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Original Article

Agreement of Carbon Dioxide Levels Measured by Arterial, Transcutaneous and End Tidal Methods in Preterm Infants $\leq$28 Weeks Gestation

Lucia Liz D. Aliwalas, MD, DPPS
Laura Noble, RRT, RRCP
Karin Nesbitt, RRT, RRCP
Shafagh Fallah, MSc
Vibhuti Shah, MD, MRCP, MRCPCH
Prakesh S. Shah, MD, MRCP, MRCPCH, FRCPC

OBJECTIVE:

To assess the agreement of transcutaneous carbon dioxide ($TcPCO_2$) and end tidal carbon dioxide ($PetCO_2$) with arterial carbon dioxide ($PaCO_2$) values in infants < 28 weeks gestational age.

STUDY DESIGN:

In all, 27 ventilated preterm infants were prospectively studied. $PaCO_2$ was compared with $TcPCO_2$ and $PetCO_2$ measured at three similar time points within first 24 hours after birth.

RESULTS:

The Intraclass correlation coefficients for $TcPCO_2$ and $PaCO_2$ were 0.45, 0.73 and 0.53; and for $PetCO_2$ and $PaCO_2$ were 0.61, 0.56 and 0.57 at 4, 12 and 24 hours after birth, respectively.

CONCLUSION:

A moderate agreement with a wide variation in individual values was observed between noninvasive methods and $PaCO_2$ in preterm infants in the first 24 hours. Noninvasive monitoring methods cannot be substituted for $PaCO_2$ analyses in preterm infants during this critical period.
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Department of Pediatrics (L.L.D.A, S.F., V.S., P.S.S.), Department of Respiratory Therapy (L.N., K.N.), Mount Sinai Hospital and University of Toronto, Toronto, Ontario, Canada

Address correspondence and reprint requests to Prakesh S. Shah, MD, MRCP, MRCPCH, Department of Pediatrics, Mount Sinai Hospital and University of Toronto, 775A-600 University Avenue, Toronto, Ontario, Canada M5G 1X5

INTRODUCTION

Arterial blood gas analysis is the gold standard for assessing the adequacy of ventilation to which noninvasive monitoring methods should be correlated. In preterm neonates, arterial sample is usually obtained from indwelling catheters and less frequently from percutaneous arterial punctures. These techniques are associated with complications such arterial spasm, ischemia, infection and pain. Noninvasive monitoring of carbon dioxide such as transcutaneous partial pressure of carbon dioxide (TcPCO2) and partial pressure of end-tidal carbon dioxide in the expired air ($PetCO_2$) have shown usefulness in adults, children and full-term neonates.[1–9] These methods offer the advantages such as simplicity, reduction in blood sampling and incidence of iatrogenic anemia and cost effectiveness.

Preterm infants have a very thin layer of epidermis, which may confer an advantage of highly reliable readings of $TcPCO_2$. However, it can also predispose them to burns and skin damage from the heated electrodes.[10,11] $PetCO_2$ measurements may be more accurate in preterm infants because of their small dead space volume. However, as their tidal volumes are minimal, it may require large volume of gas to be displaced before actual reading can be obtained. Despite their widespread use, the agreement of CO_2 obtained by noninvasive and invasive methods has not been evaluated systematically in extremely preterm neonates.

The aim of this study was to assess the agreement of the CO_2 values obtained by $TcPCO_2$ and $PetCO_2$ with arterial CO_2 ($PaCO_2$) in preterm infants $\leq$28 weeks gestation in the first 24 hours of age.

METHODS

This study was approved by the Research Ethics Board of Mount Sinai Hospital, Toronto, Canada. Written informed consent was obtained from the parents of all infants prior to study entry.

Study Population

Parents of eligible infants were approached for consent after antenatal consultations or immediately after birth. Preterm neonates born at gestational age $\leq$28 completed weeks, requiring respiratory support by conventional mechanical ventilation, and those with indwelling arterial catheters were included in the study. Neonates with cardiopulmonary malformations, those requiring

high-frequency ventilation and those who had received sodium bicarbonate infusion within 60 minutes prior to blood sampling were excluded.

