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Accuracy of Transcutaneous Carbon Dioxide Levels in Comparison to Arterial Carbon Dioxide Levels in Critically Ill Children

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BACKGROUND: Widespread use of transcutaneous P_{CO_2} (P_{tcCO_2}) monitoring is currently limited by concerns many practitioners have regarding accuracy. We compared the accuracy of P_{tcCO_2} with that of P_{aCO_2} measurements in critically ill children, and we investigated whether clinical conditions associated with low cardiac output or increased subcutaneous tissue affect this accuracy. METHODS: We performed a single-center prospective study of critically ill children placed on transcutaneous monitoring. RESULTS: There were 184 children enrolled with paired P_{aCO_2} and P_{tcCO_2} values. Subjects had a median age of 31.8 mo (interquartile range 3.5–123.3 mo). Most children were mechanically ventilated ($n = 161$, 87.5%), and many had cardiac disease ($n = 76$, 41.3%). The median P_{aCO_2} was 44 mm Hg (interquartile range 39–51 mm Hg). The mean bias between P_{aCO_2} and P_{tcCO_2} was 0.6 mm Hg with 95% limits of agreement from −13.6 to 14.7 mm Hg. The P_{tcCO_2} and P_{aCO_2} were within ±5 mm Hg in 126 (68.5%) measurements. In multivariable modeling, cyanotic heart disease (odds ratio 3.5, 95% CI 1.2–10, $P = .02$) and monitor number 2 (odds ratio 3.8 95% CI 1.3–10.5, $P = .01$) remained associated with $P_{tcCO_2} \geq 5$ mm Hg higher than P_{aCO_2}. Serum lactate, fluid balance, renal failure, obesity, vasoactive-inotrope score, and acyanotic heart disease were not associated with high or low P_{tcCO_2} values. In 130 children with a second paired P_{tcCO_2} and P_{aCO_2} measurement, predicting the second measured P_{aCO_2} by subtracting the initial observed difference between the P_{tcCO_2} and P_{aCO_2} from the subsequent measured P_{tcCO_2} decreased the mean bias between observed and predicted P_{aCO_2} to 0.2 mm Hg and the 95% limits of agreement to −9.4 to 9.7 mm Hg. CONCLUSIONS: P_{tcCO_2} provides an acceptable estimate of P_{aCO_2} in many critically ill children, including those with clinical conditions that may be associated with low cardiac output or increased subcutaneous tissue, although it does not perform as well in children with cyanotic heart disease. P_{tcCO_2} may be a useful adjunct monitoring method, but it cannot reliably replace P_{aCO_2} measurement. *Key words: capnography; carbon dioxide; pediatric intensive care unit; monitoring; physiologic; respiration; artificial; heart disease.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Continuous monitoring of P_{CO_2} is indicated in many critically ill patients to gauge the adequacy of gas exchange and to guide mechanical ventilation decisions in respiratory failure. Although arterial CO_2 (P_{aCO_2}) is considered to be the most accurate P_{CO_2} measurement, it is not suitable for continuous monitoring because it is invasive

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and requires a blood draw. In mechanically ventilated children, end-tidal P_{CO_2} (P_{ETCO_2}) can provide a breath-to-breath estimate of P_{aCO_2}, but this requires an invasive cuffed airway, can only be used during conventional ventilation, and often does not reflect P_{aCO_2} in situations of cardiopulmonary disease.[1] Critical care practice would benefit from an accurate, noninvasive method for continuous CO_2 monitoring.

Transcutaneous P_{CO_2} (P_{tcCO_2}) monitors have been available since the 1980s to continuously monitor CO_2 levels, but their widespread use has been limited by the concerns many practitioners have regarding their accuracy. These monitors utilize methodology first described by Severinghaus to estimate P_{aCO_2} by measuring the diffused P_{CO_2}, after warming the skin, through a pH glass electrode.[2] Clinicians have been concerned specifically with the accuracy of P_{tcCO_2} in situations that may compromise CO_2 washout from tissue or increase the distance over which CO_2 molecules travel to the probe (eg, low cardiac output, poor skin perfusion, obesity, edema). There are a few small studies in critically ill children assessing the accuracy of P_{tcCO_2} monitors in general, and to our knowledge there are none that have assessed the impact of specific clinical conditions on accuracy. Recent reviews have called for additional study in this area.[3]

We sought to determine the accuracy of P_{tcCO_2} measurements in comparison to measurements of P_{aCO_2} in critically ill children and the clinical conditions that may affect this accuracy. We hypothesized that variables associated with low cardiac output and a large amount of subcutaneous tissue would be associated with higher P_{tcCO_2} values in children compared to P_{aCO_2}.

