

The Importance of Stabilizing PaCO₂ during Long-term Non-invasive Ventilation in Subjects with COPD

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Abstract

Objective In subjects with chronic obstructive pulmonary disease (COPD), the effect of partial pressure of CO₂ (PaCO₂) alterations during long-term non-invasive ventilation (NIV) on continuance remains uncertain. We herein investigated the utility of PaCO₂ stability during long-term NIV as a prognostic outcome.

Methods We retrospectively assessed data from 54 subjects with COPD who received long-term NIV. The annual alteration in PaCO₂ during NIV was determined using a simple linear regression method for each subject who had at least two 6-month intervals of PaCO₂ data. Annual alterations in PaCO₂ during long-term NIV and probable confounders were examined, and long-term NIV discontinuation was the major outcome.

Results Data from 37 subjects who met the criteria were analyzed. PaCO₂ during long-term NIV increased slightly in 19 subjects (group 1, <2 mm Hg/y), and increased greatly in 18 subjects (group 2, >2 mmHg/y). In the multivariate modality model, smaller annual alterations in PaCO₂ ($p=0.009$) and lower PaCO₂ 6 months after the start of long-term NIV (6 m-PaCO₂) ($p=0.03$) were associated with a significantly higher probability of continuing NIV. The 2- and 5-year probabilities of continuing NIV were 89% and 66% for group 1 and 78% and 32% for group 2, respectively.

Conclusion A lower 6 m-PaCO₂ and a lower annual alteration of PaCO₂ during long-term NIV are significant predictive variables for patients with COPD.

Key words: chronic respiratory failure, hypercapnia, home mechanical ventilation, non-invasive ventilation, partial pressure of carbon dioxide, COPD

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Introduction

Over the last three decades, home non-invasive ventilation (NIV) has been extensively used to treat subjects with chronic hypercapnic ventilatory failure (1-4). Nocturnal high-intensity NIV aimed to reduce the partial pressure of CO₂ (PaCO₂) to a near-normal range has been shown to improve daytime arterial blood gases (ABGs) and achieve a high continuation rate in patients with stable hypercapnic chronic obstructive pulmonary disease (COPD) (5, 6). We previously demonstrated that subjects with a relatively low PaCO₂ a few months after beginning NIV maintained rela-

tively low PaCO₂ levels for several years and that PaCO₂ levels a few months after NIV initiation is a significant predictive factor for rates of NIV continuation and hospitalization due to respiratory deterioration in subjects with restrictive thoracic disease (RTD) (7), as well as those with COPD (8).

However, when our data were reanalyzed to include the annual change in PaCO₂ during long-term NIV in subjects with RTD, smaller annual alterations in PaCO₂ were found to be more important for continuation than lower PaCO₂ levels a few months after NIV (9). Therefore, nocturnal high-intensity NIV for long-term treatment may not be mandatory for these subjects.

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In the present study of subjects with COPD, we retrospectively reviewed PaCO₂ data obtained at 6-month intervals and calculated their PaCO₂ alteration rates. We intended to clarify which pattern of PaCO₂ alteration during long-term NIV would be suitable for continued NIV usage. We also wanted to elucidate whether PaCO₂ levels a few months after NIV or annual PaCO₂ alteration rates throughout long-term NIV are more important for the continuation of long-term NIV.

Materials and Methods

Subjects

All subjects with COPD who had started NIV at the National Hospital Organization Minami Kyoto Hospital, the National Tokyo Hospital, or the Kyoto University Hospital between June, 1990 and August, 2007 were included in this study. A similar group was evaluated in our previous reports (8). All subjects had chronic hypercapnic ventilatory failure. The criteria to introduce NIV were based on the clinical symptoms with persistent diurnal hypercapnia (PaCO₂ >45 mmHg) and/or nocturnal hypoventilation and/or medical instability with repeated hospitalizations. Our subjects had to continue long-term NIV to survive if they did not wish to receive tracheostomy positive pressure ventilation (TPPV). Subjects with other disorders were excluded.

