Long-term reduction of hyperinflation in stable COPD by non-invasive nocturnal home ventilation

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Summary

Objective: The role of non-invasive positive pressure ventilation (NPPV) in stable COPD with chronic ventilatory failure remains controversial. The impact of long-term home nocturnal NPPV treatment on deflation has not yet been evaluated in detail.

Methods: Retrospective explorative study of 46 patients with stable COPD undergoing NPPV treatment. Effects of NPPV on bodyplethysmographic parameters, blood gas tensions and inspiratory muscle function after 6.2 (± 1.7) and 12.7 (± 2.1) months of treatment. Further, evaluation of 1-year survival, compliance and ventilation parameters.

Results: One-year survival was 89.1%. The effectiveness of ventilation was proven by a significant reduction in nocturnal and daytime $\text{PaCO}_2$. We observed a decrease in the ratio of residual volume (RV) to total lung capacity (TLC) on the average of 5.2 ± 9.8% (or 15.2 ± 29.7% pred.; $P < 0.01$) at six and 3.9 ± 9.0% (or 12.9 ± 18.6% pred.; $P < 0.001$) at 12 months. As a consequence, we found significant improvements in inspiratory capacity (IC), vital capacity (VC) and forced expiratory volume in one second (FEV$_1$). For patients with the most severe hyperinflation (RV/TLC > 75%), we found a significant positive correlation between inspiratory positive airway pressure (IPAP) and reductions in $\text{PaCO}_2$ ($r = 0.56; P < 0.05$) and RV/TLC ($r = 0.50; P < 0.05$).

Abbreviations: BE, base excess; BMI, body-ass index; CPAP, continuous positive airway pressure; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; EPAP, expiratory positive airway pressure; EELV, end-expiratory lung volume; FEV$_1$, forced expiratory volume in one second; Hb, haemoglobin; HRQL, health-related quality of life; IC, inspiratory capacity; IPAP, inspiratory positive airway pressure; LTOT, long-term oxygen therapy; NPPV, non-invasive positive pressure ventilation; $P_{100}$, mouth occlusion pressure at 100 ms; $\text{PaCO}_2$, arterial carbon dioxide tension; $\text{PaO}_2$, arterial oxygen tension; PEEP, intrinsic positive end-expiratory pressure; P$_{1\text{max}}$, maximal inspiratory pressure; RV/TLC, ratio residual volume/total lung capacity; $\text{SaO}_2$, arterial oxygen saturation; SR$_{tot}$, total specific resistance; TLC, total lung capacity; VC, vital capacity

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Conclusions: In severe hypercapnic stable COPD long-term nocturnal NPPV can reduce hyperinflation with sustained improved daytime blood gas parameters.

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Introduction

Non-invasive positive pressure ventilation (NPPV) has attained an important role in the treatment of COPD with acute respiratory failure by avoiding intubation and prolonging survival.\textsuperscript{1-4} Despite the lack of prospective controlled trials, NPPV is also an accepted treatment option for chronic ventilatory failure in patients with neuromuscular and chest wall diseases,\textsuperscript{5-9} although controversy remains regarding the effectiveness of long-term home ventilation in patients with hypercapnic but stable COPD.\textsuperscript{10} Numerous studies have described positive effects on blood gas parameters, sleep quality and hospital admission as well as on functional status and health-related quality of life.\textsuperscript{11-18} In contrast, no changes or only marginal improvements in these parameters were reported in some controlled investigations, mostly on small samples of COPD patients.\textsuperscript{19-22} However, it was noted that these results were possibly due to patient selection, ineffective ventilation, poor compliance or too short of an application time.\textsuperscript{23-25} Although there is growing evidence that at least subgroups of COPD patients profit from NPPV,\textsuperscript{26,27} the mechanisms responsible for the beneficial effects, especially improving blood gas parameters, are not completely understood and have yet to be defined. More recently, in a prospective controlled trial, it could be shown that the short-term use of NPPV during the day improves blood gas tensions in relation to a decrease in lung hyperinflation, while no relief in inspiratory muscle fatigue could be observed.\textsuperscript{28} To evaluate the impact on lung deflation of patients receiving long-term home ventilation, we performed a retrospective analysis of different lung function parameters including inspiratory capacity and respiratory muscle function in a collective of severe symptomatic COPD patients in a stable status of their disease.

