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Review Article

Hypertension and Sleep

Relationship Between Hypertension and Sleep: An Overview

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Abstract: Sleep is a necessary component of the human lifestyle. A growing number of studies have focused on the relationship between sleep and hypertension in recent years. Sleep health plays a role in the pathophysiology of hypertension, but because of the complexity of the relationship, it can be challenging to pinpoint specific sleep abnormalities linked to blood pressure elevation at the epidemiological level as well as the level of a given patient. According to the available evidence, poor sleep conditions may be an important risk factor in the pathophysiological abnormalities of hypertension and related comorbid states. According to ambulatory blood pressure studies, even minor increases in blood pressure, particularly at night, are associated with significant increases in cardiovascular morbidity and mortality. As a result, sleep-related diseases that cause blood pressure increases are expected to impact cardiovascular risk significantly. Insomnia and sleep deprivation have been linked to an increase in the incidence and prevalence of hypertension. Sleep influences autonomic nervous system function and other physiologic events that affect blood pressure. Although current evidence suggests a strong link between sleep duration and hypertension, the relationship between sleep quality and hypertension needs to be investigated further. Unfortunately, the regularity and underlying mechanism of sex differences in sleep quality and hypertension remain unknown due to differences in geography, population, confounding factors, or methods. The current evidence suggests that the link between poor sleep quality and hypertension is stronger in women than in men. Furthermore, sleep disorders alter the BP response and raise the risk of hypertension. Recent research on the effects of sleep and sleep disorders on blood pressure and hypertension will be examined.

Keywords: Hypertension, Sleep , Obstructive Sleep Apnea Syndrome, Sleep Habits, Disorders

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1. INTRODUCTION

Systemic arterial hypertension is the leading modifiable risk factor for all-cause morbidity and mortality worldwide, and it is linked to an increased risk of cardiovascular disease (CVD). Fewer than half of those with hypertension are aware of their condition, and many more are aware but untreated or inadequately treated, despite successful hypertension treatment lowering the global burden of disease and mortality.[1] Systemic arterial hypertension (also known as hypertension) is defined by persistently high blood pressure (BP) in the systemic arteries. BP is commonly expressed as the ratio of systolic BP (the pressure exerted on the arterial walls when the heart contracts) to diastolic BP (the pressure when the heart relaxes). Most patients (90-95%) have highly heterogeneous 'essential' or primary hypertension with a multifactorial gene-environment aetiology. A positive family history is common in hypertensive patients, with heritability (a measure of how much of a trait's variation is due to genetic factors) estimated between 35% and 50% in the majority of studies. [2] According to reports, the prevalence of hypertension globally might reach 24.2% for men and 20.1% for women.[3] In adults worldwide, hypertension affects roughly 26.4% of people. With 13.5% of all deaths caused by it, it ranks as the top chronic risk factor for mortality. Hypertension is also anticipated to become increasingly prevalent, impacting more than 1.5 billion people by 2025.[4,5] High blood pressure (BP) contributes to 50% of stroke and ischemic heart disease occurrences. Since blood pressure readings are usually spread throughout the population, there is no natural cutoff point above or below which "hypertension" is unquestionably present. Every 20 mmHg increase in systolic or 10 mmHg increase in diastolic blood pressure doubles the risk of cardiovascular events. [6] The danger linked with elevated blood pressure starts as low as 115/75 mmHg. The usual "dipping pattern" of blood pressure at night is described as a 10% decrease in mean systolic blood pressure values while sleeping compared to when awake. Patients are classified as "non-dippers" if their nocturnal systolic blood pressure falls by less than 10%, "reverse dippers" if their nocturnal BP values are higher than those of the day, and "severe dippers" if their nocturnal BP falls by more than 20%. It is significant since, independent of 24-hour BP values, the mean nocturnal BP level is a key predictor of cardiovascular morbidity and mortality.[7] We will see in this overview how sleep and sleep disorders can affect BP levels and profile throughout 24 hours. Four to five sleep cycles of roughly 90 minutes each make up the normal sleep architecture, which alternates cyclically between non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. While REM sleep lasts longer during the final sleep cycles, NREM sleep predominates early in the night. Normal sleep significantly impacts the cardiovascular system, with autonomic regulation differing depending on the stage of sleep. As NREM sleep progresses deeper, sympathetic nerve activity to the vasculature steadily declines. It has been shown that NREM sleep is characterized by vagal parasympathetic predominance using heart rate variability studies, with a drop in sympathetic activity that is most pronounced in slow-wave sleep. This corresponds to the nocturnal dipping pattern of BP.[8,9] During the night, normal individuals did not exhibit significant changes in cardiac output, and the nocturnal fall in arterial pressure results from a decrease in total peripheral vascular resistance. Compared with when awake, in REM sleep sympathetic activity increases significantly and is highly variable. 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 .[10-12] Hypertension is the most common preventable risk factor for CVD (including coronary heart disease, heart failure, stroke, myocardial infarction, atrial fibrillation, and peripheral artery disease), chronic kidney disease (CKD), and cognitive impairment, and is the single leading contributor to all-cause death and disability worldwide. [13] The relationship between blood pressure and the increased risk of CVD is graded and continuous, beginning as low as 115/75 mmHg, well within the normotensive range. Successful hypertension prevention and treatment are critical in reducing disease burden and promoting longevity in the world's population.[14] The majority of cases of hypertension are idiopathic, also known as essential hypertension. It has long been assumed that increasing salt consumption increases the risk of developing hypertension. [15] The patient's genetic ability to salt response is one of the factors described for the development of essential hypertension. [16,17] Between 50 and 60% of patients are salt sensitive and thus develop hypertension. [18] Multiple types of genes are involved in primary hypertension; some allelic variations of numerous genes are linked to an elevated risk of developing primary hypertension and are practically always associated with a favourable family history. The development of hypertension is influenced by a variety of environmental factors, including high Na+ intake, poor sleep quality or sleep apnea, excessive alcohol consumption, and high mental stress. Finally, as people age, their risk of getting hypertension increases due to the arterial vasculature's increasing stiffening, which is brought on by, among other things, gradually evolving changes in vascular collagen and an increase in atherosclerosis. When rheumatological or infectious illnesses like rheumatoid arthritis are present, immunological variables might also be very important. [1] Many nations have already put measures in place or are thinking about doing so to lower sodium consumption. The positive effects of a reduction in sodium intake in these populations have been supported by reports from nations with high levels of sodium intake (for example, Japan) that have effectively adopted sodium reduction strategies. A negative association between sodium consumption, all-cause mortality, and cardiovascular events may occur in people without hypertension. These findings contradict conventional notions in the field of public health regarding the significance of controlling salt intake at the population level. The basis for current policy is the correlation between sodium intake and systolic blood pressure, which reveals that levels of sodium above 1 g per day are associated with rises in systolic blood pressure. [13]

