Title: Importance of the $PaCO_2$ from 3 to 6 months after initiation of long-term noninvasive ventilation.

Running title: $PaCO_2$ after initiation of long-term NPPV

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Key Words

(1) chronic respiratory failure

(2) home mechanical ventilation

(3) noninvsive positive pressure ventilation

(4) partial pressure of carbon dioxide

(5) restricted thoracic disease

(Words count: 248)

ABSTRACT

Background: The level at which arterial carbon dioxide tension ($PaCO_2$) a few months after introduction of long-term noninvasive positive pressure ventilation (NPPV) is associated with a favorable prognosis remains uncertain.

Methods: Data on 184 post-tuberculosis patients with chronic restrictive ventilatory failure who were receiving long-term domiciliary NPPV were examined retrospectively. Average $PaCO_2$ 3 to 6 months after NPPV (3- to 6-mo $PaCO_2$) and potential confounders were analyzed with discontinuation of long-term NPPV as the primary outcome. The effects of 3- to 6-mo $PaCO_2$ on annual hospitalization rates due to respiratory deterioration from 1 year before to 3 years after the initiation of NPPV were examined. The effect of the difference between the $PaCO_2$ value at the start of NPPV (0-mo $PaCO_2$) and the $PaCO_2$ value 3- to 6-mo later (d-$PaCO_2$) on continuation rates for NPPV was also assessed in patients who initiated NPPV while in a chronic state.

Results: Patients with relatively low 3- to 6-mo $PaCO_2$ values maintained a relatively low $PaCO_2$ 6 to 36 months after NPPV ($p<0.0001$) and had significantly better continuation rates ($p<0.03$) and lower hospitalization rates from the 1st to 3rd year of NPPV ($p=0.008$, 0.049, 0.009, respectively) than those with higher levels. The 0-mo $PaCO_2$ ($p=0.26$) or d-$PaCO_2$ ($p=0.86$) had no predictive value.

Conclusion: A relatively low 3- to 6-mo $PaCO_2$ value was predictive of long-term use of NPPV. The target values for 3- to 6-mo $PaCO_2$ may, therefore, be less than 60 mmHg in post-tuberculosis patients, although more studies are needed.

(Words count: 3045)

INTRODUCTION

Domiciliary non-invasive positive pressure ventilation (NPPV) has been widely used in the treatment of patients with chronic hypercapnic respiratory failure. [1-7] NPPV has been shown to improve gas exchange, probably due to increased ventilatory response to carbon dioxide (CO_2) in patients with chronic obstructive pulmonary disease (COPD) [8] and restrictive thoracic disease (RTD) including pulmonary tuberculosis sequelae. [9,10] Arterial blood gases (ABGs) were reported to be stabilized a few months after NPPV and maintained over several years in patients with COPD [1] and RTD. [1,3,4,11] In patients with RTD, a higher nighttime $PaCO_2$ measured before the start of long-term NPPV was shown to be a significant independent predictor of mortality. [12] In contrast, a higher daytime $PaCO_2$ at the start of NPPV (0-mo $PaCO_2$) was not associated with a poor prognosis in patients with RTD [12] or COPD. [13]

Generally, ABG values and the general condition are unstable in patients during the pre-NPPV period even in those who started NPPV while in a chronic state. However, gas exchange and the clinical state markedly stabilize after institution of long-term NPPV. According to our clinical experience, medication and ventilator settings seldom needed to be changed after the clinical condition of patients was stabilized by NPPV treatment. Therefore, as prognostic factors, parameters after a few months of NPPV seem to be more important and reliable than those before starting NPPV. However, to the best of our knowledge, no report has assessed $PaCO_2$ a few months after the introduction of long-term NPPV as a possible prognostic factor.

We hypothesized that patients with a relatively low mean value of $PaCO_2$ measured between 3 and 6 months after introduction of long-term NPPV (3- to 6-mo $PaCO_2$) would have higher continuation rates of NPPV and lower hospitalization rates than those with a relatively high 3- to 6-mo $PaCO_2$. We retrospectively examined the effects of the 3- to 6-mo $PaCO_2$ level on continuation of NPPV in post-tuberculosis patients. Thus, we wanted to determine which levels of $PaCO_2$ after a few months of NPPV were suitable for those patients.

METHODS

Patients

All post-tuberculosis patients who had started NPPV at 6 hospitals affiliated with Kyoto University Hospital and the National Tokyo Hospital from June 15, 1990 to August 2, 2007 were included in this retrospective study. All patients had chronic respiratory failure with hypercapnia. The NPPV therapy was begun either after an acute episode or during the chronic state. The decision for initiation of NPPV was based on clinical symptoms with persistent hypercapnia during daytime ($PaCO_2$>45 mmHg) and/or nocturnal hypoventilation and/or clinical instability with recurrent hospitalizations. Patients with other causes of chronic respiratory failure such as neuromuscular disorders, obesity hypoventilation syndrome, bronchiectasis, idiopathic scoliosis, or COPD were excluded.

The patients were followed until November 30, 2007. Clinical assessments were performed at the end of every year from 1995 to 2002, in December 2004 and in December 2007.

The patients were divided into 3 groups according to 3- to 6-mo $PaCO_2$ levels (Group-1, 60 mmHg>, n=79; Group-2, 60 to 70 mmHg, n=61; Group-3, >70 mmHg, n=23). Measurement of 3- to 6-mo $PaCO_2$ could not be performed in 19 other patients who otherwise met criteria for study entry because of clinical instability at the time or because they did not attend outpatient clinic. The patients who started long-term NPPV while in a chronic state were divided into 3 groups according to the difference between 0-mo $PaCO_2$ and 3- to 6-mo $PaCO_2$ (d-$PaCO_2$) (Group-d1, >16 mmHg, n=33;

Group-d2, 8 to 16 mmHg, n=29; Group-d3, 8 mmHg>, n=28). Patients in the present study were also subjects of our previous study concerning ventilator modes. [7]

Measurements

Data on age at the start of NPPV, gender, presence of pulmonary lesions, duration of long-term oxygen therapy (LTOT) before the start of NPPV, status on introduction of NPPV (i.e., acute or chronic state), ventilator mode (assisted or controlled mode), other ventilator settings such as inspiratory positive airway pressure (IPAP), expiratory positive airway pressure (EPAP), respiratory rate (f_R), and tidal volume (V_T), body-mass index (BMI), vital capacity (percentage of predicted), forced expiratory volume in 1 second over forced vital capacity (FEV_1/FVC), and concurrent use of LTOT after the start of NPPV were all examined and/or documented for determination of risk factors. Annual number of hospitalizations due to respiratory deterioration (acute bronchitis, pneumonia, spontaneous pneumothorax, chronic disease progression, etc.) beginning from 1 year before to 3 years after the start of NPPV was also included in this analysis.

