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Original Article

Acute Hypercapnic Respiratory Failure in Patients with Sleep Apneas

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ABSTRACT

Introduction: Acute hypercapnic respiratory failure (AHRF) is a serious condition observed in some patients with sleep apnea-hypopnea syndrome (SAHS). The objective of the present study was to study the clinical characteristics of SAHS patients who develop AHRF and their prognosis.
Patients and method: A total of 70 consecutive SAHS patients who survived an AHRF episode and 70 SAHS patients paired by age with no previous history of AHRF were prospectively studied and followed up for 3 years.
Results: The deterioration of lung function due to obesity or concomitant chronic obstructive pulmonary diseases (COPD) was common in SAHS patients with AHRF. In the multivariate analysis, the risk factors associated with AHRF were baseline PaO_2, the theoretical percentage value of the forced vital capacity, alcohol consumption, and benzodiazepines. The mortality during follow up was higher among patients who had AHRF than in the control group. The main cause of death was respiratory, and the coexistence of COPD was identified as a mortality risk factor.
Conclusions: The development of AHRF in SAHS patients is associated with a deterioration in lung function and with alcohol and benzodiazepine consumption. The patients had a higher mortality after the AHRF episode, mainly a respiratory cause. New studies are required that evaluate the different available therapeutic options in these patients.

Insuficiencia respiratoria hipercápnica aguda en pacientes con apneas del sueño

Palabras clave:
Apneas del sueño
Insuficiencia respiratoria
Hipercapnia
Sueño
Enfermedad pulmonar obstructiva crónica

RESUMEN

Introducción: La insuficiencia respiratoria hipercápnica aguda (IRHA) es una situación grave observada en algunos pacientes con síndrome de apneas-hipopneas del sueño (SAHS). El objetivo del presente estudio fue determinar las características clínicas de los pacientes con SAHS involucradas en el desarrollo de la IRHA y su pronóstico.
Pacientes y método: Setenta pacientes con SAHS consecutivos que sobrevivieron un episodio de IRHA y 70 pacientes con SAHS apareados por edad sin antecedentes previos de IRHA fueron estudiados y seguidos de forma prospectiva durante 3 años.
Resultados: El deterioro de la función pulmonar debido a la obesidad o a la coexistencia de enfermedad pulmonar obstructiva crónica fue frecuente en los pacientes con SAHS con IRHA. En el análisis multivariante, los factores de riesgo asociados con IRHA fueron la PaO_2 basal, el porcentaje del valor teórico de la capacidad vital forzada y el consumo de alcohol y de benzodiacepinas. La mortalidad durante el seguimiento fue superior entre los pacientes que habían presentado IRHA respecto al grupo control. La principal causa de muerte fue la respiratoria, y la coexistencia de enfermedad pulmonar obstructiva crónica se identificó como un factor de riesgo de mortalidad.

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Conclusiones: El desarrollo de IRHA en pacientes con SAHS se asocia con la presencia de deterioro de la función pulmonar y con el consumo de alcohol y benzodiacepinas. Después del episodio de IRHA los pacientes presentaron una mortalidad elevada, principalmente de causa respiratoria. Se precisan nuevos estudios que evalúen las distintas alternativas terapéuticas disponibles en estos pacientes.

Introduction

Sleep apnoea-hypopnoea syndrome (SAHS) was initially described in patients with Pickwickian syndrome, now known as obesity-hypoventilation syndrome, and is characterised by the coexistence of obesity, somnolence, and hypercapnia.[1] We now know that SAHS is not present in all patients with obesity-hypoventilation syndrome and, moreover, that only a minority of patients with SAHS develop daytime hypercapnia. Although the mechanisms involved are not well understood, classical studies showed the relationship between the presence of hypercapnia in patients with stable SAHS and coexistent morbid obesity or chronic obstructive pulmonary disease (COPD).[2,3] These findings have been confirmed by more recent studies.[4-6] However, the clinical features involved in the development of acute hypercapnic respiratory failure (AHRF) in SAHS, a common emergency situation in the practice of pulmonology, have not been studied. We only have descriptions of individual cases or small studies focused on treatment during AHRF episodes.[7-11] In an attempt to determine the clinical characteristics of patients with SAHS who develop AHRF and their long-term prognosis, we prospectively studied and followed a group of SAHS patients for 3 years who had been admitted for an episode of AHRF and compared them with a group of age-matched patients with SAHS without a history of AHRF.

