Evaluating a novel formula for noninvasive estimation of arterial carbon dioxide during postresuscitation care

Short title: Formula for estimating arterial CO$_2$

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Conflicts of interest

Dr. Markus Skrifvars has received research funding from GE Healthcare and lecture fees from Covidien and BARD Medical (Ireland). Authors Erkki Heinonen and Tom Häggblom are employees of GE Healthcare.
Abstract

Background

Controlling arterial carbon dioxide is paramount in mechanically ventilated patients, and an accurate and continuous noninvasive monitoring method would optimize management in dynamic situations. In this study, we validated and further refined formulas for estimating partial pressure of carbon dioxide with respiratory gas and pulse oximetry data in mechanically ventilated cardiac arrest patients.

Methods

A total of 4,741 data sets were collected retrospectively from 233 resuscitated patients undergoing therapeutic hypothermia. The original formula used to analyze the data is

\[ \text{PaCO}_2\text{-est1} = \text{PETCO}_2 + k[(\text{PIO}_2 - \text{PETCO}_2) - \text{PaO}_2] \]

To achieve better accuracy, we further modified the formula to

\[ \text{PaCO}_2\text{-est2} = k_1 \times \text{PETCO}_2 + k_2 (\text{PIO}_2 - \text{PETCO}_2) + k_3 (100 - \text{SpO}_2) \]

The coefficients were determined by identifying the minimal difference between the measured and calculated arterial carbon dioxide values in a development set. The accuracy of these two methods was compared with the estimation of the partial pressure of carbon dioxide using end-tidal carbon dioxide.

Results

With \( \text{PaCO}_2\text{-est1} \), the mean difference between the partial pressure of carbon dioxide, and the estimated carbon dioxide was 0.08 kPa (SE ± 0.003); with \( \text{PaCO}_2\text{-est2} \) the difference was 0.036 kPa (SE ± 0.009). The mean difference between the partial pressure of carbon dioxide and end-tidal carbon dioxide was 0.72 kPa (SE ± 0.01). In a mixed linear model, there was a significant difference between the estimation using end-tidal carbon dioxide and \( \text{PaCO}_2\text{-est1} \) (p<0.001) and \( \text{PaCO}_2\text{-est2} \) (p<0.001), respectively.

Conclusions

This novel formula appears to provide an accurate, continuous, and noninvasive estimation of arterial carbon dioxide.
Introduction

Monitoring carbon dioxide is paramount in mechanically ventilated patients and commonly performed by measuring the partial pressure of carbon dioxide (PaCO₂) with arterial blood gas (ABG) analysis. Although an ABG analysis intermittently provides exact PaCO₂ values, PaCO₂ may change despite constant ventilation.

End-tidal carbon dioxide generally underestimates arterial PaCO₂. End-tidal carbon dioxide is affected by the ventilation/perfusion ratio (V/Q ratio), possible cardiac disease such as right-to-left shunt, and increased dead space. Maintaining normoventilation may be difficult under circumstances where ABG measurements is not available, including prehospital care and patient transport. The measurement of PETCO₂ with continuous capnography is used as a surrogate but may be a poor indicator of PaCO₂ because of V/Q mismatch. Dyscarbia and unintentional deviation from normoventilation have been associated with poor outcome. Therefore, seeking new dynamic methods to noninvasively estimate PaCO₂ is highly important.

We present a method for estimating the PaCO₂ level in a continuous and noninvasive way. Previously, we tested a formula for estimating arterial carbon dioxide partial pressures in an experimental model and found good agreement between this formula with measured PaCO₂ values in various physiological and pathophysiological conditions. The formula was developed based on the assumption that the degree of V/Q mismatch behind the alveolar–arterial oxygen tension difference (PA-aO₂) is similar for both O₂ and CO₂. In our previous study, the estimation of PaO₂ was evaluated purely under experimental conditions. The primary aim of the present study was to test the agreement of measured PaCO₂ and estimated PaCO₂ by the original formula in mechanically ventilated cardiac arrest (CA)
patients. The secondary aim was to validate and refine this formula to achieve a better agreement. In addition, we studied whether the accuracy of the current formulas was affected by patient temperatures and the mean arterial blood pressure levels.
Methods

Study subjects and settings

We conducted a retrospective study in mechanically ventilated adult (≥18 years of age) patients who were treated after CA in a tertiary academic hospital between October 2012 and September 2016. Research approval was obtained from the Hospital District of Helsinki and Uusimaa (HUS/420/2018 25.04.2018).

