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Review Article

Sleep Apnea-Hypopnea Syndrome Without Excessive Daytime Sleepiness

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ABSTRACT

Nowadays, sleepiness in patients with sleep apnea-hypopnea syndrome (SAHS) is understandable. It is somewhat more difficult to explain why most patients with SAHS enrolled in epidemiologic studies, even those with a high apnea-hypopnea index, do not experience excessive daytime sleepiness. The reasons for this discrepancy lie beyond mere polysomnographic events.

This review examines data from the literature that may help us understand why these patients do not experience daytime sleepiness. It also analyzes studies that support and refute sleepiness as a marker of cardiovascular risk in patients with SAHS, and discusses the mechanisms that might increase this risk.

Palabras clave:
Síndrome de apneas-hipopneas del sueño (SAHS)
Somnolencia
Riesgo cardiovascular

Síndrome de apneas-hipoapneas durante el sueño sin somnolencia

RESUMEN

La presencia de somnolencia en pacientes con síndrome de apneas-hipopneas durante el sueño (SAHS) resulta en la actualidad comprensible. Más difícil de explicar es que la mayoría de los pacientes con SAHS incluidos en estudios epidemiológicos, incluso aquellos con un alto índice de apneas-hipopneas, no presente excesiva somnolencia diurna. Los motivos van más allá de los simples eventos polisomnográficos. En este artículo se repasarán los datos de la literatura médica que pueden ayudar a comprender la falta de excesiva somnolencia diurna en estos pacientes. Además, se analizarán los estudios que defienden y niegan que la somnolencia en pacientes con SAHS sea un marcador de riesgo cardiovascular y los mecanismos por los que pudiera aumentar este riesgo.

Introduction

Although it may not appear so in principle, most patients with sleep apnea-hypopnea syndrome (SAHS) do not experience excessive daytime sleepiness (EDS). Furthermore, the prevalence of sleepiness is not substantially greater in these patients than in the general population. A recent review of the Sleep Heart Health Study showed that EDS—considered as a score greater than 10 on the Epworth Sleepiness Scale—was experienced by up to 21% of individuals who did not have sleep apnea, whereas in patients with an apnea-hypopnea index (AHI) greater than 30, only 40% of cases experienced sleepiness.[1] Similarly, a study carried out in Spain[2] revealed that only 21% of men and 26% of women with an AHI greater than 5 reported EDS, compared with 12% of men and 28% of women with an AHI lower than 5.

Reasons for the Absence of EDS in Patients With SAHS

It is no surprise that patients with SAHS experience sleepiness. In fact, when King et al[3] induced SAHS in healthy individuals by administering a nasal pressure of −10 cm H_2O, they observed that sleep latency decreased the following day. Furthermore, after a second control night during which subatmospheric pressure was withdrawn, baseline sleep latency values returned. This indicates that acute apnea leads to sleepiness. It is more difficult to explain the fact that many patients with SAHS do not experience daytime sleepiness. The theories set out below may shed some light on this discrepancy.

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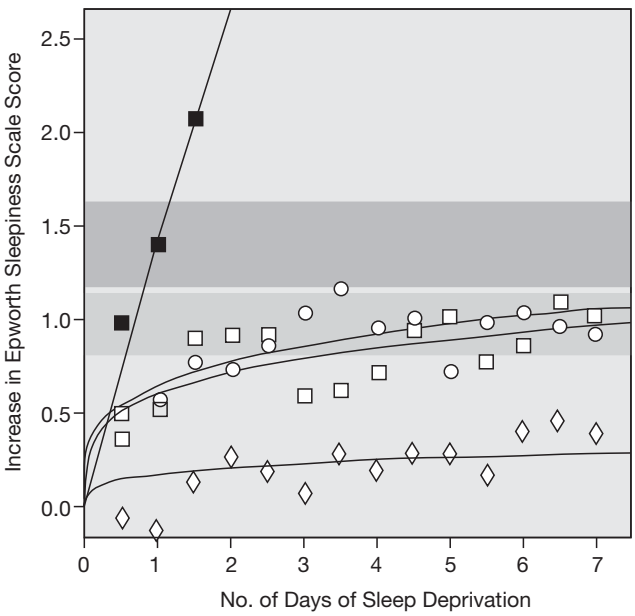

