RESPIRATORY MEDICINE

Normocapnia during nIPPV in chronic hypercapnic COPD reduces subsequent spontaneous $PaCO_2$

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Abstract Hypercapnia has been accepted during nasal intermittent positive pressure ventilation (nIPPV) and during subsequent spontaneous breathing in patients with chronic hypercapnic respiratory failure (HRF) due to COPD. We tested the hypothesis that nIPPV aimed at normalizing $PaCO_2$ will reduce $PaCO_2$ during subsequent spontaneous breathing. For that purpose 14 consecutive inpatients (age 61.4 ± 9.9 years) with chronic HRF due to COPD were established on passive pressure-controlled nIPPV in a stepwise approach. Assisted ventilation with supplemental oxygen to reach normoxemia was started followed by passive ventilation with a stepwise increment in the inspiratory pressure and finally by a stepwise increase in the respiratory rate to establish normocapnia. Baseline pulmonary function parameters were: FEV_1 0.97 ± 0.43 l, $PaCO_2$ 59.5 ± 8.4 mmHg, PaO_2 49.9 ± 7.8 mmHg, HCO_3^- 35.6 ± 5.2 mmol/l, pH 7.39 ± 0.04. Normoxemia as well as normocapnia was thus established by decreasing $PaCO_2$ by 19.5 ± 7.0 mmHg during nIPPV within 8.8 ± 3.8 days ($P < 0.001$) (inspiratory pressure 29.8 ± 3.8 mmHg, respiratory rate 22.9 ± 1.9 BPM). Spontaneous $PaCO_2$ measured 4 h after cessation of nIPPV decreased to 46.0 ± 5.5 mmHg ($P < 0.001$), and HCO_3^- decreased to 27.2 ± 3.0 mmol/l ($P < 0.001$). At 6 months of follow-up, 11 patients continued nIPPV with stable blood gases and with a decrease of $P0.1/PImax$ from 9.4 ± 4.3% to 5.9 ± 2.0% ($P < 0.005$). In conclusion, normalization of $PaCO_2$ by passive nIPPV in patients with HRF due to COPD is possible and leads to a significant reduction of $PaCO_2$ during subsequent spontaneous breathing and is associated with improved parameters of respiratory muscle function.

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INTRODUCTION

Inspiratory muscle fatigue has been recognized as a main cause of failing of the respiratory pump leading to hypercapnic respiratory failure (HRF) (1). Nasal intermittent positive pressure ventilation (nIPPV) is a well-established treatment for HRF due to chest wall deformities and neuromuscular diseases (2–7). This technique has also been increasingly used in patients with HRF due to COPD where nIPPV is usually established during stable disease (3,5–9), but also during acute exacerbation (7, 10–12) and to assist weaning from mechanical ventilation (7, 13, 14). Recent studies including patients with chronic HRF due to COPD could demonstrate improvements in $PaCO_2$ during spontaneous breathing following nIPPV (5,9,15,16). The mechanisms underlying this effect are incompletely understood, but improvements in respiratory muscle function with improved inspiratory muscle strength following appropriate unloading and resting respiratory muscles has been shown to result in a decrease of spontaneous $PaCO_2$ (7,17–19). In addition, an improved respiratory system compliance by reversing microatelectasis of the lung and resetting of the CO_2-threshold have been postulated as important factors in improving spontaneous $PaCO_2$ independently of respiratory muscle relief (7, 15).

In practice, mild-to-moderate hypercapnia has been generally accepted during nIPPV as well as during subsequent spontaneous breathing in patients with COPD despite the fact that an increased inspiratory load and a decreased inspiratory muscle strength were correlated with an elevated $PaCO_2$ (20,21). Yet, patients with normocapnic COPD have been shown to have a higher ventilatory reserve than patients with hypercapnic COPD (20). In another study, 72.8% of patients who could not be weaned from invasive ventilation using assisted ventilation modes for >70 days could be weaned within 8.9 days by passive ventilation aiming at normocapnia, and this was followed by periods of spontaneous breathing with an increase of inspiratory muscle strength (22).

