Sleep Medicine 32 (2017) 229–233

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Higher nocturnal systolic blood pressure in patients with restless legs syndrome compared with patients with insomnia

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ARTICLE INFO

Article history:
Received 11 April 2016
Received in revised form
24 July 2016
Accepted 25 July 2016
Available online 1 November 2016

Keywords:
Restless legs syndrome
Insomnia
Blood pressure
Periodic limb movements

ABSTRACT

Background: There is evidence linking restless legs syndrome (RLS) with increased blood pressure (BP), but the mechanism of this relation remains unclear. Is the BP increased due to some features of RLS or to deterioration of sleep caused by RLS? This study compared values of nocturnal BP in patients with RLS and patients with insomnia. If increased BP in RLS is a consequence of disordered sleep, then it should be similar to increased BP in insomnia.
Methods: Polysomnographic recordings of patients admitted to a sleep center with RLS or insomnia were analyzed. Demographic and clinical data, objective sleep parameters, and nocturnal BP were compared.
Results: Recordings of 35 patients with RLS and 33 patients with insomnia were analyzed. The groups did not significantly differ in terms of demographic traits or prevalence of other comorbidities. Patients with RLS had significantly higher systolic BP during the night (122.4 ± 13.8 vs 116.3 ± 13.4; $p = 0.03$) and during sleep (121.4 ± 13.3 vs 115.7 ± 13.3; $p = 0.04$). The only significant difference in sleep architecture was an increased number of periodic limb movements in sleep (PLMS) and PLMS with arousal in the RLS group (25.5 ± 24.6 vs 13.9 ± 22.7; $p = 0.02$ and 4.7 ± 5.4 vs 2.1 ± 3.4; $p = 0.01$).
Conclusion: Our results suggest that patients with RLS have higher nocturnal BP than patients with insomnia, and that increased PLMS is related to the increase in BP.

1. Introduction

Restless legs syndrome (RLS) is a neurological disorder characterized by the presence of troublesome discomfort in the lower extremities and an urge to move the legs. These symptoms appear at rest in the evening or night, and are relieved by moving the legs [1]. Another characteristic of RLS is the presence of periodic limb movements in sleep (PLMS), an involuntary flexing of the lower extremities during sleep [1]. The prevalence of RLS is estimated at 5–8.8% of the general population [2].

Epidemiologic data have shown that RLS may be related to an increased risk of hypertension [3–5] and to a nondipping pattern of circadian blood pressure (BP) changes [6]. One hypothesis explaining increased BP in RLS is based on the observation that each PLMS leads to a transient increase in BP, which results in numerous increases in BP during the night [7–9].

An alternative explanation of the relation between RLS and higher BP is that disordered nocturnal sleep (eg, short total sleep time, disturbed proportion of sleep stages, high number of awakenings) is itself a factor triggering increased nocturnal BP [10–12]. Patients with RLS have poorer nocturnal sleep compared with normal populations, which may explain the increased nocturnal BP independently of the presence of periodic limb movements.

One method of clarifying whether nocturnal BP is increased in patients with RLS due to specific clinical features of this disease (eg, presence of PLMS) or simply due to presence of sleep disturbance is to compare patients with RLS (examined group) and patients with other diseases leading to disordered sleep (control group). If nocturnal BP in patients with RLS is not significantly different from control groups, it can be concluded that disturbed sleep is sufficient to increase nocturnal BP. If, however, nocturnal BP is higher in the RLS group, some clinical features of RLS (other than disturbed sleep) may lead to increased BP.

Insomnia, primarily characterized by disordered sleep, constitutes a natural control condition for such comparisons, as it has been shown that patients with insomnia have higher nocturnal BP than healthy subjects [13].

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http://dx.doi.org/10.1016/j.sleep.2016.07.025
1389-9457/

This study compared nocturnal BP in patients with RLS and patients with disordered sleep due to insomnia. It also compared objective sleep parameters in RLS and in insomnia with regard to nocturnal BP values.

2. Methods

The protocol for this study was approved by the Independent Bioethical Committee for Scientific Research at the Medical University of Gdansk.

