TITLE:

"Mid- and long-term efficacy of NIV and CPAP in OHS"

SHORT TITLE:

PICKWICK STUDY

PARTICIPATING HOSPITALS:

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ABSTRACT

Objectives: *Primary and secondary (medium-term)*: Evaluate the medium-term efficacy of noninvasive ventilation (NIV) treatment versus continuous positive airway pressure (CPAP) and the "life style modifications" treatments in obesity hypoventilation syndrome (OHS) measuring respiratory functional (PaCO2 main outcome) and clinical improvement during sleep and wakefulness and quality of life. *Primary and secondary (long-term)*: Evaluate the long-term efficacy of NIV treatment versus CPAP treatment in OHS, with days of hospitalization analyzed as a primary variable and percentage of dropouts for medical reasons and mortality as operative variables. Oher hospital resource utilizations (hospital and ICU admissions, emergency visits and intubations), cardiovascular incidence rate, blood pressure, echocardiogram, clinical symptoms, quality of life and respiratory functional measures as secondary variables *Other objectives*: a) Investigate the importance of apneic events and leptin in the genesis of diurnal alveolar hypoventilation. b) Investigate whether metabolic and biochemical alterations and vascular endothelial dysfunctions depend on the presence of apneas and hypopneas.

Methods: Prospective, randomized open controlled trial with two parallel studies: Patients with OHS will be divided initially into two cohorts based on their apnea-hypopnea index (AHI) scores, ≥30 and <30, using conventional polysomnography. The AHI ≥30 cohort will be randomized to NIV, CPAP or "life style modifications" treatments for two months, then, "life style modifications" treatment will be re-randomized into CPAP or NIV groups to complete 36 months. The AHI <30 cohort will be randomized to NIV or "life style modifications" treatments for 36 months. Treatment efficacy at the medium and long-term will be analyzed by comparison intra and inter-group. The role of apneic events and leptin in the genesis of daytime alveolar hypoventilation will be analyzed by comparing the daytime PCO2/AHI coefficient between responders and non-responders to CPAP treatment, and the evolution of leptin levels in the four branches of the study. The role of apneic events in metabolic and biochemical alterations and endothelial dysfunction will be analyzed by comparing basal and post-treatment levels of related substances between groups, with and without significant numbers of apneic events.

BACKGROUND

Obesity is a growing phenomenon in the developed world, affecting close to one-third of the adult population, for which it is referred to as "the Twenty First Century Epidemic".

Sleep Apnea-Hypopnea Syndrome (SAHS) is a respiratory alteration related to obesity and characterized by repeated episodes of upper airway obstruction, which fragment sleep and produce intermittent hypoxia. The repercussions are excessive daytime sleepiness, traffic accidents, arterial hypertension, cardiovascular events and increased mortality (1-3). The indicated treatment in severe cases is CPAP (*continuous positive airway pressure*), which improves clinical symptoms and quality of life, and decreases the risk of traffic accidents and cardiovascular events (3).

Obesity Hypoventilation Syndrome (OHS) is another obesity-dependent pathology. It is characterized by hypercapnic chronic respiratory insufficiency which is not secondary to other causes, apneic events and alveolar hypoventilation during sleep. Its repercussions are less well known than those of SAHS, but apparently the most frequent of these is pulmonary hypertension (4) and, given the greater level of nocturnal hypoxia in these cases, there may be a greater risk of other cardiovascular events and mortality (5,6). The ideal treatment is weight loss. Return to a normal weight reverses the respiratory insufficiency, pulmonary hypertension and sleep disorders (7). The problem stems from the fact that, in these patients, it is difficult to achieve and maintain important weight loss, and bariatric surgery is an alternative for only a minority of patients due to increased mortality and rejection by patients themselves. Nevertheless, moderate weight loss achieves a decrease in PCO2, although this result has not been demonstrated over the long-term (7).

