INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

The Importance of Stabilizing $PaCO_2$ 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 CO_2 ($PaCO_2$) alterations during long-term non-invasive ventilation (NIV) on continuance remains uncertain. We herein investigated the utility of $PaCO_2$ 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 $PaCO_2$ during NIV was determined using a simple linear regression method for each subject who had at least two 6-month intervals of $PaCO_2$ data. Annual alterations in $PaCO_2$ 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. $PaCO_2$ 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 $PaCO_2$ (p=0.009) and lower $PaCO_2$ 6 months after the start of long-term NIV (6 m-$PaCO_2$) (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-$PaCO_2$ and a lower annual alteration of $PaCO_2$ 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

(Intern Med 54: 1193-1198, 2015)
(DOI: 10.2169/internalmedicine.54.4377)

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 CO_2 ($PaCO_2$) 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 $PaCO_2$ a few months after beginning NIV maintained relatively low $PaCO_2$ levels for several years and that $PaCO_2$ 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 $PaCO_2$ during long-term NIV in subjects with RTD, smaller annual alterations in $PaCO_2$ were found to be more important for continuation than lower $PaCO_2$ 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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Received for publication October 26, 2014; Accepted for publication December 15, 2014
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In the present study of subjects with COPD, we retrospectively reviewed $PaCO_2$ data obtained at 6-month intervals and calculated their $PaCO_2$ alteration rates. We intended to clarify which pattern of $PaCO_2$ alteration during long-term NIV would be suitable for continued NIV usage. We also wanted to elucidate whether $PaCO_2$ levels a few months after NIV or annual $PaCO_2$ 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 ($PaCO_2$ >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 ($\%FEV_1$), 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), $PaCO_2$ after 6 months of NIV (6 m-$PaCO_2$), and annual alterations in $PaCO_2$ 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 $PaCO_2$ during NIV was determined using a simple linear regression method for each subject who had at least two 6-month intervals of $PaCO_2$ 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 $PaCO_2$ 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 $PaCO_2$ 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 $PaCO_2$ 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 $PaCO_2$ 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).

Annual changes of $PaCO_2$	Group 1 < 2 (mmHg/y)	Group 2 > 2 (mmHg/y)	p value
(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_2O)	13.3 (5.1)	12.1 (5.3)	0.52
EPAP (cm H_2O)	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 FEV_1: 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, PaO_2: arterial oxygen tensions, $PaCO_2$: arterial carbon dioxide tensions, HCO_3^-: bicarbonate

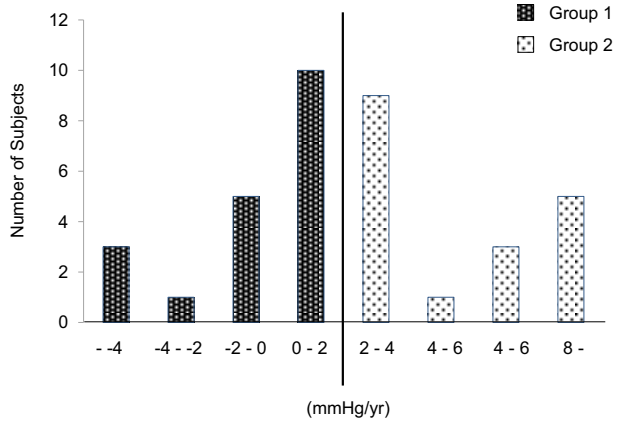

Figure 1. The distribution of annual alterations in $PaCO_2$. A total of 37 subjects were divided into two groups based on their annual alterations in $PaCO_2$ (group 1, <2 mmHg/y, n=19; group 2, >2 mmHg/y, n=18). $PaCO_2$: arterial carbon dioxide tensions

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 $PaCO_2$ as shown in Table 1. Overall, the subjects 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 $PaCO_2$ during long-term NIV

The distribution of the annual $PaCO_2$ changes is shown in Fig. 1. Two characteristic $PaCO_2$ patterns are presented in Fig. 2.

