Efficacy of Nocturnal Nasal Positive Pressure Ventilation in Hypercapnic Patients with Severe Obstructive Lung Diseases

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Background: The study objective was to investigate the efficacy of 6 months of nocturnal nasal positive pressure ventilation (NNPPV) on arterial blood gas, exercise capacity, respiratory muscle function, and the frequency of hospital admission in hypercapnic patients with severe obstructive lung diseases.

Methods: This was a prospective, randomized, controlled study. Twenty-seven patients with hypercapnic obstructive lung diseases were randomized to either the NNPPV group (N=13) or the control group (N=14). Arterial blood gas, exercise capacity and respiratory muscle function were measured before and after 6 months of NNPPV intervention. The number of hospital admissions and the length of stay during the 6-month period before and after NNPPV intervention were recorded.

Results: Subjects in the NNPPV group showed a significant reduction in arterial carbon dioxide partial pressure ($PaCO_2$), bicarbonate (HCO_3^-), and base excess (BE), compared with those before intervention and of the control group. Six-minute walk distance (6MWD) also increased significantly from 232.2 ± 79.3 m to 333.4 ± 81.3 m in the NNPPV group after 6 months of intervention. The maximum voluntary ventilation (MVV) also increased significantly after NNPPV intervention. Moreover, the NNPPV group had significantly lower frequency of admission and fewer days of hospital stay during the intervention period compared with those before intervention and of the control group.

Conclusion: Six months of NNPPV improved the arterial blood gas, increased exercise capacity and respiratory muscle endurance, and helped to reduce the frequency and the length of hospitalization in hypercapnic patients with severe obstructive lung disease.
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Key words: hypercapnic obstructive lung disease, nocturnal nasal positive pressure ventilation, 6-minute walk test, arterial blood gas.

Patients with chronic obstructive pulmonary diseases (COPD) more have frequent nocturnal oxygen desaturations than normal persons, related to episodic hypoventilation, particularly during rapid eye movement (REM) sleep.[1-3] These desaturations are associated with arousals that shorten the duration

and diminish the quality of sleep, which is an effect that is usually reversed by oxygen supplementation.[2] By assisting ventilation, nocturnal nasal positive pressure ventilation (NNPPV) offers the potential of restoring inspiratory flow rate, eliminating episodes of hypoventilation, and improving nocturnal gas exchange. Initially, the uncontrolled trials by Elliott et al. of nasal intermittent positive pressure ventilation in severe stable COPD showed improvement in the daytime and nocturnal gas exchange in small groups of patients.[4,5]

Subsequently, in a 3-month crossover trial of NNPPV, Strumpf et al. found improvement only in neuropsychologic function, but not daytime gas exchange.[6] In contrast, in a study of nearly identical design, the study by Meecham-Jones et al. showed improvement in the nocturnal and daytime gas exchange.[7] Moreover, the enhanced patient-ventilator synchrony or inpatient acclimatization might raise the possibility of better outcomes. Gay et al. had completed 3-month trial and Lin et al. completed a 2-week trial,[8,9] and their results suggested that the short treatment period led to unfavorable results. All these conflicting results highlight the need for randomized controlled, long-term trials of NNPPV. Additionally, other potential physiologic benefits on exercise tolerance,[10,11] respiratory drive and respiratory muscle function[12,13] of long-term NNPPV remain controversial and need to be elucidated.

Some series of small numbers of patients with obstructive lung diseases like cystic fibrosis and diffuse bronchiectasis and receiving NNPPV treatment have also reported to improve gas exchange and reduce the number of hospitalization days.[14,15] A similar finding was reported in an uncontrolled trial of 15 patients with hypercapnic COPD.[16] These results indicate that the effect of NNPPV on lowering the utilization of health resources for patients with chronic lung diseases deserves further examination.

Therefore, we conducted this study to investigate the efficacy of 6 months of NNPPV intervention on arterial blood gas, exercise capacity, and respiratory muscle function in patients with hypercapnic obstructive lung diseases. Furthermore, we also explored the efficacy of NNPPV on the frequency of hospitalization and the length of hospitalization for these patients.

