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【 ORIGINAL ARTICLE 】

# Low Levels of $PaO_2$ after Long-term Noninvasive Ventilation are a Poor Prognostic Factor in Patients with Restrictive Thoracic Disease

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**Abstract:**

**Objective** The effects of partial pressure of arterial oxygen ($PaO_2$) after introducing long-term noninvasive ventilation (NIV) on the prognosis of patients with restrictive thoracic disease and chronic respiratory failure are not exactly known.

**Methods** Data from 141 patients with restrictive thoracic disease under long-term nocturnal NIV were retrospectively examined. We divided the patients into 2 groups according to the daytime $PaO_2$ value while breathing spontaneously with prescribed oxygen at 12 months after introducing NIV: $PaO_2 \geq 80$ Torr group (n=76) and $PaO_2 < 80$ Torr group (n=65).

**Results** During the 4-year follow-up, the mortality was significantly higher in the $PaO_2 < 80$ Torr group than in the $PaO_2 \geq 80$ Torr group (50.8% vs. 32.9%, p=0.03). Independent factors associated with the 4-year mortality after introducing NIV determined by a multivariate logistic regression analysis were a low body mass index [odds ratio (OR) 0.87; 95% confidence interval (CI) 0.77 to 0.97; p=0.01], assisted mode with NIV (OR 4.11; 95% CI, 1.79 to 9.45; p=0.0009), hospitalization during the first year of introducing NIV (OR 1.72; 95% CI, 1.06 to 2.79; p=0.03), and daytime $PaO_2 < 80$ Torr at 12 months after introducing NIV (OR 2.30; 95% CI, 1.03 to 5.10; p=0.04).

**Conclusion** A low daytime $PaO_2$ at 12 months after introducing NIV was an independent risk factor for mortality. Keeping the daytime $PaO_2 \geq 80$ Torr through the adjustment of the nocturnal NIV settings or increased diurnal supplemental oxygen may help improve the prognosis in patients with restrictive thoracic disease who are under NIV.

**Key words:** chronic respiratory failure, noninvasive ventilation, oxygen therapy, restrictive thoracic disease

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## Introduction

Noninvasive ventilation (NIV) is widely accepted as a treatment option for patients with chronic respiratory failure arising from restrictive thoracic disease (1-3). NIV has been shown to improve the exercise capacity, sleep quality, health-related quality of life, and long-term survival in patients with chronic respiratory failure due to restrictive thoracic disease (4-8).

Improvement in gas exchange in patients after the application of NIV is an important factor that is closely related to the prognosis. Failure to improve the daytime partial pressure of arterial oxygen ($PaO_2$) after introducing NIV was reported to be a prognostic predictor in patients with acute hypoxic respiratory failure (9, 10). However, an association between prognosis and the daytime $PaO_2$ value after introducing long-term NIV in patients with chronic respiratory fail-

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ure due to restrictive thoracic disease has never been reported. In most such patients, oxygen was provided while the patient breathed spontaneously during daytime and/or while receiving NIV at night to correct hypoxemia (8, 11). Nevertheless, there are no specific recommendations about the optimum levels of daytime $PaO_2$ during spontaneous breathing with or without prescribed oxygen in patients with chronic hypercapnic respiratory failure.

In the present study, we examined the prognostic value of the daytime $PaO_2$ in patients with chronic respiratory failure due to restrictive thoracic disease who were receiving long-term nocturnal NIV.

## Materials and Methods

### Patients

All patients who had started NIV due to chronic respiratory failure with hypercapnia at six hospitals affiliated with Kyoto University Hospital and the National Tokyo Hospital from June 1990 to August 2007 were included in this retrospective study. Of the 182 patients who subsequently received NIV, 41 were excluded from the analysis because the daytime arterial blood gases (ABGs) at 12 months after the introduction of NIV were not measured; thus, data were analyzed for the remaining 141 patients. The cause of chronic respiratory failure was post-tuberculosis (n=130) or kyphoscoliosis (n=11). The introduction of NIV was either urgent for acute exacerbation of chronic respiratory failure or scheduled. Patients with other causes of chronic respiratory failure, such as neuromuscular disorders, obesity hypoventilation syndrome, bronchiectasis or chronic obstructive pulmonary disease, were excluded. The patients were followed until November 2011. This study was approved by the Ethics Committee of Kyoto University, and informed consent was obtained.

### Criteria for introducing long-term NIV

The criteria for introducing scheduled NIV were based on clinical symptoms due to hypercapnia, such as morning headache with persistent hypercapnia during the day, the partial pressure of arterial carbon dioxide ($PaCO_2$ >45 Torr), severe daytime hypercapnia ($PaCO_2$ >60 Torr) or recurrent hospitalization due to acute exacerbation following hypercapnia. For patients who received NIV urgently for acute exacerbation of chronic respiratory failure, the need to continue NIV was considered after the patients had fully recovered from their acute exacerbation. The criteria for continuing NIV after acute exacerbation of chronic respiratory failure were daytime $PaCO_2$ >60 Torr under spontaneous breathing and recurrence of symptoms resulting from hypercapnia a few days after discontinuation of NIV.

