Effect of Transcutaneous Electrode Temperature on Accuracy and Precision of Carbon Dioxide and Oxygen Measurements in the Preterm Infants

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BACKGROUND: High electrode temperature during transcutaneous monitoring is associated with skin burns in extremely premature infants. We evaluated the accuracy and precision of CO_2 and O_2 measurements using lower transcutaneous electrode temperatures below 42°C. METHODS: We enrolled 20 neonates. Two transcutaneous monitors were placed simultaneously on each neonate, with one electrode maintained at 42°C and the other randomized to temperatures of 38, 39, 40, 41, and 42°C. Arterial blood was collected twice at each temperature. RESULTS: At the time of arterial blood sampling, values for transcutaneously measured partial pressure of CO_2 (P_{tcCO_2}) were not significantly different among test temperatures. There was no evidence of skin burning at any temperature. For P_{tcCO_2}, Bland-Altman analyses of all test temperatures versus 42°C showed good precision and low bias. Transcutaneously measured partial pressure of O_2 (P_{tcO_2}) values trended arterial values but had large negative bias. CONCLUSION: Transcutaneous electrode temperatures as low as 38°C allow an assessment of P_{tcCO_2} as accurate as that with electrodes at 42°C. *Key words: transcutaneous monitoring; carbon dioxide monitoring; oxygen monitoring; electrode temperature; blood gas monitoring.* [Respir Care 2018;63(7):900–906. © 2018 Daedalus Enterprises]

Introduction

Extremes and fluctuations of arterial CO_2 and O_2 tension pose well-documented risks to the neonate, including periventricular leukomalacia,[1-3] intraventricular hemorrhage,[3-6] retinopathy of prematurity,[7] bronchopulmonary dysplasia, and mortality.[8-10]

Therefore, these levels must be closely monitored. Arterial blood sampling is the accepted standard, but this provides only a single measurement of what is often a constantly changing clinical picture. It is also invasive by nature, requiring either an indwelling catheter or multiple needle sticks and can lead to anemia, which is an already prevalent issue in premature infants.

Transcutaneous monitors can provide continuous CO_2 and O_2 monitoring. One limitation to the widespread use of transcutaneous monitors in neonatal ICUs is the previously reported association of skin burning in extremely low birthweight infants due to the elevated electrode temperature required to achieve arterialization of the capillary bed, particularly in the measurement of P_{tcO_2}.[11-13] High electrode temperature may not be needed for P_{tcCO_2} assessment.

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We hypothesized that a transcutaneous electrode temperature as low as 38°C would be accurate and precise in the measurement of CO_2 levels. We sought (1) to assess the accuracy and precision of 4 lower electrode temperatures (38, 39, 40, 41°C) compared to the recommended temperature of 42°C in the measurement of CO_2 levels in preterm infants between 1–2 kg; (2) to assess the accuracy and precision of all measured electrode temperatures (38–42°C) in the measurement of CO_2 compared to the accepted standard, arterial blood gas P_{CO_2}; (3) to reassess the accuracy and precision of P_{tcO_2} compared to P_{aO_2} and assess P_{tcO_2} at the 4 lower electrode temperatures (38, 39, 40, 41°C).

QUICK LOOK

Current knowledge

Transcutaneous monitoring provides continuous CO_2 and O_2 measurements without the need for blood sampling. Premature infants are at higher risk for complications secondary to abnormal CO_2 and O_2 levels, therefore continuous monitoring is vital. However, transcutaneous monitoring requires warming of the skin, which has been associated with skin injury in extremely low birthweight infants.

What this paper contributes to our knowledge

Transcutaneous temperatures as low as 38°C provide an accurate assessment of CO_2 compared to the previously recommended temperature of 42°C. Use of lower transcutaneous temperatures to track CO_2 trends should allow this technology to be applied in the smallest preterm infants. Transcutaneous monitoring may be useful for tracking O_2 levels.

Methods

Subjects

This study was approved by the Institutional Review Board of the University of Arkansas for Medical Sciences. A total of 20 neonates were enrolled after written parental consent was obtained. Inclusion criteria included birthweight 1–2 kg, umbilical arterial access, and hematocrit levels $> 35\%$. Exclusion criteria included pressor support, hematocrit levels $< 35\%$, congenital anomalies, nitric oxide use, persistent pulmonary hypertension, and cyanotic heart disease.