METHODS

Subjects

Patients with severe hypercapnic obstructive lung diseases from outpatient clinic of the Chang Gung Memorial Hospital were recruited for the study, if they (1) were diagnosed with obstructive lung diseases, such as chronic obstructive pulmonary disease (COPD), asthma, and bronchiectasis;[17] (2) had repeat admission due to lung deterioration despite appropriate treatments including pharmacological and oxygen therapies; (3) were well motivated patients; (4) were sleepy during daytime and/or had headache upon waking in the morning; and (5) had daytime arterial carbon dioxide partial pressure ($PaCO_2$) > 50 mmHg and pulse oxygen saturation (SpO_2) < 88% for more than 5 consecutive minutes while on usual fraction of inspired oxygen during sleep according to polysomnography.[17] Subjects were excluded from this study if they (1) were uncooperative and had poor motivation or were unable to tolerate NNPPV; (2) were diagnosed with obstructive sleep apnea diseases (i.e., apnea hypopnea index, AHI > 10 times/hour);[17] or (3) were unable to perform a 6-minute walk test (6MWT) due to a variety of other diseases (e.g., orthopedic or neuromuscular problems). All of the enrolled patients were randomly given a computer-generated number. A total of 37 patients were originally enrolled in the study, and were allocated to either the control group (with standard treatment) (N=18) or the NNPPV group (standard treatment plus NNPPV) (N=19).

Subjects in the NNPPV group were asked to use nasal positive pressure ventilation for at least 6 hours at night during sleep for 6 consecutive months. Four subjects in the NNPPV group, who were unable to tolerate this treatment within 3 months, were excluded from the data analysis. Two patients in the study group died during the study period. Four patients in the control group died during the 6-month intervention period. Therefore, a total of 13 and 14 subjects completed the study in the NNPPV and control groups, respectively. There were no significant differences between the NNPPV and control groups regarding the age, gender distribution, body mass index, apnea-hypopnea index (AHI), baseline pulmonary function and the percentage of subjects using O_2 at home (Table 1). In the NNPPV group, two

Table 1. Characteristics and Pulmonary Function of the Subjects

	NNPPV	Control	p
	(N=13)	(N=14)	
Age (yrs)	62.5 ± 11.5	65.5 ± 10.0	0.6103
Gender	3F / 10M	5F / 9M	0.5828
Weight (Kg)	55.7 ± 13.9	54.4 ± 11.4	0.9419
Height (cm)	157.5 ± 6.0	154.0 ± 10.0	0.3953
BMI (kg/m^2)	21.8 ± 4.6	23.0 ± 5.6	0.7709
AHI (times/hour)	5.3 ± 3.0	6.1 ± 2.8	0.7158
FVC (L)	1.0 ± 0.4	1.1 ± 0.3	0.3694
Predicted (%)	31.7 ± 11.2	38.5 ± 10.5	0.1146
FEV$_1$(L)	0.5 ± 0.1	0.5 ± 0.1	0.4816
Predicted (%)	19.9 ± 5.3	24.3 ± 9.1	0.4231
FEV$_1$/FVC (%)	48.2 ± 10.8	47.3 ± 18.4	0.3441
Number of subjects using O$_2$ at home	9	9	

Values given as mean$\pm$SD; BMI: body mass index; AHI: apnea hypopnea index; FVC: forced vital capacity; FEV$_1$: forced expiratory volume in one second; FEV$_1$/FVC: ratio of FEV$_1$ to FVC.

subjects had bronchiectasis, one had severe asthma and 10 had COPD. In the control group, one subject had bronchiectasis, three had severe asthma and 10 had COPD were enrolled in the control group. All subjects continued their regular regimens and dosage of bronchodilators and/or steroids prescribed by doctors. The patients were asked to stop short-acting and long-acting bronchodilators for 12 hours and 24 hours, respectively, before coming to the outpatient clinic for tests. The study was reviewed and approved by Ethical Review Committee, Chung Gung Memorial Hospital, and consent was obtained from each subject. This study was conducted from June 2001 through November 2002.