$PaCO_2$ time course before and after NIV

An analysis of the $PaCO_2$ time courses of the two groups is shown in Fig. 3. There were no significant differences in $PaCO_2$ 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 %FEV_1, lower 6 m-$PaCO_2$, higher BMI, and lower annual alterations in $PaCO_2$ during long-term NIV were all associated with higher NIV

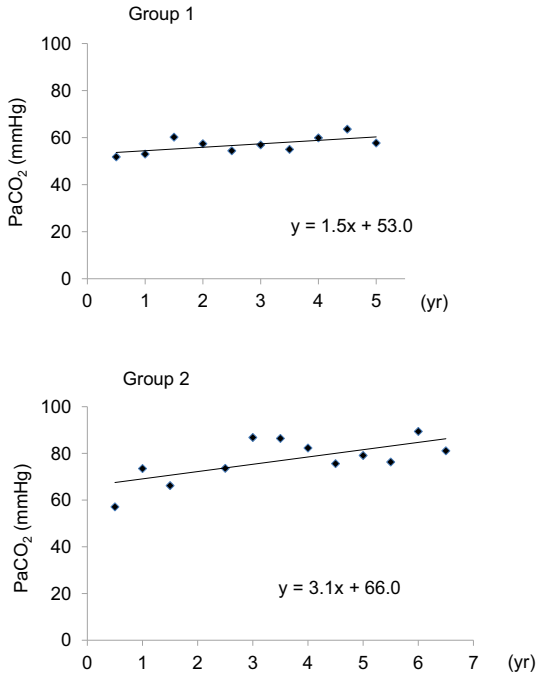

Figure 2. **Two representative patterns of $PaCO_2$ alterations during long-term non-invasive ventilation (NIV). $PaCO_2$ increased slowly in group 1 (upper panel) and rapidly in group 2 (lower panel) during long-term NIV (group 1, <2 mmHg/y, n=19; group 2, >2 mmHg/y, n=18). NIV: non-invasive ventilation,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

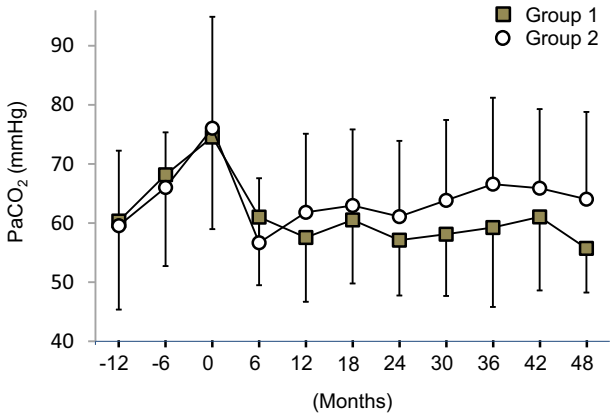

Figure 3. **The $PaCO_2$ time course during long-term non-invasive ventilation (NIV). A comparison of the subjects grouped according to their annual alteration in $PaCO_2$ (group 1, <2 mmHg/y, n=19; group 2, >2 mmHg/y, n=18). Data are presented as the means (±SDs). There were no significant differences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

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 hypothesized 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 $PaCO_2$ >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 $PaCO_2$ (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_2O)	CV	35	1.01 (0.93-1.10)	0.82
EPAP (cmH_2O)	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: sleel apnea syndrome, NA: not assesed, BMI: body mass index, CI: confidence interval, CV: continuous variable, EPAP: expiratory positive airway pressure, % predicted FEV_1: 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, $PaCO_2$: partial pressure of carbon dioxide tension, 6-mo $PaCO_2$: $PaCO_2$ 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 FEV_1: percentage of predicted value of forced expiratory volume in 1 s, NIV: non-invasive ventilation, $PaCO_2$: partial pressure of carbon dioxide tension, 6-mo $PaCO_2$: $PaCO_2$ measured at 6 months after long-term NIV initiation

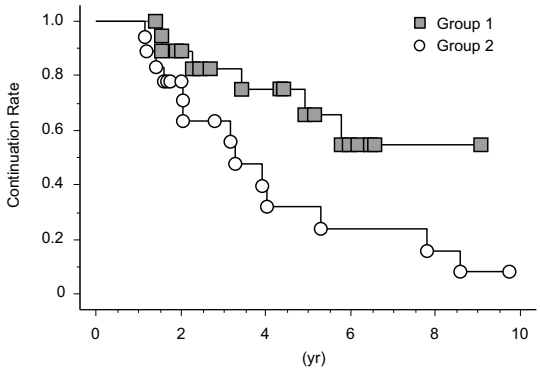

Figure 4. Kaplan-Meier curves of the continuation rates of long-term non-invasive ventilation (NIV). The subjects were divided into two groups according to their annual alterations in $PaCO_2$ (group 1, <2 mmHg/y, n=19; group 2, >2 mmHg/y, n=18). Subjects with lower annual $PaCO_2$ alterations had a 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, $PaCO_2$: arterial carbon dioxide tensions

