Short-Term Effect of Controlled Instead of Assisted Noninvasive Ventilation in Chronic Respiratory Failure Due to Chronic Obstructive Pulmonary Disease

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BACKGROUND: Noninvasive positive-pressure ventilation (NPPV) unloads respiratory muscles. Spontaneous-breathing ventilation modes require patient effort to trigger the ventilator, whereas controlled modes potentially economize on patient triggering effort and thus achieve more complete respiratory muscle rest. Data on controlled NPPV have not been published to date. We hypothesize that controlled ventilation is feasible in patients with hypercapnic chronic obstructive pulmonary disease. METHODS: We measured blood gas values, respiratory muscle strength, spontaneous breathing pattern, and lung function before and after a 3-month period of NPPV in 305 patients (213 male, mean ± SD age 61.3 ± 8.6 y). The subjects used a controlled NPPV mode when they could tolerate it. RESULTS: Ninety-one percent of the patients were able to adapt to a controlled NPPV mode. In those patients, daytime P_{CO_2} decreased from 56.7 ± 7.5 mm Hg to 47.5 ± 6.6 mm Hg ($p < 0.001$) and P_{O_2} increased from 49.2 ± 8.8 mm Hg to 56.2 ± 8.5 mm Hg ($p < 0.001$). Their mean maximum inspiratory pressure increased from 42.3 ± 16.9 cm H_2O to 48.4 ± 18.0 cm H_2O ($p < 0.001$). Their mean vital capacity increased from 1.89 ± 0.62 L to 1.99 ± 0.67 L ($p = 0.004$). And their spontaneous breathing pattern became less rapid and shallow. CONCLUSIONS: Controlled NPPV is feasible in patients with hypercapnic chronic obstructive pulmonary disease. We observed improved blood gas values, lung function, and inspiratory muscle strength. *Key words: blood gas analysis, chronic obstructive pulmonary disease, COPD, chronic respiratory failure, lung function, noninvasive ventilation.* [Respir Care 2007;52(12):1734–1740. © 2007 Daedalus Enterprises]

Introduction

Noninvasive positive-pressure ventilation (NPPV) for the treatment of chronic respiratory failure is usually applied with assisted ventilation modes such as spontaneous or spontaneous timed modes.[1–4] Assisted modes use flow-controlled and/or pressure-controlled mechanisms to trigger inspiration and expiration.[5,6]

In the presence of air leaks of the mask interface, the trigger may not accurately detect the patient's effort, which can cause asynchrony and increase the respiratory muscle burden.[7] The work to trigger the ventilator can account for up to 50% of the respiratory muscle work during invasive ventilation and up to 39% during NPPV.[8–10] Controlled ventilation modes can reduce respiratory muscle work required of the patient.[8,11–13] Data on controlled NPPV, however, have not been published to date. Our NPPV unit routinely uses a protocol in which preference is given to controlled NPPV. We hypothesized that controlled NPPV is feasible in patients with chronic respiratory failure. To test our thesis we analyzed our database on patients with chronic respiratory failure and extracted a cohort of patients with chronic respiratory failure due to chronic obstructive pulmonary disease (COPD) and who followed up after 3 months of NPPV.

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Methods

Our institutional review board reviewed and approved the study. In August 1996 we started to enter (into a digital database) data from patients with hypercapnic respiratory failure who were started on NPPV. From that database we selected patients with chronic respiratory failure due to COPD who were started on NPPV during a stable phase of their COPD. The patient had to be free of clinical signs of exacerbation for at least 1 month and was not allowed to have received antibiotics or increased doses of steroids during that 1-month period. We excluded patients who had other causes of respiratory failure, such as neuromuscular or thoracic-restrictive disease, and patients who participated in physical rehabilitation or inspiratory muscle training during the observation period. The patients were treated with supplemental oxygen, bronchodilators, and inhaled steroids, according to the current guidelines.[14] For reasons of comparability, the blood samples for blood gas analysis were taken while the patients breathed room air.

