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ORIGINAL RESEARCH

Respiratory variations in the photoplethysmographic waveform amplitude depend on type of pulse oximetry device

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Abstract Respiratory variations in the photoplethysmographic waveform amplitude predict fluid responsiveness under certain conditions. Processing of the photoplethysmographic signal may vary between different devices, and may affect respiratory amplitude variations calculated by the standard formula. The aim of the present analysis was to explore agreement between respiratory amplitude variations calculated using photoplethysmographic waveforms available from two different pulse oximeters. Analysis of registrations before and after fluid loads performed before and after open-heart surgery (aortic valve replacement and/or coronary artery bypass grafting) with patients on controlled mechanical ventilation. Photoplethysmographic (Nellcor and Masimo pulse oximeters) and arterial pressure waveforms were recorded. Amplitude variations induced by ventilation were calculated and averaged over ten respiratory cycles. Agreements for absolute values are presented in scatterplots (with least median square regression through the origin, LMSO) and Bland–Altman plots. Agreement for trending presented in a four-quadrant plot. Agreement between respiratory photoplethysmographic amplitude variations from the two pulse oximeters was poor with LMSO $\Delta POP_{Nellc} = 1.5 \times \Delta POP_{Mas}$ and bias ± limits of agreement 7.4 ± 23 %. Concordance rate with a fluid load was 91 %. Agreement between respiratory variations in the photoplethysmographic waveform amplitude calculated from the available signals output by two different pulse oximeters was poor, both evaluated by LMSO and Bland–Altman plot. Respiratory amplitude variations from the available signals output by these two pulse oximeters are not interchangeable.

Keywords Aortic valve stenosis · Blood volume · Coronary artery bypass · Monitoring · Physiologic · Photoplethysmography

1 Introduction

Dynamic variables predict fluid responsiveness in mechanically ventilated patients [1]. Many patients are not equipped with arterial catheters necessary to calculate pulse pressure variations (ΔPP) [2]. Respiratory variations in the photoplethysmographic waveform amplitude have been explored as a non-invasive alternative [3] and recommended for clinical use [4].

The photoplethysmographic waveform represents variations in the amount of infrared light detected after being transmitted through tissue [5], predominantly due to variations of blood volume [6, 7]. Respiratory variations in the photoplethysmographic waveform amplitude (ΔPOP) are calculated as the difference between the maximal and minimal amplitudes (trough to peak) divided by their mean, expressed as a percentage. Both for ΔPP and ΔPOP, it is assumed that variations in the waveform amplitude through a respiratory cycle reflect variations in left ventricular stroke volume (SV). The photoplethysmographic waveform is however a complex signal which may, depending on the measurement site, also reflect other

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phenomena such as sympathetic nervous activity and venous blood volume [8–10].

Different groups using different pulse oximeters have studied ΔPOP. When calculating ΔPOP, one needs to have access to the photoplethysmographic waveform, and typically, auto-centering and auto-scaling functions (which otherwise makes it look tidy on the monitor) are disabled. However, signals are still processed by the devices before output from the pulse oximeter. It has not been thoroughly studied if this processing affects calculation of ΔPOP.

Pleth variability index (PVI) is a commercially available variable given by the Masimo Radical 7 pulse oximeter [11] and calculated as the difference between the maximal and minimal perfusion index (PI)-values within at least one respiratory cycle divided by the maximal PI-value. PI is the fraction of the pulsatile compared to the non-pulsatile infrared signal [11]. The calculation of PVI thus differs slightly from that of ΔPOP. In a systematic review and meta-analysis, Sandroni et al. [12] concluded that ΔPOP and PVI were equally effective to predict fluid responsiveness in ventilated adult patients in sinus rhythm. The authors suggested that the main limitation was the volume of the fluid bolus, although influence of different pulse oximetry technologies was discussed. A possible influence of different pulse oximeters on calculation of ΔPOP has not been extensively studied [13].

In a study on fluid responsiveness in cardiac surgery patients [14], photoplethysmographic waveforms were sampled from two different commercially available pulse oximeters (Nellcor and Masimo). The aim of the present analysis was to explore the agreement between ΔPOP from these two devices (ΔPOP$_{Nellc}$ and ΔPOP$_{Mas}$, respectively) for absolute values and when trending a fluid load. PVI was also recorded. Furthermore, photoplethysmographic variables were compared to ΔPP.

2 Materials and methods

2.1 Patients

Data were collected in a study on fluid responsiveness in aortic stenosis (AS) patients [14]. Approval was given by the regional ethics committee (Regional Ethical Committee Sør-Øst C, Pb 1130 Blindern, 0318 Oslo, Norway; reference 2010/1629). After written informed consent, 43 patients were included; 32 scheduled for aortic valve replacement due to AS [with or without concomitant coronary artery bypass grafting (CABG)] and 11 patients scheduled for CABG only. Patients were >18 years, had sinus rhythm at inclusion, left ventricular ejection fraction >40 % and no suspected right heart failure.