Methods

The precision and accuracy of P_{tcCO_2} and P_{tcO_2} were examined at 5 different electrode temperatures (38, 39, 40, 41, and 42°C) in each infant. All newborns were monitored using 2 transcutaneous monitors applied simultaneously (TCM CombiM, Radiometer, Copenhagen, Denmark). This allowed for one electrode to remain unchanged at 42°C (ie, control) while the temperature of the other electrode was randomized to 38, 39, 40, 41, or 42°C (to assure accuracy of the control monitor). The transcutaneous electrodes were applied to the skin of the trunk as recommended by the manufacturer. The accepted standard to which the transcutaneous values were compared was the P_{aCO_2} and P_{aO_2}. After stabilization of both monitors, 2 arterial blood gases were collected at each temperature, approximately 15 min apart from an indwelling umbilical arterial catheter (for a total of 10 blood gases). For the purposes of this project, stabilization was defined as a change of $\leq$ 2 mm Hg P_{tcCO_2}over 5 min. Approximately 0.2 mL of arterial blood was collected with each sample, which totaled 2 mL of blood per subject. Total blood collected per subject was recorded during the study. Arterial blood gas sampling and readings of the P_{tcCO_2} and P_{tcO_2} levels were performed simultaneously and recorded. After changing the electrode temperature, an appropriate amount of time was allowed for calibration (usually 5–10 min) and stabilization of the new electrode temperature (usually 10–15 min). Transcutaneous data were continuously recorded and downloaded from the monitor after the study. The collection of data, per subject, took approximately 4 hours.

Statistical Analysis

For a sample size estimate, with the design of 5 repeated measurements at each pair of temperatures, a compound symmetry structure was used, and we assumed every pair had the same correlation for within-subject covariance. A sample size of 20 neonates achieved 80% power to detect a minimum difference of 0.67, 0.97, and 1.2 per standard deviation, respectively, when the correlation between observations on the same subject was 0.1, 0.5, and 0.9. We used a repeated-measures design for this study, thereby requiring substantially fewer subjects and increasing trial feasibility compared to a 2-group or *n*-group comparison study.

Summary statistics such as mean and standard deviations were reported. Several comparisons were carried out for the main analysis. Comparison of average P_{tcCO_2} or P_{tcO_2} between each of the 5 test temperatures and the control temperature were analyzed using repeated-measures analysis of variance followed by Dunnett's method adjusting for multiple comparisons. Comparison of average P_{tcCO_2} or P_{tcO_2} levels between test temperatures and blood gas measurements, and average warm-up times for stabilization between test temperatures and the con-

Table 1. Transcutaneous Test Temperatures

	Temperature	P_{tcCO_2}			P_{tcO_2}		
		Mean (SD)	95% CI vs 42°C	*P*	Mean (SD)	95% CI vs 42°C	*P*
Control	42°C	46 (5.4)	NA	NA	48 (18)	NA	NA
Test	38°C	47 (4.1)	(−3.1, 5.0)	.94	31 (8.2)	(−26.4, −6.0)	.01
	39°C	47 (4.2)	(−3.0, 5.0)	.93	32 (7.7)	(−25.9, −5.5)	.01
	40°C	49 (6.1)	(−1.1, 6.9)	.22	37 (17)	(−20.8, −0.4)	.039
	41°C	47 (5.5)	(−2.4, 5.7)	.70	36 (11)	(−21.5, −1.1)	.030

Comparisons were based on the average values of 2 repeated measurements for each subject.
NA = not applicable

Table 2. Comparison of Transcutaneous Test Temperatures vs Arterial Value

Test Temperature	CO_2			O_2		
	Transcutaneous Mean (SD)	Arterial Mean (SD)	*P*	Transcutaneous Mean (SD)	Arterial Mean (SD)	*P*
38°C	47 (4.1)	43 (4.4)	.01	31 (8.2)	64 (13)	.01
39°C	47 (4.2)	42 (3.6)	< .001	32 (7.7)	63 (13)	< .001
40°C	49 (6.1)	41 (3.4)	< .001	37 (17)	63 (12)	< .001
41°C	47 (5.5)	43 (4.4)	< .001	36 (11)	67 (11)	< .001
42°C	46 (5.4)	43 (4.7)	< .001	48 (18)	64 (13)	< .001

Comparisons were based on the average values of 2 repeated measurements for each subject.

trol temperature were analyzed by testing whether the difference was something other than zero, using the Wilcoxon signed-rank test due to the small sample size. For continuous data, the differences between test and control temperatures were assessed using generalized linear mixed-effect models.

