# **Shift work, obstructive sleep apnea** syndrome and restless legs syndrome: effects on nocturnal blood pressure

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The prevention of cardiovascular diseases (CVD) has been one of the most important issues in cardiology practice for many years. For this reason, active research is being conducted worldwide to identify new risk factors that lead to damage to the cardiovascular system. One such factor is impaired nocturnal arterial blood pressure (NBP) regulation, which is associated with an increased risk of CVD and premature death. This article reviews the current conditions that may lead to dysregulation of diurnal BP fluctuations: shift work, obstructive sleep apnea syndrome (OSAS), and restless legs syndrome (RLS). The literature review revealed a correlation between the occurrence of nocturnal arterial hypertension (AH) and the presence of OSAS or RLS in the patient, as well as the predisposing factors for nocturnal BP elevation in patients with shift work. It is obvious that patients with OSAS, RLS and shift workers need continuous BP control, including at night, to detect nocturnal AH and prescribe appropriate therapy to prevent disease progression and the increase of the cardiovascular risk.

**Keywords:** shift work, obstructive sleep apnea syndrome, restless legs syndrome, nocturnal arterial hypertension.

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## Introduction

According to the World Health Organization (WHO), cardiovascular diseases (CVD) are the leading cause of death today. Because of its social and economic importance, research is underway worldwide to identify new risk factors for CVD. One such factor is impaired nocturnal blood pressure (BP) regulation, which is associated with an increased risk of fatal cardiovascular events and premature death. However, most studies and meta-analyses addressing this issue have examined only a limited spectrum of non-cardiac nosologies that lead to inadequate reduction or increase in sleep BP, such as diabetes mellitus (DM), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and rheumatoid arthritis (RA). This paper reviews current conditions that can potentially lead to impaired regulation of diurnal BP fluctuations: shift work, obstructive sleep apnea, and restless legs syndrome.

## Shift work

Shift work is important in the implementation of 24-hour work functions, including emergency and security services, industry, food and some others. According to statistics, approximately 2.5 billion people around the world work in shifts, with 20 % of the workforce in Europe working in shifts [1]. Shift work refers to a type of activity that requires the performance of work functions outside of traditional working hours (e.g., 8:00 to 18:00, 9:00 to 17:00, etc.) [2].

### *Shift work and health effects*

Irregular work schedules can have a negative impact on a person's health. An analysis of 38 meta-analyses and 24 systematic reviews by Göran Kecklund et al. (2016) showed an association between shift work and accidents, type 2 DM, weight gain, stroke, coronary heart disease (CHD), acute sleep disturbance, cancers such as prostate and breast cancer, infectious diseases, and increased risk of cognitive and cardiometabolic disorders to the same extent as sleep deprivation [3–5]. However, the association between cancer and night shift work is not evident from a meta-analysis of 57 articles by Aishe Dun et al. (2020) [6], despite the previously observed association. A study by Bette Loef et al. (2019) of blood tests from 254 participants working night shifts (experimental group) and 57 participants in a control group (not associated with shift work) suggested an effect of the night shifts on the immune system of the respondents [4].

### *Circadian Rhythms and BP Regulation*

It is known that the shift work leads to disruption of circadian rhythms, which control not only the sleep-wake cycle, but also many metabolic processes, including BP [7, 8]. Circadian rhythms of BP are characterized by an increase of its values in the morning, 1 hour before awakening, and its decrease ("dipping") by 10-20 % at night and during sleep [2, 9]. The main component of the physiological regulation of blood pressure is the phosphorylation of glycogen synthase kinase-3ß (pGSK-3ß), which activates the WNT/B-catenin signaling pathway. The released B-catenin translocates from the cytoplasm to the nucleus of astrocytes in the supraoptic nucleus of the hypothalamus, where it induces the expression of the glutamate transporter EAAT2 and glutamine synthetase. At the next stage, the concentration of glutamate in the synaptic clefts of glutamatergic neurons decreases as a result of the function of EAAT2 and the conversion of glutamate into glutamine due to the activity of glutamine synthetase. The activity of AMPA-R and NMDA-R receptors is reduced, including on the membranes of neurons of the nucleus of the solitary tract. The intensity of signal impulses from the nucleus of the solitary tract to the neurons of the caudal part of the ventrolateral parts of the medulla oblongata inhibiting the rostral part of the ventrolateral parts of the medulla oblongata decreases, which results in suppression of the sympathetic nervous system and activation of the parasympathetic nervous system. As a result of the described process, there is an increase in BP when photons hit the retina, especially in the morning upon awakening [10]. This describes the central regulation of BP by circadian rhythms.

