CHEST®

Official publication of the American College of Chest Physicians

Mortality in Obstructive Sleep Apnea-Hypopnea Patients Treated With Positive Airway Pressure

Francisco Campos-Rodriguez, Nicolas Peña-Griñan, Nuria Reyes-Nuñez, Ines De la Cruz-Moron, Jose Perez-Ronchel, Francisco De la Vega-Gallardo and Ana Fernandez-Palacin

Chest 2005;128;624-633
DOI 10.1378/chest.128.2.624

Mortality in Obstructive Sleep Apnea-Hypopnea Patients Treated With Positive Airway Pressure*

Francisco Campos-Rodriguez, MD; Nicolas Peña-Griñan, MD; Nuria Reyes-Nuñez, MD; Ines De la Cruz-Moron, MD; Jose Perez-Ronchel, MD; Francisco De la Vega-Gallardo, MD; and Ana Fernandez-Palacin, MD

Study objectives: **The aims of this study were to analyze mortality in patients with obstructive sleep apnea-hypopnea syndrome (OSAHS) treated with positive airway pressure (PAP) and to know whether PAP compliance affects survival, as well as to investigate the prognostic value of several pretreatment variables.**

Design and patients: **A study was made of an historical cohort of 871 patients in whom OSAHS had been diagnosed by sleep study between January 1994 and December 2000 and who had been treated with PAP. Patients were followed up until December 2001. The mean (± SD) age of the group was 55.4 ± 10.6 years, the mean apnea-hypopnea index (AHI) 55.1 ± 28.7, and 80.9% were men. To assess whether mortality was influenced by PAP therapy compliance, patients were assigned to one of the following compliance categories: < 1 h/d; 1 to 6 h/d; or > 6 h/d. Survival rates were calculated according to the Kaplan-Meier method. Survival curves were compared with the log-rank test and the trend test, when necessary. Univariate and multivariate analyses using a time-dependent Cox model were performed to elicit which variables correlated with mortality.**

Setting: **Outpatient sleep disorders unit.**

Results: **By the end of the follow-up period (mean duration, 48.5 ± 22.7 months), 46 patients had died. The 5-year cumulative survival rates were significantly lower in patients who did not use PAP (compliance < 1h) than in those who used the device for > 6 h/d (85.5% [95% confidence interval (CI), 0.78 to 0.92] vs 96.4% [95% CI, 0.94 to 0.98; p < 0.00005]) and 1 to 6 h/d (85.5% [95% CI, 0.78 to 0.92] vs 91.3% [95% CI, 0.88 to 0.94; p = 0.01]), respectively. A trend in survival rates across the groups was identified (p = 0.0004). The main cause of death in 19 cases was cardiovascular disease (CVD). Variables that independently correlated with mortality in the multivariate analysis were the following PAP use categories: compliance for > 6 h/d (odds ratio [OR], 0.10; 95% CI, 0.04 to 0.29); compliance for 1 to 6 h/d (OR, 0.28; 95% CI, 0.11 to 0.69); arterial hypertension (AHT) [OR, 3.25; 95% CI, 1.24 to 8.54]; age (OR, 1.06; 95% CI, 1.01 to 1.10); and FEV_1 percent predicted (OR, 0.96; 95% CI, 0.94 to 0.98).**

Conclusion: **Mortality rates in OSAHS patients who did not receive PAP therapy were higher compared with those treated with PAP and were moderately or highly compliant with therapy. A trend in survival across compliance categories was found. Patients died mainly from CVD. Categories of PAP compliance, AHT, age, and FEV_1 percent predicted were the variables that independently predicted mortality.** ***(CHEST 2005; 128:624–633)***

Key words: arterial hypertension; compliance; continuous positive airway pressure; mortality; obstructive sleep apnea-hypopnea syndrome

Abbreviations: AHI = apnea-hypopnea index; AHT = arterial hypertension; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; CRP = limited cardiorespiratory polygraphy; CVD = cardiovascular disease; EDS = excessive daytime sleepiness; OR = odds ratio; OSAHS = obstructive sleep apnea-hypopnea syndrome; PAP = positive airway pressure; Sao_2 = arterial oxygen saturation; Sao_2m = minimum arterial oxygen saturation; Sao_2< 90% = percentage of time spent with arterial oxygen saturation at < 90%

Obstructive sleep apnea-hypopnea syndrome (OSAHS), a condition that affects about 4% of the general population,[1,2] is characterized by repetitive episodes of upper airway obstruction during sleep that provoke frequents arousals, sleep fragmentation, oxygen desaturation, and excessive daytime sleepiness (EDS). Some studies have identified OSAHS as an independent risk factor for arterial hypertension (AHT),[3,4] and probably for ischemic heart disease and stroke.[5–7] These patients also experience higher rates of traffic accidents as well as impairments in measurements of health-related

quality of life as determined by questionnaire.[8,9] Retrospective studies[10–13] carried out before the widespread application of positive airway pressure (PAP) showed that untreated patients with OSAHS had higher mortality rates compared with both the general population and treated patients. In all of these studies, the most common cause of death was cardiovascular disease (CVD).

Since the early 1980s, the development of a technique that can deliver continuous PAP (CPAP) noninvasively has provided an effective and noninvasive treatment for these patients.[14] Several trials[15–19] have shown a substantial improvement in the typical symptoms associated with this disorder, such as morning headaches, snoring, and daytime sleepiness, as well as reductions in BP, in patients undergoing this therapy. However, prospective and randomized trials comparing mortality in patients with CPAP and untreated patients are lacking, due to ethical problems. In this situation, an analysis of the outcome of an historical cohort of OSAHS patients undergoing long-term CPAP therapy could be of interest.[13,20,21] Furthermore, if different categories were defined according to CPAP compliance, comparisons among these groups would give valuable information about the effect of CPAP on OSAHS mortality.

Therefore, the aims of this study were to determine survival rates in a large, nonselected population of OSAHS patients who had been treated with PAP, to investigate whether PAP compliance affects survival, as well as to analyze the causes of mortality and the prognostic value of several pretreatment variables.