2.1. Subjects

The study design was based on a comparison of nocturnal values of BP in two groups of patients: patients with disordered sleep due to RLS, and patients with disordered sleep due to insomnia.

The following inclusion criteria were used: full polysomnographic (PSG) recordings with beat-to-beat measurement of BP and either RLS diagnosed according to the International Restless Leg Syndrome Study Group (IRLSSG) [1] diagnostic criteria or insomnia diagnosed according to the International Classification of Sleep Disorders, second edition [14]. Exclusion criteria were as follows: presence of sleep-related breathing disorders, defined as the presence of apnea/hypopnea index (AHI) greater than five; presence of diagnosed/treated mood disorders or other psychiatric conditions; and unstable intake of any drugs within the two weeks preceding PSG recordings. The selection of subjects participating in the study is shown in Fig. 1.

We performed a retrospective analysis of PSG recordings of 35 patients diagnosed with RLS and 33 patients diagnosed with insomnia. All participants were Finnish. The mean age was 48.6 ± 13.7 years in the RLS group and 46.5 ± 11.2 years in the insomnia group. There were 14 men in the RLS group and 17 men in the insomnia group. The examined and control groups were selected to detect a 10% difference in BP values with power test of 0.75 (sample size: RLS = 35, insomnia = 33; sampling ratio = 1.1 RLS/insomnia).

All patients underwent the diagnostic process in Vitalmed Helsinki Sleep Clinic. The analyzed PSG recordings were performed prior to initiation of any therapy that might interfere with sleep architecture.

2.2. PSG recordings

All the patients underwent a single night of polysomnographic recording. All recordings were performed with the SOMNOscreen