### Measurements

Patients were divided into 2 groups according to the daytime $PaO_2$ value at 12 months after the introduction of NIV: $PaO_2$≥80 Torr group (n=76) and $PaO_2$<80 Torr group (n=65).

Data were examined for the gender, age, body mass index (BMI), underlying disease, vital capacity (percentage of predicted), forced expiratory volume in 1 second over forced vital capacity ($FEV_1$/FVC), status of introduction of NIV (urgent or scheduled), duration of long-term oxygen therapy (LTOT) before the introduction of NIV, amount of oxygen during spontaneous breathing, use of oxygen therapy during spontaneous breathing, type of ventilator used (pressure preset or volume preset), ventilator mode (assisted mode or pure controlled mode) and ventilator settings, such as the inspiratory positive airway pressure (IPAP), expiratory positive airway pressure (EPAP), tidal volume, respiratory rate and amount of oxygen provided during NIV at the introduction of NIV. The annual number of hospitalizations due to respiratory deterioration (acute bronchitis, pneumonia, spontaneous pneumothorax, chronic disease progression, etc.) beginning from one year before to four years after the start of NIV and mortality in the four years after the introduction of NIV were also examined.

Daytime ABGs were measured every 6 months until 48 months after the introduction of NIV. Such measurements were made with the patient in the supine position breathing room air or prescribed oxygen without NIV support. ABGs were measured in patients who were in a stable condition without exacerbation, except for those obtained at the start of NIV from patients who had begun urgent NIV.

### Clinical protocol for introducing long-term NIV

At the start of NIV, volume preset ventilators and pressure preset ventilators using bilevel PAP devices were used with nasal masks (8, 12, 13). Both an assisted mode and a pure controlled mode were regularly used for all patients who were introduced to NIV, with the patients choosing the mode with which they felt more comfortable. The IPAP or tidal volume was progressively increased until $PaCO_2$ <60 Torr was reached. The EPAP was set as low as possible for easy expiration, while in patients with concomitant obstructive ventilatory disorders of pulmonary function and/or upper airway obstruction, the EPAP was increased to improve inspiratory triggering. On assisted ventilation, a backup respiratory rate was set approximately 4 to 5 breaths below the spontaneous breathing rate without NIV, while the respiratory rate on pure controlled ventilation was set slightly higher than the rate of a patient's own spontaneous breathing in order to suppress respiratory effort. Supplemental oxygen was added to NIV to maintain the arterial oxygen saturation ($SaO_2$) above 90% during nocturnal NIV. During the day, the flow rate for oxygen therapy was determined by the bedside clinician. The details concerning the procedure for introducing NIV have been described elsewhere (8, 12).

### Statistical analyses

Data were analyzed using the JMP software program, ver. 9.0 (SAS Institute, Cary, USA), and the values are expressed as the mean ± SD or in absolute numbers and percentages

**Table 1. Characteristics of 141 Patients Receiving NIV.**

| | $PaO_2$ <80 Torr (n=65) | $PaO_2$ ≥80 Torr (n=76) | p value |
|---|---|---|---|
| Male | 37 (56.9) | 41 (53.9) | 0.72 |
| Age (years) | 66.6±10.5 | 67.5±6.7 | 0.54 |
| BMI | 19.1±3.7 | 18.3±3.7 | 0.24 |
| Underlying disease | | | 0.56 |
| Post-tuberculosis | 59 (90.8) | 71 (93.4) | |
| Kyphoscoliosis | 6 (9.2) | 5 (6.6) | |
| %VC (%) | 31.7±7.8 | 31.0±7.9 | 0.61 |
| $FEV_1$/FVC (%) | 73.0±17.0 | 73.0±15.7 | 0.99 |
| Introduction of NIV | | | 0.13 |
| Scheduled | 40 (61.5) | 37 (48.7) | |
| Urgent | 25 (38.5) | 39 (51.3) | |
| ABGs before NIV | | | |
| pH | 7.335±0.056 | 7.332±0.050 | 0.69 |
| $PaO_2$ (Torr) | 66.3±15.9 | 77.8±21.1 | 0.0004 |
| $PaCO_2$ (Torr) | 75.9±20.4 | 80.3±16.2 | 0.15 |
| Annual hospitalization rate before NIV | 1.5±0.9 | 1.5±1.0 | 0.64 |
| Duration of LTOT before NIV (years) | 4.5±4.3 | 5.8±4.6 | 0.08 |
| Oxygen supply during spontaneous breathing (l/min) | 1.0±0.6 | 1.2±0.6 | 0.06 |
| Use of oxygen therapy during spontaneous breathing | 54 (83.1) | 74 (98.7) | 0.006 |
| Settings of NIV: | | | |
| Type of ventilator Pressure/Volume | 55/10 | 69/7 | 0.26 |
| Ventilator mode (assisted/controlled) | 26/39 | 27/49 | 0.58 |
| Pressure preset | | | |
| IPAP ($cmH_2O$) | 14.9±4.4 | 15.8±3.4 | 0.18 |
| EPAP ($cmH_2O$) | 3.7±1.2 | 3.6±1.1 | 0.72 |
| Respiratory rate | 20.5±4.5 | 21.9±4.1 | 0.12 |
| Volume preset | | | |
| Tidal volume (mL) | 585.0±109.0 | 540.0±119.0 | 0.43 |
| Respiratory rate | 22.5±5.6 | 23.7±3.9 | 0.63 |
| Amount of oxygen during NIV (l/min) | 1.5±1.0 | 1.6±0.9 | 0.32 |