Information on daytime ABGs was analyzed from 12 months before the start of NPPV to the observable end-point if available. Determinations of ABGs were made with the patient in the supine position breathing room air or prescribed oxygen without NPPV support. ABGs were obtained in patients who were in a stable condition without exacerbation except for those obtained at the start of NPPV from patients who had begun administration of NPPV during an acute state.

All data on the clinical course of patients were collected from clinical records.

Clinical protocol for introducing long-term NPPV

The precise criteria and procedure for introducing long-term NPPV have been described elsewhere.[7] At the start of NPPV, volume preset ventilators were utilized with custom fabricated nasal masks [14] or with commercially available interfaces. Pressure preset ventilators using bilevel PAP devices were applied with commercially available interfaces. Supplemental oxygen was added to NPPV to maintain an arterial oxygen saturation >95% during diurnal NPPV and >90% during nocturnal NPPV.

This study was approved by the Ethics Committee of Kyoto University, and individual consent was not obtained as stipulated by the Committee. According to the recommendation of the Ethics Committee of Kyoto University, the protocol of this study is posted on the website of our institute and all inquiries are answered.

Follow up

In Japan, patients receiving long-term NPPV and/or LTOT must attend outpatient clinic each month. ABG analysis and chest X-ray were usually performed every 3 to 6 months.

Statistical analysis

Means and standard deviations are reported for patients' characteristics and ventilator settings. One-way factorial analysis of variance (ANOVA) and post-hoc analysis (Scheffe test) were used for continuous variables and the 2 x 3 contingency table and chi-square tests for categorical variables were used to compare differences in patients' characteristics among Group-1 to -3. Comparisons of continuation rates of long-term NPPV by risk factors including 3- to 6-mo $PaCO_2$ levels were performed

using univariate and multivariate Cox proportional hazards regression analyses. 0-mo $PaCO_2$ values during periods without respiratory deterioration could be obtained only in patients starting NPPV while in a chronic state. Therefore, comparison of continuation rates of NPPV according to risk factors including d-$PaCO_2$ were performed in those who started NPPV while in a chronic state. Continuation rates of long-term NPPV were also assessed using Kaplan-Meier analyses (log-rank test). Among the three groups (Group-1 to -3), comparison of annual hospitalization rates was performed using one-way factorial ANOVA and post-hoc analysis (Scheffe test). To evaluate differences in $PaCO_2$ over time among those three groups, repeated-measures ANOVA and post-hoc analysis (Scheffe test) were used.

RESULTS

Patient characteristics

A total of 184 patients who continued receiving NPPV for more than 2 months were available for follow-up. Since two patients discontinued NPPV due to improvement in hypercapnic respiratory failure, 182 patients were available for final analysis. Table 1 shows patients' characteristics in the 3 groups according to 3- to 6-mo $PaCO_2$ levels.

Overall, patients were characterized by severe restrictive ventilatory failure, severe hypercapnia, moderate malnutrition and unstable clinical conditions. At the start of NPPV, % predicted VC was higher and the duration of LTOT before the start of NPPV was shorter in Group-1 patients than in those in Group-2 or -3. Among the patients starting NPPV while in a chronic state, Group-2 or -3 patients were more acidotic and more hypercapnic at the start of NPPV than Group-1 patients. As to ventilator settings, IPAP and f_R were higher in patients in Group-2 than in Group-1.

Overall outcome

Two patients discontinued NPPV due to improvement as mentioned above. Outcome in the remaining 182 was as follows. Two patients temporarily discontinued NPPV for several months and then restarted. After the long-term use of NPPV, 15 patients switched to long-term tracheostomy positive pressure ventilation (TPPV) for a mean (SD) duration of 2.17 (2.28) y. As of December 2007, 85 patients had died, 2 were receiving TPPV, and 95 were continuing use of NPPV.

Time course of $PaCO_2$ before and after NPPV

Comparisons of the time course of $PaCO_2$ between patients starting NPPV while in an acute state or in a chronic state are shown in Figure 1-a. Differences between the two groups were only noted at the start of NPPV. The comparison of trends of $PaCO_2$ among patients divided by 3- to 6-mo $PaCO_2$ levels (Groups-1 to -3) is shown in Figure 1-b. From 6 to 36 months after initiation of NPPV, patients with relatively low 3- to 6-mo $PaCO_2$ levels had relatively lower $PaCO_2$ values with significance than those with relatively high 3- to 6-mo $PaCO_2$ levels ($p=0.0004$). Post hoc analysis showed significant differences between Groups 1 and 2 ($p<0.0001$), between Groups 2 and 3 ($p=0.02$), and between Groups 1 and 3 ($p<0.0001$).

Comparison of continuation rate of long-term NPPV use among all cases

In the univariate analysis, female gender, a higher BMI, no parenchymal pulmonary lesions, lower annual hospitalization rates due to respiratory deterioration before NPPV, a controlled mode, and relatively low 3- to 6-mo $PaCO_2$ levels were all significantly associated with higher continuation rates of NPPV (Table 2). Patients with a longer duration of LTOT before NPPV tended to have higher continuation rates of NPPV ($p=0.11$). Ventilator settings such as IPAP, EPAP, and f_R were not related to continuation rates of NPPV.

Multivariate analysis showed that controlled ventilation, a higher BMI, female gender, and relatively low 3- to 6-mo $PaCO_2$ levels were all significantly associated with higher continuation rates of NPPV (Table 3).

Results of the Kaplan-Meier analysis showed significantly increased continuation rates of long-term NPPV in patients with relatively low 3- to 6-mo $PaCO_2$ levels

(p=0.0003; Figure 2). The 5- and 8-year probabilities of continuing NPPV for Group-1 were 70.1% and 56.0%, respectively, those for Group-2 were 55.0% and 24.3%, respectively, and those for Group-3 were 35.6% and 0%, respectively.

Comparison of continuation rate of NPPV in patients starting NPPV during the chronic state

Univariate analysis showed that a controlled mode (p=0.005), female gender (p=0.04), and relatively low 3- to 6-mo $PaCO_2$ levels (p=0.03) were all significantly associated with higher continuation rates of long-term NPPV while the 0-mo $PaCO_2$ (p=0.26) and d-$PaCO_2$ values (p=0.86) had no such significant association. By Kaplan-Meier analysis, a relatively low 3- to 6-mo $PaCO_2$ level was significantly associated with higher continuation rates of long-term NPPV (p=0.026; Figure 3).

