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SLEEP AND 3D (CANCER, CARDIOVASCULAR, METABOLIC DISEASES) (D GOZAL, SECTION EDITOR)

Periodic Leg Movements During Sleep and Cardiovascular and/or Cerebrovascular Morbidity

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Abstract

Purpose of Review To evaluate if periodic leg movements during sleep (PLMS) may be associated with increased cardiovascular or cerebrovascular morbidity

Recent Findings PLMS are accompanied by rises in hear rate and blood pressure and by important transient EEG changes indicating sleep fragmentation; in addition, PLMS have been related to elevated levels of inflammatory markers that are associated with increased cardiovascular and cerebrovascular risk and several reports have suggested that PLMS may play an important role in increasing cardiovascular risk, resulting in hypertension, cardiac ischemic disease, and cerebrovascular disease.

Summary Although a body of evidence suggests that PLMS are involved in increasing cardiovascular risk, additional studies are needed to establish the contributory role of PLMS to cardiovascular homeostasis and morbidity in patients with and without RLS, and to evaluate the role of the specific PLMS treatment to reduce the risk.

Keywords Periodic leg movements during sleep · Sleep · Restless legs syndrome · Cardiovascular risk · Cerebrovascular risk · Stroke · Heart rate · Blood pressure

Introduction

Periodic limb movements during sleep (PLMS) are sleep-related involuntary motor phenomena characterized by a sudden triple leg flexion (in the following order: ankle, knee, and hip) often bilateral, and organized into sequences of ≥4 limb movements (LM) separated by inter-movement (onset-to-onset) intervals (IMI) of 10–90 s [1•, 2]. PLMS are the most important objective manifestation and polysomnographic feature of the restless legs syndrome (RLS), and represent a supportive diagnostic criterion for RLS [3•]. In fact, about 80–90% of RLS patients have PLMS in polysomnographic evaluation (PSG), if one or more nights of recordings are available [4].

PLMS are often associated with a generalized EEG oscillatory pattern during sleep, the cyclic alternating pattern (CAP), and with autonomic sympathetic activation. Thus far, there are no clear cause/effect relationships between PLMS and CAP. The most frequently observed pattern is represented by increased slow EEG activity, soon followed by a slight, albeit significant increase in heart rate (HR), and then by the occurrence of a PLMS event, which in turn heralds or coincides with an increase in fast EEG activities and a much more consistent and robust increase in heart rate [5•, 6]. This pattern is the most frequent, but it is not stereotyped, and, as such, may present several variants, indicating that a complex mechanism underlies the association between PLMS, arousal, and autonomic activation, namely increased HR and blood pressure (BP) [7]. PLMS may occur across all sleep stages, but are more frequent in stages N1 and N2 of NREM sleep; their frequency increases with age and with several comorbidities, such as RLS [8].

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In the last several years, the interest for PLMS has increased and has particularly been focused on their association with cardiovascular function (HR and BP), with several papers indicating PLMS as a potential cardiovascular and cerebrovascular risk factor having been published [9]. The relationship between systemic hypertension and increased risk of cardiovascular disease (CVD) and stroke is well known, and hypertension is the strongest or one of the strongest risk factors for almost all the acquired CVD [7]. Thus, the potential findings on links between PLMS and hypertension justify the accrued interest on PLMS.

Our aims here are to review the data available and critically evaluate the possible relationship between PLMS and cardiovascular and cerebrovascular risk.