mean±SD or number (%)

NIV: noninvasive ventilation, $PaO_2$: partial pressure of arterial oxygen, BMI: body mass index, VC: vital capacity, $FEV_1$: forced expiratory volume in one second, FVC: forced vital capacity, ABGs: arterial blood gases, $PaCO_2$: partial pressure of arterial carbon dioxide, LTOT: long-term oxygen therapy, IPAP: inspiratory positive airway pressure, EPAP: expiratory positive airway pressure

in each group. We compared the association between the patient characteristics, overall outcome, and the value of daytime $PaO_2$ at 12 months after introducing NIV ($PaO_2$≥80 Torr group or $PaO_2$<80 Torr group). Continuous variables were tested by the unpaired *t*-test or Mann-Whitney U test. Categorical variables were compared using the $\chi^2$ test or the Fisher's exact test. Time trends in continuous variables were compared using a repeated measures analysis of variance. A p value <0.05 was considered to indicate statistical significance. Next, we investigated the associations between the patient characteristics, overall outcome, and 4-year mortality. Possible predictors of the 4-year mortality were tested by univariate and multivariate logistic regression analyses. In the logistic regression analysis of the 4-year mortality, the variables entered into the multivariate analysis were those yielding a p value <0.05 in the univariate analysis; p values <0.05 in the multivariate analysis were considered to indicate statistical significance.

## Results

### Patient characteristics

In this study, all patients received NIV only nocturnally. During spontaneous breathing without NIV, 128 patients (90.8%) received oxygen therapy. The characteristics of the 141 NIV patients are summarized in Table 1. Sixty-four (45.4%) of the 141 patients had been introduced to NIV urgently because of acute exacerbation of chronic respiratory failure. NIV was started in 124 patients (87.9%) with a pressure preset ventilator. There were no significant differences between the $PaO_2$≥80 Torr and $PaO_2$<80 Torr groups in the age, BMI, underlying disease, pulmonary function, annual hospitalization rate before NIV or NIV settings (Table 1). However, the use of oxygen therapy during spontaneous breathing without NIV was more frequent in the $PaO_2$≥80

Torr group than in the $PaO_2$<80 Torr group (p=0.006).

### Change in ABGs before and after NIV

Before the introduction of NIV, the daytime $PaO_2$ values were significantly higher in the $PaO_2$≥80 Torr group than in the $PaO_2$<80 Torr group (p=0.0004) (Fig. 1), while the pH (p=0.69) and $PaCO_2$ (p=0.15) were not significantly different between the two groups (Table 1, Fig. 2).

In both the $PaO_2$≥80 Torr and $PaO_2$<80 Torr groups, the daytime $PaO_2$ values at 12 months after the introduction of NIV were significantly greater than those before the introduction of NIV. The improvement in the daytime $PaO_2$ after 12 months of NIV was greater in the $PaO_2$≥80 Torr group than in the $PaO_2$<80 Torr group (p<0.0001) (Fig. 1). In addition, the daytime $PaO_2$ values were consistently higher in the $PaO_2$≥80 Torr group than in the $PaO_2$<80 Torr group during the 4 years after the introduction of NIV (Fig. 1).

