

Predicting Nocturnal Hypoventilation in Hypercapnic Chronic Obstructive Pulmonary Disease Patients Undergoing Long-Term Oxygen Therapy

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Key Words

Chronic obstructive pulmonary disease · Hypercapnia · Long-term oxygen therapy · Nocturnal hypoventilation

Abstract

Background: Chronic obstructive pulmonary disease (COPD) patients are very sensitive to changes in pulmonary mechanics and central ventilation control during sleep and may develop significant gas exchange alterations with increased hypoxemia and hypercapnia. Oxygen therapy improves nocturnal desaturation but can worsen hypoventilation. **Objectives:** To analyze the prevalence of nocturnal hypoventilation (NHV) in hypercapnic COPD patients and to determine predictive factors for this phenomenon. **Methods:** This was a prospective multicenter study which enrolled 80 clinically stable COPD patients with hypercapnic respiratory failure who fulfilled the conventional criteria for long-term oxygen therapy (LTOT). All patients had undergone pulmonary function testing, blood gas analysis, and respiratory polygraphy. Arterial blood gas samples were obtained while patients were awake and during sleep. NHV was considered when an increase in PaCO₂ >10 mm Hg was observed in any nocturnal

arterial blood gas sample as compared to the awake levels. **Results:** Seventeen patients (21%) developed NHV. NHV was associated with the values of BMI, hemoglobin, hematocrits, DLCO, and PaO₂ reached after oxygen administration. In the logistic regression analysis BMI (OR 1.26, 95% CI 1.068–1.481; p = 0.006) and the diurnal increase of PaO₂ after O₂ (OR 0.89, 95% CI 0.807–0.972; p = 0.010) were the variables that best discriminated with a sensitivity of 82% and a specificity of 78%. **Conclusions:** NHV is a relatively common finding in stable hypercapnic COPD patients undergoing LTOT and it is related to a higher BMI and lower PaO₂ after oxygen administration.

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Introduction

Gas exchange abnormalities in advanced chronic obstructive pulmonary disease (COPD) patients may lead to hypoxemia and hypercapnia. Continuous oxygen therapy has been shown to increase survival in patients with chronic respiratory failure (CRF) [1, 2] and may have a beneficial impact on hemodynamics [3–5], hematologic

Table 1. Clinical characteristics and pulmonary function variables in both subgroups of patients (NHV and non-NHV)

	Total	NHV (n = 17)	Non-NHV (n = 63)	p
Age, years	68 ± 7	67 ± 7	68 ± 7	0.463
BMI	27.5 ± 4.5	30 ± 4	27 ± 4	0.004
FVC, % ref.	49 ± 12	50 ± 15	49 ± 11	0.638
FEV ₁ , % ref.	23 ± 7	25 ± 7	23 ± 7	0.169
FEV ₁ /FVC, %	34 ± 9	37 ± 6	34 ± 9	0.205
TLC, % ref.	111 ± 23	109 ± 21	112 ± 23	0.774
RV, % ref.	209 ± 64	197 ± 62	211 ± 65	0.494
DLCO, %	46 ± 20	57 ± 22	44 ± 19	0.027
KCO, %	70 ± 30	89 ± 19	66 ± 30	0.028
PI _{max} , % ref.	77.5 ± 30	79 ± 51	77 ± 29	0.942
PE _{max} , % ref.	77 ± 34	73 ± 49	78 ± 33	0.856
MVV, % ref.	25 ± 7	28 ± 6	24 ± 7	0.165
CoHb, %	1.84 ± 1.34	2.5 ± 2	1.7 ± 1	0.149

Data are presented as means ± standard deviation.

NHV = Oxygen-induced nocturnal hypercapnia; ref. = reference value; KCO = DLCO adjusted to alveolar volume; CoHb = carboxyhemoglobin concentration.

characteristics [2], exercise capacity [6], and mental state [7]. However, it may also cause carbon dioxide retention which can be worse during sleep due to changes in ventilation [8, 9].

The exact consequences of hypercapnia in COPD patients are largely unknown, but the phenomenon may have a negative influence on the course of the illness. Diurnal hypercapnia has been considered a sign of poor prognosis in COPD patients undergoing long-term oxygen therapy (LTOT) [10–13]. Hypercapnia decreases myocardial contraction [14] and predisposes to arrhythmias [15]. It also decreases diaphragm contractility, favors muscle fatigue [16], and may affect sleep quality [17, 18].

