



Novel transcutaneous sensor combining optical tcPO₂ and electrochemical tcPCO₂ monitoring with reflectance pulse oximetry

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Abstract

This study investigated the accuracy, drift, and clinical usefulness of a new optical transcutaneous oxygen tension (tcPO₂) measuring technique, combined with a conventional electrochemical transcutaneous carbon dioxide (tcPCO₂) measurement and reflectance pulse oximetry in the novel transcutaneous OxiVen™ Sensor. In vitro gas studies were performed to measure accuracy and drift of tcPO₂ and tcPCO₂. Clinical usefulness for tcPO₂ and tcPCO₂ monitoring was assessed in neonates. In healthy adult volunteers, measured oxygen saturation values (SpO₂) were compared with arterially sampled oxygen saturation values (SaO₂) during controlled hypoxemia. In vitro correlation and agreement with gas mixtures of tcPO₂ ($r = 0.999$, bias 3.0 mm Hg, limits of agreement – 6.6 to 4.9 mm Hg) and tcPCO₂ ($r = 0.999$, bias 0.8 mm Hg, limits of agreement – 0.7 to 2.2 mm Hg) were excellent. In vitro drift was negligible for tcPO₂ (0.30 (0.63 SD) mm Hg/24 h) and highly acceptable for tcPCO₂ (– 2.53 (1.04 SD) mm Hg/12 h). Clinical use in neonates showed good usability and feasibility. SpO₂–SaO₂ correlation ($r = 0.979$) and agreement (bias 0.13%, limits of agreement – 3.95 to 4.21%) in healthy adult volunteers were excellent. The investigated combined tcPO₂, tcPCO₂, and SpO₂ sensor with a new oxygen fluorescence quenching technique is clinically usable and provides good overall accuracy and negligible tcPO₂ drift. Accurate and low-drift tcPO₂ monitoring offers improved measurement validity for long-term monitoring of blood and tissue oxygenation.

Keywords Transcutaneous · tcPO₂ · tcPCO₂ · Oxygen · Fluorescence quenching

1 Introduction

Transcutaneous blood gas monitoring is based on the diffusion of oxygen (O₂) and carbon dioxide (CO₂) from the blood to the skin surface [1]. Transcutaneous blood gas sensors locally heat the skin to induce vasodilation, resulting in an increase in supplied O₂ and clearance of CO₂ [2, 3]. The diffusion capacity of the skin is however markedly lower for O₂ than for CO₂ [4], additionally influenced by the thickness [5, 6] and microcirculatory condition [7] of the skin. As a consequence the measurement of transcutaneous oxygen (tcPO₂) [8] requires relatively high sensor temperatures of 43 to 44 °C [9] for tcPO₂ to correlate with arterial oxygen tension (PaO₂), which due to skin thickness only results in tcPO₂ values approaching PaO₂ in infants and young children [10–12].

Conventional transcutaneous blood gas sensors are based on the electrochemical techniques introduced by Clark [13] for tcPO₂ and Stow-Severinghaus [14] for tcPCO₂. For

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decades the Clark-type electrode has been the only clinically available technique for tcPO_2 measurements [15]. It measures oxygen by reduction, lowering the actual and thereby measured oxygen level in the superficial skin [16, 17]. Additionally there is measurement drift over time with both techniques [18], hindering usability due to reduced accuracy, frequent calibrations and membrane changes. These limitations in reliability and usability of tcPO_2 measurements [19] have held back a widespread clinical use similar to that of tcPCO_2 measurements. However, tcPO_2 offers advantages over SpO_2 in infants in which blood gas sampling is indicated for the measurement of PaO_2 , precise PaO_2 targeting is required or the oxygen dissociation curve is markedly shifted [20, 21]. In adults the use of tcPO_2 is limited to oxygen trend monitoring due to an insuperable underestimation of PaO_2 [22]. In addition measurement drift hinders clinical usability. Removing measurement drift as an influence on the measurement by implementing drift-free optical techniques could therefore significantly improve usability of tcPO_2 measurements [23]. The recently introduced OxiVenTTM Sensor (SenTec AG, Therwil, Switzerland) combines reflectance pulse oximetry and a conventional electrochemical Stow-Severinghaus-type tcPCO_2 measurement with an optical oxygen sensing technique for measuring tcPO_2 . Fluorescence quenching [24] is the optical technique used for the measurement of oxygen, making it potentially free of drift. The main challenge in the development of this sensor was to combine two optical techniques, fluorescence quenching and pulse oximetry, without mutual interference into a single sensor which also contains an electrochemical Stow-Severinghaus tcPCO_2 measurement. In this article we will discuss the technical aspects of implementing fluorescence quenching in a combined sensor, provide the first results on measurement accuracy and evaluate its clinical implications.

