Sleep Disorders, Including Sleep Apnea and Hypertension

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There is mounting evidence for an association between sleep disorders and hypertension. In obstructive sleep apnea (OSA), there are plausible biological reasons for the development of hypertension, and treatment of OSA results in modest (2–3 mm Hg), adherence-dependent decreases in blood pressure, with larger effects evident in those with resistant hypertension. However, prospective, population-based cohort studies have not yet convincingly demonstrated a link between OSA and incident hypertension, and adequately powered controlled trials of CPAP for the prevention or treatment or hypertension are lacking. While associations have been identified between short sleep duration, insomnia, restless legs syndrome (RLS), shift work, and hypertension, the causative role of these conditions/circumstances is not proven, and further well-designed pathophysiological and/or interventional studies are needed. Particular emphasis should be placed on defining subgroups of hypertensive OSA patients that stand to benefit most from OSA treatment and in understanding the link between sleep apnea and hypertensive disorders of pregnancy. Well-controlled intervention studies are needed in populations with short sleep duration, insomnia, shift work sleep disorder, and RLS to confirm their putative links with hypertension.

Keywords: blood pressure, hypertension, insomnia, restless legs, shift work, sleep apnea, sleep disorders.

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There is considerable evidence for an association between sleep disorders and hypertension. However, uncertainty remains as to the extent to which sleep disorders cause hypertension, and to what degree the treatment of sleep disorders is beneficial for blood pressure (BP) reduction.

This review presents the latest research on the link between sleep disorders and hypertension, focusing on results from epidemiological studies and potential underlying pathophysiological mechanisms. Areas for further research and clinical change are highlighted.

OSA AND HYPERTENSION

Epidemiology

Results from epidemiological studies investigating the association between obstructive sleep apnea (OSA), the most common type of sleep-disordered breathing (SDB), and hypertension have been inconsistent. While major cross-sectional studies have found an association between the 2 conditions,[1–3] conflicting results have arisen from prospective studies.[4–7] The Sleep Heart Health Study (SHHS), one of the largest community-based multicenter cross-sectional studies (6,152 participants, ≥40 years, 53% female), found an increased odds ratio (OR) of 1.37 (95% confidence interval, 1.03–1.83) for hypertension for those with severe OSA (compared with those without OSA, i.e., apnea–hypopnea index, AHI < 1.5/hour) after adjusting for confounders.[1] In the same study, when comparing highest and lowest categories of sleep time with oxygen saturation <90% (≥12% vs. <0.05%), the adjusted OR for hypertension was 1.46 [1.12–1.88].

In contrast, differing results have emerged on the association between OSA and hypertension from prospective studies.[4–7] The Wisconsin Sleep Cohort Study (n = 709) indicated that there was a dose–response association between SDB at baseline and the presence of new-onset hypertension 4 years later that was independent of known confounding factors.[4] Similarly, the Zaragoza Sleep Cohort Study (n = 1,889), a prospective observational study of patients with SDB (median follow-up 12.2 years), found that in comparison with their control group (participants without OSA), those with untreated OSA had an increased adjusted risk of new-onset hypertension, and CPAP-treated OSA was associated with a decreased adjusted risk of hypertension.[7] However, the Vitoria sleep cohort found no association between OSA and incidence of hypertension in the 1,557 participants who completed follow-up at 7.5 years (after adjustment for confounding factors).[6] Furthermore, 5-year follow-up of the SHHS found that in 2,470 participants who did not have hypertension at baseline, adjustment for BMI resulted in AHI no longer being a significant predictor of incident hypertension.[5] Reasons for these conflicting results require further investigation.