Materials and Methods

Design and Setting

Every patient in whom OSAHS who was diagnosed in the Respiratory Department of Valme University Hospital (Seville, Spain) between January 1, 1994, and December 31, 2000, was included in this historical cohort study if they fulfilled the following criteria: (1) apnea-hypopnea index (AHI) of ≥ 10 events/h in a sleep study; (2) $<20\%$ of central apneas; (3) age > 20 years; and (4) prescription of PAP (CPAP or bilevel pressure ventilation). Patients were excluded if they did not fulfill the above criteria, if the diagnosis was based exclusively on clinical grounds or sleep oximetry findings, or if they had received treatment other than PAP.

All patients were initially seen as outpatients at the Sleep Disorders Unit in the department where they had been referred with a suspected diagnosis of OSAHS by primary care or hospital-based physicians. Every patient gave a detailed clinical history and underwent a physical examination. BP, weight, height, body mass index (BMI), and fasting total cholesterol, triglyceride, and glucose levels were measured. Spirometry, arterial blood gas measurements while breathing room air, ECG, and chest radiograph examinations were also performed. All of these examinations were performed prior to the sleep study and while the patient was in a stable state.

A patient was classified as hypertensive, diabetic, hypercholesterolemic, or hypertriglyceridemic if any of these disorders had been previously diagnosed, patients were undergoing specific treatment for them, or they exhibited a systolic BP of > 140 mm Hg or a diastolic BP of > 90 mm Hg on two or more different ambulatory readings, fasting glucose levels of > 110 mg/dL on two or more determinations, and fasting cholesterol or triglyceride levels of > 200 mg/dL each. A patient was considered to be a smoker if they had smoked > 1 pack/year, irrespective of whether they were active smokers or ex-smokers. Obesity was diagnosed when BMI was > 30 kg/m^2, and COPD was diagnosed when FEV_1 was $< 80\%$ of predicted and the FEV_1/FVC ratio was $< 70\%$.

OSAHS Diagnosis and Treatment

The diagnosis of OSAHS was always based on a sleep study, either by full standard polysomnography (UltraSom; Nicolette Biomedical; Madison, WI) including EEG, electrooculogram, electromyogram, oronasal flow, thoracoabdominal movements, ECG, and arterial oxygen saturation (Sa_{O_2}), or by limited cardiorespiratory polygraphy (CRP) using a device that had previously been validated against polysomnography (Densa Pneumograph; Densa Ltd; Flint, UK[22]; or Apnoscreen II plus; Erich Jaeger Gmbh & Co KG; Wurzburg, Germany[23]). The results of every study were scored manually. Standard polysomnography was the method of choice to diagnose OSAHS in patients with cardiorespiratory disorders. Airflow was recorded with a thermistor, respiratory efforts were recorded with strain strips, and transcutaneous Sa_{O_2} was monitored continuously using a pulse oximeter (Nellcor Pulse Oxymeter N-200; Nellcor Puritan Bennett; Pleasanton, CA). An apnea was defined as the complete cessation of airflow for > 10 s and was classified either as obstructive or central based on the presence or absence of respiratory efforts. An hypopnea was defined as a reduction of $\geq 50\%$ in oronasal flow for > 10 s accompanied by a decrease of $\geq 4\%$ in Sa_{O_2}. In every patient, the AHI, the minimum Sa_{O_2} ($Sa_{O_2}m$), and the percentage of time spent with an Sa_{O_2} of $<90\%$ ($Sa_{O_2}< 90\%$) were recorded.

Once the diagnosis of OSAHS had been established, for a second night, PAP was titrated. The level of PAP was increased until respiratory events, snores, and oxygen desaturations were eliminated. CPAP was considered to be the treatment of choice unless OSAHS could not be controlled with high pressures (*ie*, 15 cm H_2O); in those cases, bilevel pressure ventilation was prescribed. This mode of treatment was also occasionally used in patients with intolerance to high CPAP pressures. Those patients who had persistent hypoxemia despite appropriate treatment were given oxygen therapy supplementary to PAP. Patients with other medical conditions were treated as necessary.

*From the Departments of Respiratory Medicine (Drs. Campos-Rodriguez, Peña-Griñan, Reyes-Nuñez, De la Cruz-Moron, Perez-Ronchel, and De la Vega-Gallardo) and Statistical Analysis (Dr. Fernandez-Palacin), Valme University Hospital, Sevilla, Spain.
Manuscript received October 29, 2003; revision accepted January 25, 2005.

Correspondence to: Francisco Campos-Rodriguez, MD, Avda Emilio Lemos No. 19, Pt 2, 4-E, 41020 Sevilla, España; e-mail: fcamposr@eresmas.com

Follow-up

Patients had check-ups at 3-month intervals after the initiation of PAP therapy during the first year and every 6 to 12 months thereafter. In these appointments, the clinical status, patient compliance, perception of benefits, and side effects were assessed. Objective compliance was established by reading the internal time counter of the devices. In those patients with intolerance to PAP or with persistent symptoms despite good compliance, a new polysomnography examination was carried out, and pressures were changed or a different mode of PAP was prescribed when needed. The follow-up ended in December 2001, and survival was assessed through attendance at the check-ups, telephone, or mail. When a patient died, information about the cause and date of death was obtained from the clinical history and their relatives. In those patients who stopped receiving PAP therapy before the termination of the study, follow-up was censored at the date of the last visit and the information generated up to that point was used.

Mortality in Different Categories of PAP Compliance and OSAHS Severity

To elicit whether mortality was influenced by PAP compliance, patients were grouped into the following four categories: (1) compliance of < 1 h/d; (2) compliance for between 1 and 6 h/d; (3) compliance for > 6 h/d; and (4) compliance not assessed (*ie*, patients in whom compliance was unavailable for the following reasons: problems with the time counter of the device; use of early devices that did not have time counters; patients in whom only subjective but not objective compliance was assessed; errors with the reading; and patients with only one to two readings in several years that cannot be considered representative of the whole period of follow-up).

To elicit whether mortality was influenced by OSAHS severity, patients were grouped into the following two categories: (1) severe OSAHS; and (2) mild-to-moderate OSAHS. To define severe OSAHS, we used a threshold of 30 apneas-hypopneas per hour, as suggested by an international classification.[24]

Statistical Analysis

A statistical software package (SPSS Inc; Chicago, IL) was used for data processing and statistical analysis. Continuous variables were expressed as the mean ± SD, and qualitative variables were expressed as a percentage. If variables were normally distributed, a *t* test or analysis of variance was used for continuous variables and a χ^2 test was used for qualitative variables; otherwise, a Mann-Whitney or a Fisher exact test, respectively, was used. Survival rates were calculated according to the Kaplan-Meier method, and survival curves were compared with the log-rank test. The log-rank test for trend was used to assess the probability that there was a trend in survival across the groups. The assumption of proportional hazards was assessed graphically using the log-minus-log survival graph.