Noninvasive Positive-Pressure Ventilation

NPPV was given overnight, either via full face mask or nasal mask. During adaptation by the respiratory physician, the primary goal was to institute a timed (controlled) mode that achieved the maximum possible P_{CO_2} reduction. For this, the expiratory positive airway pressure and respiratory rate were adapted to patient comfort by the respiratory physician at bedside, while the inspiratory positive airway pressure (IPAP) was kept low (5 cm H_2O above the expiratory positive airway pressure). Then IPAP was increased until the P_{CO_2} dropped into the normal range or the patient could not tolerate a further increase of IPAP. Increasing IPAP usually requires a parallel change of respiratory rate. For this the physician visualizes or palpates chest movements and adjusts the respiratory rate until the ventilator rate is just above the patient's rate while the patient allows passive inflation. In patients with obstructive airway disease the inspiratory time is short, which allows for longer expiration. A prolonged preset inspiratory time might affect inspiratory-pressure intolerance, whereas a shorter inspiratory time might allow for higher inspiratory pressure. A controlled mode does not allow the patient to trigger additional breaths between the mandatory delivered breaths. If the patient could not tolerate a controlled mode because of a perception of asynchrony or nightly awakenings due to asynchrony, the respiratory physician adjusted the ventilator settings during a second daytime trial. If intolerance persisted thereafter, the patient was allowed to be switched to the spontaneous timed mode with a backup frequency just below or at the spontaneous breathing frequency, determined during a 30-min NPPV trial in spontaneous mode. This mode allows the patient to trigger the ventilator at an arbitrary rate and applies a mandatory breath only when the patient's respiratory rate falls below the backup frequency. In some patients even the use of a backup frequency resulted in nighttime arousals or clinically observed asynchrony. These patients were allowed to be switched to a spontaneous-breathing mode. Follow-up was performed 3 months after starting NPPV.

Measurements and Measurement Apparatus

The following data were registered for further analysis: age, sex, body mass index, cause of respiratory failure, ventilator mode settings, hours of use, type of mask interface, daytime spontaneous respiratory rate, tidal volume, and minute ventilation 6 hours after terminating NPPV, capillary blood gas values while breathing room air (resting-level blood samples taken 6 hours after terminating NPPV, and during-ventilation sample taken at least 2 hours after starting NPPV at night), lung function variables, and inspiratory and expiratory mouth occlusion pressure 0.1 s after the onset of inspiratory effort.

Blood gas values were measured with a sensor placed on the arterialized earlobe (Omni S, Roche, Basel, Switzerland). Lung function variables and mouth occlusion pressures were measured with a plethysmograph (Masterlab, Jaeger, Hochberg, Germany). Spontaneous respiratory rate and tidal volume were measured with a pulmonary mechanics monitor (Bicore, Bear, Irvine, California). Subjects were studied while sitting upright in a comfortable chair and breathing room air. Maximum inspiratory pressure was measured with a maneuver that started from functional residual capacity. To determine the inspiratory time fraction during NPPV in spontaneous mode, we integrated a flow sensor (Pneumoflow, ResMed, Martinsried, Germany) into the tubing system distal to the Whisper Swivel valve (Respironics, Murrysville, Pennsylvania). The sensor was connected to a polygraphic platform (PolyMesam, ResMed, Martinsried, Germany), and inspiratory time was calculated as a fraction of the total breathing cycle time. Average hours of nightly use were calculated as the ratio of hours counted by the ventilator's built-in hour counter to the number of treatment days.

Statistical Analysis

Statistical analysis was performed with statistics software (SPSS 12.0, SPSS, Chicago, Illinois). Data are presented as mean ± SD. The Wilcoxon rank test was used for comparative measurements at different points in time. The Mann-Whitney U test was applied for comparison of different groups.