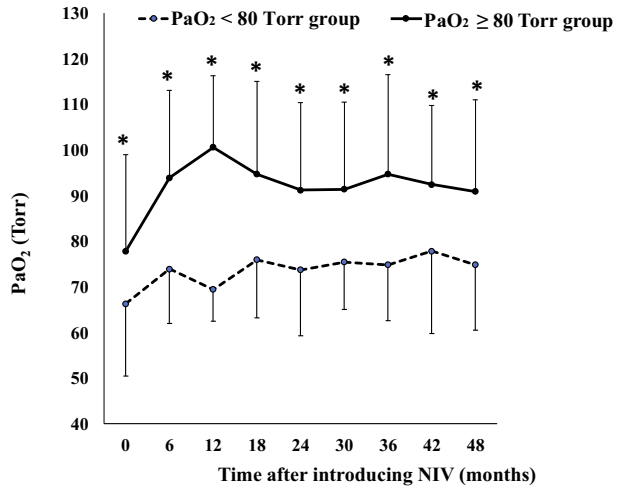


**Figure 1. Changes in the daytime $PaO_2$ in patients with $PaO_2$ ≥80 Torr and those with $PaO_2$ <80 Torr. Data are presented as the mean values ± SD. A single asterisk indicates p<0.05 between patients with $PaO_2$ ≥80 Torr and those with $PaO_2$ <80 Torr. NIV: noninvasive ventilation, $PaO_2$: partial pressure of arterial oxygen**

The daytime $PaCO_2$ values after 12 months of NIV were significantly lower than those before the introduction of NIV in both groups (Fig. 2). In contrast, there were no significant differences between the two groups in the daytime $PaCO_2$ levels (p=0.43) at 12 months after the introduction of NIV (Table 2). In addition, the differences in the daytime $PaCO_2$ values were not significant during the four years after the introduction of NIV (Fig. 2).

### Overall outcome

After the long-term use of NIV, 13 patients switched to long-term tracheostomy positive pressure ventilation (TPPV). In the 4-year follow-up period after the introduction of NIV, 58 patients died, 2 started receiving TPPV, and 81 continued the use of NIV.

After the introduction of NIV, the annual hospitalization rate due to respiratory deterioration decreased significantly in both groups (Fig. 3). There was no significant difference between the two groups in the annual hospitalization rate during the first year of NIV (p=0.70) (Table 2, Fig. 3).

Twenty-five (32.9%) of the 76 patients in the $PaO_2$≥80 Torr group died, while 33 (50.8%) of the 65 patients in the $PaO_2$<80 Torr group died (p=0.03). The survival curve shows that the patients in the daytime $PaO_2$<80 Torr group had a significantly poorer prognosis than those in the $PaO_2$≥80 Torr group (Fig. 4). In addition, the 4-year mortality due to respiratory failure was significantly higher in the $PaO_2$<80 Torr group than in the $PaO_2$≥80 Torr group (p=0.01) (Table 2).

Regarding the observation period, there were no significant differences between the $PaO_2$≥80 Torr group and $PaO_2$<

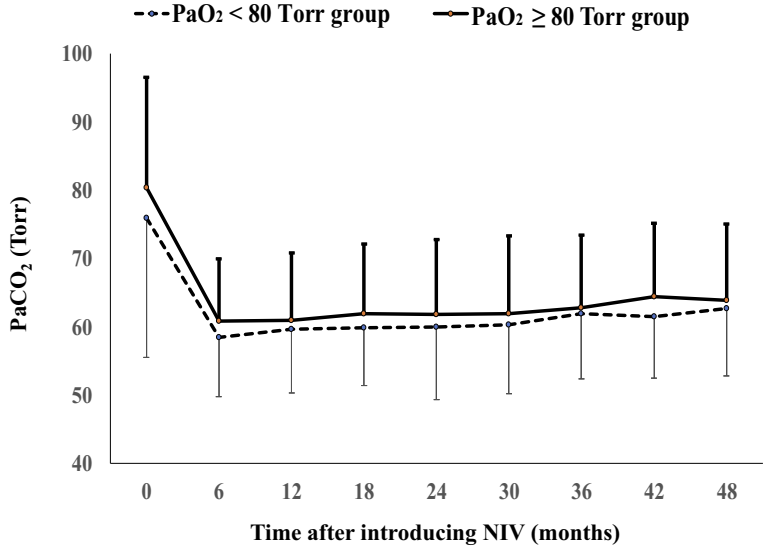


**Figure 2. Change in the daytime $PaCO_2$ in patients with $PaO_2$ ≥80 Torr and those with $PaO_2$ <80 Torr. Data are presented as the mean values ± SD. NIV: noninvasive ventilation, $PaO_2$: partial pressure of arterial oxygen, $PaCO_2$: partial pressure of arterial carbon dioxide**

**Table 2. Outcome of 141 Patients who Were Receiving NIV.**

| | $PaO_2$ <80 Torr (n=65) | $PaO_2$ ≥80 Torr (n=76) | p value |
|---|---|---|---|
| ABGs after 12 months of NIV | | | |
| pH | 7.376±0.030 | 7.368±0.029 | 0.14 |
| $PaO_2$ (Torr) | 69.4±7.0 | 100.6±15.7 | <0.0001 |
| $PaCO_2$ (Torr) | 59.6±9.3 | 60.9±9.9 | 0.43 |
| Annual hospitalization rate (1st year of NIV) | 0.5±0.7 | 0.6±0.9 | 0.70 |
| 4-year mortality, due to: | 33 (50.8) | 25 (32.9) | 0.03 |
| Respiratory failure | 30 (46.2) | 20 (26.3) | 0.01 |
| Others | 3 (4.6) | 5 (6.6) | 0.73 |
| Total observation period (years) | 5.6±2.8 | 5.2±3.6 | 0.36 |
| Mortality during total observation period | 53 (81.5) | 48 (63.2) | 0.12 |

mean±SD or number (%)