Method

Patients

All patients admitted for an episode of AHRF, defined as the presence of a carbon dioxide partial pressure ($PaCO_2$) greater than 45 mmHg and an arterial pH below 7.35, and diagnosed with SAHS in our department over a period 2 years were prospectively included in this study. A control group of 70 age-matched patients (± 5 years) with no history of AHRF was selected from among the population of patients diagnosed with SAHS in our sleep unit. After identifying a patient with SAHS with AHRF, we selected the next consecutively diagnosed patient with SAHS from our unit who met the inclusion and exclusion criteria in order to obtain the control group patients. Exclusion criteria were the presence of neuromuscular or chest wall disease, previous diagnosis of SAHS, asthma, bronchiectasis, pneumonia, diffuse interstitial lung disease, advanced neoplasia that could compromise short-term survival, lung transplantation, or inability to complete a sleep study due to clinical instability. The ethics committee of our hospital approved the study and patients gave their informed consent.

Procedures

Upon arrival in the emergency department, all patients had an arterial blood gas on room air or, in those who were started on oxygen in the ambulance during transport to hospital, on FiO_2 of 24 or 28% via a Ventimask, a chest x-ray, an electrocardiography (ECG), and a venous blood sample. Initial treatment was decided by the emergency department personnel or by the pulmonologist on call. After admission to the pulmonology department, treatment was determined by the assigned pulmonologist. The pulmonology department has a pulmonologist on call daily and maintains the sleep disordered breathing and noninvasive ventilation (NIV) programs in our hospital. For these reasons, patients in the emergency department who are candidates for NIV or for whom there is a clinical suspicion of sleep-disordered breathing are preferentially admitted to our service. Patients admitted to other services were not included in the study.

After admission, all patients with AHRF were entered into a database by one of the authors. Then those without exclusion criteria and their families were asked about the presence of somnolence, as assessed by the Epworth Sleepiness Scale (ESS)[12] and the criteria set forth by the American Academy of Sleep Medicine.[13] Furthermore, they were asked about the presence of snoring, observed apnoeic episodes, and the sensation of non-refreshing sleep. Possible responses were rated as follows: never or rarely = 0, sometimes = 1, often or always = 2. A total value for each patient was obtained by adding the scores from the three questions. In order to identify patients with SAHS, polysomnography was performed on those patients with at least one of the following characteristics: a) body mass index (BMI) greater than 25 kg/m^2, b) greater than 9 and/or mild or higher sleepiness according to the criteria of the American Academy of Sleep Medicine, and c) symptom scale total value greater than 0.

Information was collected from patients and their families about alcohol consumption, treatment with sedatives and smoking history. Patients were informed that alcoholic beverages include any type of alcohol-containing drink, including beer, wine, liquor, and long drinks. Patients were asked the type, number, and size consumed in a typical week during the past 12 months. Alcohol intake was quantified by multiplying the consumption of each type of beverage alcohol by their alcohol content. Furthermore, patients who reported alcohol consumption were asked about the frequency of consumption, and those who reported consumption that was frequent (> 4 days/week) or at night (with dinner or after 9:00 pm) were considered nocturnal drinkers. Pulmonary heart disease was diagnosed in patients with clinical signs of right heart failure and/or ventricular hypertrophy or right atrial enlargement on the electrocardiogram. To reduce the influence of fluid retention, BMI was calculated at the end of the hospital stay. Comorbidities were assessed by the Charlson Index.[14]

Spirometry and arterial blood gas measurements on room air were performed in the last 24 hours of admission. The diagnosis of COPD was established by clinical assessment and spirometry (forced expiratory volume in one second [FEV_1] < 80% of predicted value and FEV_1/Forced Vital Capacity [FVC] < 70%).