COPD. Specifically, $PaCO_2$ 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 $PaCO_2$ throughout long-term NIV improves prognosis, we should attempt to stabilize $PaCO_2$ 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 $PaCO_2$ throughout long-term NIV is the most critical prognostic factor, and the second most important factor is lower $PaCO_2$ levels a few months after NIV. Therefore, both lowering $PaCO_2$ a few months after NIV initiation and stabilizing $PaCO_2$ 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).

References

1. Leger P, Bedicam JM, Cornette A, et al. Nasal intermittent positive pressure ventilation: long-term follow-up in patients with severe chronic respiratory insufficiency. Chest **105**: 100-105, 1994.
2. Simonds AK, Elliott MW. Outcome of domiciliary nasal intermittent positive pressure ventilation in restrictive and obstructive disorders. Thorax **50**: 604-609, 1995.
3. Jager L, Franklin KA, Midgren B, Lofdahl K, Strom K. Increased survival with mechanical ventilation in posttuberculosis patients with the combination of respiratory failure and chest wall deformity. Chest **133**: 156-160, 2008.
4. Tsuboi T, Oga T, Machida K, et al. Importance of ventilator mode in long-term noninvasive positive pressure ventilation. Respir Med **103**: 1854-1861, 2009.
5. Windisch W, Kostic S, Dreher M, Virchow JC Jr, Sorichter S. Outcome of patients with stable COPD receiving controlled noninvasive positive pressure ventilation aimed at a maximal reduction of $PaCO_2$. Chest **128**: 657-662, 2005.
6. Windisch W, Haenel M, Storre JH, Dreher M. High-intensity noninvasive positive pressure ventilation for stable hypercapnic COPD. Int J Med Sci **6**: 72-76, 2009.
7. Tsuboi T, Ohi M, Machida K, et al. Importance of the $PaCO_2$ from 3 to 6 months after initiation of long-term non-invasive ventilation. Respir Med **104**: 1850-1857, 2010.
8. Tsuboi T, Oga T, Machida K, et al. $PaCO_2$ six months after initiation of long-term noninvasive ventilation in patients with COPD. Intern Med **50**: 563-570, 2011.
9. Tsuboi T, Oga T, Sumi K, Machida K, Ohi M, Chin K. The importance of controlling $PaCO_2$ throughout long-term non-invasive ventilation. Respir Care **59**: 1671-1678, 2014.
10. Tsuboi T, Ohi M, Kita H, et al. The efficacy of a custom-fabricated nasal mask on gas exchange during nasal intermittent positive pressure ventilation. Eur Respir J **13**: 152-156, 1999.
11. Barach AL. Hypercapnia in chronic obstructive lung disease: an adaptive response to low-flow oxygen therapy. Chest **66**: 112-113, 1974.
12. Petty TL. CO_2 can be good for you! Chest **129**: 494-495, 2006.
13. Elliott MW, Mulvey DA, Moxham J, Green M, Branthwaite MA. Domiciliary nocturnal nasal intermittent positive pressure ventilation in COPD: mechanisms underlying changes in arterial blood gas tensions. Eur Respir J **4**: 1044-1052, 1991.
14. Nickol AH, Hart N, Hopkinson NS, et al. Mechanisms of improvement of respiratory failure in patients with COPD treated with NIV. Int J Chro Obstruct Pulmon Dis **3**: 453-462, 2008.
15. Casanova C, Celli BR, Tost L, et al. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. Chest **118**: 1582-1590, 2000.
16. Clini E, Sturani C, Rossi A, et al. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. Eur Respir J **20**: 529-538, 2002.
17. McEvoy RD, Pierce RJ, Hillman D, et al. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomized controlled trial. Thorax **64**: 561-566, 2009.
18. Cejudo P, López-Márquez I, López-Campos JL, et al. Exercise training in patients with chronic respiratory failure due to kyphoscoliosis: a randomized controlled trial. Respir Care **59**: 375-382, 2014.