RELIABILITY OF TRANSCUTANEOUS CARBON DIOXIDE MONITORING IN PREMATURE INFANTS WITH CHRONIC LUNG DISEASE

SYNOPSIS
We studied 15 premature infants with chronic lung disease (CLD) to evaluate the reliability of using transcutaneous CO₂ (tc PCO₂) measurements in estimating arterial CO₂ (PaCO₂) values. The regression equations between tc PCO₂ (Y) and PaCO₂ (X) were Y = 0.97 + (1.78) X (torr) with r = 0.86 and Sy. x = 13.7 torr, and Y = 2.93 + (1.73) X (torr) with r = 0.84 and Sy. x = 15.6 torr for comparisons of 160 arterial samples and 87 capillary samples, respectively. We identified isolated deviant points from serial tc PCO₂ and PaCO₂ comparisons. This, together with the observed systematic fluctuations of tc PCO₂ relationship over protracted intervals accounted for the large scatter in the regression data. For the 7 CLD infants studied in time series analysis, there were 5.2 and 6.3% probabilities that this was a random phenomena for two cases. Technical errors or single physiological changes were not associated with these observations. We concluded that tc PCO₂ monitoring is clinically useful in following short-term trends of changing CO₂ status in CLD infants. However, the large scatter in our regression data would preclude using the regression equation to estimate PaCO₂ from measured tc PCO₂ in these patients.

INTRODUCTION
Infants with chronic lung disease or bronchopulmonary dysplasia (BPD) are prime candidates for extensive transcutaneous CO₂ monitoring. Hypercarbia, which develops during passive oxygenation of patients with pulmonary edema, during assisted ventilation of those with refractory hypoxia, during weaning from...
assisted ventilation, and during apneic episodes, is a frequent problem in such patients but may not be adequately predicted from the combination of transcutaneous O₂ (tc PO₂) monitoring and arterial blood gases (1). Moreover, acceptance of tc PO₂ monitoring generally is encouraged by the strong correspondence between PaCO₂ and tc PO₂ measurements [reported r values for PaCO₂ and tc PO₂ comparisons in newborn populations range from 0.79 to 0.98 (2)], the associated conservation of patient blood, relative absence of risk, convenience, and continuous nature of tc PO₂ data. On the negative side, most reports describe tc PO₂ values as 1.3 to 1.4 times greater than PaCO₂ values, so that clinician must a) decide tc PO₂ information is unique, requiring independent interpretation or b) develop schemes for estimating PaCO₂ from tc PO₂ values. Tremper et al. (3) have suggested that the tc PO₂ instrument display be adjusted to PaCO₂-like values termed “estimated PaCO₂” or “adjusted to PaCO₂” based on the equation:

\[
\text{adjusted tc PO}_2 = \frac{\text{measured tc PO}_2 - \text{intercept}}{\text{slope}}
\]

where the slope and intercept are derived from regression analysis of PaCO₂ and tc PO₂ determinations on a population of premature and term infants with mixed diagnoses.

We decided to retrospectively evaluate the reliability of tc PO₂ as an estimate of PaCO₂ and as a trend monitor of chronic lung diseased patients during the course of their therapy. We compared the regression analysis of their tc PO₂ with blood CO₂ tensions in both arterial and capillary specimens. We questioned how “estimated PaCO₂” data based on regression analysis from a mixed newborn population compared with measured blood CO₂ tension during long term therapy of these infants. Our findings are described in this report.

METHODS AND MATERIALS

Subjects of the study (n = 15) were all premature, sick infants diagnosed as having bronchopulmonary dysplasia. They were treated in the neonatal intensive care unit of University hospital during an eight-month interval and had arterial and capillary blood gas determinations performed as part of their routine management. Although all were being treated for BPD, they had a spectrum of concurrent pathologies, including anemia, sepsis, hypoglycemia, patent ductus arteriosus, intracranial hemorrhage (Grade IV), seizures, hyperbilirubinemia, and hypocalcemia. The average gestational age was 29 ± 3 wk (X ± SD). The average birth weight was 1053 ± 361 g. Ventilator regulation and FiO₂ adjustments for the infants studied were based on PaCO₂, PaO₂, and tc PO₂ measurements.