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This indicates that passive ventilation aiming at normocapnia might lead to a more significant improvement in respiratory function than assisted ventilation. In a recent study, a significant decrease in $PaCO_2$ during subsequent spontaneous breathing within the first 2 years after initiation of nIPPV was associated with long-term survival in patients with COPD suggesting that a maximal reduction of $PaCO_2$ during ventilation and spontaneous breathing might be clinically important (3). In addition, it was concluded in another study that the attempt to normalize arterial blood gas measurements (ABG) in hypercapnic COPD contributed to an improved outcome in these patients (23). Therefore, it has been suggested to adjust ventilator settings to achieve normalization of ABG with the best comfort to the patient (4,24). However, while most patients with HRF due to restrictive ventilatory disorders can be ventilated towards normocapnia, most patients with COPD remain hypercapnic even during ventilation (3,5,25). Therefore, the aim of the present study was to test the hypothesis that passive nIPPV using higher inspiratory pressures than previously reported in the literature can normalize hypercapnia in patients with chronic HRF due to COPD during ventilation assuming that this might improve the $PaCO_2$-threshold as indirectly measured by a reduction in $PaCO_2$ during subsequent spontaneous breathing.

PATIENTS AND METHODS

Patients

Fourteen consecutive patients (five female, nine male), mean age 61.4 ± 9.9 (range 49–80) years, with COPD and chronic HRF were enrolled. All had been heavy smokers (43.4 ± 13.7 packyears). Half of them were transferred from another clinic for evaluation of treatment with nIPPV. Half of them were seen as outpatients in our clinic. All patients were clinically stable with no evidence of an acute exacerbation. Three patients with minor hypercapnia ($PaCO_2 < 55$ mmHg for at least 3 months) had been established on long-term oxygen therapy (LTOT) prior to enrollment (case four, nine and twelve), but patients' symptoms worsened in terms of dyspnea on exertion and fatigue while $PaCO_2$ increased during LTOT. Eleven patients presenting with the typical symptoms of HRF such as fatigue, dyspnea and morning headache and with major hypercapnia ($PaCO_2 > 55$ mmHg for at least 3 months (except case 2)) had no LTOT prior to enrollment. None of the patients had any type of ventilatory support prior to enrollment. All patients were on antiobstructive medications (oral theophylline, inhaled formoterol and budesonide) prior to enrollment. These medications were not changed throughout the study and subsequent follow-up.

Ventilators

A pressure-controlled ventilator (PV401, Breas®, Sweden) was used. Inspiration times can be set between 0.5 and 5 s. A pressure-controlled trigger can be chosen between −2 and +8 mbar. Inspiratory pressures range from 6 to 40 mbar, and the respiratory rate can be set between 6 and 40 breaths per minute (BPM). The time in which the maximal pressure is reached can be adjusted at an arbitrary scale between 1 and 9, where higher values indicate less time needed to reach maximal pressure. Higher values between 8 and 9 were chosen in our study.

Study design

Prior to the study pulmonary function (Masterlab, Jaeger, Wuerzburg, Germany) and inspiratory mouth pressures (ZAN®, Oberthulba, Germany) were measured. Initial ABG were sampled from the radial artery (AVL Compact 2 Blood Gas Analyzer, Roswell, GA, U.S.A.) while patients were breathing room air at rest. Patients were started on nIPPV using a conventional nasal mask (Respironics®, Pittsburgh, PA, U.S.A.). After a period of acclimatization, patients were instructed to use the ventilator during the whole night and during daytime for up to 6 h (14 h/day) until normocapnia was achieved. From then on the ventilator was used during bedtime and for up to 2 h during midday (10 h/day). Patients with nasal irritations or mask leaks received an individual nasal mask. The ventilator settings were adjusted individually as described below to normalize ABG maintaining the best comfort for the patient.