Materials and methods

Patient selection

All COPD patients discharged with NPPV from the respiratory clinic in Donaustauf, University of Regensburg, Germany from 1995 to October 2003 were retrospectively collected in a computerized database. We usually initiated NPPV in severe symptomatic COPD in case of persistent hypercapnia after exhaustion of medical treatment (all patients had received \(\beta\)-agonists, anticholinergic agents, theophylline, inhaled steroids and on occasion systemic steroids). In order to examine the effects of NPPV on stable COPD, we selected the patients based on the following clinical and physiological criteria:

- severe form of the disease according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) IV;
- \(\text{FEV}_1 < 50\%\) of predicted and \(\text{PaCO}_2 > 45\text{mmHg}\) while breathing room air;
- no clinical signs of exacerbation based on the definition of Anthonisen et al.\textsuperscript{29} taken from the anamnesis;
- leucocytes \(< 10,000/ul\) at time of admission;
- \(\text{CRP} \leq 5\text{mg/dl}\) at time of admission;
- \(\text{pH} \geq 7.35\);
- current oxygen therapy (LTOT);
- no previous exposure to domiciliary NPPV;
- exclusion of patients which were switched from tracheostomy to non-invasive mask ventilation;
- exclusion of patients in which a sleep apnoea was detected (assessed by polysomnography) and/or BMI \(\geq 40\text{kg/m}^2\).

Measurements

Diurnal and nocturnal blood gas measurements (Rapidlab; Bayer Inc; East Walpole, MA, USA) were routinely taken from the hyperaemic earlobe, where the values being closest to the initiation time of NPPV and showing best oxygenation (\(\text{So}_2 > 90\%\) or \(\text{PaO}_2 > 60\text{mmHg}\)) were considered as baseline values. We registered blood gas parameters in the daytime during spontaneous breathing of room air and during long-term oxygen therapy (LTOT) using their usual oxygen flow. Whole bodyplethysmography (Masterlab; Jaeger Inc; Würzburg, Germany) was performed following the guidelines of the American Thoracic Society,\textsuperscript{30} based on the reference values of the European Community for Steel and Coal.\textsuperscript{31} Inspiratory capacity was calculated as the difference between total lung capacity and intrathoracic gas volume. Inspiratory mouth occlusion pressure at 100 ms (\(P_{0.1}\))
and maximal inspiratory mouth pressure ($P_{I\text{max}}$) were measured as previously described.\textsuperscript{32}

**Control evaluation**

Standard practice in our hospital is that all patients are reviewed after 6 and 12 months for a control evaluation. We routinely ask about adverse effects or problems such as leakage, dry mucosal, etc. by questionnaire. Furthermore, each patient is required to estimate his daily application time and quantify the therapy effect on physical capacity and symptom relief. Simultaneously, the patient's statement is compared to the time counter on the ventilator. Capillary blood gas parameters are measured twice at night during ventilation and in the daytime during spontaneous breathing 4–6 h after nocturnal NPPV under LTOT (usual oxygen flow). Ventilation parameters are adjusted to optimize blood gas parameters and nocturnal oxygen saturation. In addition, bodyplethysmography and inspiratory muscle function is performed as mentioned above.

**NPPV technique**

Before initiation of NPPV a standard commercial nasal or full facemask of different sizes and types (nasal mask Gold or Special; Resproni Inc; Murrysville, PA, USA and NV ultra mirage nasal or fullface mask; ResMed Inc; North Ryde, Australia) or, if necessary, an individually manufactured mask is fitted. Initially, the ventilator is set in the spontaneous-timed (assist-controlled) mode with low inspiratory pressure and back-up respiratory frequency. After a phase of adaptation we gradually increase the ventilation parameters to the patient’s comfort level, targeting a tidal volume of 7–10 ml/kg. Oxygen is supplemented as required to achieve an oxygen saturation of more than 90%.

The beneficial effect of the ventilation and oxygen supplementation is proven during several nights of repeated measurements of blood gas parameters at 1:00 and 4:00 a.m. from the hyperaemic earlobe. In case of a persistent hypercapnia, we increase inspiratory pressure in order to achieve more effective ventilation. In the patient sample analyzed there were four different home respirators in use, although most of our patients were ventilated with the Onyx plus (Nellcor Puritan Bennett Inc; Courtaboeuf Cedex, France) and BIPAP synchrony ST (Resproni Inc; Murrysville, PA, USA), which work in a pressure-cycled mode with a highly sensitive trigger. Additionally, a humidification system is installed if dry mucous membranes develop.