2 Methods

2.1 A novel combined transcutaneous sensor

The OxiVenTTM Sensor is the first transcutaneous sensor in which an optical tcPO_2 measurement is combined with an electrochemical Stow-Severinghaus-type tcPCO_2 measurement and reflective pulse oximetry (Fig. 1). The sensor weighs 2.7 g and has a diameter of 14 mm and a height of 9 mm. All measurements are digitized within the sensor and preprocessed. The principle of an electrolyte-filled diffusion chamber is retained for the tcPCO_2 measurement. For measuring oxygen, the sensor contains an oxygen fluorescence quenching dye surface which is back-lit by an excitation light-emitting diode. On the same side of the dye, the excitation light is measured with a wavelength-filtered photodetector. In order to provide parallel optical measurements of tcPO_2

and SpO_2 , the respective light sources emit in an alternating intermittent fashion. The sensor contains dual temperature sensing for accurate heating control. The sensor can be attached to the skin using either an ear clip or adhesive rings, minimizing pressure on the skin.

2.2 Measuring principles and technology

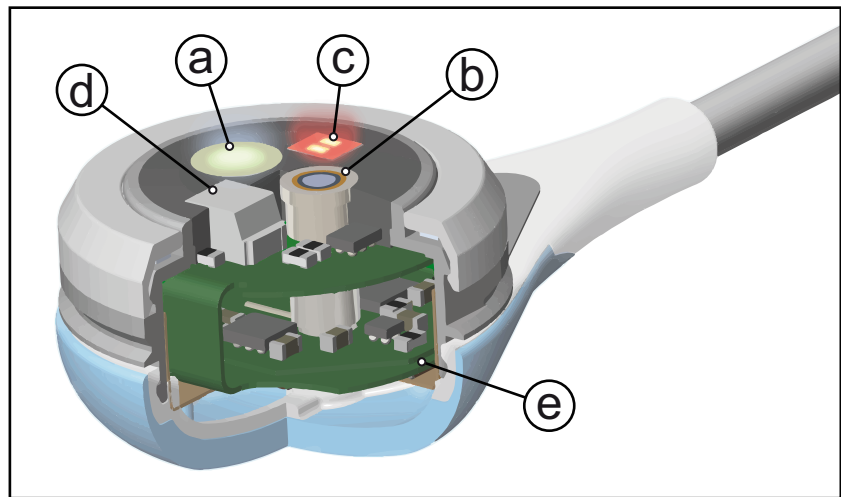
2.2.1 TCPO_2 measurement and fluorescence quenching

The OxiVenTTM Sensor measures oxygen levels with an optical technique called oxygen fluorescence quenching [24]. This technique relies on the excitation of a dye molecule by the absorption of a photon emitted by a light-emitting diode with a peak wavelength of approximately 500 nm, moving the molecule to a higher energy state. Without the presence of an oxygen molecule, the dye molecule will emit a photon at a lower specific emission wavelength (approximately 650 nm) and return to its base energy state. In the presence of an oxygen molecule, the oxygen will quench the dye and thereby prevent photon emission. In the sensing dye surface of the OxiVenTTM Sensor, fluorescence emission of each dye molecule occurs non-synchronously during a certain time interval. This results in a fluorescence intensity and decay time interval that relates to the amount of oxygen that quenches dye fluorescence. Selectively and intermittently the light intensity at the 650-nm band is measured, out of which the decay curve is reconstructed and the measured oxygen values are inferred. The oxygen diffusion to the dye results in a typical 90% response time of under 150 s. Contrary to a Clark-type electrode which reduces oxygen, influencing the oxygen level measurement itself, the fluorescence quenching technique does not affect oxygen levels.

