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Original Article

ORIGINAL ARTICLE

Characteristics and Determinants of Respiratory Event–Associated Leg Movements

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Abstract

Study Objectives: To (1) replicate the recently described distribution of respiratory event–associated leg movements (rLMs) in participants with mild-to-moderate obstructive sleep apnea syndrome (OSAS), (2) explore global and local factors associated with the presence of rLMs, and (3) investigate differences related to OSAS severity and periodic leg movements during sleep (PLMS) status.

Methods: We randomly selected six groups of participants without restless legs syndrome (12–15 participants in each group), stratified by apnea–hypopnea index (AHI) severity (AHI 10–20, 20–30, and 30–40) and PLMS status (PLMS index <15 and >15 per hr) from the population-based HypnoLaus study that assessed full polysomnography at home in participants aged 40 to 80 years, randomly selected from the population register of the city of Lausanne, Switzerland.

Results: Our results confirmed the distribution of leg movement activity at the end of respiratory events (–2.0 to +10.25 s). Mixed effects logistic regression modeling rLM-probability showed that rLMs were more frequent in participants with high-PLMS, at the end of obstructive apneas (vs. hypopneas) and in the presence of arousals at the end of the events. In participants with high-PLMS, rLM-probability decreased with time of night and was more reduced during REM sleep (vs. NREM sleep), whereas the duration of the respiratory event had a significant effect only in participants with low-PLMS.

Conclusions: We confirm the previously reported distribution of rLMs in participants with mild-to-moderate OSAS and our results suggest that rLMs are sensitive to both sleep-related and respiratory-related factors in a complex interaction with the PLMS status.

Statement of Significance

Respiratory event–associated leg movements (rLMs) are widely distributed around the end of respiratory events in participants with obstructive sleep apnea syndrome (OSAS). They are more frequent in participants with OSAS with periodic leg movements during sleep (PLMS), and in these participants, show some similarities with PLMS. Overall, rLMs appear to be sensitive markers for the OSAS-induced sleep disturbance and possibly signal a more severe form of the respiratory disorder in some participants.

Key words: periodic leg movements; obstructive sleep apnea; polysomnography

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Introduction

Periodic leg movements during sleep (PLMS) are a frequent finding in patients with obstructive sleep apnea syndrome (OSAS) [1–6]. Their pathophysiological significance, however, is currently unclear owing to inconsistent study results which range from a lack of effect of PLMS on sleepiness [3, 6–9] to PLMS being a significant predictor of mortality in patients with sleep apnea syndrome [10] and important comorbidities such as heart failure [11–13] or end stage renal disease [14, 15].

A critical issue potentially contributing to this uncertainty is the question on how to distinguish PLMS from respiratory event–associated leg movements (rLMs) in these populations. Already the first PLMS criteria introduced by Coleman in 1982 [16] and later the American Sleep Disorders Association (ASDA) in 1993 [17] excluded leg movements at the end of respiratory events from being considered as PLMS. However, quantitative criteria to identify these rLMs were only introduced in 2006 with the first, recently updated [18], criteria of the World Association of Sleep Medicine (WASM) in collaboration with the International Restless Legs Syndrome Study Group (IRLSSG) [19]. They defined rLMs as those that occurred within 0.5 s before to 0.5 s after the end of a respiratory event. Although large parts of these criteria were subsequently adopted by the American Academy of Sleep Medicine (AASM) [20], among the differences between the two sets of rules was the definition of rLMs which were defined by the AASM as any leg movement in the interval ranging from 0.5 s before the start of the respiratory event to 0.5 s after its end. It must be mentioned that neither of the two rules that defined rLMs was based on any empirical evidence. In fact, we have recently shown in patients with moderate-to-severe OSAS that the distribution of rLM is considerably wider, ranging from 2.00 s before to 10.25 s after the end of the event, and that both rules substantially underestimate the number of rLMs and overestimated the number of PLMS [21]. This definition of rLMs is now recommended in the latest WASM 2016 standards for recording and scoring leg movements [18]. However, although it is the recommended definition, it is still possible to use the prior definition (–0.5 to 0.5 s) as an alternative. The reason for this, as stated in the article, is that so far "it is only one study that has not been replicated, and it only applies to one type and range of severity of SDB" (p. 90 [18]). The first aim of the present study was therefore to replicate the distribution of rLMs in patients with mild-to-moderate OSAS.

A further area of uncertainty is the conceptual interpretation of rLMs, partly due to the large phenomenological overlap between PLMS and rLMs. Formulated provocatively, the interpretation of PLMS and rLM in patients with OSAS ranges from the suggestions that many [2] if not all LMs and even PLMS may be associated with respiratory events [22, 23] to the idea that many rLMs are in fact PLMS [24], which are temporally displaced by the respiratory events.

Given the high prevalence of PLMS in the general population [25], a priori a substantial proportion of participants with OSAS are expected to show frequent PLMS. It is currently unknown whether there are any features that reliably differ between PLMS and rLMs. To address these questions, we explored determining factors of rLMs, i.e., we investigated whether the probability to observe rLMs at the end of respiratory events was increased or decreased depending on participant characteristics: night and local sleep-related (arousal, sleep stage, and time of night) and respiratory-related factors (type and duration of event, and desaturation). To circumvent the problem of PLMS and rLMs occurring in the same participant, we specifically selected participants, all without restless legs syndrome (RLS), who had clear PLMS independent of any respiratory event and participants that had no PLMS but were matched for OSAS severity.

Methods

Participants

The HypnoLaus study included participants of the population-based CoLaus/PsyCoLaus Cohort study described previously [26–28]. Briefly, the CoLaus/PsyCoLaus study included a random sample of 6734 participants (range age: 35–75 years) selected from the residents of Lausanne city (Switzerland) between 2003 and 2006. The distribution of age groups, gender, and zip codes of participants was similar to the source population [26]. During the first follow-up of the cohort, 5 years after the initial evaluation, the HypnoLaus study evaluated the sleep characteristics in a random subset of this cohort: 3051 consecutive participants were invited to undergo a complete PSG at home, and 2168 (71.1%) accepted (51.2% women, mean age 58.4 ± 11.1 years). Both CoLaus/PsyCoLaus and HypnoLaus were approved by the Ethics Committee of the Vaud canton (CER-VD), and a written informed consent was obtained from all participants.