**Statistical analysis**

The data were collected in a data bank (Microsoft Access\textsuperscript{8}) and analyzed with SPSS software (Statistical Package for Social Science; Chicago, IL, USA). Baseline values for survivors and non-survivors and patient characteristics for responding to NPPV were compared using an unpaired t-test. For changes in functional parameters a two-related-samples test (Wilcoxon-test) was performed. Results are presented as percent (%) of change. Relationships between changes in blood gas parameters, lung volumes and inspiratory pressure were assessed using a linear regression model (Pearson-correlation). Results are shown as mean value ± standard deviation (SD). A $P$-value of $<0.05$ was considered to be significant.

**Results**

**Patient sample**

We registrated 239 patients with COPD in which NPPV was started. Thirty-seven patients (15.5%) were excluded because they were switched from tracheostomy to NPPV and 54 patients (22.6%) because of detection of a sleep apnoea syndrome. One hundred and two patients (42.7%) did not fulfil the other inclusion criteria, mostly due to exacerbation (38 patients had clinical signs for exacerbation and 64 patients elevated leucocytes or CRP). Forty-six patients (19.2%) met the inclusion criteria mentioned above. Of these patients, four died within the first 6 months and one patient between 6 and 12 months after initiation of NPPV. Thus, 1-year survival was 89.1%. One patient had to be tracheostomized a few weeks after initiation of NPPV, one patient had been admitted to another hospital for control evaluations and one patient did not come to the control investigation at 12 months. Hence, we could analyze the data of 40 patients at 6 months and 38 patients at 12 months. They were seen $6.2 \pm 1.7$ and $12.7 \pm 2.1$ months after initiation of NPPV.

**Patients characteristics at baseline**

At initiation of NPPV the median age of all 46 (8 female/38 male) patients fulfilling the inclusion criteria was 65.2 ($\pm 6.6$) years with a range from 53.1 to 77.9 years. The severity of COPD was demonstrated by a median $P_{aCO_2}$ of 55.9 ($\pm 7.3$) mmHg in the daytime during spontaneous breathing of oxygen ($0.9 \pm 1.0$ l) and an FEV$_1$ of 0.76
(±0.21) l or 29.0 (±8.2) % of predicted. Table 1 shows the data of survivors and non-survivors. Although we were aware that the size of the groups was different, it is important to note that non-survivors seem to have a more severe form of the disease and were significantly more hyperinflated (RV/TLC 73.5±8.6 vs. 78.5±7.8% or 185.0±21.2 vs. 204.6±6.1% of predicted; P<0.001).

NPPV parameters and ventilator compliance

NPPV was delivered in 42 patients through a nasal mask, in two patients through a full facemask and in two patients through an individually manufactured mask. After discharge from the hospital, the patients were ventilated with an expiratory positive airway pressure (EPAP) of 3.8 (±1.8) cm H2O, an inspiratory positive airway pressure (IPAP) of 19.9 (±4.1) cm H2O and a mean respiratory frequency of 21.3 (±3.5)/min. There were no significant changes in ventilation parameters after 6 and 12 months.

The median daily application time of NPPV, calculated via the time counter of the ventilator was 6.1 (±1.8) h from discharge to six months and 6.5 (±2.8) h from 6 to 12 months. Only two patients (5%) had ventilator use less than 3 h.

### Long-term effects of NPPV

#### Blood gas parameters

Figure 1 shows the changes in blood gas parameters during the daytime after nocturnal NPPV treatment. We found a decrease in PaCO2 of 9.3±9.9 mmHg (15.3±16.4%; P<0.001) at 6 and 11.0±9.3 mmHg (18.4±13.5%; P<0.001) at 12 months. Furthermore, PaO2 (15.6±30.5%; P<0.05 resp. 17.8±31.3%; P<0.01) and pH (0.3±0.5%; P<0.01 resp. 0.4±0.6% P<0.001) increased at 6 and 12 months while positive base excess (BE) decreased (22.0±72.4%; P<0.001 resp. 27.3±62.8%; P<0.001). In patients in which nocturnal blood gas parameter were available at baseline and control investigation at 1:00 a.m. and 4:00 a.m. as well, we saw a decrease in PaCO2 at 6 months (n = 30) from 58.3±8.2 to 47.6±8.3 mmHg (14.2±20.7%; P<0.001) resp. from 60.7±8.1 to 48.4±8.2 mmHg (15.9±20.0%; P<0.001). At 12 months (n = 28) similar reductions in PaCO2 to 46.1±7.7 mmHg (18.0±19.5%; P<0.001) at 1:00 a.m. and to 47.4±7.5 mmHg (16.9±19.2%; P<0.001) at 4:00 a.m. could be observed.