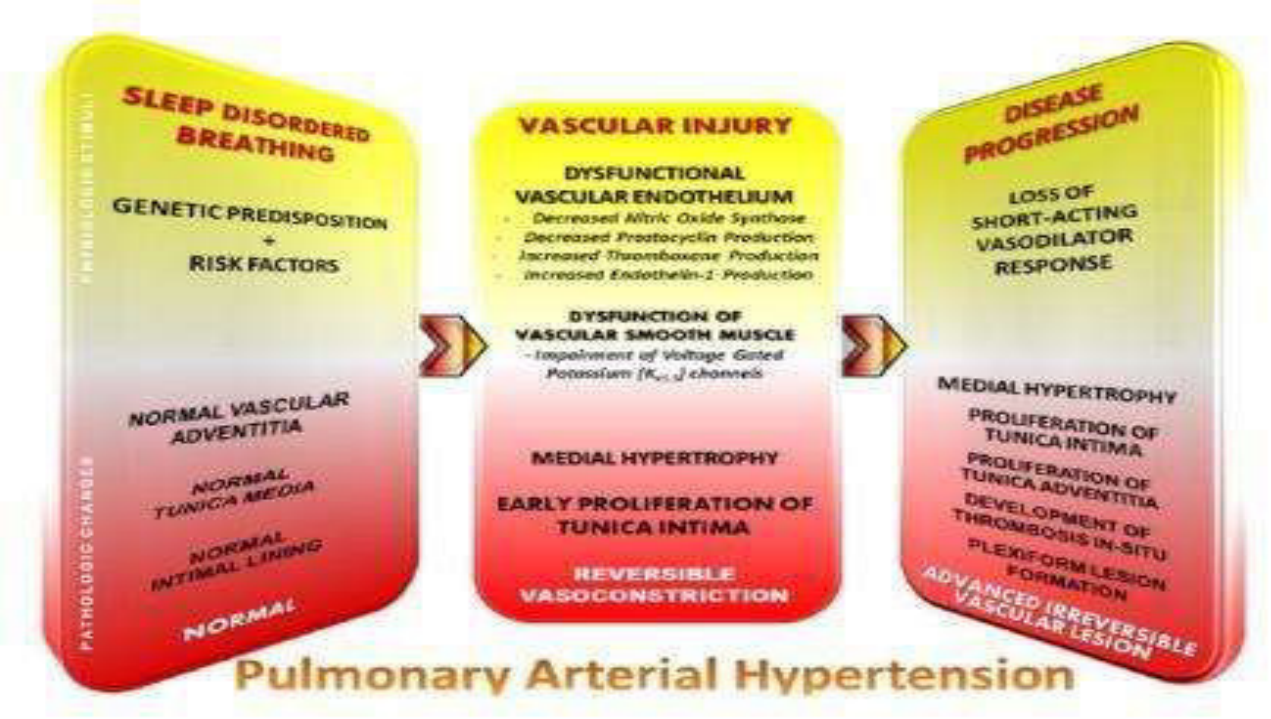


Fig 1: Pathogenesis of pulmonary hypertension[19,20]

1.1 Hypertension and sleep

Sleep is a necessary component of the human lifestyle. Many recent studies have focused on the relationship between sleep and hypertension. According to the available evidence, poor sleep conditions may be an important risk factor involved in the pathophysiological abnormalities of hypertension and related comorbid states.[21-23] As we all know; hypertension is closely related to autonomic nervous system imbalance. Sleep is essential for maintaining homeostasis and regulating the stress system. [24,25] A possible link has been discovered between sleep disorders that cause sympathetic and vagal imbalances and, ultimately, cardiac autonomic dysfunction. [26,27] Thus, some researchers have proposed that poor sleep quality may play a role in the development of hypertension by activating the sympathetic nervous system and pro-inflammatory pathways. [28-30] Although current evidence suggests a strong link between sleep duration and hypertension, the relationship between sleep quality and hypertension needs further investigation.[31,32,33,34] Unfortunately, the regularity and underlying mechanism of sex differences in sleep quality and hypertension remain unknown due to differences in geography, population, confounding factors, or methods. The current evidence suggests that the link between poor sleep quality and hypertension is stronger in women than in men. [35,36] However, several studies have found conflicting results. A cross-sectional study found that poor sleep quality was linked to an increased prevalence of hypertension only in men.[37] Another study found no significant link between sleep quality and arterial blood pressure.[38] Additionally, findings suggest that hypertension may limit sleep duration, which in turn may cause blood pressure to rise even higher. Additionally, a nonlinear link between sleep duration and hypertension is conceivable. Although the impact of sleep deprivation is more widely acknowledged, few cross-sectional research has linked long sleep duration to the prevalence of hypertension. However, no published longitudinal studies have linked long sleep duration to the incidence of hypertension. [22] Normal sleep causes a drop in blood pressure compared to wakefulness. This decrease is known as "nocturnal dipping," and it is caused in part by decreases in sympathetic output. Although arbitrary, a 10% to 20% decrease in mean nocturnal blood pressure (both systolic and diastolic) compared to mean daytime blood pressure is considered normal. A 10% decrease in nocturnal BP is defined as the absence of nocturnal dipping, or nondipping. The absence or reduction of nocturnal BP dipping is a strong, independent predictor of cardiovascular risk. According to the Ohasama study, each 5% reduction in the normal decline in nocturnal BP was associated with a 20% increased risk of cardiovascular mortality. [39] This finding has been confirmed by other studies. [40-42] Many diseases, including most secondary causes of hypertension, chronic kidney disease, diabetes, older age, resistant hypertension, and obstructive sleep apnea, are associated with decreased or absent nocturnal dipping (OSA).[43]