Polysomnography was performed in the last 48 hours of admission with clinically stable patients, without mechanical ventilation requirements for more than four days, with good nighttime sleep without wakenings due to dyspnoea, and who were able to ambulate. Polysomnography (Compumedics E Series®, Abbotsford, Australia) included recordings of oronasal flow (thermistor), thoracic and

abdominal movement, electrocardiogram, submental electromyogram, bilateral electrooculogram, electroencephalogram (C4-A1, O3-A2), arterial oxygen saturation, position, leg movements and snoring. All sleep studies were reviewed manually by an expert reader. Apnoea was defined as cessation of airflow of 10 or more seconds. Central and obstructive apnoeas were differentiated based on the presence or absence of thoracoabdominal movements. Hypopnoea was defined as more than 50% reduction in the airflow signal accompanied by cyclical desaturation greater than or equal to 4%. The apnoea-hypopnoea index (per sleep hour) (AHI) was calculated by dividing the sum of apnoeas and hypopnoeas by the total sleep time. An AHI of 10 or more per hour was considered indicative of SAHS. Patients with AHI of 30 or more per hour with somnolence underwent a nasal CPAP study with conventional polysomnography, which determined the pressure required to abolish apnoeas, hypopnoeas, snoring, and desaturations.

Treatment

Patients with SAHS were treated with nasal CPAP if they had an AHI higher than 30 per hour or significant sleepiness (ESS > 10). In patients with SAHS admitted due to AHRF and $PaCO_2$ greater than 55 at the time of discharge, nasal CPAP was replaced with NIV. Supplemental oxygen was added to nasal CPAP or NIV if the average SaO_2 during sleep with these interventions remained less than 88%. Furthermore, patients were provided with a written list of general rules for the treatment of SAHS, including recommendations for weight loss and avoidance of alcohol and sedative medications. For patients on nasal CPAP who required readmission for new episodes of AHRF or who had $PaCO_2$ greater than 50 mmHg during follow-up, CPAP was replaced with NIV.

Follow-up

Patients were seen one month after discharge or after diagnosis in the case of the control group, and spirometry and arterial blood gas analyses were repeated. Then, they were seen every 6 months over the course of 3 years. Compliance with nasal CPAP or NIV was quantified by the device's hour counter. Patients who did not come to follow-up were called by telephone and asked to come to the centre at least for the annual visit required by our health system for respiratory therapy monitoring. The vital status of patients lost to follow-up was established with the Catalan Health Service database and, in the case of a patient's death, the cause of death was researched through review of the medical record and/or through telephone contact with the family.

Statistical Analysis

Results are expressed as mean ± SD for quantitative variables and as frequencies and percentages for qualitative variables. Comparisons between groups were performed using Student's t test for paired or unpaired samples in quantitative variables, whereas in the case of qualitative variables a chi-squared test or Fisher's test was utilised. Survival curves for the two groups of patients with SAHS, with and without AHRF, were estimated using the Kaplan-Meier method and compared by log-rank test. Analysis of risk factors associated with the development of AHRF and mortality during follow-up was performed using logistic regression and Cox regression models, respectively. Selection of independent variables for multivariate analysis was based on the statistical significance obtained in the bivariate analysis ($p < 0.10$) or on their biological plausibility. We used a progressive selection procedure *(forward stepwise)* and the results were expressed as *odds ratio* or *hazard ratio* with a 95% confidence interval. All tests were performed using SPSS software, version 12 (SPSS Inc., Chicago, IL). Statistical significance was set at a p value < 0.05.

