Accuracy of a Novel Transcutaneous PCO\textsubscript{2} and PO\textsubscript{2} Sensor with Optical PO\textsubscript{2} Measurement in Neonatal Intensive Care: A Single-Centre Prospective Clinical Trial

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Keywords
Transcutaneous monitoring · Oxygen · Carbon dioxide · Neonate · Preterm infant

Abstract

Background and Objectives: Transcutaneous PCO\textsubscript{2} and PO\textsubscript{2} measurement systems offer non-invasive blood gas trend monitoring. The aim of this prospective study was to assess bias and precision of a transcutaneous PCO\textsubscript{2} and PO\textsubscript{2} measurement system incorporating a novel pO\textsubscript{2} sensor (Sentec OxiVenT™) in neonates ≥34 weeks of gestational age (GA) admitted to intensive care. Methods: Transcutaneous PCO\textsubscript{2} and PO\textsubscript{2} were compared to arterial and capillary blood gas measurements. Bias and precision were calculated by fitting linear mixed models to account for repeated measurements, and influence of clinical covariates on bias and precision was assessed. Results: We obtained 611 paired transcutaneous and blood gas measurements in 110 patients (median GA 38.3 [interquartile range 36.1–39.7] weeks; age 9 [4–15] days; weight 3,000 [2,500–3,500] g). Transcutaneous PCO\textsubscript{2} showed significant bias to arterial PCO\textsubscript{2} (+0.61; 95% confidence interval 0.46, 0.76 kPa), but not to capillary PCO\textsubscript{2} (−0.23; −0.46, 0.002 kPa). Bias of transcutaneous PO\textsubscript{2} was significant to arterial PO\textsubscript{2} (−2.50; −2.94, −2.06 kPa), while no significant bias compared to capillary PO\textsubscript{2} was observed (+0.17; −0.30, 0.64 kPa). Precision intervals were ±1.8/2.0 kPa for arterial versus capillary PCO\textsubscript{2} and ±4.9/3.3 kPa for arterial versus capillary PO\textsubscript{2} comparisons, respectively. Further, sensor operating temperature (43°C vs. 42°C), soft tissue oedema, vasoactive drugs, weight, and GA significantly altered bias (p < 0.05).

Conclusions: The tested transcutaneous blood gas measurement system showed no significant bias compared to capillary PCO\textsubscript{2} and PO\textsubscript{2}, acceptable bias to arterial PCO\textsubscript{2}, and limited agreement with arterial PO\textsubscript{2}. Precision intervals were wide for all comparisons.

Introduction

Transcutaneous blood gas monitoring represents standard of care in neonatal intensive care units [1–4]. To date, the majority of transcutaneous sensors employ electrochemical measurement principles like oxygen reduction for PO\textsubscript{2} and pH-changes in buffered electrolyte solution for PCO\textsubscript{2} [5, 6]. These techniques are prone to loss of accuracy over time [5, 6]. Recently, a new optic PO\textsubscript{2} measurement principle, the fluorescence-quench technique, has been developed and incorporated into a novel...
transcutaneous sensor. Benefits of optic PO2 measurements should be high stability over time without relevant drift and absence of need for semipermeable membranes [7]. Until now, this sensor has not been tested in late pre-term and term birth children and its accuracy is unknown.

The aim of this prospective trial was to test the accuracy of the new transcutaneous CO2 and O2 Sentec OxiVenT™ sensor (Sentec, Therwil, Switzerland) in late pre-term and term birth neonates in intensive care setting. Primary objective was to examine bias and precision in comparison to arterial and capillary blood gas values. We hypothesized that the transcutaneous Sentec OxiVenT™ system provides clinically useful bias and precision (±1 to 1.5 kPa; 1 kPa = 7.5 mm Hg) for PCO2 and PO2. Secondary objective was to explore which clinical factors influence sensor’s accuracy. Safety objective was to assess risk of thermic tissue damage at 42° and 43°C sensor temperatures.

**Methods**

This study was designed as single-centre prospective non-randomized clinical trial. It was conducted in late preterm and term birth neonates admitted to the tertiary care intensive care unit or to the intermediate care neonatology unit of the University Children’s Hospital of Zurich, Switzerland.