1.2 Epidemiology

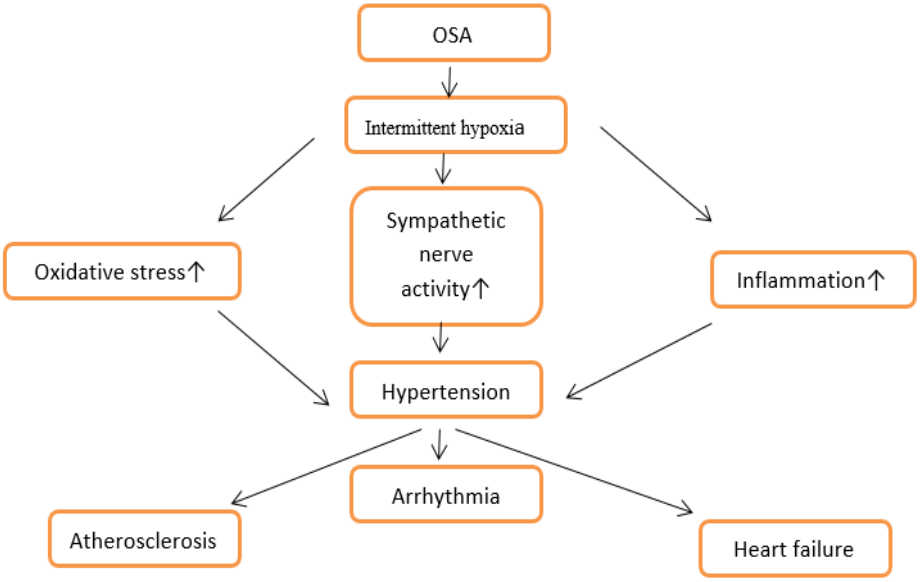
More than one billion adults worldwide have hypertension, affecting up to 45% of the adult population. The high prevalence of hypertension is consistent across all socioeconomic and income strata, and it rises with age, accounting for up to 60% of the population over 60. [44] Epidemiological research on the connection between children's and teenagers' blood pressure and sleep duration has yielded conflicting results. Decreases in total sleep time were linked to rises in blood pressure at follow-up in two longitudinal investigations of youth. Children's cross-sectional research has produced mixed results. In one cross-sectional research of children, those who slept the longest had marginally lower mean arterial pressure than those who slept the least. Still, another study observed no correlation between the amount of sleep and 24-hour ambulatory blood pressure. Short sleep duration was exclusively connected with hypertension prevalence in male children between the ages of 11 and 14 years old, according to a cross-sectional study that included both female and male children and adolescents. [31]

The Lancet published a global health survey report in 2010 that included patient data from 67 countries and identified hypertension as the leading cause of death and disability-adjusted life years worldwide since 1990. In the United States, HTN alone is responsible for more cardiovascular disease-related deaths than any other modifiable risk factor, and it ranks second only to smoking as a preventable cause of death for any reason.[45] Studies on young and middle-aged adults provide the strongest support for a link between sleep duration and hypertension. Significant correlations between short sleep duration and the risk of hypertension in young and middle-aged adults were found in five longitudinal investigations. According to three cross-sectional studies, individuals with low sleep duration had considerably higher blood pressure. Short sleep duration alone was not linked to the prevalence of hypertension, according to Bansil et al., but short sleep duration combined with sleep disturbances was. Another study discovered that the incidence of hypertension was connected with short sleep duration in combination with chronic insomnia but not with short sleep length alone. [31] According to recent estimates, the number of hypertensive patients could rise by 15 to 20%, reaching close to 1.5 billion by 2025.[4]

1.3 Common intermediary mechanisms for the link between sleep habits, sleep disorders and hypertension.

Strong evidence exists for a connection between OSA and both incidents and prevalent hypertension. CPAP therapy has a significant but modest effect on the onset and management of hypertension in OSA patients. Both short and extended sleep durations have been linked in population studies to an increased risk of hypertension. However, the data quality was compromised because the research relied on self-reported sleep length and had inconsistent cutoffs for defining short and long sleep duration. Short sleep duration and hypertension appear to be more closely related in women than in men, occur more commonly in younger subjects than in older subjects, and vary by geographic area and ethnicity. However, most sleep deprivation studies have shown an immediate effect on blood pressure, supporting the idea that chronically low sleep duration may harm BP regulation. Last but not least, sleep disorders like RLS/PLMs and narcolepsy may impact blood pressure control. Still, the current evidence is based on a small number of population/experimental or mechanistic studies, making a case for additional research into the connection between these conditions and hypertension. Relatively in OSA has a substantial causal relationship between sleep disorders and the onset of hypertension been established; sleep duration has only weaker support. The most widely accepted theory linking sleep problems or bad sleeping habits to the onset of hypertension is that changes in sleep quantity or quality cause the loss of the nocturnal BP dip connected to NREM sleep, which is the first step toward the hypertension condition. Loss of the BP dipping pattern is primarily caused by an increase in nocturnal sympathetic activity, which in turn causes a permanently higher sympathetic tone throughout the day. CPAP therapy reduces the levels of urine catecholamines and the muscle sympathetic nerve activity linked to OSA.[46,47,48] Lack of sleep has also been proven to raise the sympathetic tone, and PLMs cause a spike in blood pressure because of an abrupt increase in sympathetic activity.[49,50] Sleep issues affect the levels of various hormones that have vasoactive effects in addition to variations in catecholamine levels.[51] Compared to controls, angiotensin II and aldosterone levels are higher in OSA patients. Additionally, OSA would be predicted to stimulate the hypothalamic-pituitary-adrenal (HPA) axis because nocturnal awakenings have been linked to pulsatile cortisol release. Tomfohr et al. recently examined several research that addressed this issue; however, the heterogeneity of the investigations precluded the pooling of the findings for a metaanalysis.[51,52]When the effects of CPAP therapy on cortisol levels are examined, mixed results have been observed regarding cortisol levels in OSA patients compared to controls. Methodological biases, including uneven sampling timing collection and infrequent sampling, could cause such disparities. Multiple measures of cortisol were taken via venous blood sample over 24 hours before and during treatment with 3-mo of CPAP in two recent investigations. In 10 newly diagnosed men with largely severe OSA, Henley et al. took blood samples every 10 minutes over the course of 24 hours. They discovered that three months of CPAP therapy generally resulted in lower cortisol levels. Blood samples were taken every 30 minutes for 24 hours from obese patients with OSA, obese patients without OSA, and non-obese controls.[53,54] The non-obese controls had the greatest cortisol levels during a 24-hour period, but obese men with OSA had greater cortisol levels than obese men without OSA. After three months of CPAP therapy, they discovered a tendency towards an overall decrease in 24-hour cortisol levels. 24-hour urine-free cortisol levels were positively linked with overall awake time in 17 young adults with chronic insomnia.[55] Two controlled investigations involving 12 patients later corroborated these findings: A different study found no difference in cortisol levels but a decrease in melatonin secretion in patients with insomnia compared to control patients. Adrenocorticotrophic hormone (ACTH) and cortisol secretions were significantly higher in young men and women with insomnia than in non-insomniac controls.[56-58] Ten patients with persistent primary insomnia participated in a cross-over trial by Roden beck et al. to examine the effects of the tricyclic antidepressant doxepin on nocturnal sleep and plasma cortisol levels. [59]The antidepressant medication considerably increased sleep quality while lowering mean cortisol levels. Overall, these findings point to a cross-sectional link between insomnia and activation of the HPA axis, albeit it is unclear whether this association is causal or a product of other factors. The quantity of sleep, sleep disturbances, and endothelial dysfunction are also connected to inflammation, oxidative stress, and endothelial dysfunction, which may affect the onset and progression of hypertension.[60,61,62] For instance, interleukin-6 (IL-6) levels increased (in both men and women), and tumour necrosis factor (TNF)-alpha levels increased (in men only) after a week of mild sleep deprivation (from 8 hours per night to 6 hours per night).[63] A rise in plasma IL-6 and urinary levels of prostaglandin metabolites D2 and E2 were also seen in laboratory tests with more severe sleep deprivation (4 hours/night). The effect of OSA on BP appears to be driven by elevated sympathetic activity (and stimulation of the HPA axis, albeit with less convincing evidence). [64,65] In NC, RLS, and sleep loss cases, sympathetic activity is also elevated. However, these ailments have various pathophysiologies and stimulate sympathetic activity in various ways. The effect of intermittent hypoxia appears to be significant in the increase in sympathetic activity linked to OSA.[66,67] Indeed, intermittent hypoxia could elevate sympathetic tone in both animal models subjected to intermittent hypoxia alone and in healthy human volunteers subjected to intermittent hypoxia in a "tent" that we constructed. The intensity of oxygen desaturation throughout

