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【 ORIGINAL ARTICLE 】

Usefulness of Measurement of End-tidal CO_2 Using a Portable Capnometer in Patients with Chronic Respiratory Failure Receiving Long-term Oxygen Therapy

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Abstract:

Objective Patients with chronic respiratory failure requiring long-term oxygen therapy (LTOT) are at a risk of CO_2 retention because of excessive oxygen administration. The CapnoEye™ is a novel portable capnometer that can measure end-tidal CO_2 ($EtCO_2$) noninvasively. This retrospective study evaluated the usefulness of this device.

Methods $EtCO_2$ was measured using the CapnoEye™. The $EtCO_2$ and partial pressure of venous carbon dioxide ($PvCO_2$) were analyzed, and other clinical data were assessed.

Patients Sixty-one consecutive patients with chronic respiratory failure receiving LTOT in the outpatient department at the Japanese Red Cross Medical Center between July 2017 and March 2018 were retrospectively reviewed.

Results There was a significant correlation between $EtCO_2$ and $PvCO_2$ (r=0.63) in the total study population as well as in the COPD group (r=0.65) and ILD group (r=0.67). The $PvCO_2$ and $EtCO_2$ gradient was correlated with only the body mass index in a multivariate analysis (p=0.0235). The $EtCO_2$ levels on the day of admission were significantly higher than those in the same patients when they were in a stable condition (p=0.0049). There was a significant correlation between $\Delta EtCO_2$ and $\Delta PvCO_2$ (r=0.4). A receiver-operating characteristic curve analysis revealed the optimal cut-off $EtCO_2$ value for identifying hypercapnia to be 34 mmHg (p=0.0005).

Conclusion The evaluation of $EtCO_2$ by the CapnoEye™ was useful for predicting $PvCO_2$. The body mass index was identified as a possible predictor of the $PvCO_2$ and $EtCO_2$ gradient. An increase in $EtCO_2$ may indicate deterioration of the respiratory status in patients with chronic respiratory failure receiving LTOT.

Key words: CapnoEye™, long-term oxygen therapy, end-tidal CO_2, portable capnometer, chronic obstructive pulmonary disease, interstitial lung disease

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Introduction

Supplemental long-term oxygen therapy (LTOT) improves the survival, exercise capacity, and quality of life in patients with chronic obstructive pulmonary disease (COPD) and hypoxemia (1) as well as in those with sequelae of tuberculosis (2). LTOT has also been reported to improve the quality of life in patients with chronic interstitial lung disease (ILD) (3). The number of patients receiving LTOT has increased in Japan (4) and is likely to continue to increase because of the aging population.

According to the Global Initiative for Chronic Obstructive Lung Disease guideline, LTOT is indicated in patients who have a PaO_2 ≤55 Torr or an SaO_2 ≤88% with or without hypercapnia and in those with a PaO_2 of 55-60 Torr or an SaO_2 of 88% if there is evidence of pulmonary hypertension suggesting congestive heart failure (1).

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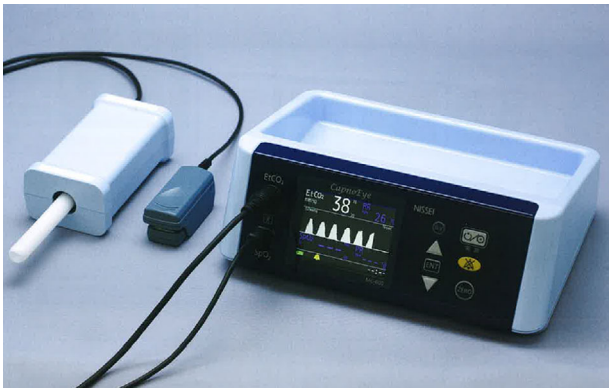

Figure 1. The CapnoEye™ capnometer. The CapnoEye™ can measure $EtCO_2$ six times during spontaneous breathing. The $EtCO_2$ is measured while holding the $EtCO_2$ sensor with the hand opposite to the one with the SpO_2 sensor attached and placing the mouthpiece in the mouth. $EtCO_2$, end-tidal carbon dioxide.

After oxygen therapy is started, blood gases should be checked to ensure that oxygenation is satisfactory without retention of CO_2 and/or worsening acidosis. An American Thoracic Society/European Respiratory Society position paper reported that an arterial blood gas (ABG) analysis was the preferred method for determining the need for oxygen, as it includes acid-base information (5). Patients with chronic respiratory failure who need LTOT are at risk of CO_2 retention as a result of the administration of excessive oxygen; therefore, it is important to monitor the blood CO_2 level regularly. However, the evaluation of the blood CO_2 level every time a patient visits the outpatient department is difficult because blood gas sampling is invasive and painful.

End-tidal CO_2 ($EtCO_2$), which is measured using a capnometer, is positively correlated with blood CO_2 (6) and is now part of the standard of care for all mechanically ventilated patients receiving general anesthesia and routine monitoring in intensive-care settings (7). In July 2018, the CapnoEye™ MC600 (Nissei, Osaka, Japan), a novel capnometer that measures the $EtCO_2$ level correctly in patients who are breathing spontaneously (Fig. 1), was approved for use in Japan, but its clinical value in patients receiving LTOT remains unclear.

The blood CO_2 levels need to be measured noninvasively in outpatients with chronic respiratory failure because of the difficulties inherent in routine measurement of blood arterial CO_2. The aim of this study was to evaluate the ability of the CapnoEye™ MC600 to measure $EtCO_2$ and to assess the relationship between $EtCO_2$ and the PCO_2 level in patients receiving LTOT.