Results

201 patients were admitted with AHRF during the study period. Patient selection is shown in figure 1.

SAHS was diagnosed in 70 patients, 49 (70%) required admission due to respiratory illness in the last 3 years. These readmissions were more frequent in patients with associated COPD (28/32 in patients with COPD versus 21/38 in patients without COPD, $p < 0.05$). Arterial blood gas values at admission were: pH 7.29 (0.07), PaO_2/FiO_2 of 206 (34) mmHg and $PaCO_2$ of 72.8 (16.6) mmHg. Fifty-one patients (73%) required mechanical ventilation (45 invasive and 6 noninvasive) for 4.6 days (5.8), while the remaining 19 (27%) were initially treated in the emergency department and later on in the pulmonology unit with oxygen along with other medical treatment and did not require mechanical ventilation. The average hospital stay was 15.5 days (8.3). At discharge, 51 patients (73%) had $PaCO_2$ above 45 mmHg.

Compared with the control group (table 1 and 2), patients with SAHS with AHRF were more obese and had increased somnolence and comorbidity, consumed more tobacco and alcohol, had more frequent nocturnal alcohol consumption, more commonly had associated COPD, increased worsening of spirometric values, and more severe SAHS. Logistic regression analysis included the following variables: sex, BMI, alcohol consumption (g/day), nocturnal alcohol intake, the Charlson Index, use of sedatives, baseline PaO_2 and $PaCO_2$, the presence of COPD, FVC (percentage of predicted value) and AHI. As detailed in table 3, significant predictors of development of AHRF in the multivariate analysis were alcohol consumption, use of sedatives, baseline PaO_2 and FVC.

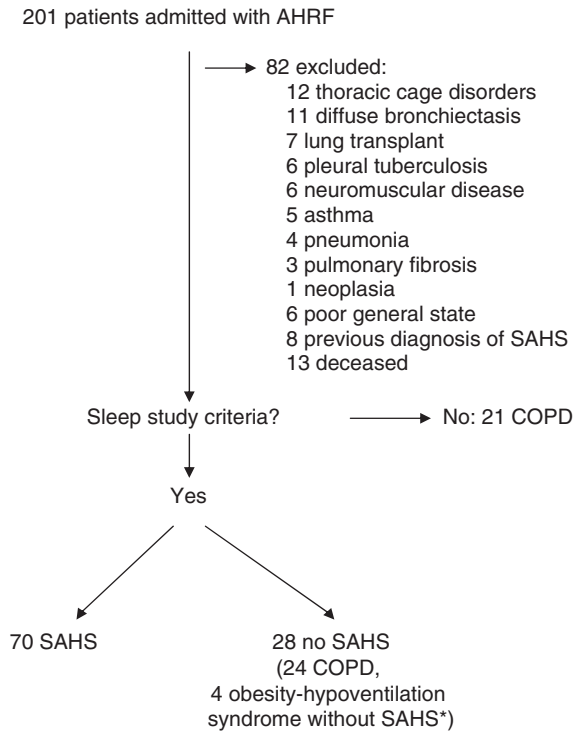

Figure 1. Patient selection. AHRF indicates acute hypercapnic respiratory failure; COPD, chronic obstructive pulmonary diseases; SAHS, sleep apnea-hypopnea syndrome. *Patients with BMI > 30 kg/m², hypercapnia, and AHI < 10.