In the first phase, univariate analysis based on a proportional hazards model was performed to determine any relationship between mortality and the following independent pretreatment variables: age; sex; BMI; obesity; smoking history; COPD; AHT; diabetes mellitus; hypercholesterolemia; hypertriglyceridemia; Po_2; Pco_2; FEV_1 percent predicted; FVC percent predicted; FEV_1/FVC ratio; Sao_2m; $Sao_2 < 90\%$; AHI; OSAHS severity; and categories of PAP compliance. Variables found to be significant (*ie*, $p \leq 0.10$) were included in a multivariate analysis using a time-dependent Cox model, as the assumption of proportional hazards was not verified. The interaction between OSAHS severity and categories of PAP compliance was included in the Cox analysis. The results of Cox multivariate analysis were expressed as the odds ratio (OR) with 95% confidence intervals (CIs). Two-tailed p values of < 0.05 were considered to be significant.

Results

Characteristics of the Patients

Eight hundred eighty-eight patients fulfilled the inclusion criteria, but 17 of them (1.9%) could not be located and were not considered in later analyses. The study population consisted of 871 patients, including 705 men (80.9%) and 166 women (19.1%), with a mean age of 55.4 ± 10.6 years. Baseline characteristics are shown in Table 1. The diagnosis of OSAHS was established by polysomnography in 249 patients (28.6%), and by CRP in 622 patients (71.4%), with a mean AHI of 55.1 ± 28.7 events/h, an Sao_2m of 69.0 ± 14.7%, and an $Sao_2 < 90\%$ of 30.4 ± 30.9%. Following the American Academy of Sleep Medicine classification,[24] 655 patients (75.2%) had severe OSAHS and 216 patients (24.71%) had mild-to-moderate OSAHS. In 793 patients (91%), CPAP was prescribed, with a mean level of 10.1 ± 2.1 cm H_2O, while in the remaining 78 patients (9%) use of a bilevel pressure ventilation device was necessary. Most patients had associated comorbidities, such as obesity (81.9%), hypercholesterolemia (66.9%), or AHT (61.1%). It is of interest to note that COPD was present in 19.1% of the patients, coinciding with the heavy smoking of the study population. In most patients with COPD, OSAHS was diagnosed by polysomnography (145 of 161 patients; 90%). Thirty-two additional OSAHS patients who were not prescribed or refused PAP were analyzed separately.

Follow-up

The mean duration of follow-up was 48.5 ± 22.7 months (range, 0 to 103 months), and during this time modifications in PAP were made in 157 patients (18%). These modifications included changes in pressure levels in 102 patients (65%) and changes of the device in the other 55 patients (35%). Most of these patients (*ie*, 44 of 55 patients) were transferred from therapy with CPAP to bilevel pressure ventilation. In 749 patients (85.9%), objective compliance could be assessed, with an average of 5.2 ± 2.7 h/d.

Treatment with PAP was withdrawn in 51 patients (5.8%) before the end point for reasons other than death. The withdrawal was due to poor compliance in 39 patients, 9 patients were considered to be cured, and 3 patients moved to another province. The survival of these 51 patients was censored on the date of the last visit and were included in the

Table 1—*Baseline Characteristics of the Sample Population*

Characteristics	PAP Compliance			
	> 6 h/d (n = 322)	1–6 h/d (n = 342)	< 1 h/d (n = 85)	Ignored (n = 122)
Age, yr	55.1 ± 10.6	55.4 ± 10.2	56.3 ± 12.0	55.6 ± 10.8
Male gender	260 (80.7)	273 (79.8)	70 (82.3)	102 (83.6)
BMI, kg/m^2	36.7 ± 6.5	34.5 ± 5.4	35.6 ± 7.4	35.5 ± 6.2
Obesity	279 (86.6)	273 (79.8)	67 (78.8)	97 (79.5)
Arterial hypertension	198 (61.4)	208 (60.8)	47 (55.2)	79 (64.7)
Diabetes mellitus	126 (39.1)	108 (31.5)	31 (36.4)	47 (38.8)
Hypercholesterolemia	207 (64.2)	223 (65.2)	59 (69.4)	90 (74.3)
Hypertriglyceridemia	108 (33.5)	108 (31.5)	34 (40)	40 (32.7)
Smokers	215 (66.7)	222 (64.9)	58 (68.2)	82 (67.2)
Tobacco consumption, packs/yr	47.2 ± 30.1	48.2 ± 30	50.1 ± 38.0	44.5 ± 33.1
COPD	68 (21.1)	50 (14.6)	13 (15.2)	30 (24.5)
Po_2, mm Hg	73.5 ± 13.7	78.2 ± 12.7†	78.4 ± 12.4‡	75.2 ± 11.6
Pco_2, mm Hg	43.0 ± 5.3	42.7 ± 5.2	42.3 ± 3.8	41.2 ± 5.1
FEV_1, % predicted	79.9 ± 22.0	86.6 ± 22.3†	84.5 ± 19.5	77.9 ± 23.8
FVC, % predicted	84.6 ± 13.7	89.0 ± 19.8†	86.2 ± 20.9	82.3 ± 18.7
FEV_1/FVC ratio	77.1 ± 9.9	78.3 ± 8.7	78.8 ± 10.8	75.7 ± 11.4
AHI, events/h	60.0 ± 29.6	52.1 ± 26.8†	48.8 ± 27.3‡	53.7 ± 29.8
Sao_2m, %	68.3 ± 20.4	70.7 ± 14.4	71.1 ± 14.3	67.2 ± 13.9
Sao_2 90%, %	34.0 ± 31.1	25.7 ± 29.6†	25.9 ± 28.0‡	31.3 ± 30.5
Compliance, h/d	7.6 ± 1.2	3.9 ± 1.4†	0.3 ± 0.2‡§	

*Values given as the mean ± SD or No. (%).
†$p < 0.05$ (patients with PAP compliance for > 6 h/d vs patients with PAP compliance for 1 to 6 h/d).
‡$p < 0.05$ (patients with PAP compliance for > 6 h/d vs patients with PAP compliance for < 1 h/d).
§$p < 0.05$ (patients with PAP compliance for 1 to 6 h/d vs patients with PAP compliance for < 1 h/d).

analysis. The characteristics of this group of patients did not differ from those of the other patients.

