Noninvasive Mechanical Ventilation in Patients With Obesity Hypoventilation Syndrome. Long-term Outcome and Prognostic Factors

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ABSTRACT

Introduction: Obesity is associated with 2 closely related respiratory diseases: obesity hypoventilation syndrome (OHS) and obstructive sleep apnea–hypopnea syndrome (OSAHS). It has been shown that noninvasive ventilation during sleep produces clinical and functional improvement in these patients. The long-term survival rate with this treatment, and the difference in clinical progress in OHS patients with and without OSAHS are analyzed.

Methodology: Longitudinal, observational study with a cohort of patients diagnosed with OHS, included in a home ventilation program over a period of 12 years, divided into 2 groups: pure OHS and OSAHS-associated OHS. Bi-level positive airway pressure ventilation was administered. During the follow-up period, symptoms, exacerbations and hospitalizations, blood gas tests and pulmonary function tests, and survival rates were monitored and compared.

Results: Eighty-three patients were eligible for analysis, 60 women (72.3%) and 23 men (27.7%), with a mean survival time of 8.47 years. Fifty patients (60.2%) were included in the group without OSAHS (OHS) and 33 (39.8%) in the OSAHS-associated OHS group (OHS–OSAHS). PaCO₂ in the OHS group was significantly higher than in the OHS–OSAHS group (P<.01). OHS patients also had a higher hospitalization rate (P<.05). There was a significant improvement in both groups in FEV₁ and FVC, and no differences between groups in PaCO₂ and PaO₂ values. There were no differences in mortality between the 2 groups, but low FVC values were predictive of mortality.

Conclusions: The use of mechanical ventilation in patients with OHS, with or without OSAHS, is an effective treatment for the correction of blood gases and functional alterations and can achieve prolonged survival rates.

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Ventilación mecánica no invasiva en pacientes con síndrome de obesidad-hipoventilación. Evolución a largo plazo y factores pronósticos

RESUMEN

Introducción: Desde el punto de vista respiratorio, la obesidad se asocia con 2 enfermedades muy relacionadas: el síndrome de obesidad-hipoventilación (SOH) y el síndrome de apnea-hipopnea del sueño (SAHS). Se ha demostrado que el tratamiento con ventilación mecánica no invasiva durante el sueño produce una mejoría clínica y funcional en estos pacientes. Analizamos a largo plazo la supervivencia con este tratamiento, y la diferencia en la evolución entre pacientes con SOH y con SAHS asociado.

Metodología: Estudio longitudinal, observacional, de una cohorte de pacientes diagnosticados de SOH e incluidos en un programa de ventilación domiciliaria a lo largo de 12 años, distribuidos en 2 grupos:

Palabras clave:
Síndrome de obesidad-hipoventilación
Síndrome de apnea del sueño
Ventilación mecánica no invasiva


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Introduction

 Obesity is the most prevalent metabolic disease in the Western world. It is associated with high rates of morbidity and mortality, and has been recognized by the World Health Organization as a serious health, social and economic problem.1 It produces significant changes in the physiology of the respiratory system that can give rise to a wide spectrum of clinical manifestations, ranging from secondary dyspnea and restrictive ventilatory defect to hypercapnic respiratory failure characteristic of obesity-hyperventilation syndrome (OHS).2–4.

OHS was first described in 19565 and is currently defined as a condition characterized by obesity, hypercapnia and respiratory changes during sleep, in the absence of any other disease that could explain respiratory failure.6 Despite the passage of time, the pathogenesis of this entity has still not been fully explained, although it seems to have a multifactorial origin in which altered ventilatory mechanics, muscle dysfunction secondary to obesity and ventilation control play an important role.6–8 Many authors consider it as simply a progressive form of the obstructive sleep apnea–hypopnea syndrome (OSAHS) in some obese subjects.9 However, although respiratory disorders during sleep are a defining condition for OHS, they are not always associated with OSAHS10 and it remains unknown which subgroup will progress the best. The prevalence of OHS in the general obese population is not precisely defined, but in obese patients with OHS it ranges between 10% and 20%.11–12 Studies in hospitalized obese patients have shown greater prevalence, also revealing increased mortality rates in this group.13