For each neonate, measurements of P_{tcCO_2} and P_{tcO_2} between the 2 blood gas draws were used for analysis of agreement. Agreement between test and control temperatures, as well as test temperatures versus arterial measurements of P_{tcCO_2} and P_{tcO_2} was assessed using Bland-Altman plots. Limits of agreements and mean difference were reported. *P* values < .05 indicate statistical significance. All statistical analysis was performed using STATA 14.2 (StataCorp, College Station, Texas) or R v.3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Twenty infants were enrolled. Subject characteristics were (mean ± SD) gestational age 30 ± 2 wk, birthweight 1,449 ± 304 g, weight at study 1,378 ± 323 g, and age at study 2 ± 1 d. P_{tcCO_2} levels of the control and test sites at 42°C were not different (45.5 ± 1.0 vs 45.7 ± 1.2 mm Hg, *P* = .87). However, P_{tcO_2} levels of the control and test sites were different (57.9 ± 3.2 vs 47.6 ± 4.0, *P* = .02). At the time of blood gas analyses, the mean P_{tcCO_2} among all test temperatures versus control (42°C) were not different, while for P_{tcO_2} there were significant differences between test and control sites for all temperatures (Table 1). The differences between P_{tcCO_2} and P_{aCO_2} values were similar at all temperatures, while P_{tcO_2} values varied markedly with large mean differences compared to blood gas values (Table 2).

Figure 1 shows continuous data for both P_{tcCO_2} and P_{tcO_2} at the lowest test temperature of 38°C versus control (42°C). For P_{tcCO_2}, while differences were statistically significant (longitudinal analysis, test of fixed effects, *P* = .005), they are not clinically important. For P_{tcO_2}, the difference between 42°C versus 38°C is quite large. For both P_{tcCO_2} and P_{tcO_2}, results at 38°C aligned well with results at 42°C. Bland-Altman analysis of 38°C versus the control of 42°C showed an average bias of 2.2 for P_{tcCO_2} at 38°C. Bias is defined as the tendency of a statistic to overestimate or underestimate a parameter. The 95% limit of agreement is between −7.04 and 11.44, which indicates poor precision (Fig. 2A). Precision refers to how close measurements from different samples are to each other. Results of other test temperatures versus control for P_{tcCO_2} were similar (not shown). Analysis of P_{tcCO_2} versus P_{CO_2} at 38°C showed a positive bias of 4.85 and poor precision with a 95% limit of agreement between −2.69 and 13.39 (Fig. 2B). For P_{tcO_2}, 38°C versus 42°C (Fig. 3A), Bland-Altman analysis showed poor precision and a strong negative bias of −26.1

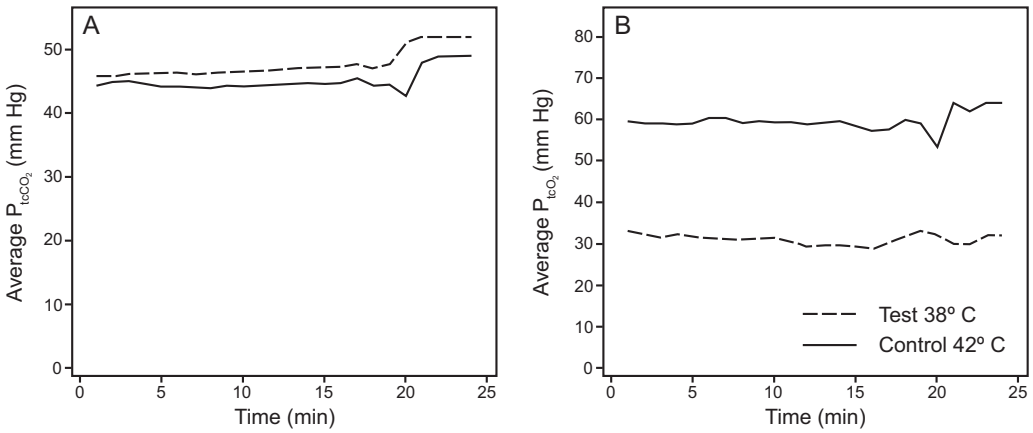

Fig. 1. Continuous data comparing the average P_{tcCO_2} at the lowest test temperature of 38°C versus the recommended temperature of 42°C. The time period shown is between the 2 blood gas draws for each subject at the represented temperatures. Subjects varied in time between blood gas draws. Higher P_{tcCO_2} noted between approximately 20–25 min reflect a smaller *n*. $P = .005$.