2.2 Study protocol

Patients were premedicated with morphine/scopolamine. After induction of general anesthesia with diazepam, fentanyl and propofol, patients were mechanically ventilated in a volume-controlled mode, and anesthesia maintained with sevoflurane 1–1.5 %. Before surgery, patients were placed in the horizontal position, and a fluid load performed by rapid infusion of 750 ml acetated Ringer's solution via a peripheral vein. Registrations were obtained before and after the fluid load, and completed before surgery was commenced.

After surgery, patients were taken to the intensive care unit (ICU) and mechanically ventilated in a pressure-controlled mode. Registrations were obtained before and after fluid loads, which were performed with a smaller volume than the preoperative load (500 ml acetated Ringer's solution, 250 ml hydroxyl ethyl starch 130/0.4, 250 ml packed red blood cells or 250 ml plasma). Registrations were obtained if patients were on no or stable infusions of sedative and vasoactive drugs.

2.3 Signal acquisition and analysis

In the operating room (OR), a 5-lead ECG was attached and a 20G catheter placed in the left radial artery. Finger probes (DS-100A; Nellcor, Boulder, CO, USA) from a Nellcor pulse oximeter (Nellcor OxiMax/Tram451N; General Electric Healthcare, Milwaukee, WI, USA) and Masimo Radical 7, software 7.3.1.1 with a LNOP DC-I probe (Masimo Corp., Irvine, CA, USA) were placed on the right 2 and 3 fingers and covered from ambient light. Photoplethysmographic waveform from the Nellcor pulse oximeter and arterial pressure waveform were extracted from the analog output of a TramRac4A (General Electric Healthcare). Photoplethysmographic waveform from the Radical 7 was extracted by its analog output. Waveforms were sampled via a NIDAQPad-6015 analog–digital converter (National Instruments, Austin, TX, USA) at 400 Hz and stored on a laptop computer. ΔPOP and ΔPP were calculated in a custom made program in LabVIEW (National Instruments), where each respiratory cycle (determined by the thoracic impedance from the ECG-leads), was manually delimitated and the maximal and minimal amplitudes of the waveforms verified before calculating ΔPOP and ΔPP. ΔPOP and ΔPP were calculated as follows:

$$\Delta POP = \frac{POPmax - POPmin}{\frac{POPmax + POPmin}{2}} \times 100 \%$$

$$\Delta PP = \frac{PPmax - PPmin}{\frac{PPmax + PPmin}{2}} \times 100 \%$$

Table 1 Patient characteristics (n = 38)

Female [n (%)]	9 (24)
Age (years)	66 (11)
Height (cm)	174 (8)
Weight (kg)	80 (12)
Tidal volume (ml/kg ideal body weight)	9.0 (0.9)

Data are mean (SD) unless otherwise stated

Table 2 Hemodynamic measurements

	Before fluid load	After fluid load	p
MAP (mmHg)	61 (12)	70 (13)	<0.001
CVP (mmHg)	7.2 (6–10)	10 (8–12)	<0.001
SV (ml)	65 (51–89)	83 (58–104)	<0.001
ΔPP (%)	11 (5)	6 (3)	<0.001
ΔPOP$_{Nellc}$ (%)	19 (11–27)	12 (8–18)	<0.001
ΔPOP$_{Mas}$ (%)	10 (8–17)	7 (4–9)	<0.001
ΔPVI (%)	11 (7–14)	8 (5–11)	0.025

Data are mean (SD) or median (25th–75th percentiles) after performing Kolmogorov–Smirnov test for normality. Comparisons by paired samples t test or Wilcoxon test

MAP mean arterial pressure, *CVP* central venous pressure, *SV* stroke volume, *ΔPOP$_{Nellc}$* respiratory photoplethysmographic waveform amplitude variations by Nellcor pulse oximeter, *ΔPOP$_{Mas}$* respiratory photoplethysmographic waveform amplitude variations by Masimo pulse oximeter, *ΔPP* pulse pressure variation, *PVI* pleth variability index

POP$_{max}$ and PP$_{max}$ are maximal and POP$_{min}$ and PP$_{min}$ minimal amplitudes of the photoplethysmographic and arterial pressure waveforms within one respiratory cycle, respectively.

SV was measured by an oesophageal Doppler (DP-12 probe; CardioQ; Deltex Medical, Chichester, UK). An increase in SV >15 % with the fluid load defined a responder. Data were downloaded beat-by-beat from the serial output of the oesophageal Doppler monitor. PVI was downloaded at 0.5 Hz by the TrendCom software (Masimo). Other hemodynamic data were downloaded at 1 Hz from a Solar 8500 or 9000 (General Electric Healthcare), using custom made software in LabVIEW (National Instuments).

ΔPOP and ΔPP-values were averaged over 10 respiratory cycles ($\approx$ 1 min). Respiratory cycles with extrasystoles or obvious disturbances were omitted. SV, PVI and other hemodynamic data were averaged over 1 min. Registrations were made before and after the fluid loads, giving two observations per fluid load.