However, there is also a peripheral regulation, which has been linked at the molecular level to the interaction of the clock proteins CLOCK (circadian locomoter output cycles protein kaput), BMAL1 (for brain and muscle aryl hydrocarbon receptor nuclear translocator (ARNT)-like protein 1), period and cryptochrome: CLOCK and BMAL1 heterodimerize as transcription factors and bind to the promoter regions of tissue-specific target genes involved in the regulation of physiological functions, as well as to the promoter regions of the period and cryptochrome genes, which encode the proteins of the same name,

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via an E-box. According to the negative feedback mechanism, accumulation and penetration of period and cryptochrome protein molecules into the nucleus under the influence of RORα/β/γ and REV-ERBα/β proteins (retinoic acid-related orphan receptors and nuclear receptor subfamily 1 group D member, respectively) inhibits CLOCK and BMAL1, thus stopping the transcription process. The described process has a 24-hour rhythm and is found in cells of smooth muscle tissue, perivascular adipose tissue, liver, adrenal glands, and kidneys, where active substances (serotonin, phenylephrine, angiotensinogen, beta-hydroxybutyrate, IGF, corticosterone, aldosterone, and others) are released, causing changes in vascular wall tone and physiological blood pressure fluctuations [11, 12].

Disruption of such a complex mechanism of regulation of diurnal BP variation leads to the launch of an equally complex pathogenetic mechanism of AH, including both central and peripheral changes in circadian rhythms [11]. In particular, it is of interest to study the relationship between circadian rhythm disturbances and the development of nocturnal arterial hypertension (NAH).

### *Shift work and AH*

AH is one of the pathological conditions caused by shift work. Compared to people with regular work schedules, AH and its progression from mild to severe stage are more common in shift workers [13, 14]. A meta-analysis of 45 studies by Sara Gamboa Madeira et al. (20–21) [1] also found significant increases in systolic (by 2.52 mm Hg, 95 % CI 0.75–4.29) and diastolic BP (1.76 mm Hg, 95 % CI 0.41–3. 12) in participants with regular night shifts, but did not show a significant increase in the risk of developing AH in such participants, in contrast to previous studies, which may be explained by the larger sample size in some previous studies, the age of the participants, the presence of specific conditions in individuals in the study population (pregnancy, sleep disorders, etc.), and differences in the definition of AH. The importance of considering the last factor, the definition of AH, was also noted in a study by Masoud Khosravipour et al. (2021), where the characteristics of AH (ACC/AHA and ESC/ESH criteria) were selected and different results were obtained regarding the incidence of AH development among workers with a 12-hour night shift, depending on the characteristics of the definition. However, despite the differences described, the results of the study showed a higher incidence of AH among "night workers" compared to workers with regular schedules [15].

Shift work and NAH. Shift work is a factor that leads to changes in BP variability and sympathetic nervous system transformation from dipper to non-dipper type [16]. There are data showing that patients with AH who are accustomed to sleeping less than 6 hours (short sleepers) are twice as likely to develop resistance to the antihypertensive drug they are taking than patients with longer sleep duration [24]. In the AAC (American Association of Cardiology) guidelines, night work is considered a factor leading to inadequate nocturnal BP reduction [17]. The development of drug resistance in certain subgroups of patients and inadequate nocturnal BP reduction are characteristics of nocturnal hypertension [17], but no studies were found that examined nocturnal BP levels and the extent of nocturnal BP reduction in this cohort of patients. Given the lack of consensus, it seems reasonable to conduct studies aimed at assessing the risk of developing NAS in patients working shifts and suffering from sleep deprivation.

### *Cardiovascular risk, circadian disruption and shift work*

Circadian disruption due to shift work is associated with an increased cardiovascular risk, which has been repeatedly demonstrated in studies [18, 19]. The first meta-analysis demonstrating the association between shift work and increased likelihood of CVD, including 34 research papers and a total of 2,011,935 participants, was conducted by Manav V. Vyas et al. (2012) in 2012 [19]. The meta-analysis found that shift work was associated with the development of myocardial infarction (OR 1.23, 95 % CI 1.15–1.31), ischemic stroke (OR 1.05, CI 1.01–1.09), and increased risk of vascular events (OR 1.24, CI 1.10–1.39).