the night is correlated with aberrant respiratory episodes, increased sympathetic activity, and abrupt increases in blood pressure. The primary factor causing the adrenergic and renin-angiotensin systems' overactivity is intermittent hypoxia caused by respiratory events. Of course, sleep deprivation is not linked to intermittent hypoxia, but it is possible that the decrease in NREM sleep time is the cause of the observed increase in sympathetic activity. The idea that disturbed NREM sleep quantity or quality may be the mechanism by which sleep deprivation or RLS leads to an increase in sympathetic tone is supported by the association between selective deprivation in slow-wave sleep and a reduction in the amplitude of the nocturnal dip in blood pressure. On the other hand, the peculiarity of the anomalous nocturnal BP pattern in NC may have some connection to the rise in blood pressure during REM sleep.[68]



Flow chart summarizes several methods via which OSA causes cardiovascular disease and hypertension[69]

1.4 The Role of Sleep Quantity

1.4.1 Sleep Deprivation

Studies on short-term sleep deprivation showed changes in heart rate and blood pressure. In a cross-sectional study with two 24 h-ABPM, spaced one week apart, 18 healthy young men and women were enrolled, according to Lusardi et al. [70.] The patients were requested to sleep their regular 8 hours one night (from 21:00 to 7:00) however just the first part of that night's sleep period (about 2:30 to 7:00 hours, or 43% of the overall amount) was allowed. The night of limited sleep was linked to an increase in systolic blood pressure, diastolic blood pressure, and heart rate between 21:00 and 02:00 h and during the morning after 07:00 h compared to average sleep length. 18 men who had been forced to work long hours were subjected to 24 h-ABPM by Tochikubo et al.[71] A typical workday with 8 hours of sleep on average was used for 24 h-ABPM, as was a day with less sleep (mean period of sleep of 3.6 h). The day following a sleepless night differed from the day following a typical sleep; systolic, diastolic blood pressure, heart rate, and norepinephrine urine excretion all rose. Because of the sympathetic nervous system's activation, short-term sleep loss appears to be linked to elevated blood pressure and heart rate. Thirty-six participants with mild hypertension who were left untreated also produced similar outcomes.[72] In a recent investigation on 13 healthy Caucasian men, Dettoni et al. also discovered an increase in sympathetic activation. [73] After two washout nights in a cross-over design, these guys spent five nights at home with no sleep restrictions, followed by five nights of sleep restriction at home (1.5 h per night). This mild sleep loss was unaffected by the office measurements of resting heart rate and systolic and diastolic blood pressure. Nevertheless, a moderate lack of sleep was linked to a considerable rise in plasma norepinephrine levels. With alterations to sleep patterns, significant improvements were also seen in heart rate and blood pressure variability. As a result, sleep deprivation has been linked to an increase in sympathetic activation and a decrease in the parasympathetic modulation of cardiac autonomic balance, even to a relatively low degree. Such changes are thought to be caused by less NREM sleep relative to REM sleep. As a result, healthy subjects selectively deprived of slow-wave sleep by electroencephalographically guided acoustic arousal showed an attenuated dip in mean arterial blood pressure during the night's first half when NREM predominated but not during the second half of the night when REM predominated. On the other hand, several investigations on total sleep deprivation indicated that while resting muscular sympathetic nerve activity (MSNA) decreased, blood pressure increased.[74,75,76] The increase in resting blood pressure was attributed to the sympathetic arterial baroreflex being reset in the presence of a decreased MSNA. Notably, both men and women experienced a rise in blood pressure due to sleep deprivation, but only men showed changed resting MSNA.[76] While the majority of research suggests that short-term sleep loss increases nocturnal and eventually daytime blood pressure, Pagani et al. reported no difference in BP following one night of complete sleep deprivation in 12 healthy males and 12 healthy women.[77]

1.5 Sleep duration

Over the past 30 years, the average person's sleep duration has declined.[78] According to the National Sleep Foundation, mean sleep duration in the US has decreased from 9 hours per night in 1910 to 7.5 hours in 1975 and 6.8 hours in 2005. The Sleep Heart Health Study (SHHS) and the National Health and Nutrition Examination Survey (NHNES), two significant community-based cohort studies, were the first to document a link between self-reported sleep duration and hypertension. In the SHHS, Gottlieb et al. discovered a U-shaped association between self-reported sleep duration and pervasive hypertension. Sleep duration above or below the median of 7-8 hours per night was linked to an increased prevalence of hypertension in 2813 males and 3097 women aged 40-100 y. These relationships persisted even after possible confounders, including age, sex, race, obesity, the apnea-hypopnea index, or lifestyle factors, were considered. The same year, Gangwisch et al. revealed a connection between self-reported short sleep duration and incident hypertension in their longitudinal analysis of the NHNES.[79,80] Between 1982 and 1984, 4810 men and women participated in the study. Participants ranged in age from 25 to 74, and were questioned about their typical sleep length. The following 8–10 years of follow-up saw the collection of their incident hypertension data (n 1–4 647). In adjusted analyses, it was discovered that sleep durations of less than 5 h were associated with incident hypertension in subjects younger than 60 y. In contrast, sleep durations of over 9 h per night were associated with incident hypertension in subjects older than 60 y, compared to self-reported sleep durations of 7-8 h. Since these early reports, a large number of population studies have examined the connection between sleep quality and blood pressure. However, Knutson et al. found a significant association between short sleep duration and prevalent and incident hypertension in an ancillary study of coronary artery risk development in young adults (CARDIA).[81] This study used actimetry to obtain objective measurements of sleep duration. Furthermore, studies utilizing simple questionnaires may not be reliable because a significant association has been shown between sleep timing and duration measured subjectively by questionnaires and objectively by actimetry.[82] Future studies should incorporate such objective assessments into their design since the objective measurement of sleep duration continues to be the gold standard when addressing the issue of an actual link with hypertension. The variability of cutoffs used to determine short or long sleep duration makes it difficult to compare the various groups studied. Most research used 7-8 hours of sleep per night, whereas short sleep duration was defined as anything less than that and long sleep duration as anything more than that.[77]