Study Design

After providing standard resuscitation in accordance to the neonatal resuscitation protocol guidelines, umbilical vessels were catheterized upon the discretion of the attending physician. Three arterial blood gas samples were drawn: (a) first within 4 hours of age, (b) second at 12 hours of age and (c) third at 24 hours of age. These samples were analyzed immediately in the central laboratory using the CIBA - Cornings 865 series (*CIBA, USA*) blood gas analyzer. Probes for both $TcPCO_2$ and $PetCO_2$ were placed prior to blood sampling at each time. The values of the $TcPCO_2$, $PetCO_2$, mean blood pressure and ventilatory parameters at the time of sampling were recorded. If the infant was extubated prior to completion of three sampling, he/she was excluded from the study.

The Linde MicroGas 7650 (*Kontron, USA*) monitor was used for $TcPCO_2$ measurement. In this technique, CO_2 was measured potentiometrically by determining the pH of an electrolyte. The electrolyte solution was provided within a hydrophilic spacer, which was placed on top of the sensing area. The spacer was covered by a highly gas permeable, hydrophobic membrane. The sensor was heated to a constant temperature of 44°C. For the study purposes barometric pressure was set at 750 mmHg, PCO_2 temperature correction was set to auto, and the PCO_2 metabolic constant was set at 5 mmHg. Each baby had the sensor timed out at 4 hours due to concerns of skin injury, erythema and skin craters with $TcPCO_2$ probes.[11,12] The double-sided adhesive ring was applied to the sensor. A small drop of contact gel was applied to the center of the sensor. The sensor was placed over nonbony structures with gentle pressure applied to the center of the sensor to ensure removal of any air pockets and to spread the contact gel.

The Nellcor NPB-70 (*Mallinckrodt, Inc; USA.*) hand-held sidestream capnograph was used to measure the partial pressure of carbon dioxide in the expired air ($PetCO_2$) which uses microstream infrared spectroscopy to measure the concentration of the molecules that absorb infrared light. Because the absorption is proportional to the concentration of the absorbing molecule, the concentration can be determined by comparing its absorption to that of a known standard. Therefore, no compensation is required when different concentrations of nitric oxide, oxygen, anesthetic agent or water vapor are present in the inhaled or exhaled breath. A Microstream Circuit FilterLine™ H Set (Mallinckrodt Inc; USA) was used. After a 15-second self-test, the FilterLine was attached between the endotracheal tube and the ventilator circuit and the readings were recorded.

Statistical Analysis

An intraclass correlation coefficient (ICC) of 0.60 for CO_2 assessment by $PetCO_2$ or $TcPCO_2$ compared to $PaCO_2$ measurement for preterm infants has been reported in a previous study.[5] A total of 27 preterm infants were required to demonstrate an agreement level of 0.80 at a 5% type I error and 20% type II error at any time of sampling.[13] Bland Altmann analysis was used to determine precision and bias.[14] The significance of the effect of different factors such as birth weight (<750 and ≥ 750 g), mean blood pressure, mean airway pressure (≤ 7.5 and >7.5 mm of H_2O), site of transcutaneous probe application (chest and abdomen or thigh) on the differences between the measurements were analyzed using the Wilcoxon two-sample test and regression analysis.

RESULTS

The study was conducted from May to December 2003 in the neonatal intensive care unit of Mount Sinai Hospital, Toronto, Canada. A total of 26 parents were approached, 33 (16 singletons, four sets of twins, three sets of triplets) patients were enrolled in the study and 27 infants completed the study. Two infants were extubated prior to the completion of data collection of three samples, two infants did not have indwelling arterial catheter, one infant needed high-frequency oscillatory ventilation after the first sample, and in one infant $PetCO_2$ measure was not obtained for the third sample. All infants (17 male) had a diagnosis of respiratory distress syndrome. The mean (SD) gestational age was 26.3 (1.0) weeks and birth weight was 875 (141) g. All patients received surfactant (BLES™, London, ON, Canada) within 15 to 30 minutes after birth.

