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Validation of a New Transcutaneous $tcPO_2$/$tcPCO_2$ Sensor with an Optical Oxygen Measurement in Preterm Neonates

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Keywords
Transcutaneous measurements · Transcutaneous oxygen · Transcutaneous carbon dioxide · Sensor · Neonate

Abstract
Introduction: Traditional transcutaneous oxygen ($tcPO_2$) measurements are affected by measurement drift, limiting accuracy and usability. The new potentially drift-free oxygen fluorescence quenching technique has been combined in a single sensor with conventional transcutaneous carbon dioxide ($tcPCO_2$) monitoring. This study aimed to validate optical $tcPO_2$ and conventional $tcPCO_2$ against arterial blood gas samples in preterm neonates and determine measurement drift. ***Methods:*** In this prospective observational study, during regular care, transcutaneous measurements were paired to arterial blood gases from preterm neonates aged 24–31 weeks of gestational age (GA) with an arterial catheter. Samples were included based on stability criteria and stratified for sepsis status. Agreement was assessed using the Bland-Altman analysis. Measurement drift per hour was calculated. ***Results:*** Sixty-eight premature neonates were included {median (interquartile range [IQR]) GA of 26 4/7 [25 3/7–27 5/7] weeks}, resulting in 216 stable paired samples. Agreement of stable samples in neonates without sepsis ($n = 38$) and with suspected sepsis ($n = 112$) was acceptable for $tcPO_2$ and good for $tcPCO_2$. However, in stable samples of neonates with sepsis ($n = 66$), $tcPO_2$ agreement (bias and 95% limits of agreement) was −32.6 (−97.0 to 31.8) mm Hg and $tcPCO_2$ agreement was 4.2 (−10.5 to 18.9) mm Hg. The median (IQR) absolute drift values were 0.058 (0.0231–0.1013) mm Hg/h for $tcPO_2$ and 0.30 (0.11–0.64) mm Hg/h for $tcPCO_2$. ***Conclusion:*** The accuracy of optical $tcPO_2$ in premature neonates was acceptable without sepsis, while electrochemically measured $tcPCO_2$ remained accurate under all circumstances. Measurement drift was negligible for $tcPO_2$ and highly acceptable for $tcPCO_2$.

Introduction

Transcutaneous blood gas monitoring is widely used in neonatal intensive care [1, 2]. It provides a continuous, noninvasive alternative to arterial blood gas sampling for

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measuring oxygen and carbon dioxide levels. The skin is arterialized by locally applying heat, causing an increase in microcirculatory blood flow. As a consequence, arterial values of oxygen and carbon dioxide can be estimated from values measured at the skin surface [3, 4]. The agreement of transcutaneously measured blood gas values with arterial values is, however, affected by factors that influence skin gas diffusion [5–7]. The diffusion capacity of the skin for oxygen is markedly lower than that for carbon dioxide and decreases with age, allowing transcutaneous oxygen ($tcPO_2$) levels to reach arterial levels only in thin neonatal skin [8–10]. Until now, transcutaneous blood gas measurement techniques have been based on an electrochemical measurement principle [11, 12]. Binding of other substances to the electrodes causes measurement drift over time, leading to additional inaccuracy [13]. While transcutaneous carbon dioxide ($tcPCO_2$) measurements are generally considered clinically useable, oxygen measurements suffer from inherent electrode instability and the fact that the electrochemical Clark-type electrode consumes oxygen, resulting in the underestimation of oxygen levels [14]. The main reasons for the sparse use of $tcPO_2$ monitoring are the labor intensity of frequent sensor repositioning and poor measurement accuracy. In previous studies, the large variation in patient populations, applied sensor temperatures, and mixed inclusion of capillary and arterial samples have led to a large spread in, often contradicting, study results [15]. Recently, a new transcutaneous sensor has been introduced, featuring an optical fluorescence quenching oxygen measurement, combined with a conventional electrochemical carbon dioxide sensor [16]. The fluorescence quenching technique measures oxygen levels through fluorescence decay of a dye that is quenched by oxygen, resulting in reduced fluorescence intensity and decay rates [17]. This study aimed to validate this new combined transcutaneous sensor in premature neonates, by assessing agreement with arterial blood gas samples and determining drift, while ensuring accurate comparison by applying criteria for measurement stability.