2.2.2 TcPCO_2 measurement

In the OxiVenTTM Sensor, CO_2 is measured with a Stow-Severinghaus-type electrode. This technique is used in the majority of currently commercially available transcutaneous sensors and consists of a pH electrode in an electrolyte buffer containing sodium bicarbonate, covered by a gas-permeable membrane. Carbon dioxide diffuses from the skin through the membrane, where it causes a carbonic acid dissociation reaction. This in turn changes the pH of the solution, which is detected by the pH electrode and causes a potential change between the pH electrode and the reference silver/silver chloride electrode. In sensors with an electrochemical tcPO_2 (Clark-type) and tcPCO_2 measurement the Clark-type electrode and its inherent oxygen consumption influence pH within the diffusion chamber. Without this influence on the tcPCO_2 measurement, there is potentially a reduction in measurement drift. Multiple patient factors and sensor temperature influence the speed at which CO_2 diffuses from the skin, and

Fig. 1 Inside view of the fully digital OxiVenT™ Sensor, showing (a) tcPO₂ optical module, (b) tcPCO₂ electrochemical module, (c) pulse oximetry light-emitting diode, (d) pulse oximetry photodiode, and (e) flexible circuit board containing the temperature sensors and all electronic components and microprocessor



thereby the delay in measuring the changes in arterial values transcutaneously. In practice, this delay is usually 20–80 s from changes in ventilation to their effect on transcutaneous measurements [25, 26].

2.2.3 Reflective two-wavelength pulse oximetry

In pulse oximetry, the optically measured ratio between oxygenated and deoxygenated hemoglobin is used to measure oxygen saturation. By sending two light frequencies (660-nm and 880–890-nm wavelengths) through tissue, the light intensity that results after absorption of light by the two forms of hemoglobin can be used to calculate a ratio between the two. Only the pulsatile part of the signal is analyzed as it ideally represents the arterial component of the signal. Using a calibration model, based on measurements in healthy volunteers, for each ratio, this results in a specific oxygen saturation. Although a shift in the oxygen dissociation curve can influence the interpretation of SpO₂ values in relation to the actual PaO₂, this technique is one of the most used oxygen monitoring techniques. Two variants of the technique are often used; transmission and reflectance pulse oximetry. In transmission pulse oximetry the light emitter and detector are placed opposite to each other on both sides of tissue (e.g. a finger), while in reflectance pulse oximetry the emitter and detector are placed next to each other. This means that in transmission pulse oximetry the light path is linear and a relatively large part of the emitted light reaches the detector. In reflectance pulse oximetry the detected light is the part that is scattered and reflected back from the tissue, resulting in a weaker signal when compared with transmission pulse oximetry. In transcutaneous sensors the arterialization caused by locally heating the skin markedly improves the reflective signal-to-noise ratio [27].

2.3 Sensor validation methods

2.3.1 Hardware and software

All studies were performed using OxiVenT™ sensors with software versions 01.09-01.58, connected to a SenTec Digital Monitor (SDM) with software versions 08.00.0-08.01.1 (SenTec Monitoring Board) and 06.00.01-06.01.00 (Multi Parameter Board).

2.3.2 In vitro gas studies for the validation of tcPO₂ and tcPCO₂

An in vitro validation of the transcutaneous (O₂ and CO₂) measurements of the OxiVenT™ Sensor was performed with 10 sensors for each parameter in order to determine the accuracy and drift of these measurements. Prior to the protocol, the sensors were allowed to stabilize. Testing methods were in concordance with the FDA Guidance on cutaneous carbon dioxide and oxygen monitors (clause 6.2), as well as IEC 60601-2-23 [28]. Accuracy was tested by cycling through different combinations of gas concentrations of O₂ and CO₂. Each gas mixture was allowed to stabilize for 10 min, after which a data point was collected for each step. In the tcPCO₂ accuracy test, a total of 4 data points for both 3% CO₂ and 5% CO₂ as well as 8 data points for 10% CO₂ were collected. After 4 cycles, an additional measurement of nitrogen with 0% CO₂ was performed. A comparable method was used for the tcPO₂ accuracy test. This results in 4 data points for both 2% O₂ and 10% O₂ as well as 8 data points for 20% O₂ after 4 cycles. Following these 4 cycles, additional measurements with nitrogen (0% O₂) and with 100% O₂ were performed. For the drift test, the sensors were exposed to humidified test gas (20% O₂/10% CO₂) for the duration of the calibration interval (24 h for tcPO₂ and 12 h for tcPCO₂). The total drift over the calibration interval is given as a percentage of the

initial reading. In addition, the drift is given as %/h for the first hour (0–1 h) and last hour (11–12 h/23–24 h) of the calibration interval.

