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Original Article

Risk of resistant hypertension associated with restless legs syndrome and periodic limb movements during sleep: a study on 673 treated hypertensive individuals

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ABSTRACT

Objective: Given the limited data available in the literature, the aim of this study was to examine the risk of resistant hypertension (RHT) associated with restless legs syndrome (RLS) and periodic limb movements during sleep (PLMS) in a large sample of treated hypertensive individuals.
Methods: Demographic and polysomnographic (PSG) data from 673 treated hypertensive individuals recruited from the research database of the sleep laboratory of Erasme Hospital were analysed. After exclusion of the main causes of pseudo-resistance and secondary hypertension, RHT status was defined by the presence of an uncontrolled hypertension despite treatment with at least three antihypertensive agents (including a diuretic) from different classes in correct combination and at the highest tolerated doses or by the presence of controlled hypertension requiring the use of at least four antihypertensive agents. Logistic regression analyses were conducted to examine the risk of RHT associated with RLS and PLMS in treated hypertensive individuals.
Results: After adjustment for major confounding factors associated with RHT, multivariate logistic regression analysis revealed that frequent RLS (≥2 episodes/week) combined with PLMS index ≥26/h [odds ratio (OR) 2.20; 95% confidence interval (CI) 1.35–3.61, $p = 0.021$] was a significant risk factor of RHT in treated hypertensive individuals.
Conclusion: In treated hypertensive individuals, frequent RLS combined with PLMS index ≥26/h is associated with higher risk of RHT which suggests that this pathology may be a secondary cause of RHT (eg, obstructive sleep apnoea syndrome and insomnia with short sleep duration) justifying the establishment of effective treatments in this particular subpopulation.

1. Introduction

Resistant hypertension (RHT) is defined by the presence of uncontrolled hypertension despite treatment with at least three antihypertensive agents (including a diuretic) from different classes in correct combination and at the highest tolerated doses or by the presence of controlled hypertension requiring the use of at least four antihypertensive agents [1]. However, before being able to make this diagnosis of RHT, it is imperative to exclude the presence of a pseudo-resistance to antihypertensive agents potentially induced by inappropriate techniques of blood-pressure measurement, non-adherence of patients to therapeutic recommendations and white coat effect [2]. In treated hypertensive individuals, the presence of this resistance to antihypertensive agents is not uncommon since its prevalence varies from 13.72% to 16.32% depending on the type of studies considered [3]. Yet, despite this non-negligible prevalence, the pathophysiology of this resistance to antihypertensive agents is still unknown even if it appears to be multifactorial with a probable involvement of one or more of the following factors: hypervolemia (excessive sodium intake, liver failure, heart failure, drugs inducing water or sodium retention and ineffective use of diuretics); activation of the sympathetic nervous system (chronic stress, chronic pain, hyperventilation, and panic attacks); and iatrogenic factor and undiagnosed secondary hypertension [hepatic diseases, renal artery stenosis, obstructive sleep apnoea syndrome (OSAS) and endocrine pathologies] [4]. Nevertheless, RHT promotes the occurrence of kidney and cardiovascular

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complications associated with an adverse prognosis which is therefore a major public health problem [5,6].

There seems to be a particular relationship between hypertension and some untreated sleep disorders [eg, insomnia with short sleep duration, OSAS, and restless legs syndrome (RLS) alone or combined with periodic leg movements during sleep (PLMS)] [7,8]. Among these sleep disorders, RLS is a relatively frequent sensorimotor neurological disorder in the general population with an estimated prevalence of 7.3% and is characterized by typical clinical symptoms [9,10]. In 85–95% of cases, RLS may be associated with PLMS characterized by the occurrence of repeated stereotypical movements during sleep [11]. Conversely, even if these PLMS seem frequent in RLS, in 25% of patients referred for sleep examination they may also occur independently of RLS [12]. However, similarly to OSAS, both in RLS and PLMS alone or combined with RLS, there is sleep deprivation and/or a sleep fragmentation which may promote the occurrence of hypertension [13,14] through several pathophysiological mechanisms (oxidative stress, metabolic alterations, activation of the sympathetic nervous system, hyperactivity of the hypothalamic–pituitary–adrenal axis, endothelial dysfunction and decreased arterial elasticity) [15]. Despite the fact that these different mechanisms associated with RLS and PLMS may also play a role in the pathophysiology of resistance to antihypertensive agents [7], the risk of RHT associated with RLS and PLMS has not yet been investigated, unlike other untreated sleep disorders (such as insomnia with short sleep duration and OSAS) [16–18].

Our objective was to demonstrate empirically that independently of other untreated sleep disorders (eg, insomnia with short sleep duration and OSAS), there was a higher risk of RHT associated with RLS and PLMS in treated hypertensive individuals. The aim of this approach was to enable health professionals who treat those with hypertension to reference reliable data concerning this risk of RHT associated with RLS and PLMS.

2. Materials and methods

2.1. Population

The 673 treated hypertensive individuals (272 individuals with RHT and 401 individuals without RHT) were recruited from the database of the sleep laboratory of Erasme Hospital, which contains data for 3511 individuals who completed sleep laboratory monitoring in the years 2002–2014 (Fig. 1). Both the 272 individuals with RHT and the 401 individuals without RHT were referred to the sleep laboratory by physicians specializing in sleep medicine after an ambulatory consultation during which a preliminary assessment of complaints related to sleep, ongoing treatments, somatic and psychiatric comorbidities was carried out systematically, making it possible to conduct a first diagnostic hypothesis. However, the sleep laboratory was performed in individuals with RHT at the request of their treating cardiologist to exclude the presence of hypertension secondary to sleep disorder whereas it was performed in individuals without RHT to allow an objective assessment of their complaints related to sleep. Moreover, the data obtained during this ambulatory consultation are systematically checked when these individuals are admitted to the sleep laboratory.

