

# The Heart, Sleep, and Respiration

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Sleep apnea-hypopnea syndrome (SAHS) consists of recurrent episodes in which the airflow becomes limited during sleep, a consequence of anatomic-functional abnormalities of the upper airway (UA) that lead to its collapse. This leads to a reduction in oxyhemoglobin saturation (SaO<sub>2</sub>) and causes arousals from sleep. The symptoms of this syndrome include the sensation of not having been refreshed by sleep, excessive daytime sleepiness (EDS), and neuropsychiatric, respiratory and heart problems.

Epidemiological studies performed in the USA and Europe have shown that SAHS is a very prevalent disorder affecting 4%-6% of men and 2%-4% of women in the general, middle-aged adult population.<sup>1,2</sup> This prevalence, however, increases with age. It has been shown that SAHS is associated with a deterioration in quality of life, high blood pressure,<sup>3,4</sup> the development of cardiovascular and cerebrovascular disease,<sup>5</sup> and even with traffic accidents.<sup>6,7</sup> SAHS is therefore associated with excess mortality.<sup>8,9</sup>

The pathophysiology of SAHS is complex and still poorly understood. The stability of the bore of the UA depends on the action of dilatory, abductor and oropharyngeal muscles that are normally activated (in a rhythmic fashion) during inspiration. The UA collapses when, for a particular cross sectional area, the force produced by these muscles is overcome by the negative pressure generated by the inspiratory action of the diaphragm and the intercostal muscles.<sup>10</sup> The tissue pressure that leads to the collapse of the airway is known as the critical closing pressure (Pcrit). Normally, the Pcrit of the UA is negative, and is lower in normal subjects than in those who snore, and even lower in snorers with SAHS. An increase in the Pcrit

may come about because of anatomical abnormalities or a reduction in the tone of the dilatory muscles.

The factors that favor airway collapse include a narrowing of the UA (anatomical factors), an excessive loss of muscular tone (muscular factors), and defects in the normal protective reflexes (neurological factors). The factors that reduce the bore of the UA lead to an increase in resistance and the generation of negative pharyngeal pressure during inspiration. The anatomical factors involved can also influence the muscular and neurological factors. Micrognathia, for example, causes the base of the tongue to lay further back, interfering with efficiency of the genioglossus muscle. In addition, obese persons tend to have smaller lung volumes, especially smaller functional residual volumes, and this has a negative influence on the size of the airway and favors its narrowing. Moreover, contractile capacity of their muscle fibers is reduced by the fat deposits between them.

Apneas and hypopneas cause intermittent hypoxia that can give rise to cardiovascular problems. They also distort the architecture of sleep, leading to daytime hypersomnia and cognitive and psychiatric problems. Generally, but not exclusively, those who suffer apnea/hypopnea are obese, snore, and show signs of EDS. The most important risk factor is sex; the disorder affects three times more men than women of middle age, although the proportions become more balanced after the menopause and with old age. Smoking, the consumption of alcohol, sleeping on the back and obesity are aggravating factors.

The cycle of sleep, apnea-hypopnea, changes in gasometry, arousal, and the end of apnea-hypopnea is repeated time and again. Repeated arousals cause the fragmentation of sleep and give rise to the majority of neuropsychiatric problems associated with the SAHS (e.g., EDS and personality and behavioral problems). It is recommended that use be made of the conventional polysomnograph (PSG) in order to properly diagnose patients suspected of suffering this syndrome.<sup>11</sup> This apparatus allows the simultaneous recording of neurophysiological and cardiorespiratory variables reflecting the quantity and quality of sleep achieved, and also identifies any abnormal respiratory events and their

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cardiorespiratory and neurophysiological repercussions. The patient's  $\text{SaO}_2$  is measured by pulseoximetry, respiratory effort by thoraco-abdominal bands, and nasobuccal flow by pneumotachographs (using thermistors or nasal pressure probes). Electroencephalography and electrooculography allow the staging of sleep, and an electrocardiogram records any heart manifestations. Blood pressure, the transcutaneous pressure of  $\text{CO}_2$  and signs of pressure on the ventilation and other systems are also simultaneously measured. Although its use is accepted in the diagnosis of SAHS, respiratory polygraphy (RP) consists only of the analysis of cardiac and respiratory variables, and does not take into account any neurophysiological variables.<sup>12,13</sup> Its main advantages are that it is simple and cheap.

In recent years, the number of patients diagnosed with SAHS has increased, and controversy has grown around the evidence relating this syndrome to a deterioration in the quality of life, an increased risk of high blood pressure (HBP), cardiovascular and cerebrovascular problems, and the increase seen in traffic accident mortality.