The ICC, the mean differences (bias) and Standard Error of the Mean (SEM) of the differences (precision) in the readings between $PaCO_2 - TcPCO_2$ and $PaCO_2 - PetCO_2$ at 4, 12 and 24 hours are reported in Table 1. The results of the Wilcoxon two-sample test and regression analysis of the effect of the different parameters are reported in Table 2. The differences between the $PaCO_2$ and $TcPCO_2$; and $PaCO_2$ and $PetCO_2$ at 4 hours of age against gold standard $PaCO_2$ values are plotted in Figures 1 and 2.

Table 1 Intraclass Correlation Coefficient, Mean Difference and Standard Error of the Mean Difference of CO_2 Measurements from $PaCO_2$ at Three Time Points

Measurement	ICC	Mean difference	Standard error of mean difference
$TcPCO_2$ within 4 hours	0.45	2.2	2.3
$TcPCO_2$ at 12 hours	0.73	4.4	1.2
$TcPCO_2$ at 24 hours	0.53	2.6	1.8
$PetCO_2$ within 4 hours	0.61	−0.3	2.2
$PetCO_2$ at 12 hours	0.56	2.4	1.4
$PetCO_2$ at 24 hours	0.57	1.9	1.8

Table 2 Wilcoxon Two-Sample Test and Regression Analysis of Different Parameters at 4 hours of age

Variable	$TcPCO_2 - PaCO_2$ at 4 hours		$PetCO_2 - PaCO_2$ at 4 hours	
	Median (IQR)	*p*	Median (IQR)	*p*
Birth weight $\leq$750 g	2 (0,7)	0.77	−4 (−15,3)	0.45
Birth weight >750 g	4 (0,8)		−1 (−5,7)	
Site of application				
Abdomen and chest	2 (−1,7.5)	0.23		
Thigh	4 (1,16)			
MAP $\leq$7.5			0 (−6,12)	0.4
MAP >7.5			−2 (−10,2)	
MBP		0.27		

MAP — mean airway pressure in cm of H_2O; MBP — mean blood pressure in mmHg; IQR — interquartile range.

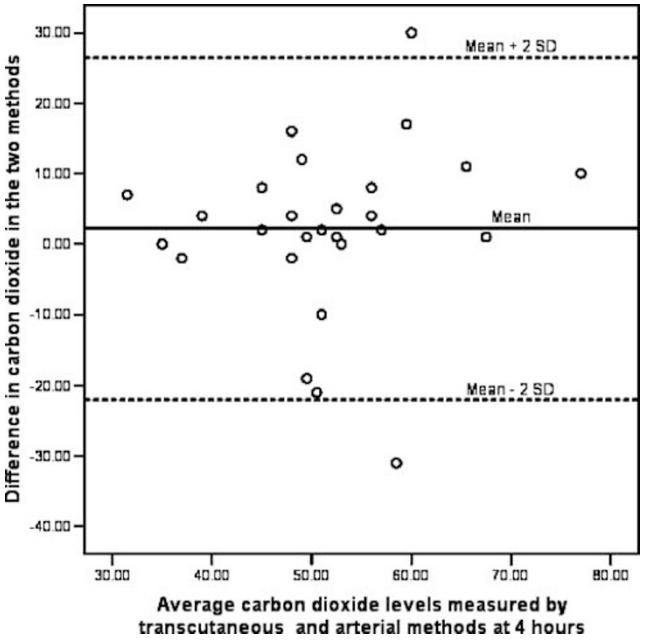

Figure 1. Bland-Altman plot of the difference between $PaCO_2$ and $TcPCO_2$ at 4 hours of age.

DISCUSSION

We found a moderate agreement between both noninvasive methods and $PaCO_2$ as reflected by the ICC values at all three time points of sampling. The values of bias and precision around the differences in the measurements reflected wide variation among individual patients. Birth weight, site of transcutaneous probe application, mean blood pressure and mean airway pressure had no influence on the agreement.

