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

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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 $PaCO_2$-est1= $PETCO_2$+k[(PIO_2-$PETCO_2$) -PaO_2]. To achieve better accuracy, we further modified the formula to $PaCO_2$-est2= k_1*$PETCO_2$ + k_2*(PIO_2-$PETCO_2$)+k_3*(100-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 $PaCO_2$-est1, the mean difference between the partial pressure of carbon dioxide, and the estimated carbon dioxide was 0.08 kPa (SE ± 0.003); with $PaCO_2$-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 $PaCO_2$-est1 ($p<0.001$) and $PaCO_2$-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 ($PaCO_2$) with arterial blood gas (ABG) analysis. Although an ABG analysis intermittently provides exact $PaCO_2$ values, $PaCO_2$ may change despite constant ventilation.

End-tidal carbon dioxide generally underestimates arterial $PaCO_2$.[1] 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.[2] Maintaining normoventilation may be difficult under circumstances where ABG measurements is not available, including prehospital care and patient transport.[3] The measurement of $PETCO_2$ with continuous capnography is used as a surrogate but may be a poor indicator of $PaCO_2$ because of V/Q mismatch. Dyscarbia and unintentional deviation from normoventilation have been associated with poor outcome.[4-5] Therefore, seeking new dynamic methods to noninvasively estimate $PaCO_2$ is highly important.[6]

We present a method for estimating the $PaCO_2$ 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 $PaCO_2$ values in various physiological and pathophysiological conditions.[7] The formula was developed based on the assumption that the degree of V/Q mismatch behind the alveolar–arterial oxygen tension difference ($PA\text{-}aO_2$) is similar for both O_2 and CO_2. In our previous study, the estimation of PaO_2 was evaluated purely under experimental conditions. The primary aim of the present study was to test the agreement of measured $PaCO_2$ and estimated $PaCO_2$ 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). [8-10]

Estimation of arterial CO_2 partial pressure

The original formula used for estimating $PaCO_2$ has been published previously and is defined as follows: [7]

$PaCO_2$-est1= $PETCO_2$+k[(PIO_2-$PETCO_2$)-PaO_2]

where $PETCO_2$ is the measured end-tidal CO_2 pressure and PIO_2 is the measured inspired O_2 pressure with the equation of FIO_2 x (barometric pressure–saturated vapor pressure of H_2O). PaO_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 $PaCO_2$ values.

Creation of the calibrated, new formula ($PaCO_2$-est2)

The relationship factors were defined by fitting the data points for the minimal difference between the blood gas measured $PaCO_2$ 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 $PETCO_2$ values. Data points having $PETCO_2$ < 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 $PETCO_2$ value of 4 kPa. The 4 kPa division value was randomly selected to reflect potentially major (< 4 kPa) and normal or minor (≥ 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:

$$\mathbf{PaCO_2\text{-}est2=k_1*PETCO_2+k_2*(PIO_2\text{-}PETCO_2)+k_3*(100\text{-}SpO_2)}$$

$PaCO_2$ 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 O_2 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 O_2 may be insufficient to fully saturate the Hb, which is measured as SpO_2 below 100%. The difference (100-SpO_2) measures the magnitude of this insufficiency. Clinician may respond to reduced SpO_2 by increasing the PIO_2. 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 SpO_2. Thus, increase on the term (100-SpO_2) of the equation indicates the increase in alveolar dead space. Again, clinician may respond to reduced SpO_2 by increasing the PIO_2 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 $PETCO_2$. This increases the second term as indication of the alveolar dead space. In addition to a V/Q mismatch, possible differences in CO_2 and O_2 alveolar exchange may cause additional differences between $PETCO_2$ and $PaCO_2$ not reflected in the O_2 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 $PaCO_2$ 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 $PaCO_2$ values.

Statistical analyses

To validate $PaCO_2$-est1 and the comparisons used between $PaCO_2$-est2 and $PETCO_2$, we calculated the mean difference with the standard deviation (SD) between the measured and estimated $PaCO_2$ values. We assessed the agreement between the measured and estimated $PaCO_2$ 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. [13] Percentage error was calculated from the SD of agreement and mean CO_2: 100* (1,96*SD/mean CO_2).

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 $PaCO_2$ and $ETCO_2$. 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 $PETCO_2$ 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_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 $PaCO_2$ values ($PaCO_2$-est1)

The mean difference between the measured and estimated $PaCO_2$ values ($PaCO_2$= $PETCO_2$+k [PIO_2-$PETCO_2$]-PaO_2) was 0.08kPa (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 $PaCO_2$-est1 and measured $PaCO_2$ values with limits of agreement and their 95% confidence intervals is presented in Figure 1.

Intraclass correlation ($PaCO_2$-est1)

The within-subject variance for the estimated $PaCO_2$ ($PaCO_2$-est1) and measured $PaCO_2$ 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 $PaCO_2$ and measured $PaCO_2$ values were τ 0.48 (SE ± 0.025, Spearman's ρ -0.105, SE ± 0.029).

Difference between the estimated and measured $PaCO_2$ values ($PaCO_2$-est2)

The data for the $PaCO_2$ 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 $PaCO_2$ and $ETCO_2$ 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 $PaCO_2$-est2 and end-tidal CO_2 in estimating $PaCO_2$ ($p < 0.001$). Also, there was a statistically significant difference ($p < 0.001$) when comparing the true and estimated values with the original, unmodified formula ($PaCO_2$-est1) and modified formula ($PaCO_2$-est2).