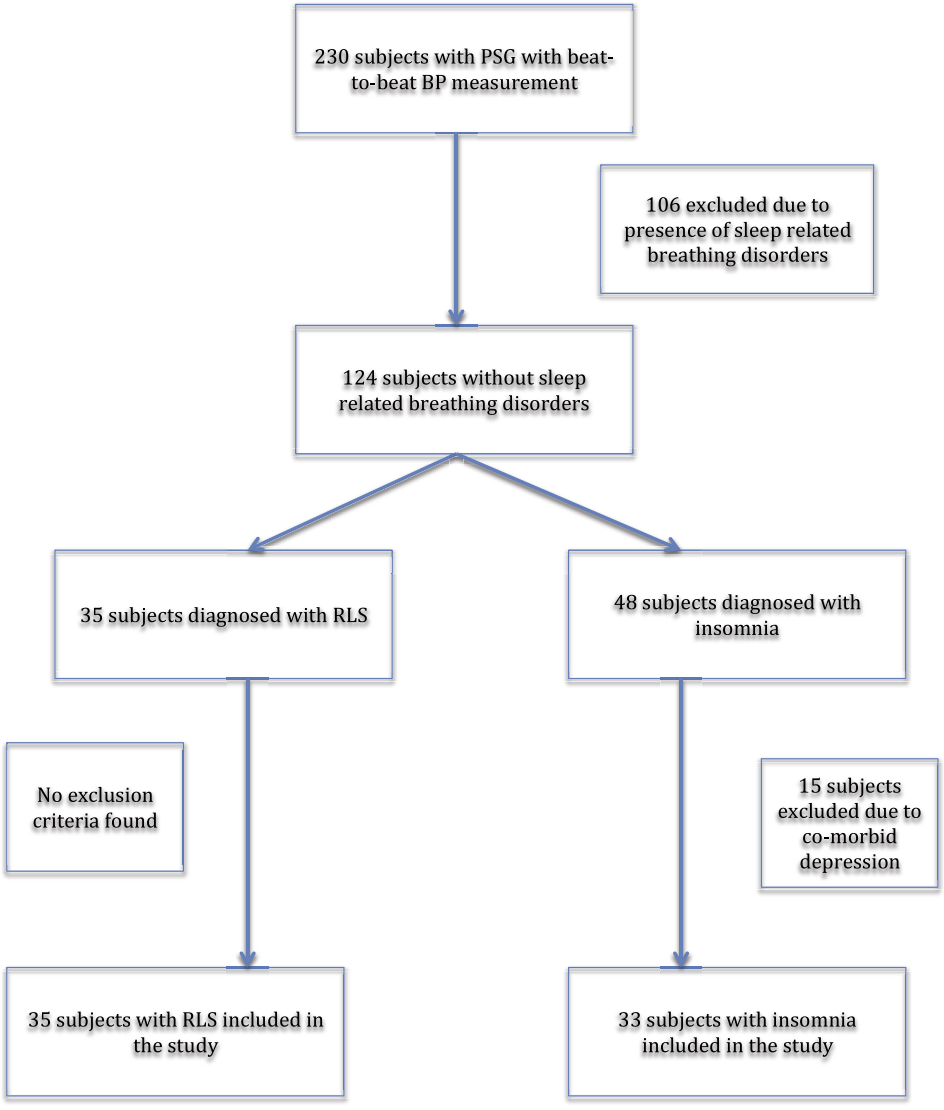

Fig. 1. Selection of subjects participating in the study. PSG – polysomnography; BP – blood pressure; RLS – restless legs syndrome.

Table 1
Demographic characteristics of the RLS group and insomnia group.

	RLS group ($n = 35$)	Insomnia group ($n = 33$)	p
Age (y, mean ± SD)	48.6 ± 13.7	46.5 ± 11.2	NS
Sex (male/female)	14/21	17/16	NS
Hypertension (%)	28.6	30.3	NS
Diabetes mellitus (%)	5.7	0	NS
History of stroke (%)	5.7	6.1	NS
Coronary heart disease (%)	2.9	0	NS
Hypercholesterolemia (%)	22.9	9.1	NS

Abbreviations: NS, not significant; SD, standard deviation.

plus PSG system (Somnomedics, Randersacker, Germany). Sleep recordings included four EEG leads, two bilateral electro-oculographic (EOG) leads, bilateral chin electromyographic (EMG) leads, and two surface EMG leads placed on the left and right anterior tibialis muscles to record periodic limb movements in sleep (PLMS). Respiration was recorded with a nasal cannula, thoracic and abdominal strain gauges, and finger oximetry. Electrocardiograms were recorded with a single precardial lead. The PSG included beat-to-beat BP measurements determined via measurement of pulse transit time (PTT) [15]. This measurement of BP was continuous, noninvasive, and did not disturb the sleep of the patients. The PTT-based measurement of BP was calibrated and validated against sphygmomanometric (cuff) measurement of BP on the brachial artery at the beginning of recording.

For each patient, recordings were begun at 9:00 p.m., one hour prior to "lights-off" (10:00 p.m.). They were stopped at 7:00 a.m., approximately 30 min after the patient was awakened. Blood pressure values measured during the periods of quiet waking activity (ie, 9:00 p.m. to 10:00 p.m. and 6:30 a.m. to 7:00 a.m.) were considered to be daytime values.

The PSG recordings were scored according to American Academy of Sleep Medicine guidelines [16]. Sleep parameters possibly related to sleep stability and BP (indicators of disordered sleep) were calculated: total sleep time (TST), sleep efficiency (SE), latency of stages 1, 2, slow wave (SWS), and rapid eye movement (REM) sleep, duration of stages 1, 2, SWS, and REM, Sleep Stage Change Index (number of transitions between the sleep stages per hour of sleep), the Wake Index (WI, number of awakenings per hour of sleep), duration of Wake after Sleep Onset (WASO), PLMS index (PLMSI), and PLMS with arousals index (PLMSA-I).

For assessment of the cardiovascular system, the following values were calculated: mean systolic BP (SBP), and diastolic BP (DBP), and heart rate during daytime, wake, and sleep periods.

2.3. Statistical analysis

Demographic, clinical data, and sleep parameters were then compared between the two groups. Statistical comparisons between the groups were performed using χ^2 tests (categorical variables) or t tests (continuous variables). A p value less than 0.05 was considered statistically significant.

