



## Editorial

AHI As an Independent Risk Factor for Sleepiness<sup>☆</sup>

## IAH como factor de riesgo independiente de la somnolencia

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In reality, I do not believe that there are currently too many doubts about the fact that an excess of obstructive hypopnea or apnea during sleep (AHI: apnea/hypopnea index) can constitute a cardiovascular risk factor, regardless of sleepiness or without the need for its manifestation. Therefore, I should begin by editing these so-called “arguments against” and transform them into “arguments to question”. And I question, fundamentally, due to the consequences that may be derived from such an affirmation.

In any case, the preponderant question that arises among assisting audiences, be they either at conferences or round tables about the vascular repercussions of sleep apnea–hypopnea syndrome (SAHS) and its implication as a risk factor, is usually: “Should asymptomatic patients with high AHI be treated?”.

And this is so because the reviews and/or proposals provided by experts in the field of the topic at hand do not usually conclude with specific recommendations in this regard, nor do they offer *a posteriori* a decisive answer. This is true even though the studies reviewed on any such occasion usually spout data in favor of the title that heads this editorial (*AHI as an Independent Risk Factor for Sleepiness*), which is still “symptomatic”.

On the other hand, there are few studies published with negative results in this regard, although they undoubtedly act as a counterpoint. Such is the case of two studies, by Barbé et al.<sup>1</sup> and Robinson et al.,<sup>2</sup> whose results showed that in non-sleepy patients with high AHI, nasal CPAP has no short-term effects on blood pressure. Few studies have dealt with this question so directly, or at least few with negative results have been published in publications with important factors.

We can weave a rather solid piece of knowledge with a thread of arguments in favor of the mentioned title, beginning with a string of epidemiologic studies (the two large cohorts in the United States: the Sleep Heart Health Study [SHHS] and the Wisconsin study). Initially, in their cross-sectional analysis, they simply showed an association with arterial hypertension (HTN),<sup>3,4</sup> but

they are now about to offer us longitudinal analyses that support that high AHI can be an independent risk factor for the development of cardiovascular pathology, fundamentally in the case of HTN,<sup>5,6</sup> having been corrected for the most common confounding factors. Furthermore, more recent results of SHHS have demonstrated a greater risk for ictus in men under the age of 70,<sup>7</sup> obviating sleepiness.

We can continue to weave the thread with the description of the physiopathological mechanisms that enable the relationship between SAHS and cardiovascular pathology at the molecular level through the release of inflammatory factors, procoagulants and the generation of oxidative stress.<sup>8–10</sup> Last of all, we can finish off with the involvement of SAHS in the genesis of arteriosclerosis as a fundamental cause of cardiovascular pathology,<sup>11,12</sup> without overlooking the possible positive correction of this factor with nasal CPAP.<sup>13</sup> Here, sleepiness is also obviated.

The strength of our weaving is reinforced by the data of studies that show greater cardiovascular mortality with the presence of SAHS<sup>14</sup> or a poorer prognosis,<sup>15</sup> and even a protector effect of treatment with nasal CPAP as evidenced by the now classic article by Marin et al.,<sup>16</sup> which shows a greater cardiovascular morbidity and mortality in those patients with AHI>30 who do not tolerate nasal CPAP. We should not forget that it is a non-randomized study and, therefore, subject to possible bias. Even so, with this limitation we should evaluate the interesting studies by Martínez-García et al.<sup>17</sup> in patients with ictus and SAHS which demonstrate that those who do not tolerate CPAP have a greater recurrence rate and mortality. Parallel or posterior to the data cited, many data have nourished the scientific literature in this direction with a policy of publications, in general, in favor of positive results, and even on occasion with questionable methodologies.

Furthermore, high AHI has been demonstrated to have deleterious effects on ischemic heart disease,<sup>18</sup> cardiac arrhythmia (fundamentally atrial fibrillation<sup>19</sup>), heart failure<sup>20</sup> or ictus,<sup>15,21</sup> resulting in poorer prognoses for both functional recuperation as well as relapses and mortality. More recently, SAHS has also been involved as a factor that contributes to the resistance to insulin and, therefore, metabolic syndrome,<sup>22</sup> in this instance

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with contradictory results and negative studies, especially for the results of nasal CPAP.<sup>23</sup>

This all seems to intertwine with the string of arguments in favor of the relationship between SAHS and cardiovascular pathology, and even the correction of the basic molecular phenomena brought about by nasal CPAP, but this does not necessarily translate into a resounding improvement in the morbidity or mortality in randomized studies when the proven effective treatment of choice, nasal CPAP, is applied for the control of sleepiness in patients diagnosed with SAHS.<sup>24</sup> And so, suddenly, the argument seems to be simply tacked together. And the fact is that the few existing studies developed as randomized clinical assays generally obtain meek results in favor of the groups treated with CPAP,<sup>25</sup> but with reductions in arterial hypertension, even in asymptomatic patients, if we consider separately the group with good compliance (CERCAS),<sup>26</sup> lower incidence of HTN (CEPECTA study)<sup>27</sup> and improvements in heart failure<sup>28</sup> or in cerebrovascular disease regarding functional recuperation.<sup>29</sup>

And, why is this so? Why does this string of arguments break when it seemed so strong and logically connected? The answer is probably multi-faceted. On one hand, perhaps it is too late to act with nasal CPAP when the vascular lesions that induce cardiovascular morbidity and mortality have already been established. On the other hand, it is obvious that, in any event, SAHS would be just another risk factor, associated with the already established and consecrated risk factors (obesity, dyslipidemia, hyperglycemia, smoking) that act as confounding factors and that, despite efforts to control them, it is often difficult to establish the importance corresponding to each factor. In addition, the methodology used up until now can be considered precarious, with few randomized assays including samples that wind up being too small in order to obtain enough statistical power and have short follow-up periods.

Therefore, given the state of the question, the main recommendations in this direction would be prudence and individualized treatment in the cases where necessary, apart from the general recommendations that we are still not prepared to issue. Moreover, in general terms, the response to the question posed should be: "It depends." Depends on what? Well, among other factors, on age,<sup>30,31</sup> the occupation of the patient, AHI values, the existence of cardiovascular comorbidity (fundamentally HTN) and its proper control.

Sleepiness is a rather unspecific symptom that is difficult to measure objectively, but what remains clear is that drowsiness improves with nasal CPAP. Nevertheless, I do not believe that in the future the debate should center around whether or not in asymptomatic patients SAHS constitutes a risk factor, or if when it is asymptomatic it should be treated (despite the fact that sleepiness is linked to certain related hormones and in the end with cardiovascular pathology and play a role in the quandary). We have several examples of asymptomatic conditions that constitute consecrated risk factors (dyslipidemia, HTN itself). The key is in demonstrating the long-term effect of nasal CPAP, with sufficient samples and by means of controlled, randomized studies. This is intended by the SAVE project (Sleep Apnea Cardiovascular Endpoints): an international, prospective, multicenter assay aimed at determining the effectiveness of nasal CPAP in the reduction of cardiovascular morbidity and mortality in patients with moderate and severe SAHS. Likewise, there is the ADVENT-HF study (Adaptive Ventilation in Heart Failure), which has a similar methodology, with servo-adaptive ventilation but in patients with heart failure, with the idea of eluding the deficiencies observed in previous experiences and undoing myths. However, we should not forget that both studies generate an ethical dilemma because not treating patients with AHI over 30 is questionable to say the least. Meanwhile, let us act with caution and common sense and call any asseverations into question.

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