The relationship between SAHS and HBP has been discussed in the literature since the 1980s. It is estimated that some 40%-60% of patients with SAHS are hypertensive and that approximately one third of patients with HBP suffer SAHS.<sup>14</sup> However, this relationship has been widely questioned since patients with these problems share certain characteristics (e.g., sex and age), and both HBP and SAHS are associated with obesity, alcohol and coffee consumption, and smoking. Patients with SAHS show cyclical increases in blood pressure related to obstructive respiratory events that occur during the night. The central and peripheral chemoreceptors, the pulmonary baroreceptors and afferent nerves, hypoxia and hypercapnia, increased negative intrathoracic pressure, and arousals from sleep, all seem to be involved. The ensuing autonomic, hemodynamic and humoral alterations translate into increased blood pressure at the end of apnea episodes. However, the debate centers on whether these transitory changes in nocturnal blood pressure could actually cause sustained HBP during the day. It has been shown that, during sleep, intermittent hypoxia in rats or intermittent occlusion of the UA in dogs causes sustained HBP after these animals wake up and begin to breath normally. In rats, the removal of the chemoreceptors prevents the development of HBP. From these experiments it can be deduced that hypoxia-hypercapnia and changes in pleural pressure are the main pathophysiological mechanisms leading to increases in sympathetic vasoconstrictory tone and the appearance of daytime HBP. There is presently much interest in biological mediators—cytokines, endothelin, and nitric oxide, etc—as factors that contribute to the development of vascular abnormalities in SAHS.

In recent years, much effort has gone into demonstrating the association between SAHS and HBP.

This is reflected in the results of 2 very large epidemiological studies of the general population. In both, HBP was defined as being greater than 140/90 mm Hg or the taking of medication to lower blood pressure. The patients were divided into severity subgroups depending upon their apnea-hypopnea index (AHI). The Wisconsin study,<sup>4</sup> a cross-sectional study with a 4 year general follow-up period (n=709) plus an 8 year follow-up for 1 subgroup (n=184), showed that SAHS patients with an AHI of >15 had an odds ratio (OR) for HBP of 2.66 (95% confidence interval [CI], 1.1-6.25). The Sleep Heart Health Study,<sup>15</sup> a cross-sectional, multicenter study involving 6841 SAHS patients, showed that, after adjusting for sex, age, body mass index, neck and waist circumference, alcohol consumption, and smoking, those with an AHI of >5 had an OR for HBP of 1.25 (95% CI, 1-1.56). The authors of both studies concluded that there is an association between SAHS and HBP, independent of any confounding factors, and that this shows a “dose-dependent” pattern with respect to the severity of SAHS. In the Wisconsin study, the 8 year follow-up allowed this relationship to be confirmed as causal. Other authors have shown that, compared to a placebo control, continuous positive airway pressure (CPAP) significantly reduces blood pressure in patients with an established diagnosis of HBP, and that the benefit is greater in patients with SAHS or those taking blood pressure lowering medication, independent of their baseline blood pressure levels.<sup>16,17</sup>

A number of cross-sectional and case-control studies have shown that nocturnal respiratory abnormalities are common in both men and women with heart disease (in its various forms), and that >30% of patients with heart failure also suffer SAHS. Schafer et al<sup>18</sup> found a high prevalence of SAHS in patients with angiographically-demonstrated heart disease and concluded that moderate SAHS (AHI>20) was an independent risk factor for myocardial infarction (OR=2.0; 95% CI, 1.0-3.8).

The Sleep Heart Health Study<sup>15</sup> evaluated the association between sleep-related breathing abnormalities and cardiovascular disease in 6481 subjects aged over 40 years. All underwent polysomnography and an association was found with coronary events (OR=1.27; 95% CI, 0.99-1.62) (although weaker than that found with heart failure and cerebrovascular accidents). It is important to remember, however, that this association does not necessarily imply causality. Patients with SAHS frequently have multiple risk factors. Therefore the evaluation of sleep-related breathing abnormalities as an independent risk factor for cardiovascular disease requires adjustments be made for confounding factors such as smoking and obesity, etc.

It has been reported that patients with heart disease and SAHS can suffer myocardial ischemia during episodes of apnea, mainly during rapid eye movement (REM) sleep. Depressions in the ST segment caused by this problem are more commonly seen in patients

with severe SAHS and in those with nocturnal angina. Patients with SAHS tend to present with myocardial infarctions at a different time (between 6.00 and 12.00 h) to those who do not suffer apnea.

