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Clinical Heterogeneity among Patients with Obesity Hypoventilation Syndrome: Therapeutic Implications

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Key Words
Obesity hypoventilation syndrome · Pickwickian syndrome · Sleep apnea · Noninvasive mechanical ventilation · Continuous positive airway pressure

Abstract
Background: Obesity hypoventilation syndrome (OHS) can be treated with noninvasive positive pressure ventilation (NIPPV). Once clinical stability is achieved, continuous positive airway pressure (CPAP) can be recommended in many cases. However, some patients respond only partially to CPAP and NIPPV is a better option for them. ***Objectives:*** To assess treatment effectiveness in 2 groups of patients: those who could be switched to CPAP after polysomnographic titration and those who required NIPPV. ***Methods:*** A prospective study of 24 OHS patients was conducted, 11 were treated with CPAP and 13 with NIPPV. Morning and evening arterial blood gases were measured. Daytime and overnight oximetric recordings were performed. A post hoc analysis compared both groups. ***Results:*** Neither group exhibited deterioration on morning-to-evening blood gases. All patients in the CPAP group presented SaO_2 of less than 90% (CT90%) for <15% of the time on nocturnal and daytime recordings. In the NIPPV group, 8 patients had either daytime or nocturnal CT90% ≥15%. There were no intergroup differences regarding age, body mass index, Epworth scale values or PaO_2/$PaCO_2$ prior to treatment. FVC in the NIPPV group was lower than in the CPAP group ($p = 0.01$). Apnea-hypopnea index was higher (56 ± 23 vs. 36 ± 23, $p = 0.049$) and baseline CT90% was lower (76 ± 19% vs. 92 ± 14%, $p = 0.03$) in the CPAP group. ***Conclusions:*** Two patient subtypes can be identified. Those controlled with CPAP have better spirometry and a significantly higher apnea-hypopnea index. None of these patients showed daytime hypoxemia and all exhibited satisfactory overnight oxygenation. However, 61% of the NIPPV group had suboptimal oximetry results. Nocturnal/diurnal oximetries should be made to assess treatment efficacy in stable OHS patients who fail to achieve good control with CPAP.

Introduction

Obesity hypoventilation syndrome (OHS) is a clinical entity characterized by the coexistence of obesity and hypercapnia during wakefulness [1]. Although its preva-

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lence is currently unknown, hypoventilation has frequently been seen to complicate severe obesity in hospitalized adults and is associated with excess morbidity and mortality [2]. In 2004 in France, OHS was recognized as the main cause of chronic respiratory failure requiring home noninvasive positive pressure ventilation (NIPPV) [3]. Surprisingly, little is known about the physiopathology of this entity and its definition remains controversial [4, 5]. Recently, we have shown that NIPPV therapy is effective in the treatment of patients with OHS, providing significant improvement in clinical status and gas exchange parameters [6]. We have also found that a second sleep study, performed once patients had stabilized, made it possible to maintain the condition of a significant number of patients by means of nasal continuous positive airway pressure (CPAP) therapy alone.

In clinical practice, arterial blood gas status is currently assessed by taking a single sample early in the morning and is the cornerstone of clinical decision making with respect to NIPPV efficacy in several conditions requiring said therapy. However, we have speculated that evening gas exchange values (immediately prior to CPAP or NIPPV) may decline compared to morning measurements (just after CPAP or NIPPV) in some patients with OHS, reflecting suboptimal control of the disease. Moreover, significant desaturations can be seen during exercise equivalent to the activities of daily living in patients without concurrent hypoxemia at rest. This finding was reported by Christensen et al. [7] in 17 patients with chronic obstructive pulmonary disease (COPD), albeit it has yet to be investigated in patients with OHS.

The purpose of this study was to assess daytime and overnight (during ventilatory support) gas exchange in 2 groups of OHS patients: those who could be switched to CPAP alone and those who continued to require NIPPV. Furthermore, it sought to identify parameters that could predict the presence of significant desaturation. Finally, a post hoc analysis was performed to compare baseline characteristics [age, body mass index (BMI), lung function, apnea-hypopnea index (AHI), Epworth sleepiness scale (ESS), PaO_2 and $PaCO_2$] in both groups at diagnosis.