PLMS and Heart Rate

Several studies have demonstrated that PLMS events are associated with autonomic activation, characterized by increases in HR, and that such increases in cardiac frequency are enhanced when PLMS are associated with arousals [10]. The first description of this association was by Winkelman et al. [11] in 1998, who demonstrated changes in HR with PLMS in eight subjects, independently of arousal. One year later, Sforza et al. [12] performed a similar study in ten patients affected by RLS/PLMS, and found that HR increases in association with PLMS were influenced by the presence of arousal and the type of PLMS. They postulated on the presence of a hierarchy of arousal starting with autonomic activation, transitioning to bursts of delta activity, alpha activity, and then to a full awakening. In 2002, Sforza et al. [13] studied 12 patients with RLS/PLMS; PLMS were divided into three groups: with arousal, without arousal, and with K-complex or delta bursts. They found an increase in HR and delta band activity before all three types of PLMS and concluded that cardiac and EEG changes occur with PLMS with or without arousal, confirming their theory of a hierarchical system of arousal. In 2003, Gosselin et al. [14] analyzed the effects of age and sex on HR activation associated with PLMS in 42 patients with RLS divided into three groups of seven men and seven women according to age. They found that PLMS events were associated with changes in HR characterized by tachycardia followed by bradycardia, with a reduction in the magnitude of both tachycardia and bradycardia with age; moreover, women showed a higher amplitude of their bradycardic responses than men. They concluded that there are age and sex differences in the magnitude of HR changes. In 2004, Ferrillo et al. [15] studied a sample of five patients with periodic limb movement disorder (PLMD) without RLS in order to describe the temporal pattern of cardiac and EEG activity changes occurring with PLMS events. They found that PLM onset was heralded by a significant activation of HR and delta activity power preceding the PLMS by 4.25 and 3 s, respectively, and followed by PLM onset, and PLM and arousal falling together. Authors concluded that all these phenomena might be linked to a common brainstem system, which receives peripheral inputs and regulates vascular, cardiac, and respiratory functions, synchronizing them with cortical activity. In 2004, Lavoie et al. [16] studied the effects of sleep stages and wakefulness on the changes in EEG activity and in HR associated with PLMS in 13 patients. They found a significant activation of EEG and HR associated with PLMs during sleep, but not during wakefulness. In 2005, Sforza et al. [17] studied the effects of PLMS on HR variability (HRV) during NREM sleep in 14 patients affected by RLS/PLMS by means of spectral analysis of R-R intervals. They found that PLMS occurrence was associated with increases in sympathetic activity without any significant changes in cardiac vagal activity. In 2007, Guggisberg et al. [18] demonstrated that the sympathetic activation associated with PLMS in patients without RLS is higher than the one elicited by other movements, and concluded that the sympathetic nervous system might have a primary role in the generation of PLMS. However, the results of these studies were possibly biased by some methodological factors [19]. In the same year, Ferri and colleagues [6] studied the changes in HR and EEG spectra in PLMS and in non-periodic LM in 16 patients with RLS. They found that EEG activation in the delta band occurred prior to PLMS and NPLMS; for isolated LMs, EEG activation preceded LM in both NREM and REM sleep, but only in NREM sleep for PLMS.

In summary, there is a considerable body of evidence that PLMS are accompanied by significant transient changes in HR, the amplitude of which is also dependent on the presence or absence of other (usually transient) sleep phenomena such as arousals and apnea; however, their interrelationships seem to be complex and not regulated by simple cause/effect mechanisms [5•].

PLMS and Blood Pressure

Various groups of investigators have shown that PLMS are associated with increases in BP [5•, 20]. However, it is not clear whether PLMS are associated with diurnal hypertension. In 2014, Izzi et al. [21] reported that RLS patients exhibit a tendency toward systemic hypertension, but the daytime cardiovascular responses do not differ between patients with PLMS and patients without PLMS. A major limitation of this study, as remarked by the authors, was the small sample of the cohort being investigated.

The first report of BP increases with PLMS was published by Ali et al. [22] in 1991 in a patient suffering from narcolepsy, even though Lugaresi et al. [23] had already mentioned implicitly this association back in 1972. In both of these

studies, BP was monitored throughout the night, and the raise in BP was augmented when PLMS were associated with EEG arousals. A more recent study [20] showed that PLMS were associated with sudden increments in systolic BP (SBP), diastolic BP (DBP), and HR, both in patients with RLS and in healthy people, but the magnitude of the changes in cardiovascular parameters were more pronounced in RLS subjects than in controls.

PLMS and Systemic Hypertension

To date, only a few studies have been conducted in order to assess the association of PLMS and systemic diurnal hypertension. In 1997, Espinar-Sierra et al. [24] found a higher frequency of PLMS in a group of patients with essential hypertension when compared to controls and also indicated that the prevalence of PLMS was proportional to the severity of hypertension, independently of other risk factors. Indeed, the prevalence of PLMS was 13% in patients with grade 1 and grade 2 hypertension, and 35.4% in patients with grade 3 hypertension.

In a large study including 861 patients, Billars et al. [25] found a linear relationship between PLMS and systemic hypertension, with higher risk being detected for subjects with PLMS index of ≥ 50/h of sleep.

Wing et al. [26] studied the effects of PLMS on nocturnal hypertension in 314 children and found that PLMS were independently associated with a wide range of BP elevations, especially nocturnal indices, and there was a trend for higher daytime BP in patients with PLMS with respect to those without PLMS.

