ORIGINAL RESEARCH

Comparison of arterial CO_2 estimation by end-tidal and transcutaneous CO_2 measurements in intubated children and variability with subject related factors

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Abstract

Transcutaneous PCO_2 ($P_{TC}CO_2$) and end-tidal PCO_2 ($P_{ET}CO_2$) measurement methods serve as alternatives to arterial PCO_2 ($PaCO_2$), providing continuous non-invasive monitoring. The objective of this study was to evaluate the $P_{TC}CO_2$ and $P_{ET}CO_2$ methods with actual $PaCO_2$ levels, and to assess the variability of measurements in relation to subject-related factors, such as skin and subcutaneous adipose tissue thickness and presence of pulmonary diseases. $P_{TC}CO_2$, $P_{ET}CO_2$ and $PaCO_2$ were measured at the same time in intubated pediatric subjects. Subjects' demographic characteristics, clinical features, laboratory parameters, skin and subcutaneous adipose tissue thickness were identified. The study was carried out on 102 subjects with a total of 1118 values for each method. In patients with non-pulmonary disease, the mean difference between $P_{TC}CO_2$ and $PaCO_2$ was − 0.29 mmHg (± 6.05), while it was 0.44 mmHg (± 6.83) bias between $P_{ET}CO_2$ and $PaCO_2$. In those with pulmonary diseases, the mean difference between $P_{TC}CO_2$ and $PaCO_2$ was − 1.27 mmHg (± 8.32), while it was − 4.65 mmHg (± 9.01) between $P_{ET}CO_2$ and $PaCO_2$. Multiple linear regression demonstrated that increased subcutaneous adipose tissue thickness, core body temperature and inotropic index were related with higher $P_{TC}CO_2$ values relative to the actual PCO_2 values. Other factors, such as skin tissue thickness, presence of pulmonary disease, measurement location and measurement times were non-significant. The $P_{TC}CO_2$ method has higher reliability than the $P_{ET}CO_2$ method, and $P_{TC}CO_2$ measurements are not influenced by most subject-related factors; however, core body temperature, inotropic index and subcutaneous adipose tissue thickness can lead to significant differences in PCO_2 measurement.

Keywords Arterial blood gas analysis · Transcutaneous CO_2 · End-tidal CO_2 · Subcutaneous adipose tissue thickness · Skin thickness · Pediatric intensive care

1 Introduction

The monitoring of carbon dioxide (CO_2) level is essential for diagnosis and therapeutic guidance in mechanically ventilated and/or tracheostomized subjects [1]. Subjects with parenchymal or non-parenchymal lung disease with invasive ventilation must be monitored to assess alveolar ventilation and also to predict the need for mechanical ventilation (MV) [1]. The current gold standard method for the measurement of partial pressure of carbon dioxide (PCO_2) is intermittent arterial blood gas (ABG) analysis. In addition to being a time-consuming invasive method, ABG does not provide continuous monitoring and measures arterial PCO_2 ($PaCO_2$) with arterial puncture which may be associated with increased blood loss, potentially-permanent vessel damage and catheter associated complications. Also it does not provide real-time measurement of PCO_2; delaying response time in critically ill patients [2]. However, although CO_2 monitoring has several non-invasive measurement techniques, $PaCO_2$ analysis remains as the gold standard method. With today's technology, it is

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not possible for any non-invasive method to entirely replace $PaCO_2$ measurements.

Ideally, non-invasive techniques of measurement should be available for continuous monitoring of oxygenation and ventilation status. For instance, pulse oximetry has proven to be a rapid, reliable and non-invasive measurement of oxygen saturation by using a non-adhesive skin sensor, but there is no similar method for measuring CO_2 levels transcutaneously [3]. Transcutaneous PCO_2 ($P_{TC}CO_2$) and end-tidal PCO_2 ($P_{ET}CO_2$) measurements serve as alternatives to $PaCO_2$ measurement and provide continuous and non-invasive monitoring of subject. The essence of non-invasive gas monitoring is to provide information about alveolar ventilation and circulatory gas levels without the need for repetitive blood sampling [1–4].

$P_{ET}CO_2$ monitoring via capnometer provides information on the adequacy of ventilation and displays the waveform of PCO_2 in exhaled air [4]. Detection of exhaled PCO_2 has proven to be a valuable mechanism to confirm tracheal intubation and recognize accidental esophageal intubations, among other critical patient safety benefits [2]. The safety enhancements provided by CO_2 monitoring also include the detection of invasive airway disconnection, dislodgement or obstruction, postoperative monitoring of respiratory depression, prediction of underlying airway or lung pathologies, and monitoring the effectiveness of cardiopulmonary resuscitation [5, 6].

$P_{TC}CO_2$ monitors perform measurements based on the capillary bed and provide continuous information about transcutaneous CO_2 through the local application of heat and measurement by electrodes [7]. Transcutaneous monitors have been more widely used in neonates because of their thinner skin which minimizes resistance to gas diffusion [8]. There are numerous studies which show good correlations between non-invasive carbon dioxide measurement methods and $PaCO_2$ values, both in the pediatric [9–13] and adult population [14, 15]. However, other authors have not been able to confirm these results, while some studies demonstrate conflicting findings [16–18].

The objective of this study was to evaluate the relationships between the $P_{TC}CO_2$ and $P_{ET}CO_2$ methods and the gold standard ABG analysis in mechanically ventilated children in the pediatric intensive care unit. The secondary objective was to assess the variability of $P_{TC}CO_2$ measurements in relation to subject-related factors, such as skin and subcutaneous adipose tissue thickness and pulmonary diseases.