The ventilator was used during the initiation of nIPPV with inspiratory pressures between 12 and 18 mbar and a low trigger threshold (−0.5 to −0.1 mbar). Oxygen saturation was measured continuously by pulse oxymetry. Supplemental oxygen was added to maintain $SaO_2 > 95\%$. Subsequently, the inspiratory pressure was increased stepwise until a further increase was not tolerated by the patient. Next, the respiratory rate was increased beyond the spontaneous rate to establish passive ventilation. Further increases in respiratory rate were aimed at a progressive decrease of $PaCO_2$ towards normocapnia. In some cases, the inspiratory pressure had to be decreased slightly to allow a further increase in the respiratory rate while maintaining an I:E ratio of approximately 1:2.

ABG drawn from the radial artery were measured daily once in the early morning while on nIPPV (for at least 4 h during night). Settings were increased when ABG during nIPPV still revealed hypercapnia. Further ABG during nIPPV were drawn later in the day in order to verify the adjustment of the ventilator. In addition, ABG were drawn during spontaneous breathing at least 4 h after cessation of ventilation on days when normo-

capnia during nIPPV had been achieved. Patients were discharged when normocapnia ($PaCO_2$ 37–43 mmHg) during nIPPV had been achieved or $PaCO_2$ did not show a further decrease during nIPPV for a minimum of 3 days. A follow-up was carried out at 6 weeks and 6 months after initiation of nIPPV with measurements of ABG, mouth occlusion pressures, and pulmonary function testing together with a detailed non-standardized history in order to investigate long-term effects of nIPPV aimed at achieving normocapnia.

Statistical analysis

Statistical analysis was performed using Sigma-Stat (Version 2.03, SPSS Inc., Chicago, IL, U.S.A.). Data are presented as mean $\pm$ standard deviation after testing for normal distribution. Statistical analysis of all data was performed with the paired *t*-test, one-way ANOVA for repeated measurements with pairwise multiple comparison using the Student–Newman–Keuls method and with the Pearson product moment correlation. Statistical significance was assumed with a *P*-value of <0.05.

RESULTS

All patients enrolled were hypoxemic and hypercapnic, and had signs and symptoms of COPD for >3 months (Table 1). Body mass index was $28.4 \pm 7.2\ kg/m^2$. Pulmonary function testing revealed a severe airflow obstruction with an FEV_1 of 0.97 ± 0.43 l and an FEV_1/VC-ratio of $45 \pm 9.7\%$. $PaCO_2$ was correlated to FEV_1 ($r = -0.57$, $P < 0.05$) and to HCO_3^- ($r = -0.76$, $P < 0.005$). Inspiratory mouth pressures with a $P0.1$ of 0.48 ± 0.25 kPa and a $PImax$ of 4.6 ± 1.7 kPa ($P0.1/PImax$ $10.9 \pm 5.4\%$) indicated an increased inspiratory load and decreased inspiratory muscle strength (20,21,26). $P0.1/PImax$ was correlated to FEV_1 ($r = -0.77$, $P < 0.005$) and to IVC ($r = -0.81$, $P < 0.005$).

All patients were established on nIPPV using a nasal mask. Ventilation parameters are given in Table 2. In all patients, the respiratory rate could be increased inducing totally passive ventilation. Five patients did not tolerate the Respironics® mask because of major leakage, one patient additionally suffered from soreness on the bridge of the nose and subsequently developed a local ulcer. All were successfully switched to an individually adapted nose mask. In two patients, symptoms of gastric distension were successfully treated by individual positioning during ventilation, a mild reduction in inspiratory pressures and oral dimeticon t.i.d. 80 mg.

$PaCO_2$ values decreased progressively to a mean $PaCO_2$ of 40.0 ± 4.6 mmHg ($P < 0.001$) following initiation of nIPPV, corresponding to an average drop in $PaCO_2$ of 19.5 ± 7.0 mmHg (Fig. 1). This was reflected by an increase in pH from 7.39 ± 0.04 to 7.45 ± 0.04 ($P < 0.001$). HCO_3^- levels decreased from 35.6 ± 5.2 to 28.5 ± 2.1 mmol/l ($P < 0.001$). Since oxygen was supplemented during nIPPV, mean PaO_2 increased from 49.9 ± 7.8 to 75.0 ± 9.3 mmHg ($P < 0.001$). In all patients, the mean supplemental oxygen flow rate was 1.5 ± 1.0 l/min at the time of optimal ventilation, whereas three patients did not require further additional treatment with oxygen once $PaCO_2$ had returned to normal.

