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Original Article

Limitations of End-Tidal CO_2 Measured with a Portable Capnometer to Estimate $PaCO_2$ for Patients with Respiratory Disease

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Abstract

OBJECTIVE: This study evaluated the relationship between end-tidal carbon dioxide ($EtCO_2$) measured with a portable capnometer and $PaCO_2$ in respiratory disease patients.

MATERIAL AND METHODS: We retrospectively reviewed patients whose $EtCO_2$, measured with a portable capnometer using a mouthpiece, and $PaCO_2$ were simultaneously assessed at a single center from August 2017 to September 2018. The primary outcome was the relationship between $EtCO_2$ and $PaCO_2$. We conducted subgroup analyses in patients with interstitial lung disease (ILD), with and without O_2 supplementation. The relationship between $EtCO_2$ and $PaCO_2$ was analyzed using Spearman's rank test and Bland–Altman analysis.

RESULTS: A total of 100 patients were registered in this study. There was a moderate correlation between $EtCO_2$ and $PaCO_2$ (rho = 0.41). The Bland–Altman plot showed that the mean bias was 0.32 mmHg (95% CI: −1.28 to 1.92), the limits of agreement (LOA) were −15.48 and 16.13 mmHg, and the percent error was 38.49%. The LOA in patients with ILD were −15.12 and 13.75 mmHg. In patients with O_2 supplementation, the mean bias was greater, and the LOA were wider than in those without O_2 supplementation (mean bias: 7.17 vs. −1.18 mmHg, respectively; LOA: −14.29 and 28.62 mmHg vs. −13.82 and 11.46 mmHg, respectively).

CONCLUSION: In the clinical setting, the relationship between $EtCO_2$ and $PaCO_2$ was poor in patients with respiratory disease, especially in those receiving O_2 supplementation, compared with that reported in previous studies. It may be difficult to precisely estimate $PaCO_2$ in patients with respiratory disease based on measurements of $EtCO_2$.

KEYWORDS: Capnography, carbon dioxide, blood gas analysis, interstitial lung disease
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INTRODUCTION

PaO_2 and $PaCO_2$ are necessary measures for the management of patients with respiratory disease or respiratory failure.[1-4] However, arterial blood sampling through an arterial puncture to measure PaO_2 and $PaCO_2$ may cause complications, such as pain, bleeding, and neuropathy.[5-8] Pulse oximetry is widely used to evaluate oxygenation owing to its non-invasiveness.[9] Similar to pulse oximetry, non-invasive portable devices to estimate $PaCO_2$ are useful. Transcutaneous monitoring of CO_2 is a non-invasive approach to estimate $PaCO_2$. However, there are factors to be considered when using the transcutaneous monitoring system, including the need for frequent calibration, replacement of sensor membranes, and assessment of the skin integrity under the sensor. In addition, capillary blood sampling is another option for estimating $PaCO_2$.[10] However, obtaining capillary $PaCO_2$ through a skin prick of the earlobe is a painful procedure.

It has been reported that end-tidal CO_2 ($EtCO_2$) significantly relates with $PaCO_2$.[11-14] Non-invasive measurement of $EtCO_2$ using a portable device is useful in-home care, anesthesia, and emergency situations.[9,15,16] However, some studies have reported differences between $EtCO_2$ and $PaCO_2$ depending on the status of the patients, such as tachypnea, ventilation-perfusion inequality, and airway dead space.[11,17,18] It is unclear whether $EtCO_2$ relates with $PaCO_2$ even in patients with respiratory disease and this status. To the best of our knowledge, no studies have investigated the relationship between $EtCO_2$ and $PaCO_2$ in patients with respiratory disease alone. We hypothesized that $EtCO_2$ measured using a capnometer in patients with the respiratory disease might be useful as a substitute for $PaCO_2$. The aim of this study was to evaluate the relationship between $EtCO_2$ measured using a portable capnometer and $PaCO_2$ in patients with respiratory disease.

MATERIAL AND METHODS

Design

This was a cross-sectional, single-center, retrospective study. This study was approved by the institutional review board at the National Hospital Organization Kinki-Chuo Chest Medical Center (approval number 664). We used an opt-out method

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Figure 1. The CapnoEye® MC-600.

instead of obtaining written informed consent, thereby allowing patients and their families to refuse participation in the study.

