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Sleep-related leg movements in obstructive sleep apnea: definitions, determinants, and clinical consequences

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ABSTRACT

Study objectives: To investigate (1) the effect of different scoring rules on leg movement (LM) classification in patients with obstructive sleep apnea (OSA), (2) determinants of respiratory event related leg movements (rLM), and (3) to relate LM parameters to clinical outcomes.

Methods: (1) LM classification was compared between the WASM 2006 and the WASM 2016 rules in 336 participants with $AHI \geq 5$; (2) determinants and features of rLM were investigated with logistic mixed regression in 172 participants with $AHI \geq 10$ and $RDI \geq 15$, and (3) LM parameters were compared for patients with and without cardiovascular events and related to CPAP adherence.

Results: WASM-2016 scoring significantly reduced PLMS frequency in OSA participants even when only considering the new periodicity criteria. Probability of rLM was strongly increased when respiratory events ended with an arousal, but rLM probability was lower for hypopneas and RERAs than for obstructive apneas. In participants with frequent non-respiratory PLMS, rLM were more frequent and behaved more PLMS-like. In participants without PLMS, rLM probability mostly depended on respiratory event features. LM parameters were neither related to cardiovascular event risk nor to CPAP-adherence.

Conclusions: It is likely that the PLMS frequency in OSA populations has been previously overestimated. Our results suggest that there are two types of rLM, true periodic ones that happen to synchronize with the respiratory events, and periodic appearing but respiratory driven LM, and that the presence of non-respiratory PLMS is instrumental in distinguishing between the two.

KEY WORDS

periodic leg movements, obstructive sleep apnea, arousal, respiratory event related leg movements, sleep, CPAP, polysomnography, cardiovascular disease

STATEMENT OF SIGNIFICANCE

Applying the newest WASM 2016 to the classification of LM in OSA patients strongly suggests that both the frequency of PLMS and the frequency of people with frequent PLMS and OSA has been overestimated, possibly considerably so. Our results further argue that people with PLMS independent of respiratory events will have frequent respiratory event related LM that are most likely *true* periodic LM and which are expected to persist with CPAP treatment. In people without PLMS, respiratory event related LM are driven by respiratory factors and could therefore signal a more severe form of this disorder. Both, non-respiratory PLMS frequency and rLM probability are promising clinical stratification factors in OSA.

INTRODUCTION

Leg movements (LM) are frequent during sleep and several types of sleep-related LM can be distinguished.¹ Major clinical interest has focused on periodic leg movements, i.e. stereotyped and repetitive LM that typically occur every 20 to 40 sec and may include hundreds of LM in a single night.² Frequent periodic leg movements during sleep (PLMS) are found in the majority of patients with restless legs syndrome,^{2,3} but also in patients with other sleep disorders,⁴⁻⁹ major medical or neurological disorders such as chronic heart failure^{10,11} or Parkinson's disease and even in 25% of the general population.¹²

Currently there are two sets of rules to define periodic leg movements: the American Academy of Sleep Medicine (AASM) rules¹³ - The AASM Manual for the Scoring of Sleep and Associated Events, version 2.5 – and the WASM 2016 rules¹⁴, created by the World Association of Sleep Medicine (WASM) together with the International and the European Restless Legs Syndrome Study Groups (IRLSSG and EURLSSG). The WASM 2016 rules¹⁴ are a major revision of the WASM 2006¹⁵ rules especially with regard to the criteria that define periodicity. The AASM rules¹³, although far from identical to the WASM 2006 rules, are nevertheless more similar to the 2006 rule set than the 2016 revision.