Collected data

From the hospital laboratory records, we collected the data of temperature-corrected PaCO$_2$ samples taken within the first 48 hours of ICU admission. Physiological data, including respiratory gas values, peripheral oxygen saturation (SpO$_2$), and body temperature at the time points corresponding to each ABG sampling, were collected from the ICU electronic patient data management system (Picis, Wakefield, MA, USA). Patient characteristics, such as age, height, weight, and gender, were collected from the ICU electronic patient data management system. Comorbidities and resuscitation factors were collected from electronic patient medical records (Uranus, CGI, Canada). Organ dysfunction and severity of illness scores (Sequential Organ Failure Assessment [SOFA]; the Simplified Acute Physiology Score II [SAPS II]); and the Acute Physiology and Chronic Health Evaluation II [APACHE II]) scores were retrieved from the Finnish Intensive Care Quality Consortium Database (Tieto Healthcare & Welfare Oy, Espoo, Finland).
Estimation of arterial CO\textsubscript{2} partial pressure

The original formula used for estimating PaCO\textsubscript{2} has been published previously and is defined as follows: \(^7\)

\[ \text{PaCO}_2\text{-est1} = \text{PETCO}_2 + k[(\text{PIO}_{2}\text{-PETCO}_2) - \text{PaO}_2] \]

where PETCO\textsubscript{2} is the measured end-tidal CO\textsubscript{2} pressure and PIO\textsubscript{2} is the measured inspired O\textsubscript{2} pressure with the equation of FIO\textsubscript{2} x (barometric pressure–saturated vapor pressure of H\textsubscript{2}O). PaO\textsubscript{2} is estimated from the oxygen dissociation curve. \(^{11}\) This formula was developed further in an attempt to improve accuracy. The patient population was divided randomly into derivation and validation groups. Using linear regression, we used derivation data to compose the new, calibrated formula and to determine the calibration factors that would minimize the difference between estimated and measured PaCO\textsubscript{2} values.

Creation of the calibrated, new formula (PaCO\textsubscript{2}-est2)

The relationship factors were defined by fitting the data points for the minimal difference between the blood gas measured PaCO\textsubscript{2} and the novel formula estimated value. For this purpose, 6,580 data points measured from the 233 patients were divided into two groups according to PETCO\textsubscript{2} values. Data points having PETCO\textsubscript{2} < 3 kPa were excluded as potentially artifactual, for example, a leak caused by side-steam gas sampling. The remaining data were randomly allocated to a derivation group of 50 patients. The remaining 183 patients composed the validation group. The 1008 data sets of the derivation group were divided according to a PETCO\textsubscript{2} value of 4 kPa. The 4 kPa division value was randomly selected to reflect potentially major (< 4 kPa) and normal or minor (\(\geq 4\) kPa) V/Q mismatches that could result in different relationship factors. We defined different validation coefficients, called k-factors, for data sets depending on the measured carbon dioxide level, keeping the 4 kPa
threshold. The potentially major V/Q mismatch group included 255 data sets, and the potentially normal or minor mismatch group included 753 data sets. The remaining data sets—3,504 in total—composed the validation group. The study flowchart is presented in Supplementary Figure 1.

Using the least square fitting to minimize the difference between the estimated PaCO\(_2\) and ABG PaCO\(_2\) values, the equation coefficients were determined for both the major and the normal or minor V/Q mismatch groups separately. These coefficients were then used to calculate the estimated PaCO\(_2\) for the validation group data points comprising the presented validation result statistics. The values for the coefficients are presented in Table 1.

