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Research Paper

High-intensity non-invasive positive pressure ventilation for stable hypercapnic COPD

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Abstract

Background: The objective of the present analysis is to describe the outcomes of high-intensity non-invasive positive pressure ventilation (NPPV) aimed at maximally decreasing $PaCO_2$ as an alternative to conventional NPPV with lower ventilator settings in stable hypercapnic COPD patients.

Methods: Physiological parameters, exacerbation rates and long-term survival were assessed in 73 COPD patients (mean FEV_1 30±12 %predicted) who were established on high-intensity NPPV due to chronic hypercapnic respiratory failure between March 1997 and May 2006.

Results: Controlled NPPV with breathing frequencies of 21±3 breath/min and mean inspiratory/expiratory positive airway pressures of 28±5/5±1 cmH_2O led to significant improvements in blood gases, lung function and hematocrit after two months. Only sixteen patients (22%) required hospitalisation due to exacerbation during the first year, with anaemia increasing the risk for exacerbation. Two- and five-year survival rates of all patients were 82% and 58%, respectively. The five year survival rate was 32% and 83% in patients with low (≤39%) and high (≥55%) hematocrit, respectively.

Conclusion: High-intensity NPPV improves blood gases, lung function and hematocrit, and is also associated with low exacerbation rates and a favourable long-term outcome. The current report strongly emphasises the need for randomised controlled trials evaluating the role of high-intensity NPPV in stable hypercapnic COPD patients.

Key words: COPD, exacerbation, hematocrit, non-invasive ventilation, survival

Introduction

The effectiveness of non-invasive positive pressure ventilation (NPPV) as a treatment for chronic hypercapnic respiratory failure (HRF) arising from COPD [1] remains debatable. Although long-term NPPV is currently used in the treatment of COPD patients in Europe [2], clinical outcomes such as survival, exacerbation and hospitalization rates have not been clearly established in favor of NPPV [3, 4, 5]. However, most studies have used low levels of inspiratory support with inspiratory positive airway pressures (IPAP) ranging from 12 to 18cmH_2O. These settings have not been shown to significantly improve physiological parameters, particularly elevated $PaCO_2$ levels [3, 4, 6]. In contrast, we have recently shown that NPPV is well tolerated and leads to a substantial improvement in blood gases and alveolar ventilation during spontaneous breathing when ventilator settings are markedly increased [7, 8, 9, 10]. Since this approach uses more intense ventilator settings, we have labeled this form of treatment

"high-intensity NPPV".

The aim of the present report is to describe the physiological and blood gas parameters, hospital admissions and mortality in patients with stable, hypercapnic COPD treated with high-intensity NPPV.

Materials and Methods

The study protocol was approved by the Institutional Review Board for Human Studies at the Albert-Ludwigs University, Freiburg, Germany, and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

High-intensity NPPV

All patients were hospitalized to establish high-intensity NPPV. The assist/control mode is used for high-intensity NPPV, preferably in a pressure-limited mode [7, 8, 9]. The major target for the ventilatory adjustments (mainly increasing IPAP and respiratory rate) is to achieve normocapnia. The initial settings consist of the lowest back-up rates and trigger threshold, with avoidance of auto triggering; these settings are used in conjunction with low IPAP levels, typically ranging between 12 and 16 cmH_2O, and the lowest expiratory positive airway pressures (EPAP) levels. Subsequently, IPAP is carefully increased, step by step, prior to the point where it is no longer tolerated by the patient. Next, the respiratory rate is increased beyond the spontaneous rate to establish controlled ventilation, while EPAP is set in order to avoid dynamic hyperinflation; this is usually between 3 and 6 cmH_2O, depending on individual tolerance. NPPV is first used during daytime under careful supervision, with the main aim of establishing NPPV tolerance. When the patient is able to tolerate NPPV for more than two hours, further ventilator adjustments are performed in order to optimise alveolar ventilation according to the results of arterial blood gas (ABG) analysis. Further increases in respiratory rate are aimed at a progressive decrease in $PaCO_2$ towards normocapnia, whilst maintaining an I:E ratio of approximately 1:2. Once daytime NPPV is tolerated, nocturnal NPPV is commenced. The settings are individually modified according to the patient's comfort and nocturnal ABG. Nasal masks are initially used, but patients are switched to oronasal masks if there is increasing nocturnal $PaCO_2$, indicative of leakage. Passive humidification with a heat and moisture exchanger is used according to patient comfort, with a switch to active humidication using a humidifier if airway dryness persists. Finally, patients are instructed to use the ventilator for the entire night, as well as during any naps taken during the daytime.