The Bland-Altman plots demonstrating the agreement between the $PaCO_2$-est2 and measured $PaCO_2$ values, as well as the $PaCO_2$ ($PETCO_2$) and measured $PaCO_2$ values with limits of agreement and their 95% confidence intervals, are presented in Figure 2a and 2b, respectively. The accuracy of the $PaCO_2$-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). $PaCO_2$-est2 was superior to $PaCO_2$-est1a nd end-tidal CO_2 at different temperature and blood pressure levels.

The effect of time

The mean difference between the measured $PaCO_2$ values and estimated $PaCO_2$ values in the first three hours was 0.12kPa (SE +/- 0.041) when using $PaCO_2$-est2. The SD of the differences was 0.73. The mean difference between the measured and estimated PCO_2

values changed over time according to the linear mixed model analysis. These changes, however, were not significant ($p=0.06$). The mean differences between the measured and estimated $PaCO_2$ levels by both methods—$PETCO_2$ and $PaCO_2$-est2—on three-hour intervals starting from the first ABG sample are presented in Figure 3.

The effect of different carbon dioxide and inspired oxygen levels on the accuracy of $PaCO_2$-est2

Estimations carried out with PaCO2-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 SpO_2 for estimating $PaCO_2$ noninvasively in mechanically ventilated patients. We found a good agreement between measured and estimated $PaCO_2$ 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 $PaCO_2$ 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 $PETCO_2$ and arterial $PaCO_2$, especially with temperature corrected $PaCO_2$. [15 -16] By contrast, with respiratory or cardiac failure, the gap between $PaCO_2$ and $ETCO_2$ widens because of V/Q mismatch, which results in lower alveolar and expired breathing gas CO_2 levels. In some studies, there has been a strong agreement between $PETCO_2$ and $PaCO_2$. [17-19] Other studies have reported that the gradient between $PETCO_2$ and $PaCO_2$ 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 $PETCO_2$ and $PaCO_2$ 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 CO_2 and $PtcCO_2$ and show similar results with high $PaCO_2$ levels, which can be the result of increased dead space and shunting. [22-23]. The method underestimated the highest $PaCO_2$ values, which may occur with large alveolar dead space. The $PACO_2$ of perfused alveoli equilibrates with blood concentration to maximum venous CO_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 $PETCO_2$ reduction corresponding to the amount of dead space ventilation. The alveolar dead space effect on oxygen is minor: the PAO_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_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 $PaCO_2$.

Patient temperatures did not affect the formula's accuracy. This is important because patients in prehospital care are more likely to suffer from hypothermia[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 $PETCO_2$ and $PaCO_2$ has been reported to increase over time. [25]

There was a statistically significant difference between the $PaCO_2$ estimates obtained using the two formulas ($PaCO_2$-est1 and $PaCO_2$-est2). An improvement regarding $PaCO_2$-est2 compared with $PaCO_2$-est1 is that $PaCO_2$-est2 utilizes data directly from the pulse oximeter instead of PaO_2 estimated by SpO_2 obtained from the oxygen dissociation curve.

In emergency care despite its unreliability for determining the adequacy of ventilation[26], $PETCO_2$ is a useful tool in verifying the correct positioning of an endotracheal tube. [27] Transcutaneous CO_2 is routinely used in neonatal ICUs. [28] In adults, $PtcCO_2$ has shown conflicting results[29-30] and may be affected by hypotension, peripheral perfusion disturbances and the use of vasoconstrictors. [31-32] Transcutaneous PCO_2 appears to be a more accurate method compared with $PETCO_2$, but its accuracy might deteriorate with extreme $PaCO_2$ values and is also affected by V/Q mismatch. [33-34, 23].

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, $PETCO_2$ does not correlate with $PaCO_2$ values, but unfortunately, the CO value was not available for assessment in this case. [35] 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 $PaCO_2$ values has good agreement with measured ABG values and outperforms $PETCO_2$ in accuracy. Within certain limits, it offers a noninvasive and continuous method for assessing $PaCO_2$.

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References

1. Hemmati N, Zokaei AH, Karbasforooshan A. Correlation between end-tidal and arterial carbon dioxide partial pressure in patients undergoing craniotomy. *J Inj Violence Res* 2012; 4.

2. Yamanaka MK, Sue DY. Comparison of arterial-end-tidal PCO2 difference and dead space/tidal volume ratio in respiratory failure. *Chest* 1987;92:832-5.

3. Davis DP, Idris AH, Sise MJ, Kennedy F, Eastman AB, Velky T, et al. Early ventilation and outcome in patients with moderate to severe traumatic brain injury*. *Crit Care Med* 2006;34:1202-8.

4. Helmerhorst HJF, Roos-Blom M-J, van Westerloo DJ, Abu-Hanna A, de Keizer NF, de Jonge E. Associations of arterial carbon dioxide and arterial oxygen concentrations with hospital mortality after resuscitation from CA. *Crit Care* 2015;19:348.

5. Hope Kilgannon J, Hunter BR, Puskarich MA, Shea L, Fuller BM, Jones C, et al. Partial pressure of arterial carbon dioxide after resuscitation from CA and neurological outcome: a prospective multi-center protocol-directed cohort study. *Resuscitation* 2019;135:212-20.

6. Nassar B, Schmidt G. Estimating arterial partial pressure of carbon dioxide in ventilated patients: How valid are surrogate measures? *Ann Am Thorac Soc* 2017;14:1005-14

7. Rentola R, Hästbacka J, Heinonen E, Rosenberg P, Häggblom T, Skrifvars M. Estimation of arterial carbon dioxide based on end-tidal gas pressure and oxygen saturation. *J Clin Med* 2018;7:290.

8. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On

behalf of the Working Group 1. *Intens Care Med* 1996;22:707-10.

9. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993;270:2957-63.

10. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818-29.

11. Aaron S. Nunn's applied respiratory physiology, 5th ed. ; Butterworth-Heinemann, Oxford, 2003.

12. Subramani S, Kanthakumar P, Maneksh D, Sidharthan A, Rao SV, Parasuraman V, et al. O_2-CO_2 diagram as a tool for comprehension of blood gas abnormalities. *Adv Physiol Educ* 2011;35:314-20.

13. Olofsen E, Dahan A, Borsboom G, Drummond G. Improvements in the application and reporting of advanced Bland-Altman methods of comparison. *J Clin Monit Comput* 2015; 29:127-39.

14. Bendjelid K, Schütz N, Stotz M, Gerard I, Suter PM, Romand J-A. Transcutaneous PCO2 monitoring in critically ill adults: clinical evaluation of a new sensor. *Crit Care Med* 2005; 33:2203-6.

15. Schmitz BD, Shapiro BA. Capnography. *Respir Care Clin of N A*, 1995; 1:107-17.

16. Losa-Reyna J, Torres-Peralta R, Henriquez JJ, Calbet JA. Arterial to end-tidal Pco2 difference during exercise in normoxia and severe acute hypoxia: importance of blood temperature correction. Physiol Rep. 2015;3(10):e12512. doi:10.14814/phy2.12512

17. Wu C-H, Chou H-C, Hsieh W-S, Chen W-K, Huang P-Y, Tsao P-N. Good estimation of arterial carbon dioxide by end-tidal carbon dioxide monitoring in the neonatal intensive care unit. *Pediatr Pulm* 2003;35:292-5.

18. McSwain SD, Hamel DS, Smith PB, Gentile MA, Srinivasan S, Meliones JN, et al. End-tidal

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

19. Takano Y, Sakamoto O, Kiyofuji C, Ito K. A comparison of the end-tidal CO_2 measured by portable capnometer and the arterial PCO2 in spontaneously breathing patients. *Resp Med* 2003;97:476-81.

20. Husaini J, Choy YC. End-tidal to arterial carbon dioxide partial pressure difference during craniotomy in anaesthetised patients. *Med J Malaysia* 2008;63:384-7.

21. Belpomme V, Ricard-Hibon A, Devoir C, Dileseigres S, Devaud ML, Chollet C, et al. Correlation of arterial Pco2 and Petco2 in prehospital controlled ventilation. *Am Journal Emerg Med* 2005;23:852-9.

22. Lee S-W, Hong Y-S, Han C, Kim SJ, Moon SW, Shin JH, et al. Concordance of end-tidal carbon dioxide and arterial carbon dioxide in severe traumatic brain injury. *J Traum* 2009;67:526-30.

23. Ruiz Y, Farrero E, Córdoba A, González N, Dorca J, Prats E. Transcutaneous carbon dioxide monitoring in subjects with acute respiratory failure and severe hypercapnia. *Respir Care* 2016;61:428-33.

24. Haverkamp FJC, Giesbrecht GG, Tan ECTH. The prehospital management of hypothermia — an up-to-date overview. *Injury* 2018;49:149-64.

25. Seguin P, Bleichner JP, Branger B, Guillou YM, Feuillu A, Mallédant Y. The measurement of end-tidal carbon dioxide (PETCO2) is not a significant parameter to monitor in patients with severe traumatic brain injury. *Can J Anaesth* 2001;48:396-400.

26. Prause G, Hetz H, Lauda P, Pojer H, Smolle-Juettner F, Smolle J. A comparison of the end-tidal-CO_2 documented by capnometry and the arterial pCO2 in emergency patients. *Resuscitation* 1997;35:145-8.

27. Varon AJ, Morrina J, Civetta JM. Clinical utility of a colorimetric end-tidal CO_2 detector in cardiopulmonary resuscitation and emergency intubation. *Journal of Clinical Monitoring* 1991;7:289-93.

28. Tobias JD, Wilson WR Jr, Meyer DJ. Transcutaneous monitoring of carbon dioxide tension after cardiothoracic surgery in infants and children. *Anesth Analg* 1999;88:531-4.

29. Gancel P-E, Roupie E, Guittet L, Laplume S, Terzi N. Accuracy of a transcutaneous carbon dioxide pressure monitoring device in emergency room patients with acute respiratory failure. *Intensive Care Med* 2011;37:348-51.

30. Sanders MH, Kern NB, Costantino JP, Stiller RA, Studnicki K, Coates J, et al. Accuracy of end-tidal and transcutaneous PCO2 monitoring during sleep. *Chest* 1994;106:472-83.

31. Clark JS, Votteri B, Ariagno RL, Cheung P, Eichhorn JH, Fallat RJ, et al. Noninvasive assessment of blood gases. *Am Rev Respir Dis* 1992;145:220-32.

32. Santos LJ, Varon J, Pic-Aluas L, Combs AH. Practical uses of end-tidal carbon dioxide monitoring in the emergency department. *J Emerg Med* 12:633-44.

33. Hirabayashi M, Fujiwara C, Ohtani N, Kagawa S, Kamide M. Transcutaneous P_{CO2} monitors are more accurate than end-tidal monitors. *J Anesth* 2009;23:198-202.