2.4 Statistics

Bland–Altman calculations were performed in MedCalc Statistical Software version 13.0.6 (MedCalc Software bvba, Ostend, Belgium) with multiple measurements per subject [15]. Bias values in Bland–Altman plots were compared by unpaired t tests, unequal variances assumed. Limits of agreement compared by F tests. Trending abilities are presented using a four-quadrant plot where the concordance rate represents the fraction of observations (outside a central exclusion zone) in the upper right and lower left quadrants. Cutoff for trending fluid responsiveness for ΔPP has been estimated to approximately 3 % [16]. We are not aware of corresponding data for ΔPOP, but arbitrarily set the central exclusion zone to 5 %. Abilities to predict fluid responsiveness are presented as areas under receiver operating characteristics curves (AUC$_{ROC}$) with 95 % exact binomial confidence intervals. Least median squares regressions through the origin (LMSO) [17] were performed in the MASS package in R 3.1.2 (R Foundation for Statistical Computing, Vienna,

Austria). As data were sampled in another study, separate sample size-calculations were not performed for the analyses in the present manuscript.

3 Results

One patient in the AS group was excluded due to arterial waveform dampening and in four patients, analog data were lost, giving 38 patients for analysis (27 in the AS group and 11 in the CABG-group). In one CABG-patient, analog data before the preoperative fluid load were lost. In one AS patient, the Masimo pulse oximeter (ΔPOP$_{Mas}$ and PVI) did not function during a postoperative fluid load. One AS-patient had frequent extrasystoles before surgery, and was only studied postoperatively. One preoperative fluid load was performed in each patient (26 in AS-patients and 11 in CABG-patients). Postoperatively, 27 fluid loads were performed in 19 AS patients, and three fluid loads were performed in three CABG-patients. Patient characteristics are presented in Table 1, hemodynamic data in Table 2.

Scatterplots with LMSO are presented in Fig. 1. Results from Bland–Altman plots are presented in Fig. 2 and Table 3. There were wide limits of agreement between ΔPOP$_{Nellc}$ and ΔPOP$_{Mas}$ with bias $\pm$ LOA 7.4 $\pm$ 23 % and a percentage error of 164 %. Results from AS-patients and CABG-patients are also presented separately (Table 3).

The agreement between ΔPP and the photoplethysmographic variables (ΔPOP$_{Nellc}$, ΔPOP$_{Mas}$ and PVI) was calculated and compared. The bias was higher (unpaired
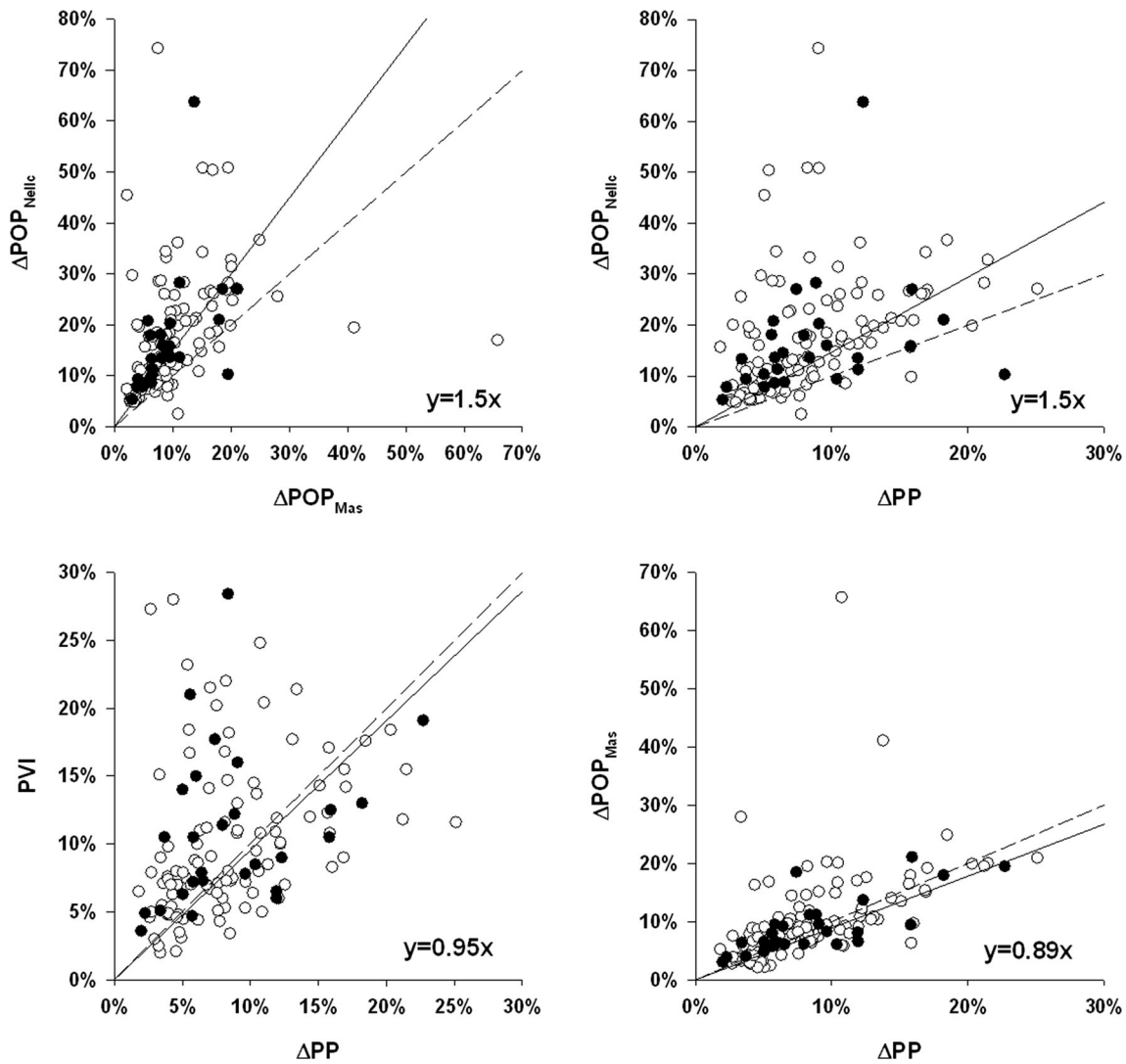
Fig. 1 Scatterplots with lines of identity (y = x) dashed, and least mean squares regression lines through the origin (LMSO) solid. Regression coefficient is for LMSO slope. *Black dots* are from coronary artery bypass grafting patients, *circles* are from aortic stenosis patients. ΔPOP_{Nellc} respiratory photoplethysmographic waveform amplitude variations by Nellcor pulse oximeter, ΔPOP_{Mas} respiratory photoplethysmographic waveform amplitude variations by Masimo pulse oximeter, *PVI* pleth variability index, ΔPP pulse pressure variation