Figure 1. Increased sleepiness on the Epworth Sleepiness Scale in a group of healthy individuals after total and partial sleep deprivation. Adapted from van Dongen et al.[4]

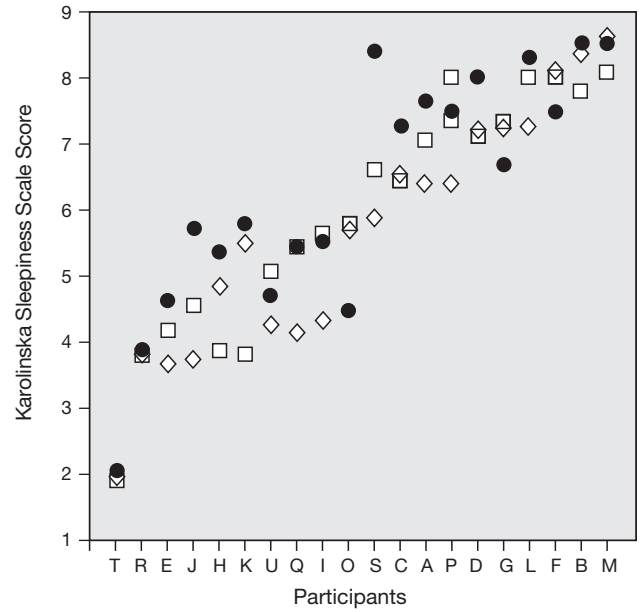

Figure 2. Karolinska Sleepiness Scale score in healthy participants after 36 hours of total sleep deprivation on 3 different occasions. Each participant is represented by a letter. Adapted from van Dongen.[6]

Adaptation Over Time

First, patients with SAHS who do not present sleepiness might have adapted to a chronic disease over time. Van Dongen et al[4] studied a group of healthy individuals to compare sleepiness brought on by total sleep deprivation (3 nights without sleep) with that brought on by partial deprivation (4, 6, or 8 h/d, maintained for 14 days). They observed that total sleep deprivation had an acute response with a progressive increase in sleepiness during the 3-day study period. However, chronic restriction of sleep periods had an acute effect at the outset, but there was no greater increase after the second or third days, thus indicating the existence of an adaptation mechanism (Figure 1).

In another study that pointed to adaptation to EDS over time, Bjorvatn et al[5] evaluated a group of 17 individuals who complained of problems adjusting to shift work. Their sleepiness was monitored for 14 consecutive days during which time they worked a night shift the first week and switched to a day shift the second week. Subjective sleepiness was found to be high at the beginning of the week they worked the night shift, only to decrease during the rest of the week. When they switched to the day shift, sleepiness increased once again and, as the week went on, it began to decrease again.

Vulnerability and Resistance to Sleep

Van Dongen[6] exposed a group of 21 healthy participants to 36 hours of total sleep deprivation and measured their subjective sleepiness. This experiment was performed on 3 occasions for each individual. Sleepiness was measured using the Karolinska Sleepiness Scale and was found to differ between the individuals. The differences remained stable throughout the 3 experiments. In other words, some people were vulnerable to total sleep deprivation, whereas others were resistant. Figure 2 shows the participants in the experiment represented by different letters and the 3 scores on the Karolinska scale.

Evidence for hypoxia as a cause of sleepiness is presented below; however, here we discuss the study by Sanfilippo-Cohn et al[7] as a justification for the theory of individual vulnerability to sleepiness. The authors randomly induced intermittent hypoxia or normoxia in a group of male and female mice. In the male mice, intermittent hypoxia caused a decrease in sleep latency and greater rapid eye movement (REM), non-REM, and total sleep time. However, the female mice were resistant to the effect of intermittent hypoxia on objective sleep and sleep time.

Sympathetic and Parasympathetic Activity

At the end of the 1980s, increased daytime sleepiness was observed to correlate with the activity of the autonomic nervous system in patients with SAHS. Pressman and Fry[8] studied a group of patients with SAHS and determined the degree of sympathetic and parasympathetic activity using the pupil light reflex. They found that increased sleep latency in the multiple sleep latency test correlated with increased parasympathetic activity and that subjective somnolence correlated indirectly with the degree of sympathetic activity.