In multivariate analysis according to risk factors of ventilator mode, 3- to 6-mo $PaCO_2$ levels and gender, the controlled mode (p=0.007) and relatively low 3- to 6-mo $PaCO_2$ levels (p=0.04) were significantly associated with higher continuation rates of long-term NPPV.

Comparison of annual hospitalization rate among three groups divided by 3- to 6-mo $PaCO_2$ levels

Patients with relatively low 3- to 6-mo $PaCO_2$ levels had significantly lower hospitalization rates due to respiratory deterioration than those with relatively high 3- to 6-mo $PaCO_2$ levels. Mean (SD) of hospitalization rates in Group-1 to -3 were 0.23 (0.60), 0.31 (0.62), and 0.82 (1.53), respectively, in the 1st year, 0.21 (0.53), 0.41 (0.63), and 0.53 (0.62), respectively, in the 2nd year, and 0.18 (0.43), 0.49 (0.68), and

0.50 (0.52), respectively, in the 3rd year of long-term NPPV. There was no significant difference in hospitalization rates for the year preceding NPPV in Group-1 to -3 (1.27 (0.96), 1.61 (1.07), and 1.43 (0.99), respectively.

DISCUSSION

In the present study, patients that had relatively low daytime $PaCO_2$ levels a few months after NPPV had significantly higher continuation rates of NPPV and significantly lower hospitalization rates due to respiratory deterioration from the first to the third years of NPPV. Such patients had also maintained relatively low $PaCO_2$ levels from 6 to 36 months after NPPV. Neither the $PaCO_2$ level at the start of NPPV nor improvement in $PaCO_2$ after use of NPPV was a significant predictive variable.

In general, patients with hypercapnic respiratory failure started long-term NPPV during either an acute or chronic state.[1, 2] The patients in the chronic state might not have been completely stable while receiving only LTOT. Actually, most of our patients who were considered to have a chronic status had experienced gradual deterioration of their symptoms over a long period even though their respiratory condition was not acutely aggravated. Their $PaCO_2$ had increased slowly during the pre-NPPV period as shown in Figure 1-a. Midgren had reported the same findings concerning $PaCO_2$ during the pre-NPPV period in post-polio patients.[15] Therefore, even in patients for whom noninvasive ventilation was initiated during the chronic state, the ABG level before NPPV might be inappropriate as a predictive variable. Furthermore, since the elevated $PaCO_2$ is effectively corrected within a few months of NPPV, it is unlikely to have any lasting predictive value for latter outcome.

The persistent CO_2 retention in patients with chronic ventilatory failure might reflect an adaptive mechanism that permits a lower level of alveolar ventilation, thus resulting in unloading of the overburdened respiratory muscles leading to decreased

dyspnea, particularly while LTOT is administered. [16, 17] It is presumed by some that this compensatory mechanism reveals the wisdom of nature. [17] However, ventilatory support such as NPPV should be implemented if hypercapnic ventilatory failure progresses over limits of this compensation. [8-10, 18-21] An improvement in daytime $PaCO_2$ after initiation of NPPV was shown to be correlated with the change in $PaCO_2$ while receiving nocturnal NPPV [18, 22] and the principal mechanism underlying the long-term improvement in daytime $PaCO_2$ was demonstrated to be an increased ventilatory response to CO_2. [8-10]

The present study showed that patients with relatively low 3- to 6-mo $PaCO_2$ values were able to maintain relatively low daytime $PaCO_2$ levels for several years and that the continuation rate of NPPV was higher and the hospitalization rate due to respiratory deterioration was lower in these patients than in those with relatively high 3- to 6-mo $PaCO_2$ values. Elliott emphasized that hypercapnia is a poor prognostic sign and that more aggressive ventilation might have resulted in a larger decrease in daytime $PaCO_2$. [21] Tuggey et al. showed that greater minute ventilation can be achieved by using higher IPAP or larger V_T during controlled NPPV. [20] Reduction in daytime $PaCO_2$ within the first 3 months of NPPV was reported to be positively correlated with support pressure. [11] Windisch et al. found that the $PaCO_2$ value during controlled NPPV using high f_R and high inspiratory pressure decreased to a normocapnic level. [18] They also suggested that nocturnal NPPV with ventilator settings aimed at maximally decreasing $PaCO_2$ could decrease daytime $PaCO_2$ sufficiently and provide additional clinical benefits such as prolongation of life. [17,19]

Dellborg et al. showed that improvements in morning $PaCO_2$ during NPPV correlated significantly with improvements in symptoms and sleep quality after 9 months of NPPV, which indicates the importance of lowering $PaCO_2$ during nocturnal NPPV.[23] These reports support the beneficial effect of nocturnal high intensity NPPV in reducing nocturnal and, therefore, daytime $PaCO_2$ values .

The present study also showed that patients with relatively high 3- to 6-mo $PaCO_2$ values retained relatively high $PaCO_2$ levels throughout their clinical course, although long-term NPPV decreased the $PaCO_2$ level in all 3 groups (Figure 1-b). Patients with relatively high 3- to 6-mo $PaCO_2$ levels had longer periods of LTOT before the initiation of NPPV and more severe ventilatory defects at the start of NPPV. These results indicate the possibility that patients with more advanced disease tend to have higher daytime $PaCO_2$ than those with less advanced disease, with and without application of long-term NPPV. Therefore, it remains unclear whether reducing the nocturnal $PaCO_2$ to a nearly normocapnic level in every patient is possible. Besides, whether a greater reduction in daytime $PaCO_2$ is beneficial in every patient has not been clarified. The excessive resetting of $PaCO_2$ might theoretically augment patients' dyspnea in spontaneous breathing because there is a possibility that, to keep $PaCO_2$ at the set low level, patients have to increase and maintain ventilation exceeding the capacity of their respiratory muscles.