t tests, unequal variances assumed, both $p < 0.001$) and limits of agreement were wider (F tests, both $p < 0.001$) for ΔPP versus ΔPOP_{Nellc} than for both ΔPP versus PVI and ΔPP versus ΔPOP_{Mas}.

Assessment of trending with fluid loads is presented in Fig. 3. Concordance rate was 91 %. The abilities to predict fluid responsiveness are presented in Table 4.

4 Discussion

The main finding of this analysis was the poor agreement between ΔPOP calculated from two different commercially available pulse oximeters both judged by LMSO and

Bland–Altman plots. ΔPOP_{Mas} agreed better than ΔPOP_{Nellc} with ΔPP. The results indicate that the photoplethysmographic waveform from the two pulse oximeters cannot be used interchangeably to calculate ΔPOP.

ΔPOP has been explored as a non-invasive alternative to ΔPP or SV variation [3, 13]. The photoplethysmographic waveform is however influenced by other phenomena than respiratory variations in SV [6, 10, 18, 19]. The photoplethysmographic signal presented on the monitor screen as well as the signals extracted from analog outputs are highly processed, e.g. by bandpass filtering, auto-centering and amplitude adjustment [20]. As stated by Feldman [21], signal processing in commercial, proprietary algorithms complicates the use of these devices in research. From a
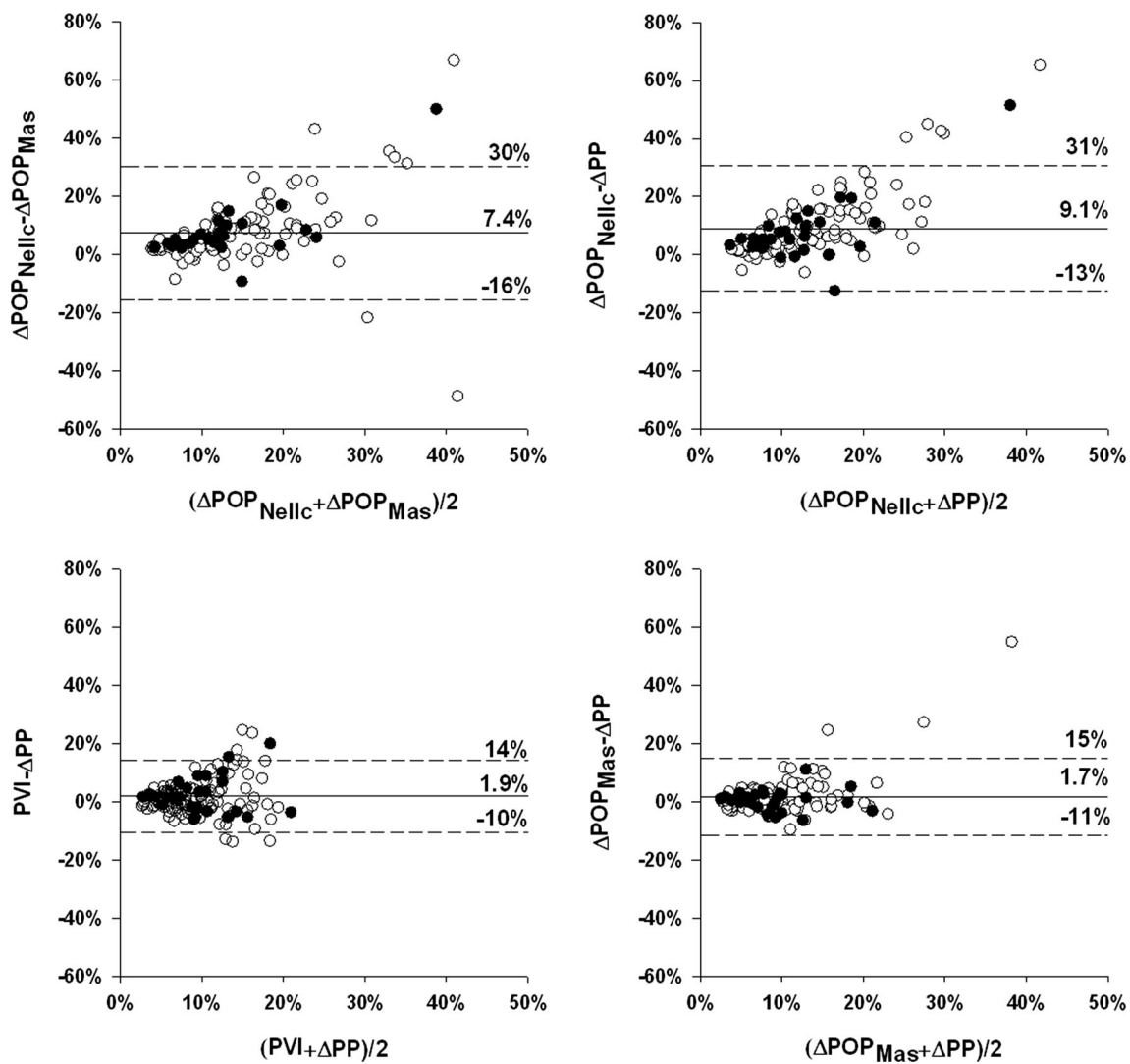
Fig. 2 Bland–Altman plots. *Solid lines* are bias and *dashed lines* are limits of agreement. *Black dots* are from coronary artery bypass grafting patients, *circles* are from aortic stenosis patients. *ΔPOP_Nellc* respiratory photoplethysmographic waveform amplitude variations by Nellcor pulse oximeter, *ΔPOP_Mas* respiratory photoplethysmographic waveform amplitude variations by Masimo pulse oximeter, *PVI* pleth variability index, *ΔPP* pulse pressure variation

