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CLINICAL REVIEW

Hypertension and sleep: Overview of a tight relationship

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SUMMARY

Autonomic cardiovascular control changes across sleep stages. Thus, blood pressure (BP), heart rate and peripheral vascular resistance progressively decrease in non-rapid eye movement sleep. Any deterioration in sleep quality or quantity may be associated with an increase in nocturnal BP which could participate in the development or poor control of hypertension. In the present report, sleep problems/disorders, which impact either the quality or quantity of sleep, are reviewed for their interaction with BP regulation and their potential association with prevalent or incident hypertension. Obstructive sleep apnea syndrome, sleep duration/deprivation, insomnia, restless legs syndrome and narcolepsy are successively reviewed. Obstructive sleep apnea is clearly associated with the development of hypertension that is only slightly reduced by continuous positive airway pressure treatment. Shorter and longer sleep durations are associated with prevalent or incident hypertension but age, gender, environmental exposures and ethnic differences are clear confounders. Insomnia with objective short sleep duration, restless legs syndrome and narcolepsy may impact BP control, needing additional studies to establish their impact in the development of permanent hypertension. Addressing sleep disorders or sleep habits seems a relevant issue when considering the risk of developing hypertension or the control of pre-existent hypertension. Combined sleep problems may have potential synergistic deleterious effects.

Introduction

Hypertension affects about 26.4% of the adult population worldwide. It ranks as the leading chronic risk factor for mortality, accounting for 13.5% of all deaths. Moreover, its prevalence is projected to grow and hypertension is expected to affect more than 1.5 billion people by 2025. Half of all strokes and ischemic heart disease events are attributable to high blood pressure (BP) [1,2]. BP values are normally distributed in the population and there is no natural threshold above which "hypertension" definitively exists and below which it does not. The risk associated with raised BP is continuous from as low as 115/75 mmHg, and the number of cardiovascular events doubles with each 20 mmHg increase for systolic or 10 mmHg increase for diastolic BP [3]. Nevertheless, certain definitions are used in the literature as well as in clinical practice in an effort to clarify the disease specificity/severity. According to the seventh report of the Joint National Committee [4], when BP is elevated above normal, but not to the level considered as hypertension, it is called "prehypertension". Prehypertension is BP values with a systolic BP from 120 to 139 mmHg or a diastolic BP from 80 to 89 mmHg. Values greater than or equal to 140/90 mmHg are considered as "hypertension" [3]. A normal BP profile is also characterized by a 10% fall in mean systolic BP values whilst sleeping compared to when awake, which is defined as the normal "dipping pattern" of BP at night. Patients are considered as "non-dippers" if they have a day–night systolic BP fall less than 10%; as "reverse dippers" if their night-time BP values exceed those of daytime, while "extreme dippers" present with a nocturnal BP fall of more than 20%. It is of note that there is increasing evidence that the mean nocturnal BP level is a major indicator of cardiovascular morbidity and mortality irrespective of the 24-h BP levels [5]. In this review we will see that sleep and sleep disorders can impact BP values and profile throughout 24 h.

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Abbreviations

ABPM	ambulatory blood pressure monitoring
ACTH	adrenocorticotrophic hormone
BP	blood pressure
BMI	body mass index
CARDIA	coronary artery risk development in young adults
CI	confidence interval
CPAP	continuous positive airway pressure
HPA	hypothalamus pituitary axis
PLMs	periodic limb movements in sleep
MADs	mandibular advancement devices
MSNA	muscle sympathetic nerve activity
NC	narcolepsy–cataplexy
NHNES	national health and nutrition examination survey
NREM	non-rapid eye movement sleep
OSA	obstructive sleep apnea
REM	rapid eye movement
RLS	restless legs syndrome
SHHS	sleep heart health study

Normal sleep architecture consists of four to five sleep cycles of approximately 90 min duration ach, with a cyclic alternation between non-rapid eye movement (NREM) and rapid eye movement (REM) sleep (Fig. 1A). NREM sleep is prominent at the beginning of the night whereas the duration of REM sleep increases during the last sleep cycles. The cardiovascular system is markedly affected by normal sleep with differential autonomic regulation during the different sleep stages [6,7]. Sympathetic nerve activity to the vasculature continuously decreases with the progressive deepening of NREM sleep [8–10]. Using heart rate variability analysis, it has been demonstrated that NREM sleep is indeed characterized by vagal parasympathetic predominance, with a decline in sympathetic activity that is most marked in slow-wave sleep (Fig. 1A). As a consequence, BP and heart rate decrease throughout NREM sleep, particularly during slow-wave sleep. This corresponds to the nocturnal dipping pattern of BP. During the night, normal individuals did not exhibit significant changes in cardiac output and the nocturnal fall in arterial pressure is actually the result of a decrease in total peripheral vascular resistance. Compared with when awake, in REM sleep sympathetic activity increases significantly and is highly variable (Fig. 1B). Particularly during the phasic component of REM, BP is highly changeable and approaches wakefulness levels. Baroreflex sensitivity increases during sleep but is more effective in buffering increases in BP during REM episodes occurring at the end of the sleep period, than earlier in the night (Fig. 1C). Such a physiological setting permits the s hypothesis that the regulation of nocturnal BP could be linked to sleep characteristics. Thus, sleep problems could be involved in the pathogenesis of non-dipping, prehypertension and subsequently in hypertension. Any disturbance in sleep quantity or quality, both explained either by delirious sleep habits or sleep disorders may contribute to the development of hypertension or an increase in its severity.