2 Materials and methods

2.1 Subjects

This is a single-center, prospective and comparative study approved by the Clinical Research Ethics Committee of Istanbul Medeniyet University Goztepe Training and Research Hospital (study registration number: 2017-9375).

The study evaluated all children aged between 1 month and 17 years that had been intubated with cuffed ETT due to a definite indication for mechanical ventilation. The intubations were performed with single-lumen cuffed ETT with appropriate size for age and weight. Among these patients, those who accepted invasive monitoring of arterial blood pressure and provided informed consent (from the parents or legal guardians) were included in the study. The presence of any one of the following characteristics was defined as grounds for exclusion from the study: sampling performed with venous blood, non-compliance to the study protocol (premature discontinuation of measurement, incorrect installation of sensor or signal abnormality of monitor or backup), use of uncuffed endotracheal tubes, determination of any type of air leakage in the lung (pneumothorax, pneumomediastinum etc.).

2.2 Measurements

We used two non-invasive CO_2 measurement methods (end-tidal CO_2; PetCO$_2$ and transcutaneous CO_2; PtcCO$_2$) and an invasive CO_2 measurement method ($PaCO_2$) via ABG, in mechanically ventilated children admitted to Istanbul Medeniyet University Hospital, Pediatric Intensive Care Unit (PICU) between November 2017 and June 2019.

2.2.1 Transcutaneous CO$_2$ measurements

Transcutaneous CO_2 was measured by using a TCM4 $P_{TC}CO_2/P_{TC}O_2$ device (Radiometer™, Copenhangen, Denmark, TCM4® series CombiM). The electrode membrane device was cleaned and calibrated at the beginning of measurement and repetitive calibration was applied every four hours. A small drop of sensor gel was applied to the center of the sensor membrane's surface. The purpose of using sensor gel is to enable gas diffusion by moisturizing the skin. The electrode temperature was set to 44.0 °C to enhance sufficient blood flow in the capillaries to allow for PCO_2 measurement in accordance with the manufacturer's recommendations. There are three preselected locations in the supine position: (a) second intercostal space in the midclavicular line, (b) lateral surface of abdomen at the level of the umbilicus in the midclavicular line and (c) inner surface of the thigh. New fixation rings were used at each transcutaneous CO_2 measurement location. The transcutaneous sensor was applied to the child's chest, thigh or abdomen and was allowed to stabilize for at least 15 min prior to data recording.

2.2.2 End-tidal CO_2 measurements

The CO_2 sensor (Mainstream Capnostat 5 EtCO$_2$ Sensor, Philips Healthcare, Eindhoven, Netherlands) was placed next to the tracheal cannula or intubation tube and was connected to the monitor (MX 600 Philips Intellivue™, Amsterdam, The Netherlands) for display. Calibration of the $P_{ET}CO_2$ sensor was performed by zeroing of the sensor in room air. Calibration was done prior to measurements for each subject.

2.2.3 Arteriel blood gas analysis

PCO_2 measurements from ABG were analyzed at the bedside using an ABL 90 FLEX blood gas analyzer (Radiometer, Medical ApS, Copenhagen, Denmark) within 3 min of collection. As soon as blood samples were taken for ABG analysis, $P_{TC}CO_2$ and $P_{ET}CO_2$ measurements were recorded simultaneously.

2.2.4 Measurement of skin and subcutaneous adipose tissue thickness

The same radiologist performed skin and subcutaneous adipose tissue thickness measurements via ultrasonography at the point where transcutaneous CO_2 sensors were placed. A linear L12-3 probe was used (EPIQ 7C, Philips, Bothell, Seattle, WA, USA). Patients were in the supine position and measurements were performed without applying pressure to the probe at the CO_2 ring localizations (chest, abdomen and thigh).

2.3 Study procedure

Transcutaneous CO_2 measurement was initiated from chest location in each subject. Then, thigh and abdomen measurements were taken respectively. At the 15th minute and 3rd hour after sensor fixation and calibration, $P_{TC}CO_2$–$P_{ET}CO_2$ and $PaCO_2$ measurements were recorded simultaneously for each location starting from the chest location (Fig. 1). The measurement protocol was planned to be performed in two cycles per subject –each cycle containing 6 readings (chest, thigh and abdomen readings on the 15th minute and 3rd hour), unless subjects expired or were extubated before the two cycles were complete. Subjects who could not complete at least one cycle protocol (at least two measurements per location with a total of 6 readings) were excluded from all analyses (Fig. 2). The results were recorded after sensor fixation at three locations sequentially and were compared with $PaCO_2$ and $P_{ET}CO_2$ results that were measured simultaneously.

Finally, a total of 1118 pairs of measurements were recorded for each measurement method. The maximum acceptable difference between $PaCO_2$ and non-invasive CO_2 measurements ($P_{TC}CO_2$ and $P_{ET}CO_2$) was defined as ± 4 mmHg [19].