Interventions

The subjects received nocturnal ventilation that was delivered using the bi-level positive airway pressure (BiPAP) system (Respironics, Inc.; Murrysville, Penn, USA) via nasal masks (Respironics) during their hospital stays. Appropriate settings of inspiratory and expiratory pressures and volumes were set to achieve optimal daytime PaCO$_2$ value. The peak inspiratory pressure was 11.8 ± 0.6 cmH$_2$O, and the positive expiratory pressure was 4.5 ± 0.4 cmH$_2$O (N=13). Subjects in the NNPPV group were instructed to use nasal ventilation at night during sleep. The compliance with NNPPV in the hospital

was monitored and observed by nurses and recorded in a daily log. After discharge, the compliance with NNPPV was evaluated by reviewing the subjects' self log records. The average duration of nocturnal use calculated from log records was 7.8 ± 0.5 hours/ day (N=13). The telephone follow-up interviews for the subjects in the NNPPV group were done every 2 weeks by a respiratory therapist to assess the compliance. The time that patients for the ventilators at home was assessed by interviewing them and their family and by calculations from the time-counter on the ventilator equipment. Side effects due to the prolonged use of NNPPV were also recorded during the follow-up interviews. Subjects came to our clinic for appropriate medication each month, and there was no specific outpatient-based rehabilitation program offered to them.

Measurements

Baseline data were measured before subjects were committed to NNPPV. The measurements included arterial blood gas tensions, pulmonary function test, 6-minute walk test, and respiratory muscle function. All measurements were repeated 6 months after beginning the study. Arterial blood samples were taken while breathing room air for at least 1 hour at rest. Four of the patients could not tolerate room air breathing, and oxygen at the concentration of two liters per minute was supplied via nasal cannula, so we calculated the ratio of arterial oxygen partial pressure to oxygen fraction of inspired gas (PaO$_2$/FiO$_2$) for comparison. The two liters per minute nasal cannula for a stable COPD was estimated as FiO$_2$ 28%.[18] Arterial blood gas analysis was performed using a gas analyzer (Corning 278 blood Gas Analyzer, Ciba-Corning Diagnostics Co, Mass, USA). Forced vital capacity (FVC), forced expiratory volume in the first second (FEV$_1$), and maximum voluntary ventilation (MVV) were measured using a portable spirometry (Spiro analyzer ST 250, Fukuda, Sangyo, Japan) according to the recommendations of the American Thoracic Society.[19] Exercise capacity was measured using a 6MWT.[20] Subjects were instructed to walk from end to end of the corridor and to cover as much distance as possible in the allotted period of 6 minutes. Subjects were encouraged every 30 seconds using two phrases: "You are doing well" or "Keep up the good work." They were allowed to stop and rest during the test, but were

instructed to resume walking as soon as they felt able to do so. Subjects took the test without O_2 supplement and modified Borg scale[21] were measured at rest (RBorg) and immediately after 6MWT (ExBorg). The distances walked in 6 minutes (6MWD) were recorded.

The mouth occlusion pressure at maximum inspiratory (Pimax), maximum expiration (Pemax), and 0.1 second ($P_{0.1}$) were measured using a plethysomnograph pulmonary function test (Erich Jaeger, Hoechberg, Germany). The mouthpiece was connected to a pneumotach apparatus with a shutter valve. The shutter that consisted of an electronically controlled magnetic valve was activated at end-expiration at irregular intervals during measurement. At the end of expiration, the shutter was set automatically. In addition, at 0.1 second, the inspiratory mouth pressure ($P_{0.1}$) was measured while the patient attempted to inhale. One trial ended after the shutter was set for about 10-15 times. The mouth occlusion pressure was expressed as absolute value (kPa). The $P_{0.1}$ data was obtained from the mean calculated value of the last 10 breaths. The Pimax and Pemax were measured while the patient performed at maximal inspiratory and maximum expiratory effort, respectively. As soon as the patient started to inhale, the shutter was closed and the pressure was measured automatically. Maneuvers were repeated until three measurements with less than 5 % variability were recorded. The highest value obtained was used for analysis.

Data analysis

Results were given as mean±SD. Length of hospital stay and numbers of admissions were recorded from the medical charts. The total number of hospital stays during the 6-month period before study (baseline) and during the trial were recorded. Wilcoxon-signed rank test was used to compare the differences between pre- and post-interventions in the same group. Mann-Whitney rank sum test was used to compare the differences of pre- and post-intervention between the study and control groups. A p value less than 0.05 was considered statistically significant.