clinical point of view, all the devices (and software versions) may need to be validated for relevant end points before clinical implementation. From a research point of view, the proprietary signal processing complicates physiological interpretation.

Processing of photoplethysmographic signals probably vary between the two measuring devices (an example presented in Fig. 4). Baseline variations with the respiration seem to be more pronounced in the signal from the Nellcor device, compared to the Masimo device, affecting calculation of ΔPOP. The Masimo Radical 7 pulse oximeter also calculates PVI, specifically intended to reflect respiratory SV variations. The photoplethysmographic signal may have been processed to reduce the influence of other phenomena, making this particular device especially prone to give different results compared to other pulse oximeters. As baseline modulations synchronous with respiration seemed to be more pronounced in the Nellcor photoplethysmographic signal, this signal was also analyzed after filtering with a 3rd order Butterworth highpass filter with 0.4 Hz cutoff. This did however not substantially improve the agreement with ΔPP (LMSO slope 1.4, Bland–Altman bias ± LOA 9.2 ± 19 %). Which signal processing is the best when using the photoplethysmographic signal to predict fluid responsiveness is beyond the scope of this article, but both amplitude modulations with each heartbeat as well as baseline modulations with respiration might be related to volume status [22]. Whether the complexity of the photoplethysmographic signal represents a limitation or an opportunity is

Table 3 Results of Bland–Altman plots

	n (observations)	Bias ± LOA (%)
ΔPOP_{Nellc} versus ΔPOP_{Mas}	132	7.4 ± 23
AS-patients	105	7.4 ± 24
CABG-patients	27	7.3 ± 20
ΔPOP_{Nellc} versus ΔPP	134	9.1 ± 22
AS-patients	107	9.4 ± 22
CABG-patients	27	7.8 ± 22
ΔPOP_{Mas} versus ΔPP	132	1.7 ± 13
AS-patients	105	2.0 ± 14*
CABG-patients	27	0.5 ± 6.9*
PVI versus ΔPP	129	1.9 ± 12
AS-patients	102	1.8 ± 12
CABG-patients	27	2.3 ± 13