One hundred acutely ill premature newborns (including the 15 subjects who later developed BPD) formed the reference group whose tc PO₂ and PaCO₂ comparisons were used to derive the population regression data with which to calculate “estimated PaCO₂” values on BPD infants. Diagnosis for the reference group patients was diverse but most had hyaline membrane disease. For regression analysis, we used only one randomly selected transcutaneous and blood CO₂ tension comparison made on each infant. This reference group’s least squares regression relationship between tc PO₂ (Y) and PaCO₂ (X) was:

\[ Y = -2.8 + (1.86) (X) \text{ (torr)} \]

where \( r = 0.86 \) and \( S_{xy} = 12.9 \) torr as reported elsewhere (8).

Sixteen acutely ill premature neonates without diagnosed BPD who received tc PO₂ for routine management constituted the control group for the randomness time series analysis (9). PaCO₂ and tc PO₂ comparisons (n = 39) from the control group were limited to one set per day every third day for each infant. Three or fewer comparisons per infant were used. The interval studied was 23 d. These comparisons were “random”. They demonstrated that any time dependent instrument, operator, or other method related factors did not account for the time series findings with the BPD patient data.

We determined tc PO₂ with three different carbon dioxide monitors of the same design (model TCM 20, Radiometer America Inc., Cleveland, OH 44145). Two point calibrations were performed at the beginning of each monitoring session with dry CO₂ standard gases (5% and 10% CO₂ in N₂). In vivo drift was determined at the end of each monitoring session. The maximum allowable drift was 4 torr. Calibrations and patient measurements were made with the electrode temperature at 44°C. Heater power and tc PO₂ measurements were recorded by an external recorder.

We determined blood gases in duplicate on two blood gas analyzers (Model 813, Instrumentation Laboratory Inc., Lexington, MA 02173). Standard assay protocols and quality control routines were used (10). Imprecision of PaCO₂ measurements as determined by analysis of tonometersed blood or commercial control solutions is approximately 3% CV (11).

For BPD patients, a total of 247 blood gas measurements (160 by arterial sample and 87 by capillary sample) were compared with tc PO₂ concurrently monitored. The arterial blood samples were collected from umbilical, radial or dorsalis pedis arteries. Capillary blood samples were collected from the heel area according to standard protocol. The term PaCO₂ will be used for blood CO₂ tensions in either arterial and capillary specimens throughout this report unless noted otherwise. Temperature corrections were not made on either transcutaneous or blood gas data.

There were 221 separate tc PO₂ monitoring sessions on the BPD patients. The mean duration per session was about 3 h (range: about 1 to 5 h). Transcutaneous tc PO₂ electrodes were placed on the shoulder, chest, abdomen or thigh.

Electrode placement site, monitoring duration, quality control and calibration data for blood gas analyzers and monitors, drift, patient information and patient respiratory therapy were recorded, analyzed and reviewed for significance.

RESULTS

To evaluate how reliably tc PO₂ could be used as an estimate of PaCO₂ in chronic lung disease patients, we reviewed 1) the regression relationship of tc PO₂ and PaCO₂ segmented into arterial and capillary groups; 2) the relative agreement of serial tc PO₂ in the seven infants most frequently monitored during this study; and 3) the distribution of PaCO₂: tc PO₂ ratios for paired measurements.

Table 1 shows the regression analysis of arterial and capillary blood PaCO₂ with concurrently measured transcutaneous CO₂ tensions. The measurements were all accepted as valid; i.e., no quality control deviations were apparent to technologists or nurses working with the patients or instruments.