Materials and Methods

The study protocol was approved on June 1, 2018, by our institutional review board (approval number 680). The requirement for written informed consent was waived due to the use of an opt-out method (8). The study population consisted of 61 consecutive outpatients with chronic respiratory failure who received LTOT and underwent blood sampling between July 2017 and March 2018.

$EtCO_2$ measurements

The mainstream $EtCO_2$ level was measured using the CapnoEye™. Patients performed a tidal volume (TV) maneuver with the mouthpiece at a constant flow rate and in a relaxed position six times while holding the $EtCO_2$ sensor with the hand opposite to the one with the SpO_2 sensor attached. The $EtCO_2$ was analyzed automatically as the average of the readings obtained during the six TV maneuvers and displayed on the monitor. The measurements were supported by experienced technicians in all cases.

Data collection

The flow of the enrolled patients throughout the study is shown in Fig. 2. Between July 2017 and March 2018, 89 patients who visited our outpatient department and received LTOT were considered for enrollment. Twenty-eight patients were excluded because a lack of either $EtCO_2$ or partial pressure of venous carbon dioxide ($PvCO_2$) data, thus leaving 61 patients for inclusion in the study. The correlations between $EtCO_2$, $PvCO_2$, and pulmonary function tests were analyzed in these 61 patients (Method 1). Forty of these patients were excluded because they were not admitted for an observation period, thereby leaving 21 patients who had been admitted for additional analysis. The baseline data for these 21 patients were collected when they were in a stable condition, i.e., with stable vital signs, a normal level of consciousness, and an assessment of at least one month before the most recent admission. The $EtCO_2$ data at baseline were compared with those obtained during the admission period and correlations between $\Delta EtCO_2$, $\Delta PvCO_2$, and pulmonary function tests were sought (Method 2).

Pulmonary function tests were performed using a rolling seal-type spirometer (Fudac-77; Fukuda Denshi, Tokyo, Japan). The medical records of each patient were also reviewed.

Statistical analyses

Correlations were analyzed using the Spearman's rank correlation coefficient. The change in the $EtCO_2$ level according to the respiratory status in the same patients was analyzed using Wilcoxon's signed rank test. A multiple regression analysis was used to predict the values of dependent and independent variables. Logistic regression and receiver-operating characteristic curve analyses were used to evaluate the diagnostic performance of $EtCO_2$. The descriptive data are shown as the median, frequency, and percentage. All reported p-values are two-sided. The data were analyzed using the JMP 9 software program, version 9.0.3 (SAS Institute, Cary, USA). A p value <0.05 was considered statistically significant.

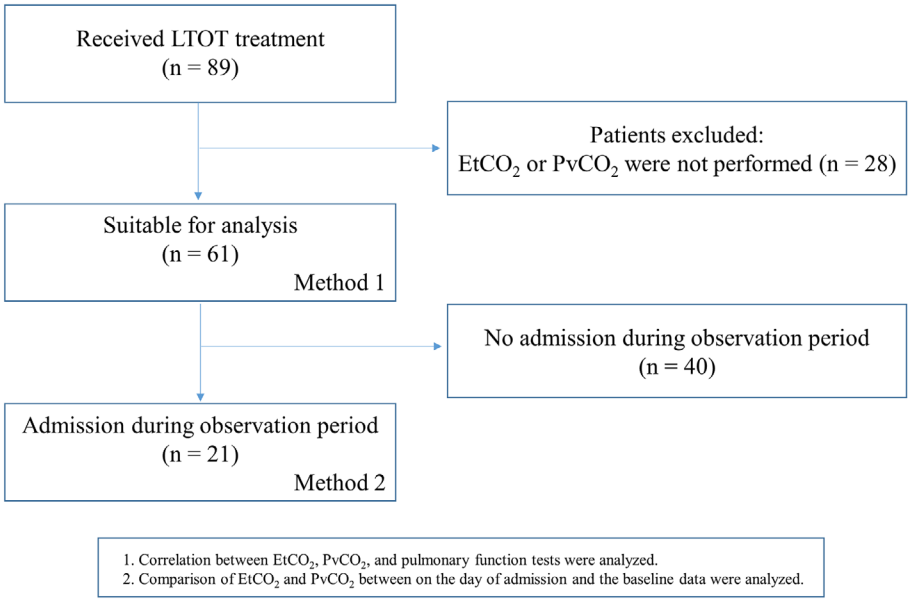

Figure 2. Consort flow diagram. Of the 89 patients screened, 28 were excluded because neither the $EtCO_2$ or $PvCO_2$ measurements were recorded, thus leaving 61 patients for enrolment in the study (Method 1). Next, a further 40 patients were excluded because they were not admitted during the observation period, thereby leaving 21 patients who had been admitted for further analysis (Method 2).

Results

The characteristics of the 61 patients [36 men, 25 women; median age 74 (34-96) years old] who received LTOT at our hospital during the study period are shown in Tables 1 and 2. All patients had a Glasgow Coma Scale score >13, indicating a clear consciousness level. None of the patients were ventilated via tracheostomy. Eight patients required noninvasive positive pressure ventilation for COPD, ILD, or sequelae of tuberculosis. Fifty-four patients required oxygen therapy for 24 hours, and 7 required it only when sleeping or on exertion.