NIV: noninvasive ventilation, $PaO_2$: partial pressure of arterial oxygen, ABGs: arterial blood gases, $PaCO_2$: partial pressure of arterial carbon dioxide

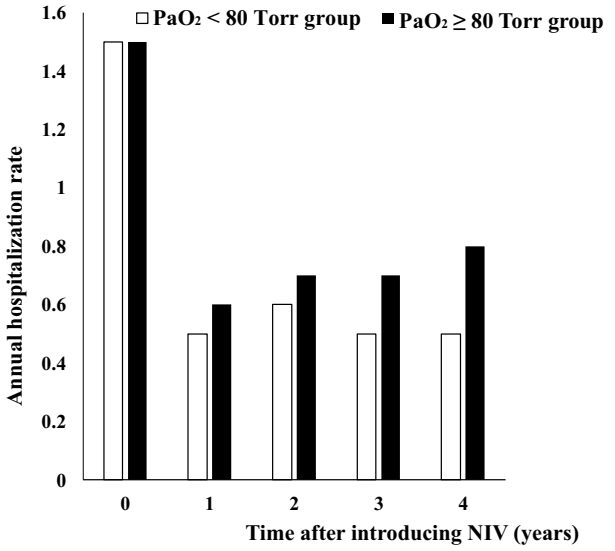


**Figure 3. Annual hospitalization rate before and after the introduction of NIV in the $PaO_2$ ≥80 Torr group and $PaO_2$ <80 Torr group. NIV: noninvasive ventilation, $PaO_2$: partial pressure of arterial oxygen**

80 Torr group ($PaO_2$≥80 Torr group: 5.6±2.8 years vs. $PaO_2$< 80 Torr group: 5.2±3.6 years; p=0.36). A significant difference in mortality between the $PaO_2$≥80 Torr group and the $PaO_2$<80 Torr group was observed until 7 years after introducing NIV (p=0.02), but the difference was lost in the analysis of the entire observation period (p=0.12).

### *A logistic regression analysis of the 4-year mortality after the introduction of NIV*

Among the 26 factors evaluated (those listed in Tables 1 and 2 and $PaO_2$<80 Torr after 12 months of NIV), the univariate analysis showed that 5 factors had a significant association with the 4-year mortality after introducing NIV (Table 3). Among the variables that had very strong co-linearity (r>0.70) with each other, such as the daytime $PaO_2$ after 12 months of NIV, and daytime $PaO_2$<80 Torr after 12 months of NIV, one was selected.

In the multivariate forward logistic analysis of factors related to the 4-year mortality after introducing NIV, a low BMI [odds ratio (OR) 0.87; 95% confidence interval (CI) 0.77 to 0.97; p=0.01], ventilator mode of NIV (assisted mode) (OR 4.11; 95% CI, 1.79 to 9.45; p=0.0009), increased annual hospitalization rate during the first year after introducing NIV (OR 1.72; 95% CI, 1.06 to 2.79; p=0.03) and daytime $PaO_2$<80 Torr after 12 months of NIV (OR 2.30; 95% CI, 1.03 to 5.10; p=0.04) were found to be significant risk factors for the 4-year mortality after the introduction of NIV (Table 4). On substituting the daytime $PaO_2$ after 12 months of NIV for daytime $PaO_2$<80 Torr after 12 months of NIV, a low BMI, assisted mode in NIV, a high annual hospitalization rate and a low $PaO_2$ value after 12 months of NIV remained significant risk factors for the 4-year mortality after the introduction of NIV (Table 4).

## Discussion

Although the data were retrospective, this long-term NIV study of patients with restrictive thoracic disease showed that patients with daytime $PaO_2$<80 Torr at 12 months after the introduction of NIV had a significantly higher mortality rate than those with daytime $PaO_2$≥80 Torr. In addition, our study revealed the following significant factors to be predictive of the 4-year mortality following NIV: a low BMI, assisted mode in NIV, a high annual hospitalization rate during the first year after the introduction of NIV and daytime $PaO_2$<80 Torr after 12 months of NIV or low $PaO_2$ value after 12 months of NIV. These results suggest that the daytime $PaO_2$ value after 12 months of NIV may be a useful marker for predicting the prognosis in patients with restrictive thoracic disease who are receiving long-term NIV therapy.