The serial simultaneous tc PO₂ and PaCO₂ determinations on the two most frequently monitored infants are plotted in Figures 1A and 1B. The tc PO₂
Figure 1
Transcutaneous $\mathrm{PCO}_2$ and blood $\mathrm{PCO}_2$ comparisons made on two chronic lung diseased premature infants (patients A and B) plotted in time sequence by day. Arterial blood specimens are noted with (O); capillary blood specimens with (△). The three most unusual comparisons for each patient are labeled a, b and c.

| TABLE 1: REGRESSION OF ARTERIAL AND CAPILLARY BLOOD $\mathrm{PaCO}_2$ WITH CONCURRENTLY MEASURED TC $\mathrm{PCO}_2$ TENSIONS IN PREMATURE INFANTS WITH CHRONIC LUNG DISEASE$^1$ |
|----------------------------------|-----------------|-----------------|
| **BLOOD SAMPLE**                | **Arterial**    | **Capillary**   |
| $n$                              | 160             | 87              |
| Regression line                  | $\text{tc } \mathrm{PCO}_2 = 0.97 + 1.78 \times (\mathrm{PaCO}_2)$ | $\text{tc } \mathrm{PCO}_2 = 2.93 + 1.73 \times (\mathrm{PaCO}_2)$ |
| $r$                              | 0.86            | 0.84            |
| Standard deviation of intercept  | 4.0 torr        | 7.1 torr        |
| $S_yx$                           | 13.7 torr       | 15.6 torr       |
| Observed tc $\mathrm{PCO}_2$ range | 38 — 169 torr | 48 — 160 torr |
| Observed Pa$\mathrm{CO}_2$ range | 20 — 93 torr    | 31 — 87 torr   |
| Mean tc $\mathrm{PCO}_2$         | 83 torr         | 102 torr        |
| Mean Pa$\mathrm{CO}_2$           | 48 torr         | 58 torr         |
| Mean of ratios Pa$\mathrm{CO}_2$/tc $\mathrm{PCO}_2$ | 0.57            | 0.58            |

$^1$Fifteen infants were studied
blood PCO₂ difference (ΔCO₂ or tc: blood bias) showed a gaussian distribution for these patients. For patient A, Figure 1, the ΔCO₂ = 59 ± 18 torr (X ± SD). For patient B of that figure, the ΔCO₂ = 32 ± 14 torr. No reason was found to disregard any of the extreme positive or negative values. The extremes of ΔCO₂ (e.g. sets marked a, b and c) were not statistically associated with the fluctuations in patient body temperature, hematocrit, coincident arterial pH, PaO₂, FIO₂, the presence or absence of forced ventilation, patient age, sex or weight. Of the six comparisons labeled (a), (b), or (c) in Figure 1, four were made with abdominal to electrode placement. Concurrent heater power tracings were not remarkable indicating tissue perfusion was unperturbed and probe attachment satisfactory. The duplication of blood gas analyses, specimen integrity notes, calibration, maintenance, and other control data were consistent with acceptable test performance. The transcutaneous measurement drift in vivo was less than 4 torr in each instance.

To evaluate the long-term reliability of tc PCO₂ for estimating PaCO₂ in individual CLD patients, we examined the data from the seven most frequently monitored CLD patients. We calculated the difference between “estimated PaCO₂” and observed PaCO₂, where “estimated PaCO₂” was derived by inserting the observed tc PCO₂ value in the regression equation for the NICU population in general i.e. tc PCO₂ = -2.8 + (1.86) (PaCO₂) (6). Figures 2A and 2B illustrate the differences for the same infants whose data are shown in Figure 1. Of the 54 comparisons for infant A, 91% were different by more than 10 torr. Of the 61 comparisons for infant B, only 8% were different by more than 10 torr. The estimates were more likely to be high for infant A while most were low for infant B.

The influence of time on these matched comparisons was examined. For 2 of 7 the patients, the sequential estimated PaCO₂ values deviated from observed PaCO₂ with a unidirectional bias for protracted intervals. The probability that these single direction deviations could be random were only 5.2 and 6.3% for the two worst cases. The other 5 on whom there were enough comparisons for valid statistical analysis were as random as the control group. Figures 1A and 2A illustrate a random series of tc PCO₂ and PaCO₂ observations and of differences between estimated PaCO₂ and corresponding PaCO₂. Figures 1B and 2B illustrate a series with 6.3% probability of being random. In it there are more low estimates of PaCO₂ from day 15 through day 28 than at other times in the series.