2.3.3 Clinical use of tcPO₂ and tcPCO₂

At the Neonatal Intensive Care Unit at Erasmus MC – Sophia Children’s Hospital (Rotterdam, the Netherlands), transcutaneous blood gas monitoring in preterm (24–32 weeks GA) and term neonates is performed as standard care. Existing, local, age-specific protocols for sensor temperatures and site times were applied for extreme preterm neonates (< 26 weeks GA: 42 °C, 2 h) and less preterm and term neonates (≥ 26 weeks GA: 43 °C, 3 h). tcPCO₂ was calibrated initially, and when the site time elapsed, tcPO₂ was calibrated initially and daily for verification during a tcPCO₂ calibration. Several clinical examples were selected to demonstrate the usability and feasibility of transcutaneous blood gas monitoring of tcPO₂ and tcPCO₂ with the OxiVenT™ Sensor during various clinical events. SpO₂ measurements (Masimo SET®, Masimo, Irvine, CA, USA) were recorded simultaneously with averaging over 12 s.

2.3.4 Validation of SpO₂ in healthy volunteers

Validation of the OxiVenT™ Sensor SpO₂ measurements was performed with a clinical study in healthy volunteers at the University of California (San Francisco, USA). Approval from the institutional IRB was obtained for the study protocol. The study was carried out according to the FDA Guidance on the validation of SpO₂ accuracy [29] and ISO 80601-2-61 [30]. The healthy volunteers underwent a desaturation protocol consisting of stepwise adjustments of the fraction of inspired oxygen (FiO₂), targeting specific arterial oxygen saturation (SaO₂) level plateaus. A total of two “runs” per volunteer were performed. Every SpO₂ plateau was held for about 30–60 s. Two blood samples were collected during the saturation plateaus. Each run was then ended by several breaths of 100% O₂ followed by room air while taking another sample pair of blood samples. The number of plateaus per “run” was adapted to the tolerance of the subjects to the desaturation protocol. SpO₂ was measured with several sensors on 5 different application sites; *earlobe, forehead, cheek, upper arm, and shoulder blade*. SpO₂ averaging time was set to 6 s. The sensor temperature was set to 44 °C for most sensors. For increasing statistical variety, several measurements were done at 37 °C and 41 °C.

2.4 Statistical analysis

Descriptive statistics (mean/standard deviation or median/range, depending on the distribution of the data) are given for demographic data (age, gender, and BMI). Correlation

and Bland-Altman analyses were performed in order to determine Pearson’s correlation coefficient (r), bias (d), and standard deviation (SD). In concordance with the uniformity of data presentation that follows from guideline ISO 80601-2-61:2011, the accuracy root mean square error (A_{rms}) was calculated with limits of agreement that did not take repeated measurements into account

($A_{rms} = \sqrt{\frac{\sum_{i=1}^n (\hat{y}_i - y_i)^2}{n}} = \sqrt{d^2 + SD^2}$ $A_{rms} = \sqrt{\frac{\sum_{i=1}^n (\hat{y}_i - y_i)^2}{n}} = \sqrt{d^2 + SD^2}$). In this formula, \hat{y}_i is the SpO₂ value for iteration number i , y_i is the measured SaO₂ value for the iteration number i , n is the number of samples, and d is the bias. The presented limits of agreement and the between-subject variance were calculated according to the methods of repeated measurements as described by Bland and Altman [31].

3 Results

3.1 In vitro accuracy and drift of tcPO₂ and tcPCO₂

A total of 17 tcPCO₂ and 18 tcPO₂ data points were collected with each of the 10 sensors. The number of available data points and the correlation and Bland-Altman analyses of the tcPO₂ and tcPCO₂ data compared with the gas O₂ and CO₂ partial pressures are shown in Fig. 2 and summarized in Table 1. At oxygen tensions of over 700 mm Hg, agreement of tcPO₂ with the reference gas has decreased, underestimating the pO₂. Measurement drift over different intervals shows a very small overall O₂ drift (Table 2). Drift of tcPCO₂ is notably highest during the first hour, tcPO₂ drift is not equally affected.

3.2 Clinical use of tcPO₂ and tcPCO₂

Four examples of clinical events were selected from patient files, are shown in Fig. 3, and include tcPO₂ and tcPCO₂ data, as well as the SpO₂ data obtained from standard of care pulse oximetry. These examples contain both cardiorespiratory patient events and related clinical interventions. A tcPO₂ response time of approximately 2 min longer when compared with SpO₂ and a consequential dampening effect can be observed.