Major changes, listed in the method part (section: leg movement scoring), included new rules specifying several new conditions that end a possible PLM series: any LM with an inter-movement interval below 10 s – the new lower limit of the PLM inter-movement interval – and so-called non-candidate LM, i.e. long unilateral LM (> 10 s) or bilateral LM that are long (> 15 s), contain one or more unilateral LM (> 10s) or contain more than 4 LM. The major motivation for these changes was to prevent the possibility that merely unspecific increased LM result in increased PLM. This had been a concern with the WASM 2006 rules, which in certain situations acted as a “pattern extractor”, ignoring all non-fitting LM, and where the PLM index then reflected the number of LM rather

than the true periodic ones.¹⁶ It must be noted that these rule changes have only minor effects on the classification of true periodic LM, such as in patients with RLS,^{16,17} but their effect is unknown for other groups of sleep disorders. This pertains especially to people with obstructive sleep apnea (OSA), since a further major change concerned the definition of respiratory event related LM (rLM). These had been defined as LM within the interval of ± 0.5 s around the end of the respiratory event¹⁵. Recent research, however, has shown that in people with OSA, LM are systematically increased over a much wider interval, i.e. from 2 s before to 10.25 s after the end of the respiratory event¹⁸, a finding which has been recently replicated in an independent sample.¹⁹ Given these major rule changes, the first aim of the present study was to compare the classification of sleep-related LM in a large population of patients with OSA and to trace any systematic differences by comparing the classifications based on the 2006 rules to the 2016 rules with either the new rLM definition, the 2006 rLM definition, or ignoring rLM status altogether.

A further challenge to the evaluation of LM in OSA subjects is that many respiratory events appear in series^{20,21} and therefore the accompanying LM – the rLM – appear periodic, making the distinction between *true* periodic LM and periodic appearing rLM particularly difficult. Complicating matters further, we have recently shown that rLM are more frequent in participants with OSA and frequent non-respiratory event associated PLMS (nrPLMS index > 15/h) and that in these subjects the rLM seem to behave more PLMS-like, i.e. their frequency decreases over the course of the night and is decreased during REM sleep. On the other hand, in subjects without nrPLMS, the rLM were mostly affected by respiratory factors, such as the duration of the respiratory event. These intriguing results suggest that there might be two types of rLM: true periodic ones possibly temporally displaced or paced by the respiratory events, and purely respiratory related ones, possibly AHI-independent markers of OSA severity, signaling the presence of frequent arousals, a higher proportion of apneas, and respiratory events of longer duration. The second aim of the present study was therefore to replicate these sleep and

respiratory-related factors as important determinants of rLM probability including the differential regulation in participants with vs. without frequent PLMS.

Lastly, we also aimed to address a possible functional relationship between sleep-related LM and clinically meaningful, prospective outcomes in people with OSA. Utilizing health information collected over a 5-year follow-up²² period we explored whether sleep- or leg movement parameters at baseline were related to the risk for first-ever cardiovascular events and CPAP adherence.

In summary, the present study aimed to investigate the effect of different scoring rules on LM classification in patients with OSA, tried to replicate and extend recent findings regarding the complex and differential regulation of rLM in participants with OSA with and without frequent PLMS, and address a possible functional role of LM parameters by relating these to the development of first ever cardiovascular events and CPAP adherence over a 5-year follow-up period.

METHODS

Participants and procedures

From all ambulatory and clinical polysomnographies recorded between 2009 and 2010 at the Center for Sleep and Wake Disorders (Haaglanden Medisch Centrum, The Hague, The Netherlands, $n = 2820$), we selected recordings from all patients older than 18 years and with a respiratory disturbance index (RDI) ≥ 5 ($n = 1168$). A total of 58 recordings were excluded because of repeated recordings in the same patients ($n = 40$) or recording during OSA treatment (CPAP: $n = 15$, mandibular advancement device: $n = 3$). All remaining 1110 patients received a questionnaire by mail. The study was conducted with the approval of the local ethics review board (METC 15-084).²²

Of the 1110 patients, 554 responded (50%). Three patients were subsequently excluded, because it was not possible to retrieve their original raw data. From all participants with valid follow-up data ($n = 551$), we selected patients without cardiovascular events at baseline ($n = 483$), a total sleep time of at least 4 hours ($n = 470$), an AHI equal or higher than 5 ($n = 409$), and with predominantly obstructive respiratory events (% of central events $< 50\%$, $n = 388$). In addition, we also excluded participants with outlying high AHI values ($75\%+$ interquartile range (IQR): > 51 , $n = 29$), outlying leg movement indices during sleep (LMI, $75\%+$ IQR: > 97 , $n = 16$), as well as 7 participants with significant artefacts in leg recordings. The final sample included 336 participants and is described in Table 1.