Although it is widely accepted that oxygen-induced hypercapnia may develop during COPD exacerbations, few studies have analyzed this phenomenon in stable COPD patients or during sleep. It has recently been suggested that oxygen-induced nocturnal hypoventilation (NHV) could be more frequent than has been thought to date [19, 20].

The aims of the present study were to analyze the prevalence of oxygen-induced nocturnal hypercapnia in COPD patients who fulfilled the conventional criteria for domiciliary oxygen therapy, and to determine which factors may predict this phenomenon.

Methods

From October 1999 to November 2004 we prospectively enrolled stable hypercapnic COPD patients with CRF. Patients were selectively recruited from the outpatient respiratory clinics at 3 tertiary teaching hospitals in Catalonia, Spain. The study protocol was approved by the hospital ethics committee at each center and all the patients accepted to participate in the study. All patients fulfilled the conventional criteria for LTOT [21–23] and had been clinically stable for at least 4 weeks prior to the study. All of them had undergone pulmonary function testing, including spirometry and the determination of static pulmonary volumes, DLCO (PFL 2450; SensorMedics, Yorba Linda, Calif., USA), inspiratory and expiratory maximal pressures (Manometer 163; Sibelmed, Barcelona, Spain), and routine blood tests. A respiratory polygraph (Sibelhome 300; Sibelmed) was used to screen for sleep-related respiratory disturbances.

All participants were hospitalized for the study. Nocturnal studies with and without oxygen were performed in a consecutive and randomized way. Oxygen saturation was recorded overnight with a pulse oximeter (Minolta Pulsox 5; AVL, Switzerland). Arterial blood gases were determined at night (3 a.m.), early in the morning (7 a.m.), and during the day (ABL 500; Radiometer, Copenhagen, Denmark). A radial artery catheter (Vygon, Ecouen, France) was inserted and all arterial blood gas samples were obtained with the patient in supine position after at least 15 min of rest. Oxygen flow was adjusted during the day while the patients rested to keep SpO₂ ≥ 90% and, once adjusted, it was not subsequently modified during the period of observation. Oxygen was administered through a concentrator (Zéfir, Cedex, France) and nasal prongs. Oxygen-induced NHV was considered when an increase in PaCO₂ > 10 mm Hg was observed in any of the nocturnal samples of arterial blood gases in relation to the daytime samples.

Results are presented as means ± standard deviation. Statistical differences between the variables analyzed and the development of NHV were explored using a 2-tailed paired t test for the quantitative variables and a χ^2 or Fisher's exact test for the categorical variables. $p < 0.05$ was considered significant. Variables related to NHV and those considered clinically important were later included in a logistic regression multivariate model in order to determine a predictive model.

Results

Eighty consecutive COPD patients with CRF and a chronic airflow limitation (FEV₁ < 80% of predicted value and FEV₁/FVC < 70% [21, 22]) were included. The patients' demographic and pulmonary function characteristics are shown in tables 1 and 2. All patients had a severe airflow limitation and respiratory failure with hypercapnia while awake. The conventional pharmacological treatment for all patients included salmeterol, ipratropium bromide, and inhaled budesonide. Eleven patients (14%) received treatment with systemic corticosteroids and 17 (21%) with theophylline. Forty-five (56%) patients