The inclusion criteria were age $\geq$18 years, the presence of hypertension meeting the diagnostic criteria of the World Health Organization (WHO) [19] and an adequate adherence to the therapeutic recommendations [compliance with antihypertensive agents and adherence to lifestyle modifications (lower-salt diet, weight loss attempt in obese, and overweight, and moderation of alcohol intake)]. The exclusion criteria included the presence of an uncontrolled severe psychiatric disorder, presence of uncontrolled severe somatic disease (chronic liver disease, chronic pancreatic disease, chronic pulmonary disease, severe cardiovascular disease, severe renal disease, autoimmune disease and pathologies altering the activity of the hypothalamic–pituitary–adrenal axis [eg, Cushing's syndrome]), presence of inflammatory or infectious disease, presence or history of cranial trauma, presence or history of central nervous system injury that could involve respiratory centres in the brain, presence or history of craniofacial or thoracic cavity malformations, presence of pregnancy, presence of OSAS already known or course of treatment before sleep laboratory, presence of PLMS/RLS already known or course of treatment before sleep laboratory, presence of predominantly central apnoea syndrome, presence of narcolepsy or primary hypersomnia, presence of parasomnia, and presence or history of substance abuse.

2.2. Methods

2.2.1. Ethics approval and consent to participate

This research protocol was approved by the Hospital and Medical School Ethics Committee of the Erasme Hospital (Brussels University Clinics) (Erasme Reference: P2019/051). At Erasme Hospital, all patients are informed that their data could be used retrospectively for scientific research. If patients do not wish for their data to be used, they must inform the hospital, at which time, this directive is indicated in their medical records, and any future use of their data is prohibited.

2.2.2. Medical and psychiatric evaluation of participants

All individuals upon admission to the sleep laboratory of Erasme Hospital had their medical records reviewed and a complete somatic check-up performed, including a blood test, electrocardiogram, a daytime electroencephalogram, urinalysis, and a chest X-ray (only for those aged over 45 years). These steps allowed for a systematic diagnosis of potential somatic pathologies present in patients admitted to our unit.

The diagnosis of RHT was made before admission to the sleep laboratory following a comprehensive and systematic cardiological assessment (including a 24-h ambulatory blood pressure monitoring) during a specialized consultation on the management of hypertension on the basis of the following criteria [20]. (1) The presence of uncontrolled hypertension (defined as the presence of systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg) despite treatment with at least three antihypertensive agents (including a diuretic) from different classes in correct combination and at the highest tolerated doses or the presence of controlled hypertension (defined as the presence of systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg) requiring the use of at least four antihypertensive agents. (2) Exclusion of the main causes of pseudo-resistance to antihypertensive agents (inappropriate techniques of blood pressure measurement, non-adherence of patients to therapeutic recommendations and white coat effect). (3) Exclusion of the main causes of secondary hypertension (iatrogenic [eg, related to treatment], primary hyperaldosteronism, renal artery stenosis, renal parenchymal pathology, pheochromocytoma, thyroid pathology, Cushing's syndrome, coarctation of the aorta, intracranial tumor and OSAS already known before sleep examination).

Furthermore, during the stay at the sleep laboratory, systolic and diastolic blood pressures were manually measured on the right arm after 5 min of rest in a sitting position by well-trained nurses during at least two medical examinations in order to assess the hypertension status (controlled or uncontrolled) in all treated hypertensive individuals referred to the sleep laboratory. For individuals with a systolic blood pressure $\geq$140 mmHg and/or a diastolic blood

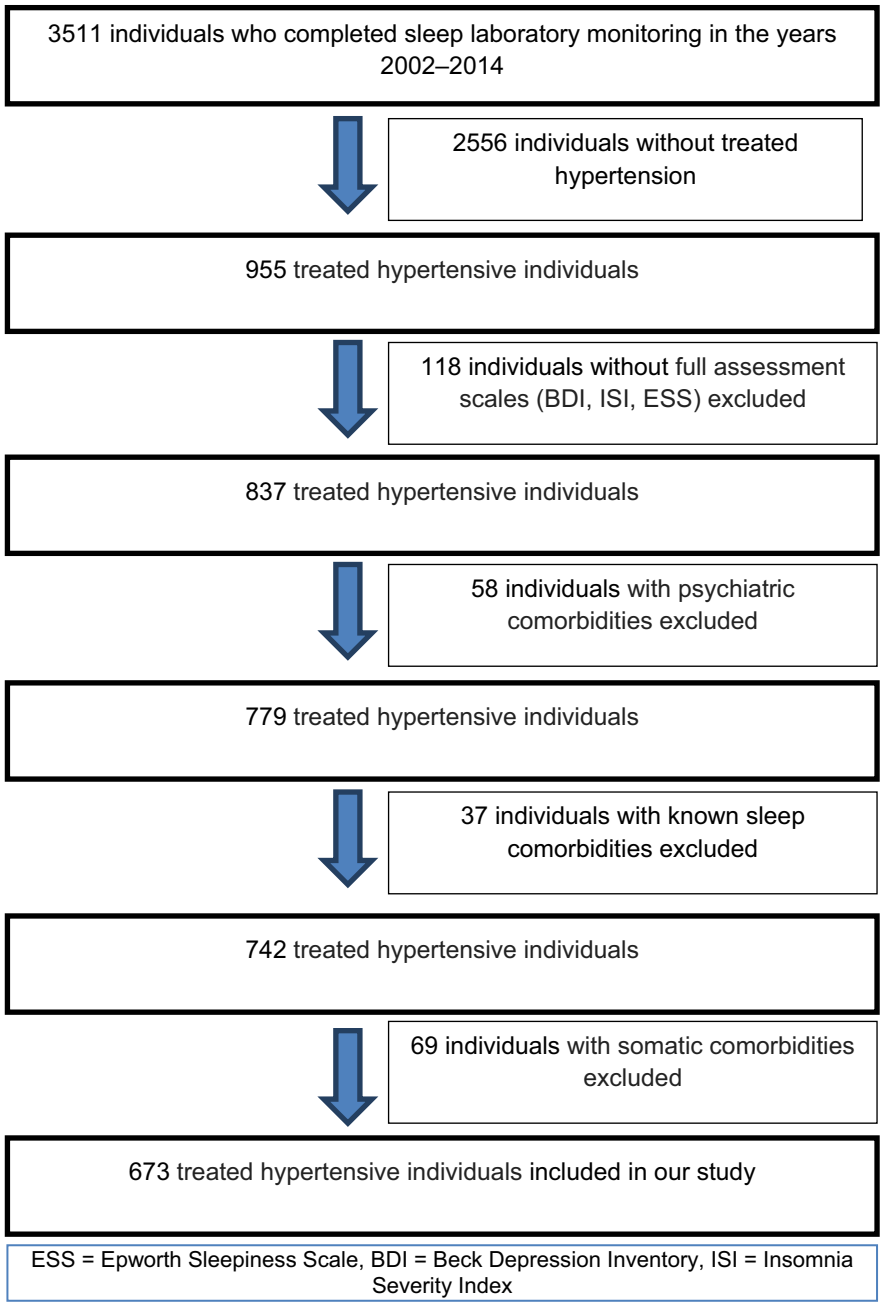

Fig. 1. Diagram of selection of treated hypertensive individuals included in our study.