Materials and Methods

Patients

Subjects were recruited from outpatient services at the Xeral-Calde Hospital, Lugo, Spain. They were diagnosed as having OHS from 2002 to 2005. Eligible patients met all of the following criteria at the time of diagnosis: (1) obesity with a BMI of >30; (2) hypercapnic respiratory failure ($PaCO_2 \geq 50$ mm Hg and $PaO_2 < 60$ mm Hg); (3) FEV_1/FVC ratio of ≥70%; (4) absence of any respiratory disorder that could account for gas exchange disturbances (such as kyphoscoliosis or diaphragmatic paralysis). Patients had been treated initially with NIPPV, using the same methodology as described in a previous cohort (fig. 1) [6]. Polysomnography was performed once they were clinically stable, 56.6 (18.4) days after the diagnosis. During a second nighttime sleep study, performed 134.2 (42.7) days after the first study, the final NIPPV settings were established. CPAP was initially tested in all patients. CPAP was adjusted with the aim of preventing periods of apnea and hypopnea during all stages of sleep. When oxygen desaturation persisted after apneas and hypopneas had been eliminated with CPAP, we changed to a bi-level positive pressure ventilation. The level of positive airway pressure that suppressed apneas and hypopneas was used during expiration and positive inspiratory pressure was gradually increased until oxygen saturation was steadily over 90% or high pressures (that is 20 cm H_2O) were reached. Oxygen was added when significant oxygen desaturation persisted despite the use of these high inspiratory pressures.

To be included in the study, patients had to be clinically stable for at least 4 weeks prior to the enrollment in the protocol. We selected the last 11 patients diagnosed as having OHS who were be-

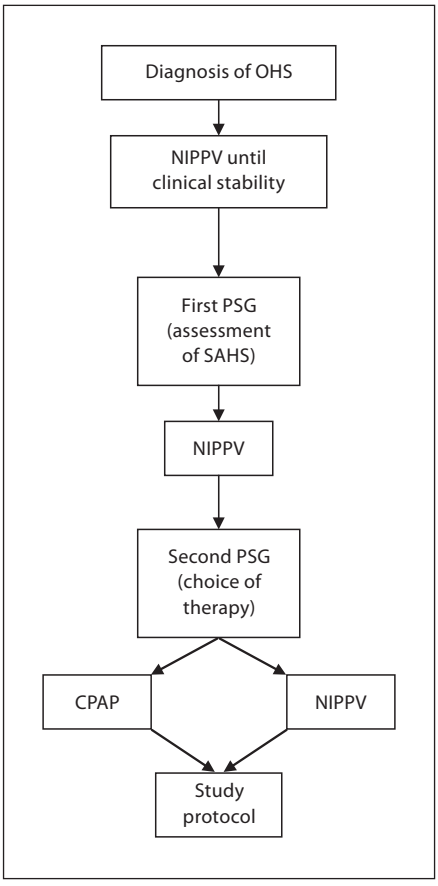

Fig. 1. Management of patients prior to inclusion in the study protocol. PSG = Polysomnography.

ing treated with CPAP and the last 13 diagnosed cases who were receiving treatment with NIPPV, after polysomnographic titration. Mean time between the second polysomnographic recording study and the inclusion in the study was 572.7 (349.9) days. Written informed consent was obtained from all study participants.

Measurements

Daytime sleepiness was evaluated according to the ESS questionnaire. Dyspnea was evaluated using the modified Medical Research Council dyspnea scale. We performed conventional spirometry with a 10-liter, closed-circuit spirograph, according to the American Thoracic Society/European Respiratory Society consensus [8]. The predicted values used were those of the European Respiratory Society [9]. Arterial blood samples were taken for gas level measurements with patients awake, seated and breathing environmental air in their rooms, and specimens were analyzed immediately (Ciba-Corning Diagnostics, Dietlikon, Switzerland). Transcutaneous oxygen saturation was measured with a pulse oximeter (Pulsox 3i; Minolta, Ramsey, N.J., USA). Mean nighttime and daytime SaO_2, percentage of recording time with SaO_2 <90% (CT90%) and the nocturnal desaturation index, defined as the number of dips in SaO_2 ≥4% per hour of recording time, were calculated using computer software (Pulsox SaO_2 analysis software DS-3; Minolta). All measurements were performed both at the time of initial diagnosis (prior to start of NIPPV) and at inclusion in the present study protocol, except for spirometry, performed only at_diagnosis, and daytime oximetry, which was only carried out at inclusion in the study protocol.