Since the work of Manav V. Vyas. et al. (2012) was limited to studies conducted before 2006, Torquati L. et al. (2018) [18] included scientific articles from 2006 to 2016 in their meta-analysis to update the association of shift work with increased cardiovascular risk. The authors assessed cardiovascular risk in 173,010 participants with regular and irregular work schedules in an analysis of 21 studies. The meta-analysis supported the assessment of higher

cardiovascular risk (likelihood of developing cardiovascular disease, including CHD, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism) among people who worked shifts (CI 1.10–1.43), although the definitions of shift work varied among the studies included in the meta-analysis.

## Obstructive sleep apnea syndrome

Obstructive sleep apnea syndrome (OSAS) is a sleep-related chronic respiratory disorder with a high prevalence worldwide, characterized by airway obstruction during sleep [20]. A recent study showed that nearly 1 billion people worldwide have manifestations of this pathology, indicating the need for further study of this condition [21]. If left untreated, OSAS can lead to the development of other pathological conditions, including AH [21]. OSAS and AH influence each other in terms of clinical presentation, therapy, and prognosis. Currently, the concept of "OSAS-associated hypertension" is used in the foreign literature.

### *Etiology and possible pathogenesis of OSAS*

The pathophysiological mechanism of OSAS development is multifactorial and variable, involving many factors, most of which are individualized for each patient. Based on our studies, the most important anatomical and functional mechanisms of OSAS development have been identified and summarized in the general concept of "PALM": P (Pcrit) — critical pharyngeal closure pressure, this term refers to anatomical features that can lead to upper airway collapse; A (Arousal threshold) — reduced respiratory arousal threshold or tendency to night arousals due to respiratory stimuli; L (Loop gain) — instability of ventilation control; M (Muscle responsiveness) — insufficient activity of the muscles that dilate the upper airway [22]. Taken together, these factors can lead to recurrent upper airway spasms, resulting in a marked decrease or complete cessation of airflow. As a result, blood oxygenation decreases, leading to sympathetic nervous system activation, catecholamine release, and sleep fragmentation.

### *OSAS-associated hypertension*

OSAS-associated hypertension occurs as a latent nocturnal hypertension with non-dipper type and pathological variability, more often resistant to drug therapy (45 %). The presence of moderate to severe obstructive apnea in a patient increases the risk of target organ damage [23, 24]. The increase in inflammatory factors in the blood that occurs with OSAS causes oxidative stress, which also increases cardiovascular risk [25]. Thus, the combination of OSAS and AH significantly worsens the patient's prognosis and requires careful evaluation for diagnosis and treatment.

OSAS is more common in patients with AH than in the general population. AH and OSAS share common risk factors, including obesity, high salt intake, advanced age, sedentary lifestyle, and diabetes [25]. Some studies have questioned the causal relationship between OSAS and AH, suggesting that the development of AH is not due to OSAS but to the same risk factor, such as obesity or diabetes [26]. A meta-analysis by Han B. et al. (2017), which included 54 original studies, found a significant association between OSAS and AH (OR = 1.798, 95 % CI 1.355–2.384). Furthermore, in a cross-sectional study group, pooled results showed that OSAS was significantly correlated with AH (OR = 1.980, 95 % CI 1.312–2.987) [27].

The common pathophysiological mechanisms for the development of OSAS and AH involve the activation of the renin-angiotensin-aldosterone system (RAAS). The hypoxemia that develops due to the sleep obstruction leads to increased synthesis and release of renin into the blood, resulting in RAAS activation, vascular constriction, and nocturnal blood pressure elevation. In addition, in the supine position, there is a distribution of fluid in the human body from the lower extremities to the neck, leading to edema of the tissues of the nasopharynx and upper airways, their obstruction and increase in BP, which is exacerbated by the activation of the RAAS by the mechanism described above and an increase in the concentration of aldosterone in the blood, which retains fluid and increases the volume of circulating blood [24]. A meta-analysis by Ze-Ning Jin et al (2016) found an increase in blood aldosterone and angiotensin II in people with OSAS and AH [28].