34. Liu S, Sun J, Chen X, Yu Y, Liu X, Liu C. The application of transcutaneous CO_2 pressure monitoring in the anesthesia of obese patients undergoing laparoscopic bariatric surgery. *PLoS ONE* 2014;9.

35. Trillò G, von Planta M, Kette F. ETCO2 monitoring during low flow states: clinical aims and limits. *Resuscitation* 1994;27:1-8.

Table 1. Coefficients k1, k2, and k3 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.

	k_1	k_2	k_3
$PETCO_2$-low (<4 kPa)	1.178	0.0132	0.0185
$PETCO_2$-high (≥ 4 kPa)	1.049	0.0162	0.0139

Table 2. Characterization of patients and various subgroups of interest

Patient characteristics	
Age, years	62 (52-67)
Male sex, n (%)	181 (81)
Height, cm	179 (172-183)
Weight, kg	85 (75-90)
Initial rhythm, n (%)	
VF	228 (97.9)
VT	2 (0.85)
PEA	2 (0.85)
Asystole	1 (0.4)
ROSC, min	20 (15-25)
Scoring model, n (IQR)	
APACHE II	25 (18-31)
SAPS	47 (35-64)
SOFA	8 (7-10)
Prevalence of lung disease, no (%)	
Asthma	18 (7.7)
COPD	11 (4.7)
Interstitial lung disease	2 (0.85)

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).

	Day 1	Day 2
FIO_2, %	35 (30-49)	35 (30-45)
SpO_2,%	99 (98-100)	99 (97-99)
PEEP, cmH_2O	7 (6-8)	7 (6-8)
HR	55 (45-68)	66 (55-79)
MAP, mmHg	78 (73-86)	77 (72-84)
$PETCO_2$, kPa	4.2 (3.8-4.7)	4.6 (4.1-5.1)
$PaCO_2$, kPa	5.0 (4.5-5.4)	5.2 (4.9-5.6)
PaO_2/FIO_2-ratio	210 (36-303)	198 (36-310)

Figure 1. The Bland-Altman plot assessing agreement between $PaCO_2$ ($PaCO_2$-est1) and measured $PaCO_2$

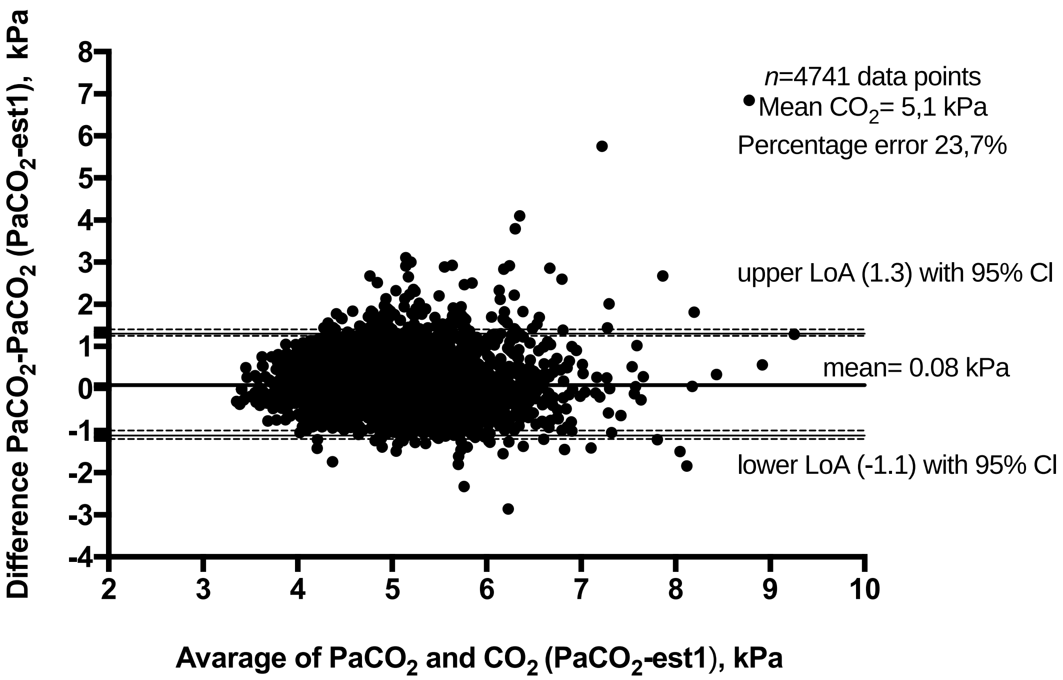


Figure 2a. The Bland-Altman plot assessing agreement between $PaCO_2$ ($PaCO_2$-est2) and measured $PaCO_2$

