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# HYPERTENSION AND SLEEP

*Jean-Louis Pépin, MD, PhD[1–4], Anne-Laure Borel, MD, PhD[2, 5], Jean-Phillipe Baguet, MD, PhD[2, 6], Renaud Tamisier, MD, PhD[1–4], Patrick Lévy, MD, PhD[1–4], Jean-Michel Mallion, MD[2, 6]*
[1]*INSERM ERI17, HP2 Laboratory (Hypoxia: Pathophysiology), Grenoble, F-38042, France*
[2]*Joseph Fourier University, Grenoble, F-38043, France*
[3]*Grenoble University Hospital, Pole de Rééducation & Physiologie, Grenoble, F-38043, France*
[4]*Grenoble University Hospital, Sleep Laboratory, EFCR, Grenoble, F-38042, France*
[5]*Grenoble University Hospital, Department of Endocrinology, Pôle Digidune, Grenoble, F-38043, France*
[6]*Grenoble University Hospital, Department of Cardiology, Grenoble, F-38043, France*

## Introduction

Cardiovascular control is markedly affected by normal sleep with a differential autonomic regulation of the cardiovascular system with the different sleep stages [1]. Blood pressure (BP) and heart rate (HR) decrease throughout non-rapid eye movement (NREM) sleep, particularly during slow-wave sleep (dipping pattern), whereas in REM sleep BP is highly variable and approximates wakefulness levels. During the night, normal individuals did not exhibit significant change in cardiac output, and the nocturnal fall in arterial pressure is actually the result of a decrease in total peripheral vascular resistance. Any disturbance in sleep quantity or quality, explained either by sleep habits or sleep disorders, may participate in hypertension development or severity.

In this article, we will successively review the different sleep disorders or sleep habits associated with hypertension and summarize the common pathophysiological intermediary mechanisms explaining the relationship.

## Obstructive sleep apnea syndrome and hypertension

Obstructive sleep apnea (OSA) is associated with changes in intra thoracic pressures during sleep reflecting variations in respiratory effort, frequent transient arousals, modifications in sleep structure, and intermittent hypoxia. All these factors have an impact on sympathetic activity and may result in long term sympathetic activation contributing to cardiovascular morbidity. During abnormal respiratory events there is a progressive increase in sympathetic activity and an acute rise in blood pressure, which correlates with the severity of oxygen desaturation. Acute respiratory events during sleep are superimposed on chronic adaptations of the cardiovascular system in response to long-term sleep apnea exposure, leading to daytime sustained elevation of sympathetic activity [2]. Obstructive sleep apnea syndrome (OSA) and hypertension are linked in a dose–response fashion. This is true even when taking into account usual confounding factors such as age, alcohol, tobacco consumption, and body mass index (BMI) [3]. Respiratory event-related intermittent hypoxia is the main stimulus leading to adrenergic and renin–angiotensin system (RAS) over-activity and thus to the development of the sustained increase in blood pressure (BP) seen in OSA patients. The endothelial dysfunction evidenced in OSAS also partly explains hypertension, owing to decreased vasodilation and enhanced vasoconstriction, resulting from NO availability reduction. Similarly, the hyperinsulinism often present in apneic subjects, especially when overweight, contributes to OSA-induced HT by favouring peripheral vasodilation impairment, endothelial dysfunction, sympathetic hyperactivity, and an increase in renal sodium reabsorption [4].

Hypertension associated with OSAS has several characteristics: diastolic and nocturnal predominance and commonly encountered masked hypertension with frequent non-dipper status. Furthermore, as OSAS is found in the vast majority of subjects with refractory hypertension, it should be systematically investigated in this situation.

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 OSAS, reduces the 24-h mean BP by approximately –2 mm Hg (pooled estimated effect). Haentjens et al. [5] looked at 12 studies assessing CPAP versus placebo (sham CPAP or pills), including a total of 512 patients. Some of the analyzed studies excluded hypertensive patients whilst others only included hypertensive patients. Furthermore, the presence of an antihypertensive treatment was not constant. This meta-analysis mainly showed that the reduction in mean BP over 24 hours with CPAP was low (–1.69 mm Hg) but significant ($p < 0.001$). This BP reduction is more marked if patients have severe OSAS and if they comply with CPAP treatment. Bazzano LA et al. [6] have taken into account 16 placebo-controlled studies comparing the effect of CPAP on BP over at least two weeks. Out of the 818 OSAS suffering patients included, the mean BP reduction with active treatment vs. placebo was –2.46 mm Hg (95% CI: –4.31 to –0.62) for SBP and –1.83 mm Hg (95% CI: –3.05 to –0.61) for DBP. The SBP and DBP falls were identical for day and night. The studies differed regarding to the BP parameters used (SBP, DBP, or mean BP), the type of control treatment used (8 used sham CPAP, 4 provided a pill, and 4 provided usual care alone), and the outcome measure (ABPM or clinical BP). Again, a significant BP reduction was associated with higher baseline BP levels, and higher BMI and severity of OSA. Mandibular advancement devices (MADs) are the only alternative treatment to CPAP. Even if available data are limited, using MADs has been reported to be associated with a significant reduction in 24-h diastolic blood pressure compared to an inactive oral appliance. The range of blood pressure decrease was similar to that achieved with CPAP [7].