The mean $PaCO_2$ after 4 h following cessation of nIPPV during subsequent spontaneous breathing was 46.0 ± 5.5 mmHg (range 36–58 mmHg) with an increase

TABLE 1. Lung function parameters and ABG prior to initiation of nIPPV

Case no.	FEV_1 (l)	VC (l)	FEV_1/VC (%)	TLC (l)	RV/TLC (%)	$PaCO_2$ (mmHg)	PaO_2 (mmHg)	HCO_3^- mmol/l	pH
1	1.00	3.1	32	7.1	0.56	67	56	44	7.43
2	1.60	3.5	47	8.0	0.56	50	49	32	7.45
3	1.40	3.0	48	6.7	0.55	58	56	37	7.42
4	0.92	1.9	49	5.9	0.68	51	54	28	7.37
5	0.87	1.5	58	4.4	0.66	60	45	35	7.42
6	0.96	2.5	39	8.5	0.71	57	60	41	7.45
7	0.68	1.5	44	7.0	0.79	64	44	36	7.34
8	0.64	2.2	30	8.4	0.74	70	39	39	7.34
9	0.43	1.2	36	5.9	0.80	50	53	32	7.40
10	1.20	2.5	50	6.1	0.59	57	47	34	7.34
11	0.93	2.4	39	5.6	0.57	55	57	30	7.38
12	1.90	3.1	61	6.1	0.49	49	58	29	7.38
13	0.57	1.0	56	7.0	0.86	74	48	37	7.35
14	0.53	1.5	36	6.7	0.78	71	33	44	7.35
Mean	0.97	2.2	45	6.7	0.67	59.5	49.9	35.6	7.39
SD	0.43	0.8	9.7	1.1	0.12	8.4	7.8	5.2	0.04

Table 2. Ventilation parameters and ABG during nIPPV + supplemental oxygen

Case no.	Pressure (mbar)	Frequency (l/min)	Insp. Time (sec)	Suppl. O_2 (l/min)	$PaCO_2$ (mmHg)	PaO_2 (mmHg)	HCO_3^- (mmol/l)	pH
1	30	22	0.9	1	36	78	29	7.51
2	32	21	0.9	2	36	78	26	7.50
3	25	22	0.8	0	39	67	28	7.47
4	24	22	1.0	0	38	84	29	7.45
5	30	20	0.9	2	48	63	32	7.37
6	28	23	0.8	0	34	68	29	7.45
7	28	26	0.7	3	40	70	30	7.48
8	36	25	0.7	1.5	47	85	28	7.43
9	24	26	0.8	1	39	72	26	7.43
10	28	23	0.9	2	37	64	26	7.43
11	33	21	0.9	2	36	90	28	7.48
12	34	21	0.8	2	40	65	28	7.45
13	32	24	0.9	2	43	78	27	7.43
14	33	24	1.0	3	47	88	33	7.39
Mean	29.8	22.9	0.9	1.5	40.0	75.0	28.5	7.45
SD	3.8	1.9	0.1	1.0	4.6	9.3	2.1	0.04

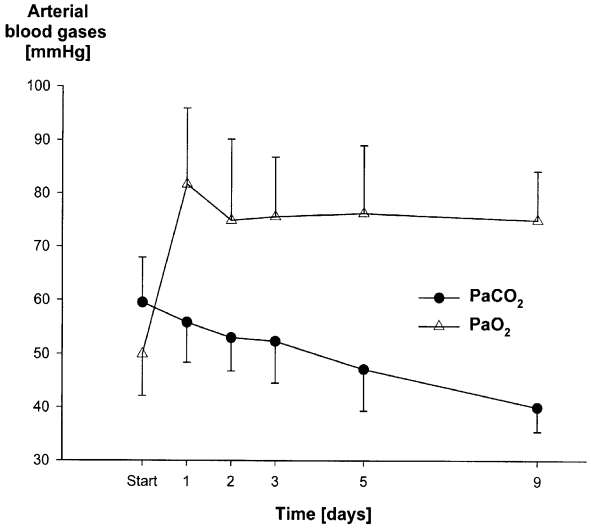

Fig. 1. Normalization of PaO_2 and $PaCO_2$ during nIPPV with supplemental oxygen ($n = 14$).

