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Commentary

Beneficial Effects of CPAP Treatment in High-risk Subgroups of OSA Patients: Some Evidence, at Last

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In the last three decades, several studies underlined the clinical and pathophysiological links between obstructive sleep apnea (OSA) and cardiovascular risk [1]. Clinically, OSA patients are generally obese, often affected by systemic hypertension, diabetes, and dyslipidemia, and show a high prevalence of cardiovascular and cerebrovascular diseases [2]. Studies aimed at dissecting the pathophysiology of cardiovascular risk in OSA identified several intermediate mechanisms. Intermittent hypoxia during sleep is considered the main pathogenetic factor, and is associated with elevated sympathetic nervous activity, nocturnal blood pressure surges at the end of apneas, endothelial cell dysfunction and oxidative stress, inflammation and accelerated atherosclerosis [2]. In patients with type 2 diabetes, OSA is highly prevalent and may worsen metabolic disturbances, not only through the metabolic effects of hypoxia, but also by inducing sleep fragmentation which also negatively affects glucose metabolism [3]. The results of a longitudinal population study in over 150,000 subjects [4] support the concept of a bidirectional relationship between OSA and diabetes [3].

Longitudinal observational studies in OSA patients showed increased cardiovascular morbidity and mortality in untreated severe OSA, and a protective effect of CPAP treatment [5]. However, randomized controlled studies (RCTs) on the effects of CPAP on cardiovascular outcomes, such as the multicenter Sleep Apnea Cardiovascular Endpoints (SAVE) study [6], failed to show any protective effect of CPAP treatment on a composite cardiovascular endpoint in non-sleepy OSA patients with known coronary or cerebrovascular disease followed for 3.7 years. A recent meta-analysis including only RCTs on this topic reached similar conclusions but found a protective effect of CPAP use for ≥4 h/night [7].

The results of the SAVE study were cautiously acknowledged by the sleep community [8], as they cannot be extrapolated to symptomatic patients with OSA and daytime sleepiness. For ethical reasons, lack of daytime sleepiness was an inclusion criteria in the SAVE study, as in other long-term RCTs, and may in part explain the low adherence to CPAP treatment (3.3 h/night) [8]. Finally, the possibility that subgroups of patients at particularly high cardiovascular risk might benefit from CPAP treatment was not tested.

The study by Quan and coworkers [9] re-analyzed the data of the SAVE study by using latent class analysis to assess whether: a) subgroups of patients may show high risk for the composite cardiovascular outcome, and b) adequate CPAP use might be protective in such subgroups. Occurrence of diabetes in OSA patients with CAD or cerebrovascular disease increased the risk for the composite outcome, while adequate CPAP treatment, i.e. at least 4 h/night, decreased cardiovascular risk in diabetic patients with OSA, with the strongest effect in patients with cerebrovascular disease.

These results suggest that CPAP treatment might be protective in diabetic OSA patients, and efforts should be made to improve CPAP adherence in these patients. According to recent studies, the detrimental effects of OSA might be especially relevant in patients with multiple comorbidities, including diabetes [10]. In such patients, CPAP treatment may prevent mortality [11] or cardiovascular events [12].

While the study by Quan and coworkers carries a more optimistic view about the effects of CPAP treatment compared to the previous results of SAVE, some points deserve comment. First, the results should be replicated in other cohorts, also in consideration of the peculiar distribution of CAD-cerebrovascular disease according to race and gender in the SAVE cohort. Second, the mechanism of the protective effect of CPAP should be clarified. To date, evidence that CPAP treatment improves glycemic control in diabetic OSA patients is lacking [13]. On the other hand, compared to usual metabolic markers, assessment of end-organ damage could provide a better estimate of the impact of OSA and its treatment in diabetic patients [14,15]. Third, phenotypic characterization of OSA patients may identify other clusters, allowing refinement of the therapeutic approach. In addition to new RCTs on the effects of OSA treatment in patients with well-defined risk profiles, analysis of "big data" in large observational cohorts of OSA patients may help to overcome the limitations of RCTs, as discussed in a recent pro-con debate [8,16].

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Physiological and clinical phenotypes are increasingly studied in OSA patients [17], but the development of personalized medicine for OSA will require model validation in different cohorts, together with new analytical approaches. The results of the new analysis of the SAVE data suggest the opportunity to treat OSA in diabetics, but the big question on the effects of CPAP on cardiovascular outcomes remains open at the moment, and awaits further study.

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