Analysis of variance was used to evaluate differences between 3 or more subgroups. Duncan's test was used for post hoc analysis. Differences were considered statistically

Table 1. Demographic Data, Ventilator Settings, and Blood Gas Data During Nighttime Ventilation in the Initial Accomodation Period

	Ventilation Type	Mean ± SD	p	*n*
Age (y)	Controlled	61.3 ± 8.7		278
	Assisted	61.5 ± 6.8	0.73	27
BMI (kg/m^2)	Controlled	24.9 ± 5.2		278
	Assisted	26.6 ± 6.7	0.12	27
IPAP (cm H_2O)	Controlled	20.1 ± 3.0		278
	Assisted	19.4 ± 3.6	0.63	27
EPAP (cm H_2O)	Controlled	5.7 ± 1.2		278
	Assisted	5.3 ± 1.5	0.32	27
Respiratory rate (breaths/min)	Controlled	18.6 ± 3.0		278
	Assisted	16.8 ± 3.1	0.003	25
T_I/T_{tot} (%)	Controlled	37.9 ± 4.7		278
	Assisted	36.9 ± 6.1	0.28	25
Hours of nightly use*	Controlled	6.0 ± 3.15		253
	Assisted	5.7 ± 3.6	0.67	22
P_{O_2} during NPPV (mm Hg)	Controlled	63.1 ± 10.7		264
	Assisted	63.1 ± 9.1	0.64	26
P_{CO_2} during NPPV (mm Hg)	Controlled	42.7 ± 6.8		264
	Assisted	46.1 ± 8.5	0.016	26
pH during NPPV	Controlled	7.40 ± 0.05		264
	Assisted	7.38 ± 0.05	0.001	26

*Hours of use were determined after 3 months of noninvasive positive-pressure ventilation (NPPV).
BMI = body mass index
IPAP = inspiratory positive airway pressure
EPAP = expiratory positive airway pressure
T_I/T_{tot} = ratio of inspiratory time to total respiratory cycle time

significant when $p < 0.05$. In case of missing values, *n* represents the number available for calculations.

Results

Until June 2005, a total of 305 (213 male) patients with chronic respiratory failure due to COPD had successfully been established on NPPV for at least 3 months. Their mean age was 61.3 ± 8.6 y. Their mean body mass index was 25.1 ± 5.3 kg/m^2. Twenty-seven patients failed to tolerate controlled bi-level positive airway pressure (BiPAP) ventilation and remained in a spontaneous timed BiPAP mode ($n = 10$) or spontaneous BiPAP mode ($n = 17$). The mean ventilator settings were: IPAP 20.3 ± 3.1 cm H_2O, expiratory positive airway pressure 5.7 ± 1.3 cm H_2O, respiratory rate 18.5 ± 3.0 breaths/min, and inspiratory time fraction 38.0 ± 4.9%. The mean NPPV use was 5.9 ± 3.2 h/night. During nighttime NPPV, the mean P_{CO_2} was 43.1 ± 7.1 mm Hg, and the mean P_{O_2} was 63.1 ± 10.5 mm Hg. Table 1 shows the demographic data, ventilator settings, and blood gas data during nighttime ventilation in the initial accommodation period. Table 2 shows the blood gas values. Table 3 shows the mouth-occlusion pressures and maximum inspiratory pressures. Table 4 shows the lung function values. Table 5 shows the tidal volumes, minute volumes, and ratios of inspiratory time to total respiratory cycle time.

To keep the data concise, the data from patients who used a spontaneous or spontaneous timed mode were analyzed together as "assisted mode."

Figure 1 shows the correlations between the P_{CO_2} change during the investigation period and the initial P_{CO_2} as well as the P_{CO_2} reduction during NPPV. Figure 2 shows the relative use of different mask types and the correlation between mask type and P_{CO_2} reduction at 3 months. There was no difference in P_{CO_2} reduction between the different mask types, as measured by one-way analysis of variance.