In this sample of 336 participants, we investigated the difference between the WASM 2006 and WASM 2016¹⁴ rules regarding the scoring and classification of leg movements. Concerning the description of features and determinants of respiratory event associated leg movements (rLM), we then selected participants with a minimum of respiratory events, i.e. an AHI of at least 10 and an RDI of at least 15 ($n = 172$). In this sample, we also explored the association between leg movement parameters and the occurrence of a new cardiovascular event during follow-up. Finally, in the group of subjects who had started CPAP treatment ($n = 101$), we investigated whether leg movement parameters were related to treatment adherence, defined as good adherence ($n = 75$, use of at least 4 h/night for at least 5 days/week) or no/poor adherence ($n = 26$, CPAP use stopped or < 4 h/night, or < 5 days/week).

Questionnaire

The mailed questionnaire included general questions about current and past medical history, in particular, the cardiovascular history and the occurrence of cardiovascular events (CVE). A cardiovascular event was defined as a transient ischemic attack (TIA), stroke (ischemic or hemorrhagic) or myocardial infarction. For all patients who indicated a first-ever cardiovascular event ($n=28$), the electronic patient record system was checked to confirm the occurrence and

nature of the cardiovascular event. Two patients without an electronic patient record available were contacted by phone to confirm the occurrence of a new CVE.

The second part of the questionnaire asked about past and current OSA treatment. Patients indicated the mode of treatment (positional therapy, oral devices, CPAP, surgery) as well as the time interval they used the respective treatment. Patients who indicated that they were currently using CPAP treatment were asked about frequency (nights/week) and duration (hours/night) of use. Electronic health records were checked for all patients who indicated that they stopped CPAP treatment (n = 51) and patients who stopped within the last 12 months (n = 24) were contacted by phone to confirm treatment cessation, with adherence status subsequently changed in 3 patients. CPAP use for 4 or more hours per night and on 5 or more nights per week was classified as good adherence, while less frequent use or cessation of CPAP treatment was classified as no/poor adherence.

Polysomnography

Polysomnography (PSG) was either performed as a home sleep study with a 24-hour recording or in the sleep lab with a standard 8-hour recording. Recording set-up and montages followed the standard procedures from the AASM 2007 guidelines²³ and included six electroencephalogram (EEG) channels, electrooculography (EOG), electromyogram (EMG) of the sub-mental muscles, EMG of the right and left anterior tibial muscles, once channel electrocardiogram (ECG), as well as airflow, thoracic and abdominal respiratory effort and oxygen saturation. Signals were acquired using SOMNOscreenTM plus devices (SOMNOmedics, Germany) and digitized using the EDF+ format.²⁴

Scoring procedures

Sleep was manually scored according to the AASM 2007²³ criteria with the exception of EEG arousal events, which were detected with an automatic detection program, which had been

validated against visual scoring in three large data sets with adequate accuracy (total $n = 2768$, sensitivity: 0.52-0.58, specificity: 0.97-0.98).^{25,26} Respiratory events were manually scored according to AASM 2007 guidelines²³. Specifically, apneas were scored when the respiratory signal peak dropped $\geq 90\%$ of baseline values lasting for ≥ 10 seconds. Apneas were classified as obstructive when there was a continued or increased inspiratory effort, and as central when there was an absent inspiratory effort. Mixed apneas were identified when there was an absent inspiratory effort in the initial portion of the event, followed by a resumption of inspiratory effort in the second part. Hypopneas were scored when the nasal pressure signal excursions dropped by $\geq 30\%$ of baseline during a period ≥ 10 seconds, and the event was followed by a $\geq 3\%$ oxygen desaturation or an arousal.

Respiratory effort-related arousals (RERA) were scored when a period of ≥ 10 seconds was identified characterized by increased respiratory effort or flattening of the inspiratory portion of the nasal pressure leading to an arousal, and the period did not meet the criteria for apnea or hypopnea.

Leg movement scoring

All leg movements (LM) were detected by an automated leg movement detection program that had been validated against manual scoring with sensitivities around 0.92 and specificity of 1²⁷ and subsequently had been adapted to the WASM 2016 rules²⁸.