This study was approved by the Ethics Committee of Kyoto University. According to the advice of the Ethics Committee of Kyoto University, the study procedure was disclosed on our institution website, and all questions from patients asked on the website form have been answered.

Measurements

The age at the initiation of NIV, gender, existence of sleep apnea syndrome (SAS), body mass index (BMI), percentage of predicted forced expiratory volume in 1 second (%FEV₁), pre-existing comorbidities (Charlson index), clinical status at the start of NIV (i.e., acute or chronic), annual hospitalization rate due to respiratory deterioration before NIV, length of long-term oxygen therapy (LTOT) before the start of NIV, ventilator mode (assisted or controlled mode), inspiratory positive airway pressure (IPAP), expiratory positive airway pressure (EPAP), respiratory rate (f_R), PaCO₂ after 6 months of NIV (6 m-PaCO₂), and annual alterations in PaCO₂ during long-term NIV were assessed to elucidate the risk factors of NIV discontinuation.

Data on 6-month intervals of daytime ABGs were collected from 12 months before NIV initiation to the observation end-point when available. ABGs were typically obtained between 9:00 and 13:00 with the subject in the supine position and spontaneously breathing prescribed oxygen. ABGs were sampled in subjects who were in a steady condition without acute exacerbations.

All of the subjects' data were gathered from their medical records.

Clinical procedure for initiating long-term NIV and follow-up

The detailed practices for introducing long-term NIV have been described elsewhere (5). Volume-targeted ventilators were utilized with either customized interfaces (10) or industrial masks. Pressure-targeted ventilators using bi-level positive airway pressure (bi-level PAP) devices were applied with industrial masks. Oxygen was added to maintain an arterial oxygen saturation >95% during diurnal NIV and >90% during nocturnal NIV.

During follow-up, all subjects who were on long-term NIV and/or LTOT had to visit an outpatient clinic once a month as required by Japanese legislation. Chest X-rays and ABGs were typically examined every 3 to 6 months.

Statistical analysis

The alteration in PaCO₂ during NIV was determined using a simple linear regression method for each subject who had at least two 6-month intervals of PaCO₂ data collected 6 to 96 months after long-term NIV initiation. The subjects were divided into two groups using the median of the distribution of PaCO₂ alterations (group 1, <2 mmHg/y, n=19; group 2, >2 mmHg/year, n=18).

The means and standard deviations were used for the subject features and ventilator settings. Mann-Whitney U tests for continuous variables and Fisher's exact tests for categorical variables were used to evaluate differences in the subject characteristics between the two groups. Continuance of long-term NIV relative to risk factors, including the annual PaCO₂ alteration, was estimated by a univariate Cox proportional hazards regression analysis. Thereafter, continuance was evaluated using a multivariate analysis that only included significant risk factors ($p < 0.1$) in the univariate analysis. Continuance of long-term NIV was also estimated and depicted by Kaplan-Meier curves (the log-rank test). The Mann-Whitney U tests were used to evaluate differences in PaCO₂ between the two groups at the same time points. For all analyses, a p value <0.05 was considered to be significant.

Results

Subject characteristics

There were 54 subjects who were on NIV for more than 2 months and were available for follow-up. Four subjects starting long-term NIV at their acute exacerbation ceased NIV within 6 months due to recovery from hypercapnia. No subjects died within 6 months of NIV. Two subjects were on NIV for less than 6 months but were still on NIV at the final follow-up time point (the last of November, 2007). Eleven subjects continued NIV for more than 6 months but had fewer than two 6-month intervals of PaCO₂ data. Ultimately, 37 subjects were included in the analyses.

Of the 37 subjects, 19 discontinued long-term NIV. Four-

Table 1. Subject Characteristics (n=37).