### *The impact of OSAS on nocturnal blood pressure*

As described above, the pathogenesis of OSAS involves factors that have a significant impact on the cardiovascular system, such as oxidative stress, hypoxia, metabolic acidosis, and excessive activation of

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the sympathetic nervous system. As a result of these factors, there may be a sustained increase in blood pressure and an increase in its diurnal variability. The most significant changes in blood pressure occur at night. During airway obstruction, the phenomenon of "paradoxical" pulse occurs, i.e., a decrease in BP ⩾ 10 mm Hg and a decrease in heart rate as a result of excessive inspiratory effort [29]. After the obstruction ceases, there is a sharp peak in BP for a few seconds, after which the BP values return to normal [29]. Based on this, we can conclude that the variability of nocturnal BP depends on the number of apnea/hypopnea attacks, but the amplitude of BP peaks depends on individual characteristics of the organism and drug therapy. Confirmation of the direct effect of OSAS on nocturnal BP peaks and their variability can be found in numerous studies [30–32], where BP values and their variability returned to normal after the application of CPAP therapy, but not all results were consistent, indicating the need for more thorough study of this problem. In addition to these findings, the CARDIA (2020) study found a pattern: a higher likelihood of having OSAS increases the likelihood of developing comorbid nocturnal hypertension (CI 1.00-1.75) [33].

## Restless legs syndrome

Restless legs syndrome (RLS) or Willis-Ekbom disease is a sensorimotor neurological disorder in which the need to move the lower extremities at rest, more often in the evening or at night during sleep, that disappears or diminishes with movement [34]. The estimated epidemiology is 5–8.8 % of the general population [35]. Periodic limb movement syndrome of sleep (PLMS) is known to occur in people with RLS. The main role in the pathogenesis of the primary form of RLS is attributed to genetically determined disorders of the dopaminergic system and iron metabolism in the brain. However, secondary forms have also been identified in the context of iron deficiency anemia, pregnancy, terminal renal failure, and vitamin B12 deficiency [36].

### *The impact of RLS on nocturnal blood pressure*

RLS, PLMS, and OSAS are the most common sleep disorders that induce nocturnal BP elevation through activation of the sympathoadrenal system and RAAS, development of oxidative stress, and further endothelial dysfunction, and thus resulting in NAH [37, 38].

A meta-analysis by Giuseppe Maiolino et al. (2021), including 7 studies and 442 patients, showed that RLS was associated with higher BP during sleep compared to controls. It should be noted that the highest BP values occurred during both periodic and non-periodic limb movements, and the duration of nocturnal BP peaks during non-periodic movements was longer in some studies included in the meta-analysis [37]. In addition, NAH in patients with RLS was more frequently observed in the elderly and was also associated with a later onset of RLS. The severity of NAH correlates with the severity of RLS, but this statement is true only for patients with diastolic non-dipper type of diastolic BP diurnal curve [39].

However, the pathogenesis of nocturnal BP elevation in patients with sleep disorders is still under study. Exploring two main hypotheses (sleep fragmentation and the presence of periodic limb movements during sleep), Mariusz Sieminski et al (2017) concluded that sleep fragmentation is not a necessary component for the development of nocturnal BP in patients with RLS. They found a strong association between nocturnal increases in both diastolic BP and systolic BP during bouts of periodic limb movements during sleep [40]. Considering the different data obtained, the authors suggest the need for more detailed study of PLMS on the pathogenesis of nocturnal AH.

Thus, RLS, both in combination with and without PLMS, leads to increased cardiovascular risk, and therefore more careful monitoring of BP, including nocturnal BP, in these patients is required.

## Conclusion

Thus, there are data suggesting an association between the occurrence of NAH and common conditions such as OSAS and RLS, as well as an increase in nocturnal BP in individuals with shift work. Studying the influence of these factors on nocturnal BP will help to clarify the specific pathogenetic links that can be acted upon to prevent the development of NAH. It is clear that patients with OSAS, RLS, and shift workers need continuous BP control, including at night, for earlier detection of NAH and prescription of appropriate therapy to prevent disease progression and increased cardiovascular risk. The issues of optimal correction of nocturnal BP levels in combination with the impact on comorbidities (RLS, OSAS, or shift work) are an ur-

gent scientific and practical task that requires further comprehensive studies.

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