Insomniac patients have been shown to have higher nighttime circulating noradrenaline levels (sympathetic arousal) than controls (Figure 3), and a negative correlation has been observed between concentrations of norepinephrine and sleep efficiency in this type of patient (Figure 4).[9]

Arzt et al[10] studied a group of 155 patients with heart failure who underwent polysomnography and who were compared with a control group of more than 1000 patients belonging to the Wisconsin cohort. For the same AHI, patients with heart failure were found to experience less subjective sleepiness despite sleeping less (total sleep time in the polysomnogram) (Figure 5). The authors state that the explanation must lie in the increased sympathetic tone experienced by patients with heart failure.

Degree of Brain Activity

Mu et al[11] studied 33 healthy participants at baseline and after 30 hours of sleep deprivation. The participants underwent magnetic resonance imaging while performing the Sternberg memory test. Ten of the 33 participants were resistant to sleep deprivation (measured using a memory test), and their brain activity (measured using magnetic resonance) was greater than that of the patients who were vulnerable to sleep deprivation (Figure 6).

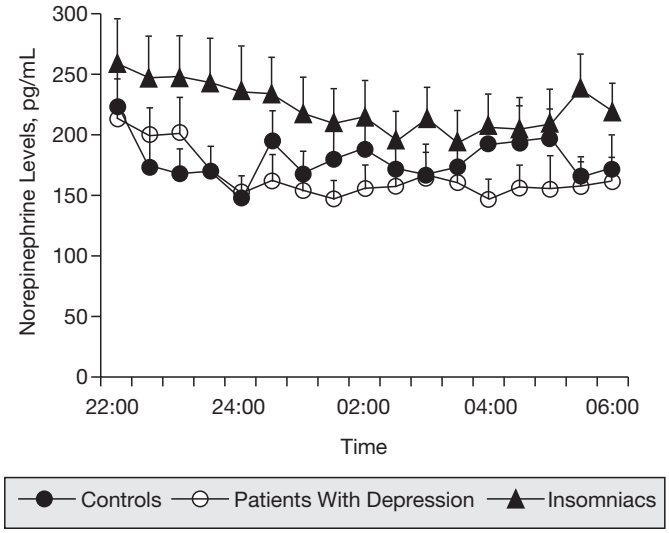

Figure 3. Nighttime circulating norepinephrine concentrations in insomniacs, patients with depression, and control participants. Adapted from Irwin M et al.[9]

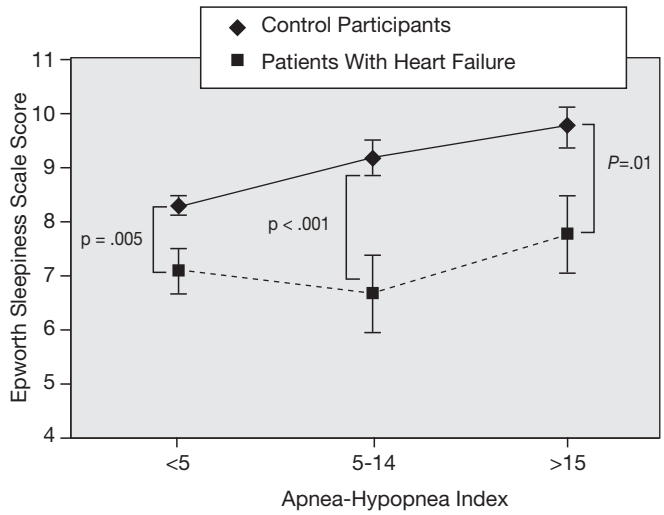

Figure 5. Epworth Sleepiness Scale score in patients with and without heart failure, for the same apnea-hypopnea index. Adapted from Arzt M et al.[10]