The potential for OSA to cause hypertension is supported by studies of OSA treatment on BP. A 2015 meta-analysis

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found that CPAP therapy (compared with inactive control, n = 44 studies) reduced systolic BP by 2.5 [1.5–3.5] mm Hg and reduced diastolic BP (DBP) by a similar amount.[8] Mandibular advancement devices resulted in equally modest decreases in systolic BP and DBP. However, whether these modest changes in BP following treatment of OSA are sufficient to prevent the onset of hypertension or to treat existing hypertension is uncertain. A parallel-group randomized controlled trial (n = 725) of CPAP treatment in nonsleepy patients with OSA found that CPAP therapy did not result in a significant reduction in the incidence of hypertension or cardiovascular events (median follow-up 4 years) compared with usual care[9]; although, this study may have been underpowered.

Pharmacological treatment of hypertension in those with comorbid OSA is generally more effective than CPAP therapy for reducing BP; for example, a study comparing CPAP with valsartan in patients with untreated hypertension and OSA found that valsartan-treated participants experienced 4 times the decrease in BP than those treated with CPAP.[10] Meta-analytical evidence indicates that treatment of OSA with CPAP is somewhat more useful in patients with hypertension that is resistant to pharmacological treatment (pooled estimated mean systolic BP change −7.21 [−9.04 to −5.38] mm Hg and mean DBP change −4.99 [−6.01 to −3.96] mm Hg).[11]

There has been increasing attention on the relationship between OSA and hypertensive disorders of pregnancy.[12–16] A prospective cohort study, in which 3,705 pregnant women had home-based objective sleep assessment, found that the early and midpregnancy adjusted ORs for pre-eclampsia when OSA was present were 1.94 [1.07–3.51] and 1.95 [1.18–3.23].[12] Those with greater severity of SDB had a higher risk of the hypertensive disorders of pregnancy.[12] Other studies have had similar findings; a 2014 meta-analysis of studies using symptom-based definitions of SDB identified a significant relationship between maternal SDB and gestational hypertension and/or pre-eclampsia (OR, 3.11 [2.28–4.25])[17]; similarly, a significant association between the same conditions was present when objective sleep recordings were used to define SDB (OR, 2.25 [1.13–4.52]).[17] Currently available research on CPAP therapy for prevention/treatment of hypertensive disorders of pregnancy is limited but is suggestive of benefit; a 2018 review described 7 previous studies, all of which had significant methodological limitations (such as small sample and short intervention periods).[18] Thus, large-scale randomized controlled trials are needed to evaluate the impact of SDB treatment on hypertensive disorders of pregnancy.

Potential mechanisms

Multiple pathways, some bidirectional, link OSA with hypertension (Figure 1). Increased BP in people with OSA is hypothesized to occur primarily due to sympathetic nervous system overactivity. Overnight intermittent hypoxia and negative intrathoracic pressure lead to chemoreceptor activation and increased sympathetic outflow that persists during wakefulness.[19] In people with OSA, changes occur in regions of the brainstem known to be responsible for setting resting sympathetic activity; changes that are reversible with CPAP therapy.[20]

Intermittent hypoxia in OSA also results in increased oxidative stress, metabolic dysregulation, and systemic inflammation, contributing to vascular remodeling, endothelial dysfunction, and atherosclerosis[21]; this predisposes the individual to hypertension, and hypertension itself is likely to contribute to vascular remodeling and endothelial dysfunction (thereby being a bidirectional relationship).[22] The hypothesis that OSA leads to endothelial dysfunction is supported by meta-analytical evidence showing that CPAP improves endothelial function in people with OSA.[23]

Increased fluid volume may also play a role in linking OSA with hypertension.[21] Fluid overload in the end-stage renal disease predisposes to SDB by increasing upper airway edema and reducing lung volume, which together decrease upper way size.[21,24–27] In pregnancy, increased fluid volume may similarly predispose the mother to OSA and the development of hypertension.[28]