The following demographic characteristics, clinical features and laboratory parameters of subjects were identified: sex, age (month) and core body temperature (sensor in the esophagus). Parameters of mechanical ventilation were also recorded, including FiO_2, peak pressure (P_{peak}) and mean airway pressure (MAP). Measurement of the non-invasive CO_2 values ($P_{TC}CO_2$ and $P_{ET}CO_2$), parameters of ABG analysis (pH, $PaCO_2$, PaO_2, HCO_3^-, base excess, haemoglobin and lactate level), inotropic index (inotropic index = dose of

Fig. 1 Flow chart of PCO_2 monitoring in mechanically ventilated subjects. *PCO$_2$* Partial pressure of carbon dioxide, *PaCO$_2$* arterial PCO_2, *t* recording time (in minutes)
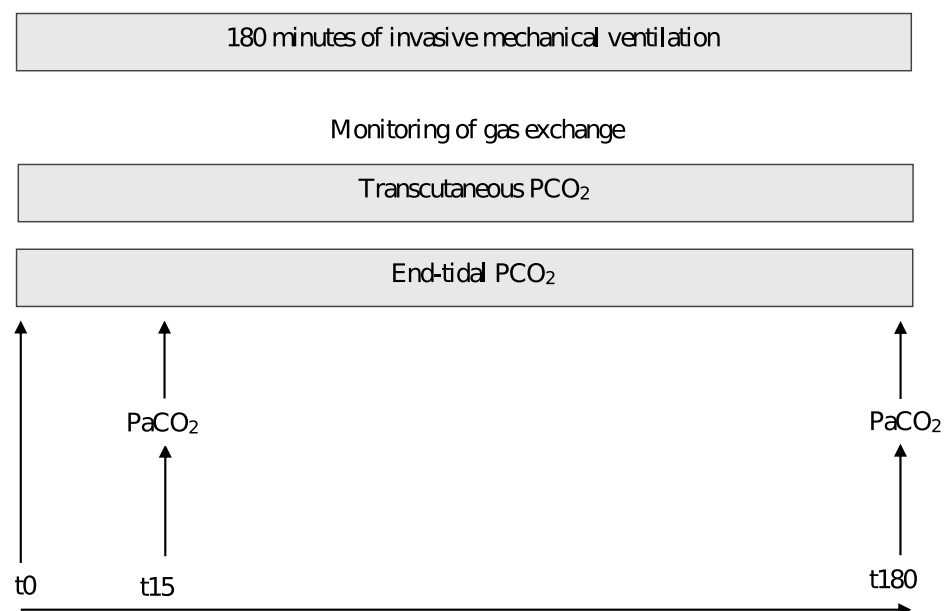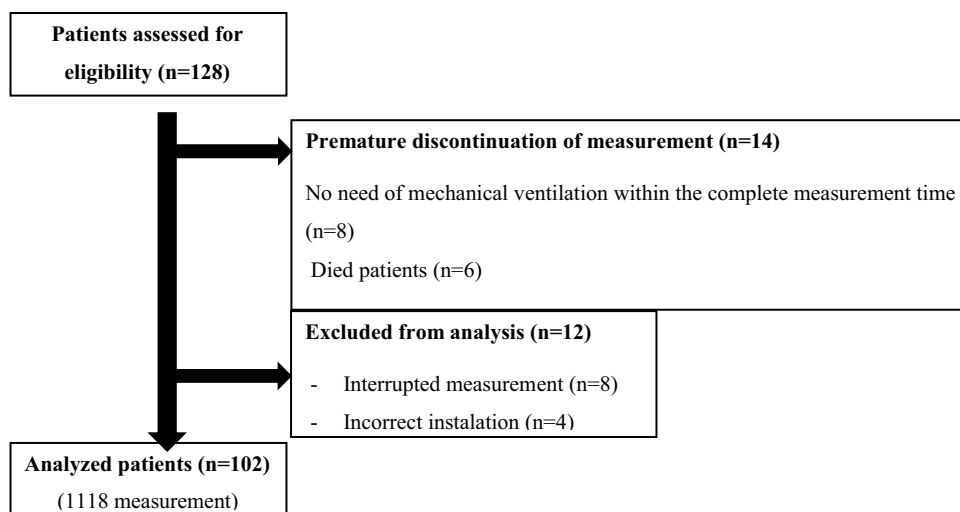
Fig. 2 Flow chart showing description of the trial

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┌─────────────────────────────┐
│   Patients assessed for      │
│   eligibility (n=128)        │
└─────────────────────────────┘
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Premature discontinuation of measurement (n=14)

No need of mechanical ventilation within the complete measurement time (n=8)

Died patients (n=6)

Excluded from analysis (n=12)

- Interrupted measurement (n=8)
- Incorrect instalation (n=4)

Analyzed patients (n=102)
(1118 measurement)

$dopamine + dobutamine + [100 \times epinephrine] + [100 \times norepinephrine] + [15 \times milrinone]$ [in microgram/kg/min]) and oxygenation index (OI) ($OI = [FiO_2 \times MAP \times 100]/PaO_2$]) [20, 21] were also included among the parameters of the study.

For subgroup analysis, subjects were divided into two groups according to presence of pulmonary disease. In these two groups, subjects with pulmonary disease (PD) were defined as $MAP \geq 14$ mmHg and/or $OI \geq 10$, and subjects with non-pulmonary disease (Non-PD) were defined as $MAP < 14$ mmHg and/or $OI < 10$). $PaCO_2$ values were compared with $P_{TC}CO_2$ and $P_{ET}CO_2$ values in both groups.

Finally, we also determined the variability in transcutaneous CO_2 measurement results and various parameters, including skin and subcutaneous adipose tissue thickness, presence of PD, measurement time, and measurement location.

2.4 Statistical analysis

Analyses were performed by using the SPSS version 21 (SPSS, Inc., Chicago, IL) or Med Calc v15.8 (Med Calc Software, Ostend, Belgium) software. Subject characteristics are described using qualitative variables (using frequencies and percentages) and quantitative variables (using means and standard deviation [SD] or median with interquartile range [IQR] depending on type of distribution). Simple linear regression analysis was performed and Pearson correlation coefficients were calculated for the assessment of the relationships between $PaCO_2$, $P_{TC}CO_2$ and $P_{ET}CO_2$. CO_2 values of the different methods were compared by using Friedman's test with Bonferroni correction method for all measurements and the Wilcoxon Signed Rank test for specific locations of $P_{TC}CO_2$ values. Bland–Altman plots were created to evaluate the agreement between measurements. We also performed multiple linear regression analysis with stepwise selection method to determine factors affecting $P_{TC}CO_2$ values. Variables with a p-value lower or equal to 0.10 in univariate analysis were included into the model. $P < 0.05$ values were accepted as statistically significant.