Materials and Methods

Study Set-Up

A prospective observational study was performed at a level III neonatal intensive care unit in the Netherlands. Neonates of 24 0/7 up to and including 31 6/7 weeks of gestational age (GA) with an arterial catheter were included upon the clinical indication for standard of care transcutaneous blood gas monitoring.

Transcutaneous Devices

Patients were provided with a SenTec OxiVenT™ Sensor (SenTec AG, Therwil, Switzerland) and a SenTec SDM-PO2 (SenTec Digital Monitor) for a minimum of 48 h or until the clinical indication ended. Sensor temperatures were set according to the department protocol: 42.0°C for extreme preterm neonates (≤25 weeks of GA) and 43.0°C for preterm neonates (26–31 weeks of GA). The site time and safety features were set to 2 h for extreme preterm neonates and 3 h for preterm neonates, automatically lowering the sensor temperature to 39°C after the measurement time elapsed. Calibration of the $tcPCO_2$ measurement was automatically required after the site time elapsed, the $tcPO_2$ measurement was calibrated automatically approximately every 24 h during a $tcPCO_2$ calibration. The SpO_2 channel was disabled in the neonatal mode of the transcutaneous monitor. Sensor membranes were changed every 30 days or earlier in case of any visible damage or recurrent calibration errors. Skin fixation adhesives and contact gel were used in accordance with manufacturer guidelines.

Parameters and Data Acquisition

$TcPO_2$ and $tcPCO_2$ measurements, quality indicators, sensor temperature, and calibration information were logged (Raspberry Pi 2 or 3 model B, Raspberry Pi Foundation, UK) at a 1 Hz rate. Arterial pressures were logged at a 1 Hz rate from the patient monitoring system (Dräger M540, Drägerwerk AG & Co., KGaA, Lübeck, Germany). Arterial blood samples were analyzed with a Radiometer ABL800 FLEX (Radiometer, Copenhagen, Denmark). Patient characteristics and arterial blood sample data were retrieved from the hospital patient information system (PDMS, Picis Clinical Solutions, Wakefield, MA, USA). The number of days between birth and the moment of blood sampling was presented as an indicator of development of the skin on the measurements. Ventilation parameters, infection laboratory parameters, and blood culture results were additionally documented.

Sample Selection

Arterial Sampling

Arterial pressure data were used to verify the arterial origin of the blood samples. For blood sampling, the connection between the arterial line and the pressure transducer was temporarily closed. The heparin lock was removed, a blood sample was taken, and the heparin lock was flushed. A clear pressure change could be observed for each of these steps, which was used to match the exact moment of blood sampling with the corresponding transcutaneous measurements (Fig. 1).

Sensor Temperature

Data pairs were excluded when blood sampling during standard care coincided with an elapsed transcutaneous measurement time.

Measurement Stability

Measurement stabilization and respiratory dynamics often lead to fluctuations in transcutaneous measurements. To guarantee a proper comparison between transcutaneous and arterial blood gas values, measurement stability criteria were applied to each sample. A parameter indicating the stability status was provided by the monitor. Additionally, around the exact moment of blood sampling, a time window of 10 min was analyzed for transcutaneous measurement stability (Fig. 1). The sample was marked

