Heart Rate and Blood Pressure Changes Associated with Periodic Limb Movements

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Over the last two decades, considerable data has been published to elaborate the association between periodic limb movements in sleep (PLMS) with heart rate (HR) and blood pressure (BP), making PLMS as a potential and an emerging cardiovascular and cerebrovascular risk factor [1]. This chapter will review the present data available to establish the relationship of PLMS with HR and BP.

HR and BP Correlate of LMS in Controls and Patients

Heart Rate and PLMS

Multiple recent studies on HR and PLMS have convincingly established that PLMS are associated with significant HR variability (HRV); PLMS with arousals are associated with a higher degree of autonomic activation. Winkelman et al. [2] first demonstrated changes in the HR with PLMS in eight patients. HR was recorded for 10 cardiac cycles before and after the onset of PLMS; no statistical significant difference was noted in HR rises with PLMS with or without arousal. HR began to peak three cycles prior to onset of PLMS, peaked at 4 cycles after and then declined below baseline at cardiac cycles 8–10. The authors concluded that pulse rate elevation occurred with PLMS irrespective of the presence of arousal. This study was

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followed by a similar study by Sforza et al. [3] where electroencephalographic (EEG) activation and tachycardia were noticed in PLMS with or without arousals. In this study 10 patients with restless legs syndrome (RLS)/PLMS were included. EEG correlates of PLMS were analyzed by visual scoring and spectral analysis during PLMS with and without arousals; also electrocardiographic R-R wave interval was analyzed. 34% of PLMS were associated with arousals lasting >3 s; 3% of PLMS were associated with arousals lasting <3 s and the rest were associated with changes in the EEG theta and delta activity. Tachycardia was seen with all types of PLMS; the authors concluded for a presence of hierarchy of arousal from autonomic activation, to bursts of delta activity, to alpha activity, and then to a full awakening. Ferri et al. [4] studied the changes in HR and EEG spectra not only in PLMS but also in nonperiodic (isolated) leg movements (NPLMS) in 16 RLS patients. EEG activation specifically in the delta band was seen prior to PLMS and NPLMS. EEG activation preceded leg movements (LM) in both NREM and REM sleep for NPLMS and only in NREM sleep for PLMS. In a subsequent study; Sforza et al. [5] studied 12 patients with RLS/PLMS. HR and EEG spectral analyses were done for 10 s before and 10 s after PLMS onset. PLMS were divided into those with arousals, without arousals and with K-complex or delta burst. The authors found an increase in HR and delta band activity before all three types of PLMS and concluded that cardiac and cerebral changes occur with PLMS with or without visible arousal and confirmed their prior theory of a hierarchy of arousal. A similar study [6] analyzed the effects of age and gender on HR changes associated with PLMS in 42 RLS patients. PLMS were again found to be associated with HR changes, i.e., tachycardia followed by bradycardia. Women were noticed to have higher amplitude of bradycardia. In 2004, Ferrillo et al. [7] studied the temporal pattern of cardiac and EEG activation changes with PLMS in NREM sleep, in 5 patients without RLS and with periodic limb movement disorder (PLMD). HR activation and delta activity power were noted 4.25 and 3 s, respectively, before PLMS onset. With the use of the spectral analysis, HRV and EEG activation were measured as a marker for autonomic activation and sleep instability [7, 8]. In one study, autonomic activation was reported several seconds before the EEG activation and movement; Guggisberg et al. [9] demonstrated that the sympathetic activation accompanying PLMS (in subjects without RLS) is greater than for all movement types, as measured by HRV spectra. However, the results of this study were possibly biased by some methodological factor [10]. Lavoie et al. [11] also demonstrated that the EEG and HR activation with PLMS is more evident during sleep than wakefulness.

Blood Pressure and PLMS

Even if already implicitly mentioned by Lugaresi et al. [12] in 1972, BP variation with periodic limb movements in sleep was first demonstrated by Ali et al. [13] in 1991 in a patient with narcolepsy. This phenomenon was separately analyzed in two different polysomnographic labs. RLS patients with PLMS were monitored

overnight with concomitant continuous BP measurement. Both studies showed statistically significant elevation of systolic and diastolic BP with periodic limb movements in sleep and wakefulness as compared to fake PLMS [14, 15]. The elevation in BP was higher in PLMS with cortical arousal, as compared with PLMS without cortical arousal. A recent study demonstrated a rise in BP with PLMS in healthy normal subjects [16]. PLMS were associated with significant increases of HR, systolic BP and diastolic BP in RLS patients and healthy subjects; however, cardiovascular increases were more pronounced in RLS subjects than healthy subjects, in agreement with a previous study which had shown the same difference for HR only [17].