Mortality Data for the Entire Sample

By the end of the study, 46 of the 871 patients (5.3%) had died. The cumulative survival rates were 96% (95% CI, 0.95 to 0.97) at 3 years and 92.1% (95% CI, 0.97 to 0.99) at 5 years. The causes of death are specified in Table 2. CVD was the main cause of death in 19 of the 46 patients, followed by neoplastic diseases in 16 patients. Three patients died of acute respiratory failure, and none died due to accidents or suicide. In two cases, the cause of death could not be elicited. These 46 patients were followed up as a group for a mean duration of 32.4 ± 22.7 months (range, 0 to 83 months).

Mortality and PAP Compliance

Seven hundred forty-nine patients (85.9%) in whom objective compliance could be assessed were analyzed. Three hundred twenty-two patients used PAP for at least 6 h/d (mean duration, 7.6 ± 1.2 h/d), 342 patients used it between 1 and 6 h/d (mean duration, 3.9 ± 1.4 h/d), and 85 had compliance for < 1 h/d (mean duration, 0.3 ± 0.2 h/d). The baseline characteristics for each group are given in Table 1. Patients in the group with compliance of > 6 h/d had higher AHI (60.0 ± 29.6 vs 48.8 ± 27.3, respectively; $p = 0.009$), lower daytime Po_2 (73.5 ± 13.7 vs 78.4 ± 12.4 mm Hg, respectively; $p = 0.003$), and had a higher $Sao_2 < 90\%$ (34.0 ± 31.1% vs 25.9 ± 28.0%, respectively; $p = 0.03$) than those patients in the group with compliance of < 1 h/d. Eleven patients (3.4%), 16 patients (4.6%), and 8 patients (9.4%), respectively, died in the group with

Table 2—*Causes of Death*

Causes	PAP Compliance			
	> 6 h/d (n = 322)	1–6 h/d (n = 342)	< 1 h/d (n = 85)	Ignored (n = 122)
Cardiovascular diseases	5	7	4	3
Myocardial infarction	4	5	2	2
Sudden death		2	1	
Congestive heart failure	1		1	1
Neoplasia	3	7	1	5
Lung	2	3		1
Head and neck		1	1	
GI	1			3
Urogenital		2		
Others		1		1
Acute respiratory failure	1		1	1
Others	1	2	1	2
Unknown	1		1	

compliance of > 6, 1 to 6, and < 1 h/d. The causes of death are shown in Table 2. The cumulative survival rates at 5 years (Fig 1) were significantly lower in patients with compliance of < 1 h/d than in those who used PAP > 6 h/d (85.5% [95% CI, 0.78 to 0.92] vs 96.4% [95% CI, 0.94 to 0.98], respectively; $p < 0.00005$) and 1 to 6 h/d (85.5% [95% CI, 0.78 to 0.92] vs 91.3% [95% CI, 0.88 to 0.94], respectively; $p = 0.01$). We also found that PAP compliance affected survival in a linear trend, such that survival was significantly better with increasing compliance ($p = 0.0004$) [Table 3].

When the group of 122 patients whose compliance could not be assessed was analyzed, the cumulative survival rates at 5 years were similar to the group with compliance of < 1 h/d (83.5% [95% CI, 0.77 to 0.90] vs 85.5% [95% CI, 0.78 to 0.92], respectively; $p = 0.11$), and were significantly lower than the group with compliance of 1 to 6 h/d (83.5% [95% CI, 0.77 to 0.90] vs 91.3% [95% CI, 0.88 to 0.94], respectively; $p = 0.004$) and > 6 h/d (83.5% [95% CI, 0.77 to 0.90] vs 96.4% [95% CI, 0.94 to 0.98], respectively; $p < 0.00005$).

Mortality and OSAHS Severity

Patients with severe OSAHS (*ie*, AHI, > 30) had similar mortality rates to those with mild-to-moderate OSAHS (35 of 657 vs 11 of 214 patients, respectively; OR, 0.96; 95% CI, 0.45 to 2.02; $p = 0.90$). When the average AHI of the sample was used to define severe OSAHS (*ie*, AHI, > 55), the results did not change (19 of 413 vs 27 of 458 patients, respectively; OR, 1.31; 95% CI, 0.69 to 2.51; $p = 0.38$). The cumulative survival rates at 5 years (Fig 2) were similar in patients with severe and mild-to-moderate OSAHS (92.8% [95% CI, 0.89 to 0.93] vs 89.8% [95% CI, 0.92 to 0.96] $p = 0.97$).

Table 3—*Survival Data Stratified by PAP Compliance Using the Log-Rank Test for Trend*

Categories of Compliance	Cases, No.	5-yr Survival Rate, %	95% CI	p Value
< 1 h/d	85	85.5	0.78–0.92	
1–6 h/d	342	91.3	0.88–0.94	0.0004
> 6 h/d	322	96.4	0.94–0.98	

Mortality in Nontreated OSAHS Patients

OSAHS was diagnosed in 32 patients, who were not treated with PAP, surgery, or mandibular advancement (mean follow-up duration, 24.4 ± 20.1 months). Twelve of these patients had symptomatic severe OSAHS and refused treatment. Nine of them had been lost to follow-up since the first check-ups. Only four patients could be contacted at the end of the study, and one of them had died (respiratory insufficiency). Twenty patients with mild-to-moderate nonsymptomatic OSAHS and without cardiovascular comorbidities did not receive treatment. Fifteen patients were discharged from follow-up because after several check-ups they had remained nonsymptomatic. Eight patients could be contacted at the end of the study, and one had died (myocardial infarction). Therefore, the outcome was available in only 12 patients (37%) with untreated OSAHS, with