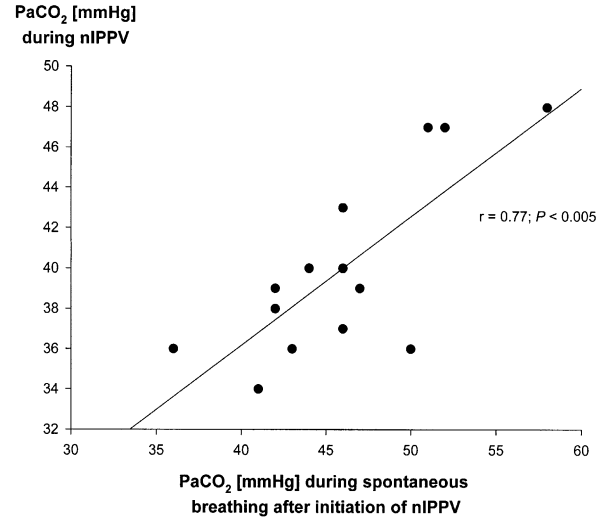

Fig. 2. Correlation (Pearson) between $PaCO_2$ during nIPPV and $PaCO_2$ during subsequent spontaneous breathing four hours after cessation of nIPPV ($n = 14$).

of 6.0 ± 3.5 mmHg compared to $PaCO_2$ during nIPPV ($P < 0.001$). The corresponding PaO_2 was 55.9 ± 8.2 mmHg (range 45–71 mmHg) with a decrease of 19.1 ± 12.7 mmHg compared to the PaO_2 during nIPPV with supplemental oxygen ($P < 0.001$), the corresponding pH was 7.43 ± 0.05 (range 7.34–7.51) with a decrease of 0.02 ± 0.06 compared to the pH during nIPPV (not significant) and the corresponding HCO_3^- was 27.2 ± 3.0 mmol/l (range 22–34 mmol/l) with a decrease of 1.3 ± 1.6 mmol/l compared to HCO_3^- during nIPPV ($P < 0.05$).

Compared to ABG prior to initiation of nIPPV the $PaCO_2$ decreased by 13.5 ± 9.3 mmHg ($P < 0.001$), the PaO_2 increased by 5.9 ± 6.1 mmHg ($P < 0.005$), the pH increased by 0.04 ± 0.05 ($P < 0.01$), and HCO_3^- decreased by 8.4 ± 5.1 mmol/l ($P < 0.001$) when patients breathed room air after 4 h following cessation of nIPPV. There was a close correlation between the $PaCO_2$ during nIPPV and the $PaCO_2$ during subsequent spontaneous breathing after initiation of nIPPV ($r = 0.77$; $P < 0.005$) (Fig. 2).

The mean number of days of nIPPV to reach normocapnia was 8.8 ± 3.8. There was a close correlation between the number of days on nIPPV to reach normocapnia and the following parameters: VC: $r = -0.74$, $P < 0.005$; FEV_1: $r = -0.73$, $P < 0.005$ (Fig. 3);

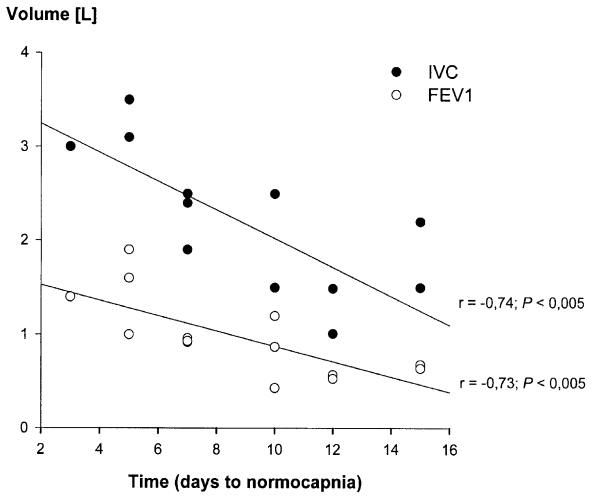

Fig. 3. Correlation (Pearson) between lung function parameters (FEV_1, VC) and the number of days to achieve normocapnia by nIPPV ($n = 14$).