Since its introduction for the treatment of OSAHS, continuous positive airway pressure (CPAP) has also become a treatment for OHS, with non-invasive mechanical ventilation (NIV) being reserved for cases that do not respond adequately to positive pressure.14–16 Numerous groups initially rejected the use of NIV as standard treatment for OHS, but it was shown that in this group of patients similar results were obtained to those observed in patients with respiratory failure due to chest wall dysfunction,17 both in acute situations or in long-term home use.18 NIV to treat night-time OHS produces clinical and functional improvement with favorable changes in blood gases, polyglobulia, respiratory function and ventilatory response to hypercapnia. These changes lead to a reduction in the number and duration of hospital admissions and visits to emergency rooms, and an improvement in quality of life and survival.19,20 However, few studies have evaluated long-term survival, and behavioral differences between patients with and without OSAHS have not been analyzed, even though it has been shown that the latter can be treated safely with CPAP.21

The aim of this study was to determine the differences in progress between patients with OHS and those with OHS and OSAHS receiving home mechanical ventilation (HV), and to identify prognostic factors for survival.

Methodology

Design

This was a prospective, longitudinal, observational study in a cohort of patients with a diagnosis of OHS seen in the Ventilatory Support Unit of our hospital over a 12-year period (from 1998 until 2010), who met all of the inclusion criteria and none of the exclusion criteria for participation in the HV program.

Population

Patients with a confirmed diagnosis of OHS and a body mass index of over 30 kg/m², respiratory failure with daytime PaCO₂ >45 mmHg and nighttime >50 mmHg, with or without associated OSAHS, were included. The patients entered the HV program in a stable state or after hospitalization for exacerbation, once clinical stability had been restored. Patients with obstructive disease defined as a FEV₁/FVC% ratio <70%, neuromuscular disease with respiratory involvement and any other respiratory disease other than OHS were excluded. Although most of the definitions of the syndrome exclude significant change in ventilatory mechanics due to obesity, patients with any FVC value were included in this study, as it was thought that this would allow better assessment of the treatment.

Study Groups

Subjects were divided into 2 groups, according to nocturnal polysomnographic results: group 1 (OHS) consisting of patients with an apnea–hypopnea index (AHI) ≤5, and group 2 (OHS–OSAHS), consisting of patients with AHI >5.

Methods

Before starting the ventilation program, a clinical questionnaire was completed for all patients, including symptoms, previous hospitalizations and intensive care admissions, spirometry data, baseline blood gases, early morning blood gases and a polysomnography study. Both spirometry and blood gases were determined according to Spanish Pulmonology and Thoracic Surgery Society guidelines.22 Sleep studies were carried out according to standard methods23 with duly validated 12-channel respiratory polygraphy (Apnoscreen II, Jaeger, Germany) or 18-channel polysomnography (Sleepscreen, Jaeger, Würzburg, Germany). Both devices measure.
airflow by thermistor and nasal cannula, producing automatic and manual readings.

Bilevel positive airway pressure (Respironics or Harmony BiPAP, Respironics, Louisville, USA) ventilators in ST mode with nasal masks were used. Positive expiratory pressure between 6 and 10 cm H2O and positive inspiratory pressure of 16 cm H2O increasing progressively until target efficacy objectives were achieved or a maximum pressure of 24 cm H2O was reached. Initial support respiratory frequency was 16 breaths per minute, with an inspiration/expiration ratio of 0.4 or an inspiratory time of 1.5 s. To facilitate patient adaptation, ventilation was initiated in 2-h periods during the day, with oxygen saturation monitoring and PaCO2 determination from blood gases at the beginning and at the end of the session. When oximetry showed persistent desaturation, oxygen supplements were added and the support pressure levels were adjusted according to final blood gas levels. Ventilation was considered to be effective when PaCO2 remained under 45 mmHg or fell from baseline value by more than 5 mmHg, with a mean oxygen saturation greater than 90%. After daytime adaptation, nighttime adaptation was undertaken. The patients’ oxygen saturation was monitored by oximetry and early morning blood gas levels. Patients with OHS–OSAHS underwent a second partially supervised polysomnography with the ventilator to adjust positive expiratory and inspiratory pressure in order to ensure control of nocturnal apnea and hypopnea events.