pressure ≥90 mmHg, blood pressures were again measured twice after a systematic rest period of an additional 5 min. The first measurement was excluded whereas the second and third measurements were averaged in order to minimize the impact of white coat effect. In addition, the characteristics of antihypertensive medication (type, number and dosage of antihypertensive agents) were systematically checked during the admission interview to the sleep laboratory. Thus, in all treated hypertensive individuals included in our study, these steps allowed confirming the hypertension status (resistant or non-resistant) highlighted during ambulatory cardiological assessment.

Patients also benefitted on the day of admission from an appointment with a unit psychiatrist who potentially assigned psychiatric diagnoses per the Diagnostic and Statistical Manual of Mental Disorders fourth edition – Text Revision criteria [21].

On admission, patients completed a series of self-questionnaires to assess the severity of their subjective complaints of depression, poor sleep, and excessive daytime sleepiness as follows: (1) The presence of depressive symptoms was investigated using the Beck Depression Inventory (BDI, reduced to 13 items). This scale consists of 13 items that can be scored from 1 to 3. The final score can vary from 0 to 39. A final score of 0–4 indicates an absence of depression, 5–7 a slight depression, 8–15 a moderate depression, and >16 severe depression [22]. (2) Daytime sleepiness was investigated using the Epworth Sleepiness Scale (ESS). This scale consists of eight questions that can be scored from 0 to 3 and assesses

sleepiness during different daytime situations. The final score varies from 0 to 24. A final score greater than 10 indicates excessive daytime sleepiness [23]. (3) The presence of insomnia symptoms was investigated using the Insomnia Severity Index (ISI). This index consists of seven questions that can be scored from 0 to 4. The final score can vary from 0 to 28. A score of 0–7 indicates a lack of insomnia, 8–14 subclinical insomnia, 15–21 moderate insomnia, and 22–28 severe insomnia [24].

To avoid missing values, individuals who did not respond fully to these questionnaires were not included in our study.

2.2.3. Sleep evaluation and study

A unit psychiatrist conducted a sleep-specific medical record systematic review on the day of admission to complete an assessment of complaints related to sleep including sleeping habits, severity of self-reported insomnia complaints (difficulty falling asleep, repeated nighttime awakenings, early morning awakening, and non-restorative sleep), insomnia duration, symptoms of sleep apnoea (snoring and self-reported apnoeas), symptoms of RLS, and nocturnal movements (eg, PLMS).

Following this systematic interview, the diagnosis of RLS was only made on the basis of the following strict diagnostic criteria [10,25]. (1) An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs). (2) The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting. (3) The urge to move or unpleasant sensations are partially or totally relieved by movement, (eg, walking or stretching), at least as long as the activity continues. (4) The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present). (5) The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioural condition (eg, myalgia, venous stasis, leg oedema, arthritis, leg cramps, positional discomfort, habitual foot tapping).

In addition, the frequency of the RLS was defined on the basis of the following criteria [26]. (1) Occasional RLS: symptoms when not treated would occur on average < 2 times/week for the past year, with at least five lifetime events; (2) Frequent RLS: symptoms when not treated would occur on average at least twice weekly for the past year.

Participants stayed in a sleep laboratory for two nights, including a first night of habituation and a night of polysomnography (PSG) from which the data were collected for analysis. The patients went to bed between 22:00 and 24:00 h and got up between 06:00 and 08:00 h, following their usual schedule. During bedtime hours, the subjects were recumbent and the lights were turned off. Daytime naps were not permitted.

The PSG recordings from our unit met the guidelines of the American Academy of Sleep Medicine (AASM) [27]. The applied PSG montage was as follows: two electro-oculogram channels, three electroencephalogram channels (Fz-Ax, Cz-Ax, and Oz-Ax, where Ax was a contralateral mastoid reference), one submental electromyogram channel, electrocardiogram, thermistors to detect the oronasal airflow, finger pulse-oximetry, a microphone to record breathing sounds and snoring, piezoelectric sensors, and leg movement electrodes. In addition, the applied polysomnography montage also included strain gauges to measure thoracic and abdominal breathing [28,29]. PSG recordings were visually scored by specialized technicians using AASM criteria [30] (inter-judge agreement score of 85%).

Apnoeas were scored if the decrease in airflow was ≥90% for at least 10 s and hypopnoeas were scored if the decrease in airflow was ≥30% for at least 10 s with a decrease in oxygen saturation of 3% or followed by a micro-arousal [31]. Apnoea–hypopnoea index (AHI) corresponds to the total number of apnoeas and hypopnoeas divided by period of sleep in hours. OSAS was considered absent when AHI was <5/h, mild when AHI was ≥5 and < 15/h, and moderate to severe when AHI was ≥15/h [32].

PLMS are characterized by repetitive extensions of the big toe and dorsiflexions of the ankle occasionally involving the knee and hip and were scored on the basis of the following strict criteria [33]. (1) Duration between 0.5 and 10 s. (2) Interval between 5 and 90 s from leg movement onset. (3) Movements had to be part of a series of ≥4 consecutive movements meeting these criteria.

PLMS index corresponds to the total number of PLMS divided by period of sleep in hours. Moderate to severe PLMS was present when PLMS index was ≥26/h [34].