Patients

We retrospectively reviewed in patients with a respiratory disease whose $EtCO_2$ (measured using a portable capnometer) and $PaCO_2$ were simultaneously measured at the National Hospital Organization Kinki-Chuo Chest Medical Center from August 2017 to September 2018.

Outcome Measurement

Medical records were retrospectively examined to gather demographic data (e.g., age, sex, classification of respiratory disease, O_2 flow rate, and O_2 therapy device) and clinical data (e.g., $EtCO_2$, $PaCO_2$, SpO_2, and respiratory rate). The primary outcome was to evaluate the relationship between $EtCO_2$ and $PaCO_2$. We conducted subgroup analyses in patients with interstitial lung disease (ILD), with and without O_2 supplementation. $EtCO_2$ was measured using the CapnoEye® MC-600 (NISSEI, Gunma, Japan) (Figure 1). The patients held a mouthpiece in their mouth and performed 6 continuous breaths through their mouth. $EtCO_2$ was measured on the basis of a nondispersive infrared absorption method, and its level was analyzed using the device's own algorithm. In addition, $PaCO_2$ was measured using the ABL800 FLEX (Radiometer, Tokyo, Japan). Arterial blood sampling was performed from the radial artery or femoral artery after 10 min of rest in the recumbent position. The time interval between the measurements of $EtCO_2$ and $PaCO_2$ was <5 min.

Main Points

- A number of factors, such as tachypnea, ventilation-perfusion inequality, and airway dead space, are described to influence differences between end-tidal carbon dioxide ($EtCO_2$) and $PaCO_2$.
- It is unclear whether $EtCO_2$ measured using a portable capnometer is related to $PaCO_2$ in patients with respiratory diseases.
- The relationship between $EtCO_2$ and $PaCO_2$ was poor in patients with respiratory disease, especially in those receiving O_2 supplementation.
- In the clinical setting, it may be difficult to precisely estimate $PaCO_2$ in patients with the respiratory disease based on measurements of $EtCO_2$.

Statistical Analysis

The results of the clinical data were presented as median (interquartile range [IQR]) or as number (%). The relationship between $EtCO_2$ and $PaCO_2$ in all patients was analyzed using Spearman's rank correlation test and Bland–Altman analysis. The latter method was also used to examine this relationship for 3 specific groups of patients: those with ILD, those with O_2 supplementation, and those without O_2 supplementation. The limits of agreement (LOA) were set at ±1.96 times the standard deviation (SD). We categorized the correlations as follows: weak, rho ≤0.35; moderate, 0.36-0.67; and strong, 0.68-1.0.[19] All analyses were performed using the EZR software, version 1.38.

RESULTS

Patients

A total of 100 patients were registered as participants in this study. The characteristics of patients are shown in Table 1. The median age was 75 years (IQR: 63-77 years), and the majority of participants (n = 73/100) were male. The major respiratory disease in this study was ILD and chronic obstructive pulmonary disease (COPD). The median respiratory rate was 14 /min (IQR: 10-18 /min). Eighteen patients received O_2 therapy.

Relationship Between $EtCO_2$ and $PaCO_2$

The median levels of $EtCO_2$ and $PaCO_2$ were 42.0 mmHg (IQR: 36.0-45.0) and 48.0 mmHg (IQR: 37.8-43.9), respectively. There was a moderate correlation between $EtCO_2$ and $PaCO_2$ (rho = 0.41, P < .001) (Figure 2A). The mean bias was 0.32 mmHg (95% CI: −1.28 to 1.92), with an upper and lower LOA of 16.13 and −15.48 mmHg, respectively (Figure 2B). The percent error was 38.49%.