The underlying diseases were COPD in 31 patients, ILD in 17, sequelae of tuberculosis in 6, and other lung disease in 7. No patient had chronic kidney disease. The median $EtCO_2$ was 31 (18-41) mmHg and the median $PvCO_2$ was 49 (25-75) mmHg. On pulmonary function testing, the patients had a median FEV_1 of 1.32 (0.43-3.01) L, a $\%FEV_1$ of 54% (25-132%), an FVC of 2.14 (0.6-4.7) L, and a %FVC of 77% (31-134%). The patient characteristics are shown according to sex in Table 1. There were significant differences in the smoking history, FVC, $FEV_1\%$, and underlying diseases between the study groups.

There were significant correlations between $EtCO_2$ and $PvCO_2$ (r=0.63), FEV_1 (r=-0.44), $\%FEV_1$ (r=-0.36), FVC (r =-0.54), and %FVC (r=-0.64) and between $\%FEV_1$ and % FVC (r=0.52; Fig. 3). A multivariate linear regression analysis was performed to determine if $PvCO_2$ could be predicted on the basis of $EtCO_2$, $\%FEV_1$, and %FVC. The findings were statistically significant for $EtCO_2$ [regression coefficient beta, 0.63; 95% confidence interval (CI) 0.58-1.48, p<0.001] and $\%FEV_1$ (regression coefficient beta, -0.3; 95% CI -0.22--0.02, p=0.0189) but not for %FVC (regression coefficient beta, -0.11; 95% CI -0.07-0.16, p=0.458). There was a significant correlation between $EtCO_2$ and $PvCO_2$ in patients with COPD (r=0.5) and in those with ILD (r=0.63; Fig. 4).

There were significant correlations between the $PvCO_2$ and $EtCO_2$ gradient and the body mass index (BMI; r=-0.35) and $\%FEV_1$ (r=-0.33); however, there was no significant correlation with the TV (r=-0.14) or %FVC (r=-0.08; Fig. 5). A multivariate linear regression analysis was performed to predict the $PvCO_2$ and $EtCO_2$ gradient based on the BMI and $\%FEV_1$. The results were statistically significant for the BMI (regression coefficient beta, -0.34; 95% CI -1.16, -0.09, p= 0.0235) but not for $\%FEV_1$ (regression coefficient beta, -0.021; 95% CI -0.15, 0.02, p=0.1476).

The median time interval between the first visit and the day of admission was 2 (1-24) months. The $EtCO_2$ levels on the day of admission were significantly higher than those in the same patients when they were in a stable condition (p= 0.0049; Fig. 6). Furthermore, there were significant correlations between $\Delta EtCO_2$ and $\Delta PvCO_2$ (r=0.4), TV (r=0.43), $\%FEV_1$ (r=-0.4), and %FVC (r=-0.45; Fig. 7) in the study population overall. However, there was no statistically significant difference between the $EtCO_2$ level on the day of admission and that in a stable condition in the COPD and ILD groups.

The receiver-operating characteristic curve for $EtCO_2$ predicting hypercapnia as $PvCO_2$>45 mmHg is shown in Fig. 8A. The area under the curve was 0.849 for $EtCO_2$. The optimum $EtCO_2$ cut-off point for identifying hypercapnia

Table 1. Demographic and Clinical Characteristics of the 61 Patients in the Study at Baseline.

	All (n=61)	Male (n=36)	Female (n=25)	p value
Age, years	74 (34-96)	75.5 (54-90)	72 (34-96)	0.7579
Smoking history, pack years	7 (0-160)	50 (0-160)	0 (0-88.5)	<0.0001
Body mass index	19 (12-39)	20.5 (14-32.6)	17.6 (12-39)	0.1164
$EtCO_2$, mmHg	31 (18-41)	34.5 (18-48)	37 (25-53)	0.2013
$PvCO_2$, mmHg	49 (25-75)	50 (25-75)	48 (33-72)	1
$PvCO_2$- $EtCO_2$	15 (-1.4, 34)	15 (-1.4, 34)	14.5 (8.5-26)	0.3589
FEV_1, L	1.32 (0.43-3.01)	1.15 (0.43-3.01)	1.4 (0.55-1.99)	0.2674
%FEV_1, %	54 (25-132)	53.9 (25-131)	66.5 (34.9-132)	0.1964
FVC, L	2.14 (0.6-4.7)	2.58 (0.6-4.7)	1.56 (0.79-2.96)	0.0057
%FVC, %	77 (31-134)	79 (31.2-134)	64.5 (39-129)	0.2184
FEV_1%, %	66.1 (23-97)	62 (23-88)	73.1 (61-97)	0.0084
TV, L	0.66 (0.21-1.4)	0.72 (0.21-1.4)	0.48 (0.37-1.17)	0.176
Oxygen flow rate at rest	2 (0-5)	2 (0-5)	2 (0-4)	0.8577
NPPV, n (%)	8	6	2	0.6363
IPAP, cmH_2O	9 (0-12)	8 (0-12)	11 (8-11)	0.4478
EPAP, cmH_2O	4 (4-8)	4 (4-8)	4	0.3291
Admission, n (%)	21	14	7	0.3606
$\Delta EtCO_2$, mmHg)	4 (-8, 16)	0 (-8, 16)	7.5 (-3, 13)	0.0543
$\Delta PvCO_2$, mmHg)	5 (-5, 21)	4 (-5, 21)	7 (-1.7, 12)	0.6926
Underlying diseases, n (%)				
COPD	31 (50.8)	23 (37.7)	8 (13.1)	0.0143
ILD	17 (27.9)	8 (13.1)	9 (14.8)	0.2379
TBsq	6 (9.8)	5 (8.2)	1 (1.6)	0.2021
Other disease	7 (11.5)	0	7 (11.5)	0.0007