We randomly selected six groups of participants according to OSAS severity (apnea–hypopnea index [AHI] 10–20, 20–30, and 30–40) and PLMS status (PLMS index < 15 and > 15, subsequently called low- and high-PLMS) with the aim to sample 15 participants in each group. An exclusion criterion was the presence of possible or probable RLS symptoms based on a questionnaire that assessed the IRLSSG criteria for the diagnosis of RLS [29]. Furthermore, exclusion criteria were the intake of beta blockers, hypnotics, and antidepressants. In total, 91 records were randomly selected from the HypnoLaus cohort, of which 13 were excluded due to signal artifacts or excessive fragmentary myoclonus that prevented the precise determination of the onset and offset of respiratory events and/or leg movements. Although not a formal inclusion criterion, we verified the presence or absence of PLMS by inspecting all individual intermovement interval plots and the periodicity index. We thus included the records of 78 participants of whom 25 had an AHI between 10 and 20 (12 with PLMS > 15, 13 without), 26 had an AHI between 20 and 30 (13 with PLMS, 13 without), and 27 had an AHI between 30 and 40 (15 with PLMS, 12 without).

Sleep Recordings

Detailed description of the PSG procedure has been described elsewhere [25]. During a visit at the Center for Investigation and Research in Sleep (Lausanne University Hospital, Switzerland), trained technicians equipped the participants with the PSG recorder (Titanium, Embla® Flaga, Reykjavik, Iceland) that included a total of 18 channels, in accordance with 2007 AASM recommended setup specifications [30]: six electroencephalography, two electrooculography, three surface electromyography (one submental, two for right and left anterior tibialis muscles), and one for electrocardiogram, nasal pressure, thoracic and abdominal belts, body position, oxygen saturation, and pulse rate. Surface leg electrodes were placed longitudinally and symmetrically around the middle of the muscle so that they were 2

to 3 cm apart or 1/3 of the length of the anterior tibialis muscle, whichever was shorter. Separate channels for both legs were used.

Scoring of Leg Movements and Respiratory Events

For the current study, in all PSG recordings, all LMs were manually rescored according to the AASM [26] and WASM/IRLSSG [19] criteria as any leg EMG increase ≥ 8 μV above the resting baseline and lasting between 0.5 and 10 s. The onset of the LMs was defined as the beginning of the EMG increase ≥ 8 μV above the resting baseline, and the end of the LM was defined as the beginning of the period where the EMG decreases for at least 0.5 s to < 2 μV above resting baseline.

Apneas, hypopneas, and respiratory effort–related arousals (RERAs) were scored according to the 2012 AASM criteria [31]. For the current study, we considered only hypopneas and apneas as respiratory events. We did not consider RERAs since these were very infrequent in this sample (RERA index of 0 in 42 participants, maximum RERA index: 3). The onset and end of all respiratory events were manually controlled and adjusted if needed. In accordance with the AASM standards [27], the onset of the hypopnea or apnea was defined as the nadir of the flow signal preceding the first breath that was clearly reduced. The end of the respiratory event was defined as the beginning of the first breath that approximated the baseline breathing amplitude.

Descriptive and Statistical Analysis

Distribution of Leg Movement Activity at the End of Respiratory Events

The distribution of leg movements at the end of respiratory events was investigated by back-averaging leg movement activity (LMA) to the end of events. The procedure was largely equivalent to the methods of our recent article [21]. In short, we selected all hypopneas and apneas that began and ended during sleep. Events where artifacts precluded the determination of the onset and end of respiratory and movement events were excluded. Back-averaging of LMA involved the following sequential steps: For each respiratory event, we selected the interval from 30 s before to 30 s after the end of the event. This 60-s interval was divided into 0.25-s bins, resulting in a segment with 240 bins for each event. Based on the information (in milliseconds) about the onset and duration of all LMs during this interval, each 0.25-s bin was classified as containing or not-containing any part of a LM, denoted as 1 or 0, respectively. LMs were considered to occur in this interval if their onset was (1) after the onset of the respiratory event, (2) before the onset of the subsequent respiratory event, and (3) nearer to the end of respiratory event in question than to the end of a previous or subsequent respiratory event. Separately for each participant, all segments were summed and standardized by the total number of respiratory events that had been considered for this participant. A value of, for example, 30 would thus signify that, for 30% of all respiratory events, a LM was present at this time point. The individually derived distribution segments were then averaged across all participants, therefore giving equal weight to each participant independently of the individual's number of respiratory or movement events.

As in our previous study [21], we used change-point analysis to derive empirically based estimates for the interval during which LMA is increased at the end of hypopneas and apneas. Change-point analysis identifies points in an ordered sequence of observations where the statistical properties (e.g., the mean) of a series change so that the property of the sequence before the change point is significantly different from the property of the sequence after the change point. In this study, the averaged distribution segments served as the input sequence. We used the binary segmentation change-point analysis [32] (implemented in the R package change point [33, 34]), which is an approximate method that uses the cumulative sums test statistic to find the optimal position of change points in the mean for data where no assumption about the distribution is made. In the case of multiple change points, the Bayesian Information Criteria (BIC) were used to select the two strongest change points. A more detailed explanation of the change-point analysis and the interpretation of the results is provided in the Supplementary Material.