Table 1
Characteristics of patients with sleep apnoea-hypopnoea syndrome

	AHRF group	Control group	p
n	70	70	
Age, years	64.1 (11.5)	63.9 (15.2)	ns
Sex, women/men	27 (39)/43 (61)	19 (27)/51 (73)	ns
BMI, kg/m^2	37.0 (7.7)	32.9 (5.1)	< 0.001
ESS	13.7 (3.1)	10.6 (4.0)	< 0.001
Charlson index 0	15 (21)	30 (43)	< 0.005
Charlson index 1	27 (39)	28 (40)	
Charlson index > 1	28 (40)	12 (17)	
Tobacco use packs/year	36.0 (30.1)	21.3 (26.2)	< 0.005
Current alcohol drinkers	34 (49)	28 (40)	ns
Alcohol consumption, g/day	28.4 (38.7)	9 (14.0)	< 0.001
Nocturnal alcohol consumption	32 (46)	12 (17)	< 0.001
Benzodiazepine use[a]	14 (20)	8 (11)	ns
FVC, percentage of predicted value	56.0 (12.0)[b]	75.0 (16.9)	< 0.001
FEV_1, percentage of predicted value	54.1 (16.2)[b]	80.9 (20.4)	< 0.001
FEV_1/FVC, %	71.1 (14.7)[b]	81.0 (8.5)	< 0.001
Arterial blood PaO_2, mmHg	64.2 (7.1)[b]	79.7 (8.2)	< 0.001
Arterial blood $PaCO_2$, mmHg	46.6 (4.3)[b]	40.7 (4.2)	< 0.001
COPD	32 (46)	8 (11)	< 0.001

AHRF indicates acute hypercapnic respiratory failure; BMI, body mass index; COPD, chronic obstruction pulmonary disease; ESS, epworth sleepiness scale; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity; ns, not significant; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; SD, standard deviation.
The data are presented in n (%) or mean (SD).
[a] Number of patients with daily benzodiazepine consumption.
[b] Values obtained 1 month after hospital discharge.

Table 2
Polysomnographic characteristics of patients with sleep apnoea-hypopnoea syndrome

	AHRF group	Control group	p
Sleep effectiveness%	71.4 (14.3)	75.0 (10.0)	ns
NREM 1+2, % TTS	76.6 (16.6)	73.7 (11.4)	ns
NREM 3+4, % TTS	10.5 (10.2)	13.7 (8.2)	< 0.05
REM, % TTS	12.9 (8.4)	12.7 (7.0)	ns
Apnoea index, n/h	36.3 (20.4)	23.9 (17.5)	< 0.001
AHI, n/h	65.3 (23.3)	48.9 (22.3)	< 0.001
AHI: < 30/h	4 (6)	19 (27)	< 0.001
AHI: ≥ 30/h	66 (94)	51 (73)	
Mean SaO_2, %	83.6 (5.2)	91.8 (3.4)	< 0.001
Minimum SaO_2, %	61.1 (8.5)	73.5 (10.7)	< 0.001
CT90,%	77.1 (22.8)	20.2 (25.2)	< 0.001

Data are presented as n (%) or mean (SD). AHI, apnoea-hypopnoea/hour sleep index; AHRF, acute hypercapnic respiratory failure; CT90, percentage of sleep time with oxygen saturation below 90%; NREM 1+2, stage 1 and 2 non-REM sleep; NREM 3+4, stage 3 and 4 non-REM sleep; ns, not significant; SaO_2; arterial oxygen saturation; SD, standard deviation.

Compared with 45 patients with "pure" COPD admitted for AHRF, patients with SAHS and COPD were of similar age (66.0 [9.7] versus 69.0 years [10.1], p not significant), but had a higher BMI (32.7 [4.8] versus 25.5 kg/m^2 [5.3], p < 0.001) and less obstruction on spirometry (FEV_1 43.1 [10.9] versus 31.3% of predicted [12], p < 0.005).