In a large multicenter study published in 2015 that included 1740 subjects, Koo et al. [27••] found that PLMS frequency was strongly associated with hypertension in African-Americans, who have been found as exhibiting a lower prevalence of PLMS [5•], with a 20% increase of odds of prevalent hypertension for every 10-unit increase in PLMS index. The trend was similar but to a lesser extent among Chinese-Americans, but not in Caucasian- or Hispanic-Americans.

Overall, studies on the association between PLMS and hypertension have suggested that hypertension may persist during daytime, but the evidence to date is not unequivocally strong, and is predicated on association studies without any well-structured and powered randomized controlled trials.

PLMS and Cardiovascular Disease

As mentioned above, several independent research groups have been studying the effects of PLMS on HR and BP. Repetitive increases in HR and BP may have an important role in increasing cardiovascular risk in patients affected by RLS/PLMS, suggesting that this sleep disorder may be a potential cardiovascular risk factor. Moreover, some early studies suggested that PLMS may worsen cardiovascular risk in patients affected by end-stage renal disease (ESRD) [28, 29] and congestive heart failure [5•, 30•].

Benz et al. [28] studied 29 consecutive patients with ESRD and reported disturbed sleep or daytime sleepiness. All patients were followed up until either their death, renal transplantation, or study termination. These investigators found that PLMS significantly predict near-term mortality, independently of other known risk factors, and the higher the PLMS index, the shorter the survival. The 20-month survival rate of patients with PLMS index < 20/h of sleep was greater than 90% vs. 50% for PLMS index > 20/h sleep, and median survival for patients with PLMS index > 80/h of sleep was only 6 months. Analogously, Lindner et al. [29] reported that PLMS index is an independent predictor of higher cardiovascular and cerebrovascular risk in patients with chronic kidney disease.

Furthermore, Yumino et al. [30•] reported that in patients with severe systolic heart failure, the presence of PLMS index ≥ 5/h sleep is associated with increased mortality risk. It should be noted that in this study, patients were older and suffered from more severe stages of heart failure. Hanly and Zuberi-Khokhar [31] studied the prevalence of PLMS and their effects on sleep and daytime alertness in 23 men with severe chronic heart failure (CHF) and 9 control subjects, by means of overnight PSG, MSLT, and Epworth Sleepiness Scale (ESS) the day after. They found that CHF patients had an increased prevalence of PLMS and associated arousals; specifically, 52% of CHF patients had PLMS versus 11% of control subjects. The authors concluded that PLMS may contribute to sleep/wake complaints in CHF patients and possibly to their impaired cardiac function.

Jahaveri et al. [32] studied the prevalence and the effects of sleep apnea and PLMS in heart failure in 100 patients with CHF but in the absence of a parallel cohort of control subjects. They found that 49% of subjects had sleep apnea and 20% had PLMS; in this study, LM associated with sleep apnea and hypopnea were not counted. In 2012, Li et al. [33] published a large-scale prospective study involving more than 70,000 women for a period of 3 years and who were free of cardiac disease (CHD) or stroke at baseline, such as to evaluate the association between RLS and CHD, and concluded that women with RLS lasting for at least 3 years had an elevated risk of CHD during a follow-up period of 6 years, suggesting that long-term RLS and RLS-associated conditions may contribute to cardiovascular risk.

The association between PLMS and CVD was also evaluated in the Outcomes of Sleep Disorders in Older Men Sleep Study (MrOS Study) [34•], in which almost 3000 elderly men were followed up for 4 years in an effort to determine if PLMS

were predictive of CVD (coronary heart disease, peripheral arterial disease, and cerebrovascular disease). The authors found that PLMS frequency was associated with incident cardiovascular disease. The Sleep Heart Health Study [35], a cross-sectional observational study including more than 1500 men and more than 1800 women with a mean age 67.9 years, concluded that RLS was associated with coronary artery disease and cardiovascular disease, and this association seemed to be stronger when RLS symptoms were more frequent or severe.

In a very recent review [4] on the clinical relevance of PLMS, we concluded that PLMS-related sympathetic changes, namely repeated transient rises in BP and HR during sleep and impaired nocturnal BP dipping, may contribute to increase cardiovascular risk, especially in elderly and in patients with RLS, but other studies are needed to determine how PLMS directly or indirectly play a role in increasing cardiovascular risk.

Finally, Zinchuk et al. [36••] carried out PSG-based cross-sectional and longitudinal analyses of obstructive sleep apnea (OSA) in a multisite, observational cohort of 1247 US Veterans; a principal components-based clustering identified different patient clusters and in the cluster "PLMS," the risk (compared with the cluster "mild (OSA)") of the combined outcome of incident transient ischemic attack, stroke, acute coronary syndrome, or death was significantly increased (hazard ratio 2.02, 95% confidence interval 1.32–3.08).