The data are presented as the median (range) or number (percentage). COPD: chronic obstructive pulmonary disease, EPAP: expiratory positive airway pressure, $EtCO_2$: end-tidal carbon dioxide, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, ILD: interstitial lung disease, IPAP: inspiratory positive airway pressure, NPPV: noninvasive positive pressure ventilation, $PvCO_2$: partial pressure of venous carbon dioxide, TBsq: sequelae of tuberculosis, TV: tidal volume

was 34 mmHg (sensitivity 79.1%, specificity 88.9%). The receiver-operating characteristic curve for $EtCO_2$ predicting hypercapnia as $PvCO_2$ >70 mmHg is shown in Fig. 8B. The area under the curve was 0.806, and the optimum cut-off point was 38 mmHg for $EtCO_2$ (sensitivity 100%, specificity 69.1%).

Discussion

This is the first report on the value of $EtCO_2$ as measured by the CapnoEye™ in patients with chronic respiratory failure receiving LTOT. There was a significant correlation of $EtCO_2$ with $PvCO_2$ and an association of the $PvCO_2$ and $EtCO_2$ gradient with BMI. The $EtCO_2$ cut-off level of 34 mmHg was useful for predicting CO_2 retention and deterioration of respiratory status in the outpatient department.

$EtCO_2$ measurements obtained by a capnometer have been widely accepted as a sensitive method for reflecting the $PaCO_2$ level in intubated and mechanically ventilated patients. However, few studies have investigated the usefulness of $EtCO_2$ in patients who are breathing spontaneously (9-11). One of the reported advantages of capnometry is its ability to obtain a reliable estimate of $EtCO_2$ during a vital capacity maneuver in patients with chronic respiratory disease who are breathing spontaneously (9). In the present study, the $EtCO_2$ value was measured using the CapnoEye™ during a TV maneuver and compared with that obtained during a vital capacity maneuver; the TV maneuver is easy for patients with respiratory failure to perform because it needs only spontaneous breathing.

It is well known that $PaCO_2$ is the gold standard for the evaluation of hypercapnia; however, $PvCO_2$ has also been reported to have good concordance with $PaCO_2$ and to be a reliable, feasible, and safe alternative to repeated ABG analyses in patients with severe hypoxemic and/or hypercapnic respiratory failure (12). Therefore, $PvCO_2$ was thought to be a useful surrogate marker of $PaCO_2$ for the evaluation of hypercapnia in the present study.

The correlation of $EtCO_2$ and $PaCO_2$ has been reported to be unreliable in some clinical situations, and no correlation was found between $EtCO_2$ and $PaCO_2$ when the physiologic dead space was substantially elevated (13-19). Physiologic dead space ventilation is the sum of the anatomic dead space from the conducting airways and the alveolar dead space arising from a disease process and/or therapy.

The $EtCO_2$ level is normally 5 mmHg lower than that of $PaCO_2$ because of the mixing of CO_2 containing alveolar gas and gas devoid of CO_2 from the anatomic dead space (20).

Table 2. Baseline Characteristics of Patients with COPD, ILD and Other Diseases.

	COPD (n=31)	ILD (n=17)	Other diseases (n=13)	p value
Age, years	75 (41-96)	72 (54-87)	74 (34-90)	0.4985
Sex, n (%)				
Male	23	8	5	0.0444
Female	8	9	8	
Smoking history, pack years	50 (0-150)	0 (0-160)	0	<0.0001
Body mass index	21 (14-28.2)	18.9 (12-39)	16.2 (14.1-19.5)	0.0079
$EtCO_2$, mmHg	34 (18-46)	36 (27-50)	42 (30-53)	0.0083
$PvCO_2$, mmHg	47 (25-75)	46 (37-72)	62 (44-73)	0.0064
$PvCO_2$- $EtCO_2$	13 (-1.4, 34)	8.5 (8-28)	19.5 (14-26)	0.075
FEV_1, L	1.14 (0.43-2.84)	1.81 (0.65-3.01)	0.77 (0.43-1.99)	0.0128
%FEV_1, %	54 (25-132)	100 (34.9-131)	46.9 (37.7-73)	0.0026
FVC, L	2.6 (0.82-4.7)	2.08 (0.98-3.39)	0.93 (0.6-3.06)	0.0015
%FVC, %	80.4 (40-134)	85.4 (41-111)	41.2 (31.2-65)	0.0006
FEV_1%, %	60.5 (23-84)	78.5 (64.3-97)	74.7 (53.2-88.9)	<0.0001
TV, L	0.72 (0.37-1.4)	0.81 (0.28-1.18)	0.45 (0.21-0.81)	0.0052
Oxygen flow rate at rest	2 (0-5)	2 (0-4)	2 (1-4)	0.8734
NPPV, n (%)	3	1	4	0.013
IPAP	10 (0-12)	0	9.5 (8-11)	0.2336
EPAP	4 (4-8)	7	4	0.2401
Admission, n (%)	10	3	8	0.1815
Δ$EtCO_2$, mmHg	1 (-8, -14)	-4 (-6, -4)	7.5 (-2, -16)	0.0755
Δ$PvCO_2$, mmHg	6 (0-12)	-1.7 (-5, -3)	7 (-1, -21)	0.0716

The data are presented as the median (range) or number (percentage). COPD: chronic obstructive pulmonary disease, EPAP: expiratory positive airway pressure, $EtCO_2$: end-tidal carbon dioxide, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, ILD: interstitial lung disease, IPAP: inspiratory positive airway pressure, NPPV: noninvasive positive pressure ventilation, $PvCO_2$: partial pressure of venous carbon dioxide, TV: tidal volume

In patients with lung disease, the additional alveolar dead space further dilutes the $EtCO_2$ relative to the $PaCO_2$ (20). For example, the normal ratio of the physiologic dead space to TV (VD/VT) is 0.2-0.35 (21) but has been found to be 0.4-0.55 in patients with acute lung injury as a result of the additional alveolar dead space (22).