1.6 Insomnia

Despite their historical connections, insomnia and short sleep duration are two distinct conditions. The symptoms of insomnia include daily effects that may or may not be attributable to an actual reduction in sleep length and unhappiness with sleep quality. As long as they choose to do so, people who sleep for short periods do not always have insomnia. It is obvious that psychiatric and psychosomatic diseases and insomnia are associated, and some insomniac patients have an inaccurate sense of sleep quality. It is debatable if sleeplessness is linked to a rise in somatic illnesses, particularly cardiovascular ones. Recent research using polysomnography has demonstrated a considerable risk of hypertension is connected with insomnia and objectively short sleep duration.[83,84]

1.7 Restless legs syndrome and periodic limb movement disorder

Leg restlessness and dysesthesia are symptoms of restless legs syndrome (RLS), which typically occur at night and during periods of inactivity. In the Wisconsin Sleep Cohort Study, self-reported RLS symptom prevalence was 10.6%, with no gender differences. The ability to fall asleep and sleep quality is hampered by unpleasant sensations and the insatiable urge to move. PLMs, which are recurrent flexions of the lower limbs while you sleep that might occasionally result in micro-arousals, are linked to RLS 80% of the time. PLMs are distinguished by sharp rises in blood pressure and spikes in sympathetic activity, whether there are micro-arousals present or not. PLMs can also occur in those who don't have RLS, and 25% of people who get routine polysomnography have them, especially those over 65. It has been proposed that RLS-related changes in sleep patterns could have a negative impact on the prevalence of hypertension. Ulfberg et al. observed that after adjusting for age, witnessed apnea, smoking, and alcohol consumption, RLS sufferers, were more likely to report hypertension among 4000 men between the ages of 18 and 64 y who self-reported having RLS. In a study by Ohayon et al. that included 18 980 people from five different countries in Europe, 732 of the participants met the criteria for RLS and had a two-fold higher risk of having high blood pressure (21.8 vs 11.1% for patients with and without RLS, respectively, for the association between hypertension and RLS after controlling for confounders). Winkelman et al. observed that patients with RLS had a greater prevalence of hypertension, but after controlling for confounding variables, the odds ratio for the cross-sectional connection between RLS and hypertension was no longer significant.[68]

1.8 Narcolepsy/cataplexy

The sleep-wake cycle is disturbed in narcolepsy cataplexy (NC) by repeated REM sleep episodes throughout the day and numerous nighttime awakenings. The condition is characterized by a significant decline in hypocretin neurons, which are believed to be important in the central control of autonomic and cardiovascular functions. Even though NC is traditionally associated with obesity, type 2 diabetes, and metabolic syndrome—all comorbidities that raise the risk of cardiovascular disease—there are very few cardiovascular investigations in patients with narcolepsy. Recently, compared to control subjects, we documented the 24 h ABPM pattern of drug-free narcolepsy patients. A "non-dipping status," defined as a drop in blood pressure during sleep of less than 10%, was discovered in one-third of patients with NC and just 4.8% of controls. Even after controlling for potential confounders, the non-dipping diastolic condition substantially correlated with the amount of REM sleep. It was highly connected with NC, with risk ratios up to 12-fold. Grimaldi et al. [80] have effectively shown that systolic BP during nighttime REM sleep was elevated in the narcoleptic group in a small, case-controlled research employing a 24-h beat by-beat measurement of blood pressure. Therefore, NC is a singular example of a rise in nocturnal BP that mostly occurs during REM sleep. Whether this molecular pathway specifically affects the likelihood of getting hypertension is unclear. PLMs and the resulting sleep disruption were also discovered to be connected to the loss of nighttime BP dropping in NC patients.[68]

1.9 Combinations of sleep problems

The cross-sectional link between sleep disorders and hypertension has only been examined in one population-based study, the NHNES. In this extensive study, which included 10,308 adult men and women, the odds ratios of hypertension were calculated based on the self-reported presence of sleep disorders (sleep apnea, insomnia, RLS, and others), short sleep duration (7 h/night), and "poor sleep" quality (one of the six following sleep problems occurring between 5 and 30 times a month: difficulty falling asleep, difficulty returning to sleep after waking up during the night, difficulty returning to sleep after waking up too early in the morning, feeling tired despite receiving enough sleep, A combination of sleep disorders, short sleep duration, and poor sleep can cause excessive daytime sleepiness, excessive daytime sleepiness, and not getting enough sleep. A single sleep disorder was not significantly connected to hypertension (OR 1.65; 95% CI 0.73-3.77), whereas combinations of sleep disorders, short sleep, and poor sleep were (OR 2.30; 95% CI 1.49-3.56) and (OR 1.84; 95% CI 1.13-2.98), respectively.[85]