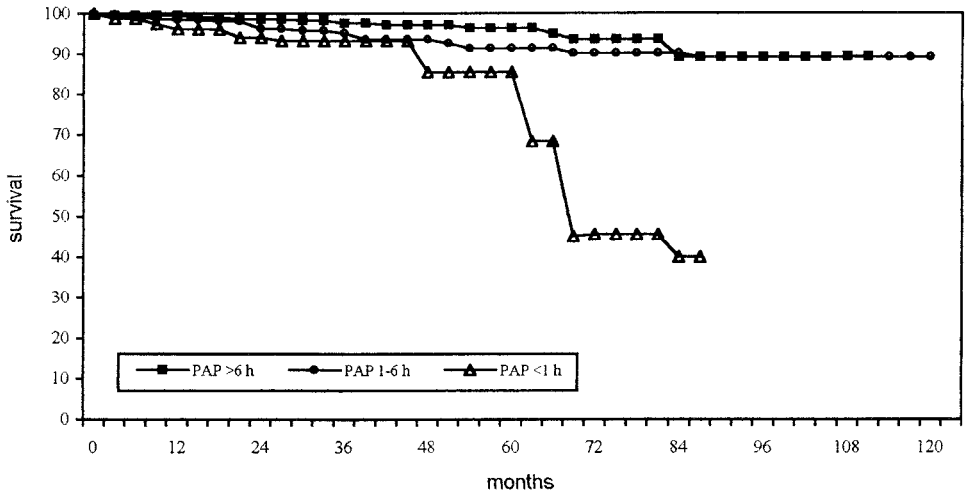

FIGURE 1. Kaplan-Meier cumulative survival rates according to categories of PAP compliance. Cumulative survival rates in the PAP > 6-h group were significantly higher than in the PAP < 1 h group ($p < 0.00005$). Cumulative survival rates in the PAP 1–6 h group were significantly higher than in the PAP < 1 h group ($p = 0.01$). Cumulative survival rates were not different in the PAP > 6 h group and the PAP 1–6 h group ($p = 0.11$)

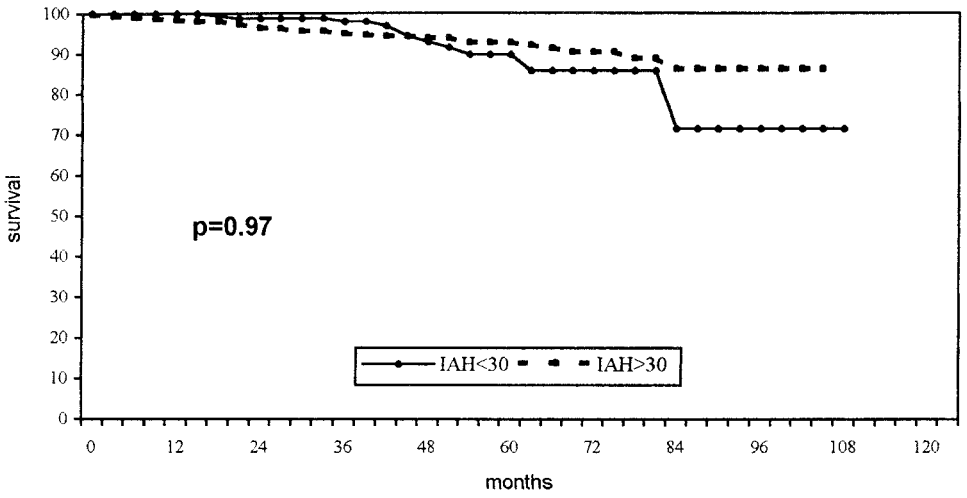

FIGURE 2. Kaplan-Meier cumulative survival rates according to OSAHS severity.

a mortality rate of 16% (2 of 12 patients) and a 5-year survival rate of 77.9% (95% CI, 0.63 to 0.92).

Univariate and Multivariate Analysis

Table 4 shows the results of the univariate analysis correlating mortality and several independent variables that had been obtained prior to the initiation of treatment. The variables finally included in the multivariate analysis were age ($p < 0.0005$), smoking habit ($p = 0.008$), AHT ($p = 0.02$), diabetes mellitus ($p = 0.009$), Po_2 ($p = 0.002$), Pco_2 ($p = 0.07$), FEV_1 percent predicted ($p < 0.0005$), FVC percent predicted ($p < 0.0005$), FEV_1/FVC ratio ($p = 0.002$),

Table 4—*Correlation Between Pretreatment Independent Variables and Death Using Univariate Analysis*

Variables	Values*	OR† (95% CI)	p Value
Age, yr	55.4 ± 10.6	1.07 (1.04–1.11)	< 0.0005
BMI, kg/m^2	35.6 ± 6.2	1.01 (0.96–1.05)	0.58
Tobacco consumption, packs/yr	33.6 ± 36.1	1.24 (1.07–1.10)	0.002
Po_2, mm Hg	76.1 ± 13.0	0.96 (0.93–0.98)	0.002
Pco_2 (mmHg)	42.0 ± 5.2	1.04 (0.99–1.10)	0.07
FEV_1, % predicted	82.4 ± 22.8	0.97 (0.95–0.98)	< 0.0005
FVC, % predicted	85.4 ± 19.6	0.96 (0.95–0.98)	< 0.0005
FEV_1/FVC ratio	77.5 ± 9.8	0.95 (0.93–0.98)	0.002
AHI, events/h	55.1 ± 28.7	0.99 (0.98–1.00)	0.45
$Sao_2 < 90\%$, %	30.4 ± 30.9	1.01 (1.00–1.02)	0.002
Sao_2m, %	69.0 ± 14.7	0.97 (0.96–0.99)	0.006
Female sex‡	19.1	1.44 (0.64–3.24)	0.36
Arterial hypertension‡	61.1	2.27 (1.12–4.58)	0.02
Hipercolesterolemia‡	66.9	1.18 (0.62–2.24)	0.61
Hypertriglyceridemia‡	33.6	1.52 (0.85–2.73)	0.12
Diabetes mellitus‡	36.0	2.19 (1.22–3.95)	0.009
COPD‡	19.1	2.62 (1.44–4.76)	0.002
Smokers > 30 packs/yr‡	45.4	2.36 (1.22–4.60)	0.008
Obesity‡§	77.1	1.08 (0.50–2.37)	0.60
Severe OSAH‡‖	75.2	0.98 (0.50–1.94)	0.97
Categories of PAP compliance‡			
< 1 h/d	9.8	1	
1–6 h/d	39.3	0.32 (0.13–0.77)	0.01
> 6 h/d	37.0	0.17 (0.06–0.43)	< 0.0005

*Values given as mean ± SD or %.
†Exponential β-statistic.
‡Categoric covariate.
§BMI > 30 kg/m^2.
‖AHI > 30.

