



Published in final edited form as:

Hypertension. 2019 October ; 74(4): 726–732. doi:10.1161/HYPERTENSIONAHA.119.13456.

Neurological Sleep Disorders and Blood Pressure: Current Evidence

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Abstract

Hypertension is a major determinant of cardiovascular morbidity and mortality and is highly prevalent in the general population. While the relationship between sleep apnea and increased blood pressure has been well documented, less recognized is emerging evidence linking sleep-related movement disorders such as restless legs syndrome/periodic limb movements of sleep and sleep-related bruxism with blood pressure (BP) dysregulation and hypertension. There is also recent literature linking narcolepsy-cataplexy with elevated BP and altered pressor responses, and there are data suggesting abnormal BP control in rapid eye movement sleep behavior disorder. It is thought that neural circulatory mechanisms, sympathetic activation in particular, comprise the predominant mediator underlying elevated BP in these neurological sleep disorders. There is very limited evidence that treating these sleep disorders may be beneficial in lowering BP primarily because this question has received very little attention. In this review, we discuss the potential pathophysiologic mechanisms underlying elevated BP in restless legs syndrome/periodic limb movements of sleep, sleep-related bruxism, narcolepsy-cataplexy and rapid eye movement sleep behavior disorder. We also examine the relationship between these sleep disorders and elevated BP and the impact of treatment of these conditions on BP control. Last, we discuss gaps in the literature evaluating the associations between these sleep disorders and elevated BP and identify areas for further research.

INTRODUCTION

Historically, research addressing the role of poor sleep in mediating the risk of hypertension has been largely dominated by studies on the effects of sleep disordered breathing on blood pressure (BP) regulation and consequent predisposition to hypertension. The association between obstructive sleep apnea (OSA) and hypertension has indeed been well described in several studies^{1, 2}. More recently, the impact of other sleep disorders on BP has been gaining attention. There is a growing body of literature linking sleep-related movement disorders including restless legs syndrome (RLS)/periodic limb movements of sleep (PLMS) and sleep-related bruxism with aberrant BP control and systemic hypertension^{3, 4, 5}. There

is also literature suggesting a relationship between other sleep disorders such as narcolepsy-cataplexy and rapid eye movement sleep behavior disorder (RBD) with abnormal BP responses^{4,5}. In normal sleep, BP is lower than wakefulness levels and is sleep-stage dependent, increasing intermittently with arousals from non-rapid eye movement sleep and during rapid eye movement (REM) sleep⁶⁻¹⁰. Autonomic mechanisms, specifically sympathetic predominance resulting from an imbalance between sympathetic and parasympathetic activity, is thought to play a key role in the pathophysiologic mechanisms underlying the relationship between these sleep disorders and hypertension, similar to that seen in the context of OSA¹¹⁻¹³. However, insufficient and disrupted sleep resulting from these conditions may play an important role in this association as well.

This review evaluates the evidence showing elevated BP in subjects with sleep-related movement disorders, narcolepsy-cataplexy and RBD, and examines possible underlying mechanisms. We further discuss the limited data regarding the effects of treatment of these sleep disorders on BP. The review is restricted to studies of adult subjects.

SLEEP-RELATED MOVEMENT DISORDERS AND HYPERTENSION

RLS/PLMS and hypertension

RLS is a fairly common condition, reported by 5-16% of the general population^{14, 15}. About 80% of patients with RLS have PLMS on polysomnography^{16, 17}. The latter are highly prevalent in the general population (21% in one study; 31% in men and 26% in women with 15 or more PLMS per hour of sleep in another study), and can be seen in patients without RLS as well, particularly in those older than 65 years^{15, 18}.

Evidence linking RLS with hypertension

A number of epidemiologic studies have shown an association between RLS and hypertension^{3, 19, 20}. Innes et al in their systematic review of 17 studies, most of which were cross-sectional in nature including the large Sleep Heart Health Study and the Wisconsin Sleep Cohort Study, found that in 10 studies there was a positive association between RLS and hypertension after accounting for common confounders such as BP, smoking status and sleep disturbances^{15, 21, 22}. RLS was positively associated with hypertension when symptom frequency exceeded more than half the days of the month^{15, 23}. It should be noted that these studies had significant variability in the definition of RLS, measurement of BP, and the use of RLS medications.