Subgroup Analysis

In 54 patients with ILD, the median respiratory rate was 14/min (IQR: 11-17/min). Eight patients received O_2 therapy. The median levels of $EtCO_2$ and $PaCO_2$ were 42.0 mmHg (IQR: 36.8-46.0 mmHg) and 41.0 mmHg (IQR: 38.1-43.8 mmHg), respectively. The mean bias was −0.69 mmHg

Table 1. Characteristics of Patients

Variable	*n* = 100
Age, median (IQR) years	70.5 (63-77)
Males/females, *n*	73/27
Respiratory disease	
ILD, *n*	54
COPD, *n*	18
Sarcoidosis, *n*	5
Lung cancer, *n*	4
Pneumonia, *n*	4
O_2 flow rate, L/m	
0, *n*	82
1-2, *n*	9
3-4, *n*	6
5-6, *n*	3
O_2 therapy device	
No device, *n*	82
Nasal cannula, *n*	15
O_2 mask, *n*	1
Reservoir nasal cannula, *n*	2
SpO_2, median (IQR) %	96 (95-97)
Respiratory rate, median (IQR)/min	14 (10-18)

IQR, interquartile range; ILD, interstitial lung disease; COPD, chronic obstructive pulmonary disease; SpO_2, saturation of percutaneous oxygen.

(95% CI: −2.66 to −1.28), and the LOA were −15.12 and 13.75 mmHg (Figure 3). The percent error was 35.32%. For 82 patients without O_2 supplementation, the median respiratory rate was 14/min (IQR: 10-16/min). The median levels of $EtCO_2$ and $PaCO_2$ were 37.0 mmHg (IQR: 42.0-45.0 mmHg) and 40.1 mmHg (IQR: 38.0-42.7 mmHg), respectively. The mean bias was −1.18 mmHg (95% CI: −2.60 to 0.24), with LOA of −13.82 and 11.46 mmHg, respectively. The percent error was 31.08% (Figure 4A). For 18 patients with O_2 supplementation, the median respiratory rate was 16/min (IQR: 12-20/min). The median levels of $EtCO_2$ and $PaCO_2$ were 39.0 mmHg (IQR: 31.3-43.0 mmHg) and 42.6 mmHg (IQR: 38.4-49.8 mmHg), respectively. The mean bias was 7.17 mmHg (95% CI: 1.72 to 12.61), with LOA of −14.29 and 28.62 mmHg, respectively. The percent error was 45.22% (Figure 4B).

DISCUSSION

In this study, we showed that $EtCO_2$ measured using the Capno-Eye® exhibited a moderate correlation (rho = 0.41) with the levels of $PaCO_2$ in patients with respiratory disease. The Bland–Altman analysis revealed that the LOA between $EtCO_2$ and $PaCO_2$ were relatively wide, both for patients with respiratory disease in general and for patients with ILD. For patients with O_2 supplementation, the discrepancy between the 2 measures was greater than for patients without O_2 supplementation.

Previous studies have reported a strong correlation between $EtCO_2$ and $PaCO_2$.[11,16] In our study, however, we observed only a moderate correlation. Barton et al.[11] showed that the correlation between $EtCO_2$ and $PaCO_2$ was strong in 76 patients who presented to the emergency department for care (r^2 = 0.772). Cinar et al.[16] showed a strong correlation between $EtCO_2$ and $PaCO_2$ (r = 0.91) in 162 patients who presented to the emergency department with acute dyspnea. In our study, the correlation between $EtCO_2$ and $PaCO_2$ (rho = 0.41) was relatively weaker than those reported in these previous studies.

Our Bland–Altman analysis revealed a smaller mean bias but wider LOA between the 2 measures than 2 other studies. One on patients under general anesthesia but without pulmonary disease found a mean bias of 6.0 mmHg, LOA of 0.3 and 11.8 mmHg, and a percent error of 18%.[15] The other, on emergency department patients, reported a mean bias of 0.5 mmHg and LOA of −10.5 and 9.5 mmHg.[16]

These differences may be the result of differences in the study populations. In our study, we included only patients with respiratory disease, and more than half of these had ILD. $EtCO_2$ is thought to be affected by various aspects of the patient's status, such as tachypnea, ventilation–perfusion inequality, and airway dead space in respiratory disease.[11,17] In patients with respiratory disease, these factors may affect the difference between $EtCO_2$ and $PaCO_2$. Similarly, Fujimoto et al.[14] reported wide LOA between these measures