Nasal CPAP was prescribed on discharge to 54 of the 70 SAHS patients admitted with AHRF, 19 of whom were also prescribed supplemental oxygen. Twelve patients were treated with home NIV (8 with a bilevel pressure ventilator and 4 with a volume ventilator) and 6 of them with supplemental oxygen. The remaining 4 patients refused this treatment. In the 65 surviving patients after 1 year follow up, the PaO_2 had significantly improved compared with discharge (61.5 [9.0] versus 66.8 [10.0], p < 0.001), while the $PaCO_2$ had decreased (49.2 [6.3] versus 46.3 [8.2], p < 0.005). Forty-seven of these 65 patients had a $PaCO_2$ greater than 45 at discharge and 24 of them remained hypercapnic at the one-year follow-up (p < 0.001). In the control group, nasal CPAP was prescribed for 60 patients (85%), and 51 of them were still using this treatment at the end of follow-up.

Compared with the previous three years, the AHRF group required fewer admissions during follow-up after SAHS diagnosis and the initiation of treatment (27 versus 49, p < 0.01). In 7 patients in this group, nasal CPAP treatment was changed to NIV during follow-up, in 5 patients due to new hospitalisations for AHRF and in 2 patients due to persistently elevated $PaCO_2$ greater than 50 mmHg.

Twenty-one patients with SAHS died during follow-up and mortality was higher among patients with AHRF (fig. 2). The causes of death were respiratory in 10 patients, cardiovascular in 7 patients, neoplasia in 3 patients (1 cavum, 1 colon, 1 lung) and pancreatitis in 1 patient. The characteristics of the patients who died during the follow-up who had AHRF compared with the survivors of that group are shown in table 4. Compared with surviving patients, patients who died were more often treated with CPAP and showed worse compliance with this treatment, with a greater number of patients with a compliance of less than 4 h/day (8/15 versus 7/32 among survivors; p < 0.05).

A Cox regression model was constructed that included the variables of age, comorbidity, FVC (percent predicted), presence of COPD, and treatment at the end of follow up. In multivariate analysis only the presence of COPD was independently associated with increased mortality *(hazard ratio* [95% confidence interval]: 3.9 [2.4 to 9.9], p < 0.02).

Discussion

In a group of patients with predominantly serious SAHS, we have found that the development of AHRF is associated with the presence of lung function impairment and the consumption of alcohol and benzodiazepines. During the follow-up period after diagnosis of SAHS and treatment, the patients required fewer hospital admissions for respiratory illness, but had high mortality. The combination of SAHS and COPD was identified as a risk factor associated with this mortality.

The main factors associated with lung function deterioration in our patients were obesity and the presence of COPD. These findings are consistent with previous observations in patients with stable

Table 3
Predisposing factors for acute hypercapnic respiratory failure by logistic regression analysis

	OR	95% confidence interval	p
Alcohol[a]	1.54	1.23-1.85	< 0.005
Benzodiazepines[b]	7.47	1.45-38.57	< 0.02
Arterial blood PaO_2	0.82	0.77-0.91	< 0.001
FVC, percentage of predicted	0.95	0.91-0.99	< 0.02

FVC indicates forced vital capacity; OR, odds ratio; PaO_2, partial pressure of oxygen.
[a] OR associated with alcohol consumption expressed in increments of 10 g/day.
[b] Daily use of benzodiazepines.

hypercapnic SAHS in which, as in our case, CO_2 retention was associated with a high BMI and hypoxaemia while awake, and increasingly so at night.[2-6,16] However, our results provide the first description of this in patients with AHRF and have several differences compared with those for stable patients. It is known that patients with the same degree of obesity may have very different effects on lung function.[15] Thus, our non-COPD patients with SAHS who were admitted with AHRF had a mean BMI of 41 kg/m^2, similar to that found on a recent review of medical literature in patients with obesity-hypoventilation syndrome.[16] In contrast, our patients had an average FVC of 58% of predicted value, lower than what is usually found in patients with obesity-hypoventilation syndrome.[16] Similarly, our patients with SAHS and associated COPD admitted for AHRF had more severe bronchial obstruction than that found in patients with both diseases in the control group and in clinical series of patients with SAHS[4,17] and in studies of the general population.[18] These findings suggest that AHRF is a complication of SAHS that affects patients with a particularly pronounced decline in pulmonary function.