Some longitudinal studies that did not support a link between RLS and increased cardiovascular disease suggested a possible inverse relationship, with a trend toward or a significant increase in the incidence of RLS in those with hypertension²⁴. It is pertinent that two other large longitudinal studies, the Physician's Health Study and the Women's Health study, failed to show that RLS (based on a 3-question survey) was a risk factor for the development of cardiovascular disease, while another study, the Nurses' Health Study, demonstrated a significant association between a diagnosis of RLS of more than 3 years duration made by a physician and incident myocardial infarction as well as fatal myocardial infarction²⁵. With regard to hypertension, in a large longitudinal study of enrollees in the

Kaiser Permanente system, a significant association was noted between “primary” RLS and hypertension, although there was no association with overall cardiovascular disease ²⁶.

Collectively, the literature available thus far suggests that a relationship between RLS and hypertension is likely, but the direction and magnitude of this relationship are unclear at this time. Additionally, the potential modification of this association by other factors including the etiology of RLS and presence of PLMS is unclear ³. Last, the day-night BP pattern carries significant clinical relevance. However, the distinction between daytime vs nighttime hypertension as an outcome is not always clear in the studies evaluating the effects of these sleep disorders on BP ²⁷.

Evidence linking PLMS with hypertension

PLMS and hypertension are commonly comorbid; an older study estimated that 18% of subjects with essential hypertension had PLMS and 36.4% with stage 3 hypertension had PLMS ²⁸.

Individual PLMS are associated with increases of 25-30 mm Hg systolic BP and 10-15 mm Hg diastolic BP, from the start of the periodic limb movement (PLM) until 10-15 seconds after the end of the movement ²⁹. Increases in heart rate (HR) followed by cortical arousal on electroencephalography may precede the PLM and persist during and shortly after the event ³⁰⁻³³. PLMS associated with arousals appear to increase the risk of hypertension compared to PLMS without arousals, possibly due to increased sympathetic activity associated with arousals (Figure 1) ^{34, 35}.

In one study, the PLM index (PLMI) was shown to be an independent predictor of cardiovascular and cerebrovascular risk scores in subjects with chronic kidney disease ³⁶. In this study, moderate disease was defined as a PLMI of 15 per hour or greater and severe disease as a PLMI of 30 per hour or greater. In another study of older male subjects without prevalent hypertension at baseline, a PLMI of more than 30 per hour increased the risk of cardiovascular disease at 4 years; however, the risk of developing incident hypertension was not known ³⁷. Koo et al in their multi-ethnic community study found that the PLMI and PLM arousal index were independently associated with prevalent hypertension, particularly in African-American subjects ³⁴, possibly suggesting ethnic-dependent vulnerability to the hypertensive effect of PLMS.

Other studies have failed to demonstrate a significant association between PLMS and hypertension. In a study of subjects with RLS, those with a PLMI of greater than 35 per hour did not have a greater prevalence of hypertension but did have left ventricular hypertrophy ³⁸. A study of subjects with OSA showed no difference in the prevalence of hypertension in those with and without concurrent PLMS (defined as a PLMI of 5 or more per hour) ³⁹. Finally, one recent population-based cohort study did not find a significant association between PLMS and hypertension after accounting for confounders ⁴⁰.