In comparison, patients with exacerbation (n = 102) in which blood gas parameters were available before initiation of NPPV and at 6 and 12 months as well (n = 40), changes in PaCO2, PaO2 and BE were even more pronounced (Table 2).

#### Lung and inspiratory muscle function after NPPV

We found a significant decrease in RV/TLC at 6 (3.9±6.4%; P<0.01) and 12 months (5.2±9.8%; P<0.001). The median decrease of RV/TLC of predicted was 15.2±29.7% (P<0.01) at 6 and

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<th>Variable</th>
<th>Survivors (n = 41)</th>
<th>Non-survivors (n = 5)</th>
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<tr>
<td>Age (yr)</td>
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<td>IC (l)</td>
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<td>RV/TLC (%)</td>
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<td>78.5±7.8</td>
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<tr>
<td>RV/TLC pred. (%)</td>
<td>185.0±21.2</td>
<td>204.6±6.1†</td>
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<td>PaO₂ (mmHg)</td>
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<td>Hb (g/dl)</td>
<td>15.2±2.1</td>
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*Data are presented as mean±SD unless otherwise indicated.

†P<0.001.

Figure 1 Changes in blood gas tensions and base excess (BE) 6 and 12 months after NPPV. *Significant difference in comparison to baseline values (P<0.001).
12.9 ± 18.9% (P < 0.001) at 12 months. Simultaneously, we observed an increase in inspiratory capacity at six (17.0 ± 38.0%; P < 0.05) and 12 months (17.1 ± 42.6%; P < 0.05) (Fig. 2). Moreover, there was also a significant increase in FEV1 (19.7 ± 33.1% resp. 18.2 ± 31.0%; P < 0.01) and VC (18.1 ± 34.1% resp. 21.0 ± 32.2%; P < 0.01) at 6 and 12 months. Again, in patients with exacerbation (n = 102) in which lung function was performed before initiation of NPPV and at 6 (n = 35) and 12 months (n = 38), changes in RV/TLC and IC were more pronounced (Table 2).

In stable COPD, improvements in FEV1 and VC were significantly correlated to the reduction in RV/TLC (r = −0.60; P < 0.001 resp. r = −0.77; P < 0.001) (Fig. 3). No changes could be detected in TLC, SRrot and FEV1/VC at these investigation points. We also found no significant improvement in the maximal inspiratory muscle force (PImax), nor in P0.1 or the quotient P0.1/PImax.

**Discussion**

The main finding of the current study is that, in stable COPD, the long-term application of nocturnal NPPV can decrease hyperinflation in terms of a reduction in RV/TLC, thereby improving inspiratory capacity. This reduction in hyperinflation is accompanied by a significant and sustained amelioration of daytime blood gas tensions, specifically a decrease in PaCO2.

**Effects and response to NPPV in comparison to previous investigations**

The long-term effects of NPPV in stable COPD are still discussed controversially.10,23,24 However, in a number of studies,11,12,14–18 NPPV has been shown to reduce daytime PaCO2, which has been
frequently explained by sensitization of central respiratory center. Nevertheless, the ability of NPPV to reduce hyperinflation was recognized more than a decade ago, but has not yet been investigated in a larger collective on a long-term basis. We detected a significant decrease in RV/TLC, on average 15.2% pred. at 6 months and 12.3% pred. at 12 months without changes in TLC, compared to baseline values. Since we found a highly positive correlation between changes in RV/TLC and FEV₁ and VC, we presume that deflation also plays a role in the improvement of these parameters. Previous long-term investigations often observed no change in most of the lung function parameters measured by bodyplethysmography or spirometry. However, Perrin et al. prospectively evaluated 14 patients on domiciliary NPPV plus LTOT and found an improvement in VC and FEV₁, but without statistical significance in their small sample of patients.

In most previous investigations, positive effects resulting from NPPV possibly were not observed for several reasons. First, in comparison to patients with neuromuscular or thoracic restrictive diseases, unsatisfactory ventilator compliance is often reported for patients with stable COPD, particularly in studies with poor response to NPPV. In an outpatient setting, Strumpf et al. even reported an intolerance rate of 63%. In contrast, we observed a high level of acceptance of NPPV, which was demonstrated by the daily duration of ventilator use. Moreover, all but one patient came to the control investigation and only one patient had to be tracheotomized. We presume, that the high compliance rate in our patients could be due to close supervision and adequate initial adaptation to NPPV. However, we should also mention, that patients refusing NPPV within the first several days and thus discharged without NPPV were not registered in this analysis.

