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 OxiVenT™ 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
decades the Clark-type electrode has been the only clinically available technique for tcPO2 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 tcPO2 measurements [19] have held back a widespread clinical use similar to that of tcPCO2 measurements. However, tcPO2 offers advantages over SpO2 in infants in which blood gas sampling is indicated for the measurement of PaO2, precise PaO2 targeting is required or the oxygen dissociation curve is markedly shifted [20, 21]. In adults the use of tcPO2 is limited to oxygen trend monitoring due to an insuperable underestimation of PaO2 [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 tcPO2 measurements [23]. The recently introduced OxiVenT™ Sensor (SenTec AG, Therwil, Switzerland) combines reflectance pulse oximetry and a conventional electrochemical Stow-Severinghaus-type tcPCO2 measurement with an optical oxygen sensing technique for measuring tcPO2. 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 tcPCO2 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 OxiVenT™ Sensor is the first transcutaneous sensor in which an optical tcPO2 measurement is combined with an electrochemical Stow-Severinghaus-type tcPCO2 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 tcPCO2 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 tcPO2 and SpO2, 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 TcPO2 measurement and fluorescence quenching

The OxiVenT™ 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 OxiVenT™ 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 TcPCO2 measurement

In the OxiVenT™ Sensor, CO2 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 tcPO2 (Clark-type) and tcPCO2 measurement the Clark-type electrode and its inherent oxygen consumption influence pH within the diffusion chamber. Without this influence on the tcPCO2 measurement, there is potentially a reduction in measurement drift. Multiple patient factors and sensor temperature influence the speed at which CO2 diffuses from the skin, and
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, a total of 4 data points for both 3% CO₂ and 5% CO₂ as well as 8 data points for 10% O₂ were collected. After 4 cycles, an additional measurement of nitrogen with 0% O₂ 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 week 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 80601-2-61:2011, the accuracy root mean square error (Arms) was calculated with limits of agreement that did not take repeated measurements into account (Arms = \sqrt{\frac{\sum (y_i - \bar{y})^2}{n}} = \sqrt{d^2 + SD^2} \text{ Arms} = \sqrt{\frac{\sum (y_i - \bar{y})^2}{n}} = \sqrt{d^2 + SD^2} ). In this formula, \( y_i \) is the SpO₂ value for iteration number i, \( \bar{y} \) 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-Altmann 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–
The correlation plot of the SaO\textsubscript{2} values with the corresponding SpO\textsubscript{2} measurements obtained with the OxiV enT™ 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 OxiV enT™ Sensor, the first combined tcPO\textsubscript{2}, tcPCO\textsubscript{2}, and SpO\textsubscript{2} transcutaneous sensor incorporating an optical tcPO\textsubscript{2} measurement that is designed to eliminate measurement drift. The in vitro results confirm a good tcPO\textsubscript{2} accuracy and negligible overall measurement drift. Decreased tcPO\textsubscript{2} accuracy and precision can be observed at very high oxygen tensions, together with underestimation of PaO\textsubscript{2}. 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. TcPCO\textsubscript{2} drift is highest during the first hour of measurement, possibly due to equilibration effects. TcPO\textsubscript{2} drift does not seem to be equally affected, providing a more consistently accurate measurement from onset. Furthermore, SpO\textsubscript{2} shows excellent correlation and agreement with SaO\textsubscript{2} 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 OxiV enT™ Sensor, an optical tcPO\textsubscript{2} measurement has been implemented for this purpose. The main patient-related limitation of transcutaneous tcPO\textsubscript{2} and tcPCO\textsubscript{2} measurements is inaccuracy due to the influence of skin thickness and microcirculatory impairment on the

### Table 1

| Measurement | Data points (n) | Accuracy (mm Hg) | Bias (mm Hg) | Limits of agreement (mm Hg) | \( r \) |
|-------------|----------------|-----------------|--------------|-----------------------------|-------|
| tcPO\textsubscript{2} | 180 | 3.0 (2.9) | −0.8 | −6.6 to 4.9 | 0.999 |
| tcPCO\textsubscript{2} | 170 | 1.1 (0.7) | 0.8 | −0.7 to 2.2 | 0.999 |

Values measured with the OxiV enT™ Sensor and compared with calibration gas mixtures.
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

| 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) |
| tcPO₂ | 0.30 (0.63) | 0.14 (0.28) | 0.03 (0.21) |
| tcPCO₂ | −2.53 (1.04) | 0.49 (0.28) | 0.18 (0.09) |

Data is shown as mean (SD)

Fig. 3 Clinical examples of tcPO₂ and tcPCO₂ measured in preterm neonates with the OxiVenT™ 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% due to retention of sputum, followed 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.
or trends is however limited and specific for patient populations. With the new OxiVen™ Sensor, the potential of optical techniques has been demonstrated. In clinical use, this combined sensor will however still require frequent calibration of the electrochemical tcPCO₂ 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 tcPO₂, tcPCO₂, and SpO₂ sensor. In vitro tcPCO₂ 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 tcPO₂ measurement is virtually drift-free in vitro. Despite showing good usability in clinical examples, the 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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