Non-invasive ventilation (NIV) consists of the application of intermittent positive pressure using nasal or naso-oral masks with the objective of improving alveolar ventilation and letting the respiratory muscles rest. A Spanish group was one of the pioneers in showing clinical improvement of arterial gasometry and sleep disorders in a series of cases (8,9). Other studies with the same design have reported similar results (5,10). In non-controlled longitudinal studies, a decrease in days of hospital admission have been observed (10,11). There are no controlled trials that have evaluated mortality, and increased mortality is only seen in series of patients treated with respect to other studies in which they were not treated (12,13). One study has reported increased mortality in a small series of cases, between treated patients and patients who refused treatment (5). Despite CPAP correcting nocturnal apneic events in patients with OHS, daytime PCO2 does not seem to return to normal in all cases. Therefore, the role of apneas and hypopneas in the development of diurnal hypercapnia is not clear and it is suspected that, in patients that respond to CPAP treatment, apneic events may predominate over alveolar hypoventilation (14,15). Daytime hypercapnia in SAHS has been associated with the event duration / inter-event duration coefficient, which would indicate that diurnal and nocturnal hypercapnia depend on insufficient recovery from the hypoventilation produced by apneic events, especially during REM sleep (16). CPAP and NIV are being used extensively to treat OHS patients in chronic conditions. Only one randomized

trial including 37 patients with mild hypercapnia (17) has shown improvement in clinical symptoms, PaCO2 and sleep disorders with NIV treatment in comparison with control group. Another randomized trial has evaluated the clinical and PaCO2 improvements with CPAP and NIV in 36 OHS patients selected for their favorable response to an initial night of CPAP treatment (18). Similar results were observed between groups but there are not large randomized, controlled trials that show which of these two treatments is more effective than the ideal treatment, which is weight loss. Neither are there controlled trials that show whether the repercussions of OHS (arterial and pulmonary hypertension, cardiovascular events, hospital admissions and mortality) decrease at all with treatment or decrease more with one type of treatment over another.

Leptin is a protein produced by adipose tissue whose functions are the reduction of appetite and the increase of energy expenditure. In obesity, there appears to be a resistance to leptin leading to hyperleptinemia. Animal studies have demonstrated that this protein is a potent stimulator of breathing and its absence (or lack of effect) can produce hypoventilation. The level of serum leptin decreases to normal limits in patients with SAHS treated with CPAP (19), but it is assumed that apneas and hypopneas are the cause of the elevated leptin levels rather than being the result of them (20). Leptinemia appears to be twice as high in patients with OHS than in patients with a similar grade of obesity and number of apneas and hypopneas, but without diurnal hypercapnia (21). Leptin levels can be reduced with NIV (22) or weight loss. These findings may indicate that leptin resistance may be the cause (20) of OHS. Nevertheless, a recent study (23) reported conflicting results: patients with OHS and a significant number of apneas and hypopneas had lower levels of leptin than those with a similar number of obstructive events but without OHS, and the level of leptin increased with NIV. In order to examine this problem in more depth, it would be interesting to test whether leptin levels decrease or increase to approach normal values (for the level of obesity) in patients with OHS that resolve their diurnal hypercapnia, especially in the group without a significant number of apneic events. Also, whether patients with OHS and obstructive events that do not resolve their hypercapnia when treated with CPAP have higher or lower leptin levels than those that revert the hypercapnia with CPAP or NIV.

SAHS has been associated with metabolic disorders and dysfunction of the vascular endothelium, which may be the consequences of intermittent hypoxia or of increased sympathetic nervous activity in these patients. These conditions can, over time, create conditions for the development of arterial and pulmonary hypertension as well as cardiovascular events. Few studies have addressed this dynamic in OHS, but it appears that the levels of some inflammatory mediators such as IL-6 could be greater in patients with OHS than in patients with SAHS but without diurnal hypercapnia (24). Neither there have been studies focused on the causes of these issues: if patients with OHS but without a significant number of apneas-hypopneas have high basal levels which decrease with treatment, or, on the contrary, if the elevation and decrease of these substances depend on the presence of apneas and hypopneas.

We proposed a broad, randomized controlled trial in patients with stable OHS, comparing efficacy in the medium (physiological variables) and long-term

(cardiovascular repercussions and days of hospitalization) of treatments with NIV, CPAP or life style modifications treatments. We will also investigate the role of apneic events and leptin resistance in the origin of daytime alveolar hyperventilation and whether metabolic, biochemical and endothelial vascular alterations depend on the presence of apneas and hypopneas.

3.3. BIBLIOGRAPHY

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HYPOTHESIS

Treatment with NIV is more effective in Obesity Hypoventilation Syndrome (OHS), in the medium and long-term, than CPAP and "life style modifications" treatments.

OBJECTIVES

Primary

Primary (medium-term): Evaluate the medium-term efficacy of NIV treatment versus CPAP and "life style modifications" treatments in OHS measuring functional outcomes (PaCO2 main variable).