Determinants of rLMs

The main focus of this study was the investigation of determinants of rLMs. To this end, we modeled the probability of rLMs with mixed effects logistic regression with a random effect for each participant and fixed effects for participant factors, night factors, and local sleep and respiratory factors, as detailed in the following. Each respiratory event was classified as 0 if there was no rLM and 1 if there was at least one rLM. Mixed effects logistic regression was then used to model this binary variable, where the log odds of the outcome are modeled as a linear combination of the predictor variables with data clustered within each participant. Across all participants, there were 12,664 respiratory events, which started and ended during sleep. We excluded 192 events where there was no rLM but LMA > 10 s. Since only a small fraction of events occurred in N3 sleep (n = 319, 2.56%), or were classified as mixed apneas (136, 1.09%) or central apneas (349, 2.80%), these were excluded from the analysis, leaving 11,629 respiratory events in which one or more rLMs were present in 39.9% cases.

As possible predictors, we considered the participant variables age, sex, body mass index (BMI), AHI group (10–20 vs. 20–30 vs. 30–40), and PLMS group (<15 vs. >15). The inclusion of participant factors tests the hypothesis that the individual's overall probability of rLM (i.e., %RLM) depends on participants' characteristics, for example, that males are more likely than females to have rLMs at the end of respiratory events. Night factors included total sleep time (TST), sleep efficiency (SE), arousal index, oxygen desaturation index (ODI), mean oxygen saturation (SpO2 mean), minimum oxygen saturation (SpO2 min), and time spend with oxygen saturation below 90% (T < 90%). Since there was only one night per participant available, the hypothesis associated with the inclusion of night factors mirrors that of the participant factors (e.g., that rLMs are more likely in nights with lower SE). Finally, we also considered several characteristics of the single respiratory events, which we called "local" factors. The local factors that were considered were sleep-related (time of the night in hours since sleep onset, sleep stage during which the respiratory event occurred, and presence of arousal at the end of the event) or respiratory event–related, including the type of respiratory event (hypopnea vs. obstructive apnea), the duration of the event, and the presence of an oxygen desaturation at the end of the event. Oxygen desaturations were classified as 0 (no desaturation), 3 to 7 (referring to magnitude of the

desaturation in %), and 8, which included all desaturations of 8% or more. The local factors test the hypothesis that rLMs are more or less likely depending on the characteristics of the respiratory event itself, for example, that rLMs are more likely to occur at the end of obstructive apneas compared with hypopneas.

Model building proceeded along the following sequential steps: first, univariable logistic mixed regression was used to identify predictor variables that were related to the probability of rLMs; second, all identified predictors were included in a common multivariable model and nonsignificant effects removed from the model. Finally, given that we found significant participant factors, we explored possible interactions between these participant factors and the significant local factors. This last step tests hypotheses such as that in participants with high-PLMS (participant factor), the likelihood of rLMs decreases over the night (local factor), whereas in participants with low-PLMS, it does not. Statistical significance of the fixed factors was tested with likelihood ratio tests comparing a model with the fixed effect to a null model for univariable regression and by comparing a full model to a model with the fixed effect dropped in the multivariable case. Results are graphically depicted by so called effect displays that show predicted probabilities with a 95% confidence interval for the response variable across the range of values for each explanatory variable, while keeping values of the other explanatory variables constant at their typical (mean) value. Effect displays were created with the R package "effects" (version 3.1-1) [35]. For comparison, we also show "raw" subgroup specific probabilities, which were derived by averaging across participants but do not take into account the remaining covariates in the model (Supplementary Material). For the sake of readability, in the description of the results, we use the term "frequency" as a short hand to mean conditional probability that is conditional on the presence of a respiratory event. Therefore, a statement such as "rLMs were more frequent during NREM sleep than REM sleep" does not necessarily mean that the absolute number of rLMs was higher during NREM sleep, but that given the same number of respiratory events in NREM and REM sleep, a higher number of events during NREM sleep was accompanied by one or more rLMs.

Two important local factors in the model were the presence of arousals and desaturations at the end of the respiratory event. To the best of our knowledge, there is no standard definition when an arousal or a desaturation is considered to be associated with a respiratory event. For this reason, we explored the distribution of arousals and desaturations at the end of respiratory events in the present sample to derive tentative definition criteria. Based on these distributions, which are described in the Supplementary Material, a respiratory event was considered to be associated with an arousal if the arousal overlapped with the end of the event or started ≤3 s after the end of the event. A respiratory event was considered to be associated with a desaturation (≥ 3%) if this desaturation overlapped with the end of the respiratory event or started ≤7 s after the end of the event.

Results

Participants

We included 78 participants of whom 25 had an AHI between 10 and 20 (12 with high-PLMS > 15, 13 with low-PLMS < 15), 26 had an AHI between 20 and 30 (13 high-PLMS, 13 low-PLMS), and 27 had an AHI between 30 and 40 (15 high-PLMS, 12 low-PLMS). A description of the standard demographic and sleep parameters is given in Table 1. The groups did not differ systematically in age, gender, or BMI. Besides the planned between-group differences in AHI and PLMS index, participants with high-PLMS had also more leg movements. Across AHI categories, the number of desaturations became more frequent and the percentage of slow wave sleep decreased significantly (Table 1). In addition, we observed an interaction between AHI severity and PLMS status for minutes of wake after sleep onset (WASO) where WASO increased with increasing AHI severity only in participants with high-PLMS (post hoc tests, $p < .05$).

Distribution of LMA at the End of Respiratory Events

The distribution of LMA at the end of respiratory events showed a systematic increase over a wide interval (Figure 1A). Change-point analysis identified this interval as ranging from –3.00 to 10.25 s when considering respiratory events that started and ended during sleep with an additional epoch of sleep before and after the event (see also Supplementary Material). The classification of respiratory events and leg movements based on the –3.00 to 10.25-s interval compared with the –2.00 to 10.25 s-interval previously identified [21] showed very little differences. The maximum absolute number leg movements that were not classified as respiratory related when considering the –2.00 to 10.25 s definition were seven leg movements per night (mean 1.1, range 0–7). Similarly, the maximum absolute number of respiratory events for which the classification changed was six events per night (mean 0.6, range 0–6). For this reason, we classified rLMs according to the published definition (–2.00–10.25 s) for all subsequent analyses. In the majority of cases, the interval from –2.00 to 10.25 s contained only one LM (75.63% ± 11.11%, range: 46.09%–96.13%), two LMs were observed in 18.56% (±7.57%) of cases, and three or more in only 5.81% (±5.42%).