1.10 Sleep and Nighttime BP

Normal sleep results in a drop in blood pressure compared to alertness. This decline, known as "nocturnal dipping," is partially caused by a drop in sympathetic output. Despite being arbitrary, a reduction of 10% to 20% in mean nocturnal blood pressure (systolic and diastolic) from mean daytime blood pressure is typical. An absence of nocturnal dipping, or nondipping, is defined as a 10% reduction in nocturnal blood pressure. A powerful, independent predictor of cardiovascular risk is the absence of or reduced nocturnal BP dropping. According to the Ohasama study, there is an average 20% increased risk of cardiovascular mortality for every 5% deficit in the normal nocturnal BP decrease.[86] Several investigations have supported this result.[87-89] Numerous illnesses, such as the majority of secondary causes of hypertension, chronic renal disease, diabetes, advanced age, resistant hypertension, and obstructive sleep apnea, are linked to decreased or absent nocturnal dipping (OSA). Large prospective studies have shown that nighttime BP predicts cardiovascular risk more accurately than daytime BP. 5,292 untreated hypertensive patients who were referred to a single hypertension clinic and were prospectively tracked for cardiovascular events participated in the Dublin Outcome Study. Ambulatory blood pressure measurements outperformed clinic blood pressure readings in predicting cardiovascular death throughout an 8.4-year median follow-up period, and nighttime blood pressure was generally the best predictor of outcome.[90] Worldwide, uncontrolled hypertension continues to be a major factor in cardiovascular morbidity and mortality. Even modest changes could significantly reduce reduced cardiovascular consequences in mean blood pressure. Data from observational studies and randomized trials, for instance, indicate that a population-wide 2-mm Hg reduction in diastolic blood pressure causes a 17% decrease in the prevalence of hypertension, a 6% reduction in the risk of coronary heart disease, and a 15% decrease in the risk of stroke and transient ischemic attack. A 10-mm Hg reduction in systolic blood pressure or a 5-mm Hg reduction in diastolic blood pressure lowers the risk of coronary heart disease events by 22% and stroke by 41%, according to a meta-analysis of randomized trials of antihypertensive drugs.[91,92]

1.11 the syndrome of obstructive sleep apnea

Obstructive sleep apnea (OSA) is now acknowledged in international guidelines from the US and Europe as a risk factor for the emergence of hypertension. A dose-response relationship exists between OSA and hypertension. This is true even after considering the typical confounding variables, including age, tobacco and alcohol use, and body mass index. The adjusted hazard ratios for incident hypertension were highest among patients with severe OSA who rejected continuous positive airway pressure (CPAP therapy) (1.96; 95% confidence interval (CI), 1.44-2.66), and among those who were not CPAP adherent (1.78; 95% CI, 1.23-2.58), according to a large prospective observational cohort followed for more than 12 years**.** However, the hazard ratio was lower in OSA patients who received more than 4 hours of CPAP therapy per night (0.71; 95% CI, 0.53-0.94). Multiple characteristics of OSA-related hypertension include the fact that it is typically mostly diastolic and nocturnal, frequently resulting in masked hypertension and non-dipper status. The fundamental cause of the rise in blood pressure in diastolic hypertension is an increase in vascular resistance brought on by sympathetic activation. OSA patients are at a greater risk of presenting with masked hypertension, which is defined as normal clinic BP but increased BP when 24-h ambulatory blood pressure monitoring (ABPM) is employed, due to its nocturnal predominance. According to Baguet et al., 130 patients with newly discovered OSA with no prior history of cardiovascular disease, Thirty per cent of the patients had disguised hypertension, and the prevalence of hypertension was 35.4%. Additionally, it has recently been reported that 24-h ABPM is the gold standard for detecting abnormal BP in OSA patients because neither clinic BP measurements (done in the doctor's office) nor home self-BP measurements (done by the patients themselves three times in the morning and three times in the evening) were sufficient to detect masked hypertension in OSA patients. Additionally, OSA should be rigorously looked at in this case as it is by far the main contributor to refractory hypertension. Regarding the specific relationship between sleep apnea and hypertension according to age, it has been established that children who have sleep apnea experience high blood pressure regardless of age, sex, race, body mass index, or waist size. This association affects left ventricular remodelling in children. Primary snoring is a clinical sign that can help doctors diagnose children with sleep-breathing difficulties, but the current literature disputes its independent link to elevated blood pressure. With age, the correlation between sleep apnea and blood pressure weakens. In addition to sleep apnea, other factors, such as sleep fragmentation in the elderly, also contribute to poor blood pressure management.[68]

1.12 Mechanisms for the link between sleep habits, sleep disorders and chronic cardiovascular diseases

There is compelling evidence linking OSA to both incident and prevalent hypertension. In OSA patients, CPAP therapy has a significant but modest effect on the onset and management of hypertension. In population studies, short and extended sleep durations have been linked to an increased risk of hypertension. The research's flaws, particularly the use of self-reported sleep length and varying cutoffs to define short and long sleep duration, however, have a negative impact on the quality of the evidence. The relationship between insufficient sleep and hypertension appears more particular to women than males, occurs more commonly in people under 60 than in people over 60, and its location- and ethnicity-dependent.