2.3. Statistical analyses

Statistical analyses were performed using Stata 14. The normal distribution of the data was verified using histograms, boxplots, and quantile–quantile plots, and the equality of variances was checked using the Levene's test.

In order to allow our analyses, we subdivided our sample of treated hypertensive individuals into a control group without RHT and a patient group with RHT. Only individuals with a diagnosis of RHT according to the diagnostic criteria of the American Heart Association at admission were included in the RHT group.

Categorical data were described with percentages and numbers, and continuous data were described with means and standard deviation or median and P25–P75. Normally distributed variables were analysed with a *t*-test. A Wilcoxon test or χ^2 test were used on asymmetric distributed or dichotomous variables.

Univariate binary logistic regression models were used to study the risk of RHT associated with RLS, PLMS, and potential confounding factors. After a review of the literature on risk factors for RHT [18,35–43], potential confounding factors included for this analysis were body mass index (BMI) (categories: <25 kg/m^2, ≥25 and < 30 kg/m^2, ≥30 kg/m^2), age (categories: <50 years, ≥50 and < 60 years, ≥60 years), BDI score (categories: <8, ≥8), ISI score (categories: <15, ≥15), ESS score (categories: ≤10, >10), benzodiazepine receptor agonists (categories: no, short half-life, intermediate half-life, long half-life), sleep duration (categories: <4 h, ≥4 h and <7 h, ≥7 h), AHI (categories: <5/h, ≥5/h and <15/h, ≥15/h), and as binary variables gender, snoring, antidepressants therapy, alcohol, smoking, caffeine, type 2 diabetes, and hypertriglyceridemia.

In multivariate binary logistic regression models, the risk of RHT associated with RLS and PLMS was adjusted only for confounding factors significantly associated with RHT. These confounding factors were entered in a hierarchical way, adjusting for BDI score, ISI score, ESS score and antidepressants therapy in Model 1, and adding gender, age and BMI in Model 2. Model 3 further included hypertriglyceridemia and type 2 diabetes. Finally, Model 4 added sleep duration, snoring and OSAS severity.

The adequacy of Model 4 was verified by the Hosmer and Lemeshow test and the specificity of the model by Link Test. The numbers of subjects by risk factors, outliers, and collinearity between risk factors that may cause problems, have also been verified.

A *p*-value of less than 0.05 was considered significant.

Table 1
Polysomnographic data ($N = 673$).

	Whole Sample ($N = 673$)	Subjects without resistant hypertension ($N = 401$)	Subjects with resistant hypertension ($N = 272$)	p
SL (min)	22.0 (13.0–38.5)	24.5 (13.7–44.3)	20.5 (12.3–33.3)	<0.001[a]
SE (%)	77.1 (66.7–84.0)	77.7 (66.7–84.7)	76.2 (66.1–83.3)	0.329[a]
SPT (min)	444.5 ± 62.6	446.0 ± 65.1	442.2 ± 58.9	0.437[b]
TST (min)	365.6 ± 75.3	370.9 ± 74.5	357.6 ± 76.0	0.024[b]
% stage 1	8.0 (5.2–11.2)	8.2 (5.4–11.3)	7.7 (4.7–11.1)	0.125[a]
% stage 2	54.9 ± 10.8	54.9 ± 10.8	54.7 ± 11.4	0.790[b]
% SWS	1.2 (0.0–4.8)	1.5 (0.0–5.3)	0.8 (0.0–3.9)	0.073[a]
% REM	15.1 ± 6.2	15.5 ± 6.0	14.5 ± 6.4	0.034[b]
REM latency (min)	85.0 (59.3–140.8)	84.5 (59.5–138.7)	85.7 (58.7–148.7)	0.530[a]
% WASO	15.1 (9.3–23.6)	14.1 (8.9–21.4)	16.5 (10.0–25.0)	0.019[a]
Number of awakenings	35 (24–52)	34 (24–47)	37.5 (24–59.5)	0.035[a]
Micro-arousal index	10 (6–17)	10 (6–16)	10 (6–19)	0.351[a]
AHI	2 (2–21)	5 (2–16)	7 (2–24)	0.017[a]
ODI	3 (1–9)	2 (1–7)	4 (1–11.5)	<0.001[a]
Total time under 90% of SaO_2 (min)	12.0 (1.0–68.0)	6.5 (0.3–41.7)	18.0 (2.5–106.7)	<0.001[a]
PLMS index	19.7 (8.9–38.4)	18.6 (7.8–35.3)	20.9 (9.9–43.2)	0.042[a]

AHI, apnea–hypopnea index; ODI, oxygen desaturation index; PLMS, periodic limb movements during sleep; REM, rapid eye movement sleep; SaO_2, oxygen saturation; SE, sleep efficiency; SL, sleep latency; SPT, sleep period time; SWS, slow-wave sleep; TST, total sleep time; WASO, wake after sleep onset.
[a] Wilcoxon test.
[b] *t*-test.

3. Results

3.1. Polysomnographic data (Table 1)

Compared to those without RHT, individuals with RHT have a decrease in sleep latency [24.5 (13.7–44.3) vs 20.5 (12.3–33.3), $p < 0.001$], total sleep time (370.9 ± 74.5 vs 357.6 ± 76.0, $p = 0.024$) and rapid eye movement (REM) sleep (15.5 ± 6.0 vs 14.5 ± 6.4, $p = 0.034$) whereas they show an increase in wake after sleep onset [14.1 (8.9–21.4) vs 16.5 (10.0–25.0), $p = 0.019$], number of awakenings [34 (24–47) vs 37.5 (24–59.5), $p = 0.035$], AHI [5 (2–16) vs 7 (2–24), $p = 0.017$], oxygen desaturation index [2 (1–7) vs 4 (1–11.5), $p < 0.001$], total time under 90% of SaO_2 [6.5 (0.3–41.7) vs 18.0 (2.5–106.7), $p < 0.001$] and PLMS index [18.6 (7.8–35.3) vs 20.9 (9.9–43.2), $p = 0.042$]. There are no significant differences for stage 1, stage 2, slow-wave sleep, sleep efficiency, sleep period time, REM latency and micro-arousal index.