In addition to a low BMI (14), the assisted mode in NIV (8) and a high annual hospitalization rate (15), which were all shown to have a negative impact on the prognosis in patients with chronic respiratory failure, a daytime $PaO_2$<

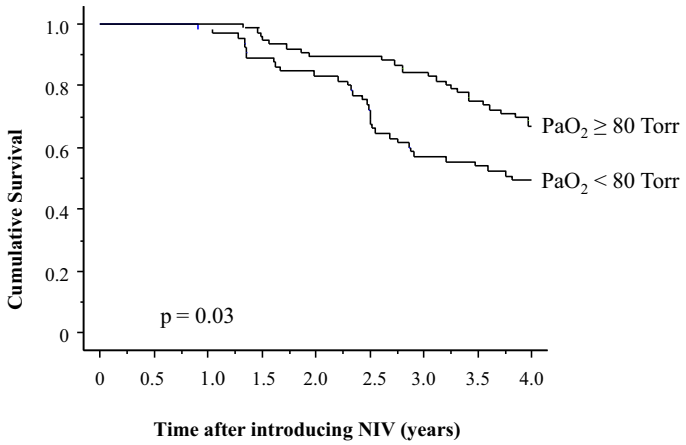


**Figure 4. Survival curve following NIV in the $PaO_2$ ≥80 Torr group and $PaO_2$ <80 Torr group. Patients with a daytime $PaO_2$ <80 Torr had a significantly poorer prognosis than those with $PaO_2$ ≥80 Torr (p=0.03). NIV: noninvasive ventilation, $PaO_2$: partial pressure of arterial oxygen**

**Table 3. Univariate Analysis of Factors Related to 4-year Mortality Rate.**

| | OR | 95% CI | p value |
|---|---|---|---|
| Male | 0.99 | 0.50 to 1.94 | 0.98 |
| Age (years) | 1.03 | 0.99 to 1.07 | 0.17 |
| BMI | 0.90 | 0.81 to 0.99 | 0.04 |
| Underlying disease | | | |
| Post-tuberculosis | 3.41 | 0.71 to 16.39 | 0.13 |
| Kyphoscoliosis | | | |
| %VC (%) | 1.01 | 0.97 to 1.06 | 0.67 |
| $FEV_1$/FVC (%) | 1.01 | 0.99 to 1.04 | 0.30 |
| Introduction of NIV | | | |
| Scheduled | 0.92 | 0.47 to 1.81 | 0.82 |
| Urgent | | | |
| ABGs before NIV | | | |
| pH | 0.64 | | 0.89 |
| $PaO_2$ (Torr) | 0.99 | 0.97 to 1.01 | 0.33 |
| $PaCO_2$ (Torr) | 1.01 | 0.99 to 1.02 | 0.61 |
| Annual hospitalization rate before NIV | 1.06 | 0.75 to 1.48 | 0.76 |
| Duration of LTOT before NIV (years) | 0.94 | 0.87 to 1.02 | 0.14 |
| Oxygen supply during spontaneous breathing (l/min) | 0.89 | 0.50 to 1.55 | 0.67 |
| Use of oxygen therapy during spontaneous breathing | 0.57 | 0.18 to 1.79 | 0.33 |
| Settings of NIV: | | | |
| Volume preset | 1.00 | 0.36 to 2.81 | 0.99 |
| Assisted mode | 2.80 | 1.38 to 5.65 | 0.004 |
| IPAP ($cmH_2O$) | 1.08 | 0.88 to 1.32 | 0.49 |
| EPAP ($cmH_2O$) | 1.03 | 0.54 to 1.99 | 0.92 |
| Respiratory rate | 0.94 | 0.87 to 1.03 | 0.17 |
| Tidal volume (mL) | 1.00 | 0.99 to 1.01 | 0.60 |
| Amount of oxygen during NIV (l/min) | 0.83 | 0.57 to 1.20 | 0.32 |
| ABGs after 12 months of NIV | | | |
| pH | 2.40 | | 0.88 |
| $PaO_2$ (Torr) | 0.88 | 0.80 to 0.98 | 0.03 |
| $PaCO_2$ (Torr) | 1.02 | 0.99 to 1.06 | 0.24 |
| $PaO_2$ <80 Torr after 12 months of NIV | 2.10 | 1.06 to 4.16 | 0.03 |
| Annual hospitalization rate (1st year of NIV) | 1.70 | 1.10 to 2.63 | 0.02 |

OR: odds ratio, 95%CI: 95% confidence interval, BMI: body mass index, VC: vital capacity, $FEV_1$: forced expiratory volume in one second, FVC: forced vital capacity, NIV: noninvasive ventilation, ABGs: arterial blood gases, $PaO_2$: partial pressure of arterial oxygen, $PaCO_2$: partial pressure of arterial carbon dioxide, LTOT: long-term oxygen therapy, IPAP: inspiratory positive airway pressure, EPAP: expiratory positive airway pressure