	Group 1 < 2 (mmHg/y)	Group 2 > 2 (mmHg/y)	p value
Annual changes of PaCO ₂ (n)	19	18	
Age at start of NIV (y)	69.3 (5.4)	71.1 (7.5)	0.27
Gender (male/female)	17/2	11/7	0.001
SAS (+/-)	3/16	0/18	0.23
BMI (kg/m ²)	21.7 (4.4)	17.7 (3.6)	0.02
%predicted FEV ₁ (%)	20.9 (6.5)	20.5 (5.6)	0.84
Charlson comorbidity index	1.0 (1.0)	0.7(1.0)	0.84
Patients' state at start of NIV (acute/chronic)	6/13	9/9	0.42
Annual hospitalization rate due to respiratory deterioration before NIV	0.9 (0.8)	2.0 (1.2)	0.01
Duration of LTOT before NIV (y)	3.5 (3.2)	2.9 (2.5)	0.63
Ventilator mode (assisted/controlled)	15/4	13/5	0.30
IPAP (cm H ₂ O)	13.3 (5.1)	12.1 (5.3)	0.52
EPAP (cm H ₂ O)	5.8 (3.8)	3.5 (1.9)	0.04
Respiratory rate	16.4 (6.1)	16.6 (4.5)	0.85
ABGs six months after start of NIV	n=17	n=17	
pH	7.37 (0.04)	7.39 (0.04)	0.12
PaO ₂ (mmHg)	83.1 (15.3)	78.0 (11.8)	0.46
PaCO ₂ (mmHg)	61.0 (12.6)	56.7 (10.9)	0.43
HCO ₃ ⁻ (mmol/L)	34.7 (4.9)	33.6 (4.7)	0.55

NIV: noninvasive ventilation, SAS: sleep apnea syndorome, BMI: body-mass index, % predicted FEV₁: percentage of predicted value of forced expiratory volume in 1 second, LTOT: long-term oxygen therapy, IPAP: inspiratory positive airway pressure, EPAP: expiratory positive airway pressure, ABGs: arterial blood gas analyses, PaO₂: arterial oxygen tensions, PaCO₂: arterial carbon dioxide tensions, HCO₃⁻: bicarbonate

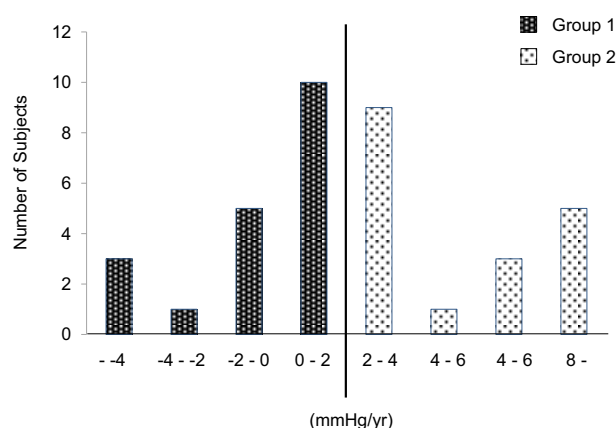


Figure 1. The distribution of annual alterations in PaCO₂. A total of 37 subjects were divided into two groups based on their annual alterations in PaCO₂ (group 1, <2 mmHg/y, n=19; group 2, >2 mmHg/y, n=18). PaCO₂: arterial carbon dioxide tensions

teen subjects died during long-term NIV, and two of them only received oxygen therapy and not NIV in the last few days of life (mostly due to delirium). Three subjects received invasive endotracheal ventilation for their acute exacerbations and died within 1 week. Two subjects were switched to TPPV due to disease progression and died after 4 and 37 months of long-term TPPV, respectively.

The subject characteristics were divided by their annual alterations in PaCO₂ as shown in Table 1. Overall, the sub-

jects were characterized by extremely severe obstructive ventilatory defects, moderate to severe hypercapnia, moderate to severe malnutrition, and an unstable clinical condition. The subjects in group 1 tended to be men and had a complicated SAS; their BMIs were higher at the start of long-term NIV, and their clinical situations were more stable compared to group 2. Among the subjects using bi-level PAP devices, group 1 had slightly higher EPAP values. However, in the subjects who did not have SAS, there was no significant difference in EPAP between the two groups (p=0.16). Furthermore, there was no significant difference in ABGs between the two groups after 6 months of NIV.