Possible mechanisms underlying RLS/PLMS and hypertension

First, sudden increases in BP seen with PLMS, probably due to sympathetic activation and vagal withdrawal, may be responsible for elevated BP in sleep seen in subjects with RLS and

frequent PLMS^{35, 41-43}. As in subjects with OSA, this is thought to be an important mechanism underlying elevated BP in individuals with RLS/PLMS during the night (although the pattern and time frame may be different than that seen in subjects with OSA) and potentially during the daytime as well⁴⁴⁻⁴⁶. Other autonomic disturbances, such as impaired BP and HR reduction in response to the head-up tilt test and Valsalva maneuvers, have been demonstrated in subjects with RLS⁴⁶. Second, difficulty with sleep initiation and/or maintenance with shortened sleep duration and sleep disruption secondary to RLS could conceivably lead to the development of hypertension²¹. Third, sleep deprivation and PLMS have been shown to be associated with aortic stiffness and may serve to elevate cardiovascular risk, including that of hypertension, in patients with RLS and PLMS^{47, 48}. Fourth, increased evening cortisol is seen in the context of sleep deprivation and higher nighttime cortisol levels have been noted in subjects with RLS, suggesting involvement of inadequate sleep and of the hypothalamic-pituitary-adrenal axis^{49, 50}. Fifth, increased inflammation has been noted in subjects with RLS and may increase the risk of hypertension although it is unclear whether inflammation is the consequence or causation of RLS⁵¹. Sixth, impaired vascular endothelial function has recently been implicated as a potential pathophysiologic mechanism for elevated BP in subjects with RLS⁵². Seventh, metabolic dysfunction in the setting of sleep deprivation in RLS/PLMS could also contribute to the risk of hypertension³. Last, iron deficiency, which is an etiologic factor for RLS, may be a cardiovascular risk factor in itself, and has been shown to be associated with diabetes mellitus type 2 and increased mortality in coronary artery disease; on the other hand, intravenous iron has been noted to improve functional status and quality of life and reduce hospitalizations in patients with heart failure⁵³. Central iron deficiency with increased dopaminergic tone in the basal ganglia may contribute to abnormalities in regulation of sympathetic tone in subjects with RLS/PLMS⁵⁴.

Effects of treatment of RLS/PLMS on blood pressure

There are a few studies examining the effects of treatment of RLS/PLMS on BP. One study showed that the use of dopamine agonist medications at night decreased the number of PLMS and PLM-related HR response in subjects with RLS but did not change tonic sympathetic-vagal regulation; however, it should be noted that these findings were noted acutely, after a single medication dose; hence the effects of chronic treatment are unknown⁵⁵. Another study reported that treatment of RLS for 3 months led to a borderline significant decline in supine BP with no change in autonomic balance during wakefulness⁵⁶. Last, a recent study of 37 subjects showed that treatment of RLS with the dopamine agonist rotigotine patch decreased the number of PLM-associated BP spikes in sleep as well as total nocturnal systolic and diastolic BP elevations⁵⁷.

Further epidemiological studies of cardiovascular markers in subjects with RLS and randomized controlled therapeutic trials are required to help determine cardiovascular risk in patients with RLS/PLMS and whether treatment of these conditions lowers BP and ameliorates overall cardiovascular risk³.

Sleep-related bruxism and hypertension

Sleep-related bruxism is seen in 10-30% of the adult general population, is associated with stress, anxiety, alcohol and tobacco use, and commonly co-exists with OSA^{58, 59}. Bruxism is thought to arise from activation of subcortical structures, with possible abnormal interaction between the central and autonomic nervous systems^{59, 60}. Sympathetic activation may result from micro-arousals, and can start before the nocturnal bruxism episode and persist during the day⁶⁰⁻⁶³. A dose-response relationship between duration of the bruxism episode and sympathetic activity has been reported⁶⁴. Increases in BP have been noted during bruxism episodes in sleep and in the daytime⁵. Conversely, hypertension was shown to be an independent predictor of the intensity of sleep-related bruxism episodes in a recent study but the direction of the relationship remains uncertain⁶⁵. Medications used in the treatment of bruxism include beta-blockers and alpha-2 adrenergic agonists which are of limited benefit; their effects on sympathetic activity and BP in the context of bruxism have not been studied⁵⁸.

NARCOLEPSY-CATAPLEXY AND HYPERTENSION

Narcolepsy-cataplexy or narcolepsy type 1 is a relatively rare condition with an incidence of 25-50 cases per 100,000 in the general population, characterized by a deficiency of hypocretin or orexin in the central nervous system, resulting in excessive daytime sleepiness as the cardinal feature⁶⁶. OSA, obesity and other endocrine and psychiatric conditions are commonly seen to coexist in subjects with narcolepsy-cataplexy⁶⁷.