Figure 1B shows the distribution of LMA for the six subgroups defined by the AHI and PLMS categories. Although the shape of the LMA distribution appears similar for all groups, a systematic increase of rLMs in participants of with high-PLMS, independent of AHI category, is prominently visible. We have quantified this as %RLM, i.e., the percentage of respiratory events where at least one rLM was observed. Figure 1C shows the individual and group average values of %RLM confirming the systematic differences between participants with high- and low-PLMS, which were formally tested and found significant in the following analyses.

Determinants of rLMs

On average, 39.9% of all respiratory events were accompanied by at least one rLM. The individual %RLM ranged from 8% to 71%, reinforcing the choice of a random participant effect, which was normally distributed (Wilks–Shapiro test, $p = .834$). In the univariate models, rLM-probability was neither associated with age ($\chi^2 = 2.87$, $p = .090$), sex ($\chi^2 = 0.01$, $p = .933$), nor BMI ($\chi^2 = 0.02$, $p = .900$). There were significant differences between participants with high- and low-PLMS ($\chi^2 = 34.59$, $p < .001$) with a significantly higher frequency of rLMs in participants with high-PLMS (Figure 1C). There was no significant difference between AHI groups ($\chi^2 = 3.30$, $p = .069$), nor was there a significant PLMS

Table 1. Description of Participants

	Group								
	1	2	3	4	5	6			
AHI	10–20	10–20	20–30	20–30	30–40	30–40			
PLMS	<15	>15	<15	>15	<15	>15			
	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD	AHI group	PLMS group	AHI × PLMS group
	n =13	*n* = 12	*n* = 13	*n* = 13	*n* = 12	*n* = 15	P*	P*	P*
Age	57.7 ± 12.6	64.1 ± 11.6	61.8 ± 12.4	60.2 ± 7.7	61.2 ± 13.0	65.4 ± 8.1	.413	.457	.747
Sex (M/F)	9/4	6/6	4/9	5/8	7/5	7/8	.556	.585	.741
BMI	26.0 ± 3.2	26.5 ± 3.7	27.8 ± 4.3	26.3 ± 3.3	26.2 ± 1.8	27.1 ± 4.6	.827	.867	.884
AHI	13.6 ± 2.4	14.9 ± 2.6	25.0 ± 2.7	23.5 ± 2.7	35.2 ± 2.8	34.6 ± 2.9	**<.001**	.5056	.1167
PLMS index	7.6 ± 4.3	46.5 ± 25.1	5.5 ± 3.8	39.3 ± 17.0	5.0 ± 3.3	39.4 ± 18.7	.5068	**<.001**	.8385
LMS index	21.0 ± 7.7[a]	62.0 ± 28.1[b]	23.7 ± 8.1[a,c]	63.7 ± 18.0[b]	28.0 ± 7.5[c]	69.8 ± 27.8[b]	.1783	**<.001**	.8854
TST	391 ± 46	421 ± 85	401 ± 51	421 ± 60	427 ± 87	392 ± 72	.1860	.0900	.0877
SE	80 ± 13	87 ± 6	84 ± 9	82 ± 8	82 ± 12	75 ± 11	.1846	.7107	.0547
N1%	11.8 ± 5.7	11.0 ± 5.0	9.9 ± 5.4	14.4 ± 6.7	14.6 ± 6.9	15.6 ± 6.7	.2853	.9467	.6002
N2%	44.3 ± 9.5	49.9 ± 8.1	47.7 ± 13.5	45.5 ± 9.5	46.4 ± 9.9	50.2 ± 10.0	.5940	.5290	.7910
N3%	21.8 ± 8.1	18.8 ± 7.3	21.3 ± 10.6	17.5 ± 7.8	14.8 ± 5.7	12.3 ± 5.3	**.0262**	.4698	.9531
REM%	22.1 ± 5.2	20.3 ± 6.0	21.1 ± 5.7	22.6 ± 4.4	24.2 ± 5.2	21.9 ± 5.6	.3390	.9200	.8570
WASO	84.1 ± 69.6	48.2 ± 27.2	60.6 ± 40.1	77.7 ± 41.9	64.6 ± 44.7	118.4 ± 59.7	.0835	.1097	**.0245**
Arousal index	20.9 ± 5.2	25.1 ± 9.9	20.9 ± 5.3	27.9 ± 6.5	24.6 ± 8.8	33.1 ± 9.2	.2410	.6530	.2950
ODI	13.9 ± 4.6	14.3 ± 3.6	22.5 ± 5.4	23.2 ± 4.4	27.7 ± 5.5	30.5 ± 6.0	**<.001**	.1821	.6785
Mean SpO2	93.7 ± 2.1	94.1 ± 1.0	93.2 ± 2.1	93.0 ± 1.6	93.8 ± 1.6	93.1 ± 2.7	.1684	.8107	.9573
T < 90%	7.5 ± 24.0	1.0 ± 1.5	8.6 ± 14.7	7.2 ± 9.7	3.2 ± 4.0	9.1 ± 25.4	.0547	.9090	.9910

AHI = apnea–hypopnea index; BMI = body mass index; F = females; LMS = leg movements during sleep; M = males; ODI = oxygen desaturation index (≥ 3%); PLMS = periodic leg movements during sleep; SE = sleep efficiency; T < 90% = time spend with oxygen saturation below 90%; TST = total sleep time; WASO = wake after sleep onset in minutes.

*p-Values based on analysis of variance (age, BMI, N1%, N2%, N3%, REM%, arousal index), logistic regression (sex), nonparametric rank–based linear model (AHI, PLMS, SE, WASO, ODI, Mean SpO2, T<90%)

group × AHI group interaction (χ^2 = 0.83, p = .361). Also, the AHI was unrelated to the rLM-probability (χ^2 = 1.97, p = .160).