PLMS and Stroke

Few studies have been performed with the aim to assess the relationship between PLMS and cerebrovascular disease. Some case reports [37–41] described PLMS onset after incident stroke, particularly those occurring in the pons, right basal ganglia, left corona radiata, left pallidum, and internal capsule.

In 2006, Elwood et al. [42] tested the hypothesis that sleep disorders are potential risk factors of ischemic stroke and CVD in a cohort of 1986 men aged 55–69 years in a 10-year-long prospective study. They found that RLS (indirectly a reporter of PLMS) was associated with a 67% increase in the relative odds for stroke compared to subjects without RLS. In a retrospective study, Coelho et al. [43] evaluated the medical history and PSG recordings of 40 patients with a history of stroke and 40 control subjects matched for age, sex, and risk factors, and found that 47.5% of patients vs. 12.5% of controls had a PLMS index > 5/h of sleep, and mean PLMS index was lower in controls than in stroke patients. Benbir and Karadeniz [44] evaluated prospectively 35 consecutive patients diagnosed with acute supratentorial ischemic stroke and 35 age- and sex-matched control subjects by means of clinical and whole night PSG assessments. They found that 77.2% of patients with stroke had a PLMS index > 5/h sleep vs. 28.5% of controls, and 54.3% of patients had a PLMS index > 15/h of sleep vs. 17.1% of controls. Territorial localization of the ischemic lesion was not related to the presence of PLMS, but all subjects had PLMS that was contralateral to the ischemic lesion, and 8 patients had bilateral PLMS. The authors concluded that lesions causing loss of cortical or subcortical inhibition on reticular formation and spinal pathways could lead to the development of PLMS. However, the major limitation of this type of studies is the lack of knowledge of the presence or absence of PLMS before the cerebrovascular event.

Walters et al. [43] assessed MRI scans from 26 patients with RLS and 241 controls from the population-based MEMO Study (memory and morbidity in Augsburg Elderly), in order to ascertain the presence of clinical stroke, silent infarction, subcortical lesions, and cortical atrophy. Among patients and controls, there were no differences in the prevalence of cardiovascular disease or risk factors. They found that the prevalence of cerebrovascular events of all types was greater in RLS patients. There were also greater extents of cortical atrophy and the volume of subcortical lesions, but these differences were not statistically different between patients and controls.

In 2016, Ferri et al. [45••] assessed the presence of silent cerebral small vessel disease (SVD) by means of MRI in 53 patients affected by RLS lasting for < 10 years, 44 with RLS lasting for > 10 years, and 74 controls. They found a significant increase in SVD in the entire group of RLS patients compared to controls. Age, duration of RLS, and interaction of age and duration of RLS were independent predictors of SVD, suggesting that long-lasting RLS and its accompanying PLMS are a risk factor for silent SVD, and perhaps for the development of clinical stroke. In particular, Ferri and colleagues speculated that not only the presence of PLMS might be, at least in part, responsible for the silent SVD found, but also the duration of their presence that is very rarely taken into account in epidemiological cross-sectional studies. Figure 1 reports a hypothetical schematic mechanism for the relationship between PLMS and cerebrovascular disease/stroke, as proposed by the authors.

In 2017, Boulos et al. [46] evaluated the association between increased PLMS index and white matter hyperintensities (WMH) in 30 patients presenting within 2 weeks of a first-ever minor stroke or high-risk transient ischemic attack. They found that greater WMH burden was correlated with elevated PLMS index and stroke infarct volume, and this relationship persisted even when controlling for vascular risk factors. These investigators concluded that PLMS may be a risk factor for or a marker of WMH.