Narcolepsy-cataplexy and elevated nocturnal blood pressure

A study employing 24-hour BP monitoring showed nocturnal non-dipping status in one-third of patients with untreated narcolepsy-cataplexy versus 5% in controls (Figure 2)⁶⁸. Non-dipping diastolic BP status was significantly associated with narcolepsy-cataplexy (OR=12) and with percentage of time in REM sleep. Another study showed non-dipping BP in most of their cohort (n=35) with narcolepsy-cataplexy⁶⁹. Finally, a small case-control study using 24-hour beat by beat measurement of BP showed an increase in systolic BP during REM sleep in subjects with narcolepsy⁷⁰. It should be noted that these studies in subjects with narcolepsy-cataplexy have demonstrated non-dipping of BP at night, and perhaps more so in REM sleep, but they have not yielded evidence of an association with prevalent or incident hypertension. Also, the effect of comorbidities on this relationship is unknown⁶⁷.

Possible mechanisms underlying narcolepsy-cataplexy and elevated blood pressure

In narcolepsy-cataplexy, there is sleep disruption with frequent awakenings^{71, 72}. Hypocretin (or orexin) is deficient in narcolepsy type 1, resulting in sleepiness, Hypocretin/orexin is also thought to play a role in modulating autonomic function, but it is worth noting that a recent study did not show a relationship between orexin levels and nondipping BP at night^{69, 73-75}. Decreased cardiovagal and sympathetic activity during wakefulness have been reported in subjects with narcolepsy^{76, 77}. Thus, mechanisms underlying elevated BP in subjects with narcolepsy-cataplexy are currently not entirely clear but may involve the orexin system and may also include sympathetic dysregulation secondary to sleep

disruption; the latter possibly occurring as part of the disorder itself or secondary to PLMS that are commonly seen in these subjects ⁴.

Effects of treatment of narcolepsy-cataplexy on blood pressure

While orexin antagonism has recently been conceptualized as having potential antihypertensive effects, as noted above there are data suggesting elevated BP in subjects with narcolepsy and there are no human studies evaluating the effects of pharmacologic interventions targeting the orexin system on BP ⁷⁸. Treatment of narcolepsy-cataplexy often requires the use of psychostimulants that can potentially adversely impact BP and other cardiovascular outcomes ^{79, 80}. One recent study showed that subjects with narcolepsy-cataplexy treated with psychostimulants had higher diastolic BP and HR than those who were untreated ⁸¹. Furthermore, psychostimulants and anti-cataplectic medications had a synergistic effect on BP. Interestingly, while the percentage of REM sleep remained an independent predictor of 24-hour BP in treated and untreated subjects, endothelial function was similar in both of these groups. Thus, there is presently no evidence that treatment of narcolepsy/cataplexy lowers BP, but may in fact raise it due to the stimulant nature of the therapeutic agents.

RBD AND HYPERTENSION

RBD is a parasomnia characterized by intermittent loss of muscle atonia during REM sleep and dream enactment, manifested in the form of complex, often violent, motor activity. Estimated to occur in 0.4-0.5% of the general population ^{82, 83, 84, 85}. RBD generally presents with late onset and is more frequent among males ⁸⁶. RBD ensues from degeneration of brainstem regions governing REM sleep, and is a well-established precursor of alpha-synucleinopathies, and mostly Parkinson's disease ⁸⁷. Manifestations of aberrant autonomic cardiovascular function have been well documented in RBD, suggesting altered sympathetic adrenergic and vagal control ^{88-91, 92}. BP dysregulation is indicated by abnormal BP response to the orthostatic standing test, head-up tilt test, and Valsalva maneuver, as well as more frequent symptoms of orthostatic hypotension ^{89, 93-97}. However, it is unclear if these changes represent part of the prodrome or the presence of the underlying alpha-synucleinopathies themselves, or whether they reflect the effects of RBD on BP. There appear to be no differences between patients with RBD and healthy subjects with regard to resting BP ⁸⁹. Thus, despite the disrupted sleep occurring in RBD, there is currently a lack of evidence that RBD may be a risk factor for development of hypertension. Studies yielding data to support or refute such an association are needed.

