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Relationship between end-tidal carbon dioxide and arterial carbon dioxide in critically ill patients on mechanical ventilation

A cross-sectional study

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Abstract

So far, only a few studies have examined and confirmed the correlation between end-expiratory carbon dioxide partial pressure ($PETCO_2$) and arterial carbon dioxide tension ($PaCO_2$) during invasive mechanical ventilation in critically ill patients. This study aimed to observe the correlation between $PaCO_2$ and $PETCO_2$ in patients on invasive mechanical ventilation.

This was a cross-sectional study of adult patients on invasive mechanical ventilation enrolled between June 2018 and March 2019. Patients requiring invasive mechanical ventilation underwent one of the following mechanical ventilation modes: assisted/controlled ventilation, synchronized intermittent mandatory ventilation, and spontaneous breathing. Subsequently, the difference and correlation between $PETCO_2$ and $PaCO_2$ were analyzed.

A total of 184 patients with 298 pairs of $PETCO_2$-$PaCO_2$ data were included in the analysis. Without distinguishing the ventilator mode, there was significant positive correlation between $PETCO_2$ and $PaCO_2$. In different ventilator modes, the correlation coefficient was 0.81 for synchronized intermittent mandatory ventilation, 0.47 for assisted/controlled ventilation, and 0.55 for spontaneous breathing, respectively. In patients with chronic obstructive pulmonary disease ($r=0.80$), multiple trauma ($r=0.64$), severe pneumonia ($r=0.60$), gastrointestinal surgery ($r=0.57$), and cerebrovascular diseases ($r=0.53$), $PETCO_2$ and $PaCO_2$ were positively correlated. For oxygenation index <200 mm Hg, correlation coefficient $r=0.69$, $P<.001$; oxygenation index ≥ 200, $r=0.73$, $P<.001$. Under different oxygenation indexes, there was no statistically significant difference between the 2 correlation coefficients. Among 116 pairs of data with oxygenation index <200 mm Hg, the difference of $PaCO_2$-$PETCO_2 \geq 10$ mm Hg was found in 25 pairs (21.55%); in 182 pairs of data with oxygenation index ≥ 200 mm Hg, the difference of $PaCO_2$-$PETCO_2 \geq 10$ mm Hg was found in 26 pairs

In patients on invasive mechanical ventilation, there was a good correlation between $PETCO_2$ and $PaCO_2$ in different ventilator modes, different disease types, and different oxygenation indexes, especially in synchronized intermittent mandatory ventilation mode and chronic obstructive pulmonary disease patients.

Abbreviations: A/C = assisted/controlled ventilation, ICU = intensive care units, $PaCO_2$ = arterial carbon dioxide tension, $PETCO_2$ = end-expiratory carbon dioxide partial pressure, SIMV = synchronized intermittent mandatory ventilation, SPONT = spontaneous breathing.

Keywords: arterial carbon dioxide tension, end-expiratory carbon dioxide partial pressure, intensive care units, invasive mechanically ventilation

1. Introduction

End-expiratory carbon dioxide partial pressure ($PETCO_2$) monitoring has been widely used in intensive care units (ICU) for patients in need of mechanical ventilation. In healthy people, the correlation between $PETCO_2$ and arterial carbon dioxide tension ($PaCO_2$) is strong. In sick patients, however, the variation is large, which may be associated with many factors.[1–3] $PETCO_2$ can exceed $PaCO_2$ or can be lower than $PaCO_2$.[4] When ventilator settings are adjusted, the correlation can be very poor or even reversed in ventilated patients. The ventilation of

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emergency patients can only be adjusted according to values derived from an arterial blood gas analysis. $PETCO_2$ measurements cannot be regarded as absolutely accurate values, except maybe in patients without primary cardiorespiratory dysfunction.[1]

So far, the relationship between $PaCO_2$ and $PETCO_2$ has been reported in several pre-clinical[5–7] and clinical studies, including children/infants,[8–11] or mechanically ventilated patients with a single disease (acute respiratory distress syndrome, neurosurgical, or postcardiac arrest patients).[12–15] Only 1 large sample study[16] analyzed the relationship between $PaCO_2$ and $PETCO_2$ in 219 arterial blood gases obtained from 87 patients. They found a good correlation between the mean of $PETCO_2$ and $PaCO_2$ when using synchronized intermittent mandatory ventilation (SIMV), continuous positive airway pressure, and T-Tube models; SIMV ($r = 0.893$, 0.841, and 0.923, respectively).[16] However, they did not conduct stratified analysis according to the disease type and severity, and its clinical significance was limited. Thus, in this study, we further examined the correlation between $PaCO_2$ and $PETCO_2$ under different ventilator modes, different disease types, and different oxygenation indexes in mechanically ventilated patients with relatively stable conditions in ICU.