QUICK LOOK

Current knowledge

There are many clinical situations in which an accurate noninvasive continuous estimate of P_{aCO_2} could be helpful in critically ill children. In small studies, transcutaneous CO_2 (P_{tcCO_2}) measurements have acceptable accuracy and may meet this need. However, certain clinical conditions (eg, low cardiac output, increased subcutaneous tissue) may affect the accuracy of P_{tcCO_2} measurements in critically ill children.

What this paper contributes to our knowledge

In a large cohort of critically ill children with a variety of clinical conditions, P_{tcCO_2} provided an acceptable estimate of P_{aCO_2}. Children with cyanotic congenital heart disease were more likely to have a falsely high P_{tcCO_2} measurement. High lactate level, vasoactive-inotrope score, acyanotic heart disease, fluid balance percentage, renal failure, breathing frequency, high bilirubin level, and obesity were not associated with either falsely high or low P_{tcCO_2} levels.

Methods

We enrolled subjects from the pediatric and cardiothoracic ICUs at Children's Hospital Los Angeles for this single-center, prospective, observational cohort study from October 2013 through March 2017. Children <21 y old with an arterial line and scheduled arterial blood gases were eligible for inclusion. Exclusion criteria included children with a skin condition precluding probe placement. This study was approved by the Institutional Review Board at Children's Hospital Los Angeles. A convenience sample was enrolled as the subjects, parents, or legal guardians were approached for informed consent based on investigator availability.

Measurements

P_{tcCO_2} was monitored with the V-Sign Sensor 2 (VS-A/P/N), which was operated by the SenTec Digital Monitor with software versions MPB-SW:V05.01.03/SMB-SW: V07.01.5 (SenTec AG, Therwil, Switzerland) in accordance with manufacturer recommendations. The sensor was placed on the chest preferentially; however, other sites were occasionally used, based primarily on parent preference or if surgical dressings impeded placement. After an initial warming phase, sensors were maintained at 42°C. Unit respiratory therapists were trained in monitor management and were responsible for calibration of the monitor and recording data. Calibration was performed at a minimum of every 8 h. P_{aCO_2} measurements from arterial blood gases, performed at the bedside using an EPOC blood gas analyzer (Alere, Waltham, Massachusetts), were done at the discretion of the primary medical team. The first paired P_{aCO_2} and P_{tcCO_2} levels obtained after study enrollment were used for analysis. Drift-corrected values of P_{tcCO_2}, accounting for P_{tcCO_2} drift over the monitoring period, were also obtained from the SenTec VSTATS software after the data were downloaded from the monitor. Drift-corrected values cannot be obtained in real time and are not available immediately to the bedside clinician. The P_{tcCO_2} trend was evaluated in the 5 min prior to and after the arterial blood gases. If there was a change of $>$ 1.5 mm Hg in P_{tcCO_2} during the 10 min surrounding the arterial blood gas measurement, the P_{tcCO_2} was discarded and the subsequently measured paired P_{tcCO_2} and P_{aCO_2} (if available) were used for that subject.

Respiratory therapists and nurses in the ICUs are trained to obtain arterial blood gases during periods of relative stability and not within 15 min of endotracheal tube suctioning or ventilator changes. From the electronic medical

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record, we obtained information on demographics, diagnoses, respiratory support, vasoactive medications, fluid balance, and laboratory values.

Variable Definition

Primary admission diagnosis was categorized as postsurgical, congenital heart disease, respiratory failure, sepsis, neurologic, and other. Subjects were classified as having cyanotic heart disease if they had a right-to-left intracardiac shunt. Subjects with surgically corrected cyanotic congenital heart disease or other cardiac abnormalities were classified as having acyanotic heart disease. Fluid balance was summed over the days of hospitalization prior to the paired set of CO_2 levels used for analysis. For subjects hospitalized $>$ 7 d, we limited the fluid balance analysis to the 7 d of hospital admission prior to the analyzed CO_2 levels. Fluid balance percentage was defined as ([fluid in − fluid out]/ICU admission weight) × 100. Subjects with a body mass index $>$ 25 kg/m^2 were considered to be obese (yes/no). Vasoactive inotrope score (VIS) was calculated as VIS = dopamine dose + dobutamine dose + 100 × epinephrine dose + 10 × milrinone dose + 10,000 × vasopressin dose + 100 × norepinephrine dose; all doses were considered as μg/kg/min except for vasopressin, which was considered as units/kg/min. Renal failure (yes/no) was defined as either a creatinine $>$ 1.5 mg/dL or requiring either hemofiltration or dialysis. A high serum lactate was defined as $>$ 20 mg/dL (yes/no). A high serum bilirubin was defined as $\geq$ 2 mg/dL (yes/no). Children who did not have an available lactate level or bilirubin were considered to have a normal serum lactate or bilirubin.