3.2. Demographic data (Table 2)

Male gender (63.8% vs 72.8%, $p = 0.015$), type 2 diabetes (39.9% vs 52.2%, $p = 0.002$), hypertriglyceridemia (39.9% vs 48.5%, $p = 0.027$), sleep duration <4 h (5.5% vs 8.8%, $p = 0.040$), snoring (77.1% vs 83.5%, $p = 0.043$), AHI ≥15/h (27.7% vs 36.8%, $p = 0.045$) and frequent RLS combined with PLMS index ≥26/h (10.5% vs 17.7%, $p = 0.046$) are more frequent in individuals with RHT. These individuals also present a BMI (29.9 ± 5.4 vs 32.1 ± 6.1, $p < 0.001$) greater and a BDI [4 (2–8) vs 3 (2–7), $p = 0.018$]/ISI score [15 (10–18) vs 13 (9–17), $p = 0.015$] lower than the individuals without RHT. In addition, compared to those without RHT, antidepressant therapy (31.7% vs 22.1%, $p = 0.006$) is less frequent in individuals with RHT. There was no significant difference in benzodiazepine receptor agonist, caffeine consumption, smoking, alcohol consumption, age and ESS score.

3.3. Univariate analysis (Table 3)

Male gender [odds ratio (OR) 1.52 (95% confidence interval (CI) 1.08–2.12], $p = 0.015$), BMI ≥30 kg/m^2 [OR 2.25 (95% CI 1.36–3.72), $p < 0.001$], age ≥60 years [OR 1.47 (95% CI 1.01–2.16), $P = 0.037$], type 2 diabetes [OR 1.65 (95% CI 1.21–2.24), $p = 0.002$], hypertriglyceridemia [OR 1.42 (95% CI 1.04–1.94), $p = 0.027$], BDI score <8 [OR 1.46 (95% CI 1.02–2.08), $p = 0.038$], ISI score <15 [OR 1.75 (95% CI 1.28–2.40), $p < 0.001$], ESS score ≤10 [OR 1.49 (95% CI 1.08–2.05), $p = 0.015$], absence of antidepressant therapy [OR 1.64 (95% CI 1.15–2.34), $p = 0.007$], sleep duration <4 h [OR 2.18 (95% CI 1.12–4.23), $p = 0.042$], snoring [OR 1.50 (95% CI 1.01–2.23), $p = 0.044$], AHI ≥15/h [OR 1.51 (95% CI 1.06–2.17), $p = 0.045$] and frequent RLS combined with PLMS index ≥26/h [OR 1.99 (95% CI 1.25–3.17), $p = 0.049$] were associated with an increased risk of RHT in treated hypertensive individuals.

3.4. Multivariate analysis (Table 4)

After adjusting for BDI score, ISI score, ESS score and antidepressant therapy (Model 1), frequent RLS combined with PLMS index ≥26/h [OR 2.11 (95% CI 1.31–3.38), $p = 0.035$] was still significantly associated with an increased risk of RHT. Adjusting additionally for gender, age and BMI (Model 2) slightly increased the risk of RHT associated with frequent RLS combined with PLMS index ≥26/hour [OR 2.14 (95% CI 1.32–3.47), $p = 0.038$]. After adjustment in addition for hypertriglyceridemia and type 2 diabetes (Model 3), this higher risk of RHT remained significant for frequent RLS combined with PLMS index ≥26/h [OR 2.17 (95% CI 1.33–3.53), $p = 0.036$]. Finally, adjusting additionally for sleep duration, snoring and OSA severity (Model 4) does not alter the significant risk of RHT associated with frequent RLS combined with PLMS index ≥26/h [OR 2.20 (95% CI 1.35–3.61), $p = 0.021$].

Despite the adjustment for major confounding factors associated with RHT in the four models studied, multivariate logistic regression analysis revealed that moderate to severe PLMS [OR 1.29 (95% CI 0.69–2.42], occasional or frequent RLS combined with PLMS index <26/h [OR 0.76 (95% CI 0.36–1.61)] and occasional RLS combined with PLMS index ≥26/h [OR 1.04 (95% CI 0.64–1.69)] remains not significantly associated with higher risk of RHT.

4. Discussion

In treated hypertensive individuals, we demonstrated a prevalence of RLS of 35.1%, which is consistent with available literature (30.0%) [44] and highlights the importance of this problem to the healthcare professionals treating this particular subpopulation.

Table 2
Sample description ($N = 673$).