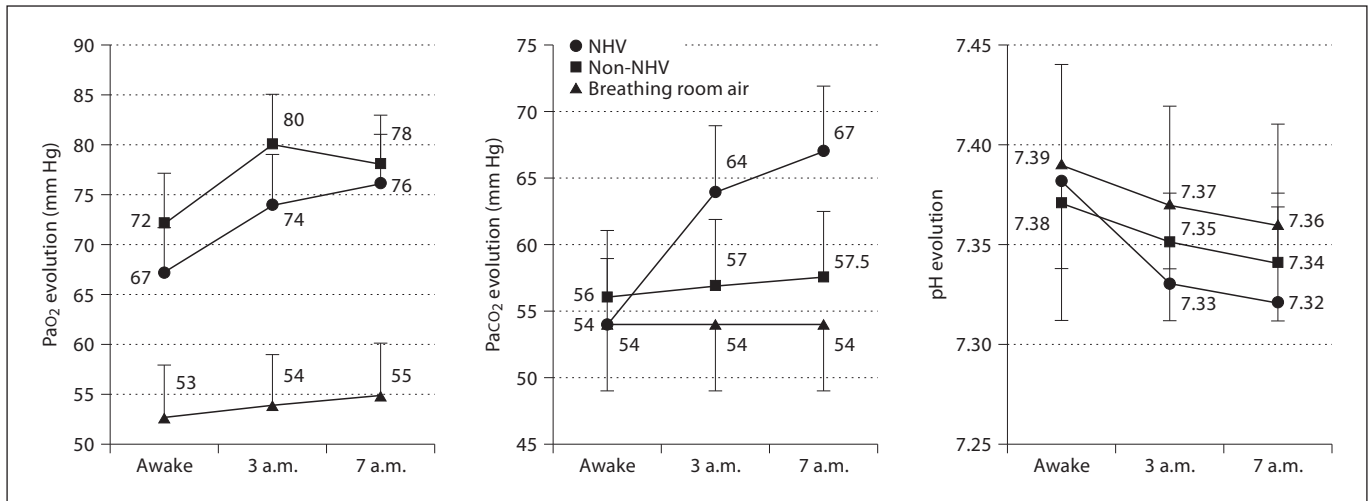


Fig. 1. Evolution of PaO₂ and pH.

Table 2. Daytime arterial blood gases (breathing room air and oxygen) in both subgroups of patients (NHV and non-NHV)

	Total	NHV (n = 17)	Non-NHV (n = 63)	p
PaO ₂ room air, mm Hg	53 ± 6	55 ± 5	53 ± 7	0.264
PaCO ₂ room air, mm Hg	54 ± 7	53 ± 6	54 ± 7	0.438
pH room air	7.39 ± 0.03	7.39 ± 0.04	7.39 ± 0.03	0.825
Bic. st. room air, mmol/l	30 ± 3	30 ± 3	30 ± 3	0.451
Dif (A-a) O ₂ , mm Hg	29 ± 9	29 ± 10	29 ± 9	0.970
PaO ₂ oxygen, mm Hg	71 ± 8	67 ± 6.77	72 ± 8.75	0.031
PaCO ₂ oxygen, mm Hg	56 ± 8	54 ± 10.73	56 ± 7.51	0.293
pH oxygen	7.37 ± 0.03	7.38 ± 0.03	7.37 ± 0.03	0.117
Bic. st. oxygen, mmol/l	30 ± 3	30 ± 3.68	30 ± 2.40	0.787
O ₂ flow, l/min	1.4 ± 0.6	1.41 ± 0.48	1.41 ± 0.62	0.995
Awake PaO ₂ difference, mm Hg	17 ± 10	12 ± 6	19 ± 10	0.008
Awake PaCO ₂ difference, mm Hg	1.75 ± 7	1.06 ± 11	1.9 ± 5	0.643

Data are presented as means ± standard deviation.

NHV = Oxygen induced nocturnal hypercapnia; Bic. st. = standard bicarbonate; Dif (A-a) O₂ = alveolar - arterial oxygen difference; awake PaO₂ difference = daytime PaO₂ breathing oxygen - PaO₂ breathing room air; awake PaCO₂ difference = daytime PaCO₂ breathing oxygen - PaCO₂ breathing room air.

were on diuretics. Sixty patients (75%) were already on LTOT and 20 patients were prescribed domiciliary oxygen therapy for the first time at enrollment.

During the night the patients slept without oxygen their PaCO₂ did not change significantly. The mean oxygen flow rate administered was 1.4 liters/min (range 0.5-4). Seventeen patients (21%) developed NHV. The changes in arterial blood gas values over time are shown in figure 1.

Body mass index (BMI), hemoglobin concentration (152 ± 12 vs. 143 ± 15 g/l; p = 0.022), hematocrits (48 ± 5 vs. 44 ± 5%; p = 0.008), and DLCO were higher in NHV patients, while PaO₂ while breathing oxygen was significantly lower (table 1). We did not find statistical differences in age, the degree of airway obstruction or hyperinflation, the apnea-hypopnea index (AHI), or nocturnal desaturation between the subgroup of patients that devel-