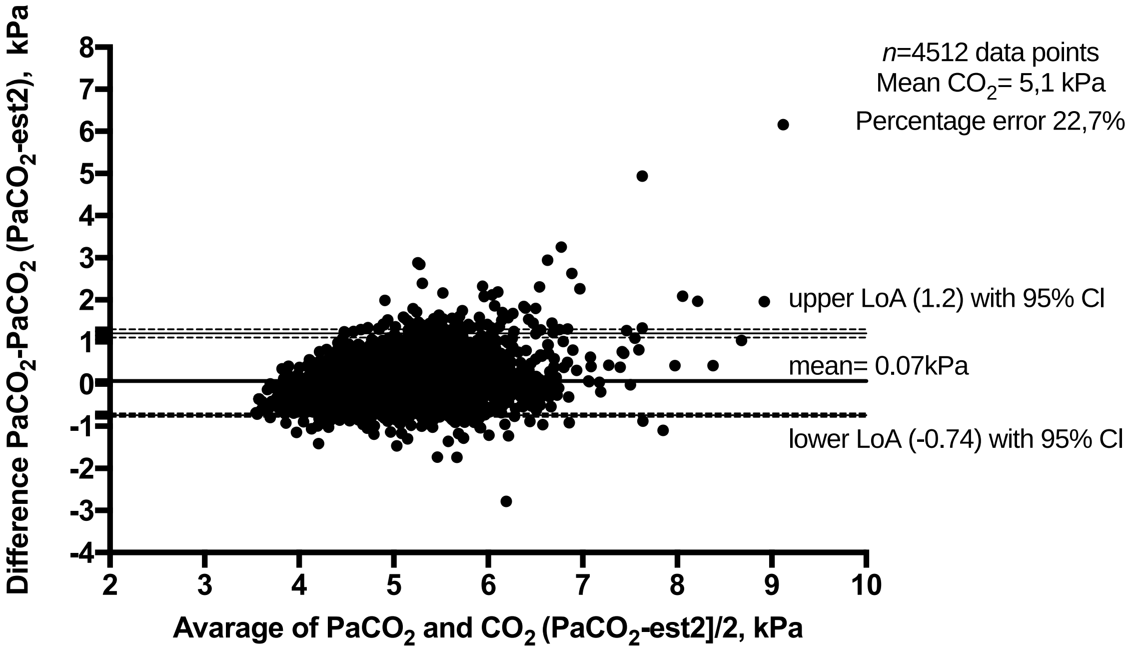


Figure 2b. The Bland-Altman plot assessing agreement between $ETCO_2$ and measured $PaCO_2$

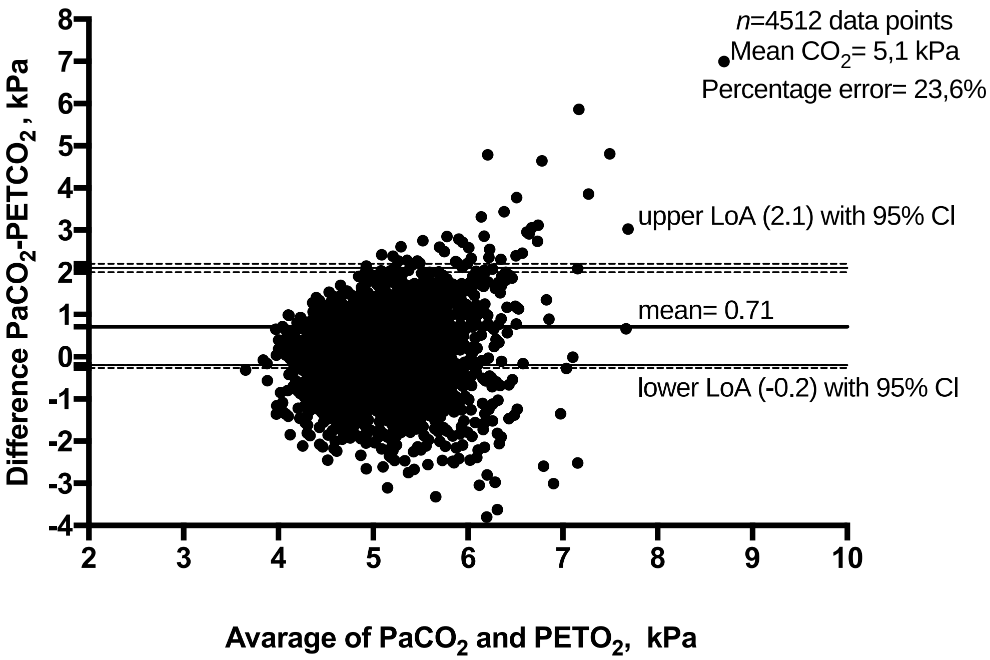


Figure 3. The mean differences between measured $PaCO_2$ and estimated $PaCO_2$, and mean differences between measured $PaCO_2$ (Formula 2) and end-tidal CO_2 at different time periods