Hand et al.[1] in a study of 12 preterm infants (51 samples) observed a linear correlation between $TcPCO_2$ and $PaCO_2$

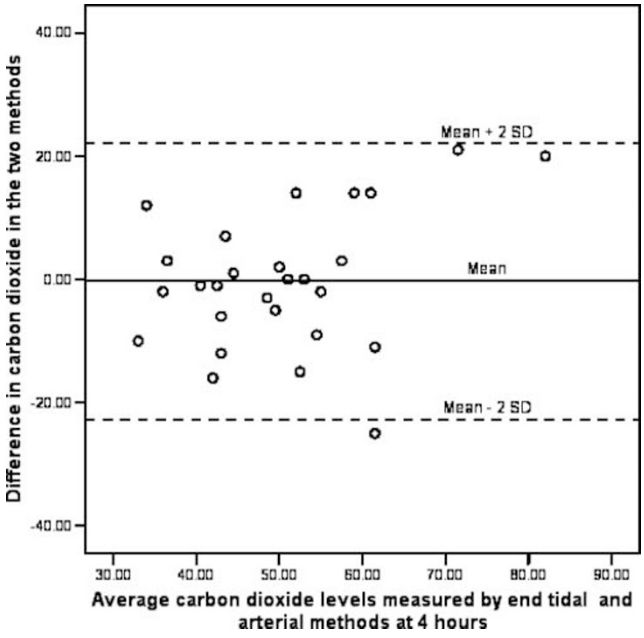

Figure 2. Bland-Altman plot of the difference between $PaCO_2$ and $PetCO_2$ at 4 hours of age.

($r = 0.71$, slope = 0.9), but not with $PetCO_2$ ($r = 0.52$, slope = 0.42). Geven et al[2] in a study of 12 infants (72 samples) observed good correlation with $TcPCO_2$ (r ranged from −0.29 to +0.95) but not $PetCO_2$ (r ranged from −0.99 to +0.97). Watkins and Weindling[3] in a study of 19 infants (69 samples) observed poor overall correlation of the $PetCO_2$ and $PaCO_2$ ($r = 0.39$, $p<0.01$). On the contrary, Wu et al[4] in a study of 60 infants observed good correlation between $PetCO_2$ and $PaCO_2$ in both term infants (44 samples, $r = 0.78$, $p<0.001$) and preterm infants (86 samples, $r = 0.85$, $p<0.001$). Nangia et al[5] in a study of 152 samples observed a significant correlation between $PaCO_2$ and $PetCO_2$ in preterm infants <32 weeks ($p = <0.01$).

Thus, previous studies to assess correlation have found conflicting results. We elected to study infants $\leq$28 weeks at birth because the number of extremely preterm infants enrolled in the previous studies is limited. We studied preterm infants in the immediate postnatal period because unintentional hypocarbia[15] is common during the initial period in preterm infants and this could lead to long-term pulmonary damage, that is, chronic lung disease of preterm infants. All the infants had similar respiratory illness pattern (RDS) and all infants were studied at the same time points in their illness. This confirms the homogeneity of our data. All infants had three sets of data that were analyzed individually allowing statistical independence of the measures. This is a unique characteristic of our study, consistently ignored in all previous studies. Multiple measures from a single patient could skew the results of correlation. We did not evaluate the agreement between $PaCO_2$ and other noninvasive methods beyond 24 hours of age as the number of infants who may get extubated remains higher and

will result in incomplete data set, however, such study will be very important for the management of infants who require mechanical ventilation beyond 24 hours of age.

Noninvasive monitoring techniques are widely accepted and used in the adult and pediatric population. In neonates, small tidal volume, higher respiratory rate resulting in shorter expiratory time could result in the lack of true alveolar gas being measured and explain wide variation in $PetCO_2$ values. Meridith and Monaco[16] reported the difference of −8 to 18 mm of Hg between $PaCO_2$ and $PetCO_2$ (similar to our findings of −22 to 21 mm of Hg) and suggested inability to predict $PaCO_2$ from $PetCO_2$, but mentioned that it may be useful for trends. Our findings confirms lack of reliability, however, due to the nature of the design of our study we are not able to comment on the usefulness to assess the changes in the trend. $TcPCO_2$ is expected to correlate well with $PaCO_2$ because of the thin layer of epidermis. Studies have shown that tissue perfusion and acidosis may alter such agreement.[17,18] Although we were not able to find differences in the correlation based on blood pressure, the sample size to assess the impact was probably inadequate. It is also possible that the technology, as currently available, is not yet ready to replace the gold standard. The apparent discrepancy in our results and that of others illustrate the need for careful and systematic evaluation of technological advances before they are adopted in the routine practice.

