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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

possible line of action in this setting is supported by the effect of sleep apnea suppression on metabolic-vascular control. A recent study reported that CPAP therapy improves glycemic control in patients with OSA and poorly controlled type 2 diabetes mellitus.[13]

ARE THE RESULTS APPLICABLE TO THE GENERAL POPULATION?

It is important to know the characteristics of the study patients: mean age 63 years, nonobese, asymptomatic, with moderate-severe OSA and a significant percentage of Asian patients. It is likely that the findings would not be directly applicable to the most common phenotype of patients with OSA (younger, obese, somnolent). Therefore, we cannot assume that CPAP therapy will reduce cardiovascular risk in patients with characteristics that differ from those of the study sample.

This has several clinical implications. First, the clinical care of patients with suspected OSA based on their symptoms will not change substantially. That is, in patients with the typical phenotype referred to sleep units for suspected OSA, these negative results will not lead to changes in the clinical care provided.

Second, the findings do not seem to warrant an active search for evidence of sleep disorders in patients with heart disease and no symptoms during the day. If the results of the SAVE study had been positive, it would have been mandatory to carry out a sleep study and apply treatment in patients with an apnea-hypopnea index of $>$ 15/h, even in the absence of symptoms. This is not justified according to the study results obtained.

MIGHT THE DIAGNOSTIC METHOD HAVE INFLUENCED THE RESULTS OF THE STUDY?

The gold standard for diagnosing OSA is a complete polysomnography study. This a complex and costly procedure that requires hospital admission and specialist interpretation of the results. The SAVE study used a simplified diagnostic method (ApneaLink, Resmed), which has good capability for identifying moderate-severe OSA in the general population. This method enabled inclusion of a large number of patients in 7 countries and facilitated a centralized analysis. Despite the simplicity of the diagnostic method used, there is no doubt that the patients included had moderate-severe OSA. All had a desaturation index at 4% $>$ 12/h and this reliably corresponds to an apnea-hypopnea index of $>$ 15/h on polysomnography.[14]

Nonetheless, a potential limitation of this method is the absence of plethysmography bands, which enable differentiation between the obstructive apneas occurring in OSA and central apneas, which are more commonly related to heart failure. In view of the current evidence on treatment of central apnea when ventricular function is depressed (left ventricular ejection fraction $\leq$45%),[15] in which treatment-induced excess mortality has been identified, one may wonder whether patients of this type were included in the SAVE study sample.

It does not seem possible that a relevant number of SAVE patients had events of central origin. First, because from the beginning patients in functional class III-IV were excluded. Second, because patients with a crescendo-decrescendo pattern typical of Cheyne Stokes respiration and indicative of central apnea were excluded. Lastly, because the efficacy of treatment was determined by memory card and the program recorded the residual respiratory events and their possible origin. In patients with numerous residual apneas, the complementary tests required to properly identify and control them were carried out.

WHEN SHOULD A CARDIOLOGIST SUSPECT OSA?

To our mind, patients with suspected OSA (showing 2 of the 3 cardinal symptoms: snoring, witnessed apneas, and drowsiness or tiredness)[16,17] and consulting in the cardiology department should still be referred to the sleep unit. At this point, we should remember that these symptoms responded positively to CPAP therapy in the SAVE study, although patients were initially considered asymptomatic. Furthermore, there was a positive response to CPAP during the day, with reductions in the number of days patients were absent from work. In this regard, the initial clinical history taking should be meticulous, and when there are doubts, CPAP therapy can be attempted and the patient reassessed in the short term.

Therefore, the SAVE study has made an important contribution to current knowledge of the relationship between OSA and cardiovascular risk and has provided an indication of future paths to be taken in research on this relationship.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Duran 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 yr. *Am J Respir Crit Care Med.* 2001;163:685–689.
2. Loke YK, Brown JWL, Kwok CS, et al. Association of obstructive sleep apnea with risk of serious cardiovascular events: systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes.* 2012;5:720–728.
3. McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med.* 2016;375:919–931.
4. Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet.* 2005;365:1046–1053.
5. Sánchez-de-la-Torre M, Campos-Rodriguez F, Barbé R. Obstructive sleep apnoea and cardiovascular disease. *Lancet Respir Med.* 2013;1:61–72.
6. Durán-Cantolla J, Aizpuru F, Montserrat JM, et al. Continuous positive airway pressure as treatment for systemic hypertension in people with obstructive sleep apnoea: randomised controlled trial. *BMJ.* 2010;341:c5991.
7. Martínez-García MA, Capote F, Campos-Rodríguez F, et al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. *JAMA.* 2013;310:2407–2415.
8. Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. *Am J Respir Crit Care Med.* 2010;182:269–277.
9. Muñoz R, Durán-Cantolla J, Martinez-Vila E, et al. Severe sleep apnea and risk of ischemic stroke in the elderly. *Stroke.* 2006;37:2317–2321.
10. Huang Z, Liu Z, Luo Q, et al. Long-term effects of continuous positive airway pressure on blood pressure and prognosis in hypertensive patients with coronary heart disease and obstructive sleep apnea: a randomized controlled trial. *Am J Hypertens.* 2014;28:300–306.
11. Garcia-Rio F, Alonso-Fernández A, Armada E, et al. CPAP effect on recurrent episodes in patients with sleep apnea and myocardial infarction. *Int J Cardiol.* 2013;168:1328–1335.
12. Barbé F, Durán-Cantolla J, Sánchez-de-la-Torre M, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. *JAMA.* 2012;307:2161–2168.
13. Martínez-Cerón E, Barquiel B, Bezos AM, et al. Effect of continuous positive airway pressure on glycemic control in patients with obstructive sleep apnea and type 2 diabetes. *Am J Respir Crit Care Med.* 2016;194:476–485.
14. Gantner D, Ge JY, Li LH, et al. Diagnostic accuracy of a questionnaire and simple home monitoring device in detecting obstructive sleep apnoea in a Chinese population at high cardiovascular risk. *Respirology.* 2010;15:952–960.
15. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med.* 2015;373:1095–1105.

16. Grupo de Trabajo de la, SEC., para la guía, ESC., 2016 sobre el diagnóstico, tratamiento de la insuficiencia cardiaca aguda, crónica. revisores expertos para la guía ESC 2016 sobre el diagnóstico y tratamiento de la insuficiencia cardiaca aguda y crónica y Comité de Guías de la SEC, Comentarios a la guía ESC 2016 sobre el diagnóstico y tratamiento de la insuficiencia cardiaca aguda y crónica. *Rev Esp Cardiol.* 2016;69:1119–1125.

17. Grupo de Trabajo de la, SEC., para la guía, ESC., 2015 sobre el tratamiento de pacientes con arritmias ventriculares, prevención de la muerte súbita cardiaca. revisores expertos para la guía ESC 2015 sobre el tratamiento de pacientes con arritmias ventriculares y prevención de la muerte súbita cardiaca y Comité de Guías de la SEC, Comentarios a la guía ESC 2015 sobre el tratamiento de pacientes con arritmias ventriculares y prevención de la muerte súbita cardiaca. *Rev Esp Cardiol.* 2016;69:94–101.