In the present work, we will successively address different sleep disorders and sleep habits reviewing their potential association with nocturnal BP control and hypertension.

Obstructive sleep apnea syndrome

Obstructive sleep apnea (OSA) is now recognized as a risk factor for the development of hypertension in European and US international guidelines. OSA and hypertension are linked in a dose–response fashion. This is true even when the usual confounding factors such as age, alcohol and/or tobacco consumption and body mass index are taken into account [11]. In a large prospective observational cohort followed for more than 12 y, it has been shown that compared with controls, the adjusted hazard ratios for incident hypertension were greatest among patients with severe OSA who declined continuous positive airway pressure (CPAP therapy) (1.96; 95% confidence interval (CI), 1.44–2.66), and among those non adherent to CPAP therapy (1.78; 95% CI, 1.23–2.58), whereas the hazard ratio was lower in patients with OSA who were treated with CPAP therapy more than 4 h per night (0.71; 95% CI, 0.53–0.94) [12]. OSA-related hypertension has several characteristics: it is commonly predominately diastolic and nocturnal leading frequently to masked hypertension and non-dipper status (Fig. 2 B_3) [13]. In diastolic hypertension the main mechanism for BP elevation is the increase in vascular resistance owing to sympathetic activation. Due to its nocturnal predominance, OSA patients are at high risk of presenting masked hypertension, i.e. normal clinic BP but elevated BP when 24-h ambulatory blood pressure monitoring (ABPM) is used. Baguet et al. [14] found that in 130 patients with newly diagnosed OSA and without cardiovascular history, the prevalence of hypertension was 35.4% and 30.0% of the patients presented with masked hypertension. Moreover, it has been recently reported that neither clinic BP measurement (in the physician's office), nor home self-BP measurements (three morning and three evening BP measurements made by the patients at home) were sufficient to detect masked hypertension in OSA patients, justifying 24-h ABPM as the gold-standard to detect abnormal BP in OSA patients [15]. In addition, OSA is by far the leading cause of refractory hypertension [16,17], and should be systematically investigated in this situation.

Regarding the specific association between sleep apnea and hypertension according to age; sleep apnea in children has been shown to impact BP, independent of age, sex, race, body mass index or waist circumference [18]. In children this association also has an impact on left ventricular remodeling [19]. Primary snoring is a clinical symptom that may lead to the diagnosis of sleep breathing disorders in children; however in the current literature its independent association with an increase in BP is disputed [20,21]. The strength of the association between sleep apnea and BP decreases with age [22]. In the elderly, sleep fragmentation due to other causes also contributes to poor BP control, independently of sleep apnea [23]. Longitudinal follow-up studies on large community-based cohorts [24] or sleep clinic based cohorts [25] reveal that the risks of "all-cause" mortality and cardiovascular mortality linearly increase with the severity of sleep apnea, independently of major confounders. Lavie et al. [26] initially proposed that sleep apnea-related mortality decreased with age such that only patients younger than 50 showed excess mortality. These results were later confirmed by Rich et al. [27]. Conversely, recent studies have shown an increased mortality rate in elderly patients with severe sleep apnea [28], particularly in OSA [29].

Three meta-analyses derived from 19 randomized controlled trials have demonstrated that continuous positive airway pressure (CPAP), the first-line therapy for moderate to severe OSA syndrome, reduces the 24-h mean BP by approximately 2 mmHg (pooled estimated effect). Haentjens et al. [30] looked at 12 studies assessing CPAP vs. placebo (sham-CPAP or pills), in a total of 512 patients. However, some of the studies included in the meta-analysis excluded hypertensive patients whilst others included only hypertensive patients. Furthermore, the presence of an anti-hypertensive treatment was not consistent. Nevertheless, they concluded that CPAP therapy induces a low (−1.69 mmHg) but significant reduction in mean 24-h BP. This BP reduction was of