Accuracy of Transcutaneous Carbon Dioxide Measurement in Premature Infants

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Background. In premature infants, maintaining blood partial pressure of carbon dioxide (pCO₂) value within a narrow range is important to avoid cerebral lesions. The aim of this study was to assess the accuracy of a noninvasive transcutaneous method (TcpCO₂), compared to blood partial pressure of carbon dioxide (pCO₂). Methods. Retrospective observational study in a tertiary neonatal intensive care unit. We analyzed the correlation between blood pCO₂ and transcutaneous values and the accuracy between the trends of blood pCO₂ and TcpCO₂ in all consecutive premature infants born at <33 weeks’ gestational age. Results. 248 infants were included (median gestational age: 29 + 5 weeks and median birth weight: 1250 g), providing 1365 pairs of TcpCO₂ and blood pCO₂ values. Pearson’s R correlation between these values was 0.58. The mean bias was −0.93 kPa with a 95% confidence limit of agreement of −4.05 to +2.16 kPa. Correlation between the trends of TcpCO₂ and blood pCO₂ values was good in only 39.6%. Conclusions. In premature infants, TcpCO₂ was poorly correlated to blood pCO₂, with a wide limit of agreement. Furthermore, concordance between trends was equally low. We warn about clinical decision-making on TcpCO₂ alone when used as continuous monitoring.

1. Background

The partial pressure of carbon dioxide (pCO₂) strongly influences cerebral perfusion in premature infants that have reduced autoregulation capacity. Thus, monitoring pCO₂ to avoid hyper- or hypocapnia and associated brain injury has become standard of care [1, 2]. Although some studies advocate “permissive hypercapnia” to limit lung injury due to mechanic ventilation, this attitude remains controversial [3]. In any case, most neonatologists consider it best practice to closely monitor pCO₂ in premature infants, especially when they are ventilated.

Currently, the gold standard to measure tissue pCO₂ is the blood gas analysis. However, this method has disadvantages, as it might contribute to spoliative anemia and is painful if done by capillary sampling. Therefore, other pCO₂ monitoring methods have been developed during the last three decades [4].

End-tidal CO₂ measurement provides a noninvasive estimate of the blood pCO₂ in ventilated patients. However, its use in premature infants is limited by the small tidal volumes and increased dead space caused by the measurement device inserted into the ventilation circuit. Furthermore, it is impossible or unreliable to use during alternate ventilation methods such as high frequency oscillation ventilation [5] or spontaneous breathing with or without continuous positive airway pressure.

Transcutaneous pCO₂ (TcpCO₂) was developed in the 1960s. A calibrated skin sensor, heated to 40–45°C (100–110°F) in order to arterialize the capillary bed and facilitate CO₂ diffusion, can then measure the pCO₂ in a thin liquid film between skin and sensor. Such devices are widely used in neonatal intensive care settings [6]. Several small studies in neonatal populations (the largest including 60 patients) have analyzed the correlation and concordance between the TcpCO₂ and blood pCO₂ [7–11]. The quality of the concordance between the two methods remains debated. One study in healthy adults has shown that very short-term trends appear accurate, with a mean TcpCO₂ lag of about one minute after acute changes in arterial pCO₂ [12]. However, no published study investigated the accuracy of TcpCO₂ trends over longer periods.
The objective of our study was to assess, in a large neonatal population, the accuracy point values as well trends of TcpCO$_2$ compared to blood pCO$_2$.

2. Methods

This retrospective observational study included all consecutive premature infants born $<33$ weeks of postmenstrual age, admitted to our tertiary Neonatal Intensive Care Unit (NICU) at Geneva University Hospital over a period of four years starting from 1/1/2009.

All data during the first 28 days of life of these neonates were prospectively recorded in our electronic clinical data system (CliniSoft®, General Electric Healthcare, Milwaukee, WI, USA).

2.1. Blood pCO$_2$ Determinations. The blood pCO$_2$ was immediately analyzed after sampling on a Radiometer ABL800 analyzer (Radiometer, Bronshøj, Denmark). All results were automatically retrieved into our clinical data system including the time of determination. As several studies suggest that arterial, venous, and capillary blood pCO$_2$ levels can be considered identical [13, 14], we did not differentiate the type of blood sample.