Aldosterone, a potent mineralocorticoid that regulates renal electrolyte balance, may also contribute to the development of hypertension in OSA.[21] OSA causes hyperaldosteronism by stimulation of the renin–angiotensin system as evidenced by reduced plasma renin and angiotensin II levels following CPAP treatment.[21,29] Hyperaldosteronism can lead to hypertension through several mechanisms including (i) a higher incidence of metabolic syndrome through altered carbohydrate metabolism, (ii) vascular remodeling *via* pathological collagen synthesis, and (iii) electrolyte imbalances leading to abnormal fluid retention.[30,31] Of particular interest is that hyperaldosteronism might also act to increase the severity of OSA. In patients with resistant hypertension, hyperaldosteronism is associated with both an increased prevalence and severity of OSA, and the severity of OSA is reduced by aldosterone blockade, and following renal denervation.[21,32,33] Thus, a bidirectional relationship may exist, whereby OSA causes hyperaldosteronism (and thereby hypertension), and this in turn increases the severity of OSA. Data from animal models suggest 2 plausible explanations. Firstly, aldosterone, which acts on central mineralocorticoid receptors, increasing brain renin–angiotensin activity and oxidative stress[34] has the potential to disrupt central nervous system respiratory control.[21] Secondly, increased aldosterone levels disrupt endothelial integrity and increase paracellular permeability, which could play a direct role in increasing para-pharyngeal edema, leading to more upper airway obstruction.[21]

Given evidence for at least 1 bidirectional pathway linking OSA and hypertension, it is interesting to note that a 2016 systematic review (11 studies) assessing the effects of antihypertensive medications on the severity of OSA found that treatment with antihypertensive agents results in a small but statistically significant reduction in the severity of OSA, with a greater reduction specifically for diuretics (likely due to a reduction in the plasma and extracellular fluid volume).[35]

Clinical implications and future research directions

Generally, improvements in BP in response to treatment of OSA using weight loss, CPAP, or mandibular advancement device therapy are modest (e.g., reductions in SDB

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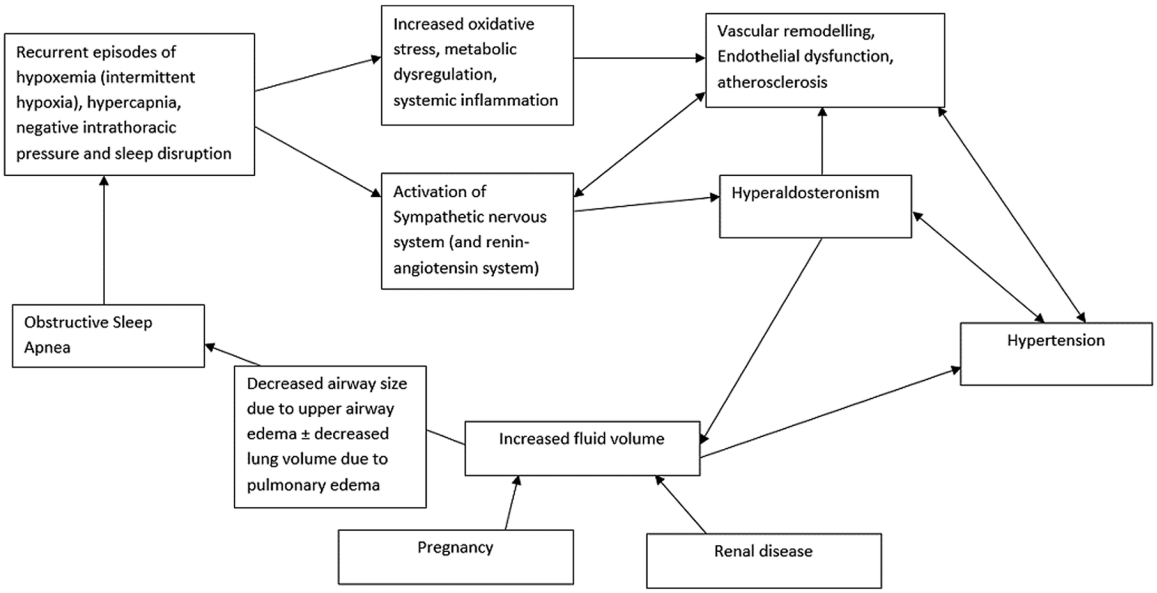