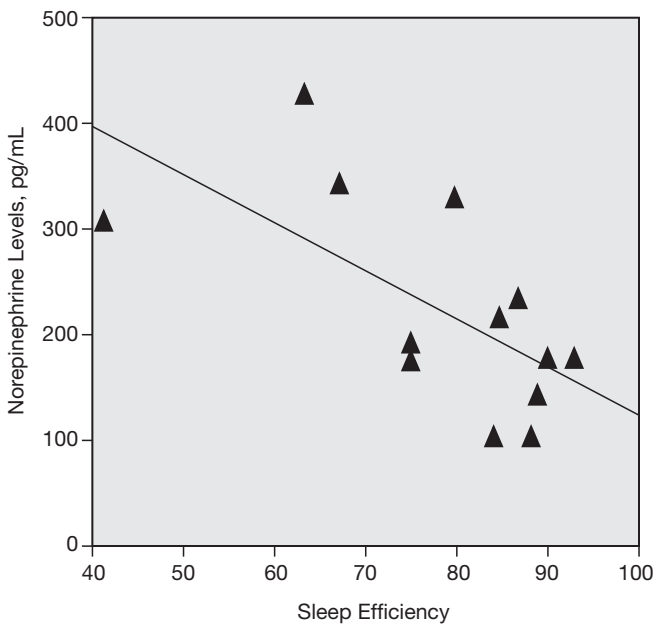

Figure 4. Inverse correlation between blood concentrations of norepinephrine and sleep quality (efficiency) in insomniacs. Adapted from Irwin M et al.[9]

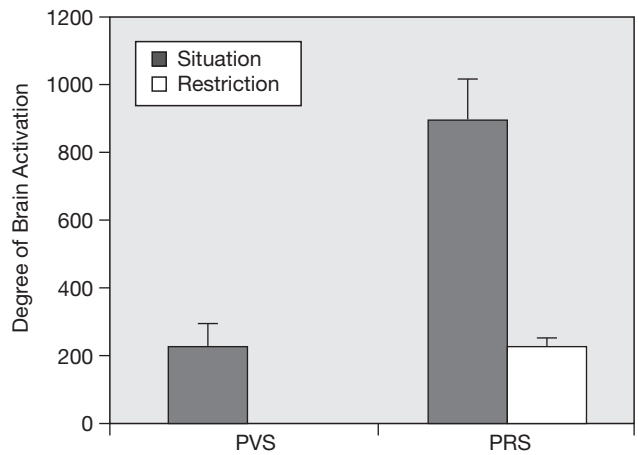

Figure 6. Brain activation measured using magnetic resonance in patients who were vulnerable and patients who were resistant to sleep deprivation. Abbreviations: PRS, patients who were resistant to sleep deprivation; PVS, patients who were vulnerable to sleep deprivation. Adapted from Mu Q et al.[11]

Arousal Threshold

Patients with SAHS who do not experience sleepiness may have a reduced arousal threshold. A recent study[12] revealed that, for the same AHI, patients with SAHS and sleepiness presented longer periods of apnea and lower minimum and mean nighttime arterial oxygen saturation. The authors suggest that this could be due to an increase in the arousal threshold of patients with EDS.

Sleepiness as a Marker of Cardiovascular Risk

Epidemiology studies, in which patients are mainly asymptomatic, have shown that SAHS is a risk factor for hypertension and other adverse cardiovascular effects.[13,14] However, it is unknown whether this risk is limited to patients with sleepiness.

Choi et al[15] used impedance cardiography to measure heart function in 86 patients with various degrees of sleepiness and of severity of SAHS. They found a negative correlation between the Epworth Sleepiness Scale score and cardiac function. Thus, the authors suggest that, within the group of patients with SAHS, sleepiness could serve to identify those patients at risk of developing cardiac function abnormalities.

Two randomized controlled studies analyze the effect of nighttime continuous positive airway pressure (CPAP) on patients with SAHS and no sleepiness.[16,17] Both studies found that CPAP did not reduce arterial pressure in these patients; therefore, they conclude that sleepiness must play an important role in the pathogenesis of hypertension in these cases.

Sleepiness: Mechanisms of Cardiovascular Injury

Abundant data in the medical literature show that both cytokines and C-reactive protein (CRP) alone, and hypoxia, through oxidative stress, are closely related to the pathogenesis of atheromatous

plaque.[18-20] Below, we analyze the evidence associating sleepiness with hypoxia and increased levels of proinflammatory cytokines and CRP.