3 Results

The study was performed in 102 subjects with 1118 measurements for each method. The descriptive factors of the study are shown in Table 1. The tolerance of skin to the electrode was quite good; there were no signs of skin irritation or erythema at the end of monitoring. The trial flow chart is shown in Fig. 2.

3.1 Comparison of the two non-invasive PCO_2 methods with ABG analysis results

The median $PaCO_2$, $P_{TC}CO_2$ and $P_{ET}CO_2$ values were 38.9 (IQR: 34.2–44.4), 38 (IQR: 34–43) and 37 (IQR: 32–44) mmHg, respectively. Results of the Bland–Altman analysis comparing $P_{TC}CO_2/PaCO_2$ and $P_{ET}CO_2/PaCO_2$ pairs are summarized in Table 2 and illustrated in Fig. 3 with regard to all subject groups and also subgroups. In all subjects, the mean difference between $P_{TC}CO_2$ and $PaCO_2$ was -0.78 (± 7.29) (95% limits of agreement -15.06 to 13.51 mmHg) with moderate correlation ($r = 0.66$, $p < 0.001$) (Fig. 3a). Similarly, the mean bias between $P_{ET}CO_2$ and $PaCO_2$ was -2.10 (± 8.39) (95% -18.54 to 14.33 mmHg) with moderate correlation ($r = 0.51$, $p < 0.001$) (Fig. 3b). Although both $P_{TC}CO_2$ and $P_{ET}CO_2$ were moderately correlated, the correlation coefficient of $P_{TC}CO_2$ was higher.

According to our findings, reliable PCO_2 measurements (within the predefined, clinically acceptable range of ± 4 mmHg) could be achieved by the $P_{TC}CO_2$ method, but not by the $P_{ET}CO_2$ method. The difference between $PaCO_2$

Table 1 Demographic, clinical and laboratory characteristics of subjects

Subjects characteristics	Values
Male sex, no (%)	57 (55.9)
Age (month), median (IQR)	23 (8–78)
Clinical data at measurement time, median (IQR)	
Body temperature (°C)	37.1 (36.7–37.6)
Inotropic index	0 (0–10)
Skin tissue thickness (mm)	1.0 (0.9–3.2)
Subcutaneous adipose tissue thickness (mm)	5.7 (3.5–10.3)
Underlying disease, no (%)	
Pulmonary disease	47 (46.1)
Bronchiolitis	20 (19.6)
Pneumonia	13 (12.8)
Acute respiratory distress syndrome	10 (9.8)
Others	4 (3.9)
Non pulmonary disease	55 (53.9)
Multiple trauma	16 (15.7)
Shock	14 (13.7)
Malignancy	10 (9.8)
Post-operative	10 (9.8)
Others	5 (4.9)
Laboratory values, median (IQR)	
Arterial blood gas analysis	
pH	7.37 (7.32–7.41)
$PaCO_2$ (mmHg)	38.9 (34.2–44.4)
PaO_2 (mmHg)	148 (110–181)
HCO_3^- (mmol/L)	22.6 (20.4–24.8)
Base excess (mmol/L)	− 2.2 (-5.0–0.4)
Haemoglobin (g/dL)	10.2 (9.2–11.5)
Lactate (mmol/L)	0.8 (0.6–1.2)
$P_{TC}CO_2$, (mmHg)	38 (34–43)
$P_{ET}CO_2$, (mmHg)	37 (32–44)
Mechanical ventilator parameters, median (IQR)	
FiO_2 (%)	40 (40–50)
P_{peak} (mmHg)	24 (19–29)
MAP (mmHg)	11.5 (9.7–13.0)
Oxygenation index	3.4 (2.4–5.3)

Inotropic index (inotropic index = dose of dopamine + dobutamine + [100 × epinephrine] + [100 × norepinephrine] + [15 × milrinone] [in microgram/kg/min]), *$PaCO_2$* arterial PCO_2, *PaO_2* arterial PO_2, *$P_{TC}CO_2$* transcutaneous PCO_2, *$P_{ET}CO_2$* end-tidal PCO_2, *P_{peak}* peak airway pressure, *MAP* mean airway pressure, *oxygenation index* (oxygenation index = [FiO_2 × MAP × 100)/PaO_2]), *IQR* interquartile range

and $P_{TC}CO_2$ was ≤ ± 4 mmHg in 662 measurements out of 1118 (59.2%) while the difference between the $PaCO_2$ and $P_{ET}CO_2$ was ≤ ± 4 mmHg in 471 measurements (42.1%) (p = 0.001).

In Fig. 4, $P_{TC}CO_2$ and $P_{ET}CO_2$ measurements are illustrated for all subjects. It was found that a 1 mm Hg increase in $P_{TC}CO_2$ values was associated with a 0.55 mm Hg increase in $P_{ET}CO_2$ values.