Thus, based on our findings of only moderate correlation and wide individual variability, we suggest that noninvasive monitoring methods, as used in the study, cannot be substituted for $PaCO_2$ analyses in preterm infants.

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References

1. Hand IL, Shepard E, Krauss AN, Auld PA. Discrepancies between transcutaneous and end tidal carbon dioxide monitoring in critically ill neonate with respiratory distress syndrome. Crit Care Med 1989;17: 556–9.
2. Geven WB, Nagler E, de Boo T, Lemmens W. Combined transcutaneous oxygen, carbon dioxide tensions and end-expired CO2 levels in severely ill newborns. Adv Exp Med Biol 1987;220:115–20.
3. Watkins AM, Weindling AM. Monitoring of end tidal CO2 in neonatal intensive care. Arch Dis Child 1987;62:837–9.
4. Wu CH, Chou HC, Hsieh WS, Chen WK, Huang PY, Tsao PN. Good estimation of arterial carbon dioxide by end tidal carbon dioxide monitoring in the neonatal intensive care unit. Pediatric Pulmonol 2003;35:292–5.
5. Nangia S, Saili A, Dutta AK. End tidal carbon dioxide monitoring — its reliability in neonates. Indian J Pediatr 1997;64:389–94.
6. Tobias JD, Meyer DJ. Noninvasive monitoring of carbon dioxide during respiratory failure in toddlers and infants: end-tidal versus transcutaneous carbon dioxide. Anesth Analg 1997;85:55–8.
7. Healey CJ, Fedullo AJ, Swinburne AJ, Wahl GA. Comparison of noninvasive measurements of carbon dioxide tensions during withdrawal from mechanical ventilation. Crit Care Med 1987;15(8):764–8.
8. Reid CW, Martineua RJ, Miller DR, Hull KA, Baines J, Sullivan PJ. Comparison of transcutaneous end tidal and arterial measurements of carbon dioxide during general anesthesia. Can J Anesth 1992;39:31–6.
9. Yamanaka MK, Sue DY. Comparison of arterial-end-tidal PCO_2 difference and dead space/tidal volume ratio in respiratory failure. Chest 1987;92: 832–5.
10. Cassady G. Transcutaneous monitoring in the newborn infant. J Pediatr 1983;103:837–48.
11. Boyle RJ, Oh W. Erythema following transcutaneous PO2 monitoring. Pediatrics 1980;65:333–4.
12. Golden SM. Skin craters — a complication of transcutaneous oxygen monitoring. Pediatrics 1981;67:514–6.
13. Walter SD, Eliasziw M. Sample size and optimal designs for reliability studies. Stat Med 1998;17:101–10.
14. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307–10.
15. Tracy M, Downe L, Holberton J. How safe is intermittent positive pressure ventilation in preterm babies ventilated from delivery to newborn intensive care unit? Arch Dis Child Fetal Neonatal Ed 2004;89:F84–7.
16. Meredith KS, Monaco FJ. Evaluation of a mainstream capnometer and end-tidal carbon dioxide monitoring in mechanically ventilated infants. Pediatr Pulmon 1990;9:254–9.
17. Cabal LA, Hodgman J, Siassi B, et al. Factors affecting heated transcutaneous PO_2 and unheated transcutaneous PCO_2 in preterm infants. Crit Care Med 1981;9:298.
18. Bhat R, Kim WD, Shukla A, et al. Simultaneous tissue pH and transcutaneous carbon dioxide monitoring in critically ill neonates. Crit Care Med 1981;9:744.