Relationship Between Hypoxia and Excessive Sleepiness

Zhan et al[21,22] showed that, when hypoxia was induced in a group of mice, waking time decreased and REM and non-REM sleep increased, whereas sleep latency was shortened. Furthermore, when nicotinamide adenine dinucleotide phosphate, an enzyme involved in the production of free radicals, was genetically suppressed in a group of mice, intermittent hypoxia was observed not to lead to the same changes in sleep structure. The authors conclude that intermittent hypoxia causes sleepiness mediated by oxidative stress.

Besides the work by Zhan et al, other animal models have produced the same results, and, although oxidative damage has not been demonstrated in the brain of patients with SAHS, systemic increased oxidative stress and its reduction with CPAP have been observed.[23]

Relationship Between Increased Levels of Proinflammatory Cytokines and Sleepiness

Ryan et al[24] measured proinflammatory cytokine concentrations in patients with various degrees of severity of SAHS and in nonapneic patients with and without sleepiness. Cytokine levels (tumor necrosis factor [TNF] α and interleukin 8) were found to be higher in patients with SAHS than in control patients, and their concentration was related to the severity of SAHS. Furthermore, in nonapneic individuals, cytokine levels are higher than in those who complain of sleepiness. This means that sleepiness itself can lead to an increase in cytokine levels, without the need for apnea to be present.

A more recent study analyzed the effect of a TNF-α–neutralizing drug (etanercept) on sleepiness in patients with sleep apnea,[25] and found a reduction in sleepiness that was 3 times greater than that observed in patients with SAHS who received CPAP. The authors suggest that proinflammatory cytokines could be mediators of sleepiness.

Relationship Between CRP and Sleepiness

Meier-Ewert et al[26] showed increased CRP levels in a group of healthy participants when sleep was totally or partially restricted. They also observed that blood pressure and heart rate increased. These authors propose that sleep deprivation may be one of the ways inflammatory processes participating in the pathogenesis of cardiovascular disease are activated.

Sleepiness and Cardiovascular Disease: Data Against

As mentioned above, sleepiness is related to a reduction in sympathetic tone; however, it is the increase in sympathetic tone that is related to cardiovascular morbidity.

In a recent study, Alonso-Fernández et al[27] showed that the nighttime ST-segment depression in patients with SAHS is related to daytime blood concentrations of epinephrine.

Kaneko et al[28] studied 24 patients with SAHS and heart failure who had scored less than 10 on the Epworth Sleepiness Scale and were randomly prescribed conventional treatment for heart failure or conventional treatment as well as CPAP. In the patients who received CPAP, the ejection fraction increased and systolic blood pressure fell. These data indicate that sleepiness does not play a pathogenic role in the cardiovascular morbidity of patients with SAHS.

Parra et al[29] studied 161 patients with a first episode of stroke and a mean (SD) score on the Epworth Sleepiness Scale of 4.8 (3.3). After almost 2 years of follow-up, they observed an increase in overall mortality in patients with an AHI greater than 30. This seems to indicate that mortality can increase in patients with SAHS who do not present sleepiness.

Finally, several studies state that no relationship whatsoever can be established between sleepiness and increased cardiovascular risk. In particular, Saletu et al[30] found no correlation between sleepiness and CRP concentrations and carotid intima-media thickness in a group of patients with SAHS. Similarly, de la Peña et al[31] analyzed inflammatory cytokine concentrations in patients with SAHS with and without sleepiness, and found no differences between them.

Conclusions

The reason why some patients with the same degree of severity of SAHS experience sleepiness and others do not is probably more complex than the evidence provided by polysomnography. We could think of sleepiness as the final level on a set of scales to which we add sleep-producing mechanisms on one side and sleep-inhibiting mechanisms on the other.

The consequences of a patient presenting sleepiness or not in the setting of SAHS remain uncertain. Current evidence is insufficient to recommend treatment in patients who do not present sleepiness, and, in most cases, this is limited to those who complain of EDS.[32] Nevertheless, a recent review on the treatment of patients with SAHS who do not present sleepiness[33] recommended considering CPAP in those cases with severe types of cardiovascular disease, such as refractory arterial hypertension.

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