We found that rLMs were more frequent in nights with a higher arousal index (χ^2 = 14.54, p < .001). No other night factors were related to rLM-probability (TST, SE, ODI, SpO2 mean, SpO2 min, T < 90%; all p > .1).

In the univariate analyses, all local factors were significantly related to rLM-probability. The strongest effect was found for the presence of arousals at the end of respiratory events (χ^2 = 1507, p < .001). Considering only the effect of arousals, the predicted rLM-probability was 0.26 (95% confidence interval [CI]: 0.22–0.29) when no arousal was present at the end of the respiratory events and 0.64 (CI 0.60–0.69) when an arousal had been observed.

In addition, rLM-probability decreased over the course of the night (χ^2 = 22.5, p < .001) and was lower in REM sleep compared with NREM sleep (χ^2 = 143.0, p < .001). The probability for rLMs was also higher at the end of obstructive apneas compared with hypopneas (χ^2 = 149.3, p < .001) and increased with the length of the respiratory events (χ^2 = 55.1, p < .001). Finally, the presence of desaturations had a significant influence on rLM-probability (χ^2 = 120.2.1, p < .001) with rLMs being more likely the larger the desaturation.

In the multivariable model, all of the above factors with the exception of the arousal index remained significantly associated with rLM-probability. In a final step, we explored the interaction between the participant factor PLMS status and the significant local factors. As detailed in Table 2, the effect of time-of-night, sleep stage, duration of the respiratory event, and magnitude of the desaturation had a significantly different effect on rLM-probability in participants with high-PLMS compared with participants with low-PLMS. An overview of the direction and magnitude of the effects is given in Figure 2 which shows the predicted probabilities for all effects in the final model, keeping the values of the other factors at their mean value (the distribution of the unadjusted individual rLM probabilities is shown in Supplementary Figure S3). As in the multivariable model, rLM-probability was notably higher in the presence of arousals and at the end of apneas compared with hypopneas in both participants with high- and low-PLMS. Interestingly, rLM frequency significantly decreased over the course of the night in participants with high-PLMS, whereas it significantly increased in participants with low-PLMS (p < .05, post hoc tests). In both groups, rLM frequency was lower during REM as compared with NREM, but the reduction during REM was more pronounced in participants with PLMS (p < .05, post hoc tests). On the other hand, only in participants with low-PLMS were rLMs more likely the longer the respiratory event (p < .05), in participants with high-PLMS, the duration of the respiratory event had no effect on rLM frequency (p > .05). Finally, the presence and magnitude of the desaturations also differentially affected rLM-probability in high- and low-participants (Figure 2). In participants with low-PLMS, desaturations had only a minor effect since rLM-probability did not differ between events with no desaturation and those with desaturations up to 7% (p > .05 for all post hoc comparisons). In participants with high-PLMS, already a desaturation of 3% increased rLM-probability compared with the absence of a desaturation and rLM frequency increased linearly with increasing magnitude of the desaturation (p < .05 for all post hoc comparisons and linear trend test).

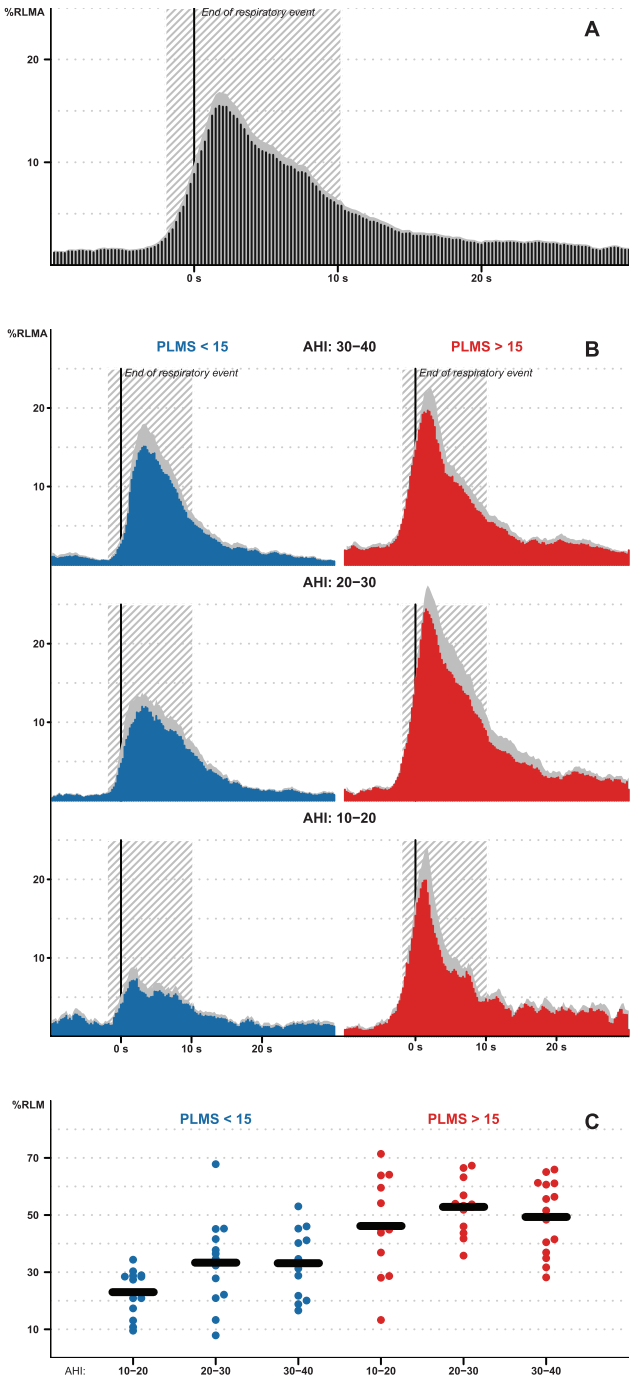

Figure 1. (A) Leg movement activity in 0.25-s bins for all participants at the end of respiratory events (0 s). The shaded background denotes the interval from –2.00 to 10.25 s, previously identified [21] as showing systematically increased leg movement activity (LMA). The *y*-axis units are %RLMA, the percentage of respiratory events with LMA present in the respective 0.25-s bin. Values are averaged %RLMA across participants, the gray band represents between-participant standard error of the mean (SEM). (B) LMA with the same specification as in (A), separately for each subgroup of participants. (C) Individual (colored points) and average (black line) %RLM, that is, the percentage of respiratory events that had at least one leg movement within –2.0 to 10.25 s of the end of the event.