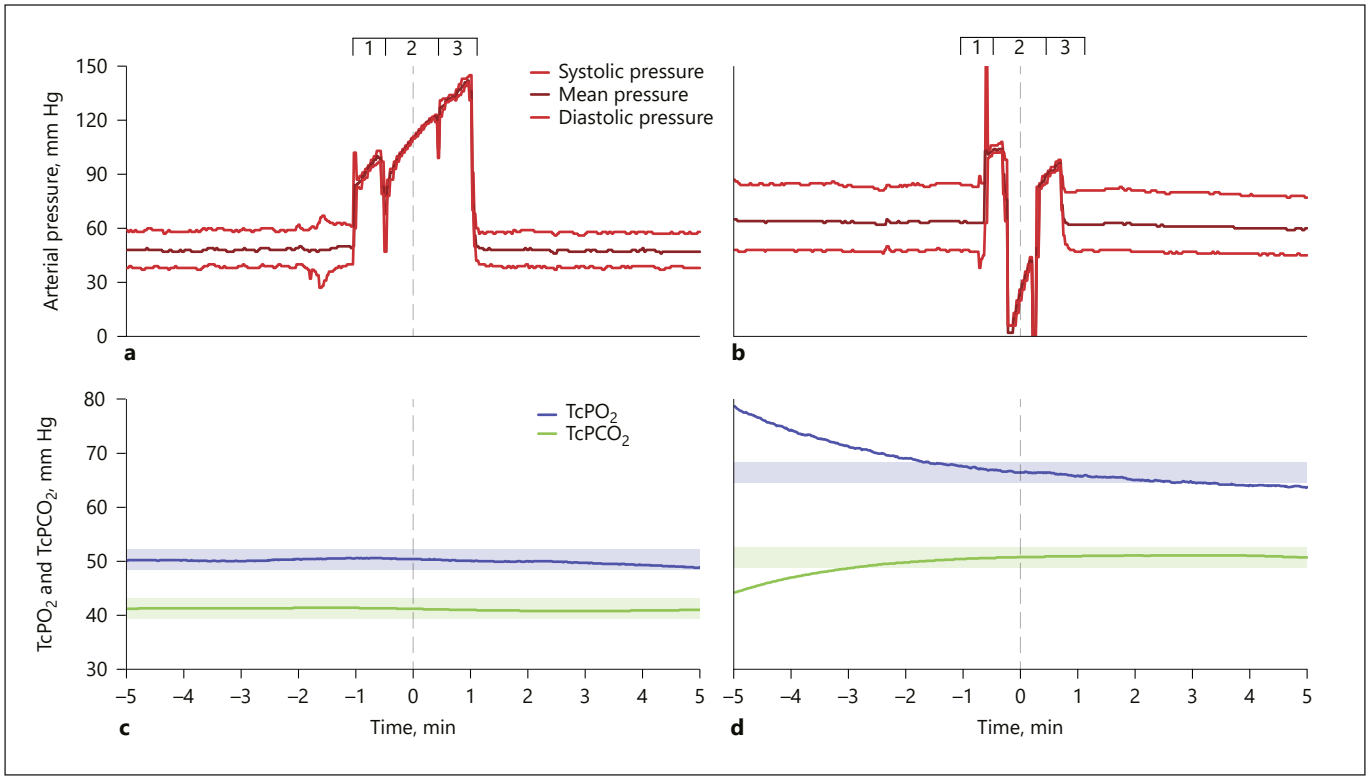

Fig. 1. Examples of arterial blood gas sample lookup for transcutaneous sample selection in 2 patients. The arterial pressure curve (**a**, **b**) and the corresponding transcutaneous measurements (**c**, **d**) were displayed for sample selection. The exact moment of blood withdrawal was identified from the arterial pressure curve: (1) heparin lock withdrawal, (2) arterial blood withdrawal, and (3) heparin lock flush. The $tcPO_2$ and $tcPCO_2$ values at the moment of blood sampling were extracted, and measurements were classified as stable when there was a relative deviation of no more than 3.75 mm Hg within the 10 min around blood withdrawal. The examples show a stable (**c**) and unstable (**d**) transcutaneous measurement. $tcPO_2$, transcutaneous oxygen; $tcPCO_2$, transcutaneous carbon dioxide.

as unstable (Fig. 1d) when either $tcPO_2$ or $tcPCO_2$ data were missing from this time interval, or a relative deviation of more than 3.75 mm Hg was present in the $tcPO_2$ and/or $tcPCO_2$ values (Fig. 1c).

Sepsis Definition

The neonate's sepsis status was defined for each data pair to indicate the influence on skin microcirculation and potential blood gas diffusion (Fig. 2b).

Analyses

Demographics

Demographic data were reported as median and interquartile range (IQR) or as *n* (%). To study significance between patient groups in the subgroup analyses, the Kruskal-Wallis and Fisher's exact tests were used for continuous and categorical variables, respectively. The significance level of statistical tests was fixed at $\alpha = 0.05$.