Figure 1. Mechanisms linking obstructive sleep apnea (OSA) with hypertension.

and/or DBP of 2–3 mm Hg), with best results often seen in those with treatment-resistant hypertension.[8,36,37] The available evidence indicates that patients with resistant hypertension and suspected OSA should be prioritized for OSA investigations and treatment. However, for the majority of patients with OSA and hypertension, the principles of management should be to control OSA-related symptoms (e.g., sleepiness, mood disturbance), when they are present, with CPAP or a similar effective treatment while ensuring that BP is optimally controlled with medication.

More research into the efficacy of OSA treatment in reducing risk of hypertensive disorders of pregnancy is needed.[16,38] Further research is also needed to ascertain which subgroups with OSA and hypertension will benefit most from OSA treatment. A recent example of this personalized approach to management of hypertension in OSA was the finding that BP reduction in response to CPAP in patients with resistant hypertension could be predicted from the levels of specific blood microRNAs.[39,40]

SLEEP DURATION ABNORMALITIES AND HYPERTENSION

Epidemiology

Sleep habits are influenced by social, cultural, behavioral, environmental, and genetic factors,[41] and these can all affect sleep quality, timing, and duration. Sleep duration is the easiest aspect of sleep to measure and the most studied thus far. It is usually defined as the self-reported average number of hours of sleep obtained in a 24-hour period. Both long and short sleep duration has been associated with adverse health outcomes, such as cardiovascular disease,[42,43] diabetes,[44,45] and poor self-rated health.[46] There is evidence suggestive of an association between variation in sleep duration and all-cause mortality.[47–49]

Short sleep duration, usually defined as <5–6 hours of sleep in a 24-hour period, has been associated with increased risk of hypertension in a number of cross-sectional studies,[41,50–52] and this association may be stronger among women. However, most studies of sleep duration and hypertension fail to account for the presence and severity of OSA, which is a confounding factor since SDB is also associated with an increased risk of hypertension. In addition, there is reliance on self-reported sleep duration rather than objective measurement using actigraphy or polysomnography. A recent meta-analysis of over 5 million participants showed that short sleep was significantly associated with hypertension (relative risk 1.17 [1.09–1.26]).[53]

Sleep extension effects on BP in short sleepers have been infrequently studied.[54] One study of 2,782 Korean participants investigated whether weekend "catch-up sleep" may lead to reduced risk of hypertension.[55] In those subjects who slept <6 hours/night, there was an increased OR for hypertension (OR, 1.73 [1.13–2.64]) compared with individuals who slept more than 7 hours a night. Interestingly, 1 hour of weekend "catch-up sleep" was associated with a significantly reduced risk for hypertension (OR, 0.83 [0.72–0.95]). This is an important area for future research.

Several studies demonstrate increased mortality in long sleepers (defined as ≥8 hours of sleep in a 24-hour period).[56] Recent meta-analyses and a systematic review have not consistently demonstrated an association between long sleep duration and the development of hypertension.[50,56,57] It is likely that long sleep duration is a marker of ill health due to another confounding factor or illness.

Potential mechanisms

Sleep has a role in altering autonomic nervous system and circadian rhythm function and other physiological events that are important in BP control.[58] During normal sleep, BP is reduced, and this is known as "nocturnal dipping." This physiological response occurs due to reduced sympathetic output, recumbency, and muscle relaxation.[59] A reduction of 10–20%

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in mean nocturnal BP (both systolic and diastolic) compared with mean daytime BP is considered normal. However, "non-dippers" have been identified; i.e., individuals whose BP does not reduce during sleep. Lack of nocturnal dipping of BP is a strong, independent predictor of cardiovascular risk, suggesting that the act of sleep itself (and potentially insufficient or poor quality sleep) plays an essential role in BP control. Few studies have investigated these proposed mechanisms.