2. Materials and methods

2.1. Study design

This was a cross-sectional study that evaluated the patients on invasive mechanical ventilation admitted to ICU of a tertiary university hospital between June 2018 and March 2019.

2.2. Eligibility criteria

Inclusion criteria were as follows: all patients underwent endotracheal intubation or tracheotomy; continued application of ventilator ≥48 hours in ICU; no vasoactive drugs were prescribed; age >18 years.

Exclusion criteria: incomplete data or patient refusal to participate.

The Institutional Review Board of Harrison International Peace Hospital (2018-1-013) approved the study protocol. Informed consent was obtained from all individual participants included in the study.

2.3. Interventions and data collection

Patients received one of the following mechanical ventilation methods: assisted/controlled ventilation (A/C), SIMV, and spontaneous breathing (SPONT) mode. The mainstream $PETCO_2$ monitor (KMI605A, Beijing Jinjiaxing Co., Ltd., Beijing, China) was used by the same doctor (with 10 years of experience) to detect $PETCO_2$. The sampling sensor was directly connected to the Y-shaped pipe of the ventilator and the endotracheal intubation or tracheotomy catheter. Blood samples of radial artery or femoral artery were collected and the arterial blood gas analysis was completed at beside (ABL90, Leidu, Denmark). $PETCO_2$ and arterial blood gas analysis were completed within 5 minutes.

2.4. Outcomes

Primary outcome measures: $PETCO_2$ and $PaCO_2$ were collected as primary outcome variables. The difference and correlation between $PETCO_2$ and $PaCO_2$ were tested in all patients.

Secondary outcome measures: The following data were collected when $PETCO_2$ and $PaCO_2$ were recorded, including age, gender, body mass index, primary disease type, mean arterial pressure, heart rate, ventilator mode and oxygenation index, Charlson comorbidity index, acute physiology and chronic health evaluation scoring system II, sequential organ failure assessment and treatments.

2.5. Statistical analysis

Assuming a type 1 error of 5% (alpha of 0.05), a power of 90% and $r = 0.50$ in preliminary, this study would require a sample size of 40 patients. To account for dropouts and incomplete data, we aimed for a sample size of 100 patients. Sample size was calculated based on both primary outcomes and the larger of the 2 calculations was utilized.

The Shapiro–Wilk test was used to verify whether all recorded variables were normally distributed ($P > .05$). Continuous data are expressed as the mean ± standard deviation. Correlations among data with measurable outcomes were analyzed using the Pearson test if distributed normally, or as median (interquartile range) and with the Spearman test if non-normally distributed. When there was a quantitative relationship between the 2 variables, linear regression was used to explore the regression equation. A P value $<.05$ was considered statistically significant.

3. Results

3.1. Patients

A total of 184 patients with 298 pairs of $PETCO_2$-$PaCO_2$ data were included in the analysis. The mean age was 68.45 ± 16.50 years, and 126 patients (68.48%) were men. Main characteristics of the patients are shown in Table 1.

3.2. Correlation analysis of $PETCO_2$ and $PaCO_2$ under different ventilator modes

Without distinguishing the ventilator mode, there was a significant positive correlation between $PETCO_2$ and $PaCO_2$; the correlation coefficient was 0.72, the linear regression equation $Y = 11.81 + 0.65x$ (Y: $PETCO_2$; x: $PaCO_2$) (Table 2 and Fig. 1). As shown in Figure 1, the majority of $PETO_2$ and $PaCO_2$ values are distributed in 20 to 60 mm Hg (black dotted frame).

Table 1

Main characteristics of 184 subjects.

Variables	Value
Age (y)	68.45 ± 16.50
Gender, male, no. (%)	126 (68.48)
BMI (kg/m^2)	23.43 ± 3.35
Temperature, °C	36.58 ± 1.67
Mean arterial pressure, mm Hg	62.66 ± 7.34
Heart rate, beats/min	90.82 ± 4.24
Charlson comorbidity index	2.12 ± 1.31
SOFA score	7.67 ± 2.20
APACHE II score	14.58 ± 3.44
Vasopressor, no. (%)	45 (24.46)
CRRT, no. (%)	31 (16.85)

APACHE II = acute physiology and chronic health evaluation scoring system II, BMI = body mass index, CRRT = continuous renal replacement therapy, SOFA = sequential organ failure assessment.

Table 2

Correlation analysis of PETCO2 and PaCO2 under different ventilator modes.