## Sleep duration and hypertension

Sleep duration has decreased in the general population over the last 30 years [8]. In the US, the National Sleep Foundation reported an increase from 12% to 16% of subjects sleeping less than 6 hours on workdays between 1998 and 2005, reflecting voluntary sleep restriction. On the other hand, the prevalence of insomnia complaints was 23% in The Atherosclerosis Risk in Communities Study (ARIC), a prospective observational cohort involving 13,563 participants aged 45 to 69 years [9]. Two major community-based cohort studies, the Sleep Heart Health Study (SHHS) [10] and the National Health and Nutrition Examination Survey (NHNES) [11] have reported a relationship between self-reported short sleep duration and prevalence and incidence of hypertension. Gottlieb et al. [10] have demonstrated from SHHS that short and long habitual sleep duration are both associated with higher prevalence of hypertension when compared with subjects sleeping between 7 and 8 hours per night, after adjustment for possible confounders such as age, sex, race, obesity, apnea–hypopnea index, or lifestyle habits. Short sleep duration was associated with higher prevalence of hypertension in the Korean National Health and Nutrition survey 2001 [12]. Subjects participating in NHNES who had self-reported less than 5 hours of sleep by night demonstrated a higher incidence of hypertension after 8 to 10 years follow-up [11]. This association persisted, even though attenuated, when analyses were adjusted for confounders, body weight in particular.

The relationship between sleep duration and hypertension is age and gender dependent. Adolescents with shorter sleep duration assessed by actigraphy demonstrated higher prevalence of prehypertension [13]. Conversely, an association between sleep restriction and incident hypertension was not found in subjects between 60 and 86 years of age in the NHNES study [11]. Hypertension was not associated with sleep duration assessed by either self-report or actigraphy in a cross-sectional study of 5058 participants, aged 58 to 98 years of age in the Rotterdam Study [14]. Finally, considering short sleep duration, hypertension was both more prevalent and more incident in women only, in the Whitehall II Study [15].

Short sleep duration and insomnia, although classically related, are different entities. Insomnia entails dissatisfaction with the quality of sleep that can be explained or not by a true reduction in sleep duration. Individuals with short sleep duration do not necessarily suffer from insomnia since they can voluntarily restrict their sleep time. Insomnia is clearly related to psychiatric and psychosomatic disorders, and some insomniac patients have a misperception of their sleep quality. Whether insomnia is associated with increased somatic disorders, cardiovascular in particular, was controversial in the literature. Recently, Vgontzas et al. [16] have demonstrated in a population based study that only insomnia associated with sleep duration < 5 hours (proven by polysomnography) is associated with a five-fold increased risk of hypertension after adjustment for other sleep disorders. Accordingly, in middle-aged subjects of the NHNES, depression was associated with increased incidence of hypertension, but the strength of this link was weakened by 33% after adjustment for both sleep duration and insomnia, suggesting that these conditions may mediate the relationship between depression and hypertension [17].

### Pathophysiological mechanisms underlying short sleep duration and hypertension association

Sleep deprivation studies in normotensive subjects have demonstrated that BP was increased after nights of sleep restriction [18, 19]. This could mainly be activation of the hypothalamic-pituitary-adrenal axis and elevated sympathetic nervous system activity [19, 20]. Sleep deprivation has also been reported to be associated with systemic inflammation [21], oxidative stress, and endothelial dysfunction — all conditions favouring the appearance of hypertension.