Clinical implications and future research directions

Public education and health practitioner education programs need to be implemented to emphasize the importance of sleep for overall health. It is recommended that adults obtain 7–9 hours of sleep in a 24-hour period.[60] It is also important to establish standardized tools for sleep extension and determine the impact of these tools on BP.

INSOMNIA AND HYPERTENSION

Epidemiology

Lack of a standardized definition of insomnia is a limiting factor for insomnia research. Most studies of insomnia use self-reported symptoms, and few utilize objective measures of sleep and sleep disruption (such as polysomnography).[61] Similarly, the measures of hypertension used within insomnia-related studies have been varied, including self-report, antihypertensive usage, and physician measured BP and 24-hour measures.

A recent meta-analysis of insomnia and hypertension has reviewed this area in detail.[62] There are inconsistent and conflicting results thus far, which is likely to be due to confounding factors including variable definitions of insomnia and hypertension, differences in the duration of insomnia and severity of insomnia symptoms, and measurement of daytime consequences. Overall conclusions suggest that when insomnia is frequent, chronic, and/or associated with short sleep, there is a strong association with BP. This may suggest that it is the short sleep duration rather than the other features of insomnia that have the most impact on BP. However, further research is needed.

Potential mechanisms

While few studies have been conducted on this topic, research has shown that both the diagnosis of insomnia and the severity of the sleep disturbance (including hyperarousal) are related to overactivation of the hypothalamic–pituitary–adrenal axis and the hypersecretion of cortisol.[61] Activation of the autonomic nervous system and the immune system and the development of inflammation due to insomnia may also contribute to hypertension. Each of these pathological changes may impact heart structure, coronary vasculature, and cardiac conduction, but more research is required.[62]

Clinical implications and future research directions

A priority for this area is adoption of a standardized definition of insomnia and hypertension as well as longer duration of follow-up (>6 months). The need to account for confounding factors, such as sleep and mood disorders, also needs to be addressed. Clinical trials are needed to determine whether treatment of insomnia leads to improved BP and/or reverses the nondipping BP pattern.

SLEEP DISRUPTION AND HYPERTENSION

Sleep disruption often occurs as a result of lifestyle or work commitments. In today's 24-hour society, demand for nighttime and rotating shift work is increasing. It is estimated that in the United States, 29% of workers engage in alternative shifts and 15% of the workforce undertake regular night shifts.[63] Similarly, a high prevalence of shift work has been reported in the European Union (23% of men, 14% of women).[64] In Australia, 16% of the workers are employed in shift working industries,[65] and in Japan, 23% of workers are engaged in this mode of work.[66]

Evidence suggests that shift work is a risk factor for hypertension and cardiovascular disease. However, there are inconsistencies in the literature, and the findings are inconclusive. An early (1999) meta-analysis on the relationship between shift work and cardiovascular disease reported mixed findings, with ORs varying from 0.4 to 3.6 (17 studies).[67] However, many of the studies were of poor quality, and there was significant heterogeneity across the studies due to methodological differences (e.g., nonstandardized definitions of shift work, length of exposure, and questionable comparison groups). A later review (2011), focusing on the link between ischemic heart disease and shift work, concluded that although there is some evidence for an increased risk, the evidence was not particularly strong due to similar methodological limitations.[68]

A 2017 meta-analysis (27 studies, 394,793 participants) concluded that there is a significant relationship between rotating shift work and hypertension;[69] there was a 31% increased risk for hypertension in longitudinal cohort studies, pooled OR 1.31 [1.07–1.60], and a 10% increased risk in cross-sectional studies OR 1.10 [1.00–1.20]. When focusing the meta-analysis on rotating shift workers only, there was a 34% increased risk of hypertension, while the set night shift workers did not show a significantly increased risk, suggesting that rotating and alternating shift schedules pose a greater insult to the cardiovascular system compared with routine night shifts. Another even more recent review also found that there is a significant association between shift work and poor health outcomes including hypertension, dyslipidemia, heart disease, diabetes, depression in men.[70]

Taken together, these recent larger and higher quality studies suggest that there is a significant association between shift work and hypertension, particularly for people working rotating shifts.