RESULTS

Arterial blood gas tensions at baseline and after the 6-month study period are shown in Table 2. After 6 months of NNPPV intervention, $PaCO_2$, arterial bicarbonate (HCO_3^-) and base excess (BE) decreased significantly from 55.2±7.1 to 42.6±5.4 mmHg, 34.5±3.6 to 26.8±3.1 meq/L, and 8.5±3.6 to 2.3±2.7 meq/L, respectively ($p<0.001$). There were significant differences between the NNPPV and control groups in the baseline and after 6 months of intervention for $PaCO_2$, HCO_3^- and BE. There were no significant differences in the changes of PaO_2/FiO_2 and pH between the groups. However, in the NNPPV group, the measurements for PaO_2/FiO_2 at baseline and after 6 months of intervention increased from 254.7±39.7 to 277.9±53.2 mmHg ($p<0.05$). No changes were found in the control group.

In the NNPPV group, 6MWD improved significantly from 232.2±79.3 m at the baseline to 333.4±81.4 m (106.8 - 429 m) after 6 months of NNPPV intervention ($p<0.001$). In contrast, 6MWD decreased significantly after the 6-month study peri-

Table 2. Arterial Blood Gases at Baseline and after the 6-month Study Period

	NNPPV (N = 13)		Control (N = 14)	
	Baseline	After	Baseline	After
pH	7.41± 0.05	7.41± 0.03	7.41± 0.07	7.39± 0.06
$PaCO_2$ (mmHg)	55.2 ± 7.1	42.6 ± 5.4[†]	53.5 ±10.4	59.0 ±15.5[‡]
PaO_2/FiO_2 (mmHg/%)	254.7 ±39.7	277.9 ±53.2*	260.9 ±54.2	265.6 ±41.8
HCO_3^- (meq/L)	34.5 ± 3.6	26.8 ± 3.1[†]	33.8 ± 4.3	35.2 ± 7.1[‡]
BE (meq/L)	8.5 ± 3.6	2.3 ± 2.7[†]	8.0 ± 4.5	8.6 ± 5.7[‡]

Values given as mean±SD; $PaCO_2$: arterial carbon dioxide partial pressure; PaO_2/FiO_2: ratio of arterial oxygen partial pressure to oxygen fraction of inspired gas; HCO_3^-: arterial bicarbonate; BE: base excess; *indicates $p<0.05$, compared to baseline; †indicates $p<0.001$, compared to baseline; ‡indicates $p<0.001$, compared to NNPPV group.

Table 3. Parameters of 6-minute Walking Test and Respiratory Muscle Function in both NNPPV and Control Groups at Baseline and after the 6-month Study Period

	NNPPV (N = 13)		Control (N = 14)	
	Baseline	After	Baseline	After
6 MWD (m)	232.2±79.3	333.4±81.3[†]	267.4±92.6	233.6±92.7 §[†]
RBorg	3.5± 1.2	2.7± 1.1	2.9± 0.8	3.1± 0.9
ExBorg	5.9± 1.6	5.8± 1.1	6.1± 1.1	6.6± 1.2
Pimax (Kpa)	4.3± 1.4	4.9± 1.9	4.4± 1.7	4.1± 1.8
Pemax (Kpa)	6.2± 1.6	7.0± 2.0	7.5± 2.6	6.7± 2.3
P0.1 (Kpa)	0.6± 0.2	0.6± 0.3	0.4± 0.2	0.6± 0.2
MVV (L/min)	18.5± 6.1	21.5± 7.3*	15.4± 3.3	15.5± 5.0‡

Values given as mean±SD; 6MWD: 6-minute walking distance; RBorg: resting Borg score; and ExBorg: Borg score at end of 6MWT; Pimax: maximum inspiratory pressure; Pemax: maximum expiratory pressure; P0.1: airway occlusion pressure at 100 msecond.; MVV: maximum voluntary ventilation; *indicates $p<0.05$, compared to baseline; †indicates $p<0.001$, compared to baseline; ‡indicates $p<0.05$, compared to NNPPV group; §indicates $p<0.01$ compared to NNPPV group.