Aggregated and separate analyses for aortic stenosis (AS) and coronary artery bypass grafting (CABG)-patients are presented

ΔPOP_{Nellc} respiratory photoplethysmographic waveform amplitude variations by Nellcor pulse oximeter, ΔPOP_{Mas} respiratory photoplethysmographic waveform amplitude variations by Masimo pulse oximeter, ΔPP pulse pressure variation, *PVI* pleth variability index

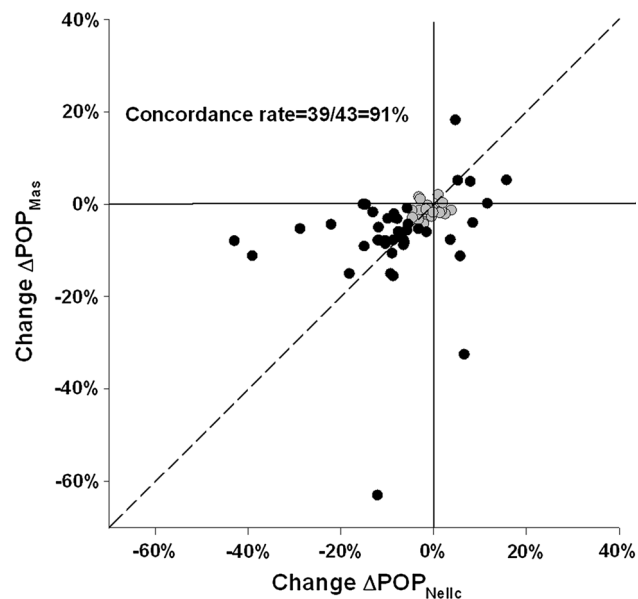* Significantly different limits of agreement ($p < 0.001$)

Fig. 3 Four quadrant scatterplot displaying the agreement between ΔPOP_{Mas} and ΔPOP_{Nellc} when trending a fluid load. A 5 % exclusion zone has been used in the calculations. Observations within the exclusion zone (marked as *grey circles*) are not used for calculations of concordance rate. ΔPOP_{Mas} respiratory photoplethysmographic waveform amplitude variations by Masimo pulse oximeter, ΔPOP_{Nellc} respiratory photoplethysmographic waveform amplitude variations by Nellcor pulse oximeter

discussed [7, 23]. The signal can be decomposed into frequencies representing the cardiac and respiratory cycles, respectively [7]. A respiratory-synchronous component can represent variations of blood volume in the venous compartment [10, 24]. If variations in SV are represented by variations in the cardiac-synchronous component, the venous component may pose a problem when using the ordinary formula to calculate ΔPOP. As some time passes from the trough to the peak in each cardiac cycle, variations in the respiratory component will cause the calculated amplitude to change, even though there is no variation in the cardiac component. This possible effect has been illustrated in a simple simulation using sine waves in Fig. 5.

ΔPOP and PVI have been recommended to predict fluid responsiveness [4]. The meta-analysis by Sandroni et al. [12] indicated that ΔPOP and PVI accurately predict fluid responsiveness when the fluid load is 500 ml, but less accurate for 250 ml. Of note, the studies using 250 ml in the meta-analysis [12] were performed during *ongoing* surgery, whereas the studies using 500 ml were performed in the ICU or in the operating room immediately after the induction of anesthesia or after surgery. Study heterogeneity was not significant after stratifying the studies according to fluid load volume. However, variations in filtering techniques in different devices could have influenced the results [12]. The present analysis shows that different devices may produce different values of ΔPOP and that ΔPOP_{Mas} and PVI agreed better than ΔPOP_{Nellc} with ΔPP.

In previous studies, our group has used both Nellcor [19, 25] and Masimo [26] pulse oximeters to calculate ΔPOP. A Nellcor pulse oximeter was used when we found larger values and larger variability for ΔPOP than for ΔPP in a study on ICU patients [19]. However, both by using Nellcor and Masimo pulse oximeters, we have found moderate or poor abilities to predict fluid responsiveness during ongoing abdominal surgery [25, 26]. Although the agreement between the ΔPOP-values was poor, their abilities to predict fluid responsiveness as judged by the AUC_{ROC}-values were quite similar.

4.1 Methodological considerations

The agreement between the waveforms could potentially be different in the two patient groups (AS and CABG-patients), influencing the results. The bias and limits of agreement were therefore also calculated separately and compared for AS and CABG patients (Table 3). The only statistically significant difference was between the LOAs of ΔPOP_{Mas} and ΔPP, influenced by outliers (Fig. 2). The overall results do therefore not seem to be specific for one patient group.

