Editorial

Obstructive sleep apnea—Hypertension link: almost there?

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High blood pressure (BP) is the dominant risk for non-transmissible chronic diseases, particularly, but not exclusively, cardiovascular disease (CVD) (1). Prevalence of hypertension is decreasing in industrialized countries, but the worldwide absolute number of individuals at risk is rising, mostly because of population ageing and the high prevalence of high BP in low and some middle-income countries (2).

Obstructive sleep apnea (OSA) is another common disease (3). Therefore, the possibility that hypertension and OSA co-exists in the same patient is high just by chance. To establish a causal relationship between them requires randomized clinical trials (RCT) showing that the treatment of OSA lowers BP. Additionally, a mechanistic explanation for the association is necessary. In this regard, there is substantial evidence that OSA leads to homeostatic cardiovascular changes potentially associated with high BP. Studies ranging from molecule (4), cell (5), and organ (6) level imply intermittent hypoxia, a landmark consequence of OSA (7), in the causation of high BP. Experimental models of OSA in dogs (8), rats (9), and mice (10) provided plausibility to causal mechanisms (11). Furthermore, experimentation in healthy human volunteers submitted to intermittent hypoxia supported the BP-rising effect of OSA (12). As a result of increased BP or due to other mechanisms, OSA has been implicated in the causation of stroke, heart failure, myocardial infarction, nocturnal sudden death, and arrhythmias (13). In face of these consequences, the diagnosis and management of OSA should be done by cardiologists, besides sleep and pulmonary specialists, neurologists, otolaryngologists, and clinicians (14).

For more than three decades, the detection of high BP in patients with OSA (15), and vice-versa (16), raised the interpretation that OSA was a risk factor for hypertension. Cross-sectional studies that identified such association were dismissed as a mere overlap of three risk factors for both diseases: sex, age, and obesity, since adjustment for adiposity and other risk factors lessened the crude risks of OSA. Eventually in the year 2000, a large cross-sectional, population-based study, managed to control for most of the confounders, identified an association of OSA and hypertension (17). In the same year, a sample followed during four years showed association of apneic events, even at a low rate, with increased risk for incident hypertension (18). This set of evidence aided the acceptance of OSA as a common cause of hypertension by the JNC, in 2003 (19).

Despite the positive associations demonstrated in a previous cohort study, more recent ones failed to confirm the OSA-hypertension connection (20,21) igniting again a debate that was considered settled.

If elimination of apneic events lowered BP, this could be considered a robust proof-of-concept for OSA causing hypertension. Besides tracheostomy, the only treatment capable of eliminating apneas is the continuous positive airway pressure (CPAP) (22). Although the efficacy of CPAP therapy is close to 100%, its effectiveness can be quite low due to poor patients' adherence and technical problems (23). Hence, most of the RCTs of CPAP as

antihypertensive cannot be used as a proof-of-concept. Adherence measured by the number of hours of CPAP used per night has been usually around 50% of sleep time, leaving a substantial number of respiratory events untreated. An additional problem is that some negative studies were not designed to assess hypertension, and employed varied methods for BP measurement [office, ambulatory blood pressure monitoring (ABPM), home BP monitoring]. Some articles reported BP changes in normotensive or controlled hypertensive subjects. Meta-analyses of studies using ABPM and resistant hypertension show significant BP reductions (24), but include articles in which the baseline BP was 129/75 mmHg (25). From a physiological point of view, only a marginal decrease in BP is expected below that level. For a trial to confirm pathophysiologically the OSA-hypertension association, it would be necessary to asses BP by ABPM (including measurement of nighttime dipping), with a sham CPAP control. Few experiments neared this goal (26).

Differently from less severe hypertension, OSA is a clear risk factor for resistant hypertension. We demonstrated, in a case-control study, an odds ratio of 4.8 (95% CI: 2.0–11.7) for OSA in patients with resistant hypertension (27). Understandably, CPAP therapy of OSA in resistant hypertensive patients—who were enrolled in the study with BP above 140/90 mmHg instead of 120/80 mmHg—showed larger effects. We conducted the first RCT controlled by sham-CPAP in resistant hypertension patients with BP of 148/88 mmHg at baseline (26).

The discrepancy between the strong association of OSA with resistant hypertension and its weak association with less severe hypertension, remains only partly explained by a biological gradient. The report from the Vitoria Sleep Cohort study advances the knowledge on this conundrum (28). This is a post hoc analysis of a longitudinal study designed to assess the association between OSA and hypertension. In the main report, the association between OSA and hypertension was non-significant after adjustment for confounding (21). In the present report, the authors explored the sex differences in the association between OSA and incidence of moderate to severe hypertension. A total of 1,521 subjects aged 30 to 70 years were followed for 7.5±0.8 years. OSA at baseline was measured by the respiratory disturbance index (RDI). Among men, the incidence of stage 2 hypertension increased in parallel with the increase in RDI. For a RDI ≥14, the odds ratio for stage-2 hypertension was 2.54 (95% CI: 1.09–5.95). The risks for women were similar, but not significant. The authors concluded that OSA is a risk for moderate to severe hypertension among men, but the lack of significance for women was due to the lack of statistical power (21 cases in 650 women versus 69 in 505 men).

The well-known a priori biological explanation for a sex difference in the OSA-hypertension relationship is the OSA-preventing effect of female hormones (29). Because around 75% of women in their sample were below 50 years old, i.e., in their reproductive age, hormonal influences might explain 77% of women being non-OSA cases. In any OSA severity category, men were twice as likely to develop stage 2 hypertension. Women older than 56 years with neck circumference >35.3 cm (n=25) were at about 30 times higher odds of incident hypertension than their younger and slimmer counterparts (n=526). While hormones and obesity explain sex differences in OSA prevalence, there is no easy way to elucidate sex differences in the consequences of OSA, namely, the incidence of stage 2 hypertension. It is necessary to consider the sample being underpowered to allow significant differences.

Beyond the sex difference, the novelty of this study was the finding of OSA being a risk factor only for stage-2 hypertension. It supports the concept of a risk gradient. Cano-Pumarega and associates' data are in a middle point of a spectrum which has at one end the low risk imparted by OSA for stage-1 hypertension and at the other extreme, the high risk for resistant hypertension. This intermediate risk for moderate to severe hypertension suggests that OSA is not a player at the inception of hypertension, when the classical pathogenic mechanisms of maladaptation to chronic sodium overload prevail. Later in life, as the prevalence of obesity and OSA increases, these two factors trigger additional mechanisms of BP increase, as sympathetic hyperactivity, oxidative stress, inflammation, and endothelial dysfunction. The addition of the OSA-mediated mechanisms will make already hypertensive individuals to progress to more advanced stages of hypertension. This is plausible considering Cano-Pumarega and associates' results for moderate to severe hypertension and the many studies at the extreme of the spectrum, involving resistant hypertension.

If such gradient is more than a statistical finding and is truly a biological, aging-dependent phenomenon, the approaches to abort the course of such irregular cardiovascular and respiratory adaptations should be focused on the prevention of obesity and hypertension at younger ages.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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