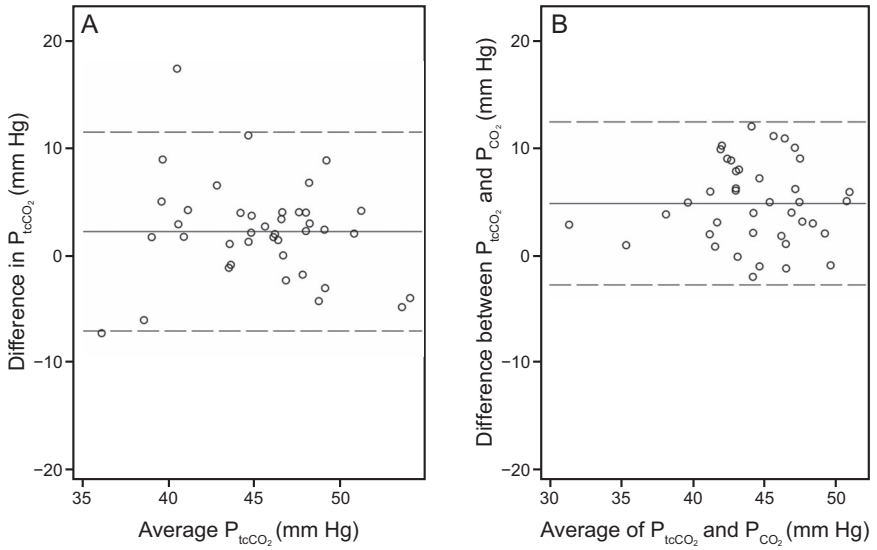

Fig. 2. A: Bland-Altman analysis of P_{tcCO_2} at 38°C versus the control of 42°C. The center horizontal line denotes an average bias of P_{tcCO_2} at 38°C of 2.2. The 95% limit of agreement is between −7.04 and 11.44, which indicates poor precision (indicated by dotted lines showing ± 1.96 SD). B: Bland-Altman analysis of P_{tcCO_2} at 38°C versus P_{aCO_2}. For P_{tcCO_2}, there was an average bias of 4.85 (center horizontal line) and poor precision (95% limit of agreement between −2.69 and 13.39, indicated by dotted lines showing ± 1.96 SD).

(95% limit of agreement between −48.51 and −3.61). Analysis of P_{O_2} versus P_{tcO_2} (Fig. 3B) showed a strongly negative bias of −31.85 and poor precision (95% limit of agreement between −64.05 and 0.35). Bland-Altman analysis was done for all test temperatures versus control as well as all temperatures versus P_{CO_2} and P_{O_2}. Electrode temperature had minimal effect on bias and precision of P_{tcO_2} measurement. However, results of P_{tcO_2} measurements were similar with strong negative biases and poor precision at all test temperatures except for 42°C. At 42°C, there was a significantly lower bias and poor precision (Table 3). Time to warm-up for each temperature was not different, ranging from 10.5 to 12.3 min.

Discussion

Extremes and fluctuations in levels of CO_2 and O_2 are known to be dangerous and can result in morbidity and mortality for premature infants. The effects of hypercapnia (both permissive and incidental) have been associated with worse neurodevelopmental outcome.[4,8-10] Hypercapnia is also associated with impaired cerebral autoregulation, leading to an increased incidence of intraventricular hemorrhage.[5] In fact, extremes and fluctuations in both hypercapnia and hypocapnia are associated with severe intraventricular hemorrhage, especially in the first few days of life.[6] Not only can over-ventilation damage the