However, most sleep deprivation studies have shown an immediate effect on blood pressure, supporting the idea that chronically low sleep duration may harm BP regulation. Last but not least, sleep disorders like RLS/PLMs and narcolepsy may have an impact on blood pressure control, but the evidence we currently have is based on a small number of population/experimental or mechanistic studies, making the case for additional research into the connection between these conditions and hypertension. Relatively in OSA has, a substantial causal relationship between sleep disorders and the onset of hypertension been established; sleep duration has only weaker support. According to the widely accepted theory linking sleep disorders or poor sleeping habits to the onset of hypertension, changes in sleep quantity or quality cause the loss of the nocturnal BP dip connected to NREM sleep, which is the first step toward the hypertension condition. Loss of the BP dipping pattern is primarily caused by an increase in nocturnal sympathetic activity, which in turn causes a permanently higher sympathetic tone throughout the day. CPAP therapy reduces the levels of urine catecholamines and the muscle sympathetic nerve activity linked to OSA. Lack of sleep has also been proven to raise sympathetic tone, and PLMs cause a spike in blood pressure due to an abrupt increase in sympathetic activity. Sleep issues affect the levels of various hormones that have vasoactive effects in addition to variations in catecholamine levels. When compared to controls, OSA patients had higher levels of angiotensin II and aldosterone. Additionally, OSA would be predicted to stimulate the hypothalamic-pituitary-adrenal (HPA) axis because nocturnal awakenings have been linked to pulsatile cortisol release. Tomfohr et al. recently examined several research that addressed this issue; however, the heterogeneity of the investigations precluded the pooling of the findings for a meta-analysis. When the effects of CPAP therapy on cortisol levels are examined, mixed results have been observed regarding cortisol levels in OSA patients compared to controls. Such differences can result from methodological biases like infrequent sampling and irregular sample collecting times. Multiple measures of cortisol were taken via venous blood sample over a 24-hour period prior to and during treatment with 3-mo of CPAP in two recent investigations. In 10 newly diagnosed men with largely severe OSA, Henley et al. took blood samples every 10 minutes over the course of 24 hours. They discovered that three months of CPAP therapy generally resulted in lower cortisol levels. Blood samples were taken every 30 minutes for 24 hours from obese patients with OSA, obese patients without OSA, and non-obese controls. The non-obese controls had the greatest cortisol levels during 24 hours, but obese men with OSA had greater cortisol levels than obese men without OSA. After three months of CPAP therapy, they discovered a tendency towards an overall decrease in 24-hour cortisol levels. Two controlled investigations involving 12 patients later corroborated these findings: A different study found no difference in cortisol levels but a decrease in melatonin secretion in patients with insomnia compared to control patients. Adrenocorticotrophic hormone (ACTH) and cortisol secretions were significantly higher in young men and women with insomnia than in non-insomniac controls. In a cross-over research, ten individuals with persistent primary insomnia were treated with the tricyclic antidepressant doxepin to see how it affected their nocturnal sleep and plasma cortisol levels. The antidepressant medication considerably increased sleep quality while lowering mean cortisol levels. These findings point to a cross-sectional relationship between insomnia and HPA axis activation. However, this research cannot determine the specifics of this connection. Additionally connected to inadequate sleep, sleep disorders, and potentially influencing the onset and development of hypertension are inflammation, oxidative stress, and endothelial dysfunction. For instance, 24 h-interleukin-6 (IL-6) levels (men and women) and 24 h tumour necrosis factor (TNF)-alpha levels (men only) increased in 20 normal sleepers who underwent one week of mild sleep loss (from 8 h/night to 6 h/night). Additionally, plasma IL-6 and urinary levels of prostaglandin metabolites D2 and E2 after sleep deprivation were found to increase in laboratory trials with more severe sleep deprivation (4 hours each night). The effect of OSA on BP appears to be driven by elevated sympathetic activity (and, to a lesser extent, by activation of the HPA axis). Sleep loss, RLS, and NC all result in increased sympathetic activity. However, the pathophysiologies of these illnesses vary, and they also affect how sympathetic activity is elevated. Intermittent hypoxia appears to play a significant role in the increase in sympathetic activity associated with OSA. Intermittent hypoxia raised sympathetic tone in animal models that were only subjected to it and healthy human volunteers exposed to it in a "tent" we created. The degree of oxygen desaturation increases during the night, along with aberrant respiratory episodes, increased sympathetic activity, and acute BP rises. The primary factor causing the adrenergic and renin-angiotensin systems' overactivity is intermittent hypoxia caused by respiratory events. Of course, sleep deprivation is not linked to intermittent hypoxia, but the decrease in NREM sleep time may cause the observed increase in sympathetic activity. It is suggested that disturbed NREM sleep quantity or quality may be the mechanism by which sleep deprivation or RLS cause an increase in sympathetic tone. The finding supports this idea that selective slow-wave sleep deprivation is associated with a reduction in the amplitude of the nocturnal dip in blood pressure. On the other hand, the uniqueness of the anomalous nocturnal BP pattern in NC may be partly attributed to the rise in blood pressure during REM sleep.[68]

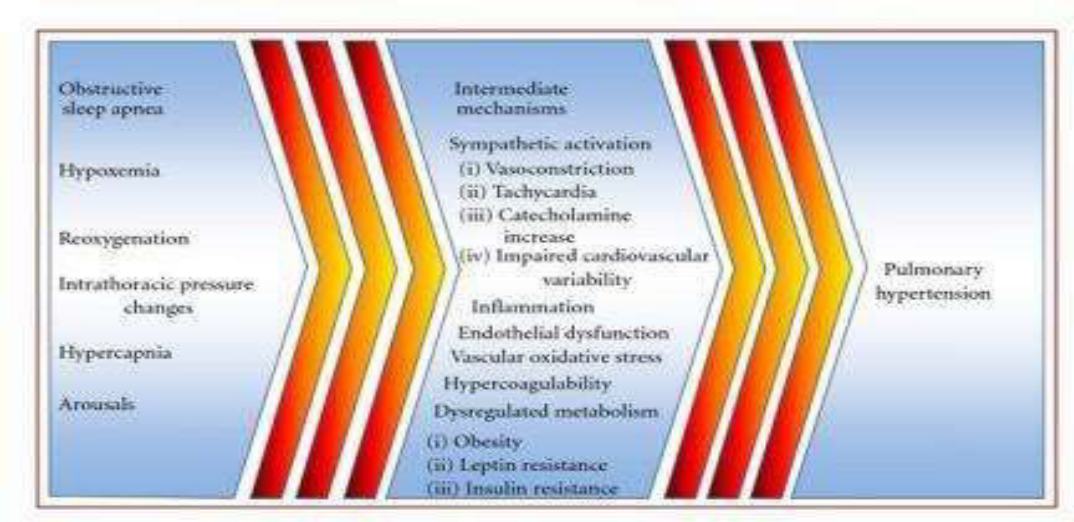


Fig2: In obstructive sleep apnea, there may be intermediary mechanisms that raise the risk of pulmonary hypertension.

These obstructive sleep apnea intermediate processes may help to start and maintain pathologic cardiovascular alterations that lead to pulmonary hypertension.[93]