Variables		Categories	%	Subjects without resistant hypertension	Subjects with resistant hypertension	p χ^2
Gender		Female ($N = 219$)	32.5%	36.2%	27.2%	0.015
		Male ($N = 454$)	67.5%	63.8%	72.8%	
Benzodiazepine receptor agonists		No ($N = 522$)	77.6%	76.6%	79.0%	0.550
		Short ($N = 83$)	12.3%	12.5%	12.1%	
		Intermediate ($N = 45$)	6.7%	6.7%	6.6%	
		Long ($N = 23$)	3.4%	4.2%	2.2%	
Antidepressant therapy		No ($N = 486$)	72.2%	68.3%	77.9%	0.006
		Yes ($N = 187$)	27.8%	31.7%	22.1%	
Caffeine		No (n = 145)	21.5%	21.0%	22.4%	0.647
		Yes (n = 528)	78.5%	79.0%	77.6%	
Smoking		No ($N = 557$)	82.8%	83.0%	82.4%	0.816
		Yes ($N = 116$)	17.2%	17.0%	17.6%	
Alcohol		No ($N = 454$)	67.5%	67.6%	67.3%	0.935
		Yes ($N = 219$)	32.5%	32.4%	32.7%	
Type 2 diabetes		No ($N = 371$)	55.1%	60.1%	47.8%	0.002
		Yes ($N = 302$)	44.9%	39.9%	52.2%	
Hypertriglyceridemia		No (n = 381)	56.6%	60.1%	51.5%	0.027
		Yes ($N = 292$)	43.4%	39.9%	48.5%	
Sleep duration (h)		≥7 (n = 172)	24.5%	27.4%	20.2%	0.040
		≥4 & <7 ($N = 483$)	68.6%	67.1%	71.0%	
		<4 ($N = 48$)	6.8%	5.5%	8.8%	
Snoring		No ($N = 137$)	20.4%	22.9%	16.5%	0.043
		Yes ($N = 536$)	79.6%	77.1%	83.5%	
AHI		<5/h ($N = 292$)	43.4%	45.6%	40.1%	0.045
		≥5/h & <15/h ($N = 170$)	25.3%	26.7%	23.1%	
		≥15/h ($N = 211$)	31.3%	27.7%	36.8%	
RLS/PLMS		No ($N = 384$)	57.6%	60.9%	51.5%	0.046
		Moderate to severe PLMS ($N = 53$)	7.9%	8.0%	7.7%	
		RLS + PLMS index <26/h ($N = 39$)	5.8%	6.0%	5.5%	
		Occasional RLS + PLMS index ≥26/h ($N = 107$)	15.9%	14.7%	17.6%	
		Frequent RLS + PLMS index ≥26/h ($N = 90$)	13.4%	10.5%	17.7%	
Resistant hypertension		No ($N = 401$)	59.6%			
		Yes ($N = 272$)	40.4%			
	Mean ± SD					t-test
BMI (kg/m^2)	30.8 ± 5.8	<25 ($N = 91$)	13.5%	29.9 ± 5.4	32.1 ± 6.1	<0.001
		≥25 & <30 ($N = 240$)	35.7%	16.2%	9.6%	0.001[a]
		≥30 ($N = 342$)	50.8%	38.9%	30.9%	
				44.9%	59.5%	
Age (years)	54.7 ± 10.1	<50 ($N = 213$)	31.7%	54.1 ± 9.6	55.5 ± 10.8	0.094
		≥50 & <60 ($N = 245$)	36.4%	32.9%	29.8%	0.037[a]
		≥60 ($N = 215$)	31.9%	38.9%	32.7%	
				28.2%	37.5%	
Systolic blood pressure (mmHg)	129.9 ± 15.8			119.8 ± 8.5	144.9 ± 11.6	<0.001
Diastolic blood pressure (mmHg)	78.0 ± 11.3			72.1 ± 8.0	86.6 ± 9.8	<0.001
	Median (P25–P75)					Wilcoxon test
BDI	4 (2–8)	<8 ($N = 493$)	72.3%	4 (2–8)	3 (2–7)	0.018
		≥8 ($N = 180$)	26.7%	70.3%	77.6%	0.037[a]
				29.7%	22.4%	
ISI	14 (10–18)	<15 ($N = 363$)	53.9%	15 (10–18)	13 (9–17)	0.015
		≥15 ($N = 310$)	46.1%	48.4%	62.1%	<0.001[a]
				51.6%	37.9%	
ESS	9 (6–13)	≤10 ($N = 413$)	61.4%	9 (6–13)	9 (6–13)	0.376
		>10 ($N = 260$)	38.6%	57.6%	66.9%	0.015[a]
				42.4%	33.1%	

AHI, apnea–hypopnea index; BDI, Beck depression inventory; BMI, body mass index; ESS; Epworth sleepiness scale; ISI, insomnia severity index; PLMS, periodic limb movements during sleep; RLS, restless legs syndrome; SD, standard deviation.
[a] χ^2.

Furthermore, this prevalence is higher than that demonstrated in the general population (7.3%) [9], which seems to confirm that RLS is more frequent in treated hypertensive individuals. Conversely, we have shown that PLMS alone are present in 7.9% of treated hypertensive patients which seems to be inferior to the prevalence of 18.0% described in the literature [45]. However, this difference in prevalence compared with the literature may be explained by the fact that in our study, we used a PLMS index ≥26/h as cut-off in order to select only moderate to severe PLMS. At the epidemiological level, it has been demonstrated that RLS (especially combined with PLMS) is associated with a higher risk of hypertension [46]. In addition, this higher risk of hypertension increases with the frequency of occurrence of RLS [47]. Moreover, in the literature, there are also arguments in favour of a potential involvement of RLS (especially combined with PLMS) in the occurrence of resistance to antihypertensive agents [7]. However,

Table 3
Univariate analysis ($N = 673$).

Variables	Subjects without resistant hypertension	Subjects with resistant hypertension	OR (CI 95%)	*p*
Sex				0.015
Female	66.2%	33.8%	1	
Male	56.4%	43.6%	1.52 (1.08–2.12)	
Benzodiazepine receptor agonists				0.564
No	58.8%	41.2%	1	
Short	60.2%	39.8%	0.94 (0.59–1.51)	
Intermediate	60.0%	40.0%	0.95 (0.51–1.77)	
Long	73.9%	26.1%	0.50 (0.20–1.30)	
Antidepressant therapy				0.007
No	56.4%	43.6%	1.64 (1.15–2.34)	
Yes	67.9%	32.1%	1	
Caffeine				0.647
No	57.9%	42.1%	1	
Yes	60.0%	40.0%	0.92 (0.63–1.33)	
Smoking				0.816
No	59.8%	40.2%	1	
Yes	58.6%	41.4%	1.05 (0.70–1.58)	
Alcohol				0.935
No	59.7%	40.3%	1	
Yes	59.4%	40.6%	1.01 (0.73–1.41)	
Type 2 diabetes				0.002
No	65.0%	35.0%	1	
Yes	53.0%	47.0%	1.65 (1.21–2.24)	
Hypertriglyceridemia				0.027
No	63.3%	36.7%	1	
Yes	54.8%	45.2%	1.42 (1.04–1.94)	
Sleep duration (h)				0.042
≥7	66.7%	33.3%	1	
≥4 & <7	58.2%	41.8%	1.43 (0.99–2.08)	
<4	47.8%	52.2%	2.18 (1.12–4.23)	
Snoring				0.044
No	67.2%	32.8%	1	
Yes	57.7%	42.3%	1.50 (1.01–2.23)	
AHI				0.045
<5/h	62.7%	37.3%	1	
≥5/h & <15/h	62.9%	37.1%	0.99 (0.67–1.46)	
≥15/h	52.6%	47.4%	1.51 (1.06–2.17)	
RLS/PLMS				0.049
No	63.5%	36.5%	1	
Moderate to severe PLMS	60.4%	39.6%	1.14 (0.64–2.06)	
RLS + PLMS index <26/h	61.5%	38.5%	1.09 (0.55–2.15)	
Occasional RLS + PLMS index ≥26/h	55.1%	44.9%	1.42 (0.92–2.19)	
Frequent RLS + PLMS index ≥26/h	46.7%	53.3%	1.99 (1.25–3.17)	
BMI (kg/m^2)				<0.001
<25	71.4%	28.6%	1	
≥25 & <30	65.0%	35.0%	1.35 (0.80–2.28)	
≥30	52.6%	47.4%	2.25 (1.36–3.72)	
Age (years)				0.037
<50	62.0%	38.0%	1	
≥50 & <60	63.7%	36.3%	0.93 (0.64–1.36)	
≥60	52.6%	47.4%	1.47 (1.01–2.16)	
BDI				0.038
<8	57.2%	42.8%	1.46 (1.02–2.08)	
≥8	66.1%	33.9%	1	
ISI				<0.001
<15	53.4%	46.6%	1.75 (1.28–2.40)	
≥15	66.8%	33.2%	1	
ESS				0.015
≤10	55.9%	44.1%	1.49 (1.08–2.05)	
>10	65.4%	34.6%	1	