The new WASM 2016¹⁴ rules introduced the distinction between leg movements (LM) and candidate LM (CLM) with LM being all LM with a duration of 0.5 s or longer. Leg movements that are longer than 10 s are not candidate LM (nonCLM) and are not evaluated for periodicity but can end a PLM series. Within this group of LM, CLM are those that are either unilateral LM between 0.5 and 10 s or bilateral LM with total duration equal or below 15 s, not containing more than 4 LM, and not containing any LM with duration longer than 10 s. LMs that are not CLM are called nonCLM. Only CLM are evaluated for periodicity but nonCLM do end a

PLM series. PLM series are also ended with any LM occurring within 10 s of the last CLM. In addition, the inter-movement interval (IMI) between CLM that constitute a PLM series is between 10 and 90 s, and no longer 5 to 90 s as in the WASM 2006 rules. A further major change concerned the definition of rLM: in the 2006 rules, only LM that occurred between ± 0.5 s around the end of respiratory events were considered rLM and excluded from any periodicity evaluation. In the 2016 rules, the preferred definition is to consider rLM as occurring within 2 s before to 10.25 s after the end of the respiratory event. Although rLM are disregarded when computing the standard PLMS index (nrPLMSI), there is also the option to include all CLM – respiratory event associated (rCLM) and not respiratory event associated (nrCLM) – in the PLMS index (PLMSI).

To explore the effect of these rule changes, we have systematically compared 4 different sets of rules (for details see Table 2):

- (1) the WASM 2006 rules with PLMS defined by inter-movement intervals (IMI) of 5- 90 s and rLM defined within the interval of ± 0.5 s around the end of the respiratory event
- (2) the WASM 2016 rules with PLMS defined by IMIs of 10 – 90 s, PLMS series ended with IMIs < 10 s, and rLM defined within the interval of ± 0.5 s around the end of the respiratory event
- (3) the WASM 2016 rules as in (2) but with rLM defined within the interval of -2 s to +10.25 s around the end of the respiratory event;
- (4) the WASM 2016 rules as in (2) but without defining rLM.

The scoring of leg movements, i.e. the post-processing of the detected LM with classification as periodic, isolated, or respiratory event associated LM, used modified and adapted versions of the freely available PLMS scoring programs for EDF+ files: PLMScoRe²⁹ and the Polyman Report Generator³⁰.

Determinants and features of respiratory event associated leg movements

We also investigated possible determinants of rLM with a methodology that closely followed the approach of Fulda, Heinzer, and Haba-Rubio.¹⁹ In short, we modeled the probability of rLMs with mixed effects logistic regression with a random effect for each participant (see statistical analysis). As possible determinants we investigated the same factors that had already been shown to determine rLM probability in a previous study:¹⁹ the presence of arousals (yes/no) and/or oxygen desaturations ($\geq 3\%$, yes/no) at the end of the respiratory event, the sleep stage (N1, N2, REM), the type of respiratory event (respiratory effort related arousal (RERA), hypopnea, obstructive apnea), duration of the respiratory event (in seconds), time of night (in full hours from sleep onset). In addition, we also explored whether PLMS status (non-respiratory PLMS index $>$ vs. $<$ 15/h) had a main effect or interacted with any of the above factors. The presence of an arousal at the end of a respiratory event was determined when the arousal overlapped with the end of the respiratory event or started ≤ 3 s after the end of the event; the presence of an oxygen desaturation ($\geq 3\%$) was assumed when the oxygen desaturation overlapped with the end of the event or started ≤ 7 s after the end of the event.¹⁹

From a total of 30608 respiratory events during sleep, we included 26581 (86.8%) events after excluding the infrequent respiratory events that occurred during N3 sleep ($n = 1166$, 3.8%) or were central ($n = 1638$, 5.6%), mixed ($n = 834$, 2.8%), or undefined apneas ($n = 117$, 0.4%), as well as those events where the first rLM was not a candidate leg movements (CLM), i.e. a unilateral LM longer than 10 s or bilateral LM with more than 4 unilateral LM, one or more non-CLM, or total length above 15 s ($n = 272$, 1.0%).