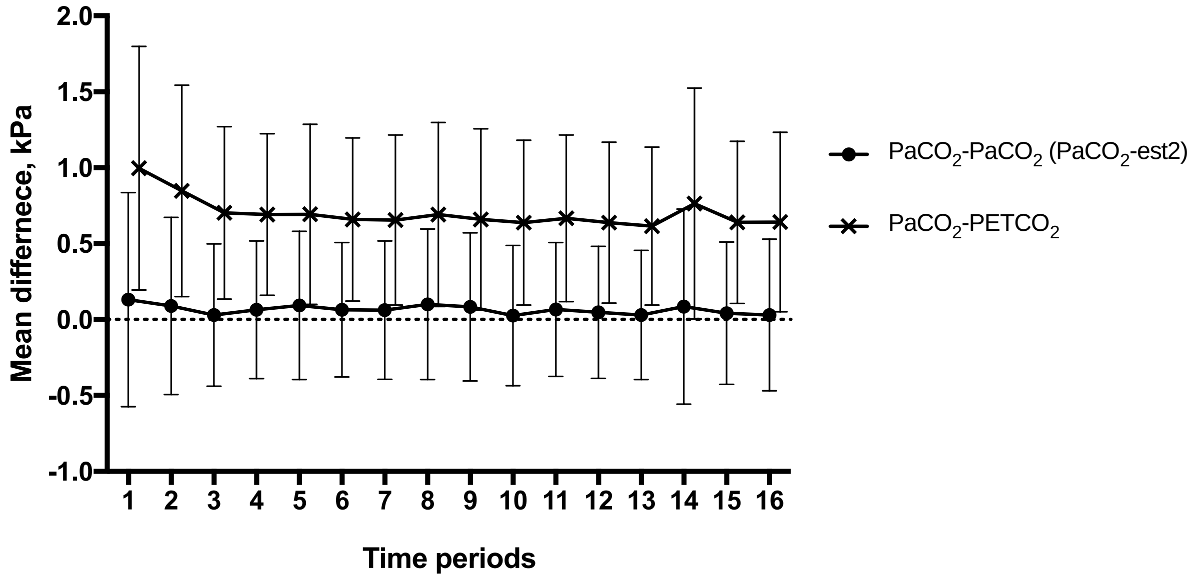


Figure 4a. The mean differences between measured $PaCO_2$ and estimated $PaCO_2$ (Formula 2) , and mean differences between measured $PaCO_2$ and end-tidal CO_2 at CO_2 deciles

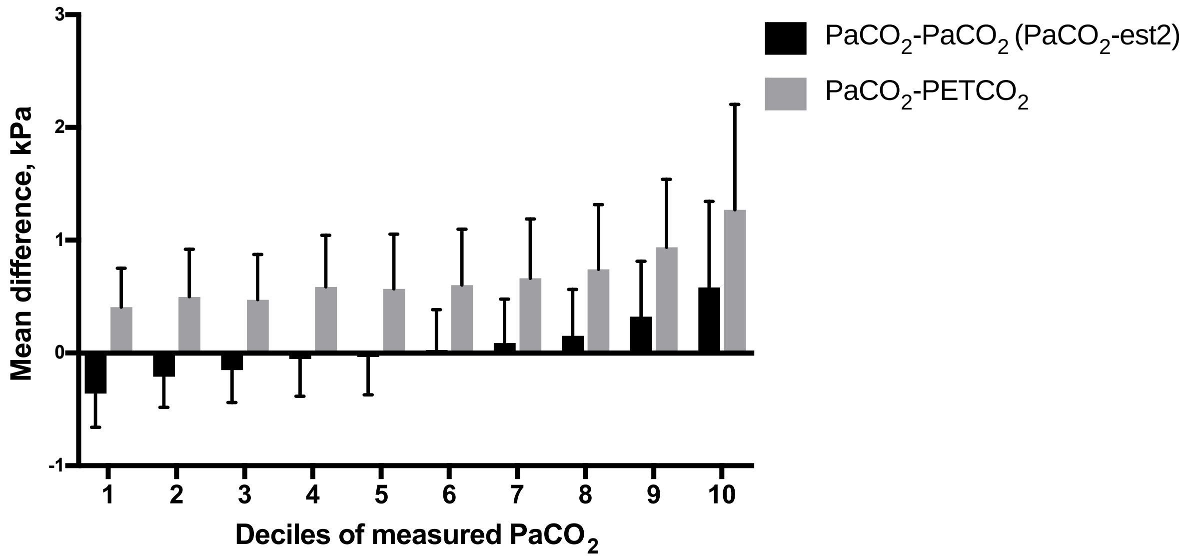
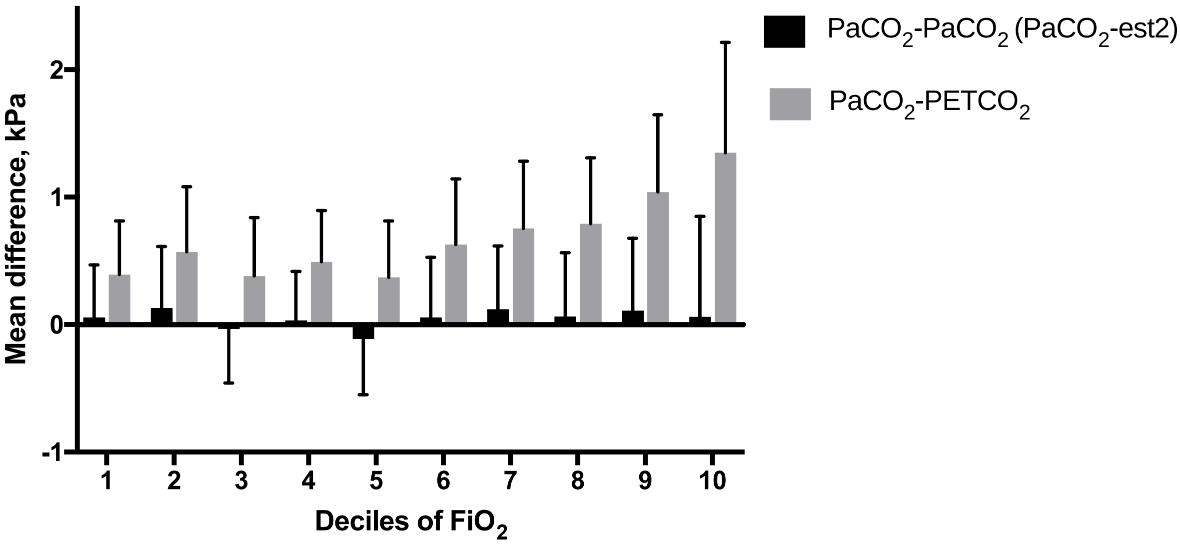
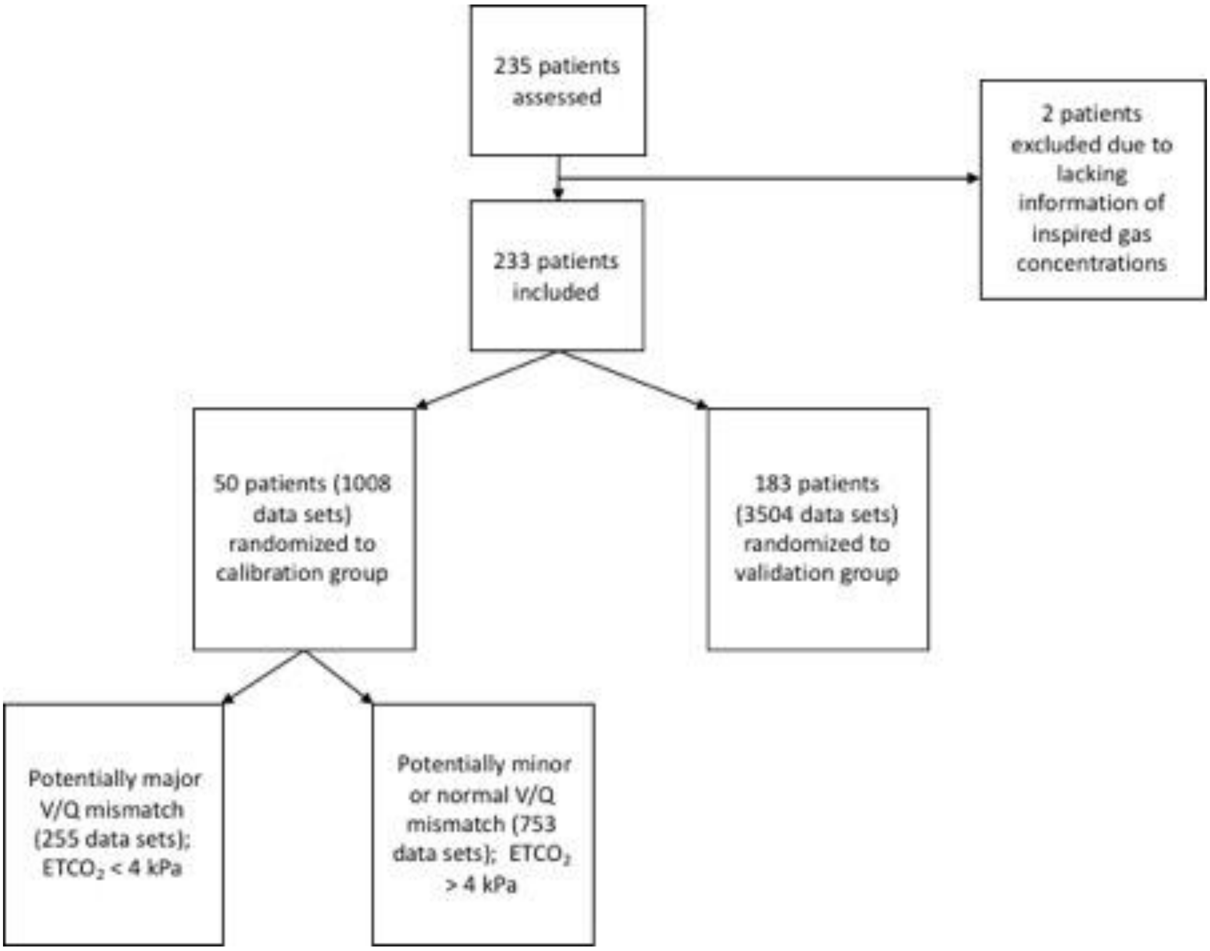