AHI, apnea–hypopnea index; BDI, Beck depression inventory; BMI, body mass index; CI, confidence interval; ESS, Epworth sleepiness scale; ISI, insomnia severity index; OR, odds ratio; PLMS, periodic limb movements during sleep; RLS, restless legs syndrome.

in our study, we highlighted that in treated hypertensive individuals, frequent RLS (≥2 episodes/week) combined with PLMS index ≥26/h is associated with a higher risk of RHT, unlike moderate to severe PLMS, occasional or frequent RLS combined with PLMS index <26/h and occasional RLS combined with PLMS index ≥26/h. Thus, in treated hypertensive individuals with RHT, it seems important to systematically look for frequent RLS combined with PLMS index ≥26/h in order to allow a better management of this pathology and avoid the negative consequences associated with the occurrence of resistance to antihypertensive agents.

In treated hypertensive individuals, several elements may provide a better understanding of the role played by frequent RLS combined with PLMS index ≥26/h in the pathophysiology of

Table 4
Multivariate analysis ($N = 673$).

Variables	Model 1 OR adjusted (CI 95%)	p	Model 2 OR adjusted (CI 95%)	p	Model 3 OR adjusted (CI 95%)	p	Model 4 OR adjusted (CI 95%)	p
RLS/PLMS		0.035		0.038		0.036		0.021
No	1		1		1		1	
Moderate to severe PLMS	1.15 (0.63–2.09)		1.21 (0.66–2.34)		1.18 (0.63–2.18)		1.29 (0.69–2.42)	
RLS + PLMS index <26/h	1.11 (0.56–2.21)		0.87 (0.42–1.79)		0.88 (0.43–1.82)		0.76 (0.36–1.61)	
Occasional RLS + PLMS index ≥26/h	1.40 (0.90–2.17)		1.20 (0.75–1.90)		1.12 (0.70–1.79)		1.04 (0.64–1.69)	
Frequent RLS + PLMS index ≥26/h	2.11 (1.31–3.38)		2.14 (1.32–3.47)		2.17 (1.33–3.53)		2.20 (1.35–3.61)	
BDI		0.766		0.649		0.663		0.609
<8	1.06 (0.71–1.58)		1.10 (0.73–1.65)		1.09 (0.73–1.65)		1.11 (0.74–1.68)	
≥8	1		1		1		1	
ISI		0.009		0.019		0.018		0.022
<15	1.57 (1.12–2.21)		1.52 (1.07–2.15)		1.52 (1.07–2.16)		1.51 (1.06–2.16)	
≥15	1		1		1		1	
ESS		0.057		0.033		0.032		0.037
≤10	1.38 (0.99–1.93)		1.46 (1.03–2.06)		1.47 (1.03–2.08)		1.46 (1.02–2.08)	
>10	1		1		1		1	
Antidepressant therapy		0.067		0.224		0.122		0.110
No	1.43 (0.98–2.09)		1.28 (0.86–1.91)		1.38 (0.92–2.08)		1.40 (0.93–2.12)	
Yes	1		1		1		1	
Gender				0.162		0.507		0.612
Female			1		1		1	
Male			1.30 (0.90–1.87)		1.14 (0.78–1.67)		1.11 (0.75–1.65)	
Age (years)				0.092		0.089		0.104
<50			1		1		1	
≥50 & <60			0.84 (0.57–1.26)		0.80 (0.53–1.21)		0.80 (0.53–1.22)	
≥60			1.32 (0.86–2.02)		1.27 (0.82–1.96)		1.25 (0.79–1.97)	
BMI (kg/m^2)				<0.001		0.002		0.004
<25			1		1		1	
≥25 & <30			1.14 (0.66–1.99)		1.04 (0.60–1.83)		1.05 (0.60–1.85)	
≥30			2.24 (1.33–3.78)		1.92 (1.12–3.30)		1.89 (1.09–3.27)	
Type 2 diabetes						0.105		0.123
No					1		1	
Yes					1.33 (0.94–1.89)		1.32 (0.93–1.87)	
Hypertriglyceridemia						0.108		0.087
No					1		1	
Yes					1.33 (0.94–1.88)		1.36 (0.96–1.93)	
Sleep duration (hours)								0.185
≥7							1	
≥4 & <7							1.25 (0.83–1.88)	
<4							1.99 (0.95–4.19)	
Snoring								0.053
No							1	
Yes							1.52 (0.99–2.32)	
AHI								0.522
<5/h							1	
≥5/h & <15/h							0.79 (0.51–1.22)	
≥15/h							0.97 (0.63–1.48)	