Primary (long-term): Evaluate the long-term efficacy of NIV treatment versus CPAP treatments in OHS on hospital resource utilization with days of hospitalization analyzed as a primary variable and percentage of dropouts for medical reasons and mortality as operative variables.

Secondary

- Evaluate the efficacy in the medium and long-term of NIV treatment as compared with CPAP or "life style modifications" treatments for OHS, analyzing the following variables:
    a. Other hospital resource utilization as hospital and ICU admissions emergency department visits and intubations.
    b. Clinical symptoms, including excessive daytime sleepiness.
    c. Quality of life.
    d. Arterial blood gases.
    e. Sleep quality, apnea-hypopnea index (AHI) and oxygen saturation (SaO2) during sleep.
    f. Analytic determinations: biochemical, related to the vascular endothelium, renin-angiotensin-aldosterone axis and the sympathetic nervous system.
    g. Echocardiograph: pulmonary systolic pressure and left ventricle function.
    h. Standardized arterial pressure measures.
    i. The incidence of cardiovascular events, including arterial hypertension.
- Investigate the importance of apneic events and leptin in the genesis of diurnal alveolar hypoventilation.
- Investigate whether metabolic and biochemical alterations and vascular endothelial dysfunctions depend on the presence of apneas and hypopneas.

METHOD

1) Subjects

a) Study Ambit:

Patients referred to the pulmonology consultations of the following hospitals: Complejo Hospitalario San Pedro de Alcántara (Cáceres), Hospital Arnau de Vilanova (Lérida), Hospital San Pablo (Barcelona), Hospital Txagorritxu (Vitoria), Hospital Universitario Virgen del Rocío (Sevilla), Hospital Universitario de Valdecilla (Santander), Hospital La Paz (Madrid), Hospital Xeral-Calde (Lugo), Hospital 12 de Octubre (Madrid)**,** Fundación Jimenez-Diaz (Madrid), Hospital Gregorio Marañon (Madrid), Hospital Universitario General Yagüe (Burgos), Hospital Virgen de la Macarena (Sevilla), Hospital Miguel Servet (Zaragoza), Hospital San Juan (Alicante) y Complejo Hospitalario Universitario Insular (Las Palmas).

For the following conditions:

Respiratory insufficiency, stable hypercapnia (PH ≥7.35 without symptoms of clinical worsening for two months) secondary to obesity (OHS).

b) Study subjects:

i) Recruitment: The aforementioned patients will be submitted to a conventional polysomnographic study (PSG). The technical characteristics, definitions and staging of polysomnographic studies will be those recommended internationally. Patients will be recruited consecutively. Patients with an AHI <30 will be assigned to the non-sleep apnea (OSA) or the light-to-moderate cohort and those with an AHI ≥30 to the severe OSA cohort. The former cohort of patients will be randomly assigned to NIV or "life style modifications" treatments. The second one will be randomized to "life style modifications" or NIV or CPAP treatments for assessing the medium term (2 months). Then, "life style modifications" group will be re-randomized to NIV or CPAP to continue 36 months (long-term assessment), (See Figure).

ii) The Definition of OHS:

1) Obesity (BMI≥30).

2) Hypercapnic respiratory insufficiency (PCO2>45 mm Hg) not secondary to other causes.