**Table 4. Multivariate Forward Logistic Regression Analysis of the 4-year Mortality Rate.**

| Model 1. | | | | |
|---|---|---|---|---|
| | OR | 95% CI | p value | |
| BMI | 0.87 | 0.77 to 0.97 | 0.01 | |
| Ventilator mode for NIV: Assisted mode | 4.11 | 1.79 to 9.45 | 0.0009 | |
| $PaO_2$ <80 Torr after 12 months of NIV | 2.30 | 1.03 to 5.10 | 0.04 | |
| Annual hospitalization rate (1st year of NIV) | 1.72 | 1.06 to 2.79 | 0.03 | |
| R square of the model | | | | 0.150 |

| Model 2. | | | | |
|---|---|---|---|---|
| | OR | 95% CI | p value | |
| BMI | 0.87 | 0.77 to 0.97 | 0.01 | |
| Ventilator mode for NIV: Assisted mode | 4.00 | 1.74 to 9.20 | 0.001 | |
| $PaO_2$ after 12 months of NIV | 0.89 | 0.80 to 0.98 | 0.04 | |
| Annual hospitalization rate (1st year of NIV) | 1.71 | 1.05 to 2.78 | 0.03 | |
| R square of the model | | | | 0.144 |

OR: odds ratio, 95%CI: 95% confidence interval, BMI: body mass index, NIV: noninvasive ventilation, $PaO_2$: partial pressure of arterial oxygen

80 Torr after 12 months of NIV was an independent risk factor for the 4-year mortality after introducing NIV. Both a low BMI (indicating malnutrition) and hospital admissions due to respiratory deterioration reflect severe illness. It has been assumed that a controlled mode achieves passive ventilation, leading to better unloading of respiratory muscles so that improvement in respiratory muscle strength can thus be achieved (8). In addition, keeping the daytime $PaO_2$ high helps prevents severe hypoxia on effort and reduces the cardiac load.

In previous reports, it was shown that a relatively low $PaCO_2$ value a few months after initiating NIV was a good prognostic factor for hospitalization due to respiratory deterioration and for mortality in patients with chronic restrictive ventilatory failure (12, 16, 17). However, using ABG data obtained over a longer period of time after the introduction of NIV in the present study, we found that the $PaO_2$ rather than the $PaCO_2$ after 12 months of NIV was an independent prognostic factor for mortality. The loss of predictability with $PaCO_2$ after a year of NIV can be attributed to the fact that many patients with a high $PaCO_2$ after a few months of NIV die within a year (12). Long-term oxygen therapy reportedly did not provide any benefit with respect to the time until death or until the first hospitalization in patients with stable chronic obstructive pulmonary disease and moderate desaturation (18). In contrast, there have been no specific recommendations regarding the prescription of oxygen for patients receiving NIV due to restrictive ventilatory failure. In the present study, the proportion of those using oxygen therapy during spontaneous breathing without NIV was significantly lower in the $PaO_2$<80 Torr group than in the $PaO_2$ ≥80 Torr group. Generally, as with our study, many clinicians prescribe a small amount of oxygen for LTOT or NIV therapy because an extremely high $PaO_2$ can generate potentially detrimental effects, including $CO_2$ retention, which is mediated by mechanisms such as hypoventilation, ventilation/perfusion redistribution or the Haldane effect. However, the present study found no significant differences between the two groups in the annual hospitalization rate due to respiratory deterioration, including $CO_2$ retention, from the first to the fourth year of NIV. Based on these results, keeping the daytime $PaO_2$≥80 Torr by increasing the amount of oxygen is unlikely to cause $CO_2$ retention and should be considered as a therapeutic option that may help improve the prognosis in patients with chronic restrictive ventilatory failure who are receiving nocturnal NIV.

Both $PaO_2$ values before the introduction of NIV and those after 12 months of NIV were significantly lower in the $PaO_2$<80 Torr group than in the $PaO_2$≥80 Torr group in this study. In detail, the $PaO_2$ values after 12 months of NIV in the $PaO_2$≥80 Torr group were quite high at 100.6±15.7 Torr. Patients with chronic respiratory failure are often complicated with pulmonary hypertension, which is likely the result of a number of factors, including pulmonary vasoconstriction caused by alveolar hypoxia (19), acidemia (19), hypercapnia (20), distortion of pulmonary vessels by parenchymal changes, and increased cardiac output and blood viscosity from polycythemia secondary to hypoxia. Pulmonary hypertension itself causes hypoxia through ventilation/perfusion inequality, a shunt and a low mixed venous $PaO_2$ through a low cardiac output, so patients with both chronic respiratory failure and pulmonary hypertension may have more severe hypoxia than those without pulmonary hypertension. Although this study did not investigate the presence of pulmonary hypertension in these patient groups, there is a possibility that the $PaO_2$<80 Torr patients had a significantly higher rate of pulmonary hypertension than those in the $PaO_2$≥80 Torr group, which would lead to severe hypoxia. In addition, the presence of pulmonary hypertension might have influenced the improvement of the $PaO_2$ values after

NIV.