COPD ($p = 0.002$), $Sao_2 < 90\%$ ($p = 0.002$), Sao_2m ($p = 0.006$), and categories of PAP compliance ($p = 0.01$ and $p < 0.0005$). The interaction between OSAHS severity and categories of PAP compliance was included in the multivariate analysis.

The results of the multivariate analysis using a time-dependent Cox model are shown in Table 5. The independent variables finally included in the equation were categories of PAP compliance, AHT, age and FEV_1 percent predicted.

Discussion

This study shows that OSAHS patients who used PAP for < 1 h/d had significantly lower survival rates compared to patients who had high compliance (> 6 h/d) or even moderate compliance (1 to 6 h/d). This association between compliance and mortality was independent of other covariates. This study also shows that there was a trend in survival across the groups, such that survival was significantly better with increasing compliance. The main cause of death was CVD followed by neoplasia. The variables that independently predicted death prior to the commencement of PAP therapy were categories of PAP compliance, AHT, FEV_1 percent predicted, and age. The severity of OSAHS was not a predictor of death in treated patients.

Our sample was made up of 871 patients with a firm diagnosis of OSAHS that had been established by a sleep study and had been treated with PAP. All of these patients were referred to our Sleep Disorders Unit due to a suspicion of OSAHS. They were not selected patients and had similar characteristics to patients in other series. Most of the patients had associated comorbidities such as hypertension, hyperlipidemia, or obesity. Therefore, this sample is representative of OSAHS patients who had been treated at home with PAP. A possible bias could arise from the 51 patients in whom PAP therapy was withdrawn before the termination of the study. However, the pretreatment variables collected for this group were not different from those of the rest of the patients who had been followed up until the end point of the study. Also, careful follow-up showed that all 51 patients were alive when PAP therapy was stopped. The diagnosis of OSAHS in COPD patients could be another bias. However, in 90% of these patients the diagnosis of OSAHS was based on polysomnography findings, and in the other 10%, CRP showed typical OSAHS findings with an AHI of > 30. In every case, the study was performed with the patient in a stable state. Therefore, we think that patients with overlap syndrome in our study have been correctly classified. A final bias could be the lack of a control group composed of patients who had "never" been treated with PAP. For that purpose, 32 patients in whom OSAHS had been diagnosed during the study period, and who had not been treated with PAP, surgery, or mandibular advancement, were included. Twelve of these patients had severe symptomatic OSAHS but had refused treatment, and 20 patients had mild nonsymptomatic OSAHS without cardiovascular comorbidities (treatment not prescribed). Unfortunately, only 12 patients could be contacted by the time of the termination of the study (most patients had been discharged from or lost to follow-up) to know whether they were alive or dead. Although the 5-year survival rate of 77.9% would suggest that mortality in this group is similar to that of patients with compliance of < 1h/d and is clearly lower than patients with moderate/high compliance, we think that this figure has to be interpreted with caution, and comparison with the study sample is not adequate, as the final outcome was ignored in 62% of the patients in this group.

The 5-year cumulative survival rates for the whole sample, and the groups with compliance of > 6, 1 to 6, and < 1 h/d were 92.1%, 96.4%, 91.3% and 85.5%, respectively. It is remarkable that OSAHS patients who used PAP for > 6 h/d had significantly higher cumulative survival rates than patients who used PAP for < 1 h/d, despite having a higher baseline AHI, lower daytime Po_2, and higher $Sao_2 < 90\%$. Even patients with only moderate compliance (*ie*, 1 to 6 h/d) had significantly higher survival rates than noncompliant patients. Another important finding is that there was a trend in survival across the groups; that is, survival improves as compliance increases. Remarkably, this association between compliance and mortality was independent of other covariates, as shown by the inclusion of the PAP use categories in the final Cox model. These data suggest that the excess of mortality in untreated OSAHS patients reported by some authors[10–12,25] would disappear if adequate treatment with PAP were established and the patient were compliant. A bias that could affect the power of the study is the

Table 5—*Results of the Multivariate Analysis Using a Time-Dependent Cox Model*

Variables	OR	95% CI	p Value
Arterial hypertension	3.25	1.24–8.54	0.01
Age	1.06	1.01–1.10	0.01
FEV_1 percent predicted	0.96	0.94–0.98	< 0.0005
PAP use categories			< 0.0005
< 1 h/d	1		
1–6 h/d	0.28	0.11–0.69	0.006
> 6 h/d	0.10	0.04–0.29	< 0.0005

selection criteria of the groups. As the performance of a prospective, randomized study was not possible for ethical reasons, we decided to perform a retrospective cohort study, and the following three categories of PAP compliance were defined: <1 h/d; 1 to 6 h/d; and >6 h/d. Patients in the group with compliance for <1 h/d had an average PAP use of 0.3 h/d and could be considered as "nontreated." On the other hand, patients with >6 h/d of use (mean, 7.6 h/d) undoubtedly had good compliance. Finally, a third group made up of patients with intermediate compliance (1 to 6 h/d; mean, 3.9 h/d) was included in the analysis. Although the number of subjects in each group was unbalanced and compliance in the group of patients with 1 to 6 h/d of PAP use was heterogeneous (range, 1.5 to 2 to 5.5 to 6 h/d), we think that the results are strong enough to show that adequate PAP treatment could influence survival in OSAHS patients independently of other variables. The sample of 122 patients (14%) in whom compliance could not be assessed represents another important bias, as it was not included in the mortality analysis. Although the baseline characteristics of this group did not differ from the rest, the cumulative survival rate was similar to that of noncompliant patients and was lower than moderate or highly compliant patients. We do not know whether these lower survival rates are related to bad compliance (it was unavailable) or depends on other factors, but even if these patients were included in the group with <1 h/d compliance, the 5-year survival rates for this new group of 207 patients with bad/unknown compliance would be 83.5% (95% CI, 0.78 to 0.88), which is similar to survival rates previously obtained for the group of 85 patients with compliance of < 1 h/d and is still significantly lower than those in patients with moderate or high compliance.