In the present study, the BMI was the only factor found to have a negative effect on the $PvCO_2$ and $EtCO_2$ gradient in a multivariate analysis, with no significant effect of TV. These findings are similar to those of Ickx et al., who found that the $PaCO_2$ and $EtCO_2$ gradient was negatively correlated with weight in small children and attributed this finding to the high ratio of dead space to TV (V_D/V_T) (23). Therefore, in the present study, the $PvCO_2$ and $EtCO_2$ gradient may have been correlated with dead space.

In general, in patients with COPD, progressive airflow limitations and emphysematous destruction were considered to increase the alveolar dead space, which might have caused the inequality in the ventilation/perfusion (V/Q) ratio. However, Sandek et al. found no significant correlation between the air flow obstruction measured by spirometry and the V/Q ratio (24). In the present study, %FEV_1 was not a significant independent predictor of the $PvCO_2$ and $EtCO_2$ gradient. This finding is consistent with a previous speculation that inequality in the V/Q ratio might be buffered by underlying pathophysiological processes, including hypoxic vasoconstriction and active collateral ventilation (24, 25).

The positive mechanical pressure used when measuring $EtCO_2$ in intubated and mechanically ventilated patients might increase the ventilation of the atelectatic lobe and reduce intravascular pulmonary fluid iatrogenically, leading to a V/Q mismatch and additional alveolar dead space (26). The mechanical dead space added by the endotracheal tube might further increase the $PvCO_2$ and $EtCO_2$ gradient. In our study, the exclusion of mechanically ventilated patients resulted in a reduction in dead space ventilation and might explain the strong correlation found between $PvCO_2$ and $EtCO_2$ even in patients with chronic respiratory failure.

$EtCO_2$ was correlated with both FEV_1 and FVC in this study. There has been a similar report of a significant correlation of FEV_1 with $EtCO_2$ measured using a capnometer (11, 12); however, to our knowledge, this is the first report of a correlation between $EtCO_2$ and FVC. Although the mechanism underlying the elevation of $EtCO_2$ in response to decreases in FEV_1 remains unclear, a reduced FEV_1 value is associated with the severity of obstructive lung disease, and obstruction of the terminal bronchi has been cited as a reason for hypoventilation of the alveoli and a cause of CO_2 retention (27, 28). In the present study, FVC was strongly correlated with FEV_1, so FEV_1 may be a confounding factor that influenced the correlation between $EtCO_2$ and FVC.

$EtCO_2$ has previously been reported to be correlated with PCO_2 in patients with COPD (9); however, there has been no study of the correlation between $EtCO_2$ and PCO_2 in pa-