Figure 3 shows the frequency distribution of the PaCO₂: tc PCO₂ ratio for all comparisons (n = 247) on the 15 infants with chronic lung disease. The group distribution of ratios was 0.57 ± 0.10 (X ± SD). The PaCO₂: tc PCO₂ ratios for the infants A and B in Figure 1 were 0.54 ± 0.09 and 0.59 ± 0.11 respectively. They have representative means and precision for the individual data sets. Among all comparisons there are 6 extreme sets with ratios > 0.8. These extremes are derived from measurements on 5 infants.

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![Patient A, Patient B graphs](image-url)

Figure 2
Time series representation of the deviation of estimated PaCO₂ from observed PaCO₂ on two chronic lung diseased premature infants (patients A and B) over protracted time periods. Points a, b and c denote three extreme deviants of PaCO₂ estimation in each patient. See also Figure 1.
The standard error of the estimates reported here as 13.7 torr and 15.6 torr, for arterial and capillary specimens respectively, are large. Scatter in regression studies has not been generally quantitated in clinical evaluations. Only values reported for newborns are 6.3 torr (13) 6.2 torr (7) and 4.2 torr (5). As there is no difference between the data for the two specimen types here, blood collection probably did not contribute to this scatter. Moreover, our measurements are well controlled in that our blood gas instruments do not have a capillary versus macro sampling bias, blood gas analyses are duplicated to confirm results, our staffs are continuously indoctrinated to note exact times of blood sampling and blood analysis, electrode drift is within the acceptable limits, and the strip chart recorders continuously monitor heater power and tc PCO₂ etc. Thus the technical factors contributing imprecision to this study were limited. We believe that it is representative of the tc PCO₂ and PaCO₂ comparisons likely to be made for daily care in a tertiary hospital's NICU.

Figures 1 and 2 reinforce the suggestion that the wide confidence intervals about our regression lines accurately reflect tissue and blood CO₂ tension status in a sick premature population where weaning is the major use of monitoring. First, there were transient intervals of non-randomness in the tc PCO₂ to PaCO₂ relationship measured. This may be expected in a typical neonatal intensive care setting. Bhat et al reported that the Δ CO₂ (tc PCO₂—PaCO₂) in infants was affected by hypoxia and acidosis but not blood pressures so long as they were above 30 mmHg (14).
Tremper et al (3) reported that the \( \Delta CO_2 \) among adults in shock, defined by a cardiac index \( < 1.5 \text{ L/min.m}^2 \), averaged 61 torr compared with 23 torr for hemodynamically stable patients. Brunstler et al found that only systolic blood pressures below 15 mmHg was consistently associated with deviant transcutaneous and blood comparisons (n = 78) on 24 infants, 23 of whom were mechanically ventilated (5). In the experience, body temperature (33.5–38.1°C), hematocrit (28–65%), and pH (6.89 to 7.61 units) were not implicated. In their regression study the standard error of the estimate was 4.15 torr. (excluding data derived on patients with low blood pressure) Finally, the existence of variable tc PCO2: PaCO2 relationships specific in chronic lung disease infants is suggested by Philip who quotes Peabody as reporting that infants with bronchopulmonary dysplasia may require a correction factor (e.g. 2.0) which is different from other children's (e.g. 1.3 or 1.4) (15). While we believe intervals of hypoxia, acidosis, edema, anemia, and/or hypermetabolic states might account for the transient deviant blood and transcutaneous comparisons we described, regression analysis failed to statistically identify a single explanation. Moreover, our patients were in physiological disequilibrium as they were almost all undergoing mechanical ventilation at the time of data collection. There may be transient tissue CO2 build up associated with incomplete tissue washout (16) or lung inefficiency.

