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Editorial

Does Minimally Symptomatic Sleep Apnea Constitute a Cardiovascular Risk Factor?

¿La apnea del sueño paucisintomática es un factor de riesgo cardiovascular?

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Few authors currently doubt the association between sleep apnea-hypopnea syndrome (SAHS) and increased cardiovascular risk. There are more and more studies being published that directly implicate SAHS with hypertension (HTN),[1] the risk for atherosclerosis,[2] endothelial dysfunction[3] and ischemic heart disease.[4] One of the more extensively-documented associations relates SAHS with HTN. SAHS is an independent risk factor for the appearance of HTN[1] and its presence makes the control of HTN difficult.[5] Although the pathogenic mechanisms involved have not been fully revealed, an increase in sympathetic activity has been demonstrated,[6] which would justify the non-dipper or even riser behavior of some of these patients.

Atherosclerosis and endothelial dysfunction have been proposed as two of the mechanisms involved in the risk of cardiovascular disease, measured fundamentally by oxidative stress and the inflammation associated with SAHS.[2,3] Clinically, the association of SAHS with the cardiovascular event is not as strong as with HTN. SAHS is probably an independent risk factor for coronary disease, and it has been associated with higher cardiovascular-related mortality.[7] Retrospective studies in an extensive patient population show greater cardiovascular mortality in patients with more serious SAHS, and observational studies show a reduction of said mortality in subjects that follow treatment with continuous positive airway pressure (CPAP).[8] Nevertheless, and in spite of the greater prevalence of this disease in patients with acute myocardial infarction, there is an important underdiagnosis of SAHS in this group of patients[9] and there is no established clinical recommendation for screening for the presence of sleep-related respiratory disorders in patients that have presented acute coronary syndrome.

It is likely that the cardiovascular risk is not the same in all SAHS patients. It is certainly influenced by the presence of other risk factors (obesity, tobacco habit, diabetes, dyslipidemia) and it is probably related to the severity of SAHS. In theory, the severity of SAHS can be established by the apnea-hypopnea index (AHI) during sleep (which defines the disease), its direct consequences (basically intermittent hypoxemia) or based on the clinical presentation of the disease. On this point, the presence or absence of sleepiness has been proposed as a marker for cardiovascular risk. This speculation is fundamentally based on the lack of response in blood pressure after CPAP treatment in minimally-symptomatic patients,[10] which has led to the suggestion of a common pathogenic pathway associating the presence of symptomatology and cardiovascular risk.[11] This common pathway would be based on the existing relationship between the processes causing excessive daytime sleepiness and the causes of the inflammation/oxidative stress that produce cardiovascular risk. Involved in these processes is the susceptibility of the individual to the effects of the arousals or desaturation associated with apneic events. The response to these alterations would be mediated by different substances (probably neuropeptides and cytokines) involved in both pathways (sleepiness/cardiovascular risk).

Recent studies, however, demonstrate that CPAP treatment lowers blood pressure levels in minimally-symptomatic SAHS patients with hypertension, although prolonged treatments with high compliance rates were necessary to obtain this effect.[12] These results would indicate an increase in cardiovascular risk produced by SAHS, even in patients with fewer symptoms. Therefore, cardiovascular risk would be directly associated with AHI and not symptomatology. Increased endothelial dysfunction and arterial stiffness have been demonstrated in asymptomatic patients,[13] while SAHS has been shown to increase cardiovascular risk in patients with metabolic syndrome, regardless of daytime sleepiness.[14] Along this same line, different meta-analyses

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have not found evidence that daytime sleepiness influences the response of blood pressure when SAHS patients initiate CPAP treatment.[15] The effect of CPAP on blood pressure is intensified the severer the SAHS and the better the compliance with CPAP treatment. Even though modest, the reductions in blood pressure produced by CPAP should not be underrated, as small reductions in blood pressure translate into an important reduction in future cardiovascular risk. Likewise, CPAP treatment seems to have a protective effect in patients with coronary disease and SAHS,[16] while causing an improvement in the symptoms of incipient atherosclerosis in patients treated with CPAP.[17]

A recently-published issue of Archivos de Bronconeumología[18] included a study that determined whether there were differences related to the frequency of cardiovascular disorders in highly-symptomatic patients when compared to minimally-symptomatic ones. The authors found no differences in the prevalence of cardiovascular comorbidity present in the subjects that had sleepiness when compared to those who did not. The results of this paper support the idea that it is the AHI, and not sleepiness, which plays a fundamental role in the development of cardiovascular pathology in SAHS patients, although it must be taken into account that, as a main limitation, the study was retrospective.

It has been widely demonstrated, and is beyond question, that CPAP is effective in the treatment of symptomatic SAHS. In addition, the existence of cardiovascular risk has limited therapeutic implications in symptomatic patients, in whom the indication for CPAP has already been established. The same does not hold true, however, with the choice of treatment in patients with minimally-symptomatic SAHS. Even the document of consensus leaves to the personal discretion of the specialist the decision of whether to prescribe CPAP to those patients with asymptomatic severe SAHS and those subjects with non-severe SAHS and comorbidity.[19] The main problem of this indication is its inherent subjectivity, as "personal discretion" may vary between specialists. On the other hand, the consensus document does not specify what is referred to by "comorbidity". Is it cardiovascular comorbidity? And if so, is it diagnosed HTN, poorly-controlled HTN, the presence of previous ischemic events or simply high cholesterol levels? Therefore, it is necessary to specify what patient groups would benefit from treatment and to what extent, and whether CPAP would be the treatment of choice.

Two important aspects that should be kept in mind in treating this patient population are the difficulty entailed in the adaptation to CPAP treatment of minimally-symptomatic patients and its economic implications. If we add the fact that, in order to experience a benefit, these patients will require higher compliance, the difficulty is even greater. Cost-effectiveness studies are necessary in this type of population to consider their treatment. Likewise, it is also necessary to evaluate therapeutic alternatives to CPAP, such as truly effective weight control programs or mandibular advancement prostheses. It is probable that these two modes of therapy would be preferred when AHI is treated as a cardiovascular risk factor.

The health-care challenge in the near future will be the diagnosis and therapeutic management of subjects with nocturnal respiratory disorders in two different scenarios: *a)* coexistence of other cardiovascular risk factors; and *b)* population with established cardiovascular disease. Regarding primary prevention (scenario 1), we are still far from having evidence to justify such attention. On the other hand, in scenario 2 there are different studies in motion (SAVE, RICCADSA), one of which is taking place in Spain (ISAACC), which in years to come will modify our guidelines for action. In short, AHI is becoming a cardiovascular risk factor.

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