Model 1: model adjusted for BDI, ISI, ESS and antidepressant therapy. Model 2: model adjusted for BDI, ISI, ESS, antidepressant therapy, gender, age and BMI. Model 3: model adjusted for BDI, ISI, ESS, antidepressant therapy, gender, age, BMI, type 2 diabetes and hypertriglyceridaemia. Model 4: model adjusted for BDI, ISI, ESS, antidepressant therapy, gender, age, BMI, type 2 diabetes, hypertriglyceridaemia, sleep duration, snoring and AHI. AHI, apnea–hypopnea index; BDI, beck depression inventory; BMI, body mass index; CI, confidence interval; ESS, Epworth sleepiness scale; ISI, insomnia severity index; OR, odds ratio; PLMS, periodic limb movements during sleep; RLS, restless legs syndrome.

resistance to antihypertensive agents. Indeed, in RLS, there is a sleep-onset and/or sleep-maintenance insomnia [48] inducing sleep deprivation [49–52]; which in turn may promote the development of hypertension through neural autonomic control changes, endothelial dysfunction, metabolic deregulation, increased oxidative stress, inflammation, altered coagulatory responses and accelerated atherosclerosis [53]. Alternately, this involvement of RLS in the pathogenesis of cardiovascular complications seems to be mediated by its frequency of occurrence [54]. Furthermore, unlike PLMS without RLS whose clinical significance is controversial [55], it has been shown in the literature that PLMS combined with RLS induces excessive sleep fragmentation characterized by an excess of micro-arousals which may promote the occurrence of hypertension via sympathetic hyperactivity [56]. However, even if RLS alone or combined with PLMS seems to promote the appearance of pathophysiologic mechanisms favouring the occurrence of hypertension, only frequent RLS combined with PLMS index ≥26/h seem to be associated with development of resistance to antihypertensive agents; probably through the combined presence of recurrent sleep deprivation and excessive sleep fragmentation potentiating these various deleterious mechanisms for blood pressure regulation [57].

Among the treatments used in the management of RLS alone or combined with PLMS, dopaminergic agonists are generally recommended in the first line [58] given the involvement of dopaminergic neurotransmission dysfunction in the pathophysiology of this entity [59]. Yet, other drugs have also been shown to be effective in treatment of RLS alone or combined with PLMS: calcium channel alpha-2-delta ligands (modulating the activity of calcium channels which allows a reduction of neurotransmitter release and an attenuation of postsynaptic excitability), opioids (acting on the endogenous opioid system which allows modulation of sensory and

motor activity) and benzodiazepine receptor agonists (potentiating the inhibitory effect of the GABA system by modulating the activation of chloride channels) [60,61]. Moreover, in individuals with RLS alone or combined with PLMS, these different treatments may allow a reduction in recurrent sleep deprivation by attenuating the clinical symptoms of RLS as well as an improvement in excessive sleep fragmentation by decreasing the occurrence of PLMS [62]. However, this improvement in sleep related to these different treatments could allow a better blood pressure control in treated hypertensive individuals with frequent RLS combined with PLMS due to an attenuation of deleterious mechanisms for blood pressure regulation induced by the combined presence of recurrent sleep deprivation and excessive sleep fragmentation in these individuals [57]. In this context, in treated hypertensive individuals, it therefore seems essential to treat the frequent RLS combined with PLMS index $\geq$26/h in order to prevent the occurrence of resistance to antihypertensive agents and its negative consequences on cardiovascular outcome in this particular subpopulation.

Conversely, it has been shown that some antihypertensive agents may have an impact on the severity of the clinical symptoms of RLS. Indeed, some alpha-2 agonists and beta-blockers may relieve the clinical symptoms of RLS [63,64] whereas some calcium channel blockers are associated with an increase in complaints related to RLS [65]. In treated hypertensive individuals, in the case of the presence of frequent RLS combined with PLMS index $\geq$26/h, it therefore seems necessary to adequately choose the antihypertensive agents used in order to avoid an exacerbation of clinical symptoms of RLS that could induce suboptimal blood pressure control via an increase in the deleterious mechanisms for blood pressure regulation related to RLS [66].

Among sleep disorders, it has been shown that OSAS played a major role in the development of resistance to antihypertensive agents [67], which justifies systematic screening and treatment of this syndrome given its high prevalence in individuals with hypertension [68,69]. Alternately, the co-occurrence of OSAS and RLS combined with PLMS is common [70] and could lead to the development of a synergy between these two pathologies at the level of the pathophysiological mechanisms involved in the development of resistance to antihypertensive agents (oxidative stress, metabolic alterations, activation of the sympathetic nervous system, hyperactivity of the hypothalamic–pituitary–adrenal axis, endothelial dysfunction and decreased arterial elasticity) [15]. Thus, in individuals with RHT, in case of co-occurrence of OSAS and RLS combined with PLMS, it seems essential to perform a combined management of these two pathologies to avoid the maintenance of cardiometabolic alterations favouring the persistence of RHT and its negative consequences on the cardiovascular outcome.

In the future, prospective studies should be conducted with the subpopulation of treated hypertensive individuals to validate this risk of RHT associated with frequent RLS combined with PLMS index $\geq$26/h highlighted in our study.

4.1. Limitations

The results obtained in our study come from retrospective data that, even if they have been encoded in a systematic manner, cannot be verified directly with the subject in most cases, which means that our results need to be replicated in prospective studies. We did not score PLMS according to the revised criteria of World Association of Sleep Medicine [71] but according to the current criteria of American Academy of Sleep Medicine which may possibly limit the interpretation of our results. Moreover, we focused only on RHT, which means that our results cannot be generalized to other cardiovascular pathology, such as myocardial infarction and stroke. In addition, our database contains only treated hypertensive individuals who have agreed to perform a sleep laboratory test, which may also limit the generalization of results.

5. Conclusion

In treated hypertensive individuals, frequent RLS combined with PLMS index $\geq$26/h is associated with higher risk of RHT which suggests that this pathology may be a secondary cause of RHT (such as OSAS and insomnia with short sleep duration) justifying the establishment of effective treatments in this particular subpopulation.

Authors' contributions

MH: principal investigator of the study with active participation in the encoding of data, statistical analysis, interpretation of results and writing of the article. JL: Active participation in the extraction and calculation of data from polysomnography for the realization of the database. GL: Support in drafting the manuscript and supervision of research work. PH: Support in drafting the manuscript and supervision of research work. All authors read and approved the final manuscript.

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Conflict of interest

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