## Restless legs syndrome (RLS), periodic limb movement disorder and hypertension

RLS is characterized by dysaesthesia and leg restlessness occurring predominantly at night during periods of immobility [22]. Unpleasant sensations and the irresistible need to move impair the ability to fall asleep and impair

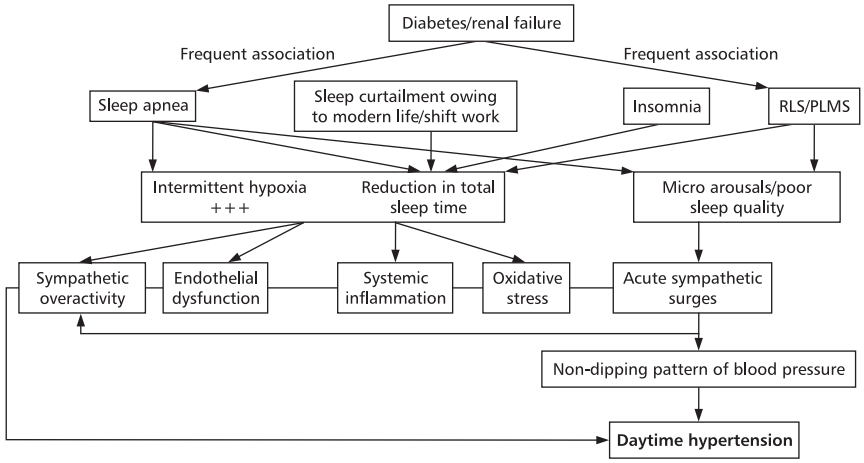


*Figure 1*. The common intermediary mechanisms for the link between sleep, sleep disorders, and hypertension. Alterations in sleep quality and sleep disorders are associated with intermediary mechanisms that favour the development of hypertension. Any combination of a pre-existing hypertension, whatever the cause, and sleep disturbances may increase hypertension severity and limit treatment efficacy

sleep quality. RLS is associated in 90% of cases with periodic limb movements in sleep (PLMS), which are repetitive flexions of the hips, knees, and ankles during sleep possibly ended by micro arousals. These micro arousals are associated with abrupt increases in blood pressure and sympathetic hyperactivity. PLMS also occur in patients without RLS and are found in 25% of patients undergoing routine polysomnography. Both RLS and PLMS are possibly associated with changes in sleep quantity and/or quality and have been incriminated as causes of hypertension [23].

Among 4000 men aged 18 to 64 years assessed by mail questionnaires, RLS sufferers were more likely to report hypertension after adjustments for age, witnessed apnea, smoking, and alcohol consumption [24]. In a study by Ohayon et al. [25] including 18,980 individuals from 5 European countries, 732 met criteria for RLS and presented with a 2-fold higher risk for elevated blood pressure (21.8 versus 11.1%, respectively, with an OR for the association between hypertension and RLS of 1.36 after adjustment for confounders). Winkelman et al. [22] studying 2821 participants in the Wisconsin Sleep Cohort found a non significant trend for the association between RLS and hypertension. The relationship seemed to be more robust only in those with severe, as opposed to moderate, RLS. This makes sense as only RLS and PLMS leading to significant impairment in sleep duration and quality are supposed to be linked with hypertension. In summary, the results of epidemiologic studies suggest a possible relationship between self-reported RLS symptoms and daytime hypertension and are more consistent when considering severe cases of RLS with daily symptoms [23].

## The common intermediary mechanisms for the link between sleep, sleep disorders, and hypertension (Figure 1)

Among the pathophysiological mechanisms associated with sleep restriction and present in different sleep disturbances such as OSAS, insomnia, and RLS/PLMS, nocturnal sympathetic activation is probably the key mechanism (Figure 1). This nocturnal sympathetic over activity limits the nocturnal BP fall and in turn leads to a diurnal permanent increase in sympathetic tone. Hypertensive subjects in whom the nocturnal BP fall is blunted (non-dipping pattern) are known to develop a higher degree of target organ damage and cardiovascular morbi-mortality. Systemic inflammation, oxidative stress, and endothelial dysfunction are also linked with sleep quantity and sleep disorders and may also influence the development and progression of hypertension. Hypertension is a frequent co morbidity of diabetes and renal failure, which are also frequently associated with OSAS and RLS/PLMS. In these situations both the primary disease and the associated sleep disorder act synergistically to elevate BP. Thus, we recently demonstrated that in type 1 diabetic subjects shorter sleep duration was associated with non-dipping pattern of BP [26]. The same detrimental situation occurs in drug-resistant hypertension. OSA is highly prevalent and present in more than 80% of the drug resistant hypertension patients. OSA suffering patients with additive shorter sleep duration exhibited higher BP values [27]. In summary, both alterations in sleep quality and sleep disorders are associated with intermediary mechanisms that favour the development of hypertension. Any combination of a pre-existing hypertension, whatever the cause, and sleep disturbances may increase hypertension severity and limit treatment efficacy.

## Conclusion and perspectives

In hypertension, sleep must be taken into account as a relevant life period [1]. Sleep restriction and sleep disorders are both and synergistically associated with increased prevalence and incidence of hypertension. Intervention studies are now needed to assess whether acting to promote voluntary longer sleep duration and/or efficiently to treat sleep disorders could prevent or reverse hypertension.

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