Annual alterations in PaCO₂ during long-term NIV

The distribution of the annual PaCO₂ changes is shown in Fig. 1. Two characteristic PaCO₂ patterns are presented in Fig. 2.

PaCO₂ time course before and after NIV

An analysis of the PaCO₂ time courses of the two groups is shown in Fig. 3. There were no significant differences in PaCO₂ between the two groups from the 12th month before NIV initiation to the 48th month after the start of NIV.

Comparison of the long-term NIV continuation rates

In the univariate analysis, higher %FEV₁, lower 6 m-PaCO₂, higher BMI, and lower annual alterations in PaCO₂ during long-term NIV were all associated with higher NIV

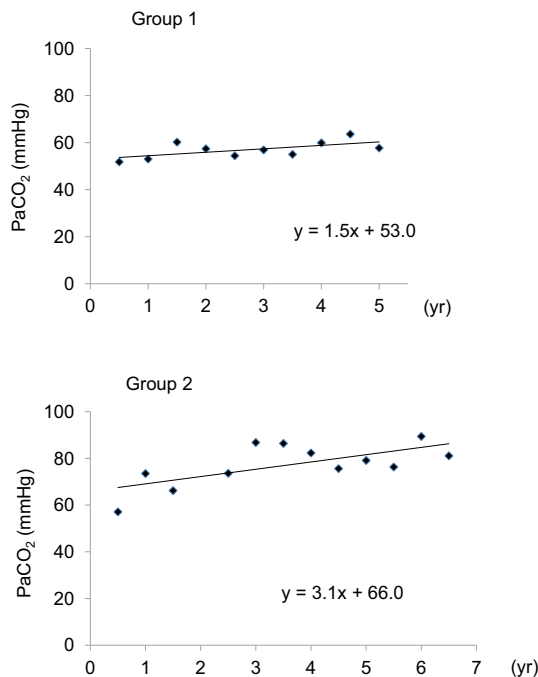


Figure 2. Two representative patterns of PaCO_2 alterations during long-term non-invasive ventilation (NIV). PaCO_2 increased slowly in group 1 (upper panel) and rapidly in group 2 (lower panel) during long-term NIV (group 1, <2 mmHg/y, $n=19$; group 2, >2 mmHg/y, $n=18$). NIV: non-invasive ventilation, PaCO_2 : arterial carbon dioxide tensions

continuation rates (Table 2).

The multivariate analysis revealed that lower annual alterations in PaCO_2 during long-term NIV ($p=0.009$) and lower 6 m- PaCO_2 ($p=0.03$) were both significantly related to higher NIV continuation rates (Table 3).

The Kaplan-Meier analysis revealed a significantly greater continuance of long-term NIV in group 1 than in group 2 ($p=0.03$, Fig. 4). The 2- and 5-year probabilities of continuing NIV were 89% and 66% for group 1 and 78% and 32% for group 2, respectively.

Discussion

After the start of long-term NIV, we observed that PaCO_2 gradually increased in most subjects with COPD. Those with lower annual alterations in PaCO_2 during long-term NIV had significantly higher NIV continuation rates. The results also indicated that a lower PaCO_2 level a few months after NIV was an important factor for prognosis.

Persistent CO_2 retention in subjects with chronic ventilatory defects may reflect an adaptive mechanism that permits a lower level of alveolar ventilation, thus unburdening overloaded respiratory muscles (11-14). In the present study, PaCO_2 increased in three-fourths of our subjects. This observation indicates that the adaptive mechanism that chronically permits hypercapnia also occurs in patients receiving long-term NIV.