Ventilator modes	Pairs	$PETCO_2$ (mm Hg)	$PaCO_2$ (mm Hg)	$PaCO_2$- $PETCO_2$ gap (mm Hg)	r	*P*
All modes	298	36.65 ± 10.31	39.40 ± 11.30	1.60 ± 7.60	0.72	<.001
A/C	30	37.33 ± 7.85	38.56 ± 8.01	1.23 ± 8.16	0.47	<.001
SIMV	127	36.20 ± 10.63	38.06 ± 12.76	1.86 ± 7.42	0.81	<.001
SPONT	68	38.16 ± 8.58	39.56 ± 7.22	1.40 ± 7.57	0.55	<.001

A/C = assisted/controlled ventilation, $PaCO_2$ = arterial carbon dioxide tension, $PETCO_2$ = end-expiratory carbon dioxide partial pressure, SIMV = synchronized intermittent mandatory ventilation, SPONT = spontaneous breathing.

When comparing different ventilator modes, only the SIMV mode showed a significant correlation (r = 0.81, $P < .001$). In both A/C and SPONT mode, the correlation was relatively weak (correlation coefficient r = 0.47 and 0.55, respectively).

3.3. Correlation analysis of $PETCO_2$ and $PaCO_2$ of different disease types

In patients with chronic obstructive pulmonary disease, multiple injuries, severe pneumonia, gastrointestinal surgery, and cerebrovascular diseases, $PETCO_2$ and $PaCO_2$ were positively correlated (the correlation coefficients were 0.80, 0.64, 0.60, 0.57, and 0.53 respectively; Table 3). For other diseases (including malignant tumors and cardiovascular disease), no correlation was found (r = 0.46, $P = .06$).

3.4. Correlation analysis of $PETCO_2$ and $PaCO_2$ with different oxygenation indexes

Oxygenation index <200 mm Hg, correlation coefficient r = 0.69, $P < .001$; oxygenation index ≥200 correlation coefficient r = 0.73, $P < .001$ (Table 4). Under different oxygenation indexes, there was no statistically significant difference between the 2 correlation coefficients (Z = 0.67, $P = .50$). Among 116 pairs of data with oxygenation index <200 mm Hg, the difference of $PaCO_2$-$PETCO_2$ ≥10 mm Hg was found in 25 pairs (21.55%); in 182 pairs of data with oxygenation index ≥200 mm Hg, the difference of $PaCO_2$-$PETCO_2$ ≥10 mm Hg was found in 26 pairs (14.29%) ($\chi 2 = 2.64$, $P = .19$).

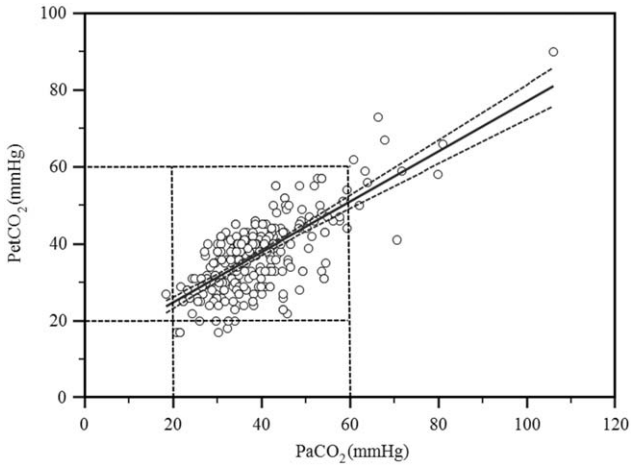

Figure 1. Scatter diagram between PETCO2 and PaCO2 for all patients. The correlation coefficient was 0.72; the linear regression equation Y = 11.81 + 0.65x (Y: PETCO2; x: PaCO2). The solid blue line is the regression line; the blue dashed line is the 95% confidence interval. The majority of PETO2 and PaCO2 values are distributed in 20 to 60 mm Hg (black dotted frame). $PaCO_2$ = arterial carbon dioxide tension, $PETCO_2$ = end-expiratory carbon dioxide partial pressure.

4. Discussion

This study showed that there was a significant positive correlation between $PETCO_2$ and $PaCO_2$ on invasive mechanical ventilation admitted to ICU, especially in SIMV mode, chronic obstructive pulmonary disease patients. Under different oxygenation indexes, the correlation remained strong.