Table 4. Number and Total Stay of Hospitalization 6 Months before and during the 6-month Study Period in both NNPPV and Control Groups.

	NNPPV (N = 13)		Control (N = 14)	
	Baseline	After	Baseline	After
Number	2.8± 1.1	0.8± 1.4‡	2.4± 0.6	3.1± 1.4 *§
Total stay (days)	39.4±14.5	10.0±22.7[†]	31.7±12.5	47.7±30.0[†] §

Values given as mean±SD; *indicates $p<0.05$, compared to baseline; † indicates $p<0.01$, compared to baseline; ‡ indicates $p<0.001$, compared to baseline; §indicates $p<0.001$, compared to NNPPV group.

od in the control group ($p<0.001$) compared to baseline (Table 3). The magnitudes of pre and post study changes of 6MWD were 101.2 m (43.6%) for the NNPPV group and -33.8 m (-12.6%) for the control group. Compared with the baseline and after 6-month NNPPV intervention, RBorg and ExBorg were not different.

Compared with the baseline, the Pimax, Pemax, and P0.1 (N=11), were not different for either group, but the changes of MVV were significantly different between the groups after the 6-month period of study. ($p<0.05$) (Table 3). The MVV increased from 18.5±6.1 to 21.5±7.3 L/min ($p<0.05$) in the NNPPV group.

During the 6-month period of using NNPPV, hospital admissions and length of stay decreased from 2.8±1.1 times to 0.8±1.4 times ($p<0.001$) and 39.4±14.5 days to 10.0±22.7 days (0-83 days) ($p<0.01$), respectively (Table 4). In contrast, during the 6-month period of study, subjects in the control group showed significantly increased the hospital admissions and length of stay from 2.4±0.6 times to 3.1±1.4 times and 31.7±12.5 days to 47.7±30.0 days ($p<0.05$ and $p<0.01$, respectively, compared with those during the 6-month period before beginning the study.

DISCUSSION

Our results revealed that the use of NNPPV in patients with severe obstructive lung diseases improved the arterial blood gas, enhanced the exercise capacity and respiratory muscle endurance. Additionally, the use of NNPPV decreased the demand of hospital admission and shortened the length of hospital stays.

Four patients in NNPPV group were withdrawn from the study within 3 months because they could

not tolerate BiPAP during sleep. The dropout rate in our study was 23.5% (4/17), which was similar to that described by Criner et al. (28%, 10/36).[22] The major causes for dropout included mask leakage, discomfort from mask headwear and nasal bridge pressure (Table 5). Further efforts in finding a way to reduce the dropout rate are needed, since NNPPV support appeared to reduce the cost of hospitalization in these patients.

Table 5. Causes of Withdrawal from Ventilatory Support in the Patients of NNPPV Group.

Causes	Patient number
Air leak	4
Headwear tight	4
Nasal bridge pressure	4
Eyes irritation	3
Nasal congestion	2
Nasal/oral dryness	2

The effect of noninvasive ventilatory support on gas exchange in patients with obstructive lung diseases was controversial. Our findings that the $PaCO_2$, HCO_3^-, and BE had improved after 6 months of NNPPV intervention are in agreement with the results of the studies by Elliott et al.[5] and Perrin et al.,[23] but different from the results of the studies by Clini et al.[10] and Casanova et al.[24] We suspected that the discrepancy was probably due to the difference in the degree of airway obstruction in the enrolled subjects. The FEV_1 was about 20% of the predicted value in our study subjects, and, in contrast, it was less severe in the study subjects of Clini et al. (average FEV_1: 31%) and Casanova et al. ($FEV_1 < 45\%$).[10,24] Additionally, in the study by Casanova et al., they did not use arterial blood gas as an enrollment criterion.[24] We calculated PaO_2/FiO_2 instead of PaO_2 to evaluate the effect of NNPPV on oxygenation, because a few patients could not tolerate the room air breathing and had received oxygen supplement. The improvement in PaO_2/FiO_2 after 6 months of NNPPV intervention confirmed the finding of Criner et al., in which PaO_2/FiO_2 also improved in 26 patients who were diagnosed with chronic respiratory failure and continued to use ventilatory support for 6 months.[22] However, no differences were found in the changes before and after study for PaO_2/FiO_2 between the groups. Thus, it remains unclear whether the improvement in PaO_2/FiO_2 was solely due to NNPPV intervention.