In patients with ischemic heart disease, the presence of sleep-associated respiratory abnormalities appears to be an indicator of poor prognosis. No controlled studies have been performed on the effect of CPAP in these patients, but isolated reports of significant improvement in nocturnal ischemic events and ST segment depression have been made.

Approximately 5%-10% of SAHS patients suffer episodes of bradyarrhythmia. Changes in the heart rate depend on the balance between sympathetic and parasympathetic tone; indeed, the bradyarrhythmias associated with SAHS are due more to an increase in parasympathetic tone than to structural abnormalities. The REM sleep period appears to be intimately related to arrhythmia, but the reason why remains unclear.

Guilleminault et al<sup>19</sup> studied 400 consecutive patients with SAHS, of whom 193 (48%) were found to have arrhythmias during 24 h electrocardiogram monitoring. Sinus block, followed by second degree atrioventricular block, were the most common causes. In 50 patients, these arrhythmias ceased after tracheostomy.

In this issue of the REVISTA ESPAÑOLA DE CARDIOLOGÍA, Martí-Almor et al<sup>20</sup> present results obtained during the study of 38 consecutive patients with sick sinus syndrome, diagnosed by Holter monitoring, and the prevalence of SAHS. The data show that 31.6% of these patients suffered sleep apnea with accompanying daytime clinical symptoms. It should be noted that none of these patients suffered abnormalities of ventricular dysfunction. The authors report that 45% of the Holter readings showed signs of tachycardia-bradycardia syndrome, with atrial fibrillation being the dominant tachycardia. In a recent paper, Gami et al<sup>21</sup> reported that 50% of their SAHS patients suffered atrial fibrillation, similar to that indicated by Martí-Almor et al.

Harbison et al<sup>22</sup> studied 45 patients with SAHS, of whom 78% had some type of heart rhythm abnormality and 18% showed clinically important arrhythmias. Treatment with CPAP for 3 months resolved all the latter. Similarly, Simantirakis et al<sup>23</sup> reported the effect of CPAP on 23 patients diagnosed with SAHS and with severe heart arrhythmias. In the first 6 months of treatment these arrhythmias disappeared completely. The work of Martí-Almor et al<sup>20</sup> goes a step further in that it shows SAHS to be 10 times more frequent in people with arrhythmias than in the general population (>31% compared to 3%-5%), although it should also be remembered that this study had no control group and did not evaluate the effect of CPAP treatment. In fact, none of the above data conclusively show a causality relationship between SAHS and heart arrhythmias.

The authors report that 63% of their patients received a pacemaker, but they give no indication of how this

affected apnea. In a small group of patients with SAHS and bradycardia or sinus arrest, Garrigue et al<sup>24</sup> reported that the implantation of a pacemaker resolved their problems of apnea, although the reason why is unclear. In addition, many of the latter patients suffered central apneas and had an abnormal ejection fraction.

Finally, it should be pointed out that there is a great lack of data on the mortality of patients with SAHS and heart arrhythmias.

A disease with a risk of cardiovascular complication, such as SAHS, necessarily has an elevated rate of mortality. Over a period of 10 years, Marín et al<sup>25</sup> followed 235 patients with severe untreated SAHS, 264 healthy men, 377 snorers, 403 with mild-moderate untreated SAHS, and 372 with SAHS treated with CPAP. The patients with severe, untreated SAHS showed a high incidence of both fatal cardiovascular events (1.06 per 100 patients per year) and non-fatal cardiovascular events (2.3 per 100 patients per year) compared to all the other groups. Multivariate analysis to take into account the effect of confounding factors showed that, compared to the healthy controls, severe, untreated SAHS significantly increased the risk of both fatal cardiovascular events (OR=2.87; 95% CI, 1.17- 7.5) and non-fatal cardiovascular events (OR=3.17; 95% CI, 1.12-7.51). In summary, the data available show greater mortality among patients with SAHS. However, it would be difficult (for ethical reasons) to perform prospective studies to assess the improvement in mortality that might be achieved by treatment.

Over the last decade, the information that has become available on SAHS and its cardiovascular consequences shows this syndrome to be a serious health problem. Sleep is now understood as a biological process which has pathophysiological relationships with respiration and cardiovascular function. Physicians should be aware of how the problems seen in everyday practice could have their origins in sleep-related abnormalities.

