Editorial

Cardiovascular risk in obstructive sleep apnoea: the power of confounders

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Obstructive sleep apnoea (OSA) is a heterogeneous and complex disease (1-3) characterized by total (apnoea) or partial (hypopnea) airflow obstruction during sleep as a consequence of increased pharyngeal muscle collapsability (3-5). This situation led to a nocturnal hypoxic burden (4) usually expressed as repeated cycles of desaturation-reoxigenation called intermittent hypoxia (IH) and sleep structure disruption associated to an increased risk or lack of control of diverse pulmonary and extrapulmonary diseases such as cardiovascular, neurocognitive, metabolic even malignant processes as has been demonstrated by numerous studies (both population-based and clinical-based) over the last decades (6,7).

Both sleep fragmentation and, more especially, IH set in motion a series of pathophysiological mechanisms similar to the ones already known to increase cardiovascular risk [sympathetic hyperactivity (8), increased insulin resistance (9) and other metabolic disorders (10), hypercoagulability states (11), and endothelial dysfunction (12)]. It is not surprising, therefore, that the risk of diabetes (9), arteriosclerosis (13,14) and high blood pressure is higher in patients with OSA (15,16) and, accordingly, that the risk of incident cardiovascular events (CVEs) is also higher, depending to a greater or lesser extent on the type of the CVE in question (6). Moreover, this relationship usually presents a dose-response pattern, so the risk increases in parallel with greater severity of OSA. Finally, a recent meta-analysis of individual data has confirmed that treatment with continuous positive airway pressure (CPAP), the treatment of choice for severe or symptomatic forms of OSA, is capable of eliminating respiratory events during sleep, including IH and sleep fragmentation, and significantly reduce the incidence of CVE, as long as the adherence to this treatment is adequate (17,18).

Longitudinal studies, usually lasting several years (depending on the sample size and the type of CVE under study), are required, however, to achieve robust conclusions about the relationship between OSA and the incidence of CVE (19). Participating subjects could present cardiovascular risk factors (related to OSA or otherwise) and

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greater or lesser control of these risk factors either at the time of entry into the study or over the course of the follow-up. The degree of control is of enormous importance, since the cardiovascular risk generated by a poorly controlled or treatment-resistant hypertensive patient is not the same as that of a well-controlled hypertensive patient and, moreover, the presence of OSA tends to hinder the control of hypertension, especially at night (20). So, in order to draw strong conclusions from such studies, some variables would have to be considered as confounding factors and the results obtained must be adjusted accordingly, and in the case of cardiovascular risk factors, the extent of them must also be taken into account as well as other variables that may be uncontrolled due to the presence of OSA, include age, obesity and diabetes (21). Thus, some studies have observed that increased cardiovascular risk of OSA disappeared in some samples when the results were adjusted for confounding variables such as age (22). These findings raise several questions, some of which still remain unanswered: Is OSA a cardiovascular risk factor "*per se*", independently of confounders? Does the greater cardiovascular risk of OSA depend on increased incidence of hypertension or its control, other factors or some combination of the above? In other words, could we normalize the known increased cardiovascular risk of OSA simply by controlling high blood pressure levels?

In a recent issue of *Cardiovascular Diagnosis and Therapy*, Yao *et al.* (23) attempt to answer this last question via a large series of hypertensive patients who underwent a polysomnographic study to analyse the presence of OSA and were followed for a median of 7 years, using as a final outcome the incidence of a MACCE and the risk of such an event in patients with OSA with both uncontrolled and controlled blood pressure levels. The authors concluded that the risk of cardiac events is 57% higher in patients with OSA, a figure that rises to 93% if their blood pressure is not under controlled. Thus, even in patients with controlled hypertension, the presence of an OSA causes a fully adjusted residual but statistically significant increase in cardiac events. No significant difference was seen between OSA and non-OSA risk in the incidence of MACCE, cerebrovascular disease or all-cause mortality.

One strength of this study is that its adjustment of the results differentiates the controlled hypertensive patients from the uncontrolled ones. Many observational studies do not even contemplate this distinction but simply adjust the results for the presence of hypertension or, occasionally, the administration of antihypertensive treatment but not for the control of blood pressure levels (15). That said, the results are not surprising given that, as previously mentioned, the potential capacity of OSA to induce an increase in the incidence of CVE is not only dependent on blood pressure levels but also on other factors similarly aggravated by OSA [such as the presence and evolution of endothelial dysfunction, arteriosclerosis, insulin resistance and hypercoagulable states (6-14)], that could explain this excess risk even when blood pressure levels are controlled. Furthermore, it is important to highlight that it is advisable to carry out 24-h blood pressure monitoring tests to study the relationship between OSA and arterial hypertension, given that one of the circumstances that characterize hypertension related to OSA is the presence of nocturnal hypertension (during sleep respiratory episodes) or changes in the circadian pattern with a greater proportion of non-dipper nocturnal patterns, even in the presence of normal daytime figures or hypertension controlled with treatment. Both these forms of hypertension have been shown to be cardiovascular risk factors, independently of the levels of daytime arterial hypertension (24). The type of antihypertensive treatment and the dosage used are other variables that must be taken into account, given that OSA usually increases blood pressure levels through sympathetic hyperactivation that occurs at night, so the use of some specific types of antihypertensives could be more effective in normalizing blood pressure levels or at the approach to night time (25). Finally, the added risk of OSA, either through high blood pressure or other mechanisms, differs according to the type of CVE. Therefore, although most studies analyse the MACCE or extended MACCE outcomes, the risk of a cardiovascular or a cerebrovascular event is probably not the same (6) (OSA is usually more closely related to cerebrovascular events and, in parallel, treatment with CPAP has shown a greater protection against stroke than coronary events) (26), so they must be studied separately with sufficient statistical power. In Yao's study (23), for example, only cardiac events were affected by the presence of OSA, unlike stroke or all-cause mortality, although it is also true that there were more cardiac events than cerebrovascular events (with a greater percentage of haemorrhagic strokes, which are risk factors and could have a different association with OSA from that with ischemic strokes).

Therefore, the study by Yao *et al.* (23) introduced the fundamental notion of trying to identify different clinical phenotypes of OSA risk according to the baseline characteristics of patients (in this case controlled and

uncontrolled hypertensive patients) and the weight that different variables of confusion add to this association. This development enhances our knowledge of the various mechanisms through which OSA indicates an increase in CVE. Future prospective studies with a sufficient sample size to be able to study the different CVEs separately, and the capacity to adjust the results for the multiple known confounding variables, are necessary in this regard.

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