Discussion

The two aims of the present study were to replicate the distribution of rLMs in patients with mild-to-moderate OSAS and to explore determining factors for rLMs. Concerning the first aim, the distribution reported here does indeed replicate the one already described in patients with moderate-to-severe OSAS [21]. Concerning the second aim, our results suggest that not all individuals with OSAS and not all respiratory events are equally likely to exhibit rLMs. Both sleep-related and respiratory-related factors have a significant effect on rLM-probability with the effect of some of them moderated by PLMS status of the individual. Independent of OSAS severity or PLMS status, rLMs are more frequent when arousals are present and when the respiratory event is an obstructive apnea. Independent of sleep-related and respiratory-related factors, rLMs are also more frequent in participants with frequent PLMS. In participants with high-PLMS, rLM-probability decreases over the course of the night and during REM sleep, whereas desaturations of any magnitude increase rLM-probability but the duration of the respiratory events has no effect. In participants with low-PLMS, rLM-probability increases over the course of the night and the decrease during REM sleep is still noticeable but significantly smaller than in participants with PLMS. Also, rLM-probability increases with the duration of respiratory events but only very large desaturations have any effect. This study therefore generated several novel findings which will be discussed in the following.

Definition of rLMs

We have recently proposed the first evidence-based definition of rLMs [21] in patients with moderate-to-severe OSAS. In that study, LMA was found to be systematically increased over an interval from 2.00 s before to 10.25 s after the end of the respiratory events. We show here that this distribution also applies to participants with mild-to-moderate OSAS, sampled from a large population-based study. In particular, the interval with increased LMA at the end of the respiratory events is nearly identical (–3.00 to 10.25 s vs. –2.00 to 10.25 s), and absolute differences in classification of rLMs are minimal. This study, therefore, provides an important replication in an independent sample and not only supports the proposed definition of rLM but extends it also to the range of mild-to-moderate OSAS. At the time of writing, the WASM 2016 standards [18] allow for the choice between two alternative definitions of rLMs with the recommended definition in patients with OSAS being the –2.00 to 10.25 s definition, the alternative being the former definition of –0.5 to 0.5 s. The results of the present study clearly support the choice of the recommended definition (–2.00 to 10.25 s) over the alternative one (–0.5 to 0.5 s) in patients with OSAS.

The finding that rLMs are more widely distributed than within 0.5 s around the end of the respiratory event has also been reported in two previous studies by Moore et al. [36] and Aritake et al. [37] Despite the important replication here, it remains, however, unclear why the distribution of rLM is so wide, considerably wider than previously assumed [19, 20]. It is not due to a multitude of LMs during this interval since our results show that in the majority of cases there is only a single LM observed at the end of the respiratory events, which is in agreement with our previous study [21]. A possible contribution may stem from the inherent imprecision in scoring start and end of LMs but particularly the end of the respiratory events. Here, we used the definition for the end of respiratory events as specified in the AASM rules [38] and manually re-scored the onset and end of all respiratory events to reduce this variability. There are very few studies that have described the exact

Table 2. Determinants of Respiratory Event–Associated Leg Movements, Final Mixed Effects Logistic Regression Model (for Details, See Methods)

Effect	χ^2	Df	P
PLMS group (high/low)	38.26	1	<.001
NREM vs. REM	85.37	1	<.001
Arousal (yes/no)	1154.76	1	<.001
Obstructive apnea vs. hypopnea	73.20	1	<.001
Desaturation (0, 3:7, >7%)	31.76	6	<.001
Time of night (hr)	5.24	1	<.001
Duration of respiratory event, s	36.65	1	<.001
PLMS group × NREM vs. REM	11.59	1	<.001
PLMS group × desaturation	20.07	6	.002
PLMS group × time of night	79.70	1	<.001
PLMS group × duration of respiratory event	15.95	1	<.001

Df = degree of freedom; PLMS = periodic leg movements during sleep.

timing of the various physiological events at the end of breathing events, and to the best of our knowledge, besides our own [21] none has described leg movements. Nevertheless, focusing on arousals at the end of respiratory events, Simms [34] et al. have described that the within participant average time from end of the event to the beginning of the arousal ranged from 0 to 4 s (across participant average 0.9 s) with a within participant standard deviation of 1.95 s. An even larger variability was already described by Younes [39] investigating arousal in relation to the respiratory events induced by dial-down of continuous positive airway pressure. Specifically, the author noted that the temporal relation between arousal and the airway opening was inconsistent between and within patients [35]. It seems therefore promising for future studies to explore whether alternative definitions of the end of respiratory events, for example, based on the abdominal and thoracic effort, and ideally based on signal analysis rather than manual scoring will yield a more concentrated distribution of rLMs and arousals.