Furthermore, the effectiveness of nocturnal ventilation in our study was confirmed by significant reductions in PaCO₂, both in the daytime and at night, similar to the favourable results reported by Meecham-Jones et al. and Elliot et al. Finally, in three controlled investigations on NPPV in chronic COPD, the patients were not in a severe hypercapnic status (46, 50.5 and 50.7 mmHg, respectively) as they were in our sample of patients.

Possible mechanisms underlying the reduction of hyperinflation

Lung hyperinflation is a major problem in COPD patients which correlates inversely with functional status and exercise tolerance. It is thought that hyperinflation is the result of “air trapping” caused by expiratory airway collapse and augmented respiratory frequency, leading to intrinsic positive end expiratory pressure (PEEP). Supplementary oxygen has been found to reduce dynamic hyperinflation in patients with expiratory flow limitation at rest and during or after exercise as well. These effects had been essentially explained by changes in ventilatory pattern. Since NPPV therapy also results in improved blood gas parameters, similar effects on respiratory pattern could play an important role in NPPV. Indeed, in stable COPD patients, a decreased respiratory frequency and augmented tidal volume during NPPV has already been observed. These effects could be preserved for spontaneous breathing at least for responders, as indicated in some clinical studies. In a controlled prospective trial, Diaz
et al. found after a 3-week study period not only a deep and slow pattern of breathing, but also a significant correlation between increase in tidal volume and a decrease in residual volume and PEEP, as well. These improvements in breathing patterns and blood gas parameters during NPPV were more pronounced at higher pressure support levels. The importance of high inspiratory pressure was also demonstrated in our study by a significant correlation between IPAP and changes in PdCO2 and RV/TLC, at least for patients with the most severe hyperinflation.

Another possible explanation for the beneficial effects on hyperinflation may be that NPPV reduces the frequency or severity of exacerbations and thereby reduces any increase in hyperinflation over time. Although the underlying reasons remain unclear, some authors have, however, described a reduction in hospitalization admissions. Although, the underlying reasons remain unclear, some authors have, however, described a reduction in hospitalization admissions.12,17

As previously discussed, effects of NPPV could also be mediated by reducing airway wall oedema, thus reducing airway narrowing and decreasing airway resistance. This could be also beneficial for mucous clearance. As a personal observation, indeed some patients report substantial secretory production during nocturnal NPPV.

In our analysis we could not detect any effects of NPPV on P0.1, Plmax or on the ratio of P0.1/Plmax, despite significant changes in lung volumes and hyperinflation. This somewhat surprising result could be explained by studies, which indicate that P0.1 often is not a valid marker for inspiratory drive in COPD.

Limitations of study

The major limitation of this long-term study is that it is retrospective and uncontrolled. To ascertain clinical stability, we based our selection criteria on recently published prospective studies. However, a clear definition of exacerbation does not exist and apparently clinically stable COPD patients also have increased circulating levels of cytokine mediators. The clinical criteria for exacerbation proposed by Anthonisen et al. seemed to be verifiable in this study since data could be taken from the anamnesis. Additionally, laboratory parameters were used to exclude patients with current severe systemic inflammation. Indeed, since changes in blood gases and lung function were, as suspected, more pronounced in patients with exacerbation, the inclusion criteria presumably were appropriate. In the absence of a control group we cannot completely discount the bias that the reported improvement in hyperinflation could be due to medical treatment. In recent years some clinical trials have demonstrated that long-acting β-agonists as well as parasympatholytic agents are able to reduce hyperinflation. However, medical therapy had been already maximized at baseline and thus should not be responsible for the described effects as has also been confirmed in the controlled, but short-term trial by Diaz et al.

In summary, we analyzed a well-selected patient group with stable COPD, showing high compliance and demonstrating effective nocturnal ventilation. Thus, we conclude that the current study supports the long-term use of NPPV as an effective modality, particularly for severe hypercapnic patients. We could demonstrate that the improvement in blood gas parameters is accompanied by a reduction in hyperinflation and an increase in inspiratory capacity. Deflation, due to an improved respiratory pattern may play a central role in the beneficial effects of NPPV in stable COPD, but this has yet to be proven in a prospective long-term controlled trial.

References

10. Rossi A, Hill NS, editors. Pro/ton editorialis: noninvasive ventilation has been shown to be effective/ineffective in stable COPD. Am J Respir Crit Care Med 2000;161:688–91.


46. Nava S, Fanfulla F, Frigerio P, et al. Physiologic evaluation of 4 weeks of nocturnal nasal positive pressure ventilation in...