During the first year of follow-up, patients were seen every 3 months. Subsequently, they attended yearly check-ups throughout their participation in the HV program. In all of the check-ups, clinical data on symptoms, exacerbations, admissions, weight changes and side effects were recorded. Compliance was evaluated with a timer and lung function tests, arterial blood gases breathing room air, nocturnal oximetry under ventilation and nocturnal blood gases, also under ventilation, were determined. Ventilation was considered appropriate if nocturnal PaCO2 under ventilation was lower than 50 mmHg, pH greater than 7.35 and oxygen saturation greater than 90% for 90% of the night. In patients with OHS/OSAHS who had basal PaCO2 of less than 45 mmHg one year after starting ventilation, nocturnal blood gases without ventilation were determined; if this figure was maintained, treatment was switched to CPAP.

### Statistical Analysis

A descriptive analysis of qualitative variables, expressed as absolute frequencies and percentages, was performed, while quantitative variables were presented as means and standard deviations (SD). For variables that did not show normal distribution or for which numbers were small (n<15), data are presented as median, interquartile range and minimum and maximum. Student’s t-test was performed for simultaneous comparison of 2 groups. To analyze changes during patient follow-up at 1, 3, 5 and 8 years, Student’s repeated measures t-test or Wilcoxon’s test were used. When the size of the groups to be compared was small or they were heterogeneous, non-parametric statistical tests were used. For qualitative variables, Pearson’s Chi-squared test was used to measure the association and compare proportions. When the groups were small, Fisher’s exact test was used. Progression to death was studied using Kaplan–Meier tests and groups were compared with the log-rank test. The relative risk of survival was estimated using a Cox regression model.

### Results

#### Initial Data

Over the 12-year period, 153 obese patients with chronic hypercapnia were included in the HV program. Of these, 70 also had airway obstruction and were excluded, leaving 83 patients: 60 women (72.3%) and 23 men (27.7%). Patients had lung function tests indicative of restrictive ventilatory defect with mean FVC of 65.9% (SD 19) and FEV1 of 66.3% (SD 19). Arterial blood gases showed overall respiratory failure, with a mean PaO2 of 52.3 mmHg (SD 16.5) and mean PaCO2 of 63.6 mmHg (SD 15.6).

Fifty patients (60.2%) were included in group 1 (OHS without OSAHS) and 33 (39.8%) in group 2, (OHS with OSAHS). Clinical and functional characteristics are listed in Table 1. In the OHS group, 82% of subjects were women, compared to 57.6% in the OHS–OSAHS group (P<0.05). PaCO2 in the OHS group was significantly higher than the OHS–OSAHS group (P<0.01) and the former also had a higher number of hospitalizations per exacerbation (P<0.05).

#### Treatment Adherence and Continuity

Mean time of continuing ventilation was 7.44 years (95% confidence interval [95% CI]: 6.22–8.65). In 21 of the 83 patients (25%), ventilation was discontinued: 12 due to improvement and 9 due to withdrawal or too few hours of use (mean 5.7±1.3 h/night, while good compliance was considered to be BiPAP...
used for over 4 h/night). Of the 12 patients who improved, 9 belonged to the OHS–OSAHS group and switched to CPAP, and 3, who improved clinically due to weight loss, were in the OHS group.

**Course of Lung Function Tests**

In both study groups, a significant improvement in both FEV₁ and in FVC had been observed by month 3. This was maintained over the first, third, fifth, eighth and tenth year of treatment, although in the last 2 evaluation points the improvement was not significant, due to the small number of patients. With regard to the blood gas figures, there was also a significant improvement in PaO₂ values, as well as a significant decrease in PaCO₂ (Table 2). No differences were found between groups in the course of lung function and blood gas parameters (Fig. 1).

**Survival and Prognostic Factors**

A total of 18 deaths (21.7% of all patients) were recorded during the follow-up period. The mean estimated survival time was 8.47 years, with a 95% CI of between 7.27 and 9.67 years. The probability of survival in the first, third, fifth, eighth and tenth year of follow-up was 93.3±3.1, 83.7±4.5, 71.9±6, 60.11±9.4 and 60.11±9.4, respectively.