iii) Inclusion Criteria

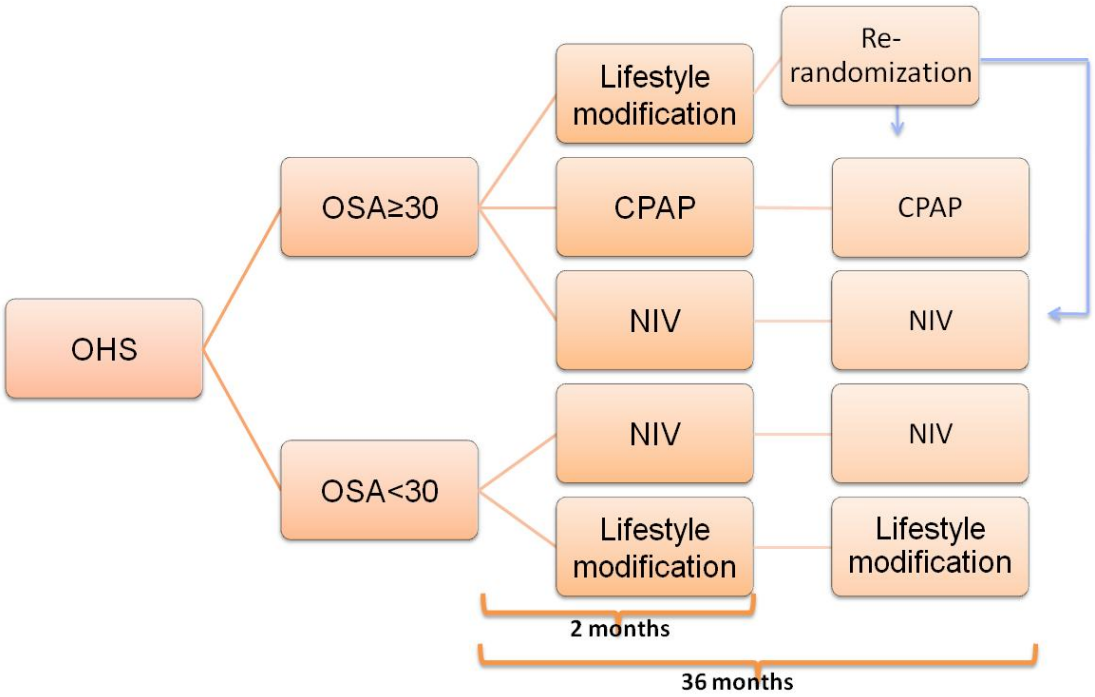
1) Age between 15 and 80 years
2) Absence of moderate or severe chronic obstructive pulmonary disease (FEV1>70% of predicted when FEV1/(FVC)>70).
3) Absence of neuromuscular disease, thoracic wall or metabolic disease that may cause diurnal hypercapnia.
4) Absence of narcolepsy or restless leg syndrome.
5) Correctly execute a 30 minute, awake CPAP/NIV treatment test

iv) Exclusion Criteria

1) Psycho-physical incapacity to complete questionnaires.
2) Patients that cannot be evaluated using quality of life questionnaires due to a previously diagnosed chronic illness (neoplasia, severe

chronic pain of any type, and any other severe chronic debilitating illness).

3) Subjects with chronic nasal obstruction that impedes the use of CPAP/NIV.
4) Lack of informed consent.



2) Sample size

The sample size has been calculated to detect differences in the primary variables and the operative variables, assuming an error α=0.05 and an error β=0.1:

- PaCO2 (medium-term efficacy): The sample size has been calculated in base to previous results where the mean PaCO2 in OHS patients treated with NIV was 45±5mmHg (Masa Chest 2001;119:1102-07). We estimated as clinically relevant to be able to detect differences among groups from 2.5 mmHg. For a standard deviation of 5 the sample size necessary to compare 2 independent means (triple comparison: severe OSA cohort), 64 patients would be needed per group. Considering a dropout rate of 20%, the number of patients per group should be 80 and 240 in total. For two comparisons in the non-severe OSA cohort, 34 patients should be necessary in each group; after a dropout rate of 20% the number of patients should be 43 per group or 86 in total.
- Days of hospitalization (long-term efficacy): The mean number of days hospitalized in patients treated with NIV was 2.5±1.1 days/year (Berg Chest 2001; 120:337-83). We estimate that it is clinically relevant to be able to detect differences between groups of 0.5 days/year (20% of the difference). With a standard deviation of 1.1, the sample size for each group would be 40. With a loss of 25% the number of patients should be 54 per group. The total sample, 108 patients for both cohorts (severe and non-severe OSA).

To conclude, the sample size of the severe OSA cohort is determined by PaCO2 measurements and a sample size of 240 patients is needed. The sample size of the non-severe OSA cohort was determined by duration of hospital stay, and for this purpose, a sample size of 108 patients is needed.
The percentage of mortality or dropouts for medical reasons (operative variables): given that these variables have been included also in order to interrupt the study in intermediate analyses, the sample should be sufficient to detect clinically relevant differences when the study has not yet been completed. In previous studies in OHS treated with NIV the overall mortality in 3 years was 12.7% (J Intern Med. 2007;261(4):375-83). For instance, with only 30 patients included we could detect 4 times more mortality between groups (i.e. from 4.2% to 17%).