Discussion

Our data suggest that controlled NPPV is feasible in patients with chronic respiratory failure due to COPD. We observed a significant reduction in daytime P_{CO_2}, increased daytime P_{O_2}, improved lung function, and improved maximum respiratory muscle strength after 3 months of NPPV.

Our investigation lacked a control group (either no mechanical ventilation or sham ventilation), so our data do not conclusively show that the observed changes are a consequence of NPPV. Randomized controlled trials, however, showed no improvement in any of the measured

Table 2. Daytime Blood Gas Values During Spontaneous Breathing of Room Air

	Ventilation Type	Before NPPV	After 3 Months of NPPV	p (before vs after)	p (controlled vs assisted)	*n*
P_{O_2} (mm Hg)	Controlled	49.2 ± 8.5	56.2 ± 8.2	< 0.001		266
	Assisted	51.4 ± 11.1	60.3 ± 10.9	< 0.001	0.45	27
P_{CO_2} (mm Hg)	Controlled	56.7 ± 7.5	47.5 ± 6.6	< 0.001		266
	Assisted	54.6 ± 6.3	48.4 ± 7.8	< 0.001	0.036	27
pH	Controlled	7.38 ± 0.05	7.41 ± 0.04	< 0.001		266
	Assisted	7.37 ± 0.05	7.40 ± 0.04	0.004	0.9	27
HCO_3 (mEq/L)	Controlled	32.5 ± 4.2	29.0 ± 4.1	< 0.001		266
	Assisted	30.9 ± 4.1	28.9 ± 3.8	0.003	0.023	27

NPPV = noninvasive positive-pressure ventilation

Table 3. Mouth-Occlusion and Maximum Inspiratory Pressures

	Ventilation Type	Before NPPV	After 3 Months of NPPV	p (before vs after)	p (controlled vs assisted)	*n*
$P_{0.1}$ (cm H_2O)	Controlled	3.86 ± 1.82	3.91 ± 1.97	0.43		247
	Assisted	3.57 ± 1.45	3.07 ± 0.85	0.1	0.06	23
MIP (cm H_2O)	Controlled	42.3 ± 16.9	48.4 ± 18.0	< 0.001		247
	Assisted	38.1 ± 19.0	41.8 ± 20.5	0.12	0.31	23
$P_{0.1\text{-max}}$	Controlled	17.8 ± 8.6	19.9 ± 8.9	< 0.001		247
	Assisted	14.2 ± 5.4	17.1 ± 7.6	0.36	0.72	23
$P_{0.1}$/MIP	Controlled	10.9 ± 7.7	9.8 ± 7.7	0.001		247
	Assisted	11.5 ± 5.9	9.5 ± 5.3	0.26	0.45	23
$P_{0.1}$/MIP	Controlled	26.7 ± 18.1	24.8 ± 17.6	0.076		247
	Assisted	30.8 ± 13.2	23.6 ± 11.4	0.2	0.33	23
MEP (cm H_2O)	Controlled	90.7 ± 36.7	102.7 ± 38.4	< 0.001		208
	Assisted	82.8 ± 39.0	88.5 ± 40.6	0.11	0.33	9

NPPV = noninvasive positive-pressure ventilation
$P_{0.1}$ = mouth occlusion pressure 0.1 s after the beginning of inspiratory effort during tidal breathing
MIP = maximum inspiratory pressure
$P_{0.1\text{-max}}$ = mouth occlusion pressure 0.1 s after the beginning of a maximal inspiratory effort
MEP = maximum expiratory pressure

variables in the control groups.[4,15–17] Given that fact, we think it is likely that there is a causal connection between the NPPV and the observed improvements in our cohort. The reduction of respiratory muscle strength due to fatigue in patients with COPD[18] and the concept of intermittent respiratory muscle rest[19] were described previously, and daytime and nighttime intermittent positive-pressure ventilation appeared to be equally effective.[20] It is not yet clear how optimal muscle rest can be accomplished.