A second explanation of our regression data scatter is also illustrated in the serial plots of figures 1 and 2 as major isolated deviations (e.g. points a, b, and c). Hazinski and Severinghaus had noted the occurrence of “single extreme and deviant points” in several published studies but considered them atypical and suggested that they could be eliminated from performance data evaluations (2). We agree that this type of observation does not reflect instrument performance but consider it the outcome of physiological phenomena. In a working NICU, we believe such “poor” tc PCO2 correlations with PaCO2 should be expected by virtue of the patient clientele.

Several authors (5,6,7) suggested that regression equations for matched tc PCO2 and PaCO2 comparisons be used to derive “estimated PaCO2” (or “adjusting tc PCO2”) values from measured tc PCO2. Adjusting instrument output with this kind of in vivo calibration is attractive as it would circumvent inevitable clinicians’ confusion in dealing with the two gas tension values simultaneously. Figure 2 demonstrates that the incidence of “poor” PaCO2 estimations varies among patients. The frequency of estimate errors greater than 10 torr for infant A was 31%. This argues against using such system for automatic PaCO2 estimation, because it is impossible to screen out inappropriate infants when we do not fully understand the precipitating phenomena. Secondly, the magnitude of exceptional residuals (to +33 torr) illustrated by points a, b, and c in series of Figure 2 also suggests a grave clinical hazard in in vivo calibration. Finally, the time dependent shift in quality of PaCO2 estimates on a given baby cannot be dealt with in a working NICU unless the physiological causes of poor correlation are taken into account. In our population, the observed scatter in the regression studies precludes using tc PCO2 to estimate PaCO2. For example, a measured tc PCO2 of 63 torr would correspond to estimated PaCO2 values between 33 and 59 torr using the prediction bands with 95% confidence for the regression equation tc PCO2 = 0.97 + (1.78) (PaCO2).

The time series analysis was done to demonstrate the pitfalls of relying on tc PCO2 measurements for too precise an estimate of PaCO2 in CLD patients and/or the inaccuracy of assuming a simple CO2 can be used to estimate PaCO2 for very long. The lack of randomness in the time series also suggests that unidentified physiological events which may last for several days are influencing the predictability of blood PCO2 from transcutaneous PCO2 measurements. These phenomena may be different from those associated with the extreme points. However, in the series for patient B, Figure 2, the extremes a, b and c occur during intervals of apparent “non-randomness.”

Figure 3 illustrates the distribution of PaCO2: tc PCO2 ratios to be experienced with this populations. We suggest that while the trends in changing tc PCO2 demonstrate shifting PaCO2 status, a change in the ratio of paired tc PCO2 and PaCO2 values is the simplest bedside indicator that the aberrant physiological phenomena we have alluded to above is occurring. It is a useful in vivo “quality control” indicator, not in the sense of identifying error per se but in the sense of masking shifts in the relationship of measureable tissue PCO2 to PaCO2. A prospective study might help to identify combinations of clinical factors which change the expected tissue: blood PCO2 status.

Contrary to our expectations, the regression studies of transcutaneous and blood PCO2 for infants with chronic lung disease were not significantly different in our, y intercept, slope, or scatter from earlier data derived for acutely ill premature infants. The data from CLD infants did demonstrate time, dependent, non-random shifts in the tc PCO2: PaCO2 relationship and interinfant differences in the frequency of such phenomena. The findings are consistent with the proposition that transcutaneous PCO2 measurements are a useful short-term trend monitor. They suggest that in vivo calibrations may sometimes be of limited value or misleading. The expected scatter in our comparisons of tc PCO2 and PaCO2 is unexplained. In view of it, we suggest that a population regression line be developed for each clinical care setting into which tc PCO2 is introduced in order to assess the relative reliability of estimating PaCO2 from tc PCO2 data.

ACKNOWLEDGEMENT

We are indebted to the staff of the University Hospital Neonatal Intensive Care Unit and the technologists of our Division, especially Claudia Bien, M.T. for their help. Radiometer America Inc. (Cleveland, OH 44145) supported the publication costs of this manuscript.

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