Study Protocol

Patients were admitted to hospital for 24 h. Baseline characteristics (those observed at the moment of diagnosis, prior to treatment with NIPPV) were collected by reviewing the patients' Xeral-Calde Hospital charts. Current demographic data, respiratory symptoms and BMI were recorded prospectively. Arterial blood samples were drawn early in the morning (30 min after CPAP or NIPPV was removed) and again in the evening, just prior to initiating ventilatory support. Patients underwent 2 oximetric studies: during the night, while on the positive pressure device, and again during the day (10:00 to 22:00 h). Patients were encouraged to stroll for 3 h in the morning and evening and to climb stairs without becoming exhausted; participants were not allowed to sleep during the day. 'Suboptimal control' was arbitrarily defined as presenting CT90% during ≥15% of the recording time.

Statistical Analysis

Unless otherwise indicated, all data are expressed as means with SD in parentheses or as percentages. Proportions were compared by Fisher's exact test. The average values of the 2 groups were compared using Student's t test for unpaired data and, when applicable, 95% confidence intervals were calculated for descriptive analysis of the data. Comparisons between baseline and post-treatment data, and between daytime and nocturnal measurements were made by means of Student's t test for paired data. Spearman correlation coefficients were used to assess the strength of associations with suboptimal control, and PaO_2, $PaCO_2$ and mean nighttime SaO_2 were used for each subject. A p value of 0.05 indicated significance for all statistical tests. These analyses were carried out using the statistical software package SPSS, version 10.0 for Windows (SPSS Inc., Chicago, Ill., USA).

Results

Baseline Characteristics

A total of 24 subjects participated in the study. Baseline data (at the time of diagnosis) for both groups of patients (those who could be switched to CPAP alone and those who required NIPPV) are shown in table 1.

As expected in light of the inclusion criteria, hypoxemia was severe with a mean PaO_2 of 50.6 (7.1) mm Hg and all patients were hypercapnic, with a mean $PaCO_2$ of 58.8 (8.6) mmHg. There were no intergroup differences with respect to clinical characteristics such as age, BMI, ESS, PaO_2 and $PaCO_2$ prior to treatment. However, FVC and FEV_1 were lower in the NIPPV group ($p = 0.014$ and $p = 0.017$, respectively). Whereas baseline nocturnal mean SaO_2 was similar in the 2 groups, CT90% was significantly higher in the NIPPV group ($p = 0.05$). In contrast, AHI was significantly higher in the CPAP group ($p = 0.049$). None of the patients included in the study had a significant number of central apneas during sleep.

Results of the NIPPV Group

Thirteen patients treated with NIPPV after polysomnographic titration agreed to participate. The mean age was 61 (14) years (range 31–79 years). Prior to polysomnographic titration, the most commonly used NIPPV modality was bi-level positive pressure ventilation (12 patients). After titration, 11 patients were treated with a bi-level device, while the remaining 2 required volume-cycled ventilation. Supplemental oxygen was needed in 8 patients.

We detected no significant change in current versus baseline BMI, with values of 43.2 (7) and 43.6 (9), respectively ($p = 0.85$). There were no significant differences between morning and evening gas exchange parameters, specifically, morning PaO_2 was 66.3 (10.6) mm Hg and evening PaO_2 65.7 (8.5) mm Hg ($p = 0.87$) and morning $PaCO_2$ was 44.3 (5.5) mm Hg and evening $PaCO_2$ 45.7 (2.6) mm Hg ($p = 0.41$). Overnight oximetric measurements, performed while the patient was on the positive pressure device, revealed a mean SaO_2 of 92.3% (2) and a CT90% of 14.8% (14.4). Daytime oximetries demonstrated a mean SaO_2 of 91.7% (1.7) and a CT90% of 18.2% (19.8). Eight patients presented either nocturnal or daytime CT90% ≥15% (table 2).

None of the variables were seen to correlate significantly with daytime or nocturnal suboptimal control (CT90% ≥15%) and patients labeled as presenting suboptimal control did not differ significantly from those who exhibited CT90% <15% values in terms of dyspnea or daytime sleepiness.