After adjustments, the formula (PaCO\(_2\)-est2) is defined as follows:

\[
\text{PaCO}_2\text{-est2}=k_1\times\text{PETCO}_2+k_2\times(\text{PIO}_2-\text{PETCO}_2)+k_3\times(100-\text{SpO}_2)
\]

PaCO\(_2\) is the arterial CO\(_2\) partial pressure, and PETCO\(_2\) and PIO\(_2\) are the end-tidal CO\(_2\) and inspired O\(_2\) pressures, respectively, recorded with a side-stream gas analyzer (GE Healthcare, Milwaukee, Wisconsin, USA). SpO\(_2\) is the peripheral hemoglobin oxygen saturation measured with a pulse oximeter.

The O\(_2\) difference in this hypothesis is based on the estimation of PETO\(_2\)-PaO\(_2\) with the aid of standard bedside monitored parameters. It is well-known that the O\(_2\) difference (PIO\(_2\)-PETO\(_2\)) is approximately PETCO\(_2\), providing an estimate for PETO\(_2\) (PIO\(_2\)-PETCO\(_2\)). 12 Conceptually, this equation is based on the hypothesis that the physiological factors causing the alveolar–arterial tension difference are similar for both O\(_2\) and CO\(_2\):

ventilation/perfusion mismatch in the form of left-to-right shunt perfusion and alveolar dead-space ventilation. The equation aims to detect the magnitude of these gas exchange disorders.
In shunt perfusion part of the pulmonary artery blood flow is passing the lungs without communicating with the alveoli. In pulmonary vein this shunted blood of venous O₂ content mix with the blood flow representing alveolar gas composition. Affinity of low oxygen saturation of the shunted perfusion reduces the mixture oxygen partial pressure from the alveolar equilibrium. Depending on the shunt, the magnitude of dissolved O₂ may be insufficient to fully saturate the Hb, which is measured as SpO₂ below 100%. The difference (100-SpO₂) measures the magnitude of this insufficiency. Clinician may respond to reduced SpO₂ by increasing the PIO₂. This compensatory action increases the second term of the equation.

In alveolar dead space no gas exchange occurs with the alveolar blood flow, which reduces SpO₂. Thus, increase on the term (100-SpO₂) of the equation indicates the increase in alveolar dead space. Again, clinician may respond to reduced SpO₂ by increasing the PIO₂ increasing respectively the second term of the equation. The gas in alveolar dead space remains in inspired concentrations and dilutes at upper respiratory tract reducing PETCO₂. This increases the second term as indication of the alveolar dead space. In addition to a V/Q mismatch, possible differences in CO₂ and O₂ alveolar exchange may cause additional differences between PETCO₂ and PaCO₂ not reflected in the O₂ difference; for example diffusion disturbance. Each factor was assigned a relationship coefficient, the values of which were determined by the calibration data points.

Measuring the change in the accuracy of estimation of PaCO₂ over time
We divided the 48-hour study period into three-hour intervals; in cases with more than one sample per three-hour period, we calculated the mean of the differences between the measured and estimated PaCO₂ values.

**Statistical analyses**

To validate PaCO₂-est1 and the comparisons used between PaCO₂-est2 and PETCO₂, we calculated the mean difference with the standard deviation (SD) between the measured and estimated PaCO₂ values. We assessed the agreement between the measured and estimated PaCO₂ values using the Bland-Altman analysis. We used the software created by Olofsen et al. for the Bland-Altman analysis, including the bias with +/-SE and the limits of agreement with 95% confidence intervals. Percentage error was calculated from the SD of agreement and mean CO₂: 100* (1,96*SD/mean CO₂).

Other analyses were performed using Statistical Package for Social Sciences (SPSS), version 25 (IBM SPSS Statistics for Macintosh, Version 24.0. Armonk, NY, IBM Corp.). Within-subject (WSV) and between-subject variances (BSV), intraclass correlations (τ), and repeatability coefficients were estimated for the differences between estimated PaCO₂ and ETCO₂. The Bland-Altman method used controls for the effect of repeated measures by calculating the within-subject and between-subject variations. The normality of the distribution of the differences between the measured and estimated values was tested using the Kolmogorov–Smirnov test.