In our study, we found an improvement in 6MWD after 6 months of NNPPV intervention. In contrast, there was a slight decrease in the 6MWD in the control group. Studies by Jones et al.[16] and Strumpf et al.[6] did not demonstrate any improvement in 6MWD but Bullemer et al[11] found a tendency of increasing 6MWD after 3 months of NNPPV in COPD patients. Clini et al.[10] reported an increase of 6MWD up to 3 years in 28 patients undergoing NNPPV. This discrepancy suggests that long-term use of NNPPV is probably needed to strengthen the exercise capacity in patients with obstructive lung diseases.

In our NNPPV group, there was an improvement in the respiratory muscle endurance (MMV), but not in the Pimax, a measure of respiratory muscle strength or $P_{0.1}$, a measure of central drive. The results were similar to the findings of Casanova et al.[24] The Pimax and $P_{0.1}$ did not change after 6-months of NNPPV. Although the diaphragmatic electromyogram (EMG) activity[25] and the pressure time product[13] can be reduced by BiPAP, in most cases this has not been documented in subjects with obstructive lung diseases and with a long-term trial[24] or short-term use.[12] The results of our study showed increased respiratory muscle endurance as evidenced by the resolution of chronic fatigue. This might not have been identified from Pimax (indicating the respiratory muscle strength). The enhanced performance may contribute to the improvement in 6MWD.

We found that the number of hospital admissions and the length of stay decreased in the NNPPV group, which was similar to the findings of Jones et al.[16] and Clini et al.[10] Recent preliminary results from two multicenter European trials comparing NNPPV with long-term oxygen therapy in COPD patients suggested that NNPPV may reduce the need for hospitalization.[26]

In conclusion, despite the heterogeneity in and the small number of our patients which may make our results different from other studies, 6 month of NNPPV used in patients with severe obstructive lung diseases improved arterial blood gas, exercise capacity, and respiratory muscle endurance. NNPPV also decreased the frequency of hospital admissions and the length of stay. In this study, we also observed

that NNPPV helped patients become free from ventilation for a period of time in daytime and, subsequently, made them able to perform more activities of daily living. Thus the deconditioning associated with chronic respiratory failure could be minimized. Further studies of the effects of NNPPV on the quality of life and the effects of initiating a rehabilitation program during the period of NNPPV intervention on preserving lung function should be encouraged.

Acknowledgments

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高二氧化碳分壓之嚴重阻塞型肺疾患者
夜間鼻罩正壓通氣治療的成效

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背　景： 本研究是探討高二氧化碳分壓之阻塞型肺疾患者，給予6個月夜間鼻罩正壓通氣治療於動脈血氣體分析值、運動量、呼吸肌功能、及再度住院次數的成效。

方　法： 這是一個前瞻性與隨機分配之對照研究。27位阻塞型肺疾病患被分至夜間鼻罩正壓氣道通氣治療組（共13人），或控制對照組（共14人）。治療前與6個月的夜間鼻罩正壓通氣治療後測量病患之動脈血壓分析值，運動量，與呼吸肌功能。治療前後6個月期間的住院次數及總住院日亦紀錄之。

結　果： 夜間鼻罩正壓通氣治療組於6個月治療後，其動脈之二氧化碳分壓，重碳酸離子，及鹼超出量皆下降，且其進步程度與控制組相比有顯著差異。與控制組相比，6分鐘行走距離及每分鐘志願通氣量皆顯著進步，6分鐘行走距離由232.2±79.3米增至333.4±81.3米。夜間鼻罩正壓通氣治療組病患6個月之住院頻率與總住院天數顯著下降。

結　論： 6個月夜間鼻罩正壓通氣治療能改善高二氧化碳分壓之嚴重阻塞型肺疾患者之動脈血氣體分析值，運動量及呼吸耐力，並且能減低住院次數及總住院天數。
(長庚醫誌 2004;27:98-106)

關鍵字： 高二氧化碳分壓之阻塞型肺疾，夜間鼻罩正壓通氣，6分鐘行走測試，動脈血氣體分析值。