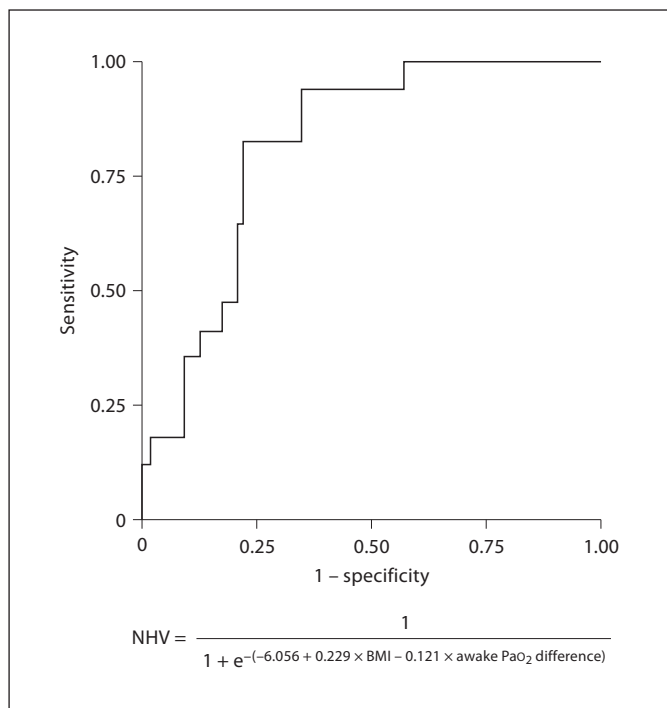


Fig. 2. Receiver operating characteristic curve to determine the best cutoff point for BMI and awake PaO₂ difference to detect NHV in COPD patients undergoing LTOT. NHV = Oxygen-induced nocturnal hypercapnia; awake PaO₂ difference (mm Hg) = daytime PaO₂ breathing oxygen – PaO₂ breathing room air.

oped NHV (NHV group) and the subgroup that did not (non-NHV group) (tables 1–3).

In the logistic regression analysis we also included the following variables: FEV₁, residual volume (RV), AHI, awake PaCO₂ with and without oxygen, mean nocturnal SpO₂, and time recorded with SpO₂ <90%. Finally, the variables that best discriminated the subgroup of patients that developed NHV were BMI (OR 1.26, 95% CI 1.068–1.481; p = 0.006) and the diurnal difference of PaO₂ (with and without oxygen) (OR 0.89, 95% CI 0.807–0.972; p = 0.010). We obtained a predictive model with a sensitivity of 82% and a specificity of 78% (fig. 2).

Discussion

NHV in stable hypercapnic COPD patients who fulfilled the conventional criteria for LTOT was relatively frequent in our sample, occurring in 21% of the study population. The variables that best predicted the development of NHV were BMI and the diurnal difference in

Table 3. Polygraphic data in NHV and non-NHV patients

	NHV (n = 17)	Non-NHV (n = 63)	p
AHI, events/h	14 ± 12	13 ± 13	0.746
Obstructive apneas, n	7 ± 11	15 ± 45	0.464
AI, events/h	1 ± 2	2 ± 7	0.492
Hypopneas, n	74 ± 69	64 ± 74	0.630
HI, events/h	12 ± 11	10 ± 11	0.461
Central apneas, n	0.71 ± 2	0.54 ± 1	0.695
Mixed apneas, n	0	0.27 ± 1	0.330
Mean SpO ₂ , %	86 ± 4	86 ± 4	0.784
CT90, %	70 ± 29	70 ± 34	0.971

Data are presented as means ± standard deviation.

AI = Apnea index; HI = hypopnea index; CT90 = recording time with SpO₂ <90%.

PaO₂ (with and without oxygen). The NHV group also had higher levels of hemoglobin concentration, hematocrits, and DLCO than the non-NHV group.

Previously, the development of significant hypercapnia (PaCO₂ 10 mm Hg above the awake values [24]) with oxygen administration in stable COPD patients was not considered a frequent or clinically important phenomenon [25]. Formerly, our group [19] and O'Donoghue et al. [26] suggested that it could be a common event (38 and 43%, respectively). Both groups analyzed nocturnal gas exchange in patients with hypercapnic respiratory failure and who fulfilled the criteria for LTOT. In our previous study [19] we included not only COPD patients but also patients with other respiratory disorders such as extrapulmonary restrictive disorders, and sleep apnea syndrome (SAS) was ruled out only by clinical symptoms. The higher prevalence of NHV found in the previous studies could have been influenced by the type of patients studied. O'Donoghue et al. [26] excluded patients with morbid obesity (BMI ≥40 kg/m²) and associated SAS (AHI ≥20). Furthermore, they used transcutaneous PCO₂ under constant polysomnographic control to define NHV. In contrast, we analyzed determinations of PaCO₂ at certain time points. Although we tried not to wake the patients, we cannot be sure that they were all fully asleep at the time of blood sampling. Nevertheless, in the study of O'Donoghue et al. [26] significant hypercapnia was still observed after awakening.