Potential mechanisms

The mechanisms underlying the link between shift work and hypertension are likely to be multifactorial and are not yet understood. Factors proposed to link the conditions include circadian misalignment, chronic sleep restriction, social

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disruption, and behavioral changes (poorer diet, reductions in physical activity) all of which increase the likelihood of obesity and hypertension.[71] A systematic review has found that there is a significant relationship between shift work and body weight, likely driven by dietary habits and reduced physical activity.[72] Circadian misalignment commonly occurs in shift workers as their behavior and environmental cycles become misaligned with their endogenous circadian rhythms. For example, an 8-day laboratory study showed that circadian misalignment increased 24-hour systolic BP and DBP by 3.0 mm Hg and 1.5 mm Hg, respectively.[71] Furthermore, there was a significant increase in cardiovascular markers including IL-6, CRP, resistin, and TNF-alpha ranging from 3% to 29%. Another contributing risk factor for hypertension in shift workers is short sleep duration. One large epidemiological study has found that short sleep significantly ($P < 0.001$) increased the risk for central obesity by 12% (adjusted HR 1.12 [1.07–1.17]), for elevated fasting glucose by 6% (adjusted HR 1.06 [1.03–1.09]), for high BP by 8% (adjusted HR 1.08 [1.04–1.13]), for low high-density lipoprotein cholesterol by 7% (adjusted HR 1.07 [1.03–1.11]), for hypertriglyceridemia by 9% (adjusted HR 1.09 [1.05–1.13]), and for metabolic syndrome by 9% (adjusted HR 1.09 [1.05–1.13]).[73] Coexisting sleep disorders in shift workers may also partly explain the increased prevalence of hypertension in this population. For example, 34% of police officers in the United States, who are frequently required to do shift work, have been found to have OSA, followed by 7% moderate-to-severe insomnia,[74] while 60% of Australian truck drivers have OSA.[75]

Clinical implications and future research directions

The major impact of shift work, particularly rotating shifts, is impaired daytime alertness and functional performance, with clear occupational safety risks. When these daytime impacts become significant enough, a formal diagnosis of shift work disorder can be made; this disorder has been found to affect 10–32% of shift workers.[76–78] The diagnostic criteria for shift work disorder are tailored to identify daytime alertness impairment, and there is a lack of evidence to suggest that individuals at high risk of shift work disorder are also the subgroup of shift workers at higher risk of hypertension or cardiovascular disease. Furthermore, there are currently no trials to indicate that BP is reduced when shift work disorder is properly managed.

The main targets for management of shift work disorder include treating comorbid sleep disorders, promoting sleep during rest periods, and promoting alertness while engaged in work through personalized sleep/wake/nap scheduling and education to improve sleep hygiene and behavioral/dietary choices.[65] It is plausible that strategies to promote sleep and wakefulness and more optimized circadian alignment would also promote improvements in cardiometabolic function and reduce BP in shift workers, but there is no evidence for this at present. While on shift, alertness is the main goal; countermeasures such as targeted caffeine, napping, and use of wakefulness promoters (e.g., modafinil or armodafinil) may be helpful in certain situations, but these agents may exacerbate hypertension.[65]

There is ongoing research into biomarkers of alertness/circadian phase as well as biomathematical modeling to help predict and efficiently treat alertness failure.[65] These decision support tools still require testing in adequately powered randomized controlled trials and will need to take into account the risk of hypertension, cardiometabolic dysfunction, and mental health problems in shift workers.