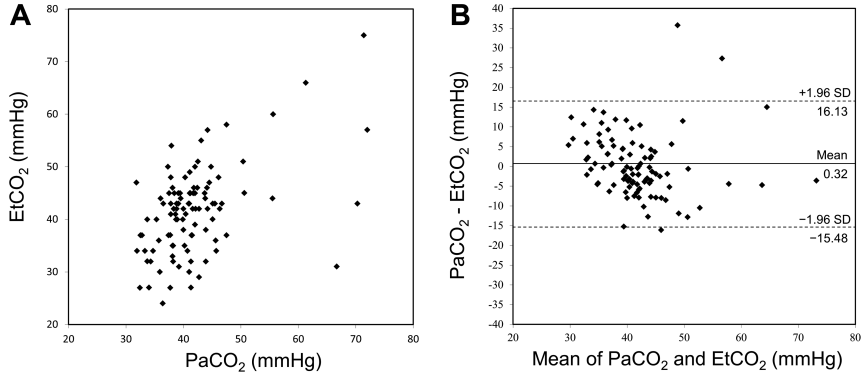

Figure 2. (A) Correlation between $EtCO_2$ and $PaCO_2$ in 100 patients with respiratory disease. (B) Bland–Altman plot showing the differences between $PaCO_2$ and $EtCO_2$ for the same patients. Mean bias = 0.32 mmHg (solid line); dashed lines indicate the upper and lower limits of agreement (± 1.96 times the standard deviation). $EtCO_2$, end-tidal carbon dioxide.

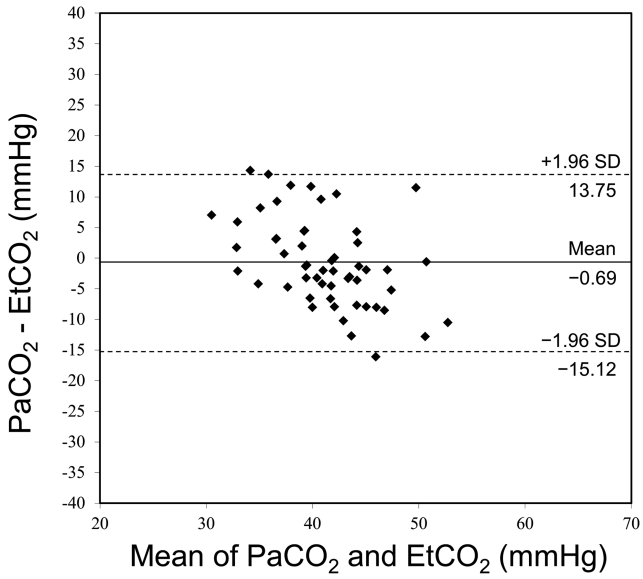

Figure 3. Bland–Altman plot showing the differences between $PaCO_2$ and $EtCO_2$ for 54 patients with ILD. Mean bias = −0.69 mmHg (solid line); dashed lines indicate the upper and lower limits of agreement (± 1.96 times the standard deviation). $EtCO_2$, end-tidal carbon dioxide; ILD, interstitial lung disease.

for patients with respiratory failure: −5.30 and 18.26 mmHg. It may thus be difficult to estimate $PaCO_2$ precisely by measuring $EtCO_2$ in patients with respiratory disease.

The LOA we observed for patients with ILD were also wider than those reported in previous studies.[15,16] This difference between $EtCO_2$ and $PaCO_2$ in these patients may be the result of several factors. First, ventilation-perfusion inequality increases in ILD, and this may partially explain the difference between the measures.[18] Another potential cause may be the effect of airway dead space. Tidal volume generally decreases in ILD, and patients may be less likely to produce a sufficiently large breath to provide an alveolar gas sample. It has been reported that the difference between $EtCO_2$ and $PaCO_2$ increases predictably with an increasing ratio of dead space to tidal volume, which supports our hypothesis.[20]

For patients with O_2 supplementation, the discrepancy between $PaCO_2$ and $EtCO_2$ was greater than for those without O_2 supplementation. The developer of the capnometer states that supplemental O_2 does not significantly affect the examination value at a flow of ≤2 L of nasal O_2.[14] However, Paul et al.[21] reported a significant inverse linear relationship between O_2 flow and $EtCO_2$ measurements taken using an $EtCO_2$-sampling cannula and mask. Although the CapnoEye® is different from the devices used in their study, cross-contamination between the O_2 flow and the expired respiratory gases may affect the $EtCO_2$ value. Based on this result, O_2 supplementation should be terminated to precisely assess $EtCO_2$ using a portable capnometer. In patients for whom it is not possible to discontinue O_2 supplementation, $EtCO_2$ measured using a portable capnometer should be interpreted with caution because its level may appear lower under O_2 supplementation. Furthermore, the LOA for patients with and without O_2 supplementation were wider than those reported in previous studies.[15,16] Regardless of O_2 supplementation, it may be difficult to estimate $PaCO_2$ precisely by measuring $EtCO_2$ in patients with respiratory disease. It is important to determine a suitable non-invasive measurement for the precise estimation of $PaCO_2$.