Agreement and Correlation

Agreement between transcutaneous measurements and arterial blood gas samples was calculated according to Bland and Altman (A-B plot), accounting for multiple measurements per patient [18]. Bias, calculated as mean difference, and limits of agreement (LoA), defined as the ±1.96 SD of the mean difference, were calculated. Pearson's correlation coefficient was calculated to determine correlations. Agreement and correlation were determined over all stable samples and in a subgroup analysis of the potentially influencing factors: GA at birth, age of the skin, weight at sampling, sepsis status, and sensor temperature.

Drift

The drift per hour of $tcPO_2$ and $tcPCO_2$ was calculated for each data pair by subtracting the calibration values after and before blood sampling. Duplicate calibration values originating from multiple data pairs within 1 calibration interval were removed. Drift is presented as median (IQR) for $tcPO_2$ and $tcPCO_2$, shown as absolute values due to the possibility of either positive or negative drift values.

Software

Statistical analyses were performed in R v3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria). A sample selection program was built in LabVIEW (National Instruments, Austin, TX, USA).

Table 1. Patient and sample characteristics of included premature neonates and data pairs

Premature neonates, *n*	68
GA at birth, weeks	26 4/7 (25 3/7–27 5/7)
Birth weight, g	803 (708–1,006)
Gender, male	45 (66.2)
Delivery mode	
Cesarean section	48 (70.6)
Vaginal	20 (29.4)
Apgar	
At min 1	5 (3–7)
At min 5	8 (6–9)
At min 10	9 (8–9)
Umbilical cord pH	7.31 (7.25–7.34)
Multiple births	11 (16.2)
Sepsis during admission	42 (61.8)
Deceased during admission	27 (39.7)
Samples per patient	9 (4–13)
Sample, *n*	**625**
GA at sample, weeks	27 6/7 (26 5/7–29 4/7)
Days since birth	6 (3–12)
Weight at sampling, g	880 (680–1,195)
Ventilation mode	
Noninvasive ventilation	3 (0.5)
Invasive ventilation	288 (46.1)
High-frequency oscillatory ventilation	334 (53.4)
Sensor temperature, °C	
42	113 (18.1)
43	512 (81.9)
PaO_2, mm Hg	57.8 (48.8–68.3)
$PaCO_2$, mm Hg	48.0 (41.3–54.0)

Values are expressed as median (IQR) or *n* (%), unless otherwise indicated. GA, gestational age; IQR, interquartile range.

Results

Patient Demographics

Between November 2015 and April 2017, 68 premature neonates were included out of a total number of 380 neonatal intensive care unit admittances aged 26–31 weeks of GA. Neonates had a median GA of 26 4/7 (IQR 25 3/7–27 5/7) weeks at birth and a median birth weight of 803 (IQR 708–1006) g (Table 1). In the study population, the incidence of sepsis was considerably higher (61.8%) than the incidence in all admitted neonates with a GA of 26–31 weeks (22.1%) during the inclusion period. Of the 42 neonates with proven sepsis, there was only 1 case of early-onset sepsis.

Sample Characteristics

A total of 625 data pairs of arterial blood gas and transcutaneous measurements were collected and analyzed (Fig. 2a; Table 1), with a median sampled PaO_2 of 57.8 (IQR 48.8–68.3) mm Hg and $PaCO_2$ of 48.0 (IQR 41.3–54.0) mm Hg. No burns or skin irritation was observed in any of the neonates. The transcutaneous sensor was placed mostly at the thorax, abdomen, and lower extremity.

Sample Stability

The stability criteria were met by 216 (34.6%) data pairs. The Bland-Altman analysis showed a bias of $tcPO_2$ and PaO_2 data pairs of −19.1 (95% LoA −64.6 to 26.5) mm Hg (Pearson's $r = 0.37$) and a $tcPCO_2$ and $PaCO_2$ bias of 4.7 (95% LoA −7.8 to 17.1) mm Hg (Pearson's $r = 0.85$).