3.2 Subgroup analyses and comparisons

Among the subjects, 46.1% (n = 47) had PD and 53.9% (n = 55) of subjects were without pulmonary disease (non-PD). In the non-PD group, the mean bias between $P_{TC}CO_2$ and $PaCO_2$ was -0.29 (± 6.05) (95% limits of agreement − 12.15 to 11.57 mmHg) (Fig. 3c), while the mean bias between $P_{ET}CO_2$ and $PaCO_2$ was 0.44 (± 6.83) (95% limits of agreement − 12.95 to 13.83 mmHg) (Fig. 3d). Correlation coefficients were r = 0.67 (p < 0.001) and r = 0.52 (p < 0.001), respectively. In the PD group, the mean bias between $P_{TC}CO_2$ and $PaCO_2$ was − 1.27 (± 8.32) (95% limits of agreement − 17.57 to 15.04 mmHg) (Fig. 3e). Whereas the mean bias between $P_{ET}CO_2$ and $PaCO_2$ was − 4.65 (± 9.01) (95% limits of agreement − 22.30 to 13.01 mmHg) (Fig. 3f). Although the mean bias for $P_{TC}CO_2$ and $P_{ET}CO_2$ were increased in the presence of PD, $P_{TC}CO_2$ was better correlated with $PaCO_2$, compared to $P_{ET}CO_2$ (respectively: r = 0.61, p < 0.001 vs. r = 0.53, p < 0.001).

We found that the absolute values of $P_{TC}CO_2$–$PaCO_2$ were significantly lower than the absolute values of $P_{ET}CO_2$–$PaCO_2$ for all subjects (p < 0.001), the non-PD group (p < 0.001) and also the PD group (p < 0.001) (Table 2).

3.3 The variability in $P_{TC}CO_2$ measurements in relation to subject-related factors

We performed multiple linear regression analysis with $P_{TC}CO_2$–$PaCO_2$ as a dependent variable to determine factors affecting differences between the measurements. We found that increased subcutaneous adipose tissue thickness (p = 0.007), body temperature (p < 0.001) and inotropic index (p = 0.002) were related with higher $P_{TC}CO_2$ values relative to actual $PaCO_2$ values (Table 3). The other factors included in the model, such as age (p = 0.061), gender (p = 0.151), skin tissue thickness (p = 0.571), PaO_2 (p = 0.725), presence of PD (p = 0.134), measurement time (p = 0.299), and measurement location (p = 0.121) were found to be non-significant.

4 Discussion

To our knowledge, this is the most comprehensive comparison between two non-invasive techniques for continuous measurement of CO_2 in pediatric subjects undergoing invasive mechanical ventilation in the PICU. It is also the largest cohort study of $P_{TC}CO_2$ and $P_{ET}CO_2$ measurement in mechanically ventilated subjects with 1118 measurements

Table 2 Results of the Bland–Altman analysis comparing $P_{TC}CO_2$/$PaCO_2$ and $P_{ET}CO_2$/$PaCO_2$ pairs

	Mean difference $\pm$ SD (mmHg)	95% CI of mean difference (mmHg)	95% LLA (mmHg)	95% ULA (mmHg)	P value
All subjects[a] (n = 102)					
$P_{TC}CO_2$–$PaCO_2$	− 0.78 ± 7.29	− 1.20; − 0.35	− 15.06	13.51	*p* < 0.001
$P_{ET}CO_2$–$PaCO_2$	− 2.10 ± 8.39	− 2.60; − 1.61	− 18.54	14.33	
Non-PD group[b] (n = 55)					
$P_{TC}CO_2$–$PaCO_2$	− 0.29 ± 6.05	− 0.79; 0.22	− 12.15	11.57	*p* < 0.001
$P_{ET}CO_2$–$PaCO_2$	0.44 ± 6.83	− 0.13; 1.01	− 12.95	13.83	
PD group[c] (n = 47)					
$P_{TC}CO_2$–$PaCO_2$	− 1.27 ± 8.32	− 1.96; − 0.57	− 17.57	15.04	*p* < 0.001
$P_{ET}CO_2$–$PaCO_2$	− 4.65 ± 9.01	− 5.40; − 3.90	− 22.30	13.01	

CI Confidence interval, *LLA* lower limit of agreement, *ULA* upper limit of agreement, *SD* standard deviation, *PCO$_2$* partial pressure of carbon dioxide, *PaCO$_2$* arterial PCO_2, *$P_{ET}CO_2$* end-tidal PCO_2, *$P_{TC}CO_2$* Transcutaneous PCO_2

[a]Overall, 1118 pairs of measurement have been assessed for analysis of all subjects

[b]Subjects with non-pulmonary disease

[c]Subjects with pulmonary disease

for each method. We also compared $P_{TC}CO_2$ values with subjects' characteristics to determine their effects on methods of $PaCO_2$ measurement. Our results demonstrated the superiority of $P_{TC}CO_2$ monitoring over $P_{ET}CO_2$ in mechanically-ventilated critically ill subjects, as demonstrated by the differences between $PaCO_2$ values and the two methods' results ($P_{TC}CO_2$ and $P_{ET}CO_2$).

In all subject groups, the mean bias between $P_{TC}CO_2$ and $PaCO_2$ was − 0.78 mmHg (± 7.29) (95% limits of agreement − 15.06 to 13.51 mmHg). In regard to $P_{ET}CO_2$ and $PaCO_2$ difference, the value was − 2.10 mmHg (± 8.39) (95% − 18.54 to 14.33 mmHg) in all subjects. There was a higher correlation between $PaCO_2$ and $P_{TC}CO_2$ values when compared to $PaCO_2$ and $P_{ET}CO_2$ (respectively, r = 0.66, p < 0.001; r = 0.51, p < 0.001). Various other studies have also found better correlations between $PaCO_2$ and $P_{TC}CO_2$ values (correlation coefficients between 0.83 and 0.99) [22–25]. The rather lower level of correlation in our study may be explained by the inclusion of only critically ill children who required endotracheal intubation, whereas, healthy patients may have demonstrated relatively stable levels throughout comparisons performed with different methods.