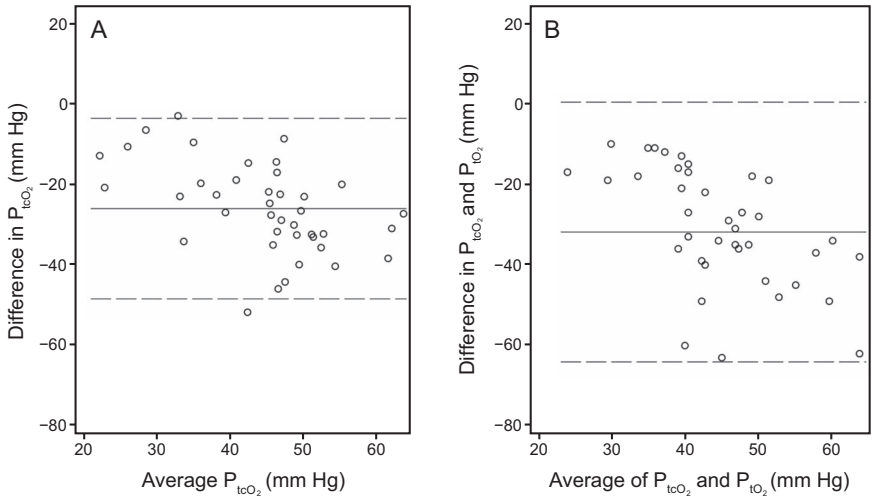

Fig. 3. A: Bland-Altman analysis of P_{tcO_2} at 38°C versus the control of 42°C. Analysis shows poor precision and strong negative bias of −26.1, shown by the center horizontal line (95% limit of agreement between −48.51 and −3.69, indicated by dotted lines showing ± 1.96 SD). B: Bland-Altman analysis of P_{tcO_2} at 38°C versus P_{aCO_2}. For P_{tcO_2}, there was a strongly negative bias of −31.85 (center horizontal line) and poor precision (95% limit of agreement between −64.05 and 0.35, indicated by dotted lines showing ± 1.96 SD).

Table 3. Bias and Precision for P_{tcCO_2} and P_{tcO_2}

	P_{tcCO_2}			P_{tcO_2}		
	Bias	95% Limit of Agreement		Bias	95% Limit of Agreement	
		Low	High		Low	High
Test vs control						
38°C vs 42°C	2.20	−7.04	11.44	−26.10	−48.51	−3.69
39°C vs 42°C	1.72	−8.29	11.74	−27.17	−48.37	−5.98
40°C vs 42°C	2.35	−6.78	11.48	−23.45	−56.37	9.47
41°C vs 42°C	1.47	−8.93	11.88	−24.37	−49.15	0.40
42°C vs 42°C	0.20	−10.63	11.03	−10.30	−48.69	28.09
Test vs arterial						
38°C vs arterial	4.85	−2.69	13.39	−31.85	−64.05	0.35
39°C vs arterial	5.50	−1.76	12.76	−31.13	−57.77	−4.48
40°C vs arterial	6.03	−3.16	15.21	−30.23	−70.90	10.45
41°C vs arterial	4.63	−3.94	13.19	−27.55	−67.04	11.94
42°C vs arterial	2.93	−8.16	14.01	−16.53	−59.69	26.64

lung, but hypocapnia has also been found to cause or worsen cerebral ischemia[1] and is known to be associated with periventricular leukomalacia.[2,3] Extremes in O_2 levels also have negative effects on the neonate. Hyperoxia is associated with periventricular leukomalacia and retinopathy of prematurity, while hypoxia has been shown to cause ischemia and is related to a higher chance of mortality.[7]

Transcutaneous monitoring provides a method to continuously monitor CO_2 and O_2, and in a recent Cochrane review, Bruschettini et al[14] called for additional studies demonstrating safety and efficacy in transcutaneous monitoring. More studies are needed to evaluate long-term outcomes of the use of transcutaneous monitoring. There is evidence of earlier diagnosis of pneumothorax prior to decompensation as well as assessment for clinical disease severity in infants with bronchiolitis using continuous transcutaneous monitoring.[15,16] Transcutaneous monitoring is not the only option for continuous monitoring of CO_2 and O_2, but at this time it is the most useful. End-tidal CO_2 monitoring has been used, but there are documented disadvantages to end-tidal monitoring that make it less feasible in the neonate. In infants with lung disease, who comprise a large proportion of neonatal subjects, ventilation-perfusion mismatch can lead to inaccurate results. Most neonates have a high breathing frequency requiring a faster response time than end-tidal sensors can deliver. This population also has a lower tidal volume resulting in proportionally increased dead

space of the sensors. In addition, end-tidal monitoring can underestimate CO_2 levels.[17-19] Monitoring end-tidal CO_2 at the distal end of a double-lumen endotracheal tube may be useful, but these tubes are not always used for neonates.[20] Given these issues, transcutaneous monitoring is the best option at this time for continuous CO_2 monitoring.