Patients and data collection

All patients presenting with stable hypercapnic COPD, as diagnosed according to international guidelines [11], and who received high-intensity NPPV between March 1997 and May 2006 at the Department of Pneumology, University Hospital Freiburg, Germany, were registered in a hospital database and included for analysis. Patients were excluded if they were established on NPPV during acute HRF (including one of the following symptoms: breathing frequency >30 per minute, pH <7.35), or received any form of invasive ventilation in the past. Furthermore, patients with obesity (BMI>35kg/m^2) were excluded.

The following data were analysed: patients' characteristics, ventilator settings, blood gases at daytime under rest, lung function testing, mouth occlusion pressures, hematocrit (three groups: ≤39, 40 to 54 and ≥55%), haemoglobin levels, and long-term survival. In addition, hospitalisation for routine check of NPPV, for management of problems related to NPPV such as mask problems and for severe exacerbation [12] during the first year of NPPV was assessed

Statistical Analysis

Statistical analysis was performed using Sigma-Stat® (Version 3.1, Systat Software, Inc., Point Richmond, California, USA). Mean values ± standard deviation were given after testing for normal distribution (Kolmogorov-Smirnov test). For non-normally distributed data, the median and interquartile ranges are given. Follow-up measurements were performed using the paired *t*- test for normally distributed data and the Wilcoxon signed rank test for non-normally distributed data. Five-year survival rates were assessed by Kaplan-Meier actuarial curve analysis. Statistical significance was assumed with a p-value <0.05.

Results

Twenty women and 53 men, for whom COPD was the leading cause of chronic HRF, and who were established on high-intensity NPPV, were identified from the database. Mean age was 64.2±9.6 years and mean body mass index (BMI) was 27.6±6.7 kg/m^2. Mean cumulative smoking history was 41.9±28.5 pack-years. Pressure-limited NPPV was applied in 69 patients (Table 1), whereas four patients were established on volume-limited NPPV, due to better tolerance with a mean tidal volume of 683±197 ml and a mean breathing frequency of 21.3±3.8/min. Changes in physiological parameters after two months of NPPV are given in Table 2. After one year of NPPV, $PaCO_2$ decreased from 51.7±6.6 to 44.9±12.7 (95%CI

-11.6/-1.9; p=0.008) while PaO_2 increased from 53.1±8.9 to 65.1±11.7 (95%CI 7.6/15.6; p<0.001). In 13 patients (18%), hematocrit was ≤39%; in 53 patients (73%), hematocrit ranged from 40 to 54%; and in seven patients (9%), hematocrit was ≥55%. Although hematocrit decreased significantly in the total group after two months of NPPV (Table 2), hematocrit increased from 36.2 (interquartile range 35.8/38.9) to 37.5 (interquartile range 36.0/39.5)% (p=0.016) in patients with an initial hematocrit ≤39%, but decreased from 55.8±0.9 to 48.2±5.7% (95%CI -13.6/-1.6; p=0.022) in patients with an initial hematocrit ≥55%, and from 46 (interquartile range 43.1/48.9) to 44.2 (interquartile range 42.1/46.3)% (p=0.008) in patients with an initial hematocrit ranging from 40 to 54%.

Table 1. Ventilator settings for 69 patients receiving pressure-limited NPPV

	Mean ± SD	Min	Max
IPAP (cmH_2O)	28.0 ± 5.4	17	42
EPAP (cmH_2O)	4.6 ± 1.3	2	9
b_f (/min)	21.0 ± 2.8	10	26
Supplemental oxygen (l/min)	1.6 ± 1.5	0	6

IPAP = inspiratory positive airway pressure, EPAP = expiratory airway pressure, b_f = breathing frequency; SD = standard deviation.

Table 2. Blood gas levels, lung function parameters, mouth occlusion pressures, hemoglobin and hematocrit prior to NPPV and 2 months after establishment of NPPV.

Variables	prior to NPPV	After 2 months of NPPV	95 % CI for the difference	p-value
pH	7.40 ± 0.04	7.40 ± 0.03	-0.01 / 0.02	0.598
$PaCO_2$ (mmHg)	51.2 ± 6.5	46.8 ± 5.8	-6.2 / -2.0	<0.001
PaO_2 (mmHg)	53.0 ± 8.1	58.0 ± 8.3	2.1 / 7.9	0.001
HCO_3^- (mmol/L)	31.3 ± 5.7	28.7 ± 5.4	-4.0 / -1.2	<0.001
TLC (%pred.)	109.2 ± 22	109.3 ± 21.6	n.f.	0.419
FVC (%pred.)	49.3 ± 13.3	54.6 ± 13.7	2.2 / 8.2	<0.001
FEV_1 (%pred.)	30.1 ± 12.2	34.6 ± 13.6	2.4 / 6.6	<0.001
FEV_1/FVC (%)	43.6 ± 10.1	45.6 ± 10.7	n.f.	0.68
P0.1 (kPa)	0.60 ± 0.57	0.46 ± 0.26	n.f.	0.056
PImax (kPa)	4.7 ± 2.3	5.6 ± 2.5	n.f.	0.501
Hb (g/dl)	14.6 ± 2.0	14.2 ± 1.7	-0.9 / -0.1	0.093
Hkt (%)	45.1 ± 6,5	43.7 ± 5.9	n.f.	0.005