3.3 Validation of SpO₂ in healthy volunteers

A total of 12 healthy volunteers participated in the study. The study demographics are shown in Table 3. At each step of the test protocol, two blood samples were drawn, of which a single-patient example is shown in Fig. 4(a). This resulted in a total of 2244 SaO₂-SpO₂ data pairs. The median of all measured SaO₂ values is 84.8% (IQR 76.1–93.4%, range 68.0–

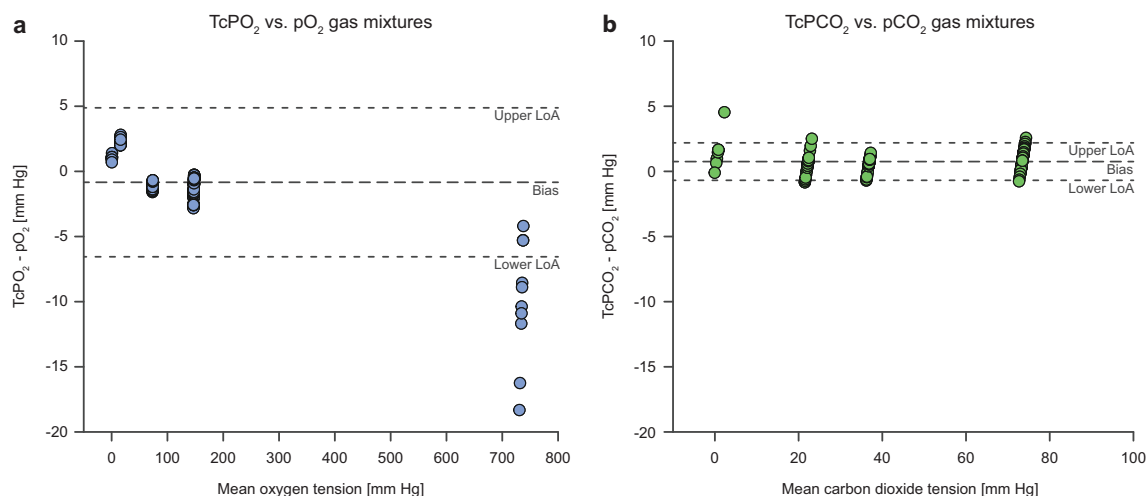


Fig. 2 Bland-Altman plots of the agreement of in vitro tcPO₂ (a) and tcPCO₂ (b) measurements with calibration gas mixtures. The accuracy, bias, and limits of agreement (LoA) for each measurement are shown in Table 1.

100.6%). The correlation plot of the SaO₂ values with the corresponding SpO₂ measurements obtained with the OxiVenTTM Sensor at all five measurement sites is shown in Fig. 4(b). The accuracy and agreement analyses for the separate measuring sites show the narrowest limits of agreement when measuring at the forehead and cheek, with the highest accuracy when measured at the forehead (Table 4).

4 Discussion

With these studies, we present data on the OxiVenTTM Sensor, the first combined tcPO₂, tcPCO₂, and SpO₂ transcutaneous sensor incorporating an optical tcPO₂ measurement that is designed to eliminate measurement drift. The in vitro results confirm a good tcPO₂ accuracy and negligible overall measurement drift. Decreased tcPO₂ accuracy and precision can be observed at very high oxygen tensions, together with underestimation of PaO₂. This is most likely a consequence of the abundance of oxygen, leading to a short fluorescence decay time in combination with a high intensity. However, these supraphysiological levels are not likely to be clinically relevant. TcPCO₂ accuracy and drift are on par with previous sensor generations [32]. TcPCO₂ drift is highest during the first hour

of measurement, possibly due to equilibration effects. TcPO₂ drift does not seem to be equally affected, providing a more consistently accurate measurement from onset. Furthermore, SpO₂ shows excellent correlation and agreement with SaO₂ values in adult volunteers, particularly when measuring at the forehead or cheek. Although transcutaneous blood gas measurements have retained their place in the clinic after the introduction of pulse oximetry, the technique has remained laborious [33–35]. When measurements are considered to be in disagreement with arterial values, they require training to be able to distinguish technical failure or measurement drift from patient factors influencing the measurement. As a consequence, transcutaneous monitoring is most often used when the required dedicated attention is outweighed by the advantages, such as in neonatal intensive care units or sleep laboratories. The logical innovation in transcutaneous blood gas monitoring is consequently the introduction of drift-free measurement techniques, making transcutaneous monitoring more accurate and easy to use. In the investigated OxiVenTTM Sensor, an optical tcPO₂ measurement has been implemented for this purpose. The main patient-related limitation of transcutaneous tcPO₂ and tcPCO₂ measurements is inaccuracy due to the influence of skin thickness and microcirculatory impairment on the