1.13 Mechanisms Linking Sleep And Blood Pressure

The suprachiasmatic nucleus, a central biological clock, evolved to use the autonomic nervous system to synchronize activity, rest, and consumption to the circadian and circannual cycles. The suprachiasmatic nucleus needs repeated inputs from light exposure, sleep, activity, and nutrition intake to entrain autonomic rhythms to the external environment. For our hunter-gatherer predecessors who lived far from the equator, these cues would have changed according to the season. The daily photoperiod is 12 hours long at the equator. As one moves away from it, the seasonal fluctuation in daylight grows to the extremes of continuous summer daylight and continuous winter darkness at the poles. Early humans most likely slept for longer than eight hours most of the time, with individuals who lived further from the equator being subjected to seasonal changes in photoperiods resulting in lower summer and longer winter sleep durations. Less sleep during the summer months led to higher average 24-hour blood pressure because blood pressure drops by 10% to 20% on average while we sleep.[94] Summertime lack of sleep also increases exposure to waking physical and psychological stimuli and to sympathetic nervous system activity that is already high. The consequences of seasonal sleep reduction on blood pressure were transient for our ancestors, but short sleep intervals and sleep interruptions are now typical throughout the year. In the 2013 International Bedroom Poll conducted by the National Sleep Foundation, more than 57% of respondents admitted sleeping less than necessary on workdays.[95] Shift work, 24-hour shopping, the Internet, cable television, dual employment, smartphones, and time zone travel are just a few potential modern distractions that interfere with sleep time and disrupt sleep rhythms. Sleep maintenance insomnia, characterized by nightly awakenings, can be exacerbated by irregular sleep patterns. Chronic sleeplessness has been linked to increased nighttime systolic blood pressure and attenuated day-to-night systolic blood pressure lowering, even in those with insomnia who compensate for nocturnal awakenings by sleeping more during the day.[36] Chronic sleep deprivation can contribute to the development and maintenance of hypertension. In experimental trials involving both normotensive and hypertensive participants, significant increases in blood pressure and sympathetic nervous system activity have been observed after nights of insufficient sleep.[96,97,98,99] Lack of sleep is a stressful state, and research has shown that stress increases salt cravings and decreases renal salt-fluid excretion. Short-term sleep deprivation has been discovered to increase appetite, particularly demands for salty snacks.[100] Lack of sleep increases the total 24-hour hemodynamic load, which over time may cause structural changes such as remodelling of the left ventricle and arteries, which eventually educate the entire cardiovascular system to function at a heightened pressure equilibrium.[101] Additionally, there is evidence to suggest that the pathophysiology of hypertension may contribute to shorter sleep duration, which may further increase blood pressure.[102] By interfering with circadian rhythmicity and autonomic balance, chronically short sleep, which is commonly defined as less than 5 or 6 hours per night in adults, might also raise the risk of hypertension. The environment sensed by the suprachiasmatic nucleus in modern industrialized society is theorized to become metabolically flattened and arrhythmic, disrupting the circadian rhythmicity of blood pressure in susceptible individuals. This is due to dramatic changes in the timing and duration of external and internal zeitgebers.[103] Disturbances in the circadian rhythmicity of numerous physiological variables, including an increased prevalence of the nondipping pattern, a shift in the daily blood pressure profile to higher values, disturbances in the diurnal rhythm of cardiac output, and increased blood pressure variability, are characteristics of hypertension. It has been demonstrated that the three main neuronal populations of the suprachiasmatic nucleus were reduced by >50% in hypertensive people who died from myocardial infarction or brain haemorrhage compared to healthy subjects.[104]

1.14 Right Heart Dysfunction and Pulmonary Hypertension In Sleep-Disordered Breathing

Often, OSA is viewed as a stand-alone risk factor for the emergence of pulmonary hypertension and the ensuing cor pulmonale. Study results, however, indicate a higher correlation between PH and obstructive ventilatory patterns shown on pulmonary function testing, as well as daytime hypercapnia and hypoxemia; most of this correlation is ascribed to underlying obstructive airway disease. PH strongly

correlates with high waking pCO_2, low waking pO_2, concomitant obstructive lung illness, and body mass index in difficult situations. [105,106,107] It has also been demonstrated that those with pulmonary hypertension have longer stretches of hypoxia. The link between PH and OSA is strongest in the presence of the mechanical effects of obesity on respiration, according to the high correlation between PH and increased BMI, decreased vital capacity, expiratory reserve volume, and total lung capacity.[108] Pressure and volume strains that are applied to the right heart repeatedly and continuously raise the wall tension in the ventricle, promoting myocardial hypertrophy. Through the activation of vascular remodelling, chronic hypoxemia brought on by sporadic nocturnal oxygen desaturations promotes the establishment of permanent PH.[109,110]

Table 1: These percentages show the frequency of symptoms obtained from

OSA patients' subjective and objective symptoms	%
Subjective symptoms	
Daytime sleepiness	67
Difficulty to have a deep sleep	57
Nocturia (≥1/night)	55
Arousals during sleep	41
Early morning arousal	35
Difficulty getting sleep	29
Nocturnal dyspnea	19
Early morning headache	16
Objective symptoms	
Snoring	76
Apnea	29

352 OSA patients from October 2015 to June 2017 with sleep apnea centre of Kyushu University[69]

2. DISCUSSION

There is no question that sleep health plays a role in the pathophysiology of hypertension, but because of the complexity of the relationship, it can be challenging to pinpoint specific sleep abnormalities linked to blood pressure elevation at the epidemiological level as well as the level of a given patient. This is mostly due to a lack of suitable methods for long-term sleep monitoring. Fortunately, advancements in low-cost wearable technologies that enable telemonitoring of blood pressure and sleep parameters can offer a fresh understanding of the relationship and support the modelling of more effective interventions with personalized care and prompt feedback from healthcare professionals to guide the necessary behavioural changes and treatments. Healthy sleep is essential for well-being, and companies and lawmakers are beginning to recognize its importance as well as the general population. [22] Regarding the neural mechanisms mediating the risk of hypertension in insomnia, several studies have found evidence suggesting abnormal neural circulatory control; in comparison to sound sleepers, insomniacs show diminished baroreflex sensitivity and increased sympathetic neural cardiovascular reactivity to stress. Insomniacs' higher levels of circulating norepinephrine, higher heart rates, and shorter pre-ejection times are likewise consistent with sympathetic upregulation, while insomniacs' higher levels of cortisol point to greater hypothalamus-pituitary-adrenal axis activity. This pattern of derangement is significant because it lends support to the idea that a hyperarousal state influences the onset and development of insomnia.[28] A 6-week sleep extension interventional trial was carried out by Harvard Medical School researchers. To extend the amount of time spent in bed by one hour each day, participants were randomly assigned to one of two groups: sleep extension or sleep maintenance. From before to after intervention, patients in the sleep extension group's average 24-hour systolic and diastolic beat-to-beat blood pressures reduced substantially (P less than 0.05) by an average of 14 and 8 mm Hg, respectively. Their average sleep duration rose by an average of 35 minutes. [31] A research by Lanfranchi et al. found that the atypical 24-hour BP profile presented by insomniacs with attenuated nocturnal dipping is related to EEG measurements of cortical activity during sleep. This further supports the idea that physiological hyperarousal contributes to BP rise in insomnia. Additionally, case-control research discovered a dose-dependent relationship between increased risk of hypertension and insomnia with physiological hyperarousal, as demonstrated by a lengthy sleep latency on the multiple sleep latency test. Emerging evidence linking sleeplessness to the advancement of renal disease is also quite fascinating. [28,83,111,112]

3. CONCLUSION

Blood pressure drops during sleep, and a drop in BP during sleep decreases cardiovascular risk. Short sleep duration is linked to hypertension, particularly in middle age. Insomnia with objectively short sleep duration is also linked to an increased risk of hypertension. RLS has a weak link to hypertension; however, PLMS raises blood pressure, especially when combined with arousal. There is no question that good and healthy sleep results in better health overall. Better sleep hygiene measurements and treatment of underlying sleep disorders can reduce the risk of many other comorbidities, especially hypertension.

4. AUTHOR CONTRIBUTION STATEMENT

All authors contributed and collaborated in data collection, extraction, paper writing, revising and production.

5. CONFLICT OF INTEREST

Conflict of interest declared none.

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