**Participants and Sample Size**

Inclusion criteria were neonates with ≥34 0/7 weeks gestational age (GA), age between first day of life and end of the neonatal period (i.e., 28 days of life or 43 6/7 weeks GA), ability of care taker to provide informed consent in German, and at least one to two expected blood gas analyses (BGA) within the upcoming 48 h for clinical reasons. Exclusion criteria were GA outside above-mentioned range, and impossibility to obtain written informed consent for any reason.

Considering the nature of the primary endpoint (evaluation of measurement bias and precision) no formal power calculation based on hypothesis testing was performed [8]. Based on simulations assuming a maximal standard deviation (SD) of $s = \pm 0.7$ kPa (i.e., expected SD of measurement differences), sample sizes of 60 patients per group (arterial and capillary sampling, respectively) were deemed sufficient to evaluate bias and precision with clinically satisfying precision (95% confidence interval [CI]). Further details on sample size calculation are available in online supplementary material (see www.karger.com doi/10.1159/000521809 for all online suppl. material).

**Study Design**

The transcutaneous sensor (Sentec OxiVenT™) being connected to the Sentec Digital Monitoring System (software version MPB-SW:V06.01.00; SMB-SW:V08.01.1) was placed with an attachment ring on left or right trunk side in thoracic (below each clavicle in midclavicular line) or abdominal (lateral of umbilicus in mid-axillary line) position. Operational temperature was 42°C for the first 24 h and 43°C for the second 24 h. During this 48 h period, the sensor was removed from the skin every 4 h, calibrated in the calibration chamber and reapplied to another of the above-mentioned positions to avoid skin burns. Each time the sensor was transiently or definitively removed from the patient (after a total of 48 h) the former placement site was under visual surveillance for thermal injury for 4 additional hours. Only arterial and capillary blood samples (55 µL) that were taken after the sensor was attached for at least 15 min (stability criterion) were used for the study.

**Variables**

Study variables are displayed in Table 1. Complete variable definitions are provided in online supplementary material.

**Statistical Analysis**

Baseline data (demographics, blood values, transcutaneous values) of all included patients were summarized as median (interquartile range [IQR]) or per cent.

**Primary Endpoint Analysis**

The agreement between transcutaneous, arterial, and capillary measurements was evaluated by Bland–Altman analysis using the statistical software R, taking into account repeated measurements for each patient by fitting a linear mixed model [9, 10]. Mean measurement difference (transcutaneous vs. BGA) was calculated as measure of bias along with 95% CIs, and limits of agreement were calculated from the precision interval (= 1.96 × total SD [s], with total $s = \sqrt{s^2} = \sqrt{(s_{inter-individual}^2 + s_{residual}^2))}$ as measure of precision. Distribution of measurement differences was assessed before the analysis, and data transformation considered if significant deviations from normal distribution were detected.

**Secondary Endpoint Analyses**

All data were combined to evaluate potential influence of covariates on bias and variance estimates in a linear mixed model [11]. Safety assessment: Occurrence of thermal injuries at transcutaneous measurement sites was summarized as proportion with 95% CIs for each time point. Since some influence of the operating temperature was suggested, this was tested in a mixed effect logistic regression model as supplemental post hoc analysis.

**Results**

**Patient Population and Measurements**

Between August 2017 and December 2018, all neonates admitted to the units (n = 498) were screened for eligibility. 129 neonates fulfilled the inclusion criteria. Consent was rejected in 11 cases, and 5 children were transferred to other hospitals before study inclusion was possible. A total of 113 patients were included in the study (characteristics: Table 1). Six hundred eleven paired transcutaneous/BGA measurements (312 for PCO2, 299 for PO2) were included in primary outcome analysis. Thirty-nine patients (34%) were treated with catecholamines at least once during the study period. Median
(IQR) PaCO_2 and PcapCO_2 were 5.8 (5.2–6.4), and 5.9 (5.3–6.9) kPa, respectively. Median (IQR) PaO_2 and PcapO_2 were 8.2 (6.1–9.9) kPa and 5.8 (4.9–7.1) kPa, respectively (Fig. 1). Median (IQR) transcutaneous PCO_2 and PO_2 measurements were 6.1 (5.4–7.1) kPa and 5.8 (4.6–7.2), respectively. All 113 patients were included in the safety analysis, with a total of 2,459 assessments (1,259 at 42°C and 1,196 at 43°C).