Statistical Analysis

Statistical analysis was performed using STATA (version 15, StataCorp, College Station, Texas). Bland-Altman analysis and graphs were created with GraphPad Prism (version 5, GraphPad Software, La Jolla, California). A descriptive initial analysis of the data was performed. Our primary outcome was the bias (mean difference) and 95% limits of agreement (mean difference ± 1.96 SD) between P_{aCO_2} and P_{tcCO_2}. A Bland-Altman plot was created to demonstrate the relationship between P_{aCO_2} and P_{tcCO_2}. A Spearman's correlation coefficient was calculated between P_{aCO_2} and P_{tcCO_2} (data were not normally distributed) to assess the strength of the relationship between the variables.

As the covariates associated with a P_{tcCO_2} value higher than the P_{aCO_2} value were hypothesized to be different than those associated with a P_{tcCO_2} value lower than the P_{aCO_2} value, measurements were categorized as $P_{tcCO_2} \geq 5$ mm Hg higher than P_{aCO_2}, P_{tcCO_2} ± 5 mm Hg of P_{aCO_2}, and $P_{tcCO_2} \geq 5$ mm Hg lower than P_{aCO_2}. These categories were used to analyze the association with covariates of low cardiac output (high lactate, VIS, cyanotic heart disease, acyanotic heart disease), increased subcutaneous tissue (fluid balance, obesity, renal failure, age), monitor performance/other (time from calibration, probe site, monitor number, study year, breathing frequency, high bilirubin) using a Kruskal-Wallis test (continuous variables) or a chi-square test (categorical variables). Multivariable modeling was used to determine the influence of covariates on the difference between P_{tcCO_2} and P_{aCO_2}. We built separate logistic regression models for the dependent variables: 1) $P_{tcCO_2} \geq 5$ mm Hg higher than P_{aCO_2} and 2) $P_{tcCO_2} \geq 5$ mm Hg lower than P_{aCO_2}. To meet assumptions of linearity in the models, VIS (0, 0–10, ≥ 10), age ($<$ 2 y, 2–10 y, ≥ 10 y), fluid balance percentage (negative, 0–10%, 10–20%, ≥ 20%), and breathing frequency ($<$ 30 breaths/min, 30–50 breaths/min, ≥ 50 breaths/min) were analyzed as categorical variables (categorization groups determined empirically). P_{aCO_2} was analyzed using categories ($<$ 35 mm Hg, 35–55 mm Hg, ≥ 55 mm Hg) to define a low and high P_{aCO_2} category ($<$ 25th percentile and $>$ 75th percentile, respectively). Variables with a univariate association of $P < .20$ were considered for a multivariable model. Variables with a significance level of $P < .05$ remained in the final multivariable model. Confounding variables were included in the final multivariable model if they changed the ß estimate by $>$ 15%. Goodness of fit was assessed with a Hosmer-Lemeshow chi-square test.

In subjects with available subsequent paired P_{aCO_2} and P_{tcCO_2} measurements, a secondary analysis examined whether the relationship between P_{tcCO_2} and P_{aCO_2} remained consistent among individual subjects over time. We approached this analysis in 2 ways. First, we used the difference between the first paired measurement of P_{tcCO_2} and P_{aCO_2} to predict the second measurement of P_{aCO_2} by subtracting the first measurement difference from the second measurement of P_{tcCO_2}. For example, if the P_{tcCO_2} was 50 mm Hg when the P_{aCO_2} was 45 mm Hg, then the assigned difference was +5 mm Hg. If the subsequent P_{tcCO_2} was 60 mm Hg, we would then predict that the P_{aCO_2} would be 55 mm Hg, maintaining this difference. Second, we considered the values for the initial difference between P_{tcCO_2} and P_{aCO_2} in the first paired measurement, the second measurement of P_{tcCO_2}, and other covariates for a linear regression prediction model for the second gas P_{aCO_2}. We reported the bias and 95% limits of agreement between the observed and predicted P_{aCO_2} values using the above 2 methods.