Table 1 In vitro accuracy of tcPO₂ (0–100%) and tcPCO₂ (0–10%) measurements

Measurement	Data points (<i>n</i>)	Accuracy (mm Hg)	Bias (mm Hg)	Limits of agreement (mm Hg)		<i>r</i>
				Lower	Upper	
		<i>A</i> _{rms}				
tcPO ₂	180	3.0 (2.9)	− 0.8	− 6.6	4.9	0.999
tcPCO ₂	170	1.1 (0.7)	0.8	− 0.7	2.2	0.999

Values measured with the OxiVenTTM Sensor and compared with calibration gas mixtures

Table 2 Data on drift of tcPO₂ (24-h calibration interval) and tcPCO₂ (12-h calibration interval)

	Total drift during calibration interval (12 h/24 h) (%)	Drift during first hour of calibration interval (%/h)	Drift during last hour of calibration interval (%/h)
tcPO ₂	0.30 (0.63)	0.14 (0.28)	0.03 (0.21)
tcPCO ₂	-2.53 (1.04)	0.49 (0.28)	0.18 (0.09)

Data is shown as mean (SD)

Table 3 Volunteers characteristics

No. of volunteers	12
Age (years)	25 (23–34)
Male/female	7/5
Skin type	
- Dark	2
- Medium	5
- Light	5

Values are listed as median (range), where applicable

diffusion of blood gases [2, 18, 36]. TcPO₂ accuracy is known to suffer more from these influences than tcPCO₂ accuracy due to the higher skin diffusion resistance to oxygen [4], leading to wide limits of agreement in clinical studies on tcPO₂ [11, 37]. In addition, the traditional electrochemical tcPO₂ sensors contained Clark-type electrodes, which consume oxygen as part of the measurement [2, 6]. The implementation of an optical measurement technique for tcPO₂ therefore potentially has a greater measurement technique-related impact on accuracy for than it would have for tcPCO₂. Clinical measurements

of tcPO₂ and tcPCO₂ in the Neonatal Intensive Care Unit suggest good usability and response to clinical events. The relatively long tcPO₂ response time makes it unsuitable for detecting apneic episodes and oxygenation dips. In adults, the inability to measure tcPO₂ values that mirror PaO₂ values limits the use in the adult population to oxygen trend monitoring. However, the improved reliability of the tcPO₂ trend could clinically have a greater impact than improved agreement with blood gas samples. Data on the user preference of using either absolute values