Table 1. Comparison of baseline data between the NIPPV and CPAP groups

	NIPPV group	CPAP group	Difference[1]	p value
Age, years	61.5 (4)	63.3 (11)	–1.83 (–12.74 to 9.09)	0.732
Sex, % males	62	91	–29 (–69 to 11)	0.166
BMI	43 (7)	44 (8)	–0.9 (–7.3 to 5.4)	0.770
ESS	15 (3)	17 (3)	–2.1 (–5.8 to 1.6)	0.251
FVC, %	57 (14)	73 (14)	–16 (–28 to –4)	0.014
FEV_1, %	65 (21)	85 (16)	–20 (–36 to –4)	0.018
FEV_1/FVC, %	79 (8)	86 (8)	–7 (–14 to 1)	0.067
PaO_2, mm Hg	49.9 (7.7)	51.3 (6.7)	–1.5 (–7.6 to 4.7)	0.632
$PaCO_2$, mm Hg	58.1 (5.9)	59.6 (11)	–1.5 (–9.0 to 5.9)	0.666
pH	7.37 (0.03)	7.34 (0.04)	0.03 (–0.001 to 0.06)	0.06
CT90%, %	92.1 (14.1)	76.3 (19.5)	15.7 (–0.0 to 31.6)	0.05
mean SaO_2, %	78.7 (5)	82.3 (4.4)	–3.6 (–8 to 0.9)	0.108
ID4%, n	34.2 (13.7)	45.4 (16.1)	–11.2 (–26.1 to 3.8)	0.134
AHI	36.5 (23.1)	56 (23)	–19 (–39 to 0)	0.049

Figures are means with SD in parentheses, unless indicated otherwise. ID4% = Number of dips in SaO_2 ≥4% per hour of recording time.

[1] Figures in parentheses are 95% confidence intervals.

Results of the CPAP Group

Eleven patients treated with CPAP following polysomnographic titration were admitted to the study. The mean age was 63 (11) years (range 40–76 years). The mean pressure was 10.4 cm H_2O and none of the patients in this group required supplemental oxygen. Changing from NIPPV to CPAP did not imply deterioration of arterial blood gas values: PaO_2 shifted from 72.6 (6.9) to 68.9 (3.8) mm Hg (p = 0.6) and $PaCO_2$ went from 41.7 (2.2) to 41.6 (4.5) mm Hg (p = 0.8).

There was a significant decrease in current versus baseline BMI, with values of 40.7 (7.7) and 44.1 (8), respectively (p = 0.002). It must be noted, however, that BMI of patients in the CPAP group did not differ significantly from that of patients in the NIPPV group (p = 0.41). PaO_2 did not differ between morning and evening measurements, at 68.9 (3.8) and 69.1 (4.4) mm Hg, respectively (p = 0.4), nor did $PaCO_2$, at 41.6 (4.5) and 40.7 (5.1) mm Hg, respectively (p = 0.36). Overnight oximetric measurements, performed while the patient was using the CPAP device, exhibited a mean SaO_2 of 92.4% (1.2) and a CT90% of 5.2% (4.6). Daytime oximetries demonstrated a mean SaO_2 of 94.1% (1.2) and a CT90% of 1.7% (2.4). No cases of suboptimal control were found in this group.

As can be seen in table 2, patients in the CPAP group had significantly better results in several nocturnal/diurnal oximetry and gasometric parameters.

Table 2. Comparison of current data between the NIPPV and CPAP groups

	NIPPV group	CPAP group	p value
Age, years	61 (14)	63 (11)	NS
BMI	43.6 (9)	40.7 (7.7)	NS
ESS	5.9 (1.8)	6.9 (1.3)	NS
MRC scale	2 (0.4)	1.8 (0.6)	NS
$mPaO_2$, mm Hg	63.3 (10.6)	68.9 (3.8)	NS
$mPaCO_2$, mm Hg	44.3 (5.5)	41.6 (4.5)	NS
$ePaO_2$, mm Hg	65.7 (8.5)	69.1 (4.4)	NS
$ePaCO_2$, mm Hg	45.7 (2.6)	40.7 (5.1)	0.0052
mean $dSaO_2$, %	91.7 (1.7)	94.1 (1.2)	0.0007
dCT90%, %	18.2 (19.8)	1.7 (2.4)	0.01
mean $nSaO_2$, %	92.3 (2)	92.4 (1.2)	NS
nCT90%, %	14.8 (14.4)	5.2 (4.6)	0.046
dCT90% ≥15%, n	5 (38%)	0	NS
nCT90% ≥15%, n	5 (38%)	0	NS

Figures are means with SD in parentheses, unless indicated otherwise. NS = Not significant; MRC = Medical Research Council; $mPaO_2$ = morning PaO_2; $mPaCO_2$ = morning $PaCO_2$; $ePaO_2$ = evening PaO_2; $ePaCO_2$ = evening $PaCO_2$; $dSaO_2$ = daytime SaO_2; dCT90% = percentage of recording time with SaO_2 <90% during the day; $nSaO_2$ = nocturnal SaO_2; nCT90% = percentage of recording time with SaO_2 <90% during the night.