The present study was not powered to demonstrate a clinically relevant difference in the ability to predict fluid responsiveness. Fluid loads pre- and postoperatively were

Table 4 Abilities to predict fluid responsiveness (>15 % increase in stroke volume measured by oesophageal Doppler) presented as areas under receiver operating characteristics curves (95 % CI)

	n (fluid loads)	ΔPP	ΔPOP_{Nellc}	ΔPOP_{Mas}	PVI
AS preoperative	26	0.75 (0.54–0.90)	0.72 (0.51–0.88)	0.72 (0.51–0.87)	0.58 (0.37–0.77)[b]
AS postoperative	27	0.95 (0.80–1.0)	0.78 (0.58–0.91)	0.81 (0.61–0.94)[a]	0.71 (0.49–0.88)[c]
CABG	13	0.98 (0.72–1.0)	0.60 (0.30–0.85)	0.76 (0.45–0.95)	0.61 (0.31–0.86)

Pre and postoperative fluid loads presented separately for aortic stenosis (AS) patients, aggregated for coronary artery bypass grafting (CABG) patients

ΔPP pulse pressure variation, *ΔPOP_Nellc* respiratory photoplethysmographic waveform amplitude variations by Nellcor pulse oximeter, *ΔPOP_Mas* respiratory photoplethysmographic waveform amplitude variations by Masimo pulse oximeter, *PVI* pleth variability index
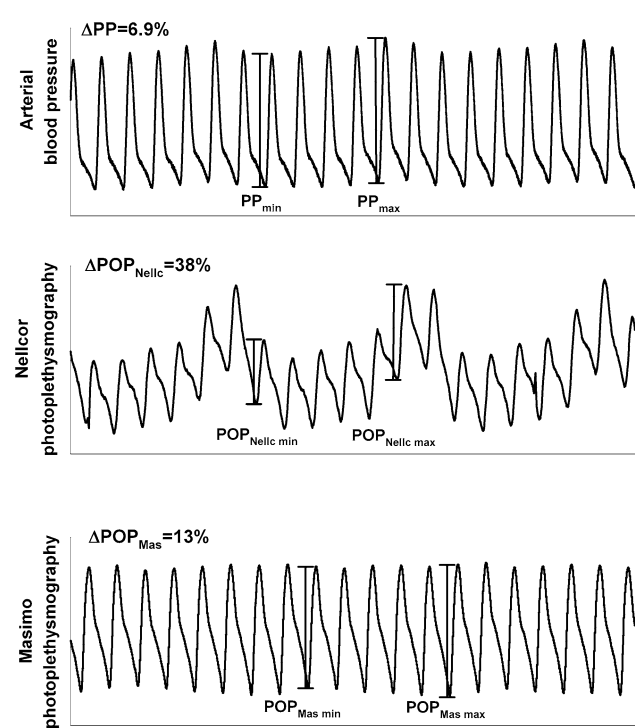
[a] n = 26, [b] n = 25, [c] n = 24

Fig. 4 Example of synchronously recorded waveforms with maximal and minimal amplitudes within one respiratory cycle marked. *ΔPP* pulse pressure variation, *ΔPOP_Nellc* respiratory photoplethysmographic waveform amplitude variations by Nellcor pulse oximeter, *ΔPOP_Mas* respiratory photoplethysmographic waveform amplitude variations by Masimo pulse oximeter

aggregated for CABG-patients, as there were few postoperative fluid loads and dynamic variables have been demonstrated to predict fluid responsiveness well both pre- and postoperatively in this patient group [1]. For AS-patients, we calculated separate AUC_ROC for pre- and postoperative fluid loads, as ΔPP only demonstrated a moderate predictive ability preoperatively [14]. ΔPP had a higher

AUC_ROC than PVI for AS patients after surgery. Otherwise, we did not demonstrate statistically significant differences in the abilities to predict fluid responsiveness for any of the variables.

For observations symmetrically distributed about the line y = x, the slope of ordinary least squares regression lines tends to deviate from 1 (y = x, line of identity) towards 0 as correlation between x and y decreases from 1 towards 0. This severely limits its use in method comparison. We are not aware of data describing the degree to which the LMSO also has this propensity.

The Bland–Altman plots were adjusted for dependence between repeated measurements within patients. *T* tests and *F* tests used when comparing bias and limits of agreement between subgroups of patients assume independent data, which repeated data (e.g. before and after a fluid load) are not. However, analyzing only measurements made before fluid loads (one observation per fluid load) gave similar results (data not shown). Postoperatively in AS-patients, some patients had repeated fluid loads, violating the assumption of independent observations in the AUC_ROC-calculations. However, analyzing only the first fluid load in each patient gave similar results (data not shown).

ΔPP, ΔPOP_Nellc and ΔPOP_Mas were calculated over ten respiratory cycles, starting synchronized with the 1 min averaging period of SV. PVI as calculated and displayed by the Masimo Radical 7 pulse oximeter was also averaged over this 1 min period. This PVI-value displayed by the device is however processed and averaged over some min, implying that the PVI-values to some extent lag behind the other variables. This could especially affect the registrations made after the fluid loads, as they were performed shortly (1–2 min) after finishing the infusion.