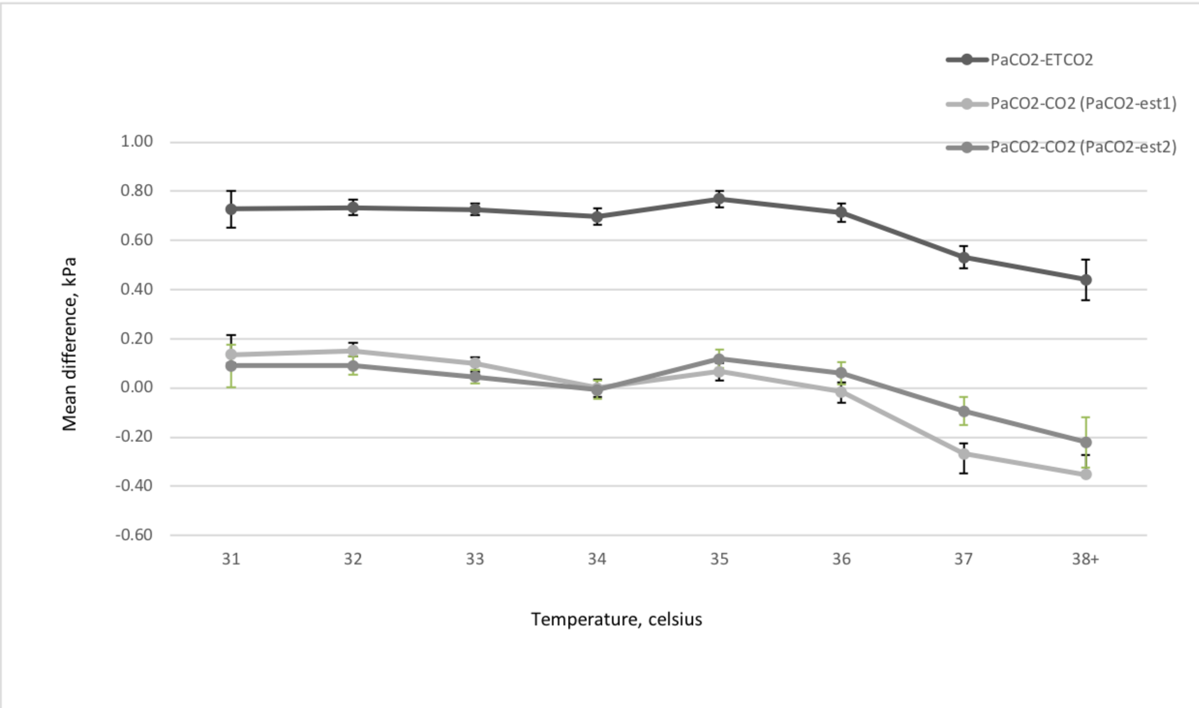
Figure 4b. The mean differences between measured $PaCO_2$ and estimated $PaCO_2$ (Formula 2) , and mean differences between measured $PaCO_2$ and end-tidal CO_2 at FIO_2 deciles