3) Design

The design of this research protocol is an open, prospective, randomized controlled trial. Consecutive patients will be included after assuring that they meet the clinical and polysomnographic criteria required, as well as the rest of the inclusion criteria and none of the exclusion criteria. This includes a treatment test, with detailed information given on the function of the equipment and the expected benefits of the treatment. Those that present any of the exclusion criteria will be registered as well as the reason for their exclusion, in the Excluded Patient_Registry. After inclusion in the protocol, patients will be randomized into three groups using a computer-generated random number list (SPSS, Chicago IL, USA), according to the following scheme:

- "Life style modifications" group (Control): It consist of a 1,000-calorie diet and to maintain proper sleep hygiene and habits (avoid supine decubitus position, maintain regular sleep habits and exercise, not take sedatives, stimulants, alcohol, tobacco or heavy meals within four hours before bedtime). Oxygen therapy should be added if on the daytime arterial blood pressure (ABG) the PaO2 was <55 mmHg or if the mean SpO2 during sleep from the pulse oximetry signal during the PSG was <88% (see annex) with the necessary flow to maintain waking SaO2 between 88%-92% or PaO2 ≥55 mmHg and for at least 17 hours/day. After 20 minutes with oxygen treatment an ABG well be performed. If PaCO2 increases ≥5 mmHg or pH gets lower than 7.35, the oxygen will be removed. During the follow-up oxygen therapy could be discontinued if daytime or nocturnal hypoxemia improved sufficiently and patients have not the previous criteria of indication.
- CPAP treatment group: In addition to lifestyle modification and oxygen (if required), a home fixed CPAP should be initiated previous conventional CPAP titration (SEPAR).
- NIV treatment groups (in patients with severe OSA and in patients with mild-moderate or no OSA): In addition to life style modification and oxygen (if required), a NIV treatment should be started. The ventilator mode will be a bilevel pressure with assured-volume. The ventilator adjustment will be firstly performed in awake situation and then during sleep by means of a PSG. In awake, EPAP will be set between 4-8 cmH2O and an IPAP between 18-22 cmH2O (EPAP included). Pressures should be adjusted to obtain the normal oxygen saturation (if

possible) measured by pulse-oximetry and patient tolerance. The respiratory rate will be adjusted between 12-15 and the target volume between 5-6 ml/kg permitting to increase the maximal pressure over previous fixed IPAP if necessary. Check of mechanical ventilation phases (trigger, pressurization and cycled) should be performed to avoid asynchronies and to refine the setting. After 30 minutes of continuous use with the patient adapted and with an adequate patient-ventilator interaction, an ABG will be carried out. The PaCO2 resulting will be used to adjust the ventilator parameters. The final adjustment will be done by means of a conventional polysomnography (PSG), increasing the EPAP if apneas appeared and the IPAP if hypopneas, flow limitation, snoring or non-apneic hypoventilation are present until oxygen saturation normalization or the optimal pressure tolerated will be reached. Full face will be initially proposed but if poor tolerance a nasal mask could be used. Humidifier will be always added for full face mask and only if necessary for nasal mask.

Patients will be instructed in the use of treatments (NIV, CPAP or oxygen), emphasizing their daily use and insisting that they maintain their hypocaloric diet, maintain proper sleep hygiene (avoid the dorsal decubitus position, maintain regular sleep habits, not take sedatives, stimulants, alcohol or heavy meals within four hours before bedtime). The treatment period will be three years.

4) Follow-up

Patients will be contacted at 30 days, and then every three months for two years. Then, patients will be contacted every six months up to three years (see table). After the ending of the three years of follow-up, patients will be followed every 3 months until the last patient included attained at least 3 years of follow-up in order to collect hospital resource utilization (see below), abandons of treatments and mortality. In patients who voluntarily abandoned the study but maintained the inform consent, the mentioned variables will be collected in the same way as during the 3 years of the study follow-up, although the patient interview can be done face-to-face or by phone.

Compliance with CPAP/NIV will be obtained by dividing the number of hours of use (from the hourly counter) by the number of days of treatment. Each patient will receive a monthly telephone contact to remind them to follow their diet treatment.

a) Treatment dropouts: patients that have been randomized and then decide to leave the study, for any reason, will be considered dropouts. Also, those patients that, for medical reasons, are unable to continue the assigned treatment will be considered dropouts. The following will be considered medical reasons:
   1. If, during the quarterly reviews, arterial blood gases pH obtained breathing room air is lower than 7.33.
   2. If a patient requires hospital admission for respiratory insufficiency, including NIV treatment for more than five days or invasive ventilation for more than three days, or if arterial gasometry at hospital discharge breathing room air registers a pH lower than 7.33.