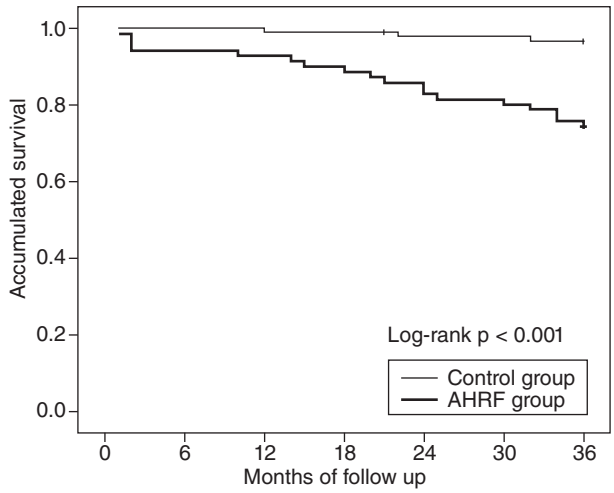

Figure 2. Kaplan-Meier survival curves for patients with sleep apnoea-hypopnoea syndrome after an episode of acute hypercapnic respiratory failure compared with patients with sleep apnoea-hypopnoea syndrome sleep with no history of acute hypercapnic respiratory failure. AHRF indicates acute hypercapnic respiratory failure.

Meanwhile, our patients with SAHS and COPD who were admitted with AHRF had less severe bronchial obstruction than that observed in patients with isolated COPD with AHRF in our series and in previous studies.[19,20] For patients with severe COPD and SAHS, Machado et al[21] recently showed that not treating SAHS is associated with higher mortality, mainly due to respiratory failure. Furthermore, Marín et al,[22] in a large prospective study of patients with COPD, showed that the coexistence of SAHS is associated with increased mortality and the number of hospitalisations for COPD exacerbation. All these findings suggest that the coexistence of SAHS promotes the development of AHRF in patients with COPD.

Furthermore, we found that chronic consumption of alcohol and/or benzodiazepines is associated with the development of AHRF. Severe alcohol consumption has been associated with the presence of hypercapnia in patients with SAHS and COPD independently of the degree of bronchial obstruction.[23] It is known that alcohol reduces nerve impulses to the motor neurons of the upper airway and increases the severity of SAHS.[24] However, previous studies in patients with stable SAHS did not relate the severity of SAHS with the development of hypercapnia,[2,3,6] pointing to other mechanisms by which alcohol might lead to the development of hypercapnia. Decreased chemoreceptor activity has also been suggested as a cause of hypercapnia in patients with SAHS,[25] and animal studies have described decreased sensitivity to alcohol-induced hypercapnia,[26] but these findings have not been confirmed in humans.[27] As an alternative mechanism, Ayappa et al showed that the development of hypercapnia is determined by the shortening of the interapnoea period.[28] This period is increased by opiate receptor blockade[29] and, based on this fact to explain our findings, we speculate that the blockade could be shortened due to the stimulation of these receptors caused by the release of endogenous opioids associated with alcohol consumption.[30]

We detected very high benzodiazepine use in our patients, more than four times that reported in our general population.[31] It is known that sedative medication should be used with caution in patients with lung disease to prevent respiratory control centre depression. Furthermore, these agents have been shown to decrease muscle tone in the upper airway and decrease wakening reactions induced by hypercapnia[32] and airway occlusion,[33] and their use is generally contraindicated in the clinical management of patients with SAHS. However, there is limited data with contradictory results on the clinical effects of benzodiazepines in patients with SAHS, with initial

Table 4
Characteristics of patients with sleep apnoea-hypopnoea syndrome presenting with acute hypercapnic respiratory failure based on their vital status at the end of follow-up