With regard to diagnostic subgroups, 14 patients (28%) in group 1 (OHS) died, while in group 2, there were 4 deaths (12.1%). Although mean survival time of patients with OHS–OSAHS (9.07

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**Table 2**

Evolution of Respiratory Function Tests and Blood Gas Levels at 3 Months and 1, 3, 5, 8 and 10 Years in the Pooled Population.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Third month</th>
<th>First year</th>
<th>Third year</th>
<th>Fifth year</th>
<th>Eighth year</th>
<th>Tenth year</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁%</td>
<td>66.3 (19)</td>
<td>76.54 (23.33)</td>
<td>78.28 (21.66)</td>
<td>75.9 (16.6)</td>
<td>73.81 (16.8)</td>
<td>72.48 (23.2)</td>
<td>68.86 (18.6)</td>
</tr>
<tr>
<td>FVC%</td>
<td>65.96 (19.1)</td>
<td>76.84 (21.61)</td>
<td>80.4 (19.8)</td>
<td>78.47 (14.3)</td>
<td>75.31 (16.6)</td>
<td>77.93 (23.12)</td>
<td>70.43 (20.4)</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>81.89 (7.25)</td>
<td>79.65 (6.25)</td>
<td>78.25 (8.35)</td>
<td>76.94 (7.06)</td>
<td>75.52 (8.3)</td>
<td>72.48 (4.7)</td>
<td>76.86 (5.27)</td>
</tr>
<tr>
<td>pH</td>
<td>7.36 (0.07)</td>
<td>7.42 (0.02)</td>
<td>7.42 (0.04)</td>
<td>7.42 (0.03)</td>
<td>7.42 (0.21)</td>
<td>7.43 (0.02)</td>
<td></td>
</tr>
<tr>
<td>PaO₂</td>
<td>52.57 (14.1)</td>
<td>60.52 (11.22)</td>
<td>63.83 (9.5)</td>
<td>65.19 (9.5)</td>
<td>61.85 (7.88)</td>
<td>61.91 (6.8)</td>
<td>59.57 (4.8)</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>61.07 (15.04)</td>
<td>42.96 (5.7)</td>
<td>43.53 (10.64)</td>
<td>40.58 (5.4)</td>
<td>42.34 (4.8)</td>
<td>41.94 (4.6)</td>
<td>42 (2)</td>
</tr>
</tbody>
</table>

FEV₁: forced expiratory volume in first second; FVC: forced vital capacity; PaO₂: pressure of oxygen in arterial blood; PaCO₂: partial pressure of carbon dioxide in arterial blood.

* P<.05 compared to baseline values.

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**Fig. 1.** Evolution of percent predicted FEV₁ and FVC pulmonary function tests by diagnostic groups. PaO₂ and PaCO₂ are expressed in mmHg. Blood gas changes are significant in both groups in the first, third and fifth years (P<.05), with no differences between groups.
years, 95% CI 7.71–10.45) was longer than that of patients with pure OHS (7.92, 95% CI 6.4–9.4), the difference was not statistically significant. Survival after the third year was greater in patients with OSH–OSAHS, but no significant differences were found between groups in accumulated survival due to the greater survival of the OHS group in the first year (Fig. 2).

A Cox regression analysis aimed at studying risk factors showed that only FVC was a predictive factor for mortality, while the other factors included in the analysis (age, sex, BMI, PaO₂, PaCO₂ and diagnostic group) had no predictive value (Table 3). Stratification according to percent predicted FVC into 4 patient subgroups (<40%, 40–59%, 60–79% and >80%) showed that mean estimated survival increased in line with FVC, and was significantly greater in patients with FVC between 60% and 79% than in those with FVC less than 40% or between 40% and 60% (Table 4). The accumulated survival analysis (Fig. 3) also found an increased probability of survival that was greater for patients with higher FVC, although because of the low number of patients in the various subgroups, the difference was only significant for those in the group with FVC between 60% and 79% vs patients with FVC between 40% and 59%.