Effects of the Interaction Between PLMS and Apnea on HR and BP

As also seen above, PLMS are embedded in a general sleep oscillatory pattern involving not only the motor system but also the autonomic function, cortical EEG activities, the respiratory system and several other functions too [18, 19]. Thus, the interaction between PLMS and these systems is of utmost importance.

The amplitude of the HR changes associated with PLMS varies with age and is higher with bilateral movements as compared to unilateral movements [4]. HRV is higher when LM are associated with respiratory events. In 2006, Yang et al. [20] demonstrated that maximal HR rise for respiratory events with leg movements (7.9 beats/min) was significantly greater than for respiratory events without leg movements (5.1 beats/min). In the context of sleep apnea, it is important to note that the interaction can be bidirectional with the rhythm of apnea events taking the lead and forcing PLMS to change their time structure with longer intervals and clustered around the end of the respiratory pauses [21, 22].

Searching for the Effects of PLMS-Related Rises in HR and BP

Repetitive abnormal HR and BP rises can play a role in increased cardiovascular risk in RLS patients with PLMS. Trotti et al. studied the level of C-reactive protein (CRP) in 137 RLS patients with PLMS and found an association of high CRP with PLMS index >45/h, suggesting again a relation between systemic inflammation, cardiovascular risk and RLS [23]; however, a prior study showed no relation of RLS and CRP and other inflammatory markers [24]. Becki et al. [25] measured the serum level of Lipoprotein-associated phospholipase A2 in 70 newly polysomnographically diagnosed PLMS patients. The levels were significantly high in patients with PLMS as compared to controls. The study also noticed a similar relation with CRP and high PLMS index. The authors concluded that risk of vascular events may be increased in patients with PLMS. Chronic sleep restriction from RLS/PLMS can

potentially increase inflammatory activity, subsequently contributing to the development of cardiovascular disease [26].

Various epidemiological, retrospective and anecdotal studies in the past two decades have shown association of vascular risk factors such as hypertension, heart disease, and stroke with RLS and PLMS.

Systemic Hypertension and PLMS

Espinar-Sierra et al. [27] in 1997, found PLMS in 18% of a group of 91 subjects with essential hypertension, a percentage considerably higher than that found in normal controls. The prevalence of PLMS was proportional to the severity of hypertension; Grade 1 and 2 hypertension had a PLMS prevalence of 13%, whereas Grade 3 hypertension had a prevalence of 36.4%. This relationship was independent of confounding risk factors such as age, sex, obesity, alcohol use, smoking, apnea severity, and use of anti-hypertensive medications. In a larger study of 861 patients, Billars et al. [28] also found a direct relation between PLMS and systemic hypertension as well. The authors found a higher risk of having hypertension in patients with PLMS index 50/h or more.

Heart Disease and PLMS

In one of the largest studies on RLS and coronary artery disease [26], more than 70,000 women, some of them with RLS were prospectively followed for 3 years and were found to have a higher risk of developing coronary artery disease. The prevalence of PLMS and their effect on sleep and daytime alertness were studied in 23 men with severe, stable congestive heart failure and 9 healthy control subjects [29]. Patients with congestive heart failure had a more frequently moderately severe PLMS, higher amount of NREM sleep and shorter mean sleep latency the day after the recording. In another large prospective case series of heart failure patients, without control group, Javaheri et al. [30] found that 20% of patients had PLMS with an average index of 35/h. PLMS also had a slightly higher number of arousals (3.4 ± 2 per hour). In a prospective study, Skomro et al. [31] enrolled 79 congestive heart failure patients who underwent echocardiogram and in lab polysomnograms. The authors found a 19% prevalence of PLMS >5/h. No difference was seen in sleep architecture or daytime sleepiness in patients with or without PLMS. This study also confirmed a significant elevation of HR after PLMS (80.1 ± 9.4 vs. 81.5 ± 9.2; $p < 0.001$). After the report of a small study indicating PLMS as a potential predictor of mortality in patients with renal insufficiency [32], in 2011 Yumino et al. [33] analyzed the relation between PLMS and mortality in patients with systolic heart failure; 218 patients with congestive heart failure were prospectively enrolled over 7 years and underwent polysomnographic studies. Eighty-one patients (37%) had PLMS >5/h; these patients were older and had lower left ventricular ejection fraction. The authors also found a significant higher mortality rate in patients with PLMS index >5/h than those with PLMS index <5/h (10.4 vs. 3.4 deaths/100 patient-years, $p = 0.002$). Even after adjusting for confounding variables, PLMS index >5/h was found to be an independent risk factor for mortality (hazard ratio 2.42, 95% CI = 1.16–5.02, $p = 0.018$). In summary, the