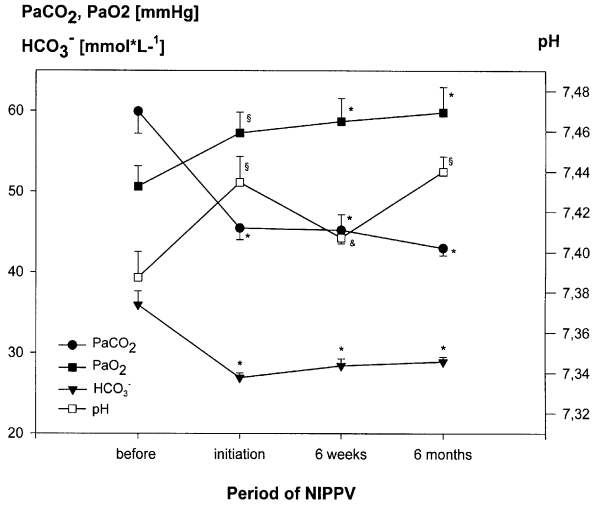

Fig. 4. $PaCO_2$, PaO_2, HCO_3^- and pH (mean ± SEM) during spontaneous breathing of ambient air following nIPPV ($n = 11$) (*$P < 0.001$, §$P < 0.005$, and &n.s. compared to values before nIPPV).

$P0.1/P\text{Imax}$: $r = 0.70$, $P < 0.05$; $PaCO_2$ prior to nIPPV: $r = 0.59$, $P < 0.05$.

The mean hospital stay was 14.1 ± 5.1 days which was correlated to the number of days on nIPPV required to reach normocapnia ($r = 0.80$; $P < 0.001$). The mean time spent on the ventilator after reaching normocapnia was 9.8 ± 2.4 h/day, most of which was during night. Each patient was discharged from hospital in a clinically stable condition and with a subjective improvement in symptoms with the exception of one patient (case five) who was unable to tolerate nIPPV at night. He was discharged without nIPPV and died 6 months later due to progressive respiratory failure. The other patients reported a good quality of sleep and were maintained on nIPPV at home.

Within the following 6 months, two additional patients discontinued nIPPV. One patient (case nine) remained normocapnic without further ventilation after initial treatment, although prior to inclusion this patient had no evidence of an acute respiratory failure. However her $PaCO_2$ was only 50 mmHg when she was entered into the study. One patient (case seven) died not due to respiratory conditions (sudden cardiac death). In the remaining 11 patients ABG remained stable for 6 weeks and 6 months after initiation of nIPPV. The $PaCO_2$ at 6 months was 38.7 ± 2.6 mmHg, the PaO_2 was 78.8 ± 14.1 mmHg, pH was 7.46 ± 0.03 and the HCO_3^- 27.8 ± 1.5 mmol/l while on nIPPV. At this follow-up visit, the $PaCO_2$ after 4 h of spontaneous breathing was 43.0 ± 1.9 mmHg, the PaO_2 was 59.8 ± 10.1 mmHg, the pH was 7.44 ± 0.02 and the HCO_3^- was 28.9 ± 1.9 mmol/l (Fig. 4). The $P0.1$ decreased significantly and $P\text{Imax}$ increased not significantly as shown in Table 3. Accordingly, this resulted in a significant decrease of the $P0.1/P\text{Imax}$-ratio (Table 3). In addition, there was no significant change in lung function parameters and hyperinflation (Table 3). The mean time on nIPPV at 6 months follow-up was 10.2 ± 3.1 h/day, most of which was during night. All patients were clinically