In practice, the differences in the range of non-invasive CO_2 measurement methods should be within the acceptable range [2, 19]. Accordingly, our results show that PCO_2 measurements within the predefined, clinically acceptable range of ± 4 mmHg could be achieved by $P_{TC}CO_2$, but not by $P_{ET}CO_2$. The difference between $PaCO_2$ and $P_{TC}CO_2$ was ≤ ± 4 mmHg in 662 measurements out of the complete set of 1118 values (59.2%) while the difference between $PaCO_2$ and $P_{ET}CO_2$ was ≤ ± 4 mmHg in 471 out of overall 1118 values (%42.1). In other studies with acceptable bias (3 to 4.5 mmHg), it was found that 29–55% of $P_{ET}CO_2$

measurements and 61–83% $P_{TC}CO_2$ measurements were within the acceptable level of bias [13, 26, 27].

There are few studies comparing the accuracy of non-invasive CO_2 measurement methods. Tobias-Meyer et al. [11] studied intubated subjects in the PICU and found that the mean bias between $P_{ET}CO_2$ and $PaCO_2$ was 6.84 mmHg (± 5.1), whereas the mean bias between $P_{TC}CO_2$ and $PaCO_2$ was 2.3 mmHg (± 1.3). Transcutaneous CO_2 monitoring is also used in subjects with spontaneous breathing or non-invasive mechanical ventilator support, in addition to its use in those with invasive mechanical ventilation. In a study of non-intubated subjects in spontaneous respiration, simultaneous $P_{ET}CO_2$, $P_{TC}CO_2$ and $PaCO_2$ measurements were performed and showed very high correlation values between $P_{TC}CO_2$ and $PaCO_2$ (r = 0.97), while moderate correlation (r = 0.62) was observed between $P_{ET}CO_2$ and $PaCO_2$ values [28].

Another strength of the current investigation lies in the subgroup analysis, where CO_2 monitoring techniques were performed similarly in subjects with regard to the presence or absence of PD. When compared with $P_{ET}CO_2$, $P_{TC}CO_2$ has been shown to be equally as accurate in children with normal respiratory function (non-PD group). The mean differences observed in the comparison of both methods with $PaCO_2$ values were found to be similar. This is in line with a recent investigation in mechanically ventilated subjects without parenchymal lung disease [29]. Therefore, it could be postulated that, even though $P_{TC}CO_2$ determination seems to be better overall, $P_{ET}CO_2$ monitoring is sufficient and accurate in subjects receiving MV, particularly if pulmonary disease is not present.

In contrast, the differences between each method and $PaCO_2$ values increased in the presence of PD; however,
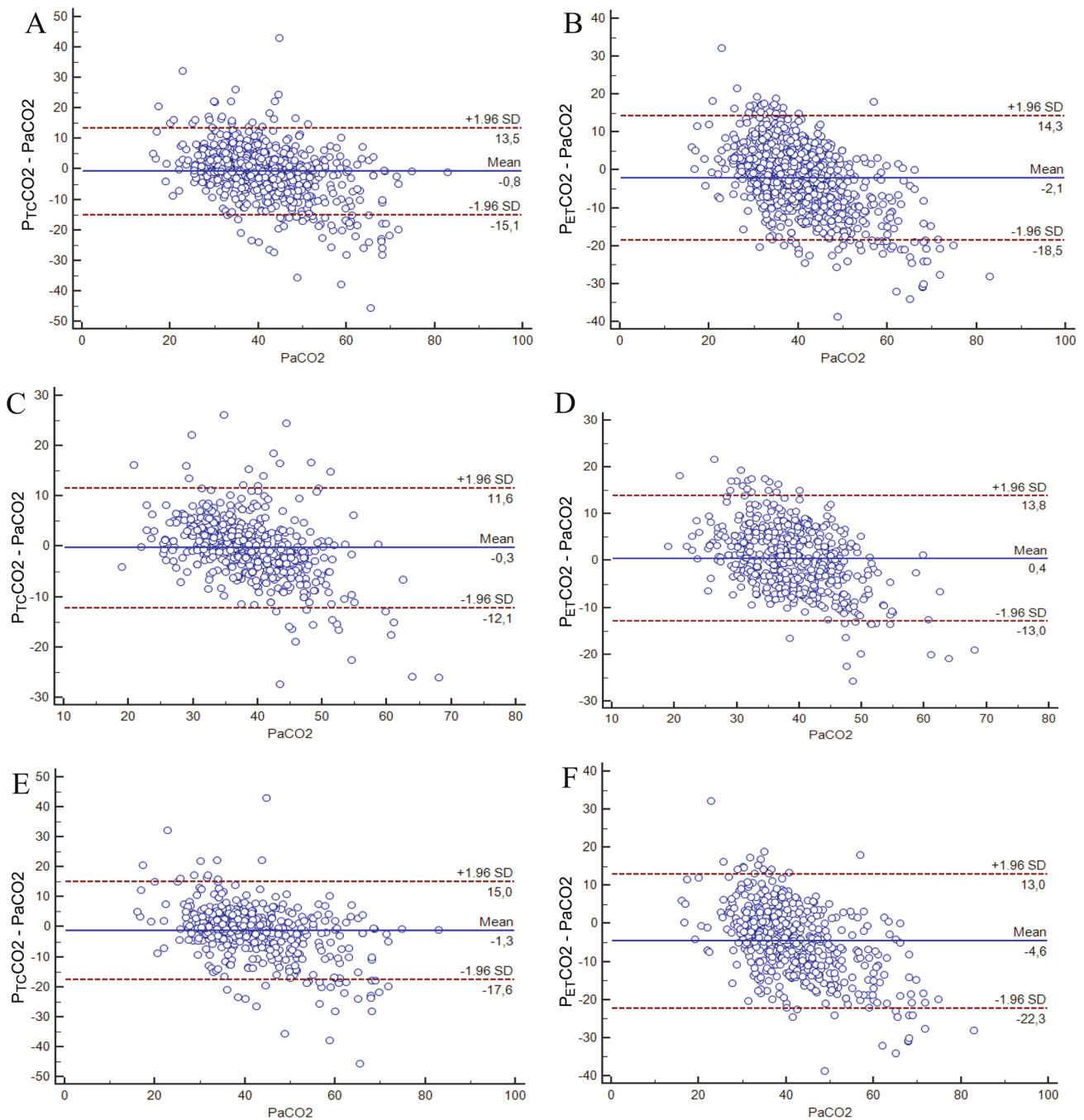
Fig. 3 Bland–Altman plots for mean $P_{TC}CO_2$ versus $PaCO_2$ and mean $P_{ET}CO_2$ versus $PaCO_2$. $PaCO_2$ and $P_{TC}CO_2$ for all subjects (**a**), $PaCO_2$ and $P_{ET}CO_2$ for all subjects (**b**), $PaCO_2$ and $P_{TC}CO_2$ for the subjects with non-pulmonary disease (**c**), $PaCO_2$ and $P_{ET}CO_2$ for the subjects with non-pulmonary disease (**d**), $PaCO_2$ and $P_{TC}CO_2$ for the subjects with pulmonary disease (**e**), $PaCO_2$ and $P_{ET}CO_2$ for the subjects with pulmonary disease (**f**). The mean difference is represented as a continuous line, and 95% limits of agreement are represented as dotted lines