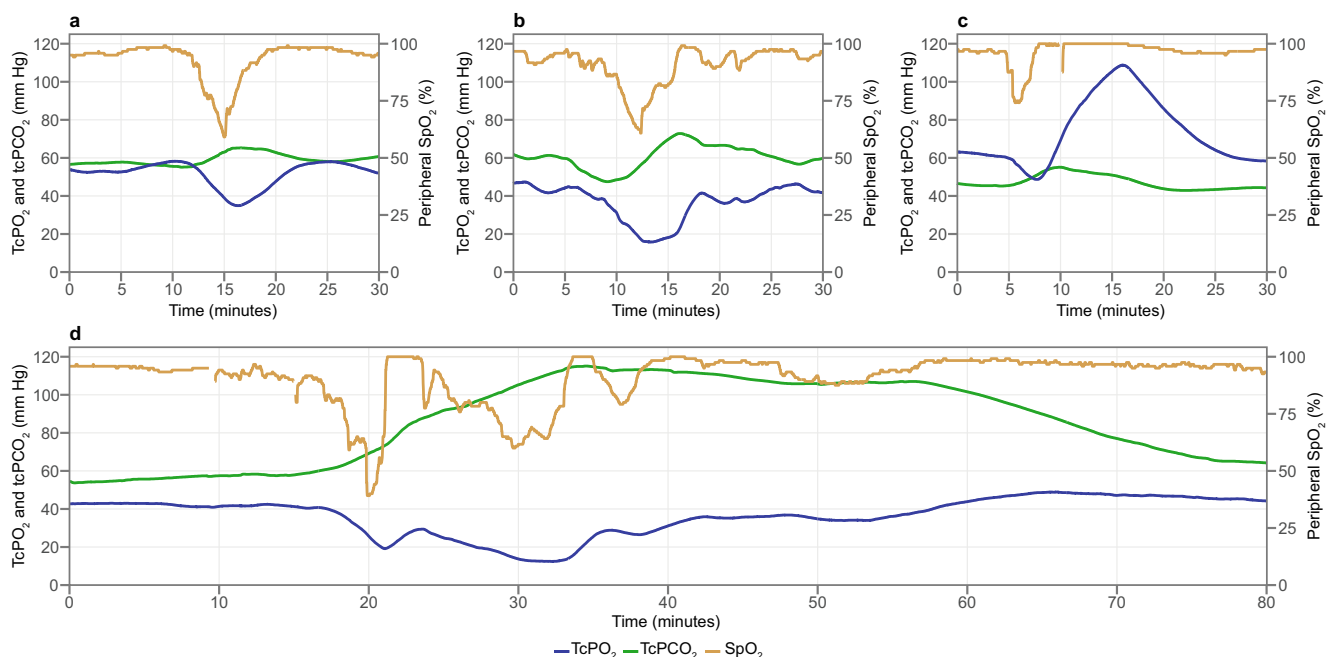
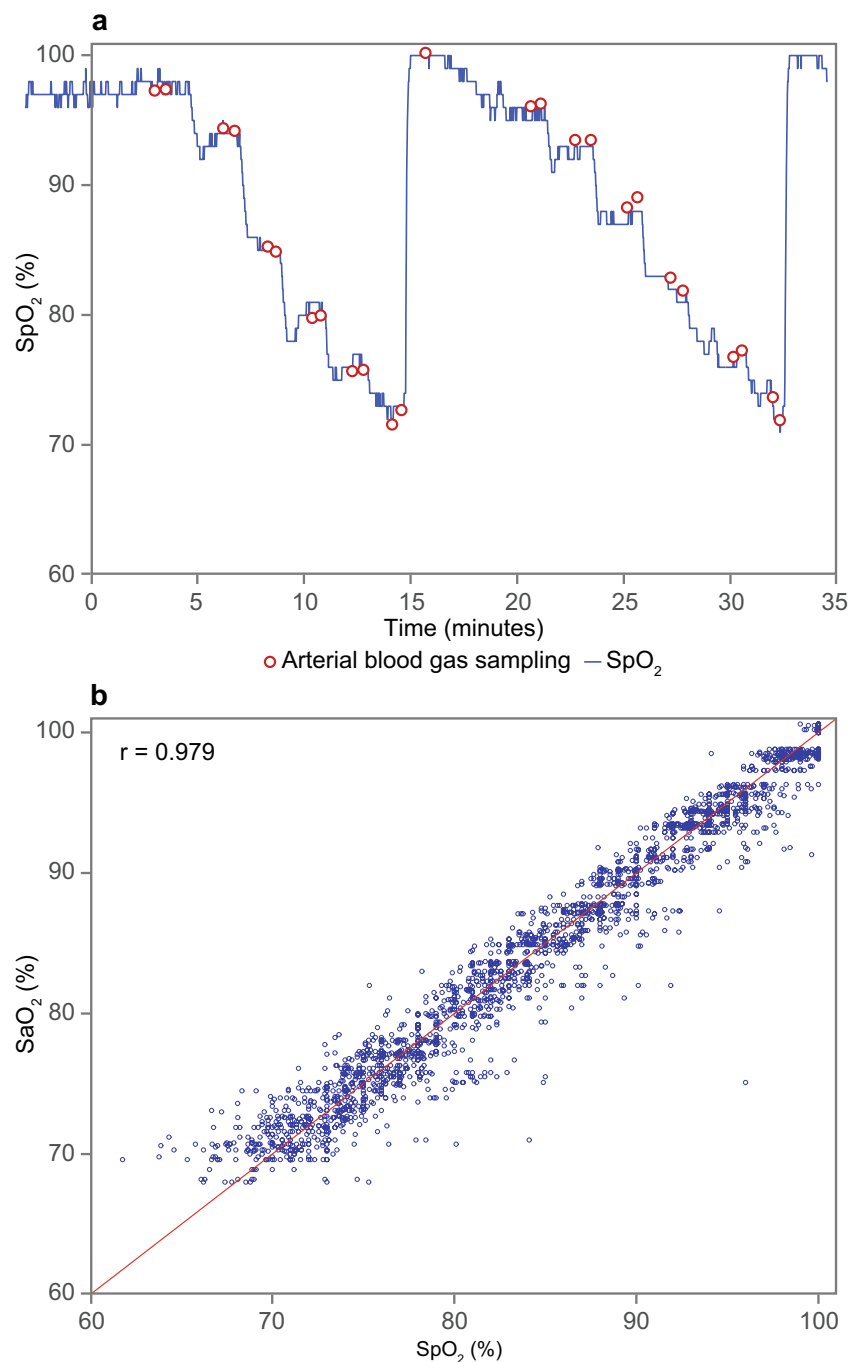