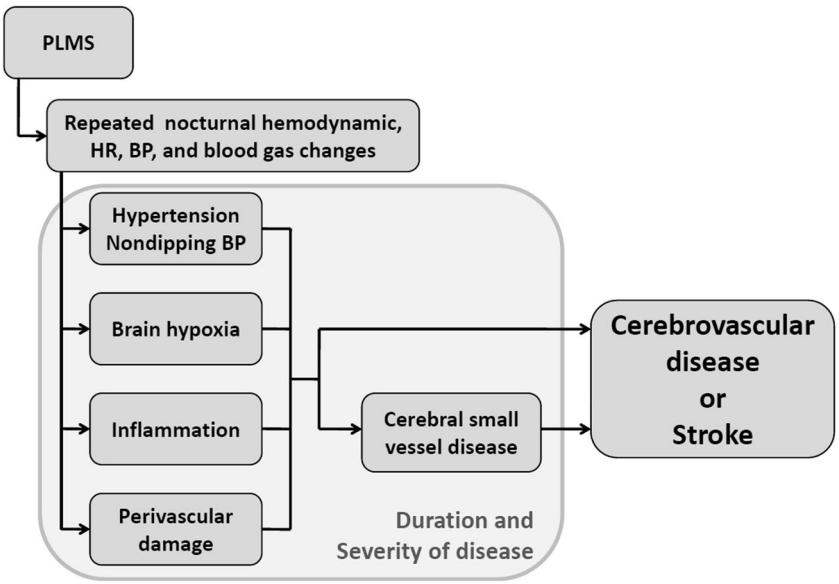

Fig. 1 Proposed hypothetical relationship between PLMS and cerebrovascular disease/stroke

PLMS, Inflammatory Response, and Cardiovascular Risk

In order to assess cardiovascular risk, Trotti et al. [46] studied systemic inflammation and PLMS in 137 RLS patients, by means of plasma levels of high-sensitivity C-reactive protein (CRP), interleukin-6, and tumor necrosis factor alpha. They found that PLMS were associated with increased levels of inflammatory markers, because of a strong association between high CRP levels and PLMS index > 45/h of sleep, suggesting a relation between RLS/PLMS, systemic inflammation, and cardiovascular risk. Conversely, Siddiqui et al. [46] did not find any differences in cytokine levels in patients with RLS. However, Becky et al. [46] demonstrated an independent linear relation between PLMS index and circulating levels of lipoprotein-associated phospholipase A2 (Lp-PLA2) and also CRP, suggesting, similar to Trotti et al. [46], that cardiovascular risk might be increased in patients with high PLMS index as indicated by inflammatory biomarkers.

Conclusion

Since 1972, when Lugaresi et al. [23] noticed the presence of periodic motor phenomena arising during sleep, both in healthy people and in subjects with sleep apnea, alveolar hypoventilation, RLS, and PLMS, it has become firmly established that PLMS are part of a complex oscillatory pattern during sleep, including cortical EEG activity, autonomic nervous system activity, and peripheral responses. These phenomena are characterized by vegetative and somatic changes (systemic arterial blood pressure, pulmonary arterial pressure, heart rate, arteriolar tone, breathing, peripheral motor neuron excitability, and level of consciousness) that tend to oscillate and to repeat themselves every 10–40 s during sleep. These complex oscillatory dynamics are also at the basis of the NREM sleep phenomenon, called cyclic alternating pattern, as reported by the group led by Terzano [47, 48].

Based on the fact that practically in all PLMS there is an increase in HR and BP, in the last years, the interest about PLMS has been increasing in a quest to evaluate potential relationships with cardiovascular and cerebrovascular risk. Overall, the evidence supports that PLMS may play an important role in increasing risk of such morbidities, although there is no conclusive evidence to indicate causality or that removing PLMS will play a major role in decreasing such risk.

Further studies are needed to establish more clearly the role of PLMS and the possible need of specific treatment (such as dopamine agonists). The American Academy of Sleep Medicine guidelines for the treatment of RLS/PLMS [49] affirm that there is no consistent evidence to treat pharmacologically PLMS alone, at least as of yet; thus, although dopamine agonists are known to reduce PLMS index, their need in the context of reducing cardiovascular remains controversial [50, 51]. Manconi et al. [51] reported that the acute administration of pramipexole at low doses reduces the number of PLMS and the amplitude of the autonomic response to residual PLMS, without any effects on sympathovagal balance, concluding that the normalization of HR responses may contribute to reduce the eventual cardiovascular risk associated with PLMS. However, Nannapaneni and Ramar [50] concluded that there is insufficient evidence for a strong recommendation to treat PLMS or PLMD specifically to reduce cardiovascular risk.

Although the current body of evidence suggests that PLMS are potentially involved in increasing cardiovascular risk,

other studies will be needed to establish the precise role of PLMS in patients with and without RLS, as far as their cardiovascular balance, and to evaluate the role of treating PLMS to reduce cardiovascular risk.

Compliance with Ethical Standards

Conflict of Interest Patrizia Congiu, Monica Puligheddu, Michela Figorilli, and Raffaele Ferri declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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