3. Death.

b) Interruption of the study: see the section on "Ethical Issues".

c) Evaluation.

Patients will be evaluated at 12 points:

- At the start of treatment (T0).
- At 30 days into follow-up (T1).
- At three months (T2)
- At six months (T3)
- At nine months (T4)
- At 12 months (T5)
- At 15 months (T6)
- At 18 months (T7)
- At 21 months (T8)
- At 24 months (T9)
- At 30 months (T10)
- At the end of the follow-up period (36 months) (T11)

At T0 and T2 all variables described in the following section will be recorded. At T1, T3, T4, T6, T7, T8 and T10, questionnaires will be administered that include clinical symptoms, side effects, number and days of hospital admission, blood pressure and arterial gasometry. At T5, T9 and T11, all variables described below will be registered, with the exception of the PSG. After the ending of the three years of follow-up, patients will be followed every 3 months until the last patient included attained 3 years of follow-up for collecting hospital resources utilization, abandons of treatments and mortality.

d) Variables:

a) Anthropometric and socio-demographic data: age, weight, size, neck and abdominal circumferences (waist and hip)
b) Arterial blood pressure using a standard protocol (Chobanian AV, Hypertension. 2003; 42(6):1206-1252.).
c) Number and days of hospital admission in the three years prior to treatment. Number and days of hospital admission during follow-up. These data will be obtained from records in the official database of the regional health system using the electronic medical record system and patient's (or family in case of dead) face-to-face interview to collect events occurred outside of the regional health system.
d) Number and days of hospital admission to the ICU in the three years prior to treatment. Number and days of hospital admission to the ICU during follow-up. These data will be obtained in similar way to number and days of hospital admission
e) Number of oro-tracheal intubations in the three years prior to treatment and the number of intubations during follow-up. These data will be obtained in similar way to number and days of hospital admission
f) Number of times treated in a hospital emergency room in the three years prior to treatment and during follow-up. These data will be obtained in similar way to number and days of hospital admission

g) Symptoms related to OSA and hypercapnic respiratory insufficiency will be collected from the questionnaire, in which the patient will be asked about their presence and intensity.
h) Level of perceived sleepiness: measured using the Epworth Sleepiness Scale. (MW Johns. The Epworth Sleepiness Scale. Sleep 1991;14:540)
i) Level of sleepiness according to the definition established by the American Thoracic Society. Sleepiness classified into four categories: none, mild, moderate, severe.
j) SAHS-related functional capacity: *Functional Outcomes of Sleep Questionnaire-- FOSQ--* y *Medical Outcome Survey --Short Form 36-- (SF 36).*
k) Subjective state of illness on a visual analogical scale.
l) Clinical history of cardiovascular risk factors (arterial hypertension (AHT), diabetes mellitus (DM), unhealthy habits and ongoing treatment, family cardiovascular history).
m) Registry of cardiovascular events (new hypertension diagnosis or anti-hypertensive treatment, atrial fibrillation, hospitalization for nonfatal myocardial infarction or instable angina, nonfatal stroke or transient ischemic attack or for heart failure episode, and cardiovascular death). These data will be obtained in similar way to number and days of hospital admission.
n) Registry of study dropouts and causes.
o) Registry of exitus and causes. These data will be obtained in similar way to number and days of hospital admission.
p) Compliance using hourly counter and a questionnaire on side effects.
q) Arterial gasometry of ambient air respired, spirometry following recommendations of the SEPAR, and the six-minute walk test.
r) PSG:
    a. AHI / hour for total sleep time, NREM and REM.
    b. Percentage of obstructive events + mixed events.
    c. Mean duration of events during total sleep time, NREM and REM.
    d. Index of arousals/hour.
    e. Total Sleep Time (TST).
    f. Sleep Efficiency (III+IV+REM/TST).
    g. Hypnogram (percentage of time in each sleep stage).
    h. Mean sleep and REM SaO2. Time with oxygen saturation below 90% (CT90).
    i. Desaturation Index.
s) Echocardiogram: the following parameters will be measured in at least three cycles.
    a. Systolic pulmonary arterial pressure (SPAP) using trans-thoracic Doppler.
    b. Mitral regurgitation peak velocity, by calculating right ventricular systolic pressure.
    c. Left heart: E-wave, A-wave, isovolumetric relaxation time, mitral deceleration time, auricular, systolic and diastolic LV diameters (mm), LV shortening fraction, LV ejection fraction, interventricular septum (mm), posterior wall of LV (mm), LV mass (gr) and LV mass index (gr/m2).