RESTLESS LEGS SYNDROME AND HYPERTENSION

Epidemiology

Restless legs syndrome (RLS) (also known as Willis Ekbom disease) is a sensorimotor disorder affecting 5–10% of the adult population and can impact significantly on sleep and general health.[79] RLS has previously been classified into primary/idiopathic and secondary; however, more recently, this system of classification has been questioned due to concerns that they may suggest inappropriate or unsubstantiated causal relationships, and the term "comorbid RLS" has been proposed to describe RLS that occurs in association with other medical conditions such as pregnancy, iron deficiency, chronic renal failure, and mental health disorders.[80]

RLS has been found to be associated with hypertension in a limited number of population-based studies; however, results have been conflicting. Methodological issues, including heterogeneity in study design, types of participants involved, diagnostic criteria used to define RLS, disease frequency and severity, duration of follow-up, adjustments for confounders, and outcomes assessed, are likely to have contributed to the variability in the findings. A cross-sectional study of women in the Nurses' Health Study II revealed a multiple adjusted OR of 1.20 [1.10–1.30] for hypertension in women with RLS compared with women without RLS symptoms.[81] Adjusted ORs were higher in women who reported more frequent RLS symptoms. A cross-sectional study involving a sample of 18,980 subjects that was representative of the general population in 5 European countries also demonstrated a significant association between RLS and high BP (OR 1.36 [1.14–1.61]), as did a Chinese population-based study (OR 4.10 [1.88–8.92]).[82,83] A retrospective cohort study conducted in the United States revealed an increase in the risk for hypertension in those with both "primary" RLS (hazard ratio [HR] 1.19 [1.12–1.25] and "secondary" RLS (HR 1.28 [1.18–1.40]).[84] However, other studies have found no correlation between RLS and hypertension after adjustment for possible confounding factors.[85–88]

Shen et al.[89] conducted a meta-analysis (9 studies, 102,408 participants) of population-based, cross-sectional studies that looked for an association between RLS and hypertension. A positive association between RLS and hypertension was found in 7 studies, while 2 studies showed no significant relationship. In the pooled analysis, the prevalence of hypertension in subjects with RLS was found to be higher than those without RLS (OR 1.36 [1.18–1.57]).

Potential mechanisms

A number of potential mediating mechanisms for the development of hypertension in patients with RLS have been proposed. In particular, increased autonomic activation from periodic limb movements of sleep (PLMS) are frequently

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seen in patient with RLS. PLMS are stereotyped, repetitive, dorsiflexion movements of the lower limbs that occur during sleep in approximately 80% of patients with RLS and may involve the upper limbs in severe cases. Individual periodic limb movements are associated with transient, large elevations in heart rate, BP, and electroencephalogram activity and have the potential to increase arousals and disturb sleep.[90] Thus, PLMS are thought to cause sympathetic nervous system hyperactivity that may increase the risk of developing hypertension.

Clinical implications and future research directions

Overall, epidemiological research indicates that RLS is associated with hypertension. While potential mechanisms have been proposed to explain a possible causative effect, insufficient research has been conducted to reach firm conclusions. Further research is needed to assess whether RLS and PLMs are causal factors in the development of hypertension, including prospective longitudinal studies, interventional studies to assess the efficacy of RLS treatment, and further investigations of the putative pathophysiological mechanisms linking RLS and hypertension.

CONCLUSION

In conclusion, while there is mounting evidence in favor of a causal link between a variety of sleep disorders and hypertension, further research is needed, in many instances, to confirm these associations, explore the impacts of sleep disorders interventions in preventing and treating hypertension, and to better understand the biological links between sleep and sleep disorders with BP control. Until then, we have enough evidence to know that adequate sleep is essential to maintain people's safety, health, and wellbeing. It would be wise therefore to encourage healthy sleep habits and seek to treat, wherever possible, sleep disorders when they occur in our patients with hypertension.

DISCLOSURE

Dr Ching Li Chai-Coetzer has received product donations from Biotech pharmaceuticals within the last 5 years; prior to that, CLC received equipment donations from ResMed, Philips Respironics, and SomnoMed. Professor R. Doug McEvoy received direct research support from Philips Respironics, Fischer Paykel, and ResMed Foundation and equipment donations from ResMed and Philips Respironics. Other authors declared no conflict of interest.

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