Subgroup and Sepsis Status Analysis

The effects of GA at birth, age of the skin, weight at the moment of blood sampling, sepsis status, and sensor temperature are shown in Table 2. Neonates in the sepsis group were older (GA: no sepsis 28 3/7 [26 4/7–29 6/7] weeks, suspected sepsis 27 6/7 [26 6/7–30 5/7] weeks, and sepsis 29 3/7 [27 6/7–31 3/7] weeks, $p = 0.001$) and had a higher weight (no sepsis 912 [622–1,260] g, suspected sepsis 930 [714–1,295] g, and sepsis 1,115 [839–1,690] g, $p = 0.002$) at the moment of blood gas sampling than the other groups, while this discrepancy was not present at birth. The Bland-Altman analysis of $tcPO_2$ and PaO_2 showed wide LoA for the sepsis group (Fig. 3). Agreement improved markedly for samples classified as suspected sepsis and no sepsis. In contrast, agreement of $tcPCO_2$ with $PaCO_2$ was minimally influenced by the sepsis status of the neonate.

Measurement Drift

Measurement drift was calculated for all unique calibrations of $tcPO_2$ ($n = 327$) and $tcPCO_2$ ($n = 573$). $TcPO_2$ drift was minimal, with a median (IQR) absolute drift of 0.058 (0.0231–0.1013) mm Hg/h, while $tcPCO_2$ drift was on par with the existing literature on $tcPCO_2$ sensors (median [IQR] drift of 0.30 [0.11–0.64] mm Hg/h) [19, 20].

Discussion

In this study, a new transcutaneous blood gas sensor using an optical technique for measuring oxygen was evaluated in a premature neonatal population during standard care. The primary outcome of this study is that