t) Measure of Biological Factors. Blood tests at baseline and post-treatment status will be recorded (after eight or nine hours of nocturnal fasting, at baseline rest in the dorsal decubitus position for 30 minutes).
   a. Biochemical studies: hemogram, hemoglobin, renal, hepatic and lipid profiles (total cholesterol, HDL and LDL, triglycerides and lipoproteins), leptin, ghrelin, adiponectin, γ-aminobutyric acid, vitamins B6-B12, and folic acid.
   b. Endothelium-dependent factors: a) plasmatic endothelin-1 using radioimmunoassay (RIA), b) nitrate and nitrite blood concentrations, using a fluorometric method, c) plasminogen activating factor (t-PA), and d) plasminogen activation inhibitor (PAI-1).
   c. Renin-angiotensin-aldosterone axis and sympathetic nervous system: a) plasmatic renin activity using second generation RIA, b) angiotensin II, c) aldosterone using RIA, d) catecholamines and metanephrine in 24-hour urine using the calorimetric method and e) serum catecholamines.
   d. Others: a) homocysteine using liquid chromatography, b) fibrinogen, c) intracellular adhesion molecules (ICAM-1), d) p-selectin, d) tumor necrosis factor (TNF-alfa), interleukin 6 (IL-6) and interleukin 1 (IL-1), e) vascular endothelial growth factor (VEGF), f) C-reactive protein, VCAM (vascular cell adhesion molecule), h) ICAM (intercellular adhesion molecule) and i) ROS (reactive oxygen species)

12 evaluations	Clinical and PFT	CV events	Hospital days	Dropouts and mortality	ABG and BP	PSG	Echo-cardiogram	Biological marquers
Baseline	x	x	x	x	x	x	x	x
30 days			x	x	x			
2 months	x	x	x	x	x	x	x	x
6 months			x	x	x			
9 months			x	x	x			
12 months	x	x	x	x	x		x	x
15 months			x	x	x			
18 months			x	x	x			
21 months			x	x	x			
24 months	x	x	x	x	x		x	x
30 months			x	x	x			
36 months	x	x	x	x	x		x	x

e) Masking strategy

Patients will continue their routine care based on regional health system requirements. Specialists implicated in the patient routine care will be not informed of the existence of this trial and there will be not any mention in the electronic health system database about it. Patients will receive information to connect with the research team if any specialist recommended a change in their mechanical treatment, NIV o CPAP. In these cases, the research team contacted with the responsible clinical specialist to agree the mechanical treatment from there on.

5) Collection and analysis of data

1) Administration of questionnaires: The tests will be administered and evaluated by trained personnel.

2) Data management: When all the questionnaires and forms have been completed, the data will be processed by computer using validated methods, which will also provide simultaneous data verification.

3) Statistical analysis:

   a) Evaluation of medium and long-term efficacy:
      i) Medium-term efficacy: Intra-group comparisons will be done for all variables between pre and post-treatment (related sample tests), although the principal analysis of efficacy will be the comparison of differences between pre and post-treatment in the different groups (ANOVA and ANCOVA). The analysis will be done both for "intention to treat" and "by protocol" for main medium-term variable (PaCO2) and the rest of variables. Treatment compliance will be also analyzed by subgroup.

      ii) Long-term efficacy: we will perform similar analysis but taking into account that for the main variable (days hospitalized), other hospital resource utilization, cardiovascular events and mortality the analysis will be centered in the comparison between arms by generalized linear model and cumulative incidence by survival analysis and Cox regression model. Continues variables with repeated measures (i.e. ABG) will be analyzed by mix linear model. Categorical variables by X^2 test. Treatment compliance will be also analyzed by subgroups preferably by the inclusion of treatment/compliance interaction in the models.
   b) The analysis of the importance of apneic events and leptin in the genesis of diurnal alveolar hypoventilation:
      i) Comparison of diurnal PaCO2/AHI and diurnal PaCO2/(event duration/AHI) coefficients between responders (normalization of diurnal hypercapnia) and non-responders, with CPAP treatment.
      ii) Evolution of leptin levels in the four branches of the study. Comparison of leptin levels between the CPAP non-responders and responders groups, and with the group of patients with OHS and an

AHI ≥30 who respond to NIV treatment (theoretical treatment of hypoventilation and obstructive events).

c) Investigate whether metabolic and biochemical alterations and endothelial dysfunction depend on the presence of apneas and hypopneas:

   i) Compare baseline and post-treatment levels of substances related to the abovementioned alterations, between groups with and without significant numbers of obstructive events.