To measure O_2 saturation, the modality used most frequently is pulse oximetry (S_{pO_2}). S_{pO_2} is widely available and easy to use, but it has weaknesses as well. Due to the O_2-dissociation curve, S_{pO_2} is unable to provide accurate estimates of P_{O_2} levels at higher O_2 saturation levels, which may be associated with very high P_{O_2}, which is harmful to the infant.[21,22] Continuous accurate monitoring of P_{O_2} could be useful to avoid hyperoxia and hypoxia. Infants with pulmonary hypertension and infants of extremely low birthweight are examples of subjects in whom very close monitoring of P_{aO_2} levels could be especially useful. It may be of more limited use in extremely premature infants, given their lower oxygenation targets. In our study, wide differences in P_{tcO_2} and P_{aO_2} occurred, even at 42°C. As noted above, there were also electrode-site differences for P_{tcO_2}. Because arterialization of the capillary bed is so important for P_{tcO_2} monitoring, perhaps a higher electrode temperature is required to accurately assess P_{tcO_2} trends. Transcutaneous monitoring may have an important role in continuous P_{O_2} assessment in larger infants who can tolerate higher electrode temperatures, and its use should perhaps be re-evaluated, particularly in the setting of pulmonary hypertension.

In our study, we assessed both P_{tcCO_2} and P_{tcO_2} at the recommended electrode temperature of 42°C and at several lower temperatures. We found that electrode temperatures as low as 38°C provide an accurate assessment of P_{CO_2} and similar trends compared to the recommended electrode temperature of 42°C. In comparison to the accepted standard of arterial blood gas measurement, transcutaneous electrode temperatures were accurate at every test temperature (38, 39, 40, 41, and 42°C), with mean differences from arterial values ranging from 2 to 8 mm Hg.

Using an older transcutaneous monitor, Sorensen et al[13] found that electrode temperatures of 40 and 41°C could be used to track P_{tcCO_2}; they recommend, however, using a correction factor of 12–15%. More recently, Hirata et al[23] found results similar to ours with electrode temperatures of 38, 39, and 40°C in comparison to a control of 42°C, but they recommended a correction factor of 6 mm Hg. Hirata et al,[23] however, did not use 2 monitors simultaneously, which is a major strength of our study. Given our average difference of 2.2 mm Hg between 38°C and 42°C, we do not feel a correction factor is needed, although occasional correlation with an arterial gas must be done. It is important to note that the limit of agreement in the neonate between arterial and transcutaneous values may be more dependent on skin perfusion due to blood flow changes in the neonatal skin. The trend in any one infant is more important than the absolute difference between the transcutaneous reading and the arterial value, therefore it may be more important to be aware of trends than to use a correction factor.

For P_{tcO_2}, transcutaneous monitoring has been associated with skin burns as well as measurement inaccuracies at lower electrode temperatures. For accurate measurement of P_{O_2} trends, transcutaneous monitoring requires an electrode temperature sufficient for arterialization of the capillary bed.[13,24] In our study we reassessed P_{tcO_2} using newer electrode technology recently developed by Radiometer (Copenhagen, Denmark). We tested this technology to assess any improvements in P_{tcO_2} measurements. The new sensors reportedly have a very small surface and a site time-heat function monitor that ensures that the heating of the sensor is automatically switched off after a monitoring session, theoretically decreasing the risk of skin damage. We found that while P_{tcO_2} values were much lower than arterial values, especially at low electrode temperatures, P_{tcO_2} appeared to track the higher electrode temperature results relatively well. Thus, following both P_{tcO_2} and P_{tcCO_2} may be clinically useful, even when low electrode temperatures are employed.

Limitations

This was a small study with an enrollment of 20 subjects. We did not include babies with birthweight of < 1 kg due to the potential of skin burns in this population at the higher electrode temperatures. The majority of our infants required only minimal respiratory support, and the study was short in duration, lasting approximately 4–5 h. It is also worth noting that, in general, the monitor performed with limited precision, likely due to changes in perfusion. For this reason, we recommend occasional correlation with an arterial blood gas.

Conclusions

Continuous CO_2 and O_2 monitoring are of utmost importance in extremely premature infants. Our results support and expand current literature. Use of transcutaneous monitor temperatures as low as 38°C allow accurate monitoring and tracking of P_{CO_2} and therefore can be used instead of the recommended 42°C. For P_{O_2}, transcutaneous monitoring may be useful for trending, although caution must be used in the interpretation of P_{tcO_2} values. Use of lower transcutaneous temperatures to track P_{CO_2} values should allow this technology to be applied in the smallest preterm infants.

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