1. **Supplementary Figure 1.** Flowchart of the study population



1. **Supplementary Figure 2.** The difference between measured and estimated $PaCO_2$ at different body temperatures.



2. **Supplementary Figure 3**. The mean differences between measured and estimated $PaCO_2$ (Formula 1, Formula 2, and end-tidal CO_2) at different mean arterial pressure levels.

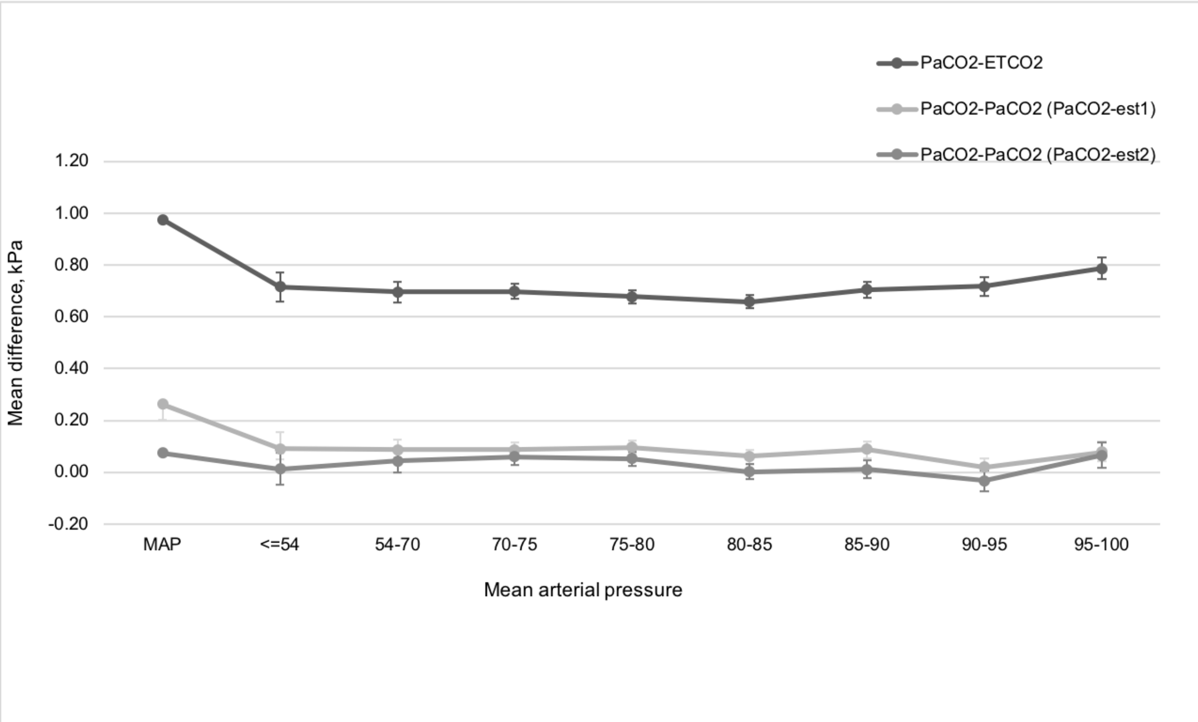


Table 2 .Patients' characteristics and pre-hospital variables. All continuous values are given as medians (interquartile range), and categorical values as percentages. Cm=centimeters, kg=kilograms, VF=ventricular fibrillation, VT=ventricular tachycardia, PEA=pulseless electrical activity, ROSC=Return 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). FIO_2=fraction of inspired oxygen, SpO_2=partial oxygen saturation of the arterial blood, PEEP=positive end-expiratory pressure, HR=heart rate, MAP=mean arterial pressure; etCO2=end-tidal carbon dioxide; $PaCO_2$=arterial partial pressure of carbon dioxide; PaO_2/FIO_2= 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, $PaCO_2$ (Formula 1), and measured $PaCO_2$ 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 $PaCO_2$ (Formula 2) and measured $PaCO_2$ values (a) and the $ETCO_2$ and measured $PaCO_2$ 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 4 b. 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 $PaCO_2$ values (Formula 1, Formula 2, and end-tidal CO_2) at different mean arterial pressure levels. $PaCO_2$=Partial pressure of arterial carbon dioxide; $ETCO_2$=end-tidal carbon dioxide.