**Table 3** Predictive Factors for Risk of Death. Results of the Cox Regression Analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>95% confidence interval</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.029</td>
<td>0.980 1.081</td>
<td>0.250</td>
</tr>
<tr>
<td>Sex</td>
<td>1.596</td>
<td>0.558 4.562</td>
<td>0.383</td>
</tr>
<tr>
<td>FVC</td>
<td>0.953</td>
<td>0.924 0.983</td>
<td>0.002</td>
</tr>
<tr>
<td>pH I</td>
<td>0.094</td>
<td>0.000 0.430</td>
<td>0.607</td>
</tr>
<tr>
<td>PaO₂ I</td>
<td>0.994</td>
<td>0.973 1.015</td>
<td>0.568</td>
</tr>
<tr>
<td>PaCO₂ I</td>
<td>1.005</td>
<td>0.966 1.045</td>
<td>0.811</td>
</tr>
<tr>
<td>BMI</td>
<td>0.981</td>
<td>0.926 1.040</td>
<td>0.523</td>
</tr>
<tr>
<td>Diagnostic group</td>
<td>0.463</td>
<td>0.172 1.245</td>
<td>0.127</td>
</tr>
</tbody>
</table>

FVC: forced vital capacity; BMI: body mass index; PaO₂: pressure of oxygen in arterial blood; PaCO₂: partial pressure of carbon dioxide in arterial blood; RR: relative risk. PaO₂ I, PaCO₂ I and pH I are baseline values determined when the patient started home ventilation.

**Fig. 2.** Accumulated survival and probability of survival stratified by diagnostic groups.

**Fig. 3.** Accumulated survival stratified by FVC.

**Discussion**

In this study, HV was found to be effective in the treatment of patients with OHS. It was associated with blood gas and functional improvement and with increased survival. Results are better in subjects with OHS–OSAHS, although the differences between these 2 groups are not significant and the only predictive factor for survival was good FVC at outset.

Historically, ventilatory support for patients with OHS was first used with concomitant OSAHS. CPAP was used initially and, if this was insufficient to control hypventilation, positive pressure ventilation was applied using either bilevel pressure or volume-controlled ventilators. Since then, long-term NIV results have been analyzed in numerous cohort studies of OHS patients, all of which have reported improvement in blood gas levels, and OHS is now among the indications given in guidelines and recommendations for the use of HV. To date, only one clinical trial has been published in which the results of NIV are compared with conventional oxygen therapy. This is a small randomized study in 36 patients with very mild hypercapnia and a follow-up period of only one month. However, despite these limitations, improvement in sleep structure and gas exchange were greater than in the control group.
Table 4
Mean Estimated Survival and Median Survival Stratified by Forced Vital Capacity Expressed in Percentage.

<table>
<thead>
<tr>
<th>FVC (%)</th>
<th>Mean estimated survival in years*</th>
<th>Median survival in years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimation</td>
<td>95% Confidence level</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower limit</td>
</tr>
<tr>
<td>&lt;40</td>
<td>1.52</td>
<td>0.236</td>
</tr>
<tr>
<td>40–59</td>
<td>4.907</td>
<td>3.564</td>
</tr>
<tr>
<td>60–79</td>
<td>8.452</td>
<td>6.946</td>
</tr>
<tr>
<td>&gt;80</td>
<td>8.131</td>
<td>5.696</td>
</tr>
<tr>
<td>Overall</td>
<td>7.391</td>
<td>6.167</td>
</tr>
</tbody>
</table>

FVC: forced vital capacity.

* In censored cases, estimated mean survival is established according to the longest time of survival observed. Median data are limited to the first 2 groups because in the rest, at least half of the patients had died during follow-up.