CONCLUSIONS

In this review, we have presented contemporary data on the nexus between neurological sleep disorders, altered BP control and hypertension risk. Available literature favors an association between RLS/PLMS and hypertension. The relationship between sleep-related bruxism and elevated BP as well as between narcolepsy-cataplexy and elevated nighttime BP requires further study. Some pathophysiologic pathways underlying the association with hypertension may be common to all of these sleep disorders, such as autonomic imbalance with increased sympathetic activity, while other mechanisms may be more specific to the

individual sleep disorders. It is notable that these disorders are highly prevalent in childhood although unlikely to be diagnosed and treated during that time; hence, autonomic dysfunction emerging in childhood may be a precursor state in these individuals manifesting with elevated BP later in life.

The mechanisms underlying elevated BP seen in subjects with RLS/PLMS may be multifactorial and include the effects of awakenings and insufficient sleep on BP, with elevated cortisol and iron deficiency potentially playing a role in addition to increased sympathetic outflow. The direction and strength of the relationship between RLS/PLMS and hypertension as well as the modifying effects of etiologic factors of sleep-related movement disorders on hypertension needs clarification. The impact of treatment of RLS/PLMS and treatment of bruxism on blood pressure also needs further study.

There is early evidence associating narcolepsy-cataplexy with elevated BP at night, particularly in REM sleep and with nocturnal non-dipping BP status. Autonomic mechanisms may be mediating factors but additional studies are required to confirm this relationship. Much needs to be clarified in terms of underlying pathophysiologic mechanisms and effects, if any, of treatment of narcolepsy-cataplexy on BP, particularly the effects of psychostimulant medication. With regard to other disorders of excessive sleepiness such as idiopathic hypersomnia, it is unknown whether there is any linkage with hypertension. Work addressing this gap is warranted.

In spite of abundant data on BP dysregulation in RBD, there is a dearth of published literature addressing whether this sleep disorder is associated with hypertension. The role of parasomnias in the development of hypertension also requires further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

SOURCES OF FUNDING

Dr. Somers is supported by research grants from the National Institutes of Health (HL 65176, HL 134885).

DISCLOSURES

Dr. Mansukhani is the principal investigator on a research grant funded by ResMed Foundation evaluating the effects of adaptive servoventilation treatment of central apnea syndromes on healthcare utilization that is not relevant to the current work. Dr. Mansukhani is the recipient of the Paul and Ruby Tsai and Family Fund Career Development Award at Mayo Clinic.

Dr. Covassin is supported by a research grant from the American Heart Association (16SDG27250156) and the Mayo Clinic Marie Ingalls Research Career Development Fund.

Dr. Somers is a Consultant for Respicardia, ResMed, U-Health, GlaxoSmithKline, Roche and Bayer. He is an investigator on the SERVE-HF Steering Committee and is working with Mayo Health Solutions and their industry partners on intellectual property related to sleep and cardiovascular disease. The Philips Respironics Foundation has provided a gift to Mayo Foundation.

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RESEARCH AGENDA

- Clarify the direction and strength of the relationship between RLS and hypertension in prospective longitudinal studies
- Ascertain the mechanistic role of etiologic factors of RLS in this relationship
- Determine whether and to what extent PLMS mediate the effects of RLS on daytime and 24-hour BP
- Epidemiologic studies on cardiovascular risk biomarkers in patients with RLS and PLMS
- Randomized controlled trials to assess whether treatment of RLS/PLMS decreases BP and overall cardiovascular risk
- Evaluation of the effects of sleep-related bruxism and its treatment on BP
- Determine whether narcolepsy is an independent risk factor for the onset or development of hypertension
- Elucidate underlying pathophysiologic mechanisms for elevated BP in narcolepsy and effects of treatment of narcolepsy on BP and on control and progression of comorbid hypertension
- Clarify the effects of RBD and other parasomnias on BP
- Investigate the cross-sectional and longitudinal association between the above mentioned sleep disorders and resistant hypertension
- Determine whether the postulated relationships are modulated by sex, race/ethnicity, and age