Other studies[13,20,21] have addressed the question of mortality in OSAHS patients treated with CPAP. Chaouat et al[21] studied 296 patients who obtained cumulative survival rates of 93% at 5 years. The authors found that mortality rates in treated patients were similar to those of the general population. Veale et al[20] also analyzed mortality in a large sample (5,669 patients) of OSAHS patients who had been treated with CPAP and found survival rates of 90% at 6 years, which is identical to that in the general population. These figures are similar to the 5-year survival of 92.1% obtained for the whole sample in our work. The main problem with these two studies is that the effect of CPAP in improving mortality was only indirectly assessed by comparison with the general population. In fact, these mortality rates of 7 to 10% at 5 years are higher than the 10-year mortality of 2 to 3% obtained by Lindberg et al[25] in patients without snoring or EDS. This study enrolled 3,100 men aged 30 to 69 years who answered a postal questionnaire including questions about snoring and EDS. The authors found that the combination of snoring and EDS carried an increased risk of mortality at 10 years (7 to 8%) compared with patients without snoring or EDS (2 to 3%). The different mortality rates in nonsnoring non-EDS patients compared to those of OSAHS patients treated with CPAP could be explained by methodological differences. While Lindberg et al[25] classified patients based on the answers to a postal questionnaire, Chaouat et al[21] and Veale et al[20] confirmed OSAHS with a sleep study. Therefore, some patients in the study by Lindberg et al[25] could have been misclassified, as OSAHS was neither confirmed nor excluded objectively. Another reason that explains this discrepancy is the subject selection. Survival data in the studies by Chaouat et al[21] and Veale et al[20] referred to the whole sample, which undoubtedly includes patients with bad compliance that will elevate mortality rates. In fact, in our study, the 5-year survival rates of a selected group of patients with very good compliance (*ie*, >6 h/d) was better than that of the whole sample (96.4% vs 92.1%, respectively), and was closer to the data reported by Lindberg et al.[25]

The only article that has compared nontreated and CPAP-treated patients is that of Marti et al,[13] who analyzed 444 patients who had been separated into the following four treatment groups: surgery (88 patients); CPAP (124 patients); weight loss (134 patients); and nontreated (98 patients). This control group was composed of patients in whom OSAHS had been diagnosed between 1982 and 1987, when CPAP was not readily available. The authors reported that survival rates were significantly lower in nontreated patients than in CPAP patients (5-year survival rate, 80% vs 97%, respectively). Our study showed a survival rate of 96.4% at 5 years in the group of patients with compliance of >6 h/d, which was very similar to that of Marti et al,[13] and also showed significantly higher survival in this group compared with patients who did not use PAP. We have also found that the level of compliance affects survival in a linear trend, and that this relationship between mortality and compliance is independent of other variables.

The main cause of death was CVD, accounting for 41.3% of all deaths. It must be emphasized that despite the theoretical beneficial effects of PAP on cardiovascular morbidity,[19,26–29] CVD remains the most prevalent cause of death in OSAHS patients, irrespective of whether patients receive treatment with PAP or not.[10–12,20,21] This may be explained by the numerous cardiovascular risk factors present in the OSAHS population,[30] some of which cannot be

improved with PAP therapy (*ie*, smoking, hyperlipidemia, and obesity). Thus, this therapy could influence some but not all of these cardiovascular risk factors, and these would still predispose patients to CVD. The second cause of death was neoplastic disease, which has been reported in previous studies.[12,20,21] Up to now, OSAHS has not been proven to be a predisposing factor for neoplasia, so these deaths do not seem to be directly attributable to the sleep disorder. However, the high prevalence of smokers in our sample (67% were smokers or ex-smokers) with a mean consumption of 49.9 ± 33.4 packs/year, which is much higher than that in the general population,[31] suggests that 7 of the 16 neoplasias (lung cancer, six patients; and mouth cancer, one patient) were directly related to tobacco use.

Variables that independently correlated with mortality in the Cox multivariate analysis were as follows: categories of PAP compliance; AHT; FEV_1 percent predicted; and age. It is of interest to note that OSAHS severity was not associated with mortality, neither when there was an apnea-hypopnea threshold of 30 events/h (recent consensus)[24] nor when 55 events/h (the average AHI of our sample) was used to define severity. Furthermore, none of the other OSAHS severity criteria that were analyzed, such as AHI, Sao_2m, or $Sao_2 < 90\%$, were included in the final equation, suggesting that, if adequately treated, OSAHS severity is not a risk factor for mortality. AHT has been an independent risk factor for death in some studies that included untreated OSAHS patients, but not in those dealing with patients receiving CPAP therapy.[12,13,20,21] In our study, AHT was a strong predictor of mortality, and those patients in whom this condition was associated with OSAHS had significantly lower cumulative survival rates than those without this comorbidity. Some epidemiologic studies[3,4] have identified OSAHS as an independent risk factor for the development of AHT, and, although CPAP therapy is expected to reduce BP levels, few adequately designed studies[18,19,32,33] have been carried out to support this theory. Therefore, we still know little about the long-term evolution of hypertension in OSAHS patients, particularly in those with refractory or badly controlled AHT, and those in whom the diagnosis and initiation of PAP therapy was delayed to a point at which vascular damage was no longer reversible. It is possible that in these patients the expected effect on cardiovascular morbidity and mortality would be small. Finally, a point we did not assess, but that could have influenced their mortality, is whether these patients were undergoing appropriate drug treatment for AHT and were in compliance with that treatment.

The other factor that significantly correlated with mortality was FEV1 percent predicted. This variable has been previously reported as an independent predictor of death in the studies of Veale et al[20] and Chaouat et al.[21] In our study, low FEV_1 percent predicted was mainly due to COPD and probably reflects that the degree of functional impairment was more important than the dichotomous variable COPD (which implies a wide range of severity) as a predictor of death. In our study, the cumulative survival rates in OSAHS patients with COPD were significantly lower than those of the group without this respiratory disease, a fact that has been previously reported by other authors.[21] The association of these two conditions, the so-called *overlap syndrome*, is not uncommon and in untreated cases is known to make a major contribution in the progression toward chronic respiratory failure and cor pulmonale.[34] Furthermore, the presence of coexisting lung disease was a predictor of death in a study involving patients with untreated OSAHS.[12]

In conclusion, this study shows a significant association between 5-year survival and increasing adherence with PAP treatment in patients with OSAHS that is independent of other covariates. CVD was the main cause of death, and PAP use groups, AHT, and FEV_1 percent predicted were the variables that best predicted death before the start of treatment.

