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Editorial

Obstructive Sleep Apnea and Cardiovascular Risk: From Evidence to Experience in Cardiology

Apnea obstructiva del sueño y riesgo cardiovascular, de la evidencia a la experiencia en cardiología

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Obstructive sleep apnea (OSA), a common disorder affecting 3% to 7% of the middle-aged population (up to 40% in some series),[1] is characterized by paused respiration during sleep. The immediate consequences of these pauses, apneas or hypopneas, are blood oxygen desaturation and restoration, changes in intrathoracic pressure, and frequent brief moments of arousal. These immediate mechanisms trigger a cascade of intermediate abnormalities, including a rise in sympathetic activity, an increase in oxidative stress, and the creation of a proinflammatory state. As a result, OAS has considerable repercussions on neurocognitive health, with a negative impact on quality of life and an increased risk of traffic accidents. However, the factor that gives OSA the greatest relevance as a public health problem is its contribution to the start or progression of various cardiovascular disorders, even to the point of increasing the patient's future cardiovascular risk.[2]

The Sleep Apnea Cardiovascular Endpoint Study (SAVE[3]) is the most important study available to date for determining the impact of apnea suppression by continuous positive airway pressure (CPAP) on cardiovascular morbidity and mortality in OSA patients. It is an open, randomized, controlled, international study, including 2717 patients with established cardiovascular or cerebrovascular disease and moderate-severe OSA. Patients were randomized to receive usual care alone (control group) or CPAP therapy plus usual care (CPAP group), and the mean duration of follow-up was 3.7 years.

With regard to the primary endpoint (a composite of death from a cardiovascular cause, acute myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or transient ischemic attack), morbidity and mortality were not lower in the group receiving CPAP (hazard ratio [HR] = 1.1; l 95% confidence interval [95% CI], 0.91-1.32; P = .34) than in patients receiving usual care. Nonetheless, CPAP therapy did result in a significant improvement in the patients' daytime sleepiness, health-related quality of life, and emotional state, in addition to reducing the number of days absent from work due to health-related causes.

As these results are important and, to a certain extent, unexpected, it seems appropriate to reflect on their interpretation and their possible repercussions on clinical practice.

DOES THIS MEAN THAT OSA IS NOT ASSOCIATED WITH HIGHER CARDIOVASCULAR RISK?

There is robust evidence relating OSA to increased cardiovascular risk. Epidemiological and longitudinal studies have shown higher cardiovascular morbidity and mortality in patients with severe, untreated OSA than in those receiving CPAP therapy or those with less severe OSA.[4,5] The strongest evidence linking OSA with cardiovascular risk is in relation to hypertension (HT). Randomized studies in OSA patients have shown a positive effect of CPAP treatment on blood pressure values,[6] with significant decreases and an impact on future cardiovascular risk. The effect is even more pronounced in patients with resistant HT, as CPAP therapy added to the usual care achieves better HT control.[7]

There is also considerable clinical and epidemiological evidence relating OSA with other cardiovascular disorders. Several studies have shown a relationship with the development and progression of ischemic heart disease, heart failure, and arrhythmias. In addition, OSA has be cited as a potential risk factor for cerebrovascular disease. Data from the

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Sleep Heart Health Study showed that OSA triples the risk of ischemic stroke in men,[8] and this association was confirmed in elderly patients.[9]

Furthermore, accumulating evidence in recent decades has linked the intermediate mechanisms of sleep apnea with the development of atherosclerosis, endothelial dysfunction–a low-grade inflammatory state–hypercoagulability, and dysregulation of lipid and carbohydrate metabolism.[5] All these data contribute to support the biological plausibility of a relationship between OSA and cardiovascular risk.

THEN, IS CPAP THERAPY UNABLE TO REDUCE OSA-ASSOCIATED CARDIOVASCULAR RISK?

Positive findings in a study such as SAVE would have reinforced the relationship between OSA and cardiovascular risk by confirming that specific treatment has an impact on risk. Nonetheless, negative findings do not necessarily question the relationship. They only indicate that the study was unable to demonstrate a risk reduction with CPAP or that the relationship may not necessarily be reversible.

Various factors could explain this absence of effect, but the most important limitation of the SAVE study may be the patients' adherence to CPAP. The mean time during which this therapy was used was 3.3 h/night. This implies that during half the night patients remained untreated, and it is precisely in the second half of the night when the most pertinent respiratory events occur in relation to the REM (rapid eye movement) phase of sleep.