A comparison of the differences between estimations provided by PaCO₂-est2 and PETCO₂ was performed using a mixed linear model in which time and measured values were treated as fixed effects, whereas subjects and formulas were treated as random effects.
Also, using a mixed linear model, we tested the accuracy of the formulas over time and whether there was any interaction between the performance of the formulas and the mean arterial blood pressure or patient temperature. We also examined the accuracy of the methods in different PaCO$_2$ and O$_2$ levels by dividing the data in deciles, according to the measured PaCO$_2$ and FIO$_2$ level.
Results

In total, we included 233 patients and collected 4,741 datasets. The basic patient characteristics are shown in Table 2. We excluded two patients because of missing data for the inspired gas O\textsubscript{2} concentrations. The mean number of ABG samples per patient was 15 (SD 10). One of the CAs was in the hospital and the other 232 were out of the hospital. All patients were treated with therapeutic hypothermia. Table 3 shows the baseline information about the ventilator parameters and hemodynamics during the 48-hour study period.

**Difference between the estimated and measured PaCO\textsubscript{2} values (PaCO\textsubscript{2}-est1)**

The mean difference between the measured and estimated PaCO\textsubscript{2} values (PaCO\textsubscript{2}= PETCO\textsubscript{2}+k [PIO\textsubscript{2}-PETCO\textsubscript{2}]-PaO\textsubscript{2}) was 0.08 kPa (SE ± 0.003). The SD of the differences was 0.62 (SE ± 0.015), percentage error was 24%. The Bland-Altman plot demonstrating the agreement between the PaCO\textsubscript{2}-est1 and measured PaCO\textsubscript{2} values with limits of agreement and their 95% confidence intervals is presented in Figure 1.

**Intraclass correlation (PaCO\textsubscript{2}-est1)**

The within-subject variance for the estimated PaCO\textsubscript{2} (PaCO\textsubscript{2}-est1) and measured PaCO\textsubscript{2} values was 0.20 (SE ± 0.004). The between-subjects variance was 0.19 (SE ± 0.018). The intraclass correlations (τ = ratio of BSV and total variance) for the estimated PaCO\textsubscript{2} and measured PaCO\textsubscript{2} values were τ 0.48 (SE ± 0.025, Spearman’s ρ -0.105, SE ± 0.029).

**Difference between the estimated and measured PaCO\textsubscript{2} values (PaCO\textsubscript{2}-est2)**
The data for the PaCO₂ values were not normally distributed (Kolmogorov–Smirnov test, p value < 0.001). The mean difference between the measured and PaCO₂-est2 values was 0.036 kPa (SE ± 0.009). The SD of the differences was 0.59 (SE ± 0.06), percentage error was 23%. The mean difference between the measured PaCO₂ and ETCO₂ values was 0.71 kPa (SE ± 0.010), percentage error was 24%. The SD of the differences was 0.62 (SE ± 0.07). There was a statistically significant difference between PaCO₂-est2 and end-tidal CO₂ in estimating PaCO₂ (p < 0.001). Also, there was a statistically significant difference (p < 0.001) when comparing the true and estimated values with the original, unmodified formula (PaCO₂-est1) and modified formula (PaCO₂-est2).

The Bland-Altman plots demonstrating the agreement between the PaCO₂-est2 and measured PaCO₂ values, as well as the PaCO₂ (PETCO₂) and measured PaCO₂ values with limits of agreement and their 95% confidence intervals, are presented in Figure 2a and 2b, respectively. The accuracy of the PaCO₂-est2 was not affected by the patients’ temperature (Supplementary Figure 1). There was no statistically significant difference between the methods at different mean arterial pressure levels (Supplementary Figure 2). PaCO₂-est2 was superior to PaCO₂-est1a nd end-tidal CO₂ at different temperature and blood pressure levels.