Fig. 3 Clinical examples of tcPO₂ and tcPCO₂ measured in preterm neonates with the OxiVenTTM Sensor during relevant events, supplemented with standard of care peripherally measured transmission pulse oximetry. These examples show the following events: (a) Very preterm neonate, born at a gestational age (GA) of 28 weeks and with a birth weight (BW) of 1200 g. Drop in oxygen saturation to 56% SpO₂ due to retention of sputum, following by suctioning, accompanied by a transient rise of tcPCO₂ and decrease of tcPO₂ down to 35 mm Hg. (b) Extreme preterm neonate, GA 27 weeks, BW 800 g. Capillary blood sampling at an extremity, leading to agitation and crying with a consequential drop in oxygen saturation to 55% and tcPO₂ to 16 mm Hg. Noteworthy is the temporary drop in tcPCO₂ due to crying,

followed by a rise due to a decline in respiratory effort. The patient's lungs were recruited due to clinical indications of bronchospasms. The FiO₂ was increased from 0.21 to 0.40 during this process. (c) Late preterm neonate, GA 36 weeks, BW 2500 g. Short period of bradycardia which was followed by a drop in oxygen saturation. As a clinical intervention, the FiO₂ was increased from 0.21 to 0.39 for 4 min, leading to a period of hyperoxia up to 109 mm Hg that was undetected by pulse oximetry. (d) Extreme preterm neonate, GA 24 weeks, BW 700 g. During nursing with patient repositioning multiple episodes of bradycardia down to 50 heart beats per minute, with drops in SpO₂ down to 40% and slow recovery. The decline in respiratory effort and slow recovery are reflected by the clear and persistent elevation of CO₂ levels

Fig. 4 (a) Single-patient example of the controlled desaturation protocol in which a stepwise decrease in SpO_2 is achieved by controlled lowering of the FiO_2 . Dots indicate the moments when an arterial blood sample was taken during a relative plateau phase. (b) Correlation plot ($r = 0.979$) of SaO_2 in % from all arterial blood samples and SpO_2 in % measured with the OxiVenTTM Sensor at the moment of blood sampling ($n = 2244$)



or trends is however limited and specific for patient populations. With the new OxiVenTTM Sensor, the potential of optical techniques has been demonstrated. In clinical use, this combined sensor will however still require frequent calibration of the electrochemical tcPCO_2 measurement, negating the potential benefit on calibration strain for both patients and personnel. Although this study provides useful information on the technical performance of this new combined sensor, clinical validation is needed to evaluate its impact and limitations.

5 Conclusion

Our results show the successful integration of a new optical oxygen measuring technique in a non-invasive, combined tcPO_2 , tcPCO_2 , and SpO_2 sensor. In vitro tcPCO_2 measurement performance is unchanged when compared with literature on previous sensor generations. Reflectance pulse oximetry correlates well in a study on healthy volunteers. The new optical tcPO_2 measurement is virtually drift-free in vitro. Despite showing good usability in clinical examples, the

Table 4 Agreement between SpO₂ and SaO₂ at different measurement sites

Application site	SaO ₂ -SpO ₂ pairs	Accuracy (%)	Bias (%)	Limits of agreement (%)		<i>r</i>
				Lower	Upper	
Earlobe	451	2.44	1.16	- 3.17	5.49	0.973
Forehead	526	1.35	- 0.29	- 2.89	2.31	0.990
Cheek	476	1.29	0.56	- 1.75	2.86	0.992
Upper arm	415	2.41	0.38	- 4.39	5.15	0.971
Shoulder blade	376	2.13	- 1.34	- 4.64	1.96	0.989
Overall	2244	2.09	0.13	- 3.17	3.98	0.979

Pooled SaO₂-SpO₂ A_{rms} (not corrected for repeated measurements), bias, limits of agreement (corrected for repeated measurements), and Pearson's correlation coefficient (not corrected for repeated measurements) per application site

clinical benefit needs to be proven. Additionally, clinical data is needed to validate this sensor to arterial blood samples in specific patient populations.

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Compliance with ethical standards

Conflict of interest The authors J. Hayoz, Ch. Ellenberger, and P.M. Schumacher are employees and shareholders of SenTec AG. J. Hayoz is a board member of SenTec AG.

Research involving human participants and/or animals All procedures performed in studies involving human participants 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 or comparable ethical standards.

Informed consent For the healthy volunteer study, informed consent was obtained from all individual participants; for the other studies, formal consent was not required.

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