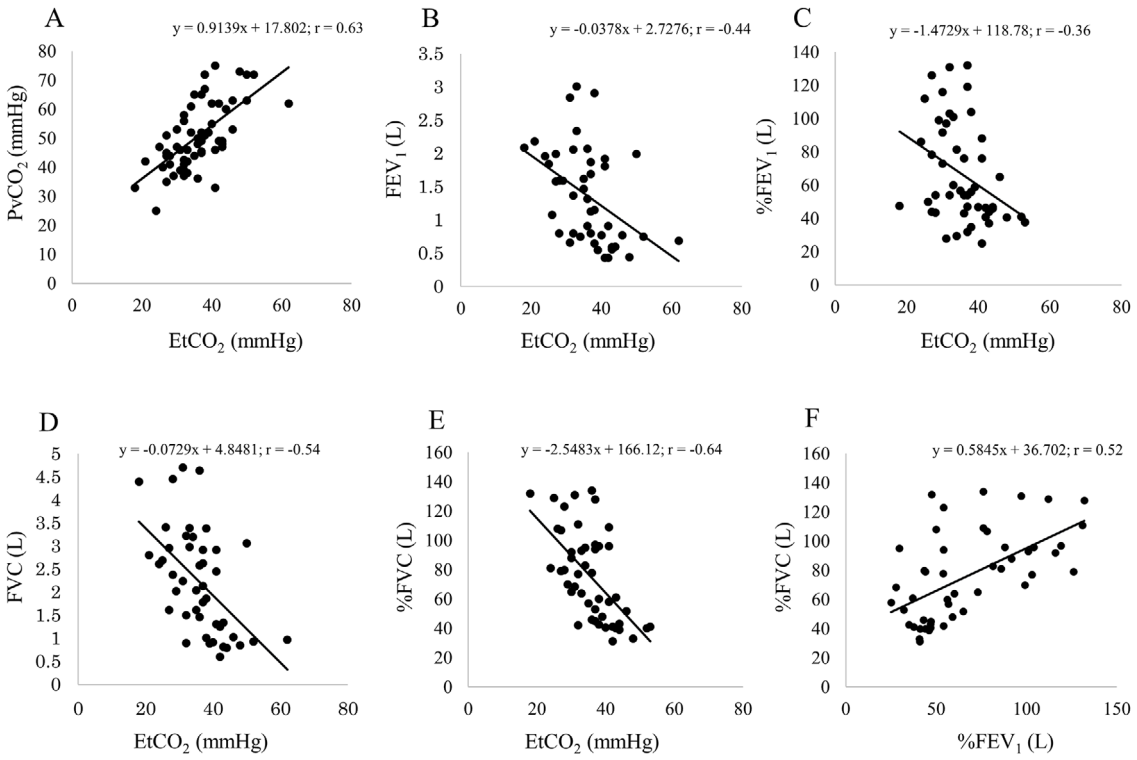

Figure 3. **Correlations of $EtCO_2$ with pulmonary function test results. $EtCO_2$ was measured in outpatients with chronic respiratory failure who were receiving long-term oxygen therapy. (A) There was a significant positive correlation of $EtCO_2$ with $PvCO_2$ (r=0.63) and (B) a significant negative correlation of $EtCO_2$ with FEV_1 (r=-0.44), (C) %FEV_1 (r=-0.36), (D) FVC (r=-0.54), and (E) %FVC (r=-0.64). (F) There was a significant positive correlation of %FEV_1 with %FVC (r=0.52). COPD: chronic obstructive pulmonary disease, $EtCO_2$: end-tidal carbon dioxide, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, ILD: interstitial lung disease, $PvCO_2$: partial pressure of venous carbon dioxide**

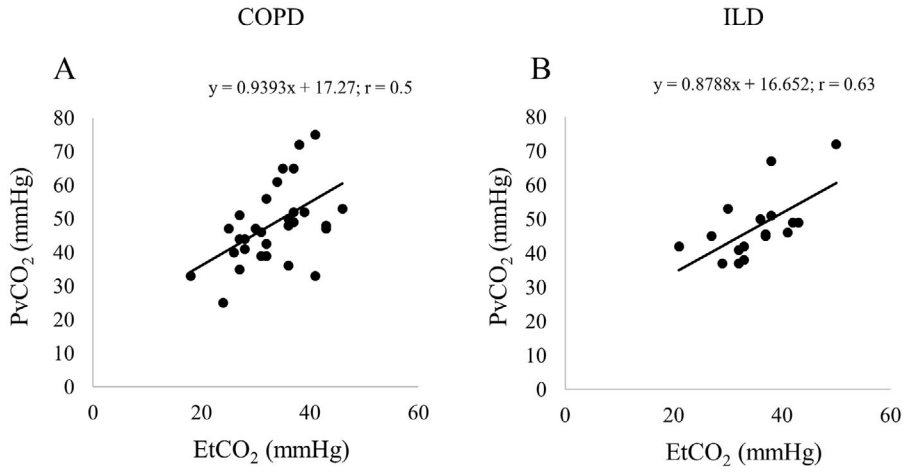

Figure 4. **Correlations of $EtCO_2$ with $PvCO_2$ in outpatients with COPD or ILD. There was a significant positive correlation of $EtCO_2$ with $PvCO_2$ in (A) outpatients with COPD (r=0.5) and (B) with ILD (r=0.63). COPD: chronic obstructive pulmonary disease, $EtCO_2$: end-tidal carbon dioxide, ILD: interstitial lung disease, $PvCO_2$: partial pressure of venous carbon dioxide**

tients with ILD. In this study, $EtCO_2$ was confirmed to be correlated with $PvCO_2$ not only in patients with COPD but also in those with ILD. This finding highlights the value of $EtCO_2$ for predicting hypercapnia in both obstructive and restrictive lung disease.

$EtCO_2$ on the day of admission was significantly higher than that recorded when the patients were in a stable condition. The $\Delta EtCO_2$ was correlated with the $\Delta PvCO_2$, suggest-