## REFERENCES

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med.* 1993;328:1230-6.
2. Durán J, Esnaola S, Ramón R, Iztueta A. 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;163:685-9.
3. Nieto FK, Young TB, Lind BK, Sahar E, Samet JM, Redline S, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. *JAMA.* 2000; 283:1829-36.
4. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med.* 2000;342:1378-84.
5. Parra O, Arboix A, Bechich S, García-Eroles L, Montserrat JM, López JA, et al. Time course of sleep-related breathing disorders in first-ever stroke or transient ischemic attack. *Am J Respir Crit Care Med.* 2000;161:375-80.
6. Terán-Santos J, Jiménez-Gómez A, Cordero-Guevara J, and the Cooperative Group Burgos-Santander. The association between

- sleep apnea and the risk of traffic accidents. *N Engl J Med*. 1999;340:847-51.
7. Barbé F, Pericás J, Muñoz A, Findley L, Antó JM, Agustí AGN. Automobile accidents in patients with sleep apnea syndrome. An epidemiological and mechanistic study. *Am J Respir Crit Care Med*. 1998;158:18-22.
  8. Lavie P, Herer P, Peled R, Berger I, Yoffe N, Zomer J, et al. Mortality in sleep apnea patients; multivariate analysis of risk factors. *Sleep*. 1995;18:149-57.
  9. He J, Kriger MH, Zorick FJ, Conway W. Mortality and apnea index in obstructive sleep apnea. *Chest*. 1988;94:9-14.
  10. Guilleminault C, Tilkian A, Dement WC. The sleep apnea syndromes. *Annu Rev Med*. 1976;27:465-85.
  11. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep*. 1999;22:667-89.
  12. Alonso Álvarez ML, Fernández Martínez de Septiem C, Alonso Mediavilla C, Martínez González M, Terán Santos J, Rodríguez Pascual L, et al. Validación de estudios polisomnográficos de mitad de noche en el síndrome de apneas-hipopneas durante el sueño. *Arch Bronconeumol*. 2000;36:180-5.
  13. Calleja JM, Esnaola S, Rubio R, Durán J. Comparison of a cardiorespiratory device vs polysomnography for diagnosis of sleep apnea. *Eur Respir J*. 2002;20:1-6.
  14. Stradling JR, Pepperell JC, Davies RJ. Sleep apnea and hypertension: proof, at last? *Thorax*. 2001;56 Suppl II:ii45-ii9.
  15. Newman AB, Nieto J, Guirdry U, Lind BK, Redline S, Sharar E, et al. Relation of sleep disordered breathing to cardiovascular risk factors. The Sleep Health Study. *Am J Epidemiol*. 2001;154:50-9.
  16. Pepperell JCT, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, et al. Ambulatory blood pressures after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet*. 2001;359:204-10.
  17. Terán Santos J, Alonso ML, Cordero J, Castrodeza J, Coma MJ. Randomized placebo controlled trial effects of continuous positive airway pressure in patients with hypertension "non dipper" without treatment and obstructive sleep apnea. *Eur Respir J*. 2005;26:723.
  18. Schafer H, Koehler U, Ewig S, Hasper E, Tasci S, Luderitz B. Obstructive sleep apnea as a risk marker in coronary artery diseases. *Cardiology*. 1999;92:79-84.
  19. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. *Am J Cardiol*. 1983;52:490-4.
  20. Martí-Almor J, Félez-Flor M, Balcells E, Cladellas M, Broquetas J, Bruguera J. Prevalencia del síndrome de apnea obstructiva del sueño en pacientes con disfunción sinusal. *Rev Esp Cardiol*. 2006;59:28-32.
  21. Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davidson DE, et al. Association of atrial fibrillation and obstructive sleep apnea. *Circulation*. 2004;110:364-7.
  22. Harbison J, O'Reilly P, McNicholas WT. Cardiac rhythm disturbances in the obstructive sleep apnea syndrome: effects of nasal continuous positive airway pressure therapy. *Chest*. 2000;118:591-5.
  23. Simantirakis EN, Schiza SI, Marketou ME, Chrysostomakis SI, Chlouverakis, Klapsinos NC, et al. Severe bradyarrhythmias in patients with sleep apnea: the effect of continuous positive airway pressure treatment: a long term evaluation using an insertable loop recorder. *Eur Heart J*. 2004;25:1070-6.
  24. Garrigue S, Bordier P, Jais P, Shah DC, Hocini M, Raheison C, et al. Benefit of atrial pacing in sleep apnea syndrome. *N Engl J Med*. 2002;346:404-12.
  25. Marín JM, Carrizo SJ, Vicente E, Agustí AG. Long term cardiovascular outcomes in men with obstructive sleep apnea-hypopnea syndrome with or without treatment with continuous positive airway pressure: an observational study. *Lancet*. 2005;365:1046-53.