Our study has several limitations. Beginning of the use of and prevalence of the use of NPPV were delayed for more than five years in Japan compared to European countries. [24] Therefore, in many post-tuberculosis patients with hypercapnic

respiratory failure, LTOT had been the only available treatment and their $PaCO_2$ values had already risen to extremely high levels before the start of long-term NPPV [7]. For this reason, in some of our patients, the daytime $PaCO_2$ value could not be reduced below 60 mmHg with long-term NPPV although both IPAP levels and improvement in daytime $PaCO_2$ values were almost equivalent to those of previous studies. [1, 2, 4, 9, 10, 11, 25, 26] The patients in those previous studies had lower $PaCO_2$ values at the start of NPPV than our patients and it was not unexpected that their $PaCO_2$ values after NPPV was lower than those of our patients [1, 2, 4, 9, 10, 11, 25, 26]. In such patients, the target values of $PaCO_2$ after NPPV can be supposed to be much lower than for our patients.

In 92% of our patients LTOT was concomitantly used immediately after the initiation of NPPV. This percentage appears to be high, but we think that the difference in percentage of LTOT usage between a previous study [12] and our study might be attributed to higher $PaCO_2$ and lower PaO_2 of our patients after initiation of long-term NPPV.

In conclusion, we first found that patients with a relatively low $PaCO_2$ a few months after NPPV maintained relatively low $PaCO_2$ levels for several years and that $PaCO_2$ a few months after the initiation of NPPV is a significant predictive variable for rates of continuation of NPPV and hospitalization rates due to respiratory deterioration. The target level of daytime $PaCO_2$ after NPPV should be less than 60 mmHg in patients with extremely severe hypercapnia like ours, although more studies are needed to clarify to what extent the daytime $PaCO_2$ value should be reduced in individual patients with moderate to severe hypercapnia.

CONFLICTS OF INTEREST

All authors have no conflicts of interest to disclose.

ACKNOWLEDGMENT

We thank Hitoshi Murao, Seisuke Niibayashi, Naoki Sakai, Susumu Oguri, Atsuo Sato, Takuya Kurasawa, Kiminobu Tanizawa, Kensaku Aihara, Yoshiko Kawabe, Kazue Shimada, Susumu Sato, Kazuo Endo, Osamu Taguchi, Kunihiko Kamakari and Koichi Shimizu for their contribution to this study.

REFERENCE

1. Leger P, Bedicam JM, Cornette A, Reybet-Degat O, Langevin B, Polu JM, Jeannin L, Robert D. Nasal intermittent positive pressure ventilation: long-term follow-up in patients with severe chronic respiratory insufficiency. Chest 1994; 105:100-5.
2. Simonds AK, Elliott MW. Outcome of domiciliary nasal intermittent positive pressure ventilation in restrictive and obstructive disorders. Thorax 1995; 50: 604-9.
3. Duiverman ML, Bladder G, Meinesz AF, Wijkstra PJ. Home mechanical ventilatory support in patients with restrictive ventilatory disorders: a 48-year experience. Respir Med 2006; 100: 56-65.
4. Brooks D, De Rosie J, Mousseau M, Avendano M, Goldstein RS. Long-term follow-up of ventilated patients with thoracic restrictive or neuromuscular disease. Can Respir J 2002; 9(2): 99-106.
5. Gustafson T, Franklin KA, Midgren B, Pehrsson K, Ranstam J, Strom K. Survival of patients with kyphoscoliosis receiving mechanical ventilation or oxygen at home. Chest 2006; 130: 1828-1833.
6. 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 2008; 133: 156-160.
7. Tsuboi T, Oga T, Machida K, Chihara Y, Matsumoto H, Niimi A, Sumi K, Ohi M, Mishima M, Chin K. Importance of ventilator mode in long-term noninvasive positive pressure ventilation. Respir Med 2009; 103: 1854-1861.
8. 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 1991; 4: 1044-1052.

9. Dellborg C, Olofson J, Hamnegard CH, Skoogh BE, Bake B. Ventilatory response to CO_2 re-breathing before and after nocturnal nasal intermittent positive pressure ventilation in patients with chronic alveolar hypoventilation. Respir Med 2000; 94: 1154-1160.
10. Nickol AH, Hart N, Hopkinson NS, Moxham J, Simonds A, Polkey MI. Mechanisms of improvement of respiratory failure in patients with restrictive thoracic disease treated with non-invasive ventilation. Thorax 2005; 60: 754-760.
11. Budweiser S, Heinemann F, Fischer W, Dobroschke J, Wild PJ, Pfeifer M. Impact of ventilation parameters and duration of ventilator use on non-invasive home ventilation in restrictive thoracic disorders. Respiration 2006; 73: 488-494.
12. Budweiser S, Murbeth RE, Jorres RA, Heinemann F, Pfeifer M. Predictors of long-term survival in patients with restrictive thoracic disorders and chronic respiratory failure undergoing non-invasive home ventilation. Respirology 2007; 12; 551-559.
13. Budweiser S, Jorres RA, Riedl T, Heinemann F, Hitzl AP, Windisch W, Pfeifer M. Predictors of survival in COPD patients with chronic hypercapnic respiratory failure receiving noninvasive home ventilation. Chest 2007; 131: 1650-1658.
14. Tsuboi T, Ohi M, Kita H, Otsuka N, Hirata H, Noguchi T, Chin K, Mishima M, Kuno K. The efficacy of a custom-fabricated nasal mask on gas exchange during nasal intermittent positive pressure ventilation. Eur Respir J 1999; 13: 152-156.
15. Midgren B. Lung function and clinical outcome in postpolio patients: a prospective

cohort study during 11 years. Eur Respir J 1997; 10: 146-149.

16. Barach AL. The adaptive function of hypercapnia. In: Petty TL ed. Chronic obstructive pulmonary disease. New York, NY: Dekker, New York, 1978.

17. Petty TL. CO_2 can be good for you! Chest 2006; 129: 494-495.

18. Windisch W, Vogel M, Sorichter S, Hennings E, Bremer H, Hamm H, Matthys H, Virchow JC Jr. Normocapnia durint nIPPV in chronic hypercapnic COPD reduces subsequent spontaneous $PaCO_2$. Respir Med 2002; 96: 572-579.

19. 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 2005; 128: 657-662.

20. Tuggey JM, Elliott MW. Titration of non-invasive positive pressure ventilation in chronic respiratory failure. Respir Med 2006; 100: 1262-1269.

21. Elliott MW. Noninvasive ventilation in chronic ventilatory failure due to chronic obstructive pulmonary disease. Eur Respir J 2002; 20: 511-514.

22. Meecham Jones DJ, Paul EA, Jones PW, Wedzicha JA. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. Am J Respir Crit Care Med 1995; 152: 538-544.

23. Dellborg C, Olofson J, Midgren B, Caro O, Bergman B, Skoogh BE. Impact of home mechanical ventilation on health-related quality of life in patients with chronic alveolar hypoventilation. A prospective study. Clin Respir J 2008; 2(1): 26-35.

24. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, Escarabill J, Farre R, Fauroux B, Robert D, Schoenhofer B, Simonds AK, Wedzicha JA. Patterns of home mechanical

ventilation use in Europe: results from the Eurovent survey. Eur Respir J 2005: 25; 1025-1031.

25. Gonzalez C, Ferris G, Diaz J, Fontana I, Nunez J, Marin J. Kyphoscoliotic ventilatory insufficiency: Effects of long-term intermittent positive-pressure ventilation. Chest 2003; 124:857-862.

26. Janssens J-P, Derivaz S, Breitenstein E, Muralt B, Fitting J-W, Chevrolet J-C, Rochat T. Changing patterns in long-term noninvasive ventilation: A 7-year prospective study in the Geneva Lake area. Chest 2003; 123: 67-79.

FIGURE LEGENDS

Figure 1-a. Time course of $PaCO_2$ values before and after NPPV.

Comparison between patients with initiation of NPPV in either an acute or chronic state. Data are presented as mean (SD). No significant difference was noted except for values at the start of NPPV.

# $p<0.05$ (compared with patients starting NPPV while in a chronic state).

Figure 1-b. Time course of $PaCO_2$ values before and after NPPV.

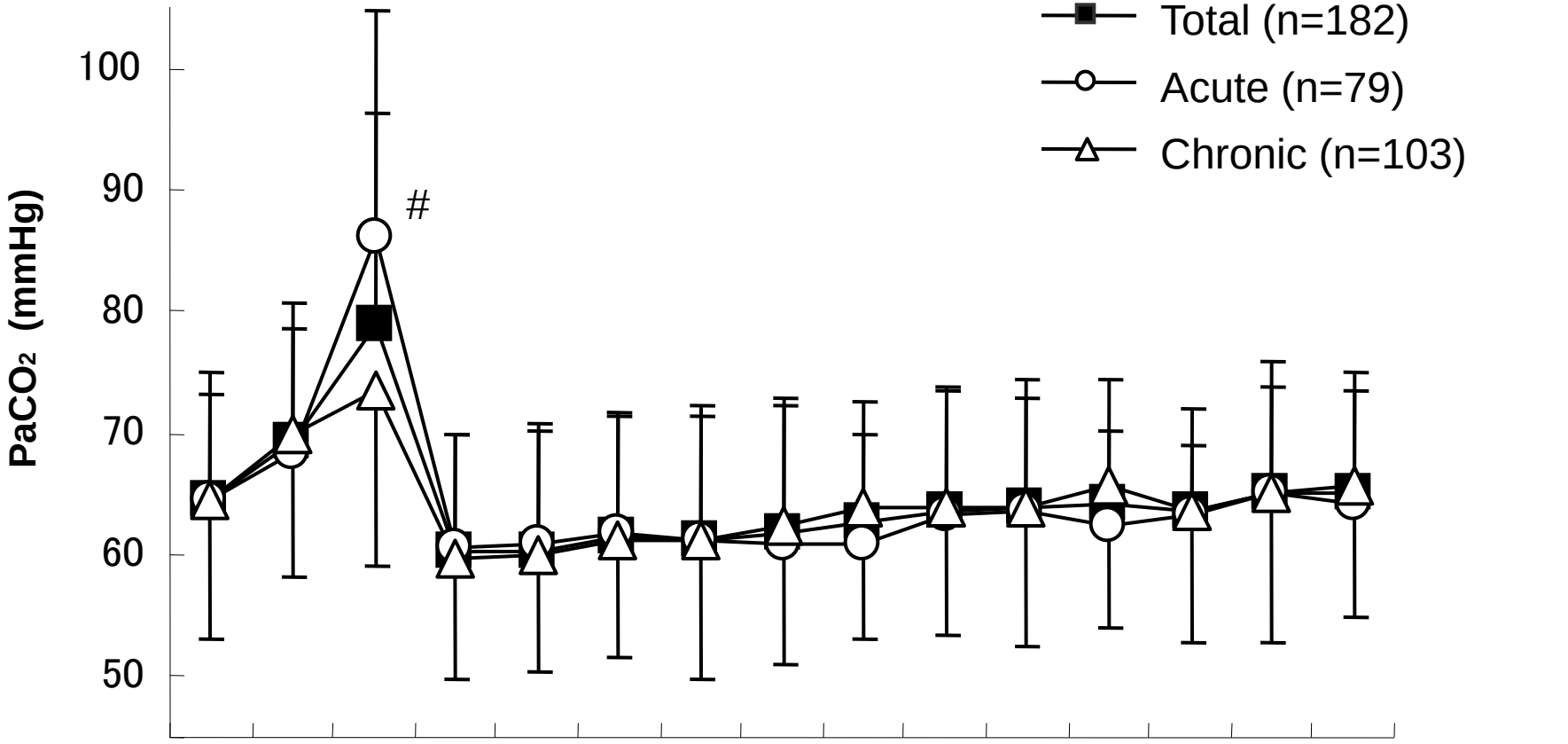
Comparison among patients grouped according to the average $PaCO_2$ 3 to 6 months after introduction of long-term NPPV (3- to 6-mo $PaCO_2$) (Group-1, 60 mmHg>; Group-2, 60 to 70 mmHg; Group-3, >70 mmHg). Data are presented as mean (SD). From 6 to 36 months after initiation of NPPV, patients with relatively high 3- to 6-mo $PaCO_2$ values had significantly higher $PaCO_2$ than those with relatively low 3- to 6-mo $PaCO_2$ ($p=0.0004$).

# $p<0.0001$ (compared to group-1), ++ $p=0.02$ (compared to group-2) by post hoc analysis.

Figure 2. Kaplan-Meier curves of continuation rates of long-term NPPV in all patients. Patients were divided into 3 groups according to the average $PaCO_2$ 3 to 6 months after introduction of long-term NPPV (3- to 6-mo $PaCO_2$) (Group-1, 60 mmHg>; Group-2, 60 to 70 mmHg; Group-3, >70 mmHg). Patients with relatively low 3- to 6-mo $PaCO_2$ values had a significantly better prognosis (log-rank test, $p=0.0003$).