$P_{TC}CO_2$ values were much more accurate compared to $P_{ET}CO_2$ values. The present and previous trials have clearly demonstrated that monitoring with $P_{ET}CO_2$ poorly estimates $PaCO_2$ in subjects with PD [9, 19, 30–33]. This is most often explained by ventilation-perfusion mismatching and dead-space ventilation, as these two factors are associated with inadequate gas exchange that cannot be identified via $P_{ET}CO_2$ [34, 35]. Therefore, it is apparent that the results of $PaCO_2$ measurements in such patients will result in a lower value relative to actual CO_2 levels [36, 37].

Fig. 4 The relationship between $P_{TC}CO_2$ and $P_{ET}CO_2$ measurements. A 1 mm Hg increase in $P_{TC}CO_2$ values was associated with a 0.55 mm Hg increase in $P_{ET}CO_2$ values
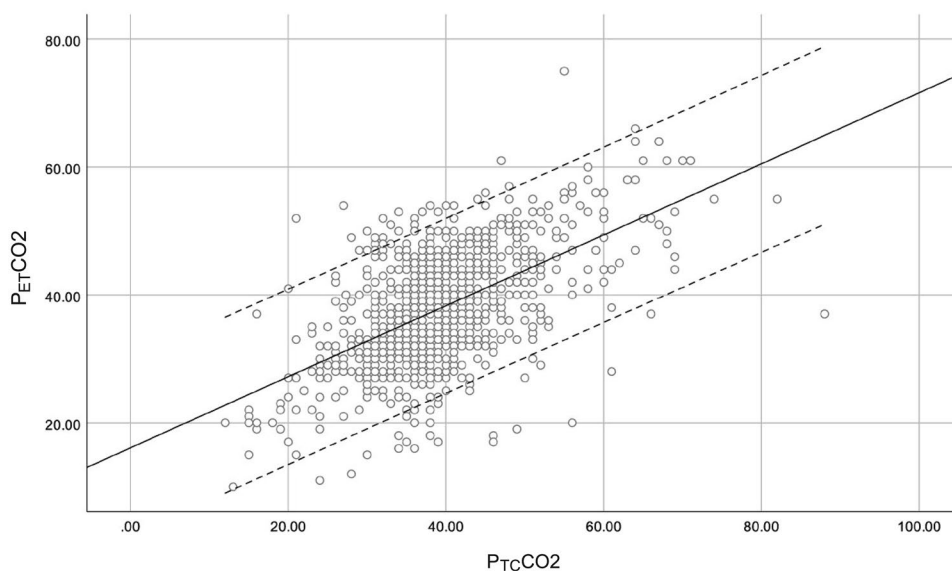

Table 3 Significant factors of the differences between measurement methods ($P_{TC}CO_2$ and $PaCO_2$), multiple linear regression analysis

Variables	Unstandardized β	Standard error	Standardized β	T	p	95.0% Confidence interval for β	
Constant	− 38.742	10.707		− 3.618	< 0.001	− 59.750	− 17.733
Subcutaneous fat tissue[*]	0.106	0.039	0.080	2.695	0.007	0.029	0.184
Body temperature	1.084	0.289	0.113	3.754	< 0.001	0.518	1.651
Inotropic index	0.035	0.011	0.094	3.132	0.002	0.013	0.057

Dependent variable: $P_{TC}CO_2$—$PaCO_2$; $R^2 = 0.043$; F = 9.968; p < 0.001

[*]Subcutaneous adipose tissue thickness

Previous reports have shown that $PaCO_2$ measurements tend to be higher than the corresponding $P_{ET}CO_2$ measurements [19, 38, 39] and the presence of PD further increases the $PaCO_2$ and $P_{ET}CO_2$ measurement gradient [40]. The results of our study are similar to the literature. However, 95% ULA values of the $P_{ET}CO_2$–$PaCO_2$ gradient were determined in the range of 13.01–15.04 mmHg, and these results are quite high compared to the literature [19]. In diseases that cause hemodynamic instability, such as sepsis and shock, $P_{ET}CO_2$ measurements tend to be higher than corresponding $PaCO_2$ measurements [41]. High 95% ULA values in our study may be associated with the presence of patients with hemodynamic instability (such as shock and multi-trauma diagnoses) in our study, and the analysis of the highest number of measurement values in the literature so far (1118 pairs).