Results

There were 200 critically ill subjects enrolled in the study. Those without a paired P_{tcCO_2} and P_{aCO_2} measure-

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Table 1. Carbon Dioxide Levels and Clinical Characteristics of Children at the Time of Measurement

	All Subjects	$P_{tcCO_2} \geq 5$ mm Hg Higher Than P_{aCO_2}	$P_{tcCO_2} \pm 5$ mm Hg of P_{aCO_2}	$P_{tcCO_2} \geq 5$ mm Hg Lower Than P_{aCO_2}	*P*
Age, months	31.8 (3.5–123.3)	4 (0.7–39.6)	40.8 (7–130.8)	69.6 (7–164.4)	.004
Probe location					.88
Chest	166 (90.2%)	35 (89.7%)	114 (90.5%)	17 (89.5%)	
Other	14 (7.6%)	3 (7.7%)	10 (7.9%)	1 (5.3%)	
Unknown	4 (2.2%)	1 (2.6%)	2 (1.6%)	1 (5.3%)	
Time from calibration, h	2.2 (1–4.6)	2.2 (1–3.6)	2.5 (1–4.8)	2 (0.9–3.8)	.55
Mechanical ventilation	161 (87.5%)	32 (82.1%)	114 (90.5%)	15 (78.9%)	.19
Frequency, breaths/min	25 (20–31)	24 (20–40)	24 (18–30)	20 (14–30)	.21
Vasoactive-inotrope score	5 (0–10)	7.5 (0–11)	2.5 (0–11.1)	2.5 (0–7.5)	.45
High bilirubin	52 (28.3%)	12 (30.8%)	33 (26.2%)	7 (36.8%)	.58
High lactate	24 (13%)	4 (10.3%)	20 (15.9%)	0 (0%)	.14
Hospital stay fluid balance					.22
Negative	37 (20.1%)	9 (23.1%)	25 (19.8%)	3 (15.8%)	
0–10%	75 (40.8%)	10 (25.6%)	55 (43.7%)	10 (52.6%)	
> 10–20%	42 (22.8%)	14 (35.9%)	26 (20.6%)	2 (10.5%)	
> 20%	30 (16.3%)	6 (15.4%)	20 (15.9%)	4 (21.1%)	
Renal failure	25 (13.6%)	2 (5.1%)	22 (17.5%)	1 (5.3%)	.08
Acyanotic heart disease	57 (31%)	14 (35.8%)	36 (28.6%)	7 (36.8%)	.58
Cyanotic heart disease	19 (10.3%)	10 (25.6%)	9 (7.1%)	0 (0%)	.001
Obesity	18 (9.8%)	2 (5.1%)	13 (10.3%)	3 (15.8%)	.4
P_{aCO_2}, mm Hg	44 (39–51)	43 (38–46)	44 (38–51)	47 (42–72)	.03
P_{tcCO_2}, mm Hg	45 (38–51)	49 (47–57)	44 (36–49)	41 (34–55)	< .001

N = 184 subjects. *P* values are for comparisons between the $P_{tcCO_2} \geq 5$ mm Hg higher than P_{aCO_2} group (*n* = 39), the $P_{tcCO_2} \pm 5$ mm Hg of P_{aCO_2} group (*n* = 126), and the $P_{tcCO_2} \geq 5$ mm Hg lower than P_{aCO_2} group (*n* = 19). Categorical values are presented as *n* (%) and were compared with a chi-square test. Continuous variables are presented as median (interquartile range) and were compared with a Kruskal-Wallis test.
P_{tcCO_2} = transcutaneous P_{CO_2}

ment after study enrollment (*n* = 9) or without paired measurements during a period of stable P_{tcCO_2} (*n* = 7) were excluded. Therefore, paired P_{tcCO_2} and P_{aCO_2} measurements obtained from 184 subjects were used for the analysis. The first recorded paired measurements were used in 153 subjects (83.2%), and in 31 subjects (16.8%) a subsequent paired measurement was used for the analysis (due to a change of > 1.5 mm Hg in P_{tcCO_2} during the 10 min surrounding the first arterial blood gas). The primary reasons for ICU admission included congenital heart disease (34.2%), respiratory failure (25%), post-surgery (12.5%), sepsis (11.4%), neurologic issue (5.4%), and other (11.4%). The median age and interquartile range (IQR) of the included subjects was 31.8 months (IQR 3.5–123.3 mo) (Table 1). Most subjects were mechanically ventilated (*n* = 161, 87.5%), and many had cardiac disease (*n* = 76, 41.3%). The median VIS was 5 (IQR 0–10.4), and 13% of subjects (*n* = 24) had a high serum lactate (> 20 mg/dL). There were 30 subjects (16.3%) with a > 20% positive fluid balance for their hospital stay at the time of the paired P_{tcCO_2} and P_{aCO_2} measurements.