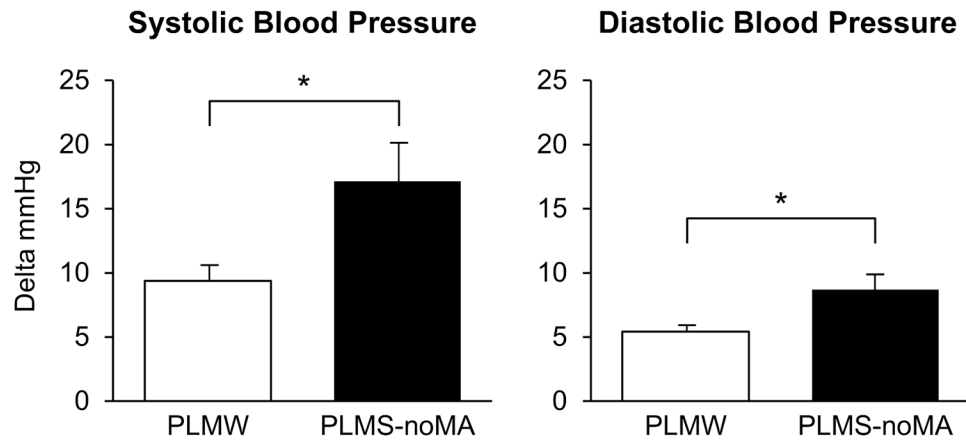


Figure 1. Mean SBP and DBP increments associated with PLMW and PLMS (reproduced with permission from ³⁵)

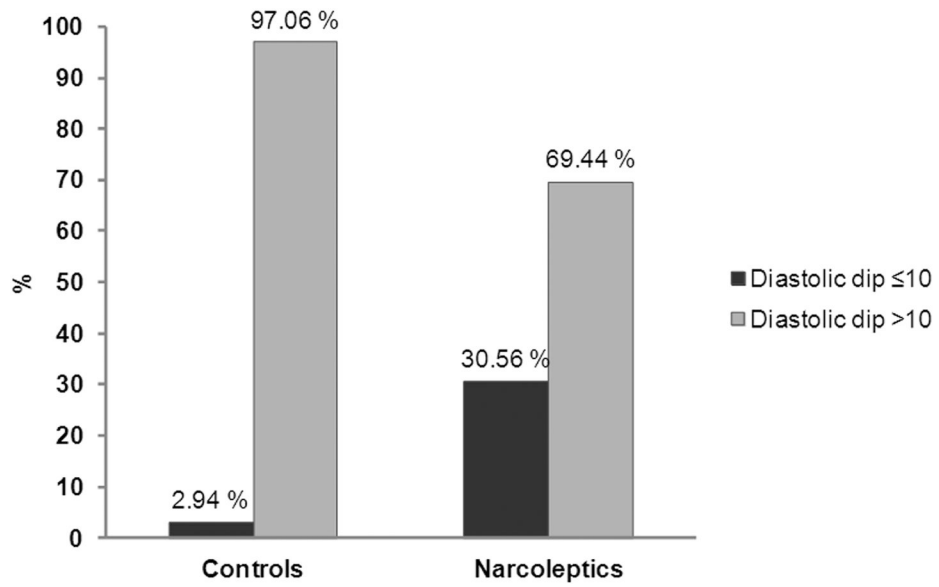


Figure 2.

Non-dipping diastolic BP profile in patients with narcolepsy-cataplexy (n=36) and in controls (n=42)

(reproduced with permission from ⁶⁸)

Abbreviations: noMA=no microarousals, SBP=systolic blood pressure, DBP=diastolic blood pressure, PLMW=periodic limb movements of wakefulness, PLMS= periodic limb movements of sleep