3. Results

3.1. Demographic data

Recordings of 35 patients with RLS and 33 patients with insomnia were included in this study. Demographic features of both groups are presented in Table 1. There were no differences between the groups regarding sex, age, BMI, or prevalence of chronic conditions. All patients diagnosed with hypertension were regularly taking antihypertensive drugs.

3.2. Sleep architecture

The sleep architecture did not differ between the groups. The only difference found was a significantly higher index of periodic limb movements in sleep (PLMSI) and periodic limb movements in sleep with arousals (PLMSA-I). The sleep characteristics of both groups are presented in Table 2.

3.3. Blood pressure

There was no significant difference between the groups in daytime SBP and DBP. Comparison of values of nocturnal BP showed that patients with RLS had higher BP values in the night and during sleep. There was no difference in DBP and heart rate. Blood pressure values are presented in Table 3.

Table 2
Sleep characteristics of patients with restless legs syndrome (RLS) or insomnia.

	RLS group ($n = 35$)	Insomnia group ($n = 33$)	p
Total sleep time (min, mean ± SD)	370.0 ± 82.6	374.1 ± 85.3	NS
Sleep efficiency (%, mean ± SD)	74.0 ± 13.7	76.3 ± 13.4	NS
Sleep latency (min, mean ± SD)	32.8 ± 36.9	27.8 ± 30.7	NS
S1% (mean ± SD)	18.1 ± 7.5	16.8 ± 8.1	NS
S2% (mean ± SD)	46.9 ± 6.9	50.2 ± 9.8	NS
SWS % (mean ± SD)	16.2 ± 7.2	14.7 ± 7.5	NS
REM % (mean ± SD)	18.5 ± 6.6	17.7 ± 7.0	NS
Sleep stage change index (mean ± SD)	18.3 ± 5.4	19.0 ± 6.2	NS
Arousal Index (mean ± SD)	17.8 ± 9.1	15.6 ± 7.7	NS
Wake Index (mean ± SD)	5.6 ± 2.5	5.5 ± 2.8	NS
WASO (min, mean ± SD)	88.4 ± 66.6	85.0 ± 60.6	NS
AHI (min, mean ± SD)	1.34 ± 1.43	1.66 ± 1.42	NS
Heart rate (beats/min; mean ± SD)	58.9 ± 7.8	59.1 ± 7.1	NS
PLMS Index (mean ± SD)	25.5 ± 24.6	13.9 ± 22.7	0.02
PLMSA Index (mean ± SD)	4.7 ± 5.4	2.1 ± 3.4	0.01

Abbreviations: AHI, apnea/hypopnea index; PLMS Index, periodic limb movements in sleep index; PLMSA Index, periodic limb movements in sleep with arousal index; SD, standard deviation; SWS, slow-wave sleep; WASO, wake after sleep onset.

Table 3
Systolic and diastolic blood pressure in patients with restless legs syndrome (RLS) or insomnia.

	RLS group ($n = 35$)	Insomnia group ($n = 33$)	p
SBP during the day (mm Hg; mean ± SD)	126.5 ± 13.9	121.9 ± 16.9	0.11
SBP during the night (mm Hg; mean ± SD)	122.4 ± 13.8	116.3 ± 13.4	0.03
SBP during the sleep period (mm Hg; mean ± SD)	121.4 ± 13.3	115.7 ± 13.3	0.04
DBP during the day (mm Hg; mean ± SD)	78.4 ± 12.2	75.1 ± 9.1	0.11
DBP during the night (mm Hg; mean ± SD)	76.5 ± 10.4	71.7 ± 14.8	0.06
DBP during the sleep period (mm Hg; mean ± SD)	76.1 ± 10.5	73.1 ± 9.1	0.1

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.

Table 4
Daytime and sleep time systolic blood pressure (SBP) and diastolic blood pressure (DBP) in restless legs syndrome (RLS) and insomnia groups.