n.f. = normality test failed. $PaCO_2$ = arterial partial pressure of carbon dioxide, PaO_2 = arterial partial pressure of oxygen, HCO_3- = bicarbonate, TLC = total lung capacity, FVC = forced vital capacity, FEV_1 = forced expiratory volume in one second, P0.1 = mouth occlusion pressure 0.1 seconds after the onset of inspiration during normal breathing, $PImax_{peak}$ = peak maximal inspiratory mouth pressure according to previous findings [21], Hb = hemoglobin, HKT = hematocrit.

Routine checks were performed 1.9±0.8 times in the first year (9.1±6.3 days in hospital). Additionally, 11 patients (15%) were admitted to hospital on 1.3±0.9 occasions for the management of problems associated with NPPV (8.0±5.8 days in hospital). Sixteen patients (22%) required hospitalisation 1.3±0.6 times (19.3±10.9 days) during the first year due to exacerbation (one of these patients died in hospital and two patients required ICU admission with one requiring intubation). Hospitalisation for an acute exacerbation was required in five patients (46%) with a hematocrit <39%, while no patient with a hematocrit >55% was hospitalised in the first year following commencement of NPPV. In all patients, two- and five-year survival rates were 82±5% and 58±8%, respectively. The median survival was 78 months. In those patients with a hematocrit <39%, five year survival was 32%, compared to 83% in those with a hematocrit >55%.

Discussion

Stable hypercapnic COPD-patients analysed in the present study performed high-intensity NPPV over several years and thereby demonstrated an improvement in blood gases; this is in agreement with previous findings [7, 8, 9]. The present study extends the existing experience with high-intensity NPPV in COPD by particularly addressing important clinical aspects of its impact on exacerbation and hospitalisation. As shown in the present study hospitalisation-rates are acceptable once high-intensity NPPV has been successfully established. Importantly, only 22% of patients required hospitalisation due to exac-

erbation during the first year, with most patients being successfully treated on the general ward. This challenges previous findings, where >50% of patients required hospitalisation during a one year follow-up, although the disease in these patients was less advanced [13].

Moreover, the five year survival rate was 58%, suggesting that high-intensity NPPV has survival benefits compared to historical data [14, 15, 16]. Anaemia was associated with higher rates of exacerbation and reduced long-term survival, confirming previous findings [17]. The present study gives uncontrolled evidence that hematocrit has an important impact on long-term outcome in COPD-patients receiving home mechanical ventilation. However, hematocrit also normalised within two months of high-intensity NPPV. In addition, there was an improvement in lung function parameters, which is in line with previous studies [8, 18]. The explanation for this observation remains unclear. However, hypercapnia, with consequent dilation of precapillary sphincters, is believed to be the predominant factor causing edema in patients with severe COPD [19]. Since this edema could also affect the bronchial tree, improvements of lung function might be attributed to the decrease in $PaCO_2$, thus reversing bronchial edema. However, this remains speculative and needs to be investigated in future studies. Finally, overall health-related quality of life has most recently been shown to increase substantially following the establishment of high-intensity NPPV, and these improvements were reported to be similar when compared to patients with neuromuscular and thoracic restrictive diseases [20].

Several questions, however, need to be addressed: Firstly, selection criteria must be established. Unfortunately, this was not performed in the present study due to its retrospective nature. Secondly, drop-outs and compliance rates have not been quantified. This seems to be important as selection of those patients who tolerate high-intensity NPPV would result in better outcomes. Therefore, prospective trials also assessing the number of patients not tolerating high-intensity NPPV are required. Thirdly, high-intensity NPPV, as described in the present study, seems to be the extreme opposite to the conventional technique of using considerably lower ventilator settings. Therefore, controlled studies are needed to compare these techniques in the future.

In conclusion, application of high-intensity NPPV, described both here and in the literature, improves alveolar ventilation and consequently blood gases during spontaneous breathing, as well as lung function and hematocrit in stable hypercapnic COPD patients. In addition, with regard to the present study, there is uncontrolled evidence of high-intensity NPPV being capable of reducing exacerbation rates and improving long-term survival. Therefore, the current report strongly emphasises the need for randomised controlled trials evaluating the role of high-intensity NPPV in COPD patients with chronic HRF.

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Competing interest

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