The median P_{aCO_2} was 44 mm Hg (IQR 39–51 mm Hg), with a range 21–194 mm Hg. The median P_{tcCO_2} was 45 mm Hg (IQR 38–51 mm Hg) with a range of 21–163 mm Hg. In 126 (68.5%) measurements, the P_{tcCO_2} was within ± 5 mm Hg of the P_{aCO_2}. In 39 (21.1%) measurements, the P_{tcCO_2} was ≥ 5 mm Hg higher than the P_{aCO_2}, and in 19 (10.3%) measurements, the P_{tcCO_2} was ≥ 5 mm Hg lower than the P_{aCO_2}. In 153 measurements (83.2%), the P_{tcCO_2} was ± 7.5 mm Hg of the P_{aCO_2}.

The mean bias between P_{aCO_2} and the P_{tcCO_2} was 0.6 mm Hg with 95% limits of agreement from −13.6 to 14.7 mm Hg (Fig. 1). The correlation between P_{aCO_2} and P_{tcCO_2} was high (r_s = 0.83).

Drift-Corrected P_{tcCO_2} Measurements

In the 162 (88%) subjects with drift-corrected data, 114 subjects (70.4%) had a drift-corrected $P_{tcCO_2} \pm 5$ mm Hg of the P_{aCO_2}. This was not significantly more than the 108 subjects (66.7%) in this subgroup who had a real-time $P_{tcCO_2} \pm 5$ mm Hg of the P_{aCO_2} (*P* = .17). The mean bias between P_{aCO_2} and the drift-corrected P_{tcCO_2} was 0.4 mm Hg with 95% limits of agreement from −11 to 11.8 mm Hg. The correlation between P_{aCO_2} and the drift-corrected P_{tcCO_2} was high (r_s = 0.86).

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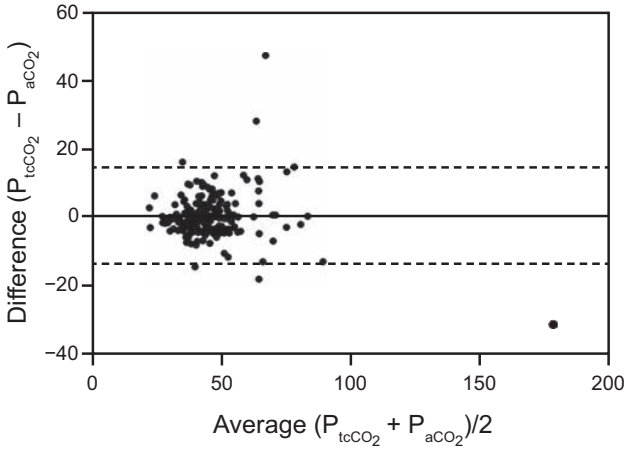

Fig. 1. Bland-Altman plot showing the difference between P_{tcCO_2} and P_{aCO_2} plotted against the average of the P_{tcCO_2} and the P_{aCO_2}. The horizontal line represents the bias (mean difference), and the dashed lines indicate the limits of agreement (± 1.96 SD).

Logistic Regression Models

Univariate risk factors for $P_{tcCO_2} \geq 5$ mm Hg higher than P_{aCO_2} included cyanotic heart disease, monitor number 2, and age < 2 y ($P < .05$). Cyanotic heart disease (odds ratio 3.5, 95% CI 1.2–10, $P = .02$) and monitor number 2 (odds ratio 3.8, 95% CI 1.3–10.5, $P = .01$) remained independently associated with $P_{tcCO_2} \geq 5$ mm Hg higher than P_{aCO_2} after controlling for age, which did not maintain an independent association (reference range 2–10 y; < 2 y: odds ratio 2.7, 95% CI 0.96–7.7, $P = .06$; ≥ 10 y: odds ratio 1.2, 95% CI 0.36–4.2, $P = .73$) but did meet a priori criteria as a confounding variable.

The only identified univariate risk factor for producing a P_{tcCO_2} at least 5 mm Hg lower than the P_{aCO_2} was $P_{aCO_2} \geq 55$ mm Hg (odds ratio 3.5 (95% CI 1.2–10), $P = .02$). There were no confounding variables that affected this relationship.