The effect of time

The mean difference between the measured PaCO₂ values and estimated PaCO₂ values in the first three hours was 0.12kPa (SE +/- 0.041) when using PaCO₂-est2. The SD of the differences was 0.73. The mean difference between the measured and estimated PCO₂
The effect of different carbon dioxide and inspired oxygen levels on the accuracy of PaCO$_2$-est2

Estimations carried out with PaCO$_2$-est2 were the most accurate in normoventilation. The differences between the measured and estimated PaCO$_2$ in PaCO$_2$ deciles are shown in Figure 4a. The difference between the measured and estimated PaCO$_2$ values was not affected by FIO$_2$ values at the same degree as PaCO$_2$ levels. The differences between the measured and estimated PaCO$_2$ values in FIO$_2$ deciles are shown in Figure 4b.

The intraclass correlation

The WSV for the estimated PaCO$_2$ and ETCO$_2$ values were 0.16 (SE ± 0.004) and 0.18 SE +/- 0.004), respectively. The intraclass correlations (τ = ratio of BSV and total variance) for the estimated PaCO$_2$ and PETCO$_2$ values were τ 0.48 (SE ± 0.028, Spearman’s ρ 0.16, SE ± 0.033) and ETCO$_2$ 0.61 (SE +/- 0.027, Spearman’s ρ -0.05 SE ± 0.034).
Discussion

We developed and validated a novel formula that utilizes respiratory gas measurements and SpO₂ for estimating PaCO₂ noninvasively in mechanically ventilated patients. We found a good agreement between measured and estimated PaCO₂ values for the novel formula and found no evidence of impaired accuracy depending on patient temperature and mean arterial pressure levels. This formula might enable reliable, noninvasive methods for monitoring mechanical ventilation. The difference between the measured and estimated PaCO₂ values in our study is below the limit of agreement of a clinically acceptable 1 kPa error.¹⁴

In healthy subjects, there is a reasonable agreement between PETCO₂ and arterial PaCO₂, especially with temperature corrected PaCO₂.¹⁵⁻¹⁶ By contrast, with respiratory or cardiac failure, the gap between PaCO₂ and ETCO₂ widens because of V/Q mismatch, which results in lower alveolar and expired breathing gas CO₂ levels. In some studies, there has been a strong agreement between PETCO₂ and PaCO₂.¹⁷⁻¹⁹ Other studies have reported that the gradient between PETCO₂ and PaCO₂ has clinically significant importance considering for example the reliability of monitoring and the adequacy of ventilation.²⁰⁻²¹ In patients with hypotension and metabolic acidosis, the gap between PETCO₂ and PaCO₂ is higher than in normotensive and stable patients.²²

The accuracy of the novel formula is the highest in the normoventilation range.

Previous studies of end-tidal CO₂ and PtcCO₂ and show similar results with high PaCO₂ levels,
which can be the result of increased dead space and shunting.\textsuperscript{22-23} The method underestimated the highest PaCO\textsubscript{2} values, which may occur with large alveolar dead space. The PACO\textsubscript{2} of perfused alveoli equilibrates with blood concentration to maximum venous CO\textsubscript{2} concentration independently of the alveolar dead space whereas in the alveolar dead space the concentration remains zero of the inspired gas. At expiration the zero concentration dead space gas dilutes the blood concentration stream from perfused alveoli causing the PETCO\textsubscript{2} reduction corresponding to the amount of dead space ventilation. The alveolar dead space effect on oxygen is minor: the PAO\textsubscript{2} of the perfused alveoli will decrease more in supplying the whole perfusion with smaller gas volume. During expiration, when mixing in the upper airways, the inspired oxygen concentration from the dead space compensates the reduced PAO\textsubscript{2} from the perfused lung regions. As a result of this compensation in oxygenation, the equation is unable to fully compensate the alveolar dead space effect on the PaCO\textsubscript{2}.

Patient temperatures did not affect the formula’s accuracy. This is important because patients in prehospital care are more likely to suffer from hypothermia\textsuperscript{24} and targeted temperature management is standard practice during the intensive care of patients after CA.