The previously cited meta-analysis[1] included one study[17] that achieved a significant reduction of daytime P_{CO_2} by applying the highest IPAP (18 cm H_2O, range 16–22 cm H_2O) among the included studies. There is increasing concern that lower inspiratory pressure might fail to achieve a clinical benefit,[21] and there is increasing evidence that higher inspiratory pressure can significantly reduce daytime P_{CO_2}.[2,17,22,23]

We found the P_{CO_2} change after 3 months to be directly correlated to the P_{CO_2} reduction achieved during the initial phase of NPPV (see Fig. 2B). This finding has been described before[17] and is consistent with the concept that overnight muscle rest improves respiratory muscle performance during the day. The P_{CO_2} reduction at 3 months correlates well with the P_{CO_2} prior to NPPV (Fig. 1A), which suggests that patients with more severe disease experience a greater benefit.

Patient-ventilator asynchrony is known to be a common problem of controlled ventilation modes,[15] but if synchrony can be achieved, a controlled mode will provide the maximum respiratory muscle rest, by avoiding the work needed to trigger the ventilator.[8,9,13,24] Ninety-one percent of our study patients were able to adapt to a controlled mode, with a mean inspiratory pressure of 20.3 ± 3.1 cm H_2O. We observed a P_{CO_2} reduction during daytime spontaneous breathing that was comparable to that in other studies that used higher inspiratory pressure during a spontaneous timed mode (IPAP of 27.7 ± 5.9 cm H_2O and 40.4 ± 5.2 cm H_2O).[2,22] Although we did not measure patient-

Table 4. Lung Function

	Ventilation Type	Before NPPV	After 3 Months of NPPV	p (before vs after)	p (controlled vs assisted)	*n*
VC (L)	Controlled	0.89 ± 0.62	1.99 ± 0.67	0.004		263
	Assisted	1.94 ± 0.66	2.09 ± 0.78	0.049	0.51	26
VC (% of predicted)	Controlled	51.3 ± 14.7	54.0 ± 15.2	0.001		263
	Assisted	49.48 ± 12.7	52.8 ± 15.1	0.086	0.74	26
FEV_1 (L)	Controlled	0.89 ± 0.35	0.95 ± 0.40	0.001		263
	Assisted	1.02 ± 0.52	1.10 ± 0.64	0.15	0.74	26
FEV_1 (% of predicted)	Controlled	50.1 ± 13.1	50.4 ± 13.4	0.72		263
	Assisted	54.9 ± 15.2	51.8 ± 14.7	0.13	0.24	26
R_{aw} (cm H_2O/L/s)	Controlled	1.28 ± 0.65	1.18 ± 0.66	0.008		217
	Assisted	1.01 ± 0.45	0.94 ± 0.50	0.09	0.7	22
TLC (L)	Controlled	5.43 ± 0.98	5.52 ± 0.98	0.11		217
	Assisted	5.94 ± 1.01	6.10 ± 0.89	0.53	0.9	22
RV (% of TLC)	Controlled	62.8 ± 11.1	62.6 ± 9.9	0.38		217
	Assisted	66.4 ± 11.3	63.3 ± 11.7	0.12	0.27	22

VC = vital capacity
FEV_1 = forced expiratory volume in the first second
R_{aw} = airway resistance
TLC = total lung capacity
RV = residual volume

Table 5. Breathing Pattern During Spontaneous Daytime Breathing

	Ventilation Type	Before NPPV	After 3 Months of NPPV	p (before vs after)	p (controlled vs assisted)	*n*
Respiratory rate	Controlled	20.0 ± 5.6	19.2 ± 4.7	0.024		261
(breaths/min)	Assisted	21.1 ± 5.5	18.9 ± 4.7	0.007	0.14	24
V_T (L)	Controlled	0.58 ± 0.20	0.66 ± 0.20	< 0.001		261
	Assisted	0.53 ± 0.19	0.55 ± 0.31	0.43	0.41	24
$\dot{V}_E$ (L)	Controlled	11.3 ± 4.1	12.5 ± 3.7	< 0.001		261
	Assisted	11.1 ± 4.8	11.6 ± 4.7	0.26	0.64	24
T_I/T_{tot} (%)	Controlled	37.8 ± 4.7	38.6 ± 4.2	0.011		261
	Assisted	40.8 ± 5.5	40.9 ± 6.1	0.91	0.39	24