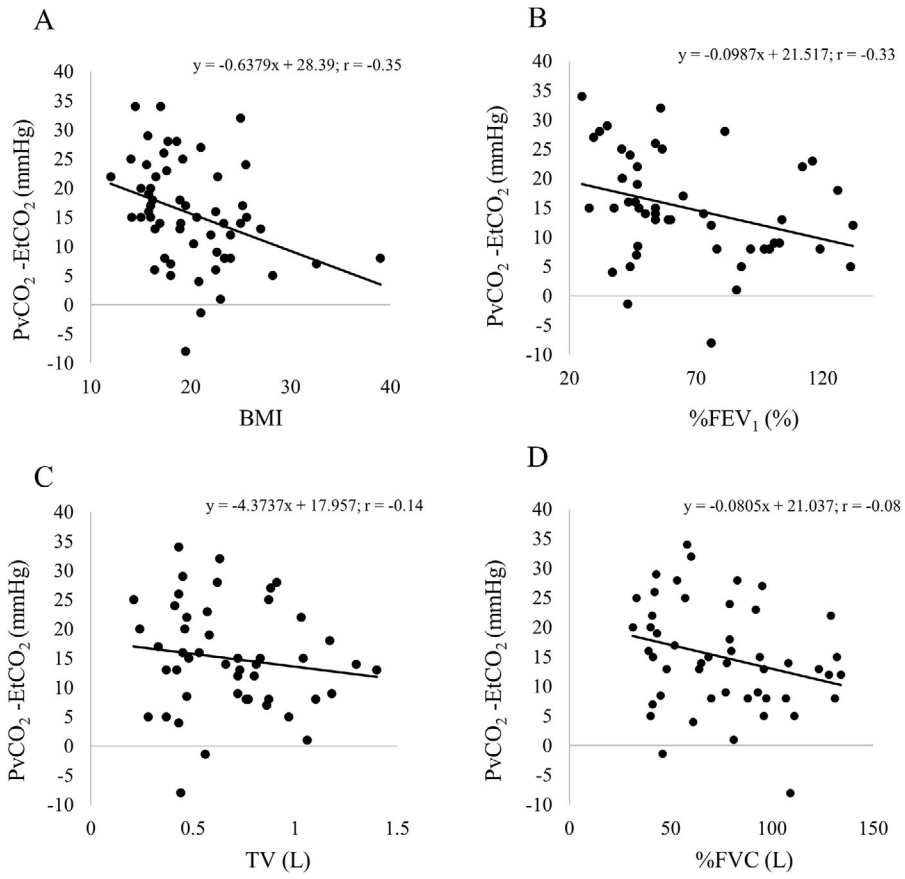

Figure 5. **Correlations of the $PvCO_2$ and $EtCO_2$ gradient with the BMI and pulmonary function test results. (A) There was a significant negative correlation of the $PvCO_2$ and $EtCO_2$ gradient with the BMI (r=-0.35) and (B) %FEV_1 (r=-0.33) and (C) no significant correlation of the $PvCO_2$ and $EtCO_2$ gradient with the TV (r=-0.14) or (D) %FVC (r=-0.08). $EtCO_2$: end-tidal carbon dioxide, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, $PvCO_2$: partial pressure of venous carbon dioxide, TV: tidal volume**

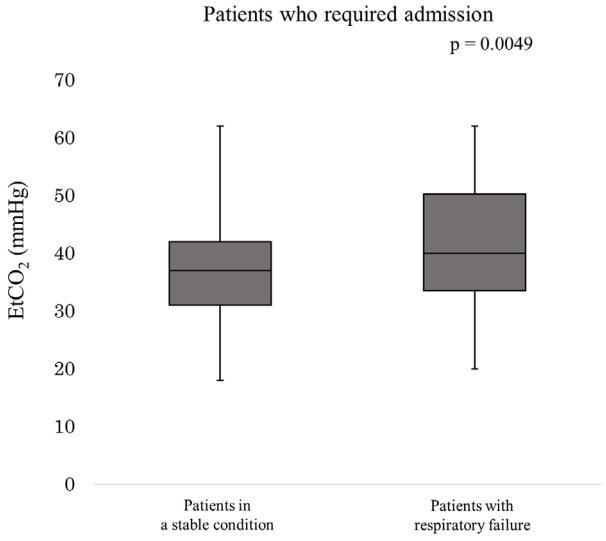

Figure 6. **A comparison of $EtCO_2$ between patients who were admitted to the hospital according to their respiratory status. The $EtCO_2$ was significantly higher in patients with respiratory failure who were admitted immediately after measurement of $EtCO_2$ than in the same patients when they were in a stable condition (p=0.0049). $EtCO_2$: end-tidal carbon dioxide**

ing that elevation of $EtCO_2$ may be a sign of an increasing $PvCO_2$ level over time. The patients in our study were in an unstable respiratory condition when they were admitted and unable to undergo respiratory function testing. However, $EtCO_2$ was measured successfully in these patients using the CapnoEye™ because the protocol required for the TV maneuver is much easier to perform than that for the VC maneuver, regardless of the respiratory status. Furthermore, the FEV_1, FVC, and TV values measured when the patients were in a stable condition were negatively correlated with the $\Delta EtCO_2$ and $\Delta PvCO_2$. Therefore, we assume that the elevation of the CO_2 level was easier to observe in patients with an impaired lung function than in those with a preserved lung function. The regular measurement of $EtCO_2$ on an outpatient basis using the CapnoEye™ may help detect deterioration of the respiratory status and the need for hospital admission in patients with respiratory failure.

It is well known that CO_2 retention depresses awareness, even to the point of total loss of consciousness, so monitoring the blood CO_2 level is an important component of the patient assessment. Previous studies that used $PvCO_2$ to screen for potential hypercapnia found that it had a sensitiv-