The mean difference between the measured and estimated values was slightly higher in the first three hours compared with the remaining 45 hours but this difference was not statistically significant. In previous studies, the difference between PETCO\textsubscript{2} and PaCO\textsubscript{2} has been reported to increase over time.\textsuperscript{25}

There was a statistically significant difference between the PaCO\textsubscript{2} estimates obtained using the two formulas (PaCO\textsubscript{2}-est1 and PaCO\textsubscript{2}-est2). An improvement regarding PaCO\textsubscript{2}-est2 compared with PaCO\textsubscript{2}-est1 is that PaCO\textsubscript{2}-est2 utilizes data directly from the
pulse oximeter instead of PaO₂ estimated by SpO₂ obtained from the oxygen dissociation curve.

In emergency care despite its unreliability for determining the adequacy of ventilation, PETCO₂ is a useful tool in verifying the correct positioning of an endotracheal tube. Transcutaneous CO₂ is routinely used in neonatal ICUs. In adults, PtcCO₂ has shown conflicting results and may be affected by hypotension, peripheral perfusion disturbances and the use of vasoconstrictors. Transcutaneous PCO₂ appears to be a more accurate method compared with PETCO₂, but its accuracy might deteriorate with extreme PaCO₂ values and is also affected by V/Q mismatch.

There are some limitations to this study. One patient was hemodynamically unstable and potentially had a very low cardiac output (CO). In conditions associated with low CO, PETCO₂ does not correlate with PaCO₂ values, but unfortunately, the CO value was not available for assessment in this case. Our next aim is to identify the limitations of the algorithm and validate the formula in different critically ill mechanically ventilated patient groups.

In conclusion the present study shows that a novel formula developed for estimating PaCO₂ values has good agreement with measured ABG values and outperforms PETCO₂ in accuracy. Within certain limits, it offers a noninvasive and continuous method for assessing PaCO₂.
Acknowledgments

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References


and arterial carbon dioxide measurements correlate across all levels of physiologic dead space. *Respir Care* 2010;55:288-93.


Table 1. Coefficients $k_1$, $k_2$, and $k_3$ for Formula 2 as determined by using 500 randomly
selected data points. The coefficients were created separately for the low and high
PETCO$_2$ groups.

<table>
<thead>
<tr>
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<th>$k_1$</th>
<th>$k_2$</th>
<th>$k_3$</th>
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<tbody>
<tr>
<td>PETCO$_2$-low (&lt;4 kPa)</td>
<td>1.178</td>
<td>0.0132</td>
<td>0.0185</td>
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<tr>
<td>PETCO$_2$-high ($\geq$ 4 kPa)</td>
<td>1.049</td>
<td>0.0162</td>
<td>0.0139</td>
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### Table 2. Characterization of patients and various subgroups of interest

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<th>Patient characteristics</th>
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<tr>
<td>Age, years</td>
<td>62 (52-67)</td>
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<tr>
<td>Male sex, n (%)</td>
<td>181 (81)</td>
<td></td>
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<tr>
<td>Height, cm</td>
<td>179 (172-183)</td>
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<tr>
<td>Weight, kg</td>
<td>85 (75-90)</td>
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<th>Initial rhythm, n (%)</th>
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<tr>
<td>VF</td>
<td>228 (97.9)</td>
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<tr>
<td>VT</td>
<td>2 (0.85)</td>
<td></td>
</tr>
<tr>
<td>PEA</td>
<td>2 (0.85)</td>
<td></td>
</tr>
<tr>
<td>Asystole</td>
<td>1 (0.4)</td>
<td></td>
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</table>

| ROSC, min              | 20 (15-25) |

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<tr>
<th>Scoring model, n (IQR)</th>
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<tr>
<td>APACHE II</td>
<td>25 (18-31)</td>
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<tr>
<td>SAPS</td>
<td>47 (35-64)</td>
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<tr>
<td>SOFA</td>
<td>8 (7-10)</td>
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<tr>
<th>Prevalence of lung disease, n (%)</th>
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<tr>
<td>Asthma</td>
<td>18 (7.7)</td>
<td></td>
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<tr>
<td>COPD</td>
<td>11 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>2 (0.85)</td>
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Table 3. Characteristics of ventilation and hemodynamic variables during first and second intensive care unit (ICU) treatment days. Data are shown as median (interquartile range).