**Primary Outcome**

Bland-Altman plots are presented in Figure 2 along with estimated bias and 95% limits of agreement (details: Table 2). Briefly, based on 95% CIs of bias estimates, PtcCO_2 was significantly higher than PaCO_2 with an estimated bias of +0.61 (95% CI: 0.46, 0.76) kPa, but not significantly different from PcapCO_2 (−0.23, −0.46; 0.002 kPa). PtcO_2 was significantly lower than PaO_2 with estimated bias of −2.50 (−2.94; −2.1) kPa, while no significant difference compared to PcapO_2 was observed (+0.17, −0.30; 0.64 kPa). Precision intervals were ±1.8/2.0 kPa for PaCO_2/PcapCO_2 and ±4.9/3.3 kPa for PaO_2/PcapO_2, respectively. For the transcutaneous-arterial PO_2 comparison a trend towards increased bias with increasing mean PO_2 was observed. A sensitivity analysis was performed to evaluate effects of outlying data. Three outlying data points were excluded from database, and analysis was re-run. Bias of transcutaneous-arterial comparisons of PCO_2 and PO_2 did not change significantly, PIs were reduced by 10% (1.61 instead of 1.79 kPa) and 13% (4.25 instead of 4.88 kPa), respectively. Influence of outlying data was small (online suppl. material).

**Secondary Outcomes**

Figure 3a b shows the above-mentioned results stratified by operational temperature, corresponding estimated bias, and 95% limits of agreement are summarized in

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**Table 1. Baseline characteristics.**

| Patient characteristics | Value | Missing data, n (%) |
|-------------------------|-------|---------------------|
| Individuals, n          | 113   | –                   |
| Age (days of life)      | 9 (4, 15) | –                  |
| Weight, g               | 3,000 (2,500, 3,500) | –             |
| Birth weight, g         | 2,910 (2,490, 3,450) | –             |
| Gestational age, weeks  | 38.3 (36.1, 39.7) | –       |
| Cyanotic heart disease with right-to-left shunt | 29 (25.7) | –  |
| Patients with oedema at study inclusion | 19 (16.8) | 2 (1.8)  |
| Patients developing oedema after study inclusion | 8 (7.1) | 24 (21.2) |
| Patients with catecholamine use | 39 (34) | –                   |
| Covariates              |       |                     |
| Paired blood samples, N (PO_2+ PCO_2) | 611 (100) | –                       |
| Blood gas sampling      |       |                     |
| Arterial                | 462 (75.6) | –                 |
| Capillary               | 149 (24.4) | –                 |
| Sensor temperature      |       |                     |
| 42°C                    | 404 (66.2) | 1 (0.2)               |
| 43°C                    | 206 (33.8) | –                 |
| Right-to-left shunt     |       |                     |
| Catecholamine points*   |       |                     |
| ≤10                     | 509 (83.6) | 2 (0.3)               |
| >10                     | 100 (16.4) | 43 (7.0)              |
| Presence of oedema      | 201 (35.4) | 157 (25.7)             |
| Duration of sensor application until measurement, h | 1.3 (0.7–2.3) | 490 (80.2) |
| Bilirubin, µmol/L       | 146 (70–196) | 490 (80.2)             |

Data are presented as median (IQR) for continuous variables or n (%) for categorical variables, respectively. Presence of oedema was defined as presence of relevant oedema on anterior-posterior chest radiographs, i.e., doubled horizontal distance between skin and rip surface on level of the sixth thoracic vertebra in the time from admission to time of blood sampling; * catecholamine points were estimated with one point for every µg/kg/min dopamine or dobutamine, 10 points for every µg/kg/min milrinone and 100 points for every µg/kg/min adrenaline or noradrenaline.
online supplementary material S5 Table. Briefly, by comparison of 95% CI of estimated bias, measurement differences were similar at both temperatures (overlapping 95% CI) with exception of PO2 measurements, for which bias was with −2.77 (−3.29; −2.26) kPa greater at 42°C compared with −1.81 (−2.30; −1.32) kPa at 43°C.