Table 3. Mouth occlusion pressures and lung function parameters in patients who continued nIPPV over a period of 6 months ($n = 11$)

	nIPPV onset	6-weeks follow-up	6-months follow-up
P0.1 (kPa)	0.46 ± 0.26	0.29 ± 0.14*	0.31 ± 0.10*
PImax (kPa)	4.9 ± 1.6	5.4 ± 1.5	5.5 ± 1.4
P0.1/PImax (%)	9.4 ± 4.3	5.2 ± 2.5***	5.9 ± 2.0**
FEV_1 (l)	1.06 ± 0.43	0.99 ± 0.44	1.06 ± 0.48
VC (l)	2.4 ± 0.7	2.2 ± 0.8	2.5 ± 0.7
FEV_1/VC (%)	44 ± 9.9	45 ± 10.3	44 ± 13.3
TLC (l)	6.9 ± 1.0	6.8 ± 1.3	6.7 ± 1.1
RV/TLC (%)	0.64 ± 0.11	0.66 ± 0.12	0.64 ± 0.12

*$P < 0.05$, ** $P < 0.005$, *** $P < 0.001$ compared to nIPPV onset.

stable, and there was no acute exacerbation or hospital admission due to respiratory events since the onset of nIPPV. All patients reported an improvement in their physical function and well-being.

Discussion

Our data show that normalization of $PaCO_2$ by nIPPV in patients with HRF due to COPD is possible and leads to a significant reduction of $PaCO_2$ during subsequent spontaneous breathing. During the initiation of nIPPV assisted ventilation with supplemental oxygen allowed normalization of PaO_2 in all patients without any significant deterioration in hypercapnia. Subsequently, ventilation parameters were increased stepwise until normocapnia was reached by passive ventilation. Almost 9 days of nIPPV were needed to achieve normocapnia. Interestingly, there was a statistically significant correlation between the time needed to achieve normocapnia and pulmonary function parameters (FEV_1 and VC), $PaCO_2$ prior to nIPPV and the $P0.1/PImax$-ratio suggesting that the time on nIPPV required to reach normocapnia is dependent on the severity of the disease. Relatively high inspiratory pressures with a mean of 29.8 ± 3.8 mbar and relatively high respiratory rates with a mean of 22.9 ± 1.9 BPM were necessary to achieve normocapnia. This is in contrast to low-pressure ventilation with e.g. BiPAP® ventilators (Respironics Inc., Murrysville, PA, U.S.A., peak inspiratory pressure: 22 cmH_2O) which were insufficient to normalize $PaCO_2$ in hypercapnic COPD. In these studies, BiPAP® in the spontaneous mode did not change hypercapnia in patients with stable COPD (27,28). In another study, nasal pressure support ventilation (PSV) with BiPAP® in the spontaneous mode increased minute ventilation (VE) by increasing tidal volume (VT) despite a reduction in respiratory rate (25). Although this resulted in a decrease in $PaCO_2$ by 7 mmHg, patients still remained hypercapnic during ventilation.