This study had some limitations. First, it was a retrospective study. However, we examined $EtCO_2$ and $PaCO_2$ in consecutive patients. Second, this study was conducted in a single

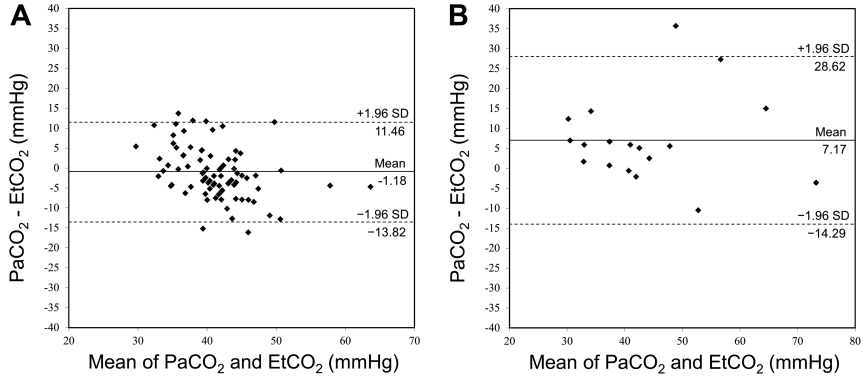

Figure 4. (A) Bland–Altman plot showing the differences between $PaCO_2$ and $EtCO_2$ for 82 patients without O_2 supplementation. Mean bias = −1.18 mmHg (solid line); dashed lines indicate the upper and lower limits of agreement (LOA) (±1.96 times the standard deviation (SD)). (B) Bland–Altman plot showing the differences between $PaCO_2$ and $EtCO_2$ for 18 patients with O_2 supplementation. Mean bias = 7.17 mmHg (solid line); dashed lines indicate the upper and lower LOA (±1.96 times the standard deviation (SD)). $EtCO_2$, end-tidal carbon dioxide.

center. Our center is a high-volume center; therefore, we were able to include patients with various respiratory diseases. Third, we could not examine the respiratory function or severity of the disease. Finally, we did not conduct a statistical calculation of the sample size.

In conclusion, in the clinical setting, the relationship between $EtCO_2$ and $PaCO_2$ was poor in patients with respiratory disease, especially in those receiving O_2 supplementation, compared with that reported in previous studies. It may be difficult to precisely estimate $PaCO_2$ by measuring $EtCO_2$ in patients with respiratory disease.

Ethics Committee Approval: This study was approved by Ethics committee of National Hospital Organization Kinki-Chuo Chest Medical Center, (Approval No: 664).

Informed Consent: We used an opt-out method, allowing patients and their families to refuse participation in the study.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – T.E., Y.M., Y.A., S.K., Y.I.; K.A., Y.I.; Design – T.E., Y.M., Y.A., S.K., Y.I.; K.A., Y.I.; Supervision – Y.M., Y.I.; Data Collection and/or Processing – T.E., Y.M., Y.A., S.K., Y.I.; K.A., K.K., N.T.; Analysis and/or Interpretation – T.E., Y.M., Y.A., S.K., Y.I.; K.A., K.K., N.T., Y.I.; Literature Search – T.E., Y.M., Y.A., S.K., Y.I.; K.A.; Writing Manuscript – T.E., Y.M., Y.A., S.K., Y.I.; K.A., Y.I.; Critical Review – T.E., Y.M., Y.I.

Conflict of Interest: Dr. Inoue received honoraria as an advisor and member of the steering committees of Boehringer Ingelheim, Shionogi, Asahi Kasei, and Savara. Dr. Inoue received a grant from Japan Agency for Medical Research and Development and the Japanese Ministry of Health, Labour, and Welfare. The other authors have no conflict of interest to declare.

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