All NIV cohort studies in patients with OSH show an improvement in gas exchange. This was also found in this study, in which correction of hypercapnia was seen from the beginning of treatment, an improvement that persisted for as long as 10 years in both OSH and OSH-OSAHS patients. This improvement has been attributed to multiple mechanisms, including recovery of sensitivity to hypercapnia, respiratory muscle rest and improvement in ventilatory mechanics.8,19,20

In patients with OHS, the use of NIV is associated with an increase in respiratory minute volume (Vₖₑ) and occlusion pressure in response to hypercapnia.24,29 A previous study performed by our group in a small series of patients also found that the use of NIV in patients with OHS was associated with an increase in the Vₖₑ/Paco₂ and P0.1/Paco₂ slope,24 but these variables were not available in most of the patients in the cohort analyzed here, so these findings cannot be confirmed. Changes in PacO₂, in addition to reflecting variations in ventilation, may also be related to an improvement in the level of pulmonary hypertension and right ventricular overload that frequently develop in these patients, and, according to some recent studies, may be reversed with the use of HV.30,31 Two important aspects to remember when considering the improvement in blood gas levels are good ventilatory support during administration and adherence to treatment. Our working procedures include nocturnal arterial blood gas monitoring for evaluating the efficacy of the ventilation, so all patients were subject to nocturnal monitoring, both at the start of ventilation and during regular check-ups, the results of which were used to adjust the ventilator parameters. Treatment adherence is known to be a prerequisite for normalizing blood gas levels, with reports indicating an association between the number of hours of ventilation and the degree of PaO₂ reduction, and only around 4.5 h of ventilation can achieve significant blood gas level improvements.32 The patients in this study received more than 4 h of ventilatory support, a factor that also contributed to the good results obtained.

With regard to changes in ventilatory mechanics, the literature is contradictory, and although the study published by Heinemann et al.26 showed that NIV in OSH patients was associated with an increase in inspiratory capacity and total lung capacity, this has not been confirmed by other authors.20,25 Although lung volumes were not measured in this study, a sustained increase in FVC was found. Other factors cannot be ruled out, but similarly to Heinemann et al., high support pressures were used in this study, which could have assisted in resolving possible microatelectasis, thus improving respiratory mechanics. Muscle rest provided by NIV may also contribute to the improvement in lung volumes,33 but since pressures were not measured in this study no conclusions could be drawn in this regard.

The most important aspect of this study is the impact of HV on mortality. Few studies have analyzed the survival of patients with OHS treated with HV for periods longer than 5 years.28,34 Our results confirm the findings of those studies, with survival rates of over 90% in the first year and 70% in the fifth. We also had good results for 8- and 10-year survival, data that has not yet been reported by other researchers. Unlike other authors,27,35 we did not find that the degree of hypoxemia or hypercapnia or pH levels had a prognostic value for patient survival, but the difference is probably due to the fact that our patients were very closely assessed before inclusion in an HV program, i.e., their situation was already stable.

None of the previous studies analyzed the impact of OSAHS associated with OHS on patient survival. In our study, after the first year of ventilation, patients with OSAHS showed a clear trend toward improved survival, although this was not statistically significant. Since patients with OHS initially had a higher level of hypoventilation than those with OHS–OSAHS, correction of airway instability in the latter may have a more favorable effect on gas exchange, but differences in other fundamental physiological aspects cannot be ruled out.

One important and hitherto unreported factor analyzed is the impact of changes in ventilatory mechanics on the clinical course. In this study, the only factor with predictive value for survival was FVC: the lower the FVC, the less chance of survival. It can be assumed that in patients with more compromised ventilation at the time of diagnosis, gas exchange alterations would already have caused irreversible structural changes that would explain their poorer progress, even after an initial improvement in blood gas levels. Moreover, as data on the cause of death are not available, we cannot rule out that patients with greater restriction did not also have greater associated comorbidity.

Interestingly, although most of the OHS patients in the series published to date also had OSAHS, these subjects were a minority in our study. This may be because our population had a greater level of hypercapnia that those of other studies, and patients were referred for respiratory failure and not because of suspected sleep apnea.

One of the most important limitations of this study is the lack of data related to the impact of comorbidity on the clinical course and survival of patients, since, although follow-up was prospective, this information was not included when the statistical analysis plan was designed. Nor is it possible to analyze which type of ventilator would be more effective or, more importantly, whether some patients could have been treated from the outset with CPAP instead of NIV.

Although some authors claim that in extremely obese patients the use of volume-cycled ventilators may be necessary, all published series have reported satisfactory results with bilevel ventilators with backup respiratory rate for avoiding central apnea events37; the efficacy of this technology is supported by our results. It has been suggested recently that the use of bilevel
Conflict of Interests
The authors state that they have no conflict of interests.

References