6) Ethical issues

a) Informed written consent: All patients will be informed in writing about the nature and goals of the study. Patients' rights will be protected at all times, as established by the Helsinki declaration.
b) During the study an authorized external committee will have access to the periodic analysis of number of dropouts for medical reasons, and mortality. They will compare results in the different groups and interrupt the study if one of the treatments is significantly worse. This may happen separately in studies with or without OSA.

7) Ending of the study

The inclusion of additional patients will be stopped when the number of patients reached the estimated sample size with dropouts included or when groups have the calculated number of patients (dropouts excluded) at the end of the follow up. Additionally, the study could be early stopped by consensus among researches if the progression of the inclusion is no the appropriated (i.e. no new inclusions in the previous year).

Annex for supplemental oxygen therapy

Criteria for oxygen supplementation

Lifestyle arm: There will be two ways to add supplemental oxygen therapy in patients randomized in this group: 1) *Daytime valuation of oxygenation based on baseline arterial blood gases (ABG):* Supplemental oxygen will be prescribed if on the ABG the PaO_2 is ≤55 mmHg on room air during wakefulness. 2) *Sleep assessment during baseline polysomnography (PSG):* The PSG will be made on room air. The choice to add oxygen will be made in the morning by the professional sleep clinicians based on the review and analysis of the PSG data. If the mean SpO_2 during sleep from the pulse oximetry signal during the PSG is ≤88%, then supplemental oxygen will be added.

CPAP and NIV arms: In patients randomized to CPAP or NIV there will be two ways to recommend supplemental oxygen. 1) *Sleep assessment during CPAP/NIV titration PSG:* all PSGs for the sleep assessment will be made on room air. The sleep clinicians, based on the evaluation and analysis of the titration PSG data, will decide, in the morning, to add oxygen. The decision to add oxygen to NIV/CPAP therapy to those who underwent CPAP or NIV titration will be made if the mean SpO_2 from the pulse oximetry during the PSG titration was ≤88% on adequate NIV/CPAP levels. 2) *Daytime assessment of oxygenation based on ABG:* In patients randomized to CPAP or NIV, oxygen can also be prescribed if PaO_2 is ≤55 mmHg on ABG obtained during the follow-up of NIV or CPAP therapy.

How to use supplemental oxygen: guide for patients

All patients needing supplemental oxygen therapy regardless of the group they came from (i.e. lifestyle, CPAP or NIV) will be suggested to use it for at least 17 hours a day including the sleep period.

Oxygen therapy will be only titrated in patients who have hypoxemia during daytime valuation on ABG with PaO_2 ≤55 mmHg. In these patients, oxygen therapy will be titrated during wakefulness to determine the necessary flow to keep waking SpO_2 between 88% and 92%. The oxygen level required to keep SpO_2 above 88% during wakefulness will be the same used during sleep (either added to the NIV/CPAP system or via nasal cannula in the lifestyle arm). For those patients who have only criterion for oxygen supplementation during sleep, oxygen will be prescribed empirically at 2 L/min flow during sleep and wakefulness. As stated before, all PSGs (baseline and follow up) will be made without supplemental oxygen. Consequently, oxygen titration during sleep will be not possible. Oxygen will be bled-in into their home NIV/CPAP system using a T-tube connector. Oxygen will be administered via nasal cannula in those patients randomized to lifestyle modification.

Discontinuation of supplemental oxygen therapy

1) *Daytime assessment of oxygenation based on baseline ABG:* Supplemental oxygen will be discontinued if on the ABG the PaO_2 is >55 mmHg on room air during wakefulness. 2) *Sleep assessment during follow-up:* Based in nocturnal oximetry on room air. If the professional sleep clinicians consider necessary to perform a nocturnal oximetry this test will be carry out without oxygen, without

NIV/CPAP device in life style modification arm and with NIV/CPAP in the other two arms. If the mean nocturnal SpO_2 is >88%, supplemental oxygen will be discontinued.