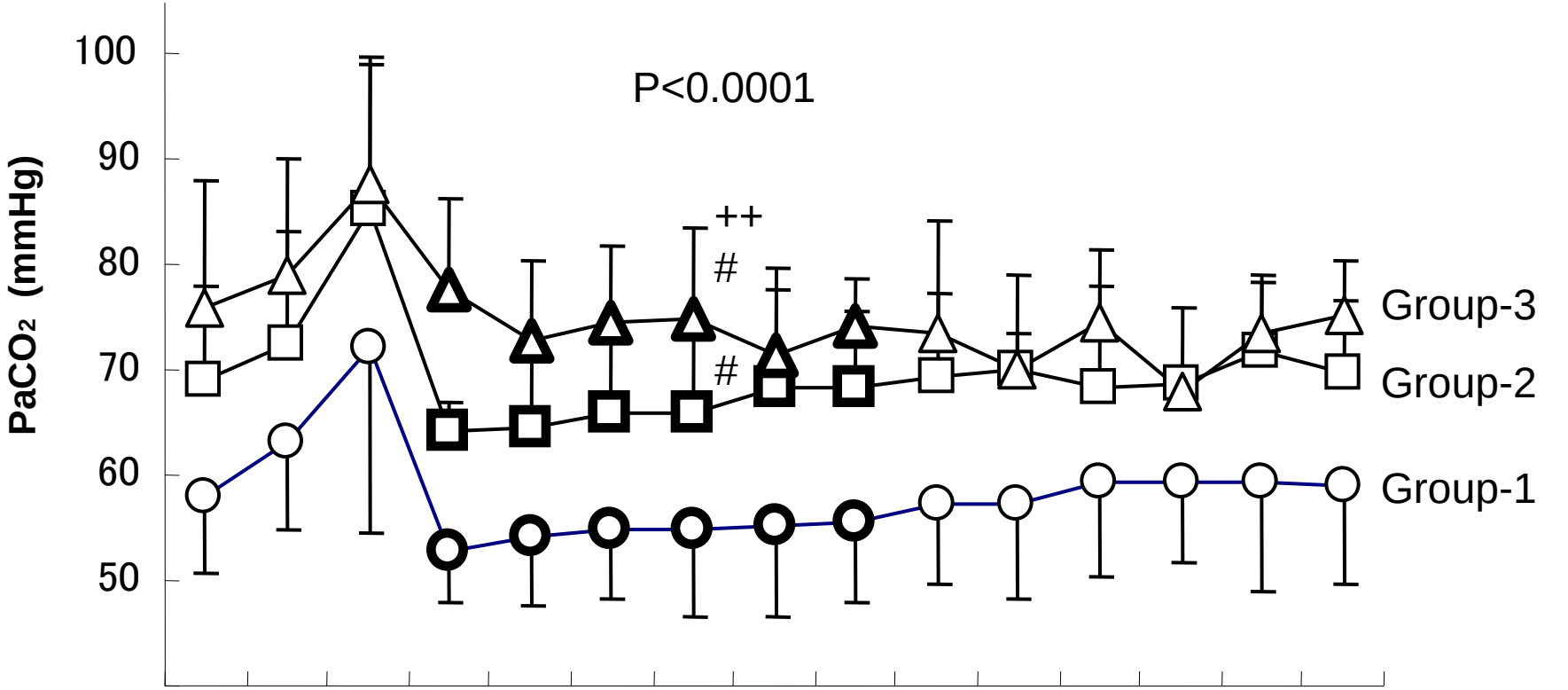
Figure 3. Kaplan-Meier curves for continuation rates of long-term NPPV in patients who began NPPV during a chronic state.

Comparisons were made among patients who were divided into 3 groups according to the average $PaCO_2$ at 3 to 6 months after introduction of long-term NPPV (3- to 6-mo $PaCO_2$) (Group-1, 60 mmHg>; Group-2, 60 to 70 mmHg; Group-3, >70 mmHg). Relatively low 3- to 6-mo $PaCO_2$ was significantly associated with higher continuation rates (log-rank test, p=0.026).



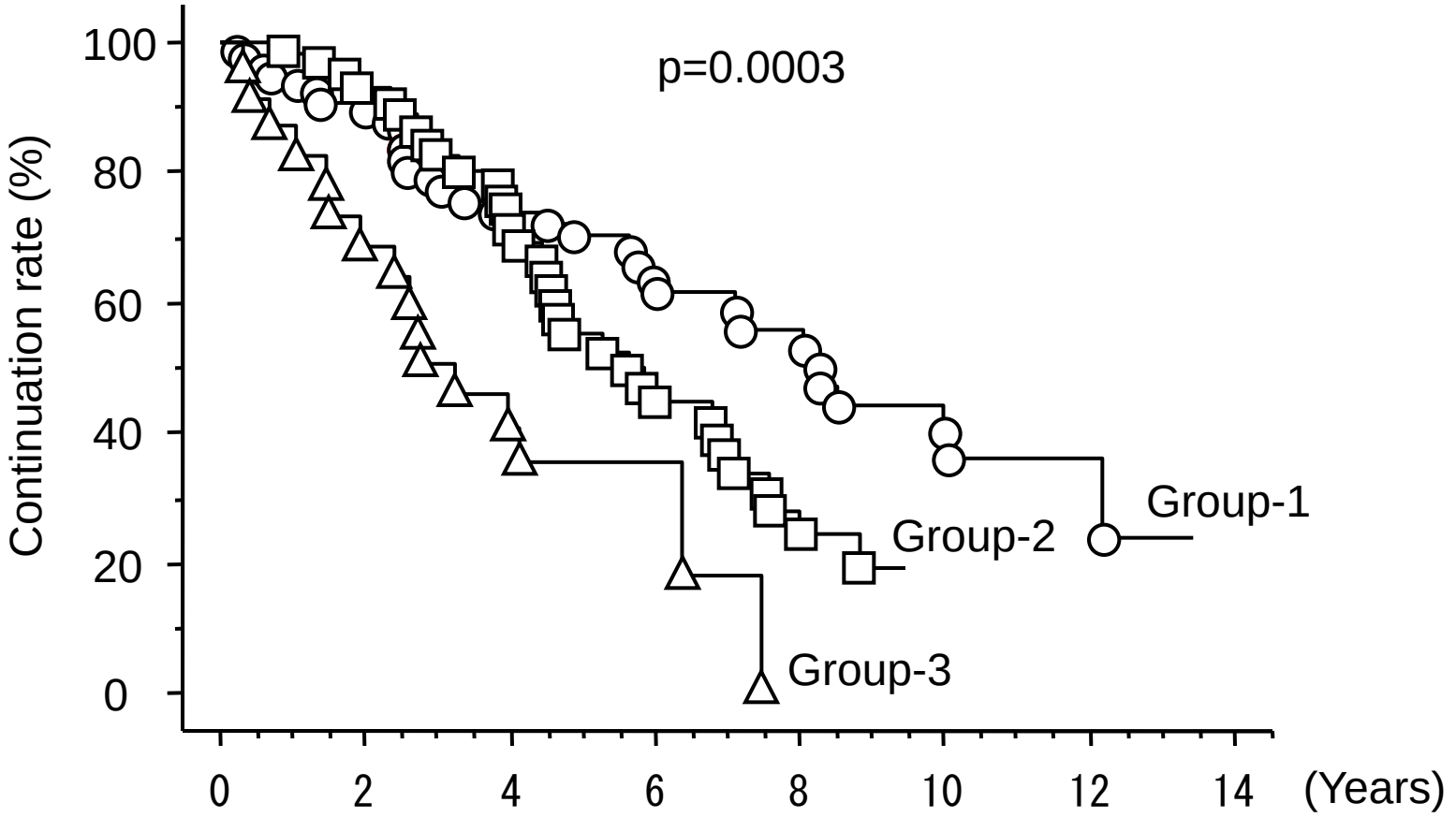
(n)	-12	-6	0	6	12	18	24	30	36	42	48	54	60	66	72
Total	84	101	176	140	139	127	112	100	84	71	69	62	53	49	37
Acute	33	42	77	61	63	55	42	43	35	30	29	29	25	22	18
Chronic	51	59	99	79	76	72	70	57	49	41	40	33	28	27	19