Several limitations associated with the present study warrant mention. First, it had a retrospective design. However, the large number of cases included in our analysis was probably sufficient to minimize the impact of this limitation. Second, the criteria used for NIV initiation in this study were different from the current guidelines in patients with restrictive thoracic disease. Third, the study period was relatively long. Therefore, improvements in general care, including the management of co-morbidities, fluids and antibiotics, might have influenced the outcome in this study, such as that related to the 4-year mortality following NIV. Fourth, our study was a multi-center study, leading to the possibility that the prognosis of the patients studied was influenced by differences in oxygen administration and NIV setting among institutions or clinicians. Fifth, there were no significant differences between the two groups in mortality throughout the entire observation period. These results suggest that the daytime $PaO_2$ value after 12 months of NIV may not be useful for predicting the prognosis in a longer-term observation period. A multi-center randomized controlled study following up on the results of the present experience would be useful for addressing these limitations.

## Conclusion

In conclusion, we demonstrated that a daytime $PaO_2$<80 Torr following 12 months of NIV was a significant predictor of the 4-year mortality after the introduction of NIV. There were no significant differences in the frequency of $CO_2$ retention between the $PaO_2$≥80 Torr group and the $PaO_2$<80 Torr group. Although a randomized controlled trial is needed, keeping the daytime $PaO_2$≥80 Torr by increasing the amount of oxygen may help improve the prognosis of restrictive thoracic disease patients who receive NIV.

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

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### *References*

1. Mehta S, Hill NS. Noninvasive ventilation. Am J Respir Crit Care Med **163**: 540-577, 2001.
2. Shneerson JM, Simonds AK. Noninvasive ventilation for chest wall and neuromuscular disorders. Eur Respir J **20**: 480-487, 2002.
3. Ozsancak A, D'Ambrosio C, Hill NS. Nocturnal noninvasive ventilation. Chest **133**: 1275-1286, 2008.
4. 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.
5. Simonds AK, Elliott MW. Outcome of domiciliary nasal intermittent positive pressure ventilation in restrictive and obstructive disorders. Thorax **50**: 604-609, 1995.
6. Janssens JP, Derivaz S, Breitenstein E, et al. Changing patterns in long-term noninvasive ventilation: a 7-year prospective study in the Geneva Lake area. Chest **123**: 67-79, 2003.
7. Gustafson T, Franklin KA, Midgren B, Pehrsson K, Ranstam J, Ström K. Survival of patients with kyphoscoliosis receiving mechanical ventilation or oxygen at home. Chest **130**: 1828-1833, 2006.
8. 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.
9. Antonelli M, Conti G, Moro ML, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive Care Med **27**: 1718-1728, 2001.
10. Antonelli M, Conti G, Esquinas A, et al. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. Crit Care Med **35**: 18-25, 2007.
11. Buyse B, Meersseman W, Demedts M. Treatment of chronic respiratory failure in kyphoscoliosis: oxygen or ventilation? Eur Respir J **22**: 525-528, 2003.
12. Tsuboi T, Ohi M, Oga T, 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.
13. 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.
14. Cano NJ, Pichard C, Roth H, et al; Clinical Research Group of the Société Francophone de Nutrition Entérale et Parentérale. C-reactive protein and body mass index predict outcome in end-stage respiratory failure. Chest **126**: 540-546, 2004.
15. Ankjærgaard KL, Rasmussen DB, Schwaner SH, Andreassen HF, Hansen EF, Wilcke JT. COPD: mortality and readmissions in relation to number of admissions with noninvasive ventilation. COPD **14**: 30-36, 2017.
16. Martí S, Pallero M, Ferrer J, et al. Predictors of mortality in chest wall disease treated with noninvasive home mechanical ventilation. Respir Med **104**: 1843-1849, 2010.
17. Midgren B. Home mechanical ventilation in chest wall disease should aim at full correction of PaCO(2). Respir Med **104**: 1765-1766, 2010.
18. Long-Term Oxygen Treatment Trial Research Group; Albert RK, Au DH, Blackford AL, et al. A randomized trial of long-term oxygen for COPD with moderate desaturation. N Engl J Med **375**: 1617-1627, 2016.
19. Enson Y, Giuntini C, Lewis ML, Morris TQ, Ferrer MI, Harvey RM. The influence of hydrogen ion concentration and hypoxia on the pulmonary circulation. J Clin Invest **43**: 1146-1162, 1964.
20. Durand J, Le Roy Ladurie M, Ranson-Bitker B. Effects of hypoxia and hypercapnia on the repartition of pulmonary blood flow in supine subjects. Respir Res **5**: 156-165, 1970.