The following variables were associated with a significant change in mean measurement difference (bias) (all \( p < 0.05 \)): BGA type (capillary vs. arterial), temperature (43°C vs. 42°C), presence of oedema, catecholamine treatment, GA, and current and birth body weight. Accounting for those variables did not improve precision to a relevant extent: the largest decrease of total SD was for PCO2 from ±1.36 (95% limits of agreement ±2.67) to ±1.26 (±2.57) kPa, and for PO2 from ±2.30 (±4.51) to ±2.22 (±4.35) kPa. Proportions of covariables among study populations are summarized in Table 1. Association of PCO2 and PO2 differences with covariables is summarized in Table 3.

**Safety**

No thermal injury or necrosis was observed. The proportion of redness was significantly higher at 43°C than at 42°C (\( p < 0.001 \)) with predicted proportions (95% CI) of 31% (26; 36) and 24% (20; 28), respectively (Fig. 3c).

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**Fig. 1.** a PCO2 and PO2 by BGA (stars) and transcutaneous system (open circles), stratified by blood gas measurement type (arterial/capillary). Sensor temperature was 42°C during the first 24 h and 43°C afterwards (dashed vertical line). b Transcutaneous versus blood gas measurements of PCO2/PO2. Diagonal lines: lines of identity. \( R \), Pearson’s correlation coefficient.

**Fig. 2.** Primary outcome. Bland-Altman plot for PCO2 (upper row) and PO2 (lower row), stratified by blood gas measurement type (arterial/capillary). Red line with red shaded area: mean difference (bias) with 95% CI. Blue lines: precision interval. Black horizontal line at delta = 0 kPa: reference line for no bias.
Discussion

In our study, we found excellent agreement of transcutaneous measurements with capillary PCO₂ and PO₂, and good agreement with arterial PCO₂. Transcutaneous PO₂ compared to arterial PO₂ showed large bias that was significantly influenced by sensor temperature. Precision intervals were wide for all comparisons. We identified a number of factors that could have relevant influence on accuracy of transcutaneous blood gas measurement.

Critically ill neonates are at risk for blood gas disturbance that might have detrimental effects on the metabolic and circulatory state of the patients. Therefore, reliable continuous blood gas trend monitoring is crucial for patients’ safety and for guiding respiratory support [12]. However, it has been demonstrated in several studies that accuracy of transcutaneous PCO₂ and PO₂ is dependent on local perfusion [12–15].

Bearing this in mind, the system tested in this study performed well and showed no difference to capillary BGA values. The results suggest correct display of the actual PCO₂ and PO₂ concentrations present in the skin capillary bed, even though the capillary blood samples were taken from small skin incisions in feet and not from trunk. Published comparisons of other transcutaneous devices to capillary blood gas values are scarce, as most comparisons are done to arterial values. Bernet et al. [16] found a small bias of −0.09 kPa and a precision interval of 1.11 kPa for the transcutaneous-capillary comparison using a different device in neonates.

The transcutaneous-arterial comparison revealed small bias of +0.58 kPa for PCO₂ and large bias of −2.47 kPa for PO₂. Further, wide precision intervals were found for all capillary and arterial comparisons. This is in line with many past studies [16–19]. Particularly, the Sentec OxiVent system was recently evaluated in very preterm neonates ≤32

| Variable | Type of BGA | Samples, n | Patients, n | Bias in kPa (95% CI) | Precision interval in kPa (95% limits of agreement) |
|----------|-------------|------------|-------------|----------------------|--------------------------------------------------|
| PCO₂ (kPa) | Arterial | 234 | 64 | +0.61 (0.46; 0.76) | ±1.79 (−1.18; 2.40) |
| | Capillary | 78 | 46 | −0.23 (−0.46; 0.002) | ±2.04 (−2.27; 1.80) |
| PO₂ (kPa) | Arterial | 228 | 63 | −2.50 (−2.94; −2.06) | ±4.94 (−7.38; 2.38) |
| | Capillary | 71 | 41 | +0.17 (−0.30; −0.64) | ±3.30 (−3.13; 3.46) |