The addition of BiPAP® to oxygen has been reported to be superior to oxygen alone to improve daytime and overnight blood gas values, sleep quality and quality of life in patients with stable hypercapnic COPD (9). However, $PaCO_2$ decreased only by a mean of 3.3 mmHg when patients were breathing room air after BiPAP®. In contrast, in our study there was a mean decrease in spontaneous $PaCO_2$ of 13.5 ± 9.3 mmHg. An increase in spontaneous PaO_2 by 5.9 mmHg following nIPPV in our study was similar to other observations (5,9). Interestingly, $PaCO_2$ during nIPPV and $PaCO_2$ during spontaneous breathing following nIPPV were well correlated suggesting that if normalization of $PaCO_2$ can be achieved by nIPPV this will also result in a reduction in $PaCO_2$ during subsequent spontaneous breathing. In contrast, patients who remain in hypercapnia even during ventilation presumably will not have a significant decrease in spontaneous $PaCO_2$. Although we did not measure CO_2-threshold, it might be, therefore, suggested that an increased CO_2-threshold in hypercapnic COPD can be temporarily decreased by more aggressive ventilation. A high correlation between the change in $PaCO_2$ following nIPPV and the increase in ventilation following CO_2-rebreathing has been reported previously (15). From these data, it was concluded that the CNS responds to an increase in load in order to prevent fatigue and not due to overt respiratory pump failure, since the reduction of $PaCO_2$ and the increase of inspiratory muscle strength did not correlate well. However, $PaCO_2$ decreased only by 7 mmHg (0.9 kPa) which could explain the lack of a significant increase of inspiratory muscle strength. In addition, it has been suggested that bicarbonate concentration is a significant determinant in setting the sensitivity of the respiratory control mechanism to the natural carbon dioxide stimulus, whereas changes in hydrogen ion activity as the crucial determinant of ventilatory response are mainly regulated by bicarbonate concentration (29). Accordingly, the application of acetazolamide (ACET) produced metabolic acidosis in COPD with a decrease in bicarbonate levels, but a decrease of $PaCO_2$ of > 5 mmHg combined with an increase in VT was observed only in six of the 15 patients (30). Furthermore, there was no correlation between the correction of $PaCO_2$ induced by ACET and the ventilatory response to exogenous $PaCO_2$ in this study indicating that the simple renal loss of bicarbonate which lowers the pH is presumably not the only mechanism by which normalization of ventilation with lowering of $PaCO_2$ occurs. Interestingly, there was a significant decrease of bicarbonate and $PaCO_2$ following nIPPV in our series. From these data it can be suggested that normalization of spontaneous $PaCO_2$ induced by acidosis-stimulated breathing will occur only if renal excretion of bicarbonate is accompanied by improvement of the respiratory muscle function. This is supported by the fact that $P0.1$ decreased following nIPPV in our series indicating unloading of the respiratory muscles, whereas P0.1 increased following application of ACET (30) which would suggest to us that ACET in contrast to nIPPV as applied in our study increase the load on the respiratory pump.

Only one patient discontinued nIPPV due to major discomfort indicating that the ventilation parameters used in our study which are considerably higher than those previously reported in the literature are well tolerated. In addition, no harmful effects of nIPPV using higher ventilation pressures occurred, and there was no increase of hyperinflation following nIPPV which could have theoretically led to harmful effects on respiratory muscle function, barotrauma or hemodynamic changes. Although up to 50% of patients suffer from gastric distension when using a volume-cycled ventilator (3,31), normocapnia was achieved during nIPPV in our study with a reduced frequency of side-effects possibly due to a more constant

peak inspiratory pressure when using a pressure-controlled ventilator. Pressure-controlled ventilation also has the advantage of leak compensation but it remains unclear to which extend this might have contributed to the successful ventilation in our study. Patients who continued home ventilation had relief of symptoms, and none of the patients was readmitted for an acute exacerbation of HRF and presented with normocapnia during the follow-up at 6 weeks and 6 months indicating clinical benefit. This was accompanied by a significant reduction in *P*0.1/*P*Imax at follow-up visits, although lung volumes and hyperinflation remained unchanged suggesting that nIPPV and not improvement in lung volumes or a decrease in hyperinflation might be responsible for the observed changes. Although we do not provide direct proof, these findings suggest alleviation of respiratory muscle fatigue due to nIPPV, possibly due to unloading of the respiratory muscles.

In conclusion, pressure-controlled ventilation can normalize $PaCO_2$ in patients with severe HRF due to COPD using relatively high inspiratory pressures and relatively high respiratory rates without major discomfort for the patient. Our data suggest that attempts to normalize $PaCO_2$ during nIPPV can lead to a prolonged improvement in $PaCO_2$ when breathing ambient air in patients with chronic HRF due to COPD. Although not tested in this study, we would speculate that this effect is due to a reduction in the CO_2-threshold of these patients induced by renal excretion of bicarbonate following improvement of respiratory muscle function. Clearly, controlled studies are needed to assess the long-term benefit of establishing normocapnia in patients with chronic HRF due to COPD.

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