Probe location, time from monitor calibration, study year, breathing frequency, high lactate level, high bilirubin level, VIS, acyanotic heart disease, fluid balance percentage, renal failure, and obesity were not associated with either high or low P_{tcCO_2} levels (all $P > .05$). In post hoc sensitivity analysis, using multiple different cutpoints, VIS remained unassociated with either high or low P_{tcCO_2} levels ($P > .05$).

Of the 4 monitors used for this study, one monitor was associated with high P_{tcCO_2} values (odds ratio 3.4, 95% CI 1.3–9.1, $P = .01$). This monitor was used on 27 subjects (14.7%). When the primary analysis was repeated without the subjects studied on this monitor, the results were similar.

Prediction Modeling

For the purpose of prediction modeling, 130 subjects (70.7%) had a second paired P_{tcCO_2} and P_{aCO_2} measurement. The median time between gases used for this analysis was 6 h (IQR 3−11 h). Most subjects ($n = 97$, 74.6%) remained in the same category ($P_{tcCO_2} \geq 5$ mm Hg higher than P_{aCO_2}, ± 5 mm Hg of P_{aCO_2}, or ≥ 5 mm Hg lower than P_{aCO_2}) from the first paired measurement to the second paired measurement (Table 2).

The mean bias between the observed and predicted P_{aCO_2} when adding the initial measurement difference between P_{aCO_2} and P_{tcCO_2} to the second paired measurement P_{tcCO_2} was 0.2 mm Hg, with 95% limits of agreement from −9.4 to 9.7 mm Hg. In multivariable linear regression modeling, including a variable for the change in P_{tcCO_2} from the first to the second measurement, we further narrowed the 95% limits of agreement between the predicted P_{aCO_2} and the observed P_{aCO_2} (bias 0 mm Hg, 95% limits of agreement from −8.3 to 8.3 mm Hg) (Table 3, Fig. 2).

Discussion

We analyzed the accuracy of P_{tcCO_2} monitoring in a large diverse population of critically ill children with an extensive range of P_{aCO_2} values, finding that P_{tcCO_2} provides a clinically useful estimate of P_{aCO_2} (± 5 mm Hg) in most clinical conditions, including many that are associated with low cardiac output or increased subcutaneous tissue. We found that subjects with cyanotic heart disease are more likely to have P_{tcCO_2} values ≥ 5 mm Hg higher than P_{aCO_2}. The specific monitor used was also important in our analysis because one of the 4 monitors we used was associated with a P_{tcCO_2} value ≥ 5 mm Hg higher than P_{aCO_2}. In secondary analyses we demonstrated that the P_{tcCO_2} and P_{aCO_2} difference can be used to improve the prediction ability of subsequent P_{tcCO_2} measurements.

Our findings are similar to previous studies in newborns, adults, and children, demonstrating a small bias and poor precision with wide limits of agreement between P_{aCO_2} and P_{tcCO_2}.[4-10] Urbano et al[5] found similar results in 11 critically ill children monitored with the SenTec monitor, a bias of −2.1 mm Hg with 95% limits of agreement of ± 10.6 mm Hg. This previous study used a range of ± 7.5 mm Hg as acceptable and found that 81.2% of measurements fell within this range.[5] This was similar to the 83.2% of measurements in our study where the P_{tcCO_2} was within ± 7.5 mm Hg of the P_{aCO_2}.

Measurement of P_{tcCO_2} requires warming of the skin to hyperperfuse capillaries and facilitate diffusion of CO_2 through the skin. Children with cyanotic heart disease, particularly in the perioperative period, often have low cardiac output with decreased skin perfusion. Decreased skin perfusion causes reduced removal of CO_2 from the

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Table 2. Category of First Paired P_{aCO_2} and P_{tcCO_2} Measurement and Second Paired Measurement

		Second Paired Measurement		
		Children With $P_{tcCO_2} \geq 5$ mm Hg Lower Than P_{aCO_2} ($n = 16$)	Children With $P_{tcCO_2} \pm 5$ mm Hg of P_{aCO_2} ($n = 87$)	Children With $P_{tcCO_2} \geq 5$ mm Hg Higher Than P_{aCO_2} ($n = 27$)
First Paired Measurement	Children with $P_{tcCO_2} \geq 5$ mm Hg lower than P_{aCO_2} ($n = 14$)	7	7	0
	Children with $P_{tcCO_2} \pm 5$ mm Hg of P_{aCO_2} ($n = 86$)	9	70	7
	Children with $P_{tcCO_2} \geq 5$ mm Hg higher than P_{aCO_2} ($n = 30$)	0	10	20