	Daytime	Sleep time	*p*
SBP in RLS group (mm Hg; mean ± SD)	126.5 ± 13.9	121.4 ± 13.3	0.02
DBP in RLS group (mm Hg; mean ± SD)	78.4 ± 12.2	76.1 ± 10.5	0.008
SBP in insomnia group (mm Hg; mean ± SD)	121.9 ± 16.9	115.7 ± 13.3	<0.001
DBP in insomnia group (mm Hg; mean ± SD)	75.1 ± 9.1	73.1 ± 9.1	0.009

Blood pressure during wakefulness differed significantly from that during sleep in both groups, such that it underwent a nocturnal (sleep-related) dip for both SBP and DBP (Table 4). Separate comparisons were performed for patients who were normotensive and hypertensive in both groups. Normotensive patients with RLS had significantly higher SBP during sleep (at night). No such difference was found in the population of hypertensive patients (Table 5).

4. Discussion

In this study, we compared patients with RLS and patients with insomnia and found that patients with RLS have higher nocturnal BP values compared with patients with insomnia.

There is some evidence in the literature for a relationship between RLS and increased (or nondipping) nocturnal BP. Erden et al., after analyzing data of 133 hypertensive and 81 normotensive subjects, found that RLS is an independent determinant for hypertension and for lack of nocturnal BP dipping [6]. Moreover, the authors observed that patients with RLS had smaller nocturnal decreases in BP [6]. Ulu et al. found that nondipping patients with RLS have more severe symptoms of the disease [11]. Additionally, patients with Parkinson disease and RLS have significantly higher nocturnal SBP than patients with Parkinson disease but no RLS [17]. Our results (showing that patients with RLS have higher values of BP), remain in concordance with the above studies.

The nature of the relation between RLS and increased nocturnal BP is not yet established. Two possible factors related to sleep in patients with RLS may contribute to increased nocturnal BP [9,18,19]. One is disruption of normal sleep architecture in RLS, and the other is the presence of PLMS.

Restless legs syndrome leads to significant disorders of sleep structure. Patients with RLS are reported to have decreased sleep efficiency and total sleep time, increased nocturnal awakenings, and increased stage shifts [20,21]. Individuals with RLS were also found to have significantly increased PLMS, although it must be remembered that PLMS are also present in other sleep disorders, such as insomnia. Ferri et al. found increased PLMS in patients with unexplained insomnia [22]. A similar fact was observed by Sivertsen et al. [23]. It was also shown that disordered sleep led to increased BP. Au et al. found that sleep duration and sleep efficiency were inversely associated with BP in a population of adolescents [24]. Adolescents with lower sleep efficiency and shorter sleep duration had higher BP values [18]. Sleep efficiency for both groups in our study was below 80%, and the groups' WASO times were both over 60 min; these values fall between those that are characteristic for individuals with extremely fragmented sleep and undisturbed sleep. However, their similarity between groups rejects the hypothesis that BP changes in this study were the result of sleep fragmentation.

Sayk et al. published evidence that disturbing sleep architecture by deprivation of slow-wave sleep reduced the nocturnal dipping of BP [19]. Although our study did not analyze correlations between sleep stage and BP, the potential for such correlations to exist suggests that this aspect deserves attention in future projects focusing on cardiovascular consequences of sleep disorders.

To explain the mechanism(s) leading to increased values of nocturnal BP, we compared two groups of patients with disordered sleep who would significantly differ only in the number of PLMS. The groups were relatively young and free of chronic comorbidities, suggesting that the sleep-related features were the most important factors influencing the nocturnal BP values. Both groups in our study had similar sleep parameters, with the only exception being significantly higher indices of PLMS and PLMS with arousal in the group of subjects with RLS. The observed difference nocturnal BP between the groups can be related to the number of PLMS.

PLMS are related to increased BP. Pennestri et al., studying a group of patients with RLS, found that each PLM was followed by a significant increase in BP. The increase was significantly higher after PLMS with microarousals [9]. This finding was confirmed by Siddiqui et al., who observed that in treated patients with RLS, there was a significant increase in SBP and DBP following PLMS, PLM in wake (PLMW), PLMS with arousal (PLMSA), and respiratory-related leg movement (RRLM). There was no increase in BP following voluntary movements of the leg [7]. Recently, Pennestri et al. compared changes in BP following PLMS in patients with RLS and in healthy subjects. That study once again confirmed the presence of significant increases in SBP and DBP in patients with RLS following PLMS, and showed that SBP and DBP significantly increased after PLMS in healthy subjects. The increase was more pronounced after PLMSA in both groups, but it was smaller in the group of healthy subjects [8].