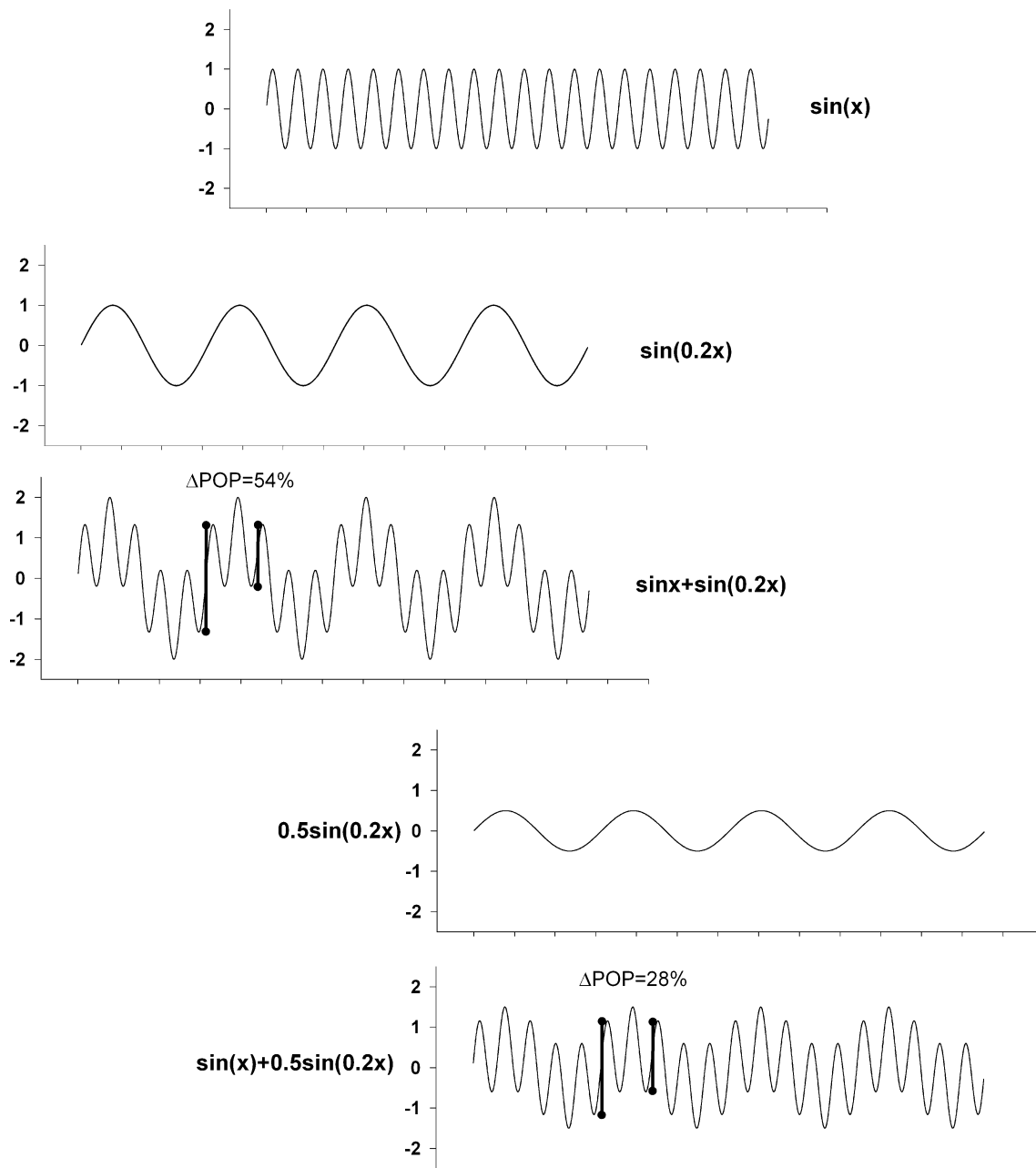In summary, ΔPOP calculated from the Nellcor and Masimo pulse oximeters do not seem to be

Fig. 5 Simulations illustrating the potential effect of the respiratory oscillation on ΔPOP. Sin(x) represents cardiac oscillations, sin(0.2x) represents respiratory oscillations, whereas sin(x) + sin(0.2x) represents the photoplethysmographic signal. Although there are no variations in the cardiac component, the respiratory component will influence the calculations of ΔPOP due to the lag between the trough and the peak. A smaller respiratory component [0.5sin(0.2x)] attenuates this effect, giving smaller calculated ΔPOP-values

interchangeable. The device used should be taken into consideration when interpreting data based on the photo-plethysmographic waveform.

Conflict of interest Pulse oximeter Masimo Radical 7 provided by Masimo Corp., which had no influence on the planning or conduction of the study. Otherwise, the authors declare no conflicts of interest. The authors declare no financial disclosures.

Ethical standard All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent Written informed consent was given by all the patients participating in the study.

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