Discussion

Relatively few articles have focused on the efficacy of NIPPV for patients with respiratory failure due to OHS [10–17]. Recently, we have demonstrated that this treatment is effective in both the acute and chronic treatment setting, providing sustained improvement of PaO_2 and $PaCO_2$. We have also found that a simple CPAP device is sufficient to achieve good clinical and gasometric control in a significant proportion of patients [6]. In the present study, we divided the patients with OHS into 2 groups with different severity of illness: those who could be switched to CPAP alone and those who continued to need NIPPV after polysomnographic titration. The objective was to assess the degree of control of the disease in each group. The results revealed that nighttime treatment with CPAP or NIPPV allows OHS patients to maintain adequate spontaneous ventilation throughout the day, as quantified by arterial blood gas values measured 12 h apart, immediately on awakening and just prior to onset of sleep. We have also determined nocturnal and daytime oxygen saturation and arbitrarily set a cutoff value for CT90% in order to assess the risk associated with significant desaturation. In the United Kingdom and Europe, desaturation below 90% for 30% of the nighttime has gained widespread acceptance as defining significant nocturnal desaturation in COPD research [18, 19]. However, in the United States, nighttime oxygen therapy is advocated for nocturnal desaturation that is less rigidly defined [20]. In the present study, patients with nocturnal or daytime CT90% >15% despite NIPPV treatment were classified as suboptimal control. We found that 8 patients in the NIPPV group (none in the CPAP group) had either a daytime or nocturnal CT90% >15%. Given that daytime PaO_2 was the best predictor of nocturnal hypoxemia in COPD [21] patients, we have attempted to identify gasometric predictors of suboptimal control; however, neither morning nor evening arterial blood gas values correlated with CT90%. Thus, direct assessment of nocturnal and daytime saturation by pulse oximetry is needed to identify suboptimal control cases.

It must be noted that the finding of suboptimal control did not imply greater dyspnea or daytime sleepiness in our patients. Certainly, the clinical implications of detecting significant desaturation in patients with OHS has yet to be elucidated. Future studies should address this question.

We do not know why some obese subjects develop respiratory failure while others do not, nor do we fully understand the pathogenesis of OHS, although it is almost certainly multifactorial. Ventilatory muscle dysfunction, abnormal load responsiveness, increased respiratory work and CO_2 production, impaired central respiratory drive and repeated airway occlusion during sleep are all possible pathophysiological components in this entity, but the precise contribution of each remains to be fully clarified [22–24]. Interestingly, we noticed that patients in the NIPPV group had significantly lower baseline FVC and FEV_1, but higher CT90% compared to patients from the CPAP group. In contrast, AHI in the CPAP group was significantly higher than in the NIPPV group. These results might reflect an intriguing possibility: the weight of the different pathophysiological mechanisms may vary in individuals with OHS. It seems that in some patients, severe obstructive sleep apnea syndrome might be a major contributor to OHS pathophysiology, with respiratory system mechanics playing only a minor role. These patients could be successfully treated with long-term CPAP. On the other hand, other patients might stand out as having moderate or severe restrictive pulmonary defects and considerable nocturnal desaturation with low AHI values. These patients would require long-term NIPPV. We admit that the sample size is small and conventional spirometry might not be the best way to explore the consequences of obesity on the respiratory system. Moreover, as a finding in a post hoc analysis, this hypothesis warrants additional investigation, and further systematic study of subjects with OHS, before and after treatment, will help to determine the contribution of each factor to respiratory failure in an individual patient.

Certain limitations of the present study must be addressed. One of them is the small patient cohort, too small to enable definitive conclusions to be drawn. However, the strict criteria used in recruiting patients for the study made it possible to include a homogeneous sample covering a wide range of obesity-induced respiratory disturbances. Our intention was to avoid confounding effects related to other respiratory disorders (like COPD) capable of producing gas exchange alterations; the obvious consequence was that fewer patients were admitted to the study. Another limitation is the theoretical variability in nocturnal desaturation between nights. This variability was demonstrated in COPD patients, both night-to-night and over a 3-week period of clinical stability [25]. However, in most obstructive sleep apnea syndrome patients, oxygen desaturation index variability is rather modest and screening can be reliably based on a single, 1-night recording [26].

Several conclusions can be drawn from this study. The group of patients treated with NIPPV exhibited worse

pulmonary function and nocturnal saturation than patients who could be treated with CPAP after polysomnographic titration. In contrast, the latter group showed significantly higher AHI. Results of arterial blood pressures showed no deterioration during the day in both groups of OHS patients. Patients in the CPAP group are well controlled and do not need further testing. A proportion of patients from the NIPPV group showed suboptimal control, but the clinical importance of this condition is not clear.

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