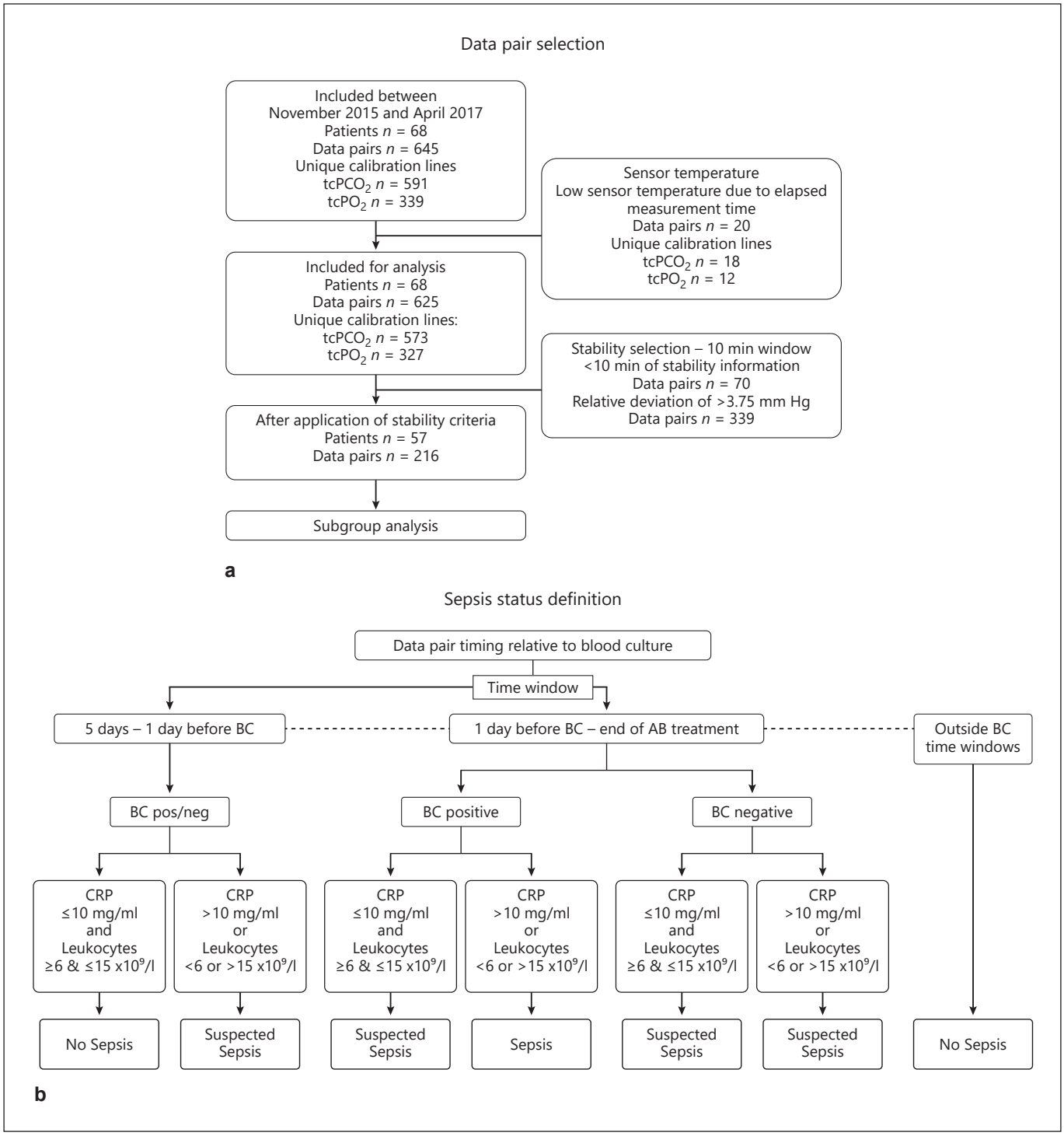

Fig. 2. a Flowchart of inclusion and exclusion of patients, data pairs, and unique calibration lines. **b** Flowchart of sepsis status definition. BC, blood culture; AB, antibiotic; CRP, C-reactive protein; $tcPO_2$, transcutaneous oxygen; $tcPCO_2$, transcutaneous carbon dioxide.

Table 2. Subgroup analysis of agreement

Parameter	Samples, *n*	$tcPO_2$-PaO_2, mm Hg			$tcPCO_2$-$PaCO_2$, mm Hg		
		bias	lower LoA-upper LoA	*R*	bias	lower LoA-upper LoA	*R*
GA at birth, weeks							
24 0/7 to 25 6/7	60	−18.6	−48.3 to 11.0	0.21	4.3	−9.6 to 18.2	0.76
26 0/7 to 27 6/7	94	−16.5	−58.1 to 25.2	0.36	4.9	−4.5 to 14.2	0.91
28 0/7 to 29 6/7	17	−19.8	−55.3 to 15.8	0.38	2.5	−4.9 to 9.9	0.95
30 0/7 to 31 6/7	45	−24.7	−95.6 to 46.1	0.49	5.5	−12.0 to 22.9	0.80
Postnatal skin age, week							
<1	132	−15.5	−61.1 to 30.2	0.50	5.0	−6.2 to 16.3	0.90
≥1	84	−24.7	−68.4 to 19.0	0.22	4.0	−10.3 to 18.4	0.78
Weight at sampling, kg							
<1	116	−15.7	−54.7 to 23.4	0.34	4.7	−6.9 to 16.3	0.86
≥1	100	−23.0	−74.6 to 28.6	0.41	4.6	−9.0 to 18.1	0.84
Sepsis status							
No sepsis	38	−16.1	−49.7 to 17.6	0.11	3.4	−3.9 to 10.7	0.95
Suspected sepsis	112	−12.1	−36.9 to 12.7	0.55	5.3	−7.1 to 17.8	0.87
Sepsis	66	−32.6	−97.0 to 31.8	0.45	4.2	−10.5 to 18.9	0.70
Sensor temperature, °C							
42	37	−19.7	−64.6 to 25.2	−0.40	7.8	−2.2 to 17.7	0.90
43	179	−18.9	−64.6 to 26.8	0.45	4.0	−8.6 to 16.6	0.84

Bias and 95% LoA in all stable samples related to GA at birth, age of the skin, weight at sampling, sepsis status, and sensor temperature. *r* represents Pearson's correlation coefficient. LOA, limits of agreement; GA, gestational age; $tcPO_2$, transcutaneous oxygen; $tcPCO_2$, transcutaneous carbon dioxide.

agreement of stable $tcPO_2$ values with PaO_2 is acceptable in suspected septic and nonseptic patients, while overall agreement of $tcPCO_2$ with $PaCO_2$ remains excellent even with sepsis. The current literature on $tcPO_2$ sensors shows similar results in terms of agreement [21, 22]. Conventional $tcPO_2$ sensors however apply a correction factor for, among other influences, the oxygen consumption of the Clark-type electrode or the so-called stirring effect [3, 14]. The investigated sensor provides the actual skin oxygen level, leading to negative agreement when oxygen diffusion is impaired. Most interesting in this study was the factor of sepsis, which caused poor agreement between $tcPO_2$ and PaO_2, potentially due to impairment of the microcirculation [23]. Contrary to $tcPO_2$, the agreement between $tcPCO_2$ and $PaCO_2$ was minimally affected by sepsis. The disparity can be explained by the higher skin diffusion capacity for carbon dioxide than for oxygen. The skin thickness in adults may have a more pronounced influence on the diffusion of and transport capacity for carbon dioxide. The effects of GA at birth in this study are also suggestive of this influence.