Determinants of rLM: The Role of Arousal and Respiratory Event Type

A novel finding of the present study is that not all respiratory events were equally likely to be accompanied by an rLM. The single most influential factor is the presence of an arousal at the end of the event which increases rLM-probability from 26% to 64%. In addition, rLMs are more likely at the end of obstructive

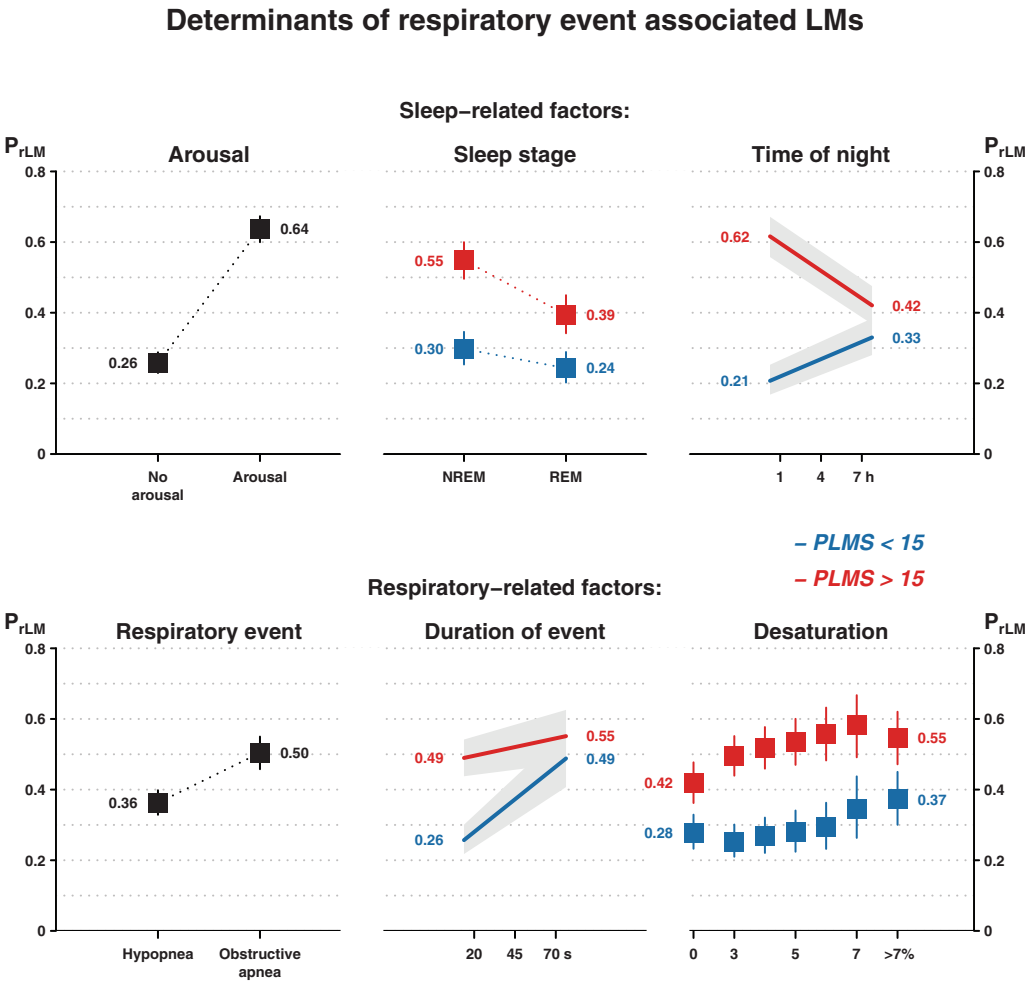

Figure 2. Effects display of the determinants of respiratory event–associated leg movements (rLMs) derived from logistic mixed regression (see Methods). The main outcome P_{rLM} refers to the probability to have one or more rLMs at the end of the respiratory event. Points or lines are predicted probabilities with 95% confidence intervals (gray background band for continuous variables, vertical lines for categorical variables) derived across the range of values for each explanatory variable, while keeping values of the other explanatory variables constant at their mean value. In the case of an interaction between PLMS status and another variable, blue symbols or line refers to participants with PLMS indices < 15 and red symbols or line to participants with PLMS indices > 15.

apneas when compared with hypopneas. So far it is unclear whether arousal and rLM are directly related to each other or whether they are indirectly linked by a common provoking mechanism. Future research is needed that specifically explores whether RERAs are affected by the same factors that affect rLM-probability and that compares the relationship between LM and arousal at the end of respiratory events and during sleep phases without respiratory events. It must be noted that the percentage of respiratory events that we find to be associated with an arousal (35%) is smaller than in previous studies [39–43]; however, these studies were based on a different definition of respiratory events, in particular hypopneas. Although not all respiratory events are associated with arousals, there are only inconsistent differences of respiratory event features that distinguish between events that end with an arousal and those that do not [39, 42, 44]. Interestingly, there is accumulated evidence that there are reliable and trait-like differences in respiratory arousal threshold in OSAS patients [40, 45]. Given the strong association between respiratory arousals and rLMs in this study, it could be expected that participants with a low arousal threshold and more arousals also have more frequent rLMs. A relation of rLMs to arousals and respiratory factors has previously been reported by Aritake et al. [37] in a study including 575 elderly men (mean age 77 years). In this study, rLMs were defined as leg movements with an onset between 5 s before to 5s after the end of respiratory events. Their measure, RRLM%, was derived by dividing the number of rLMs by the number of apneas and hypopneas. When the participant group was divided according to RRLM% quartiles, both the AHI, the obstructive apnea index, and the arousal index significantly increased across the four participant groups with the highest values in participants with the highest RRLM%. Our results support their finding concerning the relationship between arousals and rLM but we did not find a relationship between rLM-probability and AHI. Possible explanations for this discrepancy are the differences in the definition of rLM, the restricted AHI range in the present study, and the differences in sample characteristics and size.