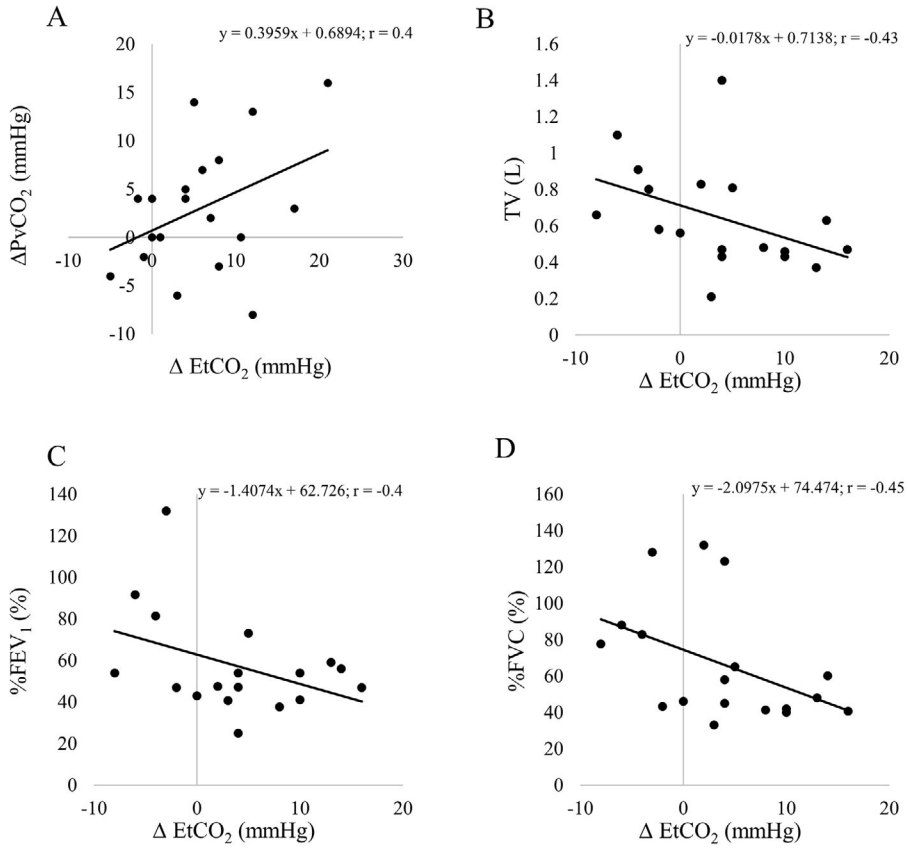

Figure 7. **Correlations of $\Delta EtCO_2$ with $\Delta PvCO_2$ and pulmonary function test results. (A) There was a significant positive correlation of $\Delta EtCO_2$ with $\Delta PvCO_2$ (r=-0.4) and a significant negative correlation of $\Delta EtCO_2$ with the (B) TV (r=-0.43), (C) $\%FEV_1$ (r=-0.4), and (D) %FVC (r=-0.45). $EtCO_2$: end-tidal carbon dioxide, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, $PvCO_2$: partial pressure of venous carbon dioxide, TV: tidal volume**

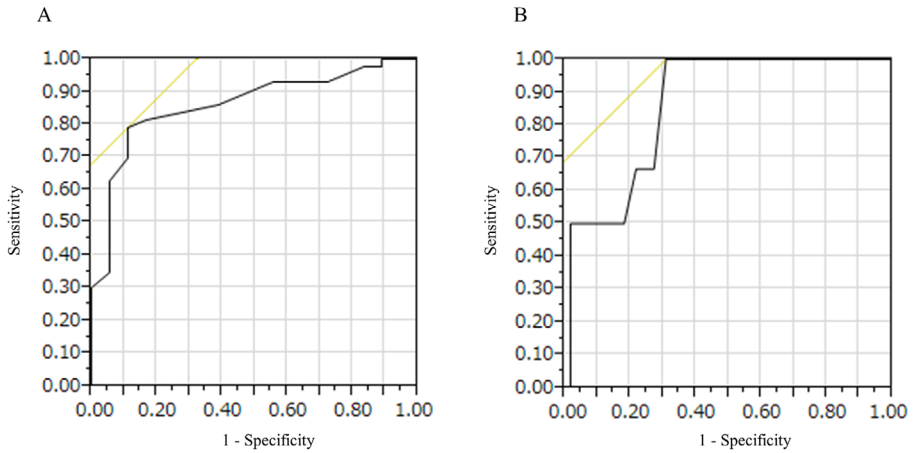

Figure 8. **Ability of the receiver-operating characteristic curve of $EtCO_2$ to predict hypercapnia. (A) A plot of the $EtCO_2$ curve for the prediction of hypercapnia defined as $PvCO_2$ >45 mmHg with an area under the curve of 0.849. (B) A plot of the $EtCO_2$ curve for the prediction of hypercapnia defined as a $PvCO_2$ of >70 mmHg with an area under the curve of 0.806.**

ity of 79% when a cut-off point of >45 mmHg was used (29). Therefore, the screening cut-off in the present study was defined as a $PvCO_2$ of >45 mmHg, and the optimum cut-off point for hypercapnia was set at an $EtCO_2$ of > 34 mmHg. Furthermore, the elevation of $PaCO_2$ to >70-75 mmHg has been reported to reduce the level of awareness (30). An $EtCO_2$ of >38 mmHg was shown to be a possible biomarker of a $PvCO_2$>70 mmHg. By determining the cut-off point for $EtCO_2$, the evaluation of the increase in $EtCO_2$ over time may be able to predict the exacerbation of

respiratory failure, thereby allowing for the early treatment and avoidance of admission.

Several limitations associated with the present study warrant mention, including its retrospective design, single-institution setting, small sample size, and inclusion of patients who needed differing oxygen flow rates. Furthermore, $PvCO_2$ was measured instead of $PaCO_2$, and the difference between the venous and arterial CO_2 levels may be influenced by the cardiac output and tissue consumption; therefore, our ability to evaluate the correlation between $EtCO_2$ and $PaCO_2$ accurately was limited. Other limitations that restricted our ability to evaluate the usefulness of $EtCO_2$ in patients with a deteriorating respiratory status included the lack of clinical data besides $EtCO_2$ and $PvCO_2$ in patients who required hospital admission. Finally, the CapnoEye™ can only evaluate $EtCO_2$ in patients who are alert and breathing spontaneously and is thus unsuitable for use with patients who are unconscious.

Conclusion

This is the first study to demonstrate the correlation of $EtCO_2$ and $PvCO_2$ with the pulmonary function in spontaneously breathing patients with chronic respiratory failure. Repeated $EtCO_2$ measurements were obtained noninvasively by the CapnoEye™. The CapnoEye™ was convenient and useful for estimating $PvCO_2$. The BMI was identified as a possible predictor of the $PvCO_2$ and $EtCO_2$ gradient. An increase in $EtCO_2$ to >34 mmHg may indicate the deterioration of the respiratory status in patients with chronic respiratory failure receiving LTOT.

The authors state that they have no Conflict of Interest (COI).

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