ACKNOWLEDGMENT: The authors thank Dr. Carmen Almeida-Gonzalez for their assistance in the statistical analysis.

References

1 Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-age adults. N Engl J Med 1993; 328:1230–1235
2 Durán J, Esnaola S, Rubio R, et al. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 years. Am J Respir Crit Care Med 2001; 163:685–689
3 Nieto FJ, Young TB, Lind BK, et al. Association of sleep disordered breathing, sleep apnea, and hypertension in a large community based study: Sleep Heart Health Study. JAMA 2000; 283:1829–1836
4 Peppard PE, Young T, Palta M, et al. Prospective study of the association between sleep disordered breathing and hypertension. N Engl J Med 2000; 342:1378–1384
5 Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001; 163:19–25
6 Mooe T, Rabben T, Wiklund U, et al. Sleep-disordered breathing in men with coronary artery disease. Chest 1996; 109:659–663
7 Parra O, Arboix A, Bechich S, et al. Time course of sleep-related breathing disorders in first-ever stroke or transient ischemic attack. Am J Respir Crit Care Med 2000; 161:375–380
8 Masa JF, Rubio M, Findley LF. Habitually sleepy drivers have a high frequency of automobile crashes associated with

respiratory disorders during sleep. Am J Respir Crit Care Med 2000; 162:1407–1412
9 Finn L, Young TB, Palta M, et al. Sleep-disordered breathing and self-reported general health status in the Wisconsin Sleep Cohort Study. Sleep 1998; 21:701–706
10 He J, Kryger MH, Zorick FJ, et al. Mortality and apnea index in obstructive sleep apnea: experience in 385 male patients. Chest 1988; 94:9–14
11 Partinen M, Jamieson A, Guilleminault C. Long-term outcome for obstructive sleep apnea syndrome patients: mortality. Chest 1998; 94:1200–1204
12 Lavie P, Herer P, Peled R, et al. Mortality in sleep apnea patients: a multivariate analysis of risk factors. Sleep 1995; 18:149–157
13 Marti S, Sampol G, Muñoz X, et al. Mortality in severe sleep apnoea/hypopnoea syndrome patients: impact of treatment. Eur Respir J 2002; 20:1511–1518
14 Sullivan CE, Issa FG, Berthon-Jones M, et al. Reversal of obstructive sleep apnoea by continuous positive airways pressure applied through the nares. Lancet 1981; 1:862–865
15 Jenkinson C, Davies RJO, Mullins R, et al. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomized prospective parallel trial. Lancet 1999; 353:2100–2105
16 Montserrat JM, Ferrer M, Hernandez L, et al. Effectiveness of CPAP therapy on daytime function in sleep apnea syndrome: a randomized controlled study with an optimized placebo. Am J Respir Crit Care Med 2001; 164:608–613
17 Findley LJ, Smith C, Hooper J, et al. Treatment with nasal CPAP decreases automobile accidents in patients with sleep apnea. Am J Respir Crit Care Med 2000; 161:857–859
18 Faccenda JF, Mackay TW, Boon NA, et al. Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. Am J Respir Crit Care Med 2001; 163:344–348
19 Pepperell JCT, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomized parallel trial. Lancet 2001; 359:204–210
20 Veale D, Chailleux E, Hoorelbeke-Ramon A, et al. Mortality of sleep apnoea patients treated by nasal continuous positive airway pressure registered in the ANTADIR observatory. Eur Respir J 2000; 15:326–331
21 Chaouat A, Weitzenblum E, Krieger J, et al. Prognostic value of lung function and pulmonary haemodynamics in OSA patients treated with CPAP. Eur Respir J 1999; 13:1091–1096
22 Carrasco O, Montserrat JM, Lloberes P, et al. Visual and different automatic scoring profiles of respiratory variables in the diagnosis of sleep apnoea-hypopnoea syndrome. Eur Respir J 1996; 9:125–130
23 Duran J, Esnaola S, Rubio R, et al. Estimación de la validez diagnóstica del sistema portátil Apnoscreen II en el diagnóstico del síndrome de apnea obstructiva durante el sueño. Arch Bronconeumol 1996; 32(suppl):3
24 American Academy of Sleep Medicine. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research; the report of an American Academy of Sleep Medicine Task Force. Sleep 1999; 22:667–689
25 Lindberg E, Janson C, Svardsudd K, et al. Increased mortality among sleepy snorers: a prospective population based study. Thorax 1998; 53:631–637
26 Somers VK, Dyken ME, Clary MP, et al. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995; 96:1897–1904
27 Malone S, Liu PP, Holloway R, et al. Obstructive sleep apnoea in patients with dilated cardiomyopathy: effects of continuous positive airway pressure. Lancet 1991; 338:1480–1484
28 Naughton MT, Benard DC, Liu PP, et al. Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. Am J Respir Crit Care Med 1995; 152:473–479
29 Logan AG, Tkacova R, Perlikowsky SM, et al. Refractory hypertension and sleep apnoea: effect of CPAP on blood pressure and baroreflex. Eur Respir J 2003; 21:241–247
30 Kiely JL, McNicholas WT. Cardiovascular risk factors in patients with obstructive sleep apnoea syndrome. Eur Respir J 2000; 16:128–133
31 Ministerio de Sanidad y Consumo. Encuesta Nacional de Salud de España, 1997. Madrid, Spain: Ministerio de Sanidad y Consumo, 1997
32 Dimsdale JE, Loredo JS, Profant J. Effect of continuous positive airway pressure on blood pressure. Hypertension 2000; 35:144–147
33 Becker HF, Jerrentrup A, Ploch T, et al. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. Circulation 2003; 107:68–73
34 Chaouat A, Weitzenblum E, Krieger J, et al. Association of chronic obstructive pulmonary disease and sleep apnea syndrome. Am J Respir Crit Care Med 1995; 151:82–86

Mortality in Obstructive Sleep Apnea-Hypopnea Patients Treated With Positive Airway Pressure

Francisco Campos-Rodriguez, Nicolas Peña-Griñan, Nuria Reyes-Nuñez, Ines De la Cruz-Moron, Jose Perez-Ronchel, Francisco De la Vega-Gallardo and Ana Fernandez-Palacin

Chest 2005;128;624-633
DOI 10.1378/chest.128.2.624