BGA: blood gas analysis. Bias: mean difference Δ (sensor-BGA). Precision interval: calculated as ±1.96 × total SD (s), with total $s = \sqrt{s^2} = \sqrt{(s_{\text{inter-individual}}^2 + s_{\text{residual}}^2)}$ estimated from linear mixed model (random intercept model). Limits of agreement: calculated as bias ± precision interval.
Table 3. Secondary outcome: associations of PCO₂ and PO₂ measurement differences with covariates

| Variable                    | PCO₂                      |          | PO₂                       |          |
|-----------------------------|---------------------------|----------|---------------------------|----------|
|                             | N  | n  | Δ mean (95 CI%) (kPa or kPa/unit) | p value | N  | n  | Δ mean (95 CI%) (kPa or kPa/unit) | p value |
| BGA type (arterial vs. capillary) | 100 | 312 | 0.62 (0.48; 0.76) | <0.001 | 96  | 299  | −2.5 (−2.91; −2.09) | <0.001 |
| Temperature (42°C vs. 43°C)  | 100 | 312 | 0.46 (0.3; 0.62)  | 0.001  | 96  | 298  | −1.97 (−2.42; −1.52) | <0.001 |
| Oedema reported (yes vs. no) | 94  | 290 | 0.18 (0.02; 0.34) | <0.001 | 91  | 278  | −1.31 (−1.78; −0.84) | 0.001  |
| Catecholamine points (≥10 vs. <10) | 99 | 310 | 0.26 (0.12; 0.4)  | 0.001  | 96  | 299  | −1.37 (−1.76; −0.98) | <0.001 |
| Bilirubin (μmol/L)           | 35  | 62  | 0.55 (0.24; 0.86) | 0.489  | 34  | 59   | −2.25 (−3.21; −1.29) | 0.112  |
| Duration of sensor application (h) | 92 | 231 | 0.32 (0.14; 0.5)  | 0.989  | 88  | 223  | −1.61 (−2.08; −1.14) | 0.52   |
| Capillary refill time (s)     | 94  | 223 | 0.3 (0.1; 0.5)    | 0.506  | 89  | 216  | −1.58 (−2.05; −1.1)  | 0.064  |
| Cyanotic heart disease (yes vs. no) | 100 | 312 | 0.34 (0.16; 0.52) | 0.872  | 96  | 299  | −1.79 (−2.28; −1.3)  | 0.144  |
| GA (weeks)                   | 100 | 312 | 0.36 (0.22; 0.5)  | 0.087  | 96  | 299  | −1.72 (−2.13; −1.3)  | 0.01   |
| Age (days of life)           | 100 | 312 | 0.35 (0.19; 0.51) | 0.429  | 96  | 299  | −1.67 (−2.1; −1.24)  | 0.296  |
| Birth weight (kg)            | 100 | 312 | 0.35 (0.21; 0.49) | 0.02   | 96  | 299  | −1.68 (−2.07; −1.29) | 0.007  |
| Weight (kg)                  | 100 | 312 | 0.37 (0.23; 0.51) | 0.012  | 96  | 299  | −1.71 (−2.12; −1.3)  | 0.006  |

Associations investigated in monovariable regression analysis accounting for repeated measurements. N, number of included individuals; n, number of included observations; Δ mean, mean difference in kPa for comparator versus reference group (e.g., BGA type: arterial vs. capillary) or in kPa per unit for continuous variables (e.g., bilirubin: in kPa/μmol/L, with reference value = median for continuous variables). p value: likelihood ratio test.