An important difficulty in studies is the sepsis status of the neonate. Sepsis is a continuously changing condition, of which the effects on the microcirculation can precede the clinical manifestation by several days [23]. In this study, the definition of sepsis was based on hospital guidelines and current literature [24]. In the sepsis group, the older age and consequent development of the neonatal skin may also influence the diffusion capacity of oxygen and thus the agreement of $tcPO_2$ with PaO_2. Whenever there is a lack of agreement of $tcPO_2$ with PaO_2, edema, impaired perfusion, or incorrect sensor placement should be considered.

Transcutaneous monitoring was mostly used to monitor CO_2 during high-frequency oscillatory ventilation, used as rescue therapy. This resulted in a high prevalence of, mostly late-onset, sepsis (61.8%) and mortality (39.7%) during admission in this study population. Unfortunately, during routine care, sensor skin locations were not registered, potentially influencing agreement due to skin microcirculation heterogeneity [14, 25]. The investigated sensor was provided with skin adhesives that performed well even under humid incubator conditions and allowed for sensor repositioning for kangaroo care.

The methodological aim of this study was to remove the cause of highly varying results on transcutaneous

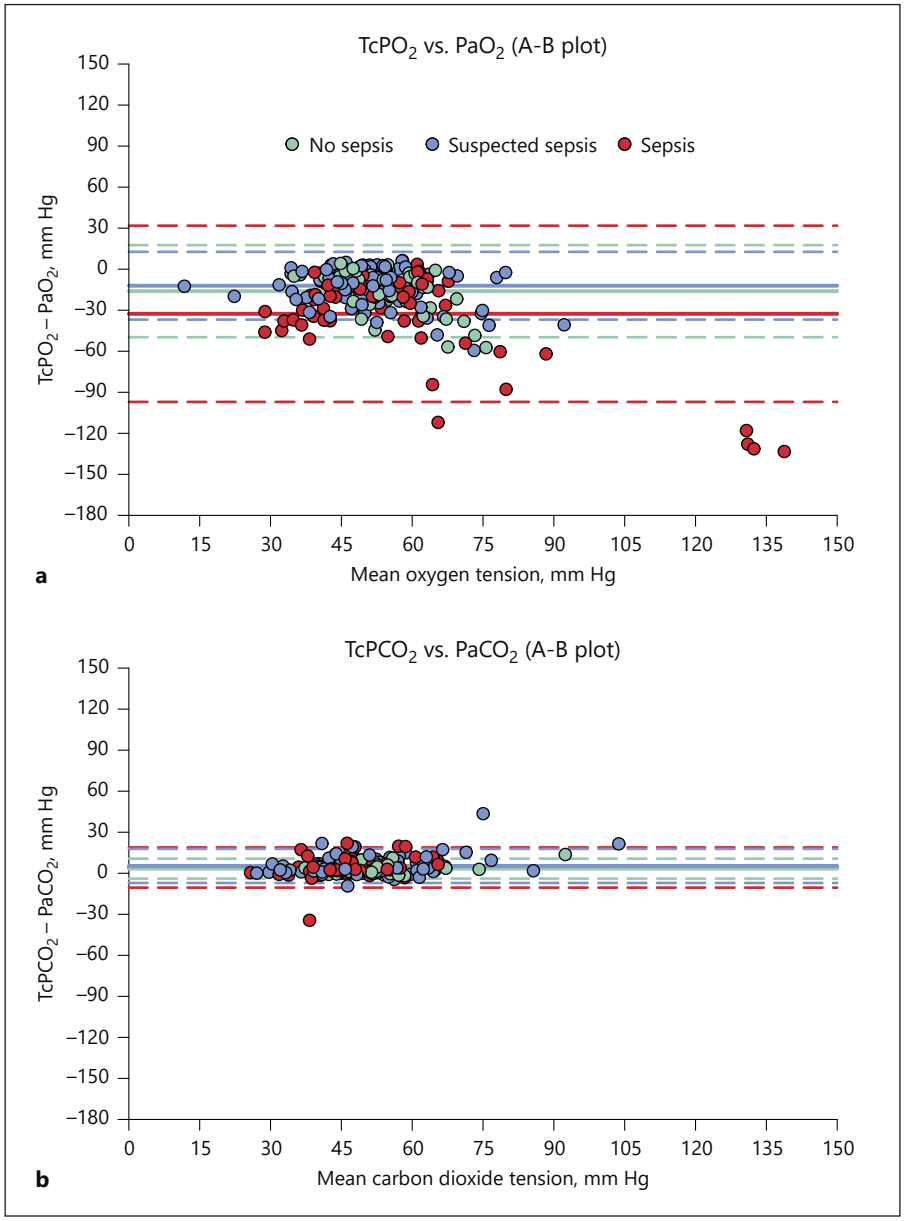

Fig. 3. Bland-Altman plot of the measured $tcPO_2$ (**a**) and $tcPCO_2$ (**b**) against arterial blood gas values for the defined sepsis status of the neonates. $tcPO_2$, transcutaneous oxygen; $tcPCO_2$, transcutaneous carbon dioxide.

monitoring in previous studies by improving the time-synchronized matching between transcutaneous measurements and arterial blood gas samples [15]. The inclusion and exclusion criteria for sample selection and measurement stability aim to improve reproducibility of future studies on transcutaneous monitoring. The criteria provide the possibility to distinguish the kinetics and dynamic properties of cardiorespiratory changes from those related to gas diffusion. The agreement analysis accounted for multiple measurements per patient, resulting in increased LoA when compared to other studies.