P_{tcCO_2} = transcutaneous P_{CO_2}

Table 3. Multivariable Predictive Linear Regression Model for Second Measurement of P_{aCO_2}

	β (95% CI)	P
P_{tcCO_2} (second measurement)	0.98 (0.92–1)	< .001
Difference between P_{tcCO_2} and P_{aCO_2} (first measurement)	0.66 (0.54–0.77)	< .001
Change in P_{tcCO_2} from first to second measurement	0.11 (0.03–0.2)	.01

$r^2 = 0.90$ ($P < .001$) for the multivariable model.
P_{tcCO_2} = transcutaneous P_{CO_2}

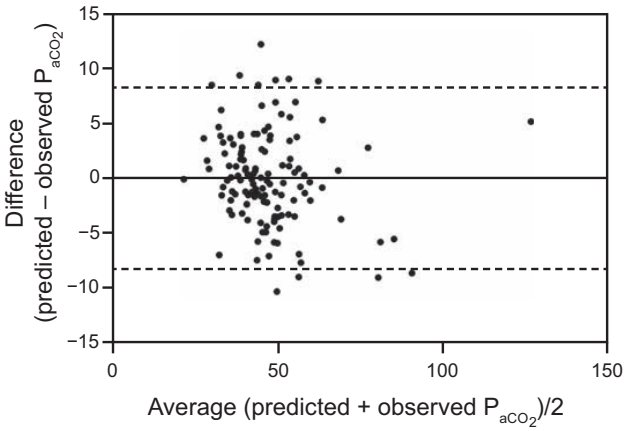

Fig. 2. Bland-Altman plot of predicted P_{aCO_2} and observed P_{aCO_2} using the developed multivariable predictive linear regression model. The difference between the predicted P_{aCO_2} and observed P_{aCO_2} is plotted against the average of the predicted P_{aCO_2} and the observed P_{aCO_2}. The horizontal line represents the bias (mean difference), and the dashed lines indicate the limits of agreement (± 1.96 SD).

skin through the blood, so it is not surprising that P_{tcCO_2} levels ≥ 5 mm Hg higher than P_{aCO_2} were associated with children with cyanotic heart disease.[1] We did not find a significant association between other markers of poor cardiac output such as high lactate level, VIS, or acyanotic heart disease and a $P_{tcCO_2} \geq 5$ mm Hg higher than P_{aCO_2}. Lactate can be elevated for reasons other than poor perfusion, which may have led to nonsignificance. In previous studies, doses of epinephrine as high as 0.3 μg/kg/min were required to observe a diminished correlation between P_{aCO_2} and P_{tcCO_2}.[11] We did not see this association in our data, although in our study only 5 subjects were on doses of vasoconstrictors this high. It is possible that many of the children in our study with acyanotic heart disease did not have low cardiac output at the time of measurement, and only the children with cyanotic heart disease had compromised cardiac output to the degree necessary to affect skin perfusion.

In 10.9% of the measurements the P_{tcCO_2} was ≥ 5 mm Hg lower than P_{aCO_2}. For some of the measurements this was in the situation of a very high P_{aCO_2}, as demonstrated by the significant association between a $P_{aCO_2} \geq 55$ mm Hg and a $P_{tcCO_2} \geq 5$ mm Hg lower than P_{aCO_2} in the multivariable analysis. The primary theoretical reason for this type of discrepancy in other measurements would be problems with either probe placement or technical drift of the measurement. Although all respiratory therapists were trained in appropriate probe placement, it was not required that they check probe placement prior to recording data. The accuracy of P_{tcCO_2} measurements may improve with more frequent monitoring of probe placement or calibration, although this would also make the monitors more cumbersome to use in a clinical setting.

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An accurate, noninvasive, and continuous method to estimate P_{aCO_2} is desirable for optimal patient care in most critically ill children. Although noninvasive continuous oxygenation monitoring is universally clinically accepted with pulse oximetry, no such method is universally accepted for CO_2 monitoring. Assessment of both oxygenation and ventilation are necessary to determine the respiratory status of a patient. High P_{aCO_2} increases blood flow to the brain and decreases blood flow to the lungs. It is imperative in situations such as increased intracranial pressure or pulmonary hypertension that clinicians closely monitor P_{aCO_2} levels as a reflection of changing pH. While P_{tcCO_2} monitoring does not have the precision to replace P_{aCO_2} measurement routinely, our data suggest that in many children it may be a useful adjunct continuous P_{CO_2} monitoring method.