weeks of GA in a neonatal intensive care unit. The results were very similar to our findings: bias for the transcutaneous-arterial-comparison was for PCO₂ 0.6 kPa with limits of agreement −1.04 to 2.3 kPa and for PO₂ −2.6 (−8.6; 3.5) kPa, respectively [15]. When comparing our results to other studies with neonates, it is important to consider that we also included critically ill patients. These patients were at risk for haemodynamic instability and changing and compromised peripheral perfusion might be the main reason for the rather wide-ranged precision intervals for all comparisons found in our and former studies [12, 14]. Therefore, transcutaneous blood gas monitoring has to be considered rather as a permanent surveillance system than as a precise diagnostic tool that displays exact arterial blood gas concentrations in central arteries. If acute transcutaneous PCO₂ and PO₂ deviations occur, one has to integrate these readings into the whole clinical picture of the patient and be cautious about interpreting these values as they might well be biased by changing peripheral skin perfusion. Control blood gas sampling may still be needed [14].

Interestingly, the same factors interfered with accuracy of both, transcutaneous PCO₂ and PO₂. Although most of the confounders were related to compromised peripheral perfusion (vasoactive drugs, oedema), we could not find prolonged capillary refill time to have relevant impact on accuracy, as we would have expected from former studies [20]. This might be due to the subjective nature of the capillary refill assessment and questions capillary refill time as surrogate marker for tissue perfusion. Sensor temperature had a significant influence on transcutaneous-arterial PO₂ bias as it was nearly halved by elevating the sensor temperature by 1°C to 43°C. Higher sensor operational temperatures usually reduce bias, but they increase the risk of burn injuries, especially in preterm children [6, 21].

The main indication of transcutaneous PO₂ monitoring is to guide inhaled oxygen concentrations for the avoidance of relevant hyperoxaemia which may be undetected with peripheral oxygen saturation monitoring alone due to the specific s-shaped form of the oxygen dissociation curve [22]. However, bias and PIs were large for the transcutaneous-arterial PO₂ comparison, limiting the ability to use the sensor for guidance of inhaled oxygen.

We did not observe any burn injuries neither with 42°C (first 24 h) nor with 43°C (second 24 h). As patients’ clinical status and perfusion might have improved over time, this might be a reason for increased accuracy of the 43°C measurements. In fact, we found a lower proportion of children with high catecholamine scores (first 24 h [42°C]: 0.23, second 24 h [43°C]: 0.14, p < 0.05, data not shown). One consequence of our data would be to recommend a sensor temperature of 43°C if PO₂ monitoring is required. However, in selected patients with fragile skin or poor peripheral perfusion, it might be indicated to reduce sensor temperature and/or attachment time to reduce the risk of burn injury.

The translational value of this study might be limited by the fact that a dedicated study team of physicians and
technicians was in charge 24/7 for sensor cleaning, maintenance, and membrane change. Therefore, the system’s operational state was kept optimal throughout the study. Under non-study conditions, the accuracy of the sensor and monitoring system could be different.

**Conclusion**

The tested transcutaneous measurement system showed no significant bias compared to capillary PCO₂ and PO₂ values and acceptable bias compared to arterial PCO₂ values. Agreement with arterial PO₂ values was limited. Precision intervals were wide for all measurements possibly due to changing and compromised peripheral perfusion. The results render the system useful for blood gas trend monitoring in critically ill neonates, but control blood gas sampling may still be needed.

**Statement of Ethics**

This study protocol was reviewed and approved by the local Swiss Ethics Committee, Approval Number KEK 2016-01356. Care takers of all neonates signed informed consent before study inclusion. The study was registered in national (Swiss National Clinical Trials Portal: KEK 2016-01356) and international (clinicaltrials.gov: NCT03060018) registries.

**Data Availability Statement**

All data generated or analysed during this study are included in this article and in online supplementary material. Further enquiries can be directed to the corresponding author.

**Conflict of Interest Statement**

The authors have no conflicts of interest relevant to this article to disclose.

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**Author Contributions**

Dr. Baumann and Prof. Bernet conceptualized and designed the study and the data collection instruments, coordinated and supervised data collection, collected data, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. Gotta carried out the statistical analyses and reviewed and revised the manuscript. Dr. Adzikah collected data and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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