<table>
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<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
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<tr>
<td>FIO₂, %</td>
<td>35 (30-49)</td>
<td>35 (30-45)</td>
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<tr>
<td>SpO₂, %</td>
<td>99 (98-100)</td>
<td>99 (97-99)</td>
</tr>
<tr>
<td>PEEP, cmH₂O</td>
<td>7 (6-8)</td>
<td>7 (6-8)</td>
</tr>
<tr>
<td>HR</td>
<td>55 (45-68)</td>
<td>66 (55-79)</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>78 (73-86)</td>
<td>77 (72-84)</td>
</tr>
<tr>
<td>PETCO₂, kPa</td>
<td>4.2 (3.8-4.7)</td>
<td>4.6 (4.1-5.1)</td>
</tr>
<tr>
<td>PaCO₂, kPa</td>
<td>5.0 (4.5-5.4)</td>
<td>5.2 (4.9-5.6)</td>
</tr>
<tr>
<td>PaO₂/FIO₂-ratio</td>
<td>210 (36-303)</td>
<td>198 (36-310)</td>
</tr>
</tbody>
</table>
Figure 1. The Bland-Altman plot assessing agreement between PaCO₂ (PaCO₂-est1) and measured PaCO₂.

- Mean CO₂ = 5.1 kPa
- Percentage error 23.7%
- n = 4741 data points
- Upper LoA (1.3) with 95% CI
- Lower LoA (-1.1) with 95% CI
- Avarage of PaCO₂ and CO₂ (PaCO₂-est1), kPa
Figure 2a. The Bland-Altman plot assessing agreement between PaCO\(_2\) (PaCO\(_2\)-est2) and measured PaCO\(_2\).

- Mean CO\(_2\) = 5.1 kPa
- Percentage error 22.7%
- Upper LoA (1.2) with 95% CI
- Lower LoA (-0.74) with 95% CI
- n = 4512 data points

The figure illustrates the agreement between estimated PaCO\(_2\) and measured PaCO\(_2\). The plot shows the difference between the two measurements against the average of the two measurements. The dotted lines represent the limits of agreement (LoA) for 95% confidence interval (CI). The solid line represents the mean difference, which is 0.07 kPa.
Figure 2b. The Bland-Altman plot assessing agreement between ETCO₂ and measured PaCO₂

- n=4512 data points
- Mean CO₂= 5.1 kPa
- Percentage error= 23.6%

- Average of PaCO₂ and PETO₂, kPa
Figure 3. The mean differences between measured PaCO\(_2\) and estimated PaCO\(_2\), and mean differences between measured PaCO\(_2\) (Formula 2) and end-tidal CO\(_2\) at different time periods.
Figure 4a. The mean differences between measured PaCO₂ and estimated PaCO₂ (Formula 2), and mean differences between measured PaCO₂ and end-tidal CO₂ at CO₂ deciles.
Figure 4b. The mean differences between measured PaCO₂ and estimated PaCO₂ (Formula 2), and mean differences between measured PaCO₂ and end-tidal CO₂ at FiO₂ deciles.
1. **Supplementary Figure 1.** Flowchart of the study population
1. **Supplementary Figure 2.** The difference between measured and estimated PaCO₂ at different body temperatures.
2. **Supplementary Figure 3.** The mean differences between measured and estimated PaCO₂ (Formula 1, Formula 2, and end-tidal CO₂) at different mean arterial pressure levels.
Table 2. Patients’ characteristics and pre-hospital variables. All continuous values are given as medians (interquartile range), and categorical values as percentages. Cm=centimeters, kg=kilograms, VF=ventricular fibrillation, VT=ventricular tachycardia, PEA=pulseless electrical activity, ROSC=Return of spontaneous circulation, COPD= chronic obstructive pulmonary disease