Although agreement was good between $P_{TC}CO_2$ and $PaCO_2$, it was still limited; most possibly due to the characteristics of our patient group. We performed multiple linear regression analysis with $P_{TC}CO_2$-$PaCO_2$ as the dependent variable to determine factors affecting differences between measurements. We found that increased body temperature

(p < 0.001) is related with falsely high $P_{TC}CO_2$ values. Compared to previous studies, we had a higher number of measurements that demonstrated similar results, somewhat contrasting to previously published findings [17, 25]. Despite frequent measurement of body temperature in these critically ill patients and setting the sensor to appropriate temperature before measurements, it is still possible that the actual local pressure at the measurement site was different from patient to patient (especially since these were all critically ill patients),thereby causing differences in results. This hypothesis is directly related to the operating principle of the sensor [42].

In this study, inotropic index was found to affect the accuracy of $P_{TC}CO_2$ measurements. There are concerns about the accuracy of $P_{TC}CO_2$ in situations that may compromise CO_2 washout from the tissue, such as poor skin perfusion and low cardiac output [36]. In the current study, increased inotropic index (p < 0.001) was related to higher $P_{TC}CO_2$ values. Although some investigators have suggested that shock does not affect $P_{TC}CO_2$ accuracy [12, 16, 17], others have confirmed that the gradient between $P_{TC}CO_2$ and $PaCO_2$ increases as tissue perfusion decreases [43–45]. In

our study, an objective marker (inotropic index) was used as a marker of shock, therefore, enabling more accurate analysis compared to other studies. We think that inotropic-induced vasoconstriction could be expected to reduce the accuracy of transcutaneous monitoring.

This is the first study to assess the associations between $P_{TC}CO_2$ – $PaCO_2$ measurements with regard to their correlation to skin and subcutaneous adipose tissue thickness. While measurements were not affected by skin thickness ($p = 0.57$), they were significantly influenced by an increase in subcutaneous fat tissue thickness ($p = 0.007$). Several studies reported conflicting results regarding the influence of skin thickness by indirect estimation of body mass index (BMI) on the diffusion of CO_2 to the skin and therefore the values of $P_{TC}CO_2$ [4, 16, 46, 47]. In our study, skin thickness and subcutaneous adipose tissue thickness (at sites of transcutaneous CO_2 sensor placement) were measured directly by using ultrasonography—leading to comparisons based on actual measurements rather than estimates. Since we were not able to find such evaluations in previous studies, we believe our study adds important data to the existing literature pertaining to transcutaneous CO_2 measurement. Based on the results of our study, we may speculate that local conditions at the site of sensor placement, including the skin-subcutaneous adipose tissue thickness and conductivity of the skin, are more important for $P_{TC}CO_2$ measurement than whole body composition. Similarly, local edema increases the distance over which CO_2 molecules travel to the probe; therefore, it could affect $P_{TC}CO_2$ measurements.

The results from our analyses have important implications for how transcutaneous CO_2 monitoring should be applied. No specific recommendations for a preferred site or sites are provided by manufacturers. Similarly, guidelines on transcutaneous CO_2 monitoring from the American Association for Respiratory Care do not provide a recommendation for the optimal site to place a transcutaneous CO_2 sensor [42]. In addition, transcutaneous CO_2 measurement was obtained from three different locations (chest, thigh and abdomen) in current study. In accordance with the literature, it was found that the measurement locations do not affect the accuracy of $P_{TC}CO_2$ measurements [4].

Although we have reached a large series of mechanically ventilated pediatric subjects and maximum number of transcutaneous CO_2 measurement in the literature, there are some limitations in the study. Firstly, transcutaneous CO_2 measurements were obtained from three different body locations of the subjects at separate times. It would be possible to compare much more collected data by increasing the number of time-points for measurement, and possibly, the number of body locations. Secondly, no evaluation was made regarding the effects of the thickness of muscle tissue at the measurement site. Thirdly, we limited our study to the TCM4 Radiometer $P_{TC}CO_2$ monitor. It is possible that other monitors

perform with higher or lower accuracy. Finally, in this study, we did not record ventilation tidal volumes during $P_{ET}CO_2$ measurements. Particularly low tidal volumes that are not sufficient to flush the anatomic dead volume may result in gas samples that do not represent the alveolar gas status. This is quite often a cause of low $P_{ET}CO_2$ measurements.

5 Conclusion

The $P_{TC}CO_2$ method has higher reliability than the $P_{ET}CO_2$ method for non-invasive monitoring of PCO_2 in children undergoing invasive MV. Especially in children with PD, it is more reliable than $P_{ET}CO_2$. However, $P_{TC}CO_2$ measurement is affected by subcutaneous fat (adipose) tissue thickness, core body temperature and inotropic index. $P_{TC}CO_2$ cannot replace ABG analysis in mechanically ventilated pediatric subjects, but it may be very useful to define early changes in ventilation, ease clinical management, and reduce the number of invasive procedures performed for arterial blood sampling.

Compliance with Ethical Standards

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