prevalence of PLMS in patients with congestive heart failure varies from 19 to 35%. PLMS index has recently been proposed as an independent risk factor for mortality.

Stroke and PLMS

Very few studies have tried to address the relation of stroke with PLMS and RLS. Only few case reports [34–36] suggested the onset of PLMS as a result of stroke. The strokes occurred in the left corona radiata, left pallidum and internal capsule, and right basal ganglia. More recently, 35 patients with acute supratentorial ischemic stroke and 35 age- and sex-matched control subjects were studied [37]; 27 patients (77.2%) had PLMS index >5/h, while only 10 participants (28.5%) in the control group had PLMS index >5/h ($p < 0.05$). A retrospective analysis [38] of 40 stroke patients and 40 controls matched for age, sex, and risk factors showed 19 patients (47.5%) and 5 controls (12.5%) had a PLMS index >5/h ($p < 0.001$). Walters et al. [39] compared the MRI scans from patients with RLS to those of control subjects without RLS; when controlled for age, gender, and comorbidities, the likelihood for any stroke was higher in patients with RLS compared to controls, but was not significant (OR 2.46; 95% CI = 0.97–6.28; $p = 0.06$). Patients with RLS also had a nonsignificantly higher incidence of silent infarctions (19.2% of patients vs. 12.0% of controls), larger subcortical lesions, and slightly higher mean cerebral atrophy scores, compared to age-matched controls without RLS.

Challenging the Cause/Effect Relationship Between PLMS and EEG or Autonomic Activations

It has been known, for decades, that the rhythm of PLMS is strictly interconnected with a general sleep oscillatory pattern. Already in 1972, Lugaresi et al. [12] showed in controls and patients with sleep apnea, primary alveolar hypoventilation, RLS and PLMS, that several vegetative and somatic phenomena (systemic arterial pressure, pulmonary arterial pressure, cardiac rate, arteriolar tone, breathing, peripheral motor neuron excitability and level of consciousness) tended to oscillate or repeat themselves periodically every 20–30 s during sleep, and especially during light sleep. This generalized, rather regular, oscillatory pattern, involving primarily the EEG, was later shown to be a feature of NREM sleep, occupying a variable portion of it, depending on age and clinical condition of the subject and was termed and coded as cyclic alternating pattern [40, 41]. As already noticed by Lugaresi et al. [12], these oscillations can be observed also without the participation of one or two of the above systems, or even involve only one parameter under analysis [18].

Regarding PLMS, a series of observational and experimental studies have been published with the aim to clarify their role and participation to this general sleep oscillatory behavior. First of all PLMS, that have been reported in patients with spinal cord injury [42–44], can occur in these patients without any accompanying HR rise and asynchronously with EEG transients [45]. This can also be observed in

other patients with an impaired anatomical connection between the spinal cord and the cortex [46].

Manconi et al. [47] have reported that different drugs can selectively abolish PLMS, without affecting EEG oscillations (dopamine agonists) or dampen EEG oscillations without modifications of PLMS (benzodiazepines). On the contrary, experimentally increasing EEG and autonomic oscillations during sleep is not accompanied by the appearance of PLMS in young normal subjects [48].

All this demonstrates that LMs during sleep can be dissociated from arousals (and its autonomic correlates) in a variety of conditions including pharmacological interventions, experimental procedures, and pathological states inducing an anatomical/functional disconnection between the spinal cord and higher nervous structures.

The possibility to dissociate events that occur often as a cluster, such as cortical arousals, autonomic events, and PLMS, suggests that the interrelationships between these events are not likely to follow the simple paradigm of any one event leading to another; however, the lack of a cause/effect relationship between these events does not exclude the possibility that, when they do occur concurrently, one modifies the biological effects of the other [20]. The resulting possibly enhanced effect may represent the basis of adverse consequences of various clinical conditions in which PLMS are particularly abundant such as RLS [1, 49] or PLMD [50].

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