V_T = tidal volume
$\dot{V}_E$ = minute volume
T_I/T_{tot} = ratio of inspiratory time to total respiratory cycle time

ventilator asynchrony, our results suggest that careful adaptation to controlled ventilation causes additional unloading of the respiratory muscles and is as effective as the combination of the spontaneous timed mode with higher inspiratory pressure. Comparisons between the groups that received controlled versus assisted ventilation must be made under the caveat that the patients were not randomized to the ventilation modes. The demographic and ventilator data (other than respiratory rate) were not different between the controlled and assisted NPPV groups, but respiratory rate was expectedly higher in the controlled NPPV group. The P_{CO_2} reduction after 3 months of NPPV was less pronounced in the assisted NPPV group than in the controlled NPPV group (see Table 2), which might indicate that muscle rest was more complete during controlled NPPV.

There is evidence that NPPV increases maximum inspiratory pressure in patients with COPD.[1,23,25,26] We observed similar findings but also saw an increase in peak expiratory pressure and the mouth occlusion pressure 0.1 s after the beginning of a maximal inspiratory effort (see Table 3). Pressures during quiet breathing were unaffected, but the ratio of mouth occlusion pressure 0.1 s after the beginning of inspiration to maximum breathing pressure dropped, which increased the pressure reserve. The increase in maximum muscle force can be the consequence of various mechanisms. First, a change in functional residual capacity can impact muscle force, because muscle fiber length prior to contraction impacts fiber force. Second, alternation between muscle rest during NPPV and increased muscle performance during spontaneous breathing can result in increased respiratory muscle

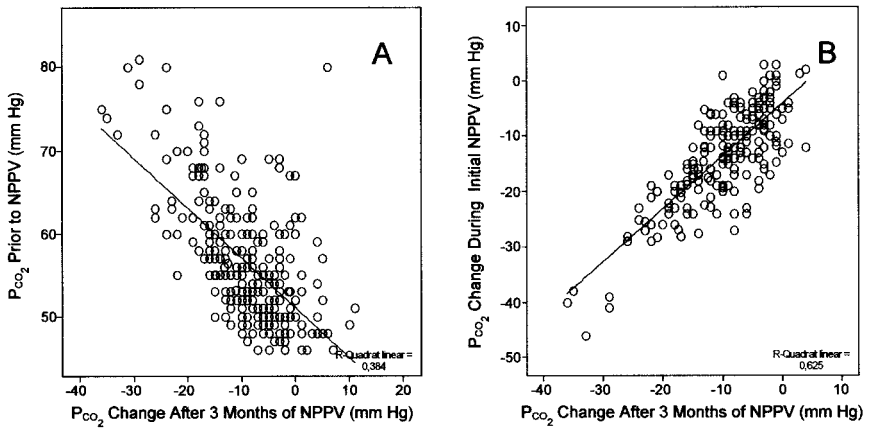

Fig. 1. A: Correlation of P_{CO_2} (during spontaneous breathing) prior to beginning noninvasive positive-pressure ventilation (NPPV) and the change in P_{CO_2} (during spontaneous breathing) after 3 months of NPPV ($r = -0.62$, $p < 0.001$). B: Correlation of P_{CO_2} reduction during initial application of NPPV and the change in P_{CO_2} during spontaneous breathing after 3 months of NPPV ($r = -0.79$, $p < 0.001$).