Because adaptations develop in difficult situations, we hy-

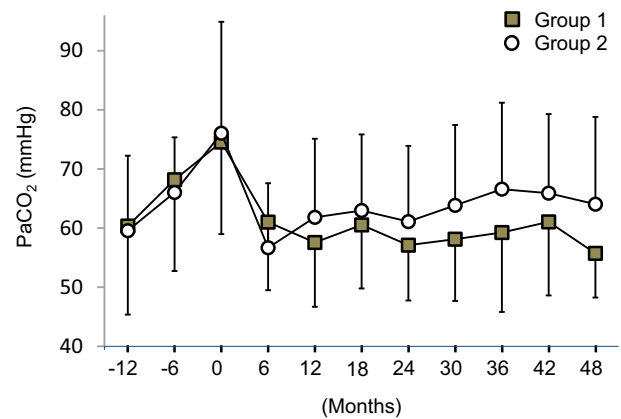


Figure 3. The PaCO_2 time course during long-term non-invasive ventilation (NIV). A comparison of the subjects grouped according to their annual alteration in PaCO_2 (group 1, <2 mmHg/y, $n=19$; group 2, >2 mmHg/y, $n=18$). Data are presented as the means ($\pm$ SDs). There were no significant differences in PaCO_2 between the two groups at any time point. NIV: non-invasive ventilation, PaCO_2 : arterial carbon dioxide tensions

pothesized that the subjects with greater annual alterations in PaCO_2 were more likely to discontinue NIV than those subjects with more stable PaCO_2 values. Indeed, we found that low annual alteration in PaCO_2 was the most important prognostic factor in COPD subjects who received long-term NIV.

We also hypothesized that low annual alteration in PaCO_2 implied a reserved capacity in respiratory muscle and that some factors should maintain and/or increase respiratory muscle capacity. Respiratory muscle rest by NIV, nutritional management, and pulmonary rehabilitation may enhance respiratory muscle capacity.

While an effect of long-term NIV on prognosis is established in subjects with RTD (1-4), there is insufficient evidence to recommend NIV as the standard therapy in stable hypercapnic patients with COPD (15-17). Several efforts have been undertaken to enhance the effectiveness of long-term NIV in subjects with COPD. Nocturnal high intensity NIV is one such effort. Windisch et al. reported that nocturnal NIV, with ventilator settings aimed at significantly reducing PaCO_2 , could satisfactorily reduce diurnal PaCO_2 and achieve other clinical gains, including extended survival (5, 6). In the present study, lower PaCO_2 levels a few months after NIV were associated with a significantly increased likelihood of long-term NIV continuance.

In our very recent study of subjects with RTD, those with an annual alteration in $\text{PaCO}_2 >1.85$ mmHg/year had a poor prognosis, which was similar to the result of the present study regarding subjects with COPD. In RTD, PaCO_2 measured a few months after long-term NIV initiation was not a significant prognostic factor (9), while subjects with COPD who had lower PaCO_2 within a few months of NIV initiation had a better prognosis. Further efforts should be made to augment the utility of long-term NIV in subjects with

Table 2. Comparisons of Continuation Rates of Long-term NIV by Several Risk Factors, Including Annual Alterations of PaCO₂ (Univariate Modality Model).

Variable	Category	n	Hazard ratio (95%CI)	p value
Age (y)	CV	37	1.00 (0.94-1.07)	0.92
Gender	female	9	(reference)	0.85
	male	28	1.11 (0.39-3.16)	
SAS	+	3	NA	NA
	-	34		
BMI (kg/m ²)	CV	31	0.87 (0.75-1.00)	0.05
% predicted FEV ₁ (%)	CV	32	0.92 (0.84-1.01)	0.08
Charlson comorbidity index	CV	37	0.77 (0.45-1.34)	0.36
Patients' state	chronic	22	(reference)	0.77
	acute	15	1.15 (0.46-2.88)	
Annual hospitalization rate due to acute respiratory episodes before NIV	CV	37	1.20 (0.85-1.69)	0.30
Duration of LTOT before NIV (y)	CV	37	1.11 (0.93-1.32)	0.24
Ventilator mode	assisted	28	(reference)	0.38
	controlled	9	1.56 (0.58-4.17)	
IPAP (cmH ₂ O)	CV	35	1.01 (0.93-1.10)	0.82
EPAP (cmH ₂ O)	CV	35	0.90 (0.75-1.07)	0.23
Respiratory rate	CV	35	1.05 (0.95-1.15)	0.32
6-mo PaCO ₂ (mmHg)	CV	34	1.03 (0.996-1.07)	0.08
Annual alterations of PaCO ₂ (mmHg/y)	CV	37	1.07 (1.02-1.12)	0.00