2.2. Transcutaneous pCO$_2$ (TcpCO$_2$) Determinations. All TcpCO$_2$ sensors (TCM4®, Radiometer, Copenhagen, Denmark) were applied according to the manufacturer's recommendations and to our unit protocol: the sensor was calibrated every two to four hours, the skin cleaned with sterile water, two to three drops of specific contact gel were applied, and sensor was placed on the inside of the infant’s thigh (on alternate sides, after each recalibration). The sensor temperature was set according to the manufacturer’s guidelines (41°C for infants 500 g to 750 g and 42°C for infants 751 g to 2000 g). The membrane was changed every 14 days.

At least once an hour, the nurse in charge of the patient manually entered the TcpCO$_2$ value into the electronic clinical data system.

2.3. Data Analysis. We considered pairs of TcpCO$_2$ and blood pCO$_2$ when both values were measured within an interval of 10 minutes.

The accuracy of point values was then assessed by three methods:

1. The proportion of values where the difference between TcpCO$_2$ and blood pCO$_2$ was less than 10% and its 95% confidence interval of agreement.
2. The correlation between TcpCO$_2$ and blood pCO$_2$ values; we considered, a priori, a good correlation defined by a Pearson $R > 0.8$.
3. A Bland-Altman plot, to report the mean bias and 95% confidence limits of agreement between the two methods [15]; TcpCO$_2$ and blood pCO$_2$ values were averaged across the range and the mean bias was calculated as the mean difference between TcpCO$_2$ and blood pCO$_2$, and the 95% confidence limits of agreement between the two methods were defined as 1.96 times the standard deviation of the mean difference between TcpCO$_2$ and blood pCO$_2$.

The accuracy of trends was assessed for all consecutive pairs of TcpCO$_2$ and blood pCO$_2$, when pairs were measured within a six-hour interval. The trends of both values were expressed in percentage of change. Concordance between TcpCO$_2$ and blood pCO$_2$ trends was defined, a priori, as good if the difference between the values was $\leq$10%, moderate if the difference was 11 to 20%, and poor if the difference was $>20$% (see examples in Table 1).

All statistical analyses were performed with SPSS version 20 for Mac (SPSS, Chicago, IL, USA).

2.4. Sample Size. We anticipated 75% of good concordance between trends of TcpCO$_2$ and blood pCO$_2$. To obtain a 95% confidence interval smaller than $\pm$5% around the proportion of good concordance, we calculated that at least 288 trends for each method would be required. We planned to include as many patients as possible, over a four-year period (to avoid historical biases), as long as the required number of inclusions would be matched.

The ethics committee of Geneva University Hospital approved the study.

3. Results

From January 1st 2009 to December 31st 2012, 248 patients were consequently included in this study. The median

### Table 1: Examples of concordance classification between blood pCO$_2$ and transcutaneous pCO$_2$.

| Example | Blood pCO$_2$ | TcpCO$_2$ | Trends’ difference | Trends’ concordance |
|---------|---------------|------------|---------------------|---------------------|
|         | $T_0$ | $T_1$ | Trend | $T_0$ | $T_1$ | Trend |                       |
| 1       | 5.2  | 5.6  | +7.7% | 5.2  | 5.2  | +0%   | 7.7% Good               |
| 2       | 5.2  | 5.6  | +7.7% | 5.2  | 6.4  | +23.1%| 15.4% Moderate           |
| 3       | 5.2  | 5.6  | +7.7% | 5.8  | 4.6  | -21.4%| 29.1% Poor               |

Four examples of blood pCO$_2$ and TcpCO$_2$ trends within six-hour periods, with difference between trends, and the qualitative assessment of the concordance. All pCO$_2$ values are in kPa.

$T_0$: measures at baseline.

$T_1$: measures within a six-hour interval.
Figure 1: Scatter plot of the blood pCO₂ and the TcpCO₂ of values measured <10 min. Scatter plot of the blood pCO₂ (x-axis) and the TcpCO₂ (y-axis) of values measured <10 minutes apart. Values are in kPa. n = 1365. Pearson’s R = 0.58 (p < .001).

Figure 2: Bland-Altman plot of the average TcpCO₂ and blood pCO₂ values. Bland-Altman plot of the average TcpCO₂ and blood pCO₂ values (x-axis) and difference between TcpCO₂ and blood pCO₂ values (y-axis). n = 1365. Mean bias = −0.93 kPa and 95% confidence limit of agreement = −4.05 to +2.16 kPa.

Figure 3: Scatter plot of the changes in blood pCO₂ and the TcpCO₂ six-hour trends. Scatter plot of the changes in blood pCO₂ (x-axis) and the TcpCO₂ (y-axis) six-hour trends. n = 313 pairs. Pearson’s R = 0.25; p < .001.