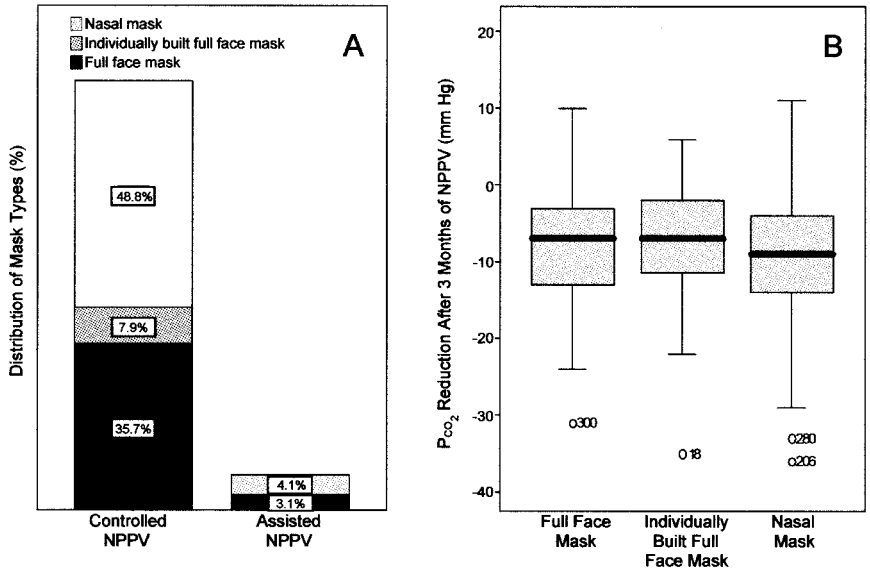

Fig. 2. A: Distribution of mask types among patients who received controlled versus assisted ventilation. B: P_{CO_2} reduction versus mask type after 3 months of noninvasive positive-pressure ventilation (NPPV). The values of outlier data points of up to 1.5 box lengths are marked with circles.

strength. Since we did not see a change in residual volume (see Table 4), the latter mechanism appears to be more likely. There is evidence for increased muscle use during spontaneous breathing in patients receiving NPPV.[27] After institution of NPPV, patients increase their spontaneous minute ventilation by increasing the tidal volume while decreasing the respiratory rate. Rapid shallow breathing is a sign of respiratory muscle fatigue,[28,29] and we can see the opposite phenomenon after the muscle rest provided by NPPV.

Changes in lung function consisted of a small but significant VC increase (see Table 4). The forced expiratory volume in the first second (FEV_1) increased in absolute value, but not as related to the VC. These observations are in line with previous findings in patients in whom NPPV significantly reduced daytime P_{CO_2}.[2] We also observed reduced airway resistance.

The type of mask did not impact the P_{CO_2} reduction at 3 months of NPPV, which suggests that, like previous studies,[30] nasal and full face mask are equally effective when used with a pressure preset ventilation mode.

Limitations

We used a nonparametric tests for comparison because not all of our data had a Gaussian distribution. This might underestimate the significance of the differences; however, application of the paired and unpaired *t* test (where appropriate) did not show other significant differences in any other comparison conducted in this study.

We did not perform polysomnography in our patients, so we cannot exclude the possibility that some improvement could be due to concomitant treatment of obstructive sleep apnea. This study was meant to pursue the clinical course of patients who successfully adapted to NPPV, at least in a spontaneous mode, and who followed up with our clinic. We did not present data from patients who failed to comply and stopped NPPV.

Conclusions

Controlled NPPV is feasible in patients with chronic respiratory failure due to COPD. In our cohort we observed significantly improved daytime blood gas values, respiratory muscle strength, and certain lung function variables. Applying a stepwise protocol with the use of a controlled rather than a spontaneous or spontaneous timed mode given first, and the increase of IPAP according to P_{CO_2} reduction and patient comfort given second priority, 91% of our patients were able to adapt to a controlled ventilation mode.

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