SAS: sleep apnea syndrome, NA: not assessed, BMI: body mass index, CI: confidence interval, CV: continuous variable, EPAP: expiratory positive airway pressure, % predicted FEV₁: percentage of predicted value of forced expiratory volume in 1 s, IPAP: inspiratory positive airway pressure, LTOT: long-term oxygen therapy, NIV: non-invasive ventilation, PaCO₂: partial pressure of carbon dioxide tension, 6-mo PaCO₂: PaCO₂ measured at 6 months after long-term NIV initiation

Table 3. Comparisons of Continuation Rates of Long-term NIV by Several Risk Factors (Multivariate Modality Model).

Variables	Category	n	Hazard ratio (95%CI)	p value
Annual alterations of PaCO ₂ (mmHg/y)	CV	37	1.08 (1.02-1.14)	0.009
6-m PaCO ₂ (mmHg)	CV	34	1.11 (1.01-1.22)	0.03
% predicted FEV ₁ (%)	CV	32	1.06 (0.92-1.23)	0.42
BMI (kg/m ²)	CV	31	1.04 (0.86-1.25)	0.70

BMI: body mass index, CI: confidence interval, CV: continuous variable, % predicted FEV₁: percentage of predicted value of forced expiratory volume in 1 s, NIV: non-invasive ventilation, PaCO₂: partial pressure of carbon dioxide tension, 6-mo PaCO₂: PaCO₂ measured at 6 months after long-term NIV initiation

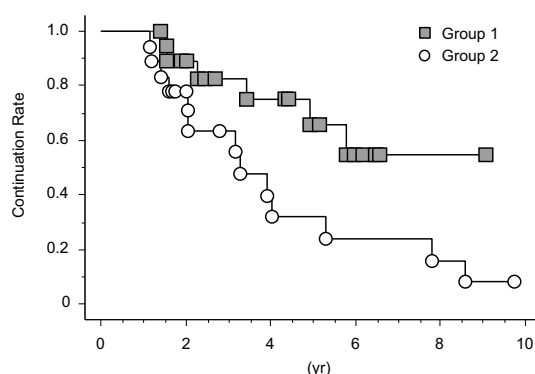


Figure 4. Kaplan-Meier curves of the continuation rates of long-term non-invasive ventilation (NIV). The subjects were divided into two groups according to their annual alterations in PaCO₂ (group 1, <2 mmHg/y, n=19; group 2, >2 mmHg/y, n=18). Subjects with lower annual PaCO₂ alterations had a significantly better prognosis (log-rank test, p=0.03). The 2- and 5-year probabilities of continuing NIV were 89% and 66% for group 1 and 78% and 32% for group 2, respectively. NIV: non-invasive ventilation, PaCO₂: arterial carbon dioxide tensions

COPD. Specifically, PaCO₂ should be reduced as low as possible within a few months and stabilized during long-term NIV.

Although a prospective study is needed to clarify whether controlling PaCO₂ throughout long-term NIV improves prognosis, we should attempt to stabilize PaCO₂ during long-term NIV by switching the ventilator type, modifying ventilator settings, augmenting NIV duration, exchanging masks, and adding dietary management and pulmonary rehabilitation (18).

In conclusion, we found that a lower annual alteration in PaCO₂ throughout long-term NIV is the most critical prognostic factor, and the second most important factor is lower PaCO₂ levels a few months after NIV. Therefore, both lowering PaCO₂ a few months after NIV initiation and stabilizing PaCO₂ throughout long-term NIV may be critical for improving the continuation rate of long-term NIV in subjects with COPD.

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

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