Several factors could have had an influence on this poor adherence. First, these were asymptomatic patients who had not consulted for any sleep problems, and this could make adaptation to the therapy more difficult. Second, as this was an intention-to-treat study, patients who promptly discontinued CPAP due to intolerance remained in the CPAP therapy arm until completion of the study even though their adherence was 0 h. This situation questions whether an intention-to-treat analysis is the most appropriate approach to use in a study involving a treatment such as CPAP (where adherence is perfectly monitored).

A per protocol analysis was carried out in 561 patients using CPAP >4 h/night and the results were compared with those of a control group. Although this subgroup also showed no significant differences in the main endpoint, we should take into consideration its small size with respect to the total CPAP group included in the intention-to-treat analysis (n = 1346), with the limitations and biases that this may imply. Nonetheless, in this patient group showing good adherence, a protective effect of CPAP was found for the aggregate of cerebrovascular diseases (with CPAP, HR = 0.52; 95% CI, 0.30-0.90; P = .02) and for acute stroke (HR = 0.56; 95% CI, 0.32-1.00; P = .05). Taking into account the limitations of the study, this possible positive effect may be an indication that the heart and brain have a differing response to respiratory sleep disorders. Based on the theory of ischemic preconditioning, one could speculate that the heart would be able to develop compensatory mechanisms that would prepare it for a new event, whereas the central nervous system, lacking these mechanisms, would be exposed to injury with all its consequences. To demonstrate this theory, studies specifically designed with this aim would be needed.

The reality, therefore, is that we cannot affirm that better treatment adherence would have yielded different results. In this line, it is interesting that some previous clinical trials[10] and observational studies[11] in much smaller samples have reported a positive effect of CPAP on reducing cardiovascular events in OSA patients with established coronary disease and achieving lengthier adherence to CPAP. Ostensibly, it is true that CPAP therapy is associated with certain adherence problems, at least in populations having these characteristics. This raises the question of whether improvements in this aspect are needed, either by reviewing the applicability of CPAP as therapy or by examining alternative treatments.

However, as was stated above, it is also worth considering that the relationship between OSA and cardiovascular complications may not be reversible after a certain time point, and that the results of epidemiological studies may be overestimated. We should bear in mind that, based on the SAVE study design, adherence of 3.3 h/night should show a relative risk reduction of 25%, according to the available epidemiologic data. Furthermore, the follow-up time was longer in epidemiologic studies[4] than randomized studies.

A brief reflection on the chronobiology of the impact of OSA in the cardiovascular domain may be of interest. Whereas the changes produced by sleep apneas may enhance the development and progression of structural abnormalities at several levels, once these are established, apnea suppression by CPAP may not necessarily cause them to remit. In short, it can be accepted that CPAP can contribute to decrease systemic inflammation, produce some degree of hemodynamic improvement, and even lower the arrhythmia burden in patients with established cardiovascular disease. However, it is more difficult to hope that it will manage to reduce established atheromatous lesions or regenerate myocardial tissue. This would highlight the need for prompt detection of OSA so that treatment for its functional effects can be established before the structural injury has become consolidated. Furthermore, it reinforces the relevance of acting in early or subclinical phases of the condition and proposes an interesting role for primary prevention, as discussed below.

CAN THESE RESULTS BE EXTRAPOLATED TO PRIMARY PRVENTION?

Patients in the SAVE study already had established cardiovascular disease. It has been speculated that the study population may have been composed of "survivors" of this first event, in whom the effect of CPAP to improve their future risk could be very limited. In addition, as they already had an event, the patients had received complete cardiovascular medical treatment as recommended in the current clinical practice guidelines, and it is likely there would be little room for improvement with any additional treatment.

It cannot be firmly ensured that these findings can be extended to primary prevention, but some data indicate that the results would be different. As mentioned, patients experiencing OSA for a lengthy time period may develop compensatory mechanisms that would be useful to overcome a cardiovascular event. Therefore, patients surviving a first event would probably be those most well protected and least likely to have a new event. What is unknown is the effect of CPAP on a first event in patients who failed to overcome it.

Although data are still emerging, there is already some evidence pointing to the usefulness of CPAP for primary prevention of cardiovascular risk. In OSA patients with no evidence of previous cardiovascular disease, CPAP therapy has been reported to reduce the development of hypertension and cardiovascular events when adherence is > 4 h.[12] Another

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