ΔPP and ΔPOP were selected from the recordings. In the study by Feissel et al.,14 calculation of ΔPOP was, as far as we understand, based on randomly selected respiratory cycles. In contrast to our study, the patients in the studies by both Feissel et al.14 and Wyffels et al.15 were more homogenous regarding cause of admission to the ICU. Fluid challenges were also used in these two studies to evaluate fluid responsiveness.

Different medications, dosages, causes of admission to the ICU, and pulse oximetry technologies could explain some of the difference between these studies and ours. However, we believe that an important reason for the different findings relates to the fact that we performed continuous calculations over a longer registration period and therefore were able to test the repeatability of ΔPP and ΔPOP. In accord with our results, it should be difficult to interpret an agreement between the two methods in ICU patients based on few randomly selected respiratory cycles. However, our study also shows that the repeatability of ΔPP is very good, and therefore very robust in different clinical situations.

Our results cannot be directly transferred to a population of surgical patients in general anesthesia, which would probably be the target group for using ΔPOP, as a noninvasive method to evaluate fluid responsiveness. During general anesthesia, intraindividual variation could be less than described in this study, because of a more suppressed sympathetic nervous system and less use of vasoactive drugs. No studies have reported intraindividual variation of ΔPOP during general anesthesia. However, a method for detection of fluid responsiveness perioperatively should be independent of the different clinical situations in the operating room, such as surgical stress reactions due to different levels of anesthesia, vasoactive drugs, or other medical interventions. Comparing the two methods on a heterogeneous group of ICU patients is therefore useful when trying to implement the method perioperatively.

Identifying the mechanisms that contributed to lack of agreement would be of interest. The amplitude of the pulse oximetry plethysmographic waveform is influenced by changes in vascular tone from all tissue compartments present in the fingertip, and vasoconstriction narrows the amplitude of the waveform. These changes can create large oscillations in skin microcirculation and were seen in 6 of the 14 patients in our study. This can be further illustrated by spectral analyzing the pulse oximetry photoplethysmographic waveform, where oscillatory components slower than those of the heartbeat and respiration are present (fig. 4). This is similar to what can be seen in skin microcirculation.6,16 Slow oscillations are related to the sympathetic nervous system and local vascular control mediated from the vascular wall, known as vasomotion. Sedative and anesthetic drugs impair these oscillations.17 To detect these oscillations, we focused on the skin microcirculation in the finger pulp, due to the presence of the highly innervated arteriovenous anastomoses. This can easily be detected with LDF. The slow oscillations, especially the large, sympathetic oscillations, can influence the calculation of ΔPOP. This can be seen when vasoconstriction occurs during a respiratory cycle which narrows the amplitude and increases ΔPOP (fig. 5). Even though this effect is reduced by averaging POP over three respiratory cycles, it is probably one of the mechanisms for the large vari-

Fig. 4. The pulse oximetry plethysmographic waveform signal from patient 14 is spectral analyzed in this three-dimensional wavelet transform. This figure illustrates the presence of large oscillations, slower than the heartbeat (1 Hz) and respiration (0.2 Hz). These oscillations are related to the sympathetic nervous system and those generated within the vascular wall and have the potential to increase the variability of respiratory variations in pulse oximetry photoplethysmographic waveform amplitude.
Spectral analyzing techniques have been tried that could identify the “pure” respiratory impact on this signal. Further investigations of these methods could be useful.

**Methodologic Considerations**

\(\Delta PP\) and \(\Delta POP\) were calculated with custom-made software in this study. Each respiratory cycle, with a corresponding interval of blood pressure and photoplethysmographic waves, was chosen manually. The calculations were then made automatically. Therefore, subjective decisions in defining which waves correspond to each respiratory cycle and starting the calculations at different respiratory cycles would give different values for \(\Delta PP\) and \(\Delta POP\). However, the average values and SD were almost identical when interobserver variability was evaluated.

The pulse oximeter used in this study has filters built in, like other commercial pulse oximeters, and the signal from the analog output is therefore not a “raw signal.” We cannot exclude the possibility that the respiratory variations could have been altered by the preprocessing. However, the pulse oximeter used in this study did not filter out respiratory variations, and the fact that some of the patients presented good correlations between \(\Delta PP\) and \(\Delta POP\) shows that the technology used in this pulse oximeter is not inferior in detecting \(\Delta POP\), compared with other pulse oximeters used in previous studies. A Nellcor OxiMax pulse oximeter was also used in the study by Cannesson et al.\(^5\)

To quantify vascular tone with LDF has limitations. LDF is a semiquantitative measurement. The LDF probe was also attached to the neighbor finger. Because of variations in skin microcirculations at different sites, perfusion values must be interpreted with caution. We could have placed the LDF probe on the finger together with the pulse oximeter. However, because there is little knowledge of how the two methods could interact, placement on separate fingers was chosen.

Because of our primary aim of investigating agreement between the two methods in a heterogeneous group of ICU patients, the patients were characterized by large variations in positive end-expiratory pressure, vasoactive medication, sedative drugs, and temperature that could influence this agreement. We believe that further de-
telled description of the characteristics, or discussion of the impact of each of them, would have limited information, because the number of patients included was few.

Conclusion

Large variability of \( \Delta \text{POP} \) and poor agreement between \( \Delta \text{PP} \) and \( \Delta \text{POP} \) limit the calculation of \( \Delta \text{POP} \) as a potential noninvasive tool for evaluation of fluid responsiveness in ICU patients. This is in contrast to \( \Delta \text{PP} \), which shows small variability. We recommend that future studies using \( \Delta \text{POP} \), as a method to identify fluid responsiveness, should document intraindividual variation.

The authors thank Lawrence Sheppard (Ph.D. Student, Department of Physics, Lancaster University, United Kingdom) for wavelet analyses.

References