Importantly, arousal and respiratory event type effects are still pronounced in the multivariable model when accounting for other factors such as the duration of the event and the magnitude of the oxygen desaturation. The result that rLM-probability is independent of the AHI but sensitive to arousal presence and respiratory event features could suggest individual rLM-probability as a possible additional and AHI-independent marker of OSAS severity. In fact, even among participants with very similar AHI (and ODI), rLM-probability varies widely which could signal that those with a higher rLM-probability may suffer from a more severe form, possibly with a stronger effect on sleep continuity or the cardiovascular system. Regarding the possible effect on the cardiovascular system, a previous study by Yang et al. [46] has shown that heart rate response at the end of respiratory events was significantly greater when a leg movement was present. Notably, this effect was independent of other features of the respiratory event.

rLMs and PLMS Status

On a group level, we have found a systematic effect of PLMS status on the propensity for rLMs. Participants with frequent PLMS outside of respiratory events are significantly more likely to have rLM at the end of a respiratory event. On average, in participants with high-PLMS, rLMs are observed in 50% of all respiratory events, whereas this percentage is 30% in participants with low-PLMS. Although this effect was strong and consistent on a group level, the distribution of individual rLM% (Figure 1C) also showed some overlap between the groups. It is important to stress that also participants with low-PLMS do have rLMs, albeit to a lower extent. This is in contrast to a previous study [24] that claimed that participants without frequent PLMS do not show rLM. This study, however, used a very narrow definition of rLM (± 0.5 s). As we have shown in our previous study [21] and confirmed here, rLMs are distributed more widely around the end of respiratory events than previously assumed. Since rLMs tend to be suppressed during the respiratory events [21] and these events have a minimum duration of 10 s, any rLM not classified as such will be very likely to fulfill the criteria for PLMS that require an intermovement interval of 5 [19] or 10 [18] s between LMs. By this mechanism, many participants with frequent, periodic respiratory events will be classified as having PLMS when not adequately accounting for the wide rLM distribution.

A further important and novel result is that rLMs "behave" differently in participants with high- vs. low-PLMS. In participants with high-PLMS, rLM-probability decreases over the course of the night and decreases strongly in REM sleep. These two features mirror those consistently shown for PLMS [47, 48] and therefore suggest that rLMs behave more PLMS-like in these participants. In low-PLMS participants, on the other hand, the duration of the respiratory events had strong and significant effect on rLM-probability. It must be remembered that in both groups, rLMs were more probably at the end of obstructive apneas compared with hypopneas and in the presence of arousals. Together these results suggest that rLM-probability is influenced by sleep-related and respiratory-related factors in both participants with high- and low-PLMS, but the specific factors differ in strength and direction between the groups.

It is tempting to speculate that in participants with high-PLMS, rLMs are "real" PLMS, possibly paced by the respiratory events. However, respiratory features also affect rLMs in participants with high-PLMS. This concerns the increase with obstructive apneas but in particular the greater sensitivity of rLM-probability to the magnitude of desaturations in participants with high-PLMS. Hypoxia has been reported to be involved in the RLS [49]; however, none of the participants in this study had RLS. It must be noted that we used an ad hoc definition for the assessment of desaturations at the end of apneas, which although based on the empirical distribution might nevertheless have influenced results, and therefore, this finding should be confirmed in future studies. The finding that rLMs in participants with OSAS with high-PLMS share similarities with PLMS and are influenced by both sleep-related and respiratory-related factors points to the possibility that in these participants, there are more than one type of rLM: PLMS-like periodic rLM and respiratory-related rLM. Future studies should therefore investigate whether there are any features of the leg movement themselves that could distinguish between the two types.

A stronger case could be made for rLM not being PLMS in participants with low-PLMS. Although this seems tautological at first glance, it must be remembered that rLMs in participants with low-PLMS may appear as periodic when the respiratory events themselves are periodic. Indeed, previous studies have found periodicities of the respiratory events with cycle lengths of around 40 s [50, 51] at the upper range of the typical PLMS

intermovement interval [48]; these participants will therefore appear to have frequent PLMS when the association of the leg movements to the respiratory events is not considered. Our results, however, suggest that these rLMs are purely respiratory related and do not share similarities to PLMS.

Strengths and Limitations

We consider the well-defined selection of participants as one of the strengths of the study. By determining PLMS status based on sleep periods free of respiratory events and supplementing the PLMS index by the periodicity index and the visual inspection of individual intermovement interval distributions, we have increased our confidence in the PLMS status of the participants. Because participants were also well matched for OSAS severity, differences between groups with and without PLMS can, in our opinion, be reasonably attributed to PLMS status. At the same time, this procedure limits the generalizability of our findings to participants without well-defined PLMS status. This applies in particular to patients with severe OSAS who will not have any sleep periods without respiratory events that allow for a reliable determination of PLMS status. In addition, by selecting participants according to PLMS status, we have inadvertently also selected for leg movement frequency as participants with high-PLMS had more periodic but also more overall leg movements than participants without PLMS. It remains to be seen whether there exists a group of participants with OSAS with a high number of nonperiodic leg movements not related to respiratory events; for now the applicability of our findings in this group is questionable. Furthermore, we have restricted the analysis to hypopneas and obstructive apneas and the characteristics of rLM near central apneas or RERAs remain unaddressed. The generalization of our findings is further limited to middle-aged and elderly participants since the HypnoLaus study included only participants between 40 and 80 years of age at the time of the sleep recording. The sample size in the current study was limited by the need to manually control all LM and respiratory events. Although this constitutes a strength of study by increasing the precision of our results, in the case of adjusting the beginning and end of respiratory events, this can also be seen as a limitation due to the inherent imprecision of human, visual scoring [52].

The development of automatic algorithms that take more than one signal into account may be helpful to increase precision and consistency of respiratory event scoring. It must be noted, however, that the identification of rLM will be less susceptible to scoring imprecision when it is based on a wider interval.

A further limitation of the present study is the ad hoc definition of the association of respiratory events to arousals and desaturations. Although we based the used definition on the empirical distribution of these events in the present study, we would have preferred to utilize an established, preferable data-based, international standard. However, we were unable to find such a standard.

In summary, we confirm the time distribution of rLMs in participants with mild-to-moderate OSAS (–2.0 to 10.25 s) and show that rLM-probability is jointly influenced by sleep-related and respiratory-related factors that suggest individual rLM-probability as a potential AHI-independent marker and/or moderator of OSAS severity. Sleep- and respiratory-related factors act partly different in participants with high- and low-PLMS, and in the former group- participants with OSAS with PLMS- point to the possibility that there are two types of rLMs.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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None declared.

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