Table 3. Hemodynamic variables and variables of ventilator settings and derived data. All continuous values are given as medians (interquartile range). FIO₂=fraction of inspired oxygen, SpO₂=partial oxygen saturation of the arterial blood, PEEP=positive end-expiratory pressure, HR=heart rate, MAP=mean arterial pressure; etCO₂=end-tidal carbon dioxide; PaCO₂=arterial partial pressure of carbon dioxide; PaO₂/FIO₂= arterial oxygen partial pressure/fractional inspired oxygen ratio

Figure 1. Bland-Altman plots with 95% limits of agreement with 95% confidence intervals demonstrating agreement between partial pressure of carbon dioxide, PaCO₂ (Formula 1), and measured PaCO₂ during the first 48 hours after admission to the ICU.

Figures 2a and 2b. Bland-Altman plots with 95% limits of agreement with 95% confidence intervals demonstrating agreement between the PaCO₂ (Formula 2) and measured PaCO₂ values (a) and the ETCO₂ and measured PaCO₂ values (b) during the first 48 hours after admission to the ICU.
**Figure 3.** Mean differences between the measured and estimated PaCO$$_2$$ values and between measured PaCO$$_2$$ and end-tidal CO$$_2$$ at different time points: First time period: 0–3 hours; 2nd: 3–6 hrs; 3rd 6–9 hrs; 4th 9–12 hrs; 5th 12–15 hrs, 6th 15–18 hrs; 7th 18–21 hrs; 8th: 21–24 hrs; 9th: 24–27 hrs; 10th 27–30 hrs; 11th 30–33 hrs; 12th: 33–36 hrs; 13th: 36–39 hrs; 14th: 39–42 hrs; 15th: 42–45 hrs; and 16th: 45–48 hrs.

**Figures 4a and 4b.** The mean differences between measured PaCO$$_2$$, estimated PaCO$$_2$$ (Formula 2) and end-tidal CO$$_2$$ values at different levels of PaCO$$_2$$. 1: PaCO$$_2$$ < 4.3 kPa; 2: PaCO$$_2$$ 4.3-4.5 kPa; 3: PaCO$$_2$$ 4.6-4.7 kPa; 4: PaCO$$_2$$ 4.8-4.9 kPa; 5: PaCO$$_2$$ 5.0-5.1 kPa; 6: PaCO$$_2$$ 5.2 kPa; 7: PaCO$$_2$$ 5.3-5.4 kPa; 8: PaCO$$_2$$ 5.5-5.6 kPa; 9: PaCO$$_2$$ 5.7-5.9 kPa; and 10: PaCO$$_2$$ > 5.9 kPa. The mean differences between the measured PaCO$$_2$$, estimated PaCO$$_2$$ (Formula 2), and end-tidal CO$$_2$$ values at different levels of FiO$$_2$$ (%). 1: FiO$$_2$$ < 26; 2: FiO$$_2$$ 26–30; 3: FiO$$_2$$ 30–30.3; 4: FiO$$_2$$ 30.3–34.6; 5: FiO$$_2$$ 34.6–35.2; 6: FiO$$_2$$ 35.2–40.0; 7: FiO$$_2$$ 40.0–45.0; 8: FiO$$_2$$ 45.0–50.33; 9: FiO$$_2$$ 50.33–60.55; and 10 FiO$$_2$$ > 60.55.

**Supplementary Figure 1.** Flowchart of the study population. V/Q mismatch=ventilation/perfusion mismatch; ETCO$$_2$$=end-tidal carbon dioxide; kPa=kilopascal

**Supplementary Figure 2.** The difference between the measured and estimated PaCO$$_2$$ values at different body temperatures. PaCO$$_2$$=Partial pressure of arterial carbon dioxide; ETCO$$_2$$=end-tidal carbon dioxide.
Supplementary Figure 3. The mean differences between the measured and estimated PaCO₂ values (Formula 1, Formula 2, and end-tidal CO₂) at different mean arterial pressure levels. PaCO₂=Partial pressure of arterial carbon dioxide; ETCO₂=end-tidal carbon dioxide.