4. Discussion

Our results suggest that transcutaneous pCO₂ with the TCM4® is not accurate in a general neonatal intensive care setting. The correlation between TcpCO₂ and blood pCO₂ was poor (Pearson’s R = 0.58) and the 95% confidence limits of agreement wide (−4.05 kPa to 2.16 kPa) in the Bland-Altman analysis. The concordance between the six-hour trends of blood pCO₂ and TcpCO₂ was also poor, with only 39.6% of good concordance.

Several studies have analyzed the accuracy and the reliability of TcpCO₂ monitoring, with conflicting results. Whereas some have described poor correlation between TcpCO₂ and blood pCO₂ [10, 16], others have shown better results [11, 17–19]. Kesten et al. have suggested very short-term trends, of a few minutes, to be accurate in healthy adults [12]. Two studies have described poor correlation blood pCO₂ values for high values [7, 10].
Our study reports 1365 pairs of TcpCO\textsubscript{2} and blood pCO\textsubscript{2} in 248 different neonatal subjects, to assess the reliability of the noninvasive technique. Our Bland-Altman analysis is in line with a worsening correlation for high values (>10 kPa), but the rather low number of data points does not allow concluding in this matter (Figure 2). However, our study, with the largest number of matching samples published so far, strongly supports the studies with poor agreement between TcpCO\textsubscript{2} and blood pCO\textsubscript{2}.

Our study is the first to report concordance between trends of TcpCO\textsubscript{2} and blood pCO\textsubscript{2} in premature infants. Indeed, although the point value correlation might be poor, most clinicians would rely on the trend of the TcpCO\textsubscript{2} as a surrogate of the blood pCO\textsubscript{2}'s changes over time. Only one-third of the samples showed a good concordance of trends over a six-hour period.

It is legitimate to wonder if such monitoring may not lead to wrong clinical decisions or increased blood sampling to confirm values. Furthermore, as the sensor heats the skin to 41–42°C, it might cause discomfort and even injure the youngest infants' very fragile skin. Finally, the use of TcpCO\textsubscript{2} is expensive. According to the manufacturer, the sensor needs recalibration every three to four hours using a specific gas cylinder. The skin fixation rings have to be relocated every 12 to 24 hours, and the sensor's membrane changed every one to two weeks. In our unit, the average yearly cost for one device used 24/7 is 10500$.

Some limitations to our study must be recognized. First, it is a retrospective study, and although the TcpCO\textsubscript{2} values were recorded prospectively into the electronic clinical data system, it is impossible to retrospectively assess the skin's perfusion at the precise time. Second, our data system does not report the heating power or the sensor temperature or the precise site of use of the sensor. Therefore, we cannot ascertain the quality of each measured value. However, our nurses are instructed to use the probe according to the manufacturer's guidelines and to record the TcpCO\textsubscript{2} value only when it has stabilized, and the large number of data points analyzed increases the credibility of our findings. Finally, the Bland-Altman analysis was not modified to adjust for multiple measures in the same patient [20]. However, the median of median number of repeated measures was low (4) compared to the number of patients (248). Furthermore, adjusting for multiple measures would only have increased the agreement limit. Despite the limitations, we would argue that our results represent very closely real life use of TcpCO\textsubscript{2} and certainly those used in our own clinical practice to take decisions.

5. Conclusion

Our data show that TcpCO\textsubscript{2} with the TCM4\textsuperscript{®} poorly correlate to blood pCO\textsubscript{2}, with a wide confidence limit of agreement. A low concordance was also noted between trends of TcpCO\textsubscript{2} and blood pCO\textsubscript{2}. We therefore warn about the sole use of TcpCO\textsubscript{2} for clinical decision-making. Prospective, short-term correlations for value points and trends need to be assessed in further research as well as in nonneonatal populations.

Abbreviations

VLBW: Very low birth weight
pCO\textsubscript{2}: Partial pressure of carbon dioxide (pCO\textsubscript{2})
TcpCO\textsubscript{2}: Transcutaneous partial pressure of carbon dioxide
NICU: Neonatal intensive care unit.

Disclosure

In particular, Radiometer did not provide funding, equipment, or consumables.

Competing Interests

The authors have no competing interests.

Authors’ Contributions

Marie Janaillac conceived of the study and its design and drafted the paper. Sonia Labarinas participated in the design of the study and helped to draft the paper. Riccardo Pfitzer participated in the design and helped to draft the paper. Oliver Karam participated in the design of the study, performed the statistical analysis, and helped to draft the paper. All authors read and approved the final paper.

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