In healthy people, the difference between $PETCO_2$ and $PaCO_2$ is generally 2 to 5 mm Hg.[17] $PaCO_2$, dead space, lung perfusion, and sampling points affect $PETCO_2$. When the dead space is large, the alveolar CO_2 ($PACO_2$) evacuation is not uniform, so $PETCO_2$ is more likely to have a lower value compared with $PaCO_2$. When the ventilation/perfusion ratio is low, the effect of shunt on $PETCO_2$ is small, and cannot easily degrade $PETCO_2$. The difference between $PETCO_2$ and $PaCO_2$ in patients with respiratory failure is large, and the difference is closely related to ventilation/perfusion. $PETCO_2$ should not be used to evaluate $PaCO_2$. In severely ill patients, pulmonary organic diseases cause increased pulmonary shunts; this mixed blood flow into the arterial system results in an increased gradient of $PETCO_2$-$PaCO_2$ difference.[4] In severe lung diseases or systemic diseases, this difference is as high as 20 mm Hg. In other words, $PETCO_2$ underestimates $PaCO_2$ levels. Sivan et al[18] found that the average difference is 3.4 ± 6.6 mm Hg. When the $PaCO_2/PACO_2$ ratio is lower than 0.3, the difference begins to increase, reaching 7.8 ± 7.3 mm Hg; when the $PaCO_2/PACO_2$ ratio is greater than 0.3, the difference is only 0 ± 3.4 mm Hg. This study did not distinguish ventilator mode and disease type, the difference was 2.75 ± 8.38 mm Hg, but stratified analysis was not based on $PaCO_2/PACO_2$.

4.1. Ventilator mode and $PETCO_2$

Weinger and Brimm[19] found a good correlation between $PaCO_2$ and $PETCO_2$ in 25 adult patients with lung disease or extrapulmonary disease using a SIMV mode; the difference between $PaCO_2$ and $PETCO_2$ was 4.24 ± 4.42 mm Hg. In patients with non-pulmonary diseases, who underwent mechanical ventilation or automatic ventilation through tracheal intubation the difference between $PaCO_2$ and $PETCO_2$ was 0.8 to 3.5 mm Hg.[20] A recent study suggested a strong correlation between $PaCO_2$ and $PETCO_2$ under the conditions of SIMV, CPAP mode, and T-tube,[16] which was consistent with our findings. However, there was only a weak correlation between $PaCO_2$ and $PETCO_2$ in A/C mode. This might be due to small sample size; only 30 sets

Table 3

Correlation analysis of $PETCO_2$ and $PaCO_2$ in different disease types.

Disease types	Cases	$PETCO_2$ (mm Hg)	$PaCO_2$ (mm Hg)	$PaCO_2$- $PETCO_2$ gap (mm Hg)	r	*P*
COPD	70	42.81 ± 12.04	48.16 ± 13.14	5.35 ± 7.97	0.80	<.001
Multiple trauma	23	41.30 ± 8.14	38.75 ± 5.50	−2.55 ± 6.25	0.64	.001
Severe pneumonia	55	32.05 ± 7.39	35.13 ± 8.13	3.08 ± 6.97	0.60	<.001
Gastrointestinal surgery	73	36.77 ± 7.53	36.13 ± 7.22	−0.64 ± 6.82	0.57	<.001
Cerebrovascular disease	56	34.79 ± 7.37	35.01 ± 7.85	0.22 ± 7.36	0.53	<.001
Others	21	32.52 ± 6.65	33.71 ± 6.77	1.19 ± 6.95	0.46	.06

COPD = chronic obstructive pulmonary disease, $PaCO_2$ = arterial carbon dioxide tension, $PETCO_2$ = end-expiratory carbon dioxide partial pressure.

Table 4

Correlation analysis of $PETCO_2$ and $PaCO_2$ with different oxygenation indexes.

Oxygenation indexes (mm Hg)	Cases	$PETCO_2$ (mm Hg)	$PaCO_2$ (mm Hg)	$PaCO_2$- $PETCO_2$ gap (mm Hg)	r	*P*
<200	116	38.72 ± 10.23	40.86 ± 10.47	2.14 ± 8.09	0.69	<.001
≥200	182	35.90 ± 8.98	37.15 ± 10.34	1.25 ± 7.26	0.73	<.001
					*Z = 0.67, *P* = .50	

* Comparison of correlation coefficients under different oxygenation indexes.

$PaCO_2$ = arterial carbon dioxide tension, $PETCO_2$ = end-expiratory carbon dioxide partial pressure.

with A/C mode were analyzed. In addition, the A/C mode in this study was mostly used for surgical postoperative or severe pneumonia patients, which requires deep sedation, analgesia, and complete control of ventilation, and alveolar minute ventilation and exhaled tidal volume are basically in a constant state, so $PETCO_2$ variation is small in this case. Even if $PaCO_2$ increases or decreases, it is difficult to stimulate the central or surrounding receptors, change the breathing frequency and tidal volume, so there is weak correlation between $PaCO_2$ and $PETCO_2$.