(Figure 1-a)

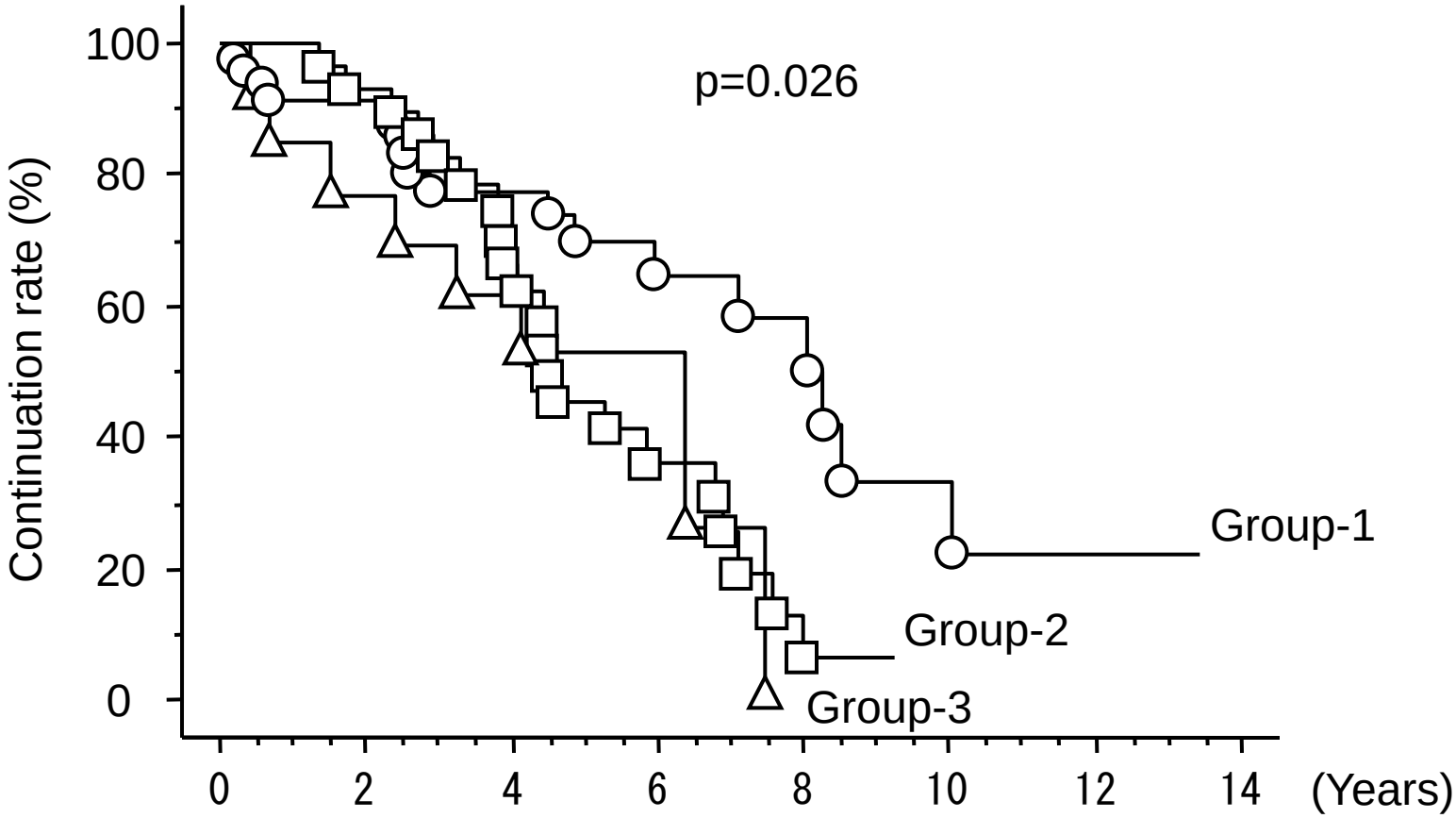


(n)	-12	-6	0	6	12	18	24	30	36	42	48	54	60	66	72
Group-1	40	44	78	68	68	59	55	49	39	34	31	29	28	26	19
Group-2	34	41	59	55	49	46	38	36	32	27	26	24	19	17	13
Group-3	7	11	23	17	17	16	14	11	8	6	6	4	3	4	3

(Figure 1-b)


p=0.0003
Continuation rate (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
(Years)
Group-1
Group-2
Group-3

(Figure 2)


p=0.026
Continuation rate (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
(Years)
Group-1
Group-2
Group-3

(Figure 3)