In agreement with O'Donoghue et al. [26] we found that the risk of developing NHV was related to the BMI. It has previously been reported that obesity increases

metabolic demands and is associated with a higher O_2 consumption and a greater CO_2 production [27]. It affects the ventilatory chemical drive [28], reduces thoracic compliance, increases inspiratory load with an increase in respiratory work, and reduces FRC [28] and inspiratory muscle strength. Altogether, obesity predisposes to a greater alteration of the V/Q relationship and facilitates hypoventilation. It is also associated with an increase in upper airway resistance, possibly leading to a higher prevalence of obstructive respiratory events during sleep. Coexistent COPD and SAS imply an aggravation of nocturnal gas exchange alterations. Some authors argue that oxygen-induced NHV only develops in patients with both of these entities [25]. However, we found no relationship between NHV and obstructive sleep-related respiratory events (AHI, apnea index, or hypopnea index). Although an AHI >5 can be considered pathologic [29], some authors established an AHI >15 as abnormal, especially in older patients [30, 31]. This cutoff avoids the false-positive diagnosis of SAS in patients with values of AHI between 5 and 15 due to hypopneas in transition to sleep, a frequent finding in patients suffering from respiratory failure.

Although a relationship between NHV and awake $PaCO_2$ has been described [26], we did not find an association of NHV with awake $PaCO_2$ (breathing room air or oxygen), the bicarbonate standard concentration, or pH. Even though the awake PaO_2 observed in patients breathing room air and the oxygen flow administered was similar in both subgroups, the PaO_2 increase observed after oxygen administration was lower in the NHV group. We can hypothesize that the oxygen concentration reached by both subgroups could be influenced by differences in VT.

The NHV group also presented higher concentrations of hemoglobin and hematocrits. Polycythemia in COPD has been related to the carboxyhemoglobin concentration, hypoxemia, and nocturnal desaturation. However, none of these factors justifies the differences observed in the present study. No current smokers were included and there were no differences between subgroups regarding carboxyhemoglobin. At rest and while breathing room air, both subgroups presented the same degree of daytime hypoxemia, and no differences in nocturnal desaturation were observed. However, hypercapnia per se can be both the cause and consequence of erythrocytosis [32]. Reduced renal flow due to an increase in $PaCO_2$ stimulates erythropoietin secretion and facilitates polycythemia. Alternatively, polycythemia could act as a negative stimulus for ventilation and thus predispose to the development of hypoventilation [32]. Strikingly, no differences

were found between the 2 subgroups in any parameter of airflow obstruction or air trapping. Only significantly higher DLCO and KCO in the NHV group as compared to non-NHV patients were observed. Erythrocytosis [33], SAS [34], and obesity [34] are associated with an improvement in diffusion indexes. In our NHV subgroup, both BMI and hemoglobin concentrations were greater than those in the group that did not develop NHV, and this could be responsible for the greater DLCO observed.

The multivariable analysis used showed that the only variables with the independent power to discriminate between the 2 subgroups were BMI and awake PaO_2 while breathing oxygen. Although not validated, this multivariate model showed a sensitivity of 82% and a specificity of 78%. Furthermore, it included variables that are simple to obtain in everyday clinical practice. It facilitates the identification of patients with NHV and allows us to optimize treatment for CRF. Nevertheless, prospective studies are needed to establish the clinical significance of this phenomenon and to evaluate the benefits of alternative treatments, such as noninvasive ventilation, in this subgroup of patients [35–37].

One of the limitations of the present study is the fact that we did not obtain nocturnal arterial blood gas measurements under polysomnographic control. Polysomnographic studies are complex and are not always available. Another limitation of our study is the lack of continuous a measurement of $PaCO_2$ by capnography. We used arterial blood gas measurements because these allowed us to monitor the pH response. Thus, although $PaCO_2$ was determined at only 2 time points during the study, the consequent decrease in pH was suggestive of a nighttime $PaCO_2$ evolution.

In conclusion, we consider that oxygen-induced nocturnal hypercapnia in stable COPD patients who fulfill the conventional criteria for LTOT is a more frequent phenomenon than generally expected. As variability in NHV prevalence seems to be related to the inclusion criteria and the form of measurement, a clear definition of NHV is needed. NHV is best predicted by a higher BMI together with a lower awake PaO_2 while breathing oxygen. Although large studies are lacking, clinicians should be aware of this phenomenon in order to provide an optimal management of CRF in COPD patients undergoing LTOT.

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