4.2. Disease type and $PETCO_2$

Kerr et al[21] reported a good correlation between $PaCO_2$ and $PETCO_2$ in adult patients with traumatic brain injury without pulmonary disease (positive end-expiratory pressure <5 cmH_2O). Another study found that $PaCO_2$ and $PETCO_2$ had a strong correlation regardless of the disease, using a ventilator, or SPONT; but the correlation coefficients were different among different diseases.[22] Barton et al reported that in non-intubated patients with different conditions in the emergency room, $PaCO_2$ and $PETCO_2$ also had a strong correlation. $PETCO_2$ monitoring may be sufficient to represent $PaCO_2$ and avoid repeated arterial blood gas analysis.[22] Tobias and Meyer[23] found that percutaneous CO_2 monitoring is more accurate than $PETCO_2$ in predicting $PaCO_2$ in infants and young children. The difference between percutaneous CO_2 and $PaCO_2$ is smaller than the deviation between $PaCO_2$ and $PETCO_2$ (2.3 ± 1.3 mm Hg and 6.8 ± 5.1 mm Hg, respectively). Continuous monitoring of $PETCO_2$ and finger oxygen saturation is safe and effective for patients after coronary artery bypass grafting. Moreover, $PETCO_2$ can predict $PaCO_2$ (r = 0.76), can easily detect hypercapnia, and has a sensitivity of 95%.[24] Consistently, in this study, we found a good correlation between $PaCO_2$ and $PETCO_2$ in patients with COPD, multiple injuries, and severe pneumonia. A correlation coefficient of 0.57 and 0.53 for gastrointestinal surgery and cerebrovascular diagnosis is weak, and clinically irrelevant, even though statistically significant.

4.3. Oxygenation index and $PETCO_2$

Previous studies have argued that the relationship between $PETCO_2$ and $PaCO_2$ in different clinical settings is controversial. McDonald et al[25] suggested a good correlation between $PETCO_2$ and $PaCO_2$ in 129 critically ill patients who received invasive mechanical ventilation through tracheal intubation. The statistical analysis of 1708 paired data showed a higher $PETCO_2$ (39.9 ± 12.7 mm Hg) compared to $PaCO_2$ (45.5 ± 14.1 mm Hg); $PETCO_2$-$PaCO_2$ difference was ≤5 mm Hg in 54%, and ≤10 mm Hg in 80% paired data. The presence of lung disease had a negative impact on the correlation between the two. In the data of 640 groups with oxygenation index <200 mm Hg, the difference of $PETCO_2$-$PaCO_2$ in 223 groups (35%) was >10 mm Hg. However, among the 1068 data sets with an oxygenation index >200 mm Hg, only 111 groups (10%) had a difference >10 mm Hg. This trend suggests that the lower the oxygenation index, the greater the difference between the two.[25] In this study, among 116 pairs of data with oxygenation index <200 mm Hg, the difference of $PaCO_2$-$PETCO_2$ ≥10 mm Hg was found in 25 pairs (21.55%); in 182 pairs of data with oxygenation index ≥200 mm Hg, the difference of $PaCO_2$-$PETCO_2$ ≥10 mm Hg was found in 26 pairs. These data suggest that the oxygenation index of adult patients was negatively correlated with the $PaCO_2$-$PETCO_2$ difference.

This study had several limitations. First of all, the $PETCO_2$ sampling sensor was directly connected to the Y-shaped pipe of the ventilator. It is necessary to ensure that the exhaled gas will not leak due to insufficient tube cuff pressure, which may be ignored by the researcher during the research process, resulting in measurement error. However, in all patients during mechanical ventilation, manually re-measure the cuff pressure every 6 to 8 hours, and the pressure is always maintained at 25 to 30 cmH_2O to minimize the possibility of air leakage. Second, although $PETCO_2$ was measured only once without the average of multiple measurements, but when recording the value, ensure that the $PETCO_2$ is in a steady state (the fluctuation range is <±2 mm Hg within 5 minutes), which may reduce the error. Finally, with the

increasing accuracy of the measuring instruments, $PETCO_2$ has become clinically applied as a substitute for $PaCO_2$. However, caution is required for its application, and use without knowing the advantages and disadvantages of this method may result in erroneous results and improper clinical interpretation. Further studies are needed to assess their suitability in different diseases and clinical situations.

5. Conclusions

In patients receiving invasive mechanical ventilation, $PETCO_2$ and $PaCO_2$ showed a good correlation in different ventilator modes, different disease types and different oxygenation indexes, especially in SIMV mode and chronic obstructive pulmonary disease patients.

Author contributions

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