Authors of those studies focused on describing short-term changes in BP related to a single PLMS. However, our study also found that subjects with sleep disorders and higher numbers of PLMs also have higher nocturnal BP values. This finding suggests that short but repetitive increases in BP related to PLMS can lead to a generalized increase in nocturnal BP. Dean et al., in an analysis of relations between sleep parameters and BP, found that increased PLMS with arousals was related to increased diastolic BP [25].

Table 5
Differences in blood pressure values in normotensive and hypertensive subgroups of patients with restless legs syndrome (RLS) or with insomnia.

	Normotensive			Hypertensive		
	RLS group ($n = 25$)	Insomnia group ($n = 23$)	*p*	RLS group ($n = 10$)	Insomnia group ($n = 10$)	*p*
SBP in night (mm Hg; mean ± SD)	120.9 ± 12.0	114.2 ± 12.1	0.03	126.0 ± 17.8	121 ± 0	0.26
DBP in night (mm Hg; mean ± SD)	76.2 ± 9.4	71.6 ± 8.9	0.05	77.5 ± 13.2	77.5 ± 8.8	0.5
SBP in sleep (mm Hg; mean ± SD)	120.3 ± 12.1	113.9 ± 12.2	0.04	124.0 ± 16.2	119.8 ± 15.5	0.28
DBP in sleep (mm Hg; mean ± SD)	75.7 ± 9.4	71.3 ± 8.9	0.05	77.1 ± 13.2	77.2 ± 8.6	0.49
Daytime SBP (mm Hg; mean ± SD)	125.2 ± 12.5	118.8 ± 15.2	0.06	129.5 ± 17.3	129.1 ± 19.0	0.48
Daytime DBP (mm Hg; mean ± SD)	78.4 ± 11.6	74.0 ± 9.0	0.08	78.5 ± 14.3	77.7 ± 9.2	0.49

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.

Our study has some limitations. First, the concept of the study allowed observation of correlations between sleep parameters and BP without a definite causal relation. Future studies should use a prospective design. Second, the study focused on objective polysomnographic data. Therefore, we used no subjective data, such as scales of the severity of insomnia and RLS. We have not yet analyzed the relationship between insomnia secondary to RLS and BP. Future projects should combine subjective and objective clinical data. It must be noted also that differences in BP found between the groups in our study were small, and resolving whether they are of clinical significance would require a different (prospective) protocol of a study. No significant differences between the groups were found in terms of comorbidities or sleep parameters; nevertheless, BP values could be affected by some uncontrolled incidental factors.

Our study showed that patients with RLS had higher nocturnal BP compared to patients with insomnia, and that the only statistically significant difference between the groups was the higher numbers of PLMS and PLMSA in the RLS group. It may therefore be suggested that patients with RLS have higher nocturnal BP related to increased numbers of PLMS and PLMSA and not related to other disturbances of sleep architecture. Our results suggest that patients diagnosed with RLS are at risk for developing high BP during the night. Ultimately, high nocturnal BP may lead to chronic nocturnal hypertension and secondary consequences such as increased cardiovascular morbidity and mortality. Diagnosis of RLS does not require sophisticated methods in most cases, and effective symptomatic therapies are available. These therapies are also shown to reduce the incidence of PLMS in patients with RLS. Some studies have shown that PLMS were a risk factor for hypertension and cardiovascular disease; therefore, proper diagnosis of RLS and therapy leading to reduction of the PLMS index may be considered to reduce the overall risk of cardiovascular morbidity [26,27].

Conflict of interest

Dr. Sieminski has nothing to disclose. Dr. Chwojnicki has nothing to disclose. Dr. Partinen reports grants from Academy of Finland, other from Bioprojet, other from Jazz Pharmaceuticals, personal fees from UCB-Pharma, personal fees from GSK, personal fees from MSD, personal fees from Orion Pharma, personal fees from Takeda, outside the submitted work.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2016.07.025.

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