	Deceased (n: 18)	Living (n: 52)	p
Age, years	67.1 (7.9)	63.1 (12.4)	ns
Sex, women/men	5/13	22/30	ns
BMI, kg/m^2	33.4 (5.1)	38.3 (8.1)	< 0.02
Charlson index 0	3	12	ns
Charlson index 1	4	23	
Charlson index > 1	11	17	
FVC, percentage of predicted value	47.17 (9.6)	55.0 (13.8)	< 0.03
FEV_1, percentage of predicted value	40.9 (14.8)	56.2 (17.6)	< 0.005
COPD	13	19	< 0.02
AHI, n/hour	54.4 (18.6)	69.1 (23.7)	0.02
Pulmonary heart disease	9	24	ns
CPAP treatment[a]	15	32	< 0.05
NIV	1	18	
Untreated	2	2	

AHI indicates apnoea-hypopnoea index per hour of sleep; BMI, body mass index; COPD, chronic obstruction pulmonary disease; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity; ns, not significant; NIV, non-invasive mechanical ventilation; SD, standard deviation.
Data are presented as n or mean (SD).
[a] Treatment at the end of follow-up.

studies reporting adverse effects[32] that have not been subsequently confirmed.[33] Our findings provide the first description that chronic use of benzodiazepines in patients with SAHS is a risk factor for the development of AHRF, suggesting the need for alternative methods of handling complaints of poor sleep quality and/or anxiety in these patients.

Patients with SAHS and AHRF in our series showed higher mortality compared with the control group during follow-up and, in contrast to the deaths of predominantly cardiovascular origin previously reported in patients with SAHS,[34-36] we found that the main cause of death in our patients was respiratory. These findings suggest that patients with SAHS who have an episode of AHRF, although they constitute a minority of patients with SAHS who are generally evaluated for sleep respiratory pathology, are a subgroup with specific clinical features and increased mortality. Previous studies have reported that the coexistence of respiratory disease is a risk factor for mortality in patients with SAHS,[34,37-39] and mortality in our patients after hospital discharge was higher among patients who had SAHS with associated COPD. We observed a reduction in the number of hospitalisations for respiratory illness during the follow-up period compared with the previous three years as well as improved arterial blood gases. This suggests that SAHS treatment is beneficial. Furthermore, lower mortality was observed in patients treated with NIV compared to patients treated with CPAP and lower adherence to CPAP treatment in patients who died during the follow-up. However, our study was not designed to evaluate different treatment options and decisions about its initiation were made in accordance with our clinical practice during the study period. Further studies are needed focusing on the treatment of these patients with randomisation to the different therapeutic options.

Several limitations of our study should be considered. Firstly, we only matched the group with AHRF and SAHS and the control group by age. However, the absence of previous descriptions of the clinical features involved in the development of AHRF in SAHS led us to believe that this is a valid initial approach to explore a wide range of biologically plausible variables. Secondly, there is a selection bias in our work and SAHS patients are over-represented with respect to all patients with AHRF admitted to a tertiary care hospital. However, this fact does not materially affect the objectives of the study which were to define the clinical characteristics and prognosis of patients with SAHS and AHRF. Thirdly, we did not perform polysomnography on all patients admitted with AHRF, and some patients with SAHS may have theoretically been overlooked. On the other hand, we believe that the criteria we used to determine the need for polysomnography were highly sensitive for detection of SAHS. Lastly, although our patients with SAHS and AHRF had a higher AHI, the fact that the control group had a higher AHI also may have limited our ability to identify the severity of SAHS as a factor relating to the development of AHRF.

In summary, we found that the presence of deteriorating lung function in relation to obesity or COPD and the consumption of alcohol and benzodiazepines are associated with the development of AHRF in patients with SAHS and that these patients represent a subgroup of SAHS patients with high mortality, mainly due to respiratory causes. Our findings stress the need for early detection of these risk factors and the need for studies focusing on the evaluation of different therapeutic alternatives.

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