Table 1. Patients'characteristics at beginning of long-term NPPV

3- to 6-mo $PaCO_2$ levels	Group-1	Group-2	Group-3	p Value
	< 60 mmHg	60 - 70 mmHg	> 70 mmHg	
(n)	79	61	23	
Age (y)	68.1 (9.0)	69.9 (6.7)	69.3 (6.7)	0.42
Gender (Female/ Male)	36/43	31/30	9/14	0.61
BMI (kg/m^2)	19.3 (3.7)	17.9 (3.4)	19.3 (3.0)	0.06
% predicted VC (%)	34.7 (8.6)	30.5 (7.8) *	29.5 (5.5) *	0.004
FEV_1/FVC (%)	70.7 (16.4)	74.9 (16.1)	71.4 (13.4)	0.33
Pulmonary lesions (+/-)	69/10	61/0	23/0	0.004
Annual hospitalization rate due to respiratory deterioration before NPPV	1.27 (0.96)	1.61 (1.07) *	1.43 (0.99)	0.14
Patients' state (Acute/Chronic)	32/47	29/32	10/13	0.71
Duration of LTOT before NPPV (y)	3.7 (3.8)	6.4 (5.0) *	7.7 (4.7) *	<0.0001
Use of LTOT after NPPV (+/-)	71/8	60/1	22/1	0.11
Oxygen supply during spontaneous breathing (l/min.)	1.1 (0.6)	1.3 (0.6)	1.4 (0.6)	0.06
Ventilator mode (Assisted/Controlled)	31/48	22/39	12/11	0.40
Bilevel PAP	n=64	n=53	n=22	
IPAP (cmH_2O)	14.2 (4.1)	16.2 (3.4) *	16.3 (3.0)	0.01
EPAP (cmH_2O)	3.6 (1.1)	3.8 (1.3)	4.3 (0.7) *	0.047
Respiratory rate	20.3 (4.5)	22.2 (3.9)	19.9 (4.0)	0.02
Volume	n=15	n=8	n=1	
Tidal Volume (ml)	578 (116)	533 (81)	620	0.54
Respiratory rate	22.5 (4.5)	25.6 (5.4)	20	0.27
Oxygen supply during NPPV (l/min.)	1.6 (0.8)	1.8 (1.0)	1.8 (0.7)	0.28
ABGs during spontaneous breathing at start of NPPV (NPPV initiated during acute state)	n=32	n=29	n=10	
pH	7.32 (0.06)	7.30 (0.05)	7.34 (0.03)	0.16
PaO_2 (mmHg)	63.4 (18.4)	57.4 (18.9)	79.8 (21.9) #	0.009
$PaCO_2$ (mmHg)	83.0 (20.9)	89.1 (15.7)	90.2 (13.6)	0.34
HCO_3^- (mmol/l)	41.4 (6.5)	42.3 (9.4)	46.9 (6.4)	0.17
ABGs during spontaneous breathing at start of NPPV (NPPV initiated during chronic state)	n=47	n=32	n=13	
pH	7.36 (0.04)	7.33 (0.04) *	7.33 (0.04) *	<0.0001
PaO_2 (mmHg)	71.1 (15.8)	82.0 (14.9) *	83.3 (22.4)	0.007
$PaCO_2$ (mmHg)	64.6 (9.7)	81.6 (11.5) *	86.1 (10.8) *	<0.0001
HCO_3^- (mmol/l)	35.9 (3.9)	42.6 (5.2) *	44.5 (5.1) *	<0.0001

Values given as mean (SD), *p<0.05 (compared to group 1), #p<0.05 (compared to group 2)

3- to 6-mo $PaCO_2$, mean value of $PaCO_2$ measured between 3 and 6 months after introduction of long-term NPPV; BMI, body mass index; VC, vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; NPPV, noninvasive positive pressure ventilation; LTOT, long-term oxygen therapy; bilevel PAP, bilevel positive airway pressure; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure; ABGs, arterial blood gas analyses; PaO_2, $PaCO_2$, arterial oxygen and carbon dioxide tensions; HCO_3^-, bicarbonate.

Table 2. Univariate modality model

Variable	Category	(n)	HR (95%CI)	p Value
Gender	Female	85	0.53 (0.34-0.83)	0.005
	Male	97	Reference	
Age **(y)**	<69	89	0.92 (0.60-1.42)	0.70
	69≦	93	Reference	
BMI (kg/m^2)	18.6≦	83	0.58 (0.37-0.91)	0.02
	<18.6	79	Reference	
% predicted VC (%)	<31.4	81	0.89 (0.56-1.41)	0.62
	31.4≦	81	Reference	
FEV_1/FVC (%)	<70	68	0.87 (0.55-1.39)	0.56
	70≦	95	Reference	
Pulmonary lesions	(-)	14	0.25 (0.08-0.81)	0.02
	(+)	168	Reference	
Patients' status	Acute	79	0.78 (0.51-1.21)	0.27
	Chronic	103	Reference	
Hospitalization rate due to acute	0-1	118	0.65 (0.42-0.99)	0.04
respiratory episodes before NPPV	2≦	64	Reference	
Duration of LTOT before NPPV (y)	4.5≦	91	0.70 (0.46-1.08)	0.11
	<4.5	91	Reference	
Use of LTOT after NPPV	(+)	170	0.79 (0.32-1.96)	0.62
	(-)	12	Reference	
Ventilator mode	Controlled	106	0.54 (0.35-0.83)	0.005
	Assisted	76	Reference	
Ventilator settings				
IPAP (cmH_2O)	continuous variable	162	0.99 (0.94-1.05)	0.82
EPAP (cmH_2O)	continuous variable	162	0.92 (0.78-1.09)	0.33
Respiratory rate (/min.)	continuous variable	182	0.96 (0.91-1.01)	0.14
3- to 6-mo $PaCO_2$ (mmHg)				0.0006
	< 60	79	0.29 (0.16-0.54)	0.0001
	60 - 70	61	0.47 (0.26-0.87)	0.02
	70 <	23	Reference	-

Table 3. Multivariate modality model

Variable		n	HR (95%CI)	p Value
Ventilator mode	Controlled	106	0.41 (0.25 - 0.68)	0.0005
	Assisted	76	Reference	
BMI (kg/m^2)	18.6≦	83	0.54 (0.32 - 0.92)	0.02
	< 18.6	79	Reference	
3- to 6-mo $PaCO_2$ (mmHg)				0.03
	< 60	79	0.37 (0.18 - 0.77)	0.008
	60 - 70	61	0.44 (0.21 - 0.89)	0.02
	70 <	23	Reference	-
Gender	Female	85	0.59 (0.36 - 0.97)	0.04
	Male	97	Reference	
Pulmonary lesions	-	14	0.30 (0.09 - 1.05)	0.06
	+	168	Reference	
Hospitalization rate due to acute respiratory episodes before NPPV	0-1	118	0.81 (0.49 - 1.34)	0.41
	2≦	64	Reference	