The investigated sensor provides a solution to the problem of $tcPO_2$ measurement drift, an inherent property of electrochemical blood gas sensors [13]. Although measurement drift is a well-known problem, few studies provide quantitative data that have been obtained during standard care. The conventional $tcPCO_2$ drift was comparable to previous studies [19, 20]. Improvements in transcutaneous measurement drift are able to significantly improve clinical usability, reliability, and accuracy. In the case of $tcPO_2$, this might even increase competition with pulse oximetry [26–28], providing trend informa-

tion on reasonable estimates of the actual PaO_2 when calibrated to an arterial blood gas sample. The investigated sensor requires regular $tcPCO_2$ calibration, limiting the long-term accuracy advantage of the drift-free $tcPO_2$ measurement. A dedicated optical $tcPO_2$ sensor that would only need measures to prevent skin burns could provide a useful complement to neonatal oxygen monitoring.

Regardless of technical performance, the microcirculatory condition of the patient and optimal timing of blood sampling during a stable phase are of great influence on agreement of the measurements with arterial values. The influence of sepsis as demonstrated in this study is one of many potential patient-related factors that should be taken into account during the clinical use of transcutaneous monitoring.

Conclusion

The investigated combined optical $tcPO_2$ and conventional $tcPCO_2$ sensor provided acceptable agreement of $tcPO_2$ with PaO_2 in premature neonates without sepsis. In the case of proven sepsis, the LoA for $tcPO_2$ with PaO_2 widened remarkably. An equally interesting finding was the excellent agreement of $tcPCO_2$ with $PaCO_2$, despite sepsis in these premature neonates. Drift was negligible during $tcPO_2$ measurement and highly acceptable when measuring $tcPCO_2$ during standard care in premature neonates.

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Statement of Ethics

The Medical Ethical Board of Erasmus University Medical Center Rotterdam approved the study protocol (MEC-2015-514). A waiver of informed consent was given as all data were collected as part of regular clinical care.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

W.W., T.G.G., R.C.J.J., and I.K.M.R. designed and set up the study. W.W. and T.E. acquired the data. W.W., T.E., and N.H.G.-P. analyzed the data. W.W. and N.H.G.-P. wrote the manuscript. T.E. and N.H.G.-P. contributed equally to this work. All authors provided input on the final manuscript.

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