Most mechanically ventilated children are monitored with end-tidal capnography because it provides breath-to-breath P_{CO_2} values, confirming appropriate endotracheal tube placement; and for some children it provides an acceptable continuous estimate of P_{aCO_2}. However, P_{ETCO_2} may be inaccurate and highly variable in periods of incomplete exhalation when dynamic hyperinflation is present.[12] Furthermore, critically ill children (particularly those with significant lung or cardiac disease) often have elevated alveolar dead space (ie, alveoli that are ventilated without perfusion).[13-15] This results in a P_{ETCO_2} that is lower than P_{aCO_2}. In small infants, some clinicians argue against using P_{ETCO_2} monitoring at all because the monitor adds airway dead space to the ventilator circuit. Furthermore, clinicians are more commonly choosing noninvasive modes of respiratory support such as high-flow humidified nasal cannula or bi-level positive airway pressure. Children on noninvasive respiratory support often have changing cardiorespiratory pathophysiology and are a population in which close monitoring of respiratory status is imperative for the detection of clinical deterioration and timely intervention. Continuous monitoring of CO_2 levels with P_{tcCO_2} has the potential to address many of the known problems with P_{ETCO_2} monitoring in some children.

In mechanically ventilated children with ARDS, concerns regarding ventilator-induced lung injury have led to guidelines that recommend permissive hypercapnia.[16] Currently, blood gases are the primary method for ventilation assessment in children with ARDS, and ventilator changes occur infrequently.[17] To prevent periods of overventilation, and thus abide by permissive hypercapnia, more frequent and accurate measurements of CO_2 to prompt ventilator changes are necessary. The limits of agreement we found for P_{tcCO_2} are likely sufficient for this purpose. Moreover, in critically ill children with acute hypoxemic respiratory failure, elevated dead space has been associated with increased mortality.[13,14] Using P_{tcCO_2}-based prediction modeling of P_{aCO_2} for dead space calculation could be feasible for noninvasive monitoring of dead space for prognostic purposes in some children.

Although some may disagree on how close a P_{tcCO_2} measurement should be to a P_{aCO_2} measurement for clinical use, values $\pm$ 5 mm Hg are close to the acceptable error of measurement within point-of-care devices for P_{aCO_2} measurements.[18] There are limits to accuracy for all measurement devices. Some of the devices that intensivists rely on heavily to be accurate often have surprisingly wide limits of agreement. For example, while pulse oximetry is considered accurate by most clinicians, research has demonstrated that, when pulse oximetry oxygen saturation values are below normal, the limits of agreement can be quite wide and are comparable to the range we found for P_{tcCO_2} in this study.[19,20]

Our study had several limitations. We chose to operate the V-Sign Sensor 2 at 42°C to limit the risk of skin blistering or burning (no patients experienced either in our study). However, a higher monitoring temperature may have improved the accuracy of P_{tcCO_2} measurements.[21] Our analysis was limited by the sample size, which may have led to a lack of power to detect some associations. For example, it is possible that, in a larger sample size, age $<$ 2 y old may have retained an independent association in the multivariable model for $P_{tcCO_2} \geq 5$ mm Hg higher than P_{aCO_2}. Furthermore, we did not measure cardiac output or subcutaneous tissue in the subjects, relying instead on surrogate measures. It is possible that measured cardiac output or subcutaneous tissue would have been more strongly associated with accuracy. We did not perform blood gases for the purposes of the study, therefore there was a variable time from monitor set up and calibration to blood gas. However, the time from calibration was not associated with accuracy in our analysis. The subjects who were selected for our study all had an arterial line in place for blood gas monitoring. In general, children with an arterial line have a higher severity of illness. It is possible that P_{tcCO_2} monitoring would perform differently in the larger population of critically ill children without an arterial line, although we would anticipate P_{tcCO_2} to perform better in this population due to the lower severity of illness, not worse. We limited our study to the SenTec P_{tcCO_2} monitor. It is possible that other monitors perform with higher or lower accuracy.

Conclusions

P_{tcCO_2} provides an acceptable estimate of P_{aCO_2} in many critically ill children, including those with clinical conditions that may be associated with low cardiac output or increased subcutaneous tissue, although it does not perform as well in children with cyanotic heart disease. P_{tcCO_2} monitoring may be useful as a noninvasive continuous method of estimating

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P_{aCO_2} in critically ill children. However, it cannot be used reliably in place of P_{aCO_2} measurements.

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