Statistical analyses

We conducted three sets of analyses. Differences in leg movement parameters between the different scoring rules were explored with the Friedman test, Wilcoxon test, and the Chi² test, as appropriate. Determinants of rLM-probability were investigated with logistic mixed effect modeling with a random effect for each participant and fixed effects for differences between sleep stages, the types of respiratory events, the presence or absence of arousals and/or oxygen desaturations, and subjects with high (> 15) or low (< 15) PLMS index, as well as for the association to OSA severity (AHI). Features of rLM were explored with linear (duration of LM) or logistic (uni- vs. bilateral LM) mixed models with a random effect for each participant and fixed effects for the differences between rLM and non-rLM, as well as rLM and PLM. Differences between participants with vs. without a new cardiovascular event or between patients with good vs. no/poor CPAP adherence were investigated using Mann-Whitney U tests or Chi² tests, as appropriate. Variables that showed significant between-group differences were then jointly entered into a logistic regression model. Multiple testing issues were addressed by Bonferroni correction and/or Tukey post-hoc tests.

RESULTS

We included 336 participants with predominantly mild to moderate OSA and the expected characteristics for these patients, i.e. mostly middle-aged (53.8 ± 10.4 years), male (67%), with increased BMI (29.6 ± 6.0 kg/m²) and a high prevalence of arterial hypertension (65%, Table 1).

Table 1. Description of participants.

	n	Sample n = 336 mean \pm SD
Age, years	336	53.8 \pm 10.4
Male, (n, %)	336	226 (67.3%)
Body mass index (BMI, kg/m ²)	284	29.6 \pm 6.0
Arterial hypertension, (n, %)	294	191 (65.0%)
Diabetes mellitus, (n, %)	294	36 (12.2%)
Smoking, (n, %)	267	50 (22.1%)
Time in bed (TIB), min	336	465.4 \pm 93.0
Sleep period time (SPT), min	336	445.7 \pm 64.6
Total sleep time (TST), min	336	396.8 \pm 63.2
Sleep efficiency (SE), %	336	86.1 \pm 9.9
Sleep onset latency (SOL), min, median [IQR]	336	6.48 [10.30]
REM latency, min, median [IQR]	336	114.5 [92.3]
N1, % of TST	336	12.2 \pm 6.8
N2, % of TST	336	54.1 \pm 9.4
N3, % of TST	336	15.0 \pm 8.6
REM, % of TST	336	18.7 \pm 5.8
Wake after sleep onset (WASO), min	336	48.8 \pm 38.5
Arousal index (Ari) , n/hour of sleep	336	15.4 \pm 8.6
Apnea-hypopnea index (AHI), n/hour of sleep	336	16.7 \pm 9.7
Oxygen desaturation index, n/hour of sleep	336	21.1 \pm 13.2

Effect of PLMs scoring rules on sleep leg movement parameters

Table 2 describes the effect of the different scoring rules on the resulting leg movement parameters. We have compared leg movement parameters for the WASM 2006 rules (rule no. 1) with the WASM 2016 rules and the following variations: rLM defined as between ± 0.5 s (rule no. 2), between -2 s and +10.25 s (rule no. 3), and rLM status ignored (rule no. 4). As detailed in Table 2, differences between the four rules for all leg movement parameters – although at times numerically small – were all statistically significant due to the fact that any difference was highly systematic, i.e. in the same direction for all participants.

There was only a small difference in the number of LM/CLM between the rules (mean difference: 0.67, range: 0-6). However, the PLMS indices showed substantial variation with a mean decrease of 5.5 (0-27) when comparing rule 1 to rule 2, i.e. the WASM 2006 and the WASM 2016 rules with the same criteria for rLM. Within the possibilities of the WASM 2016 rules, changing the criterion for rLM (rule 3 vs. rule 2) resulted in a mean reduction of 5 rLM/h of sleep (range: 0-34) and 3 PLMS/h of sleep (0-27). In terms of classification of subjects regarding a PLMS index below or above 15, according to the WASM 2006 rules, 46.7% of the participants had an elevated PLMS index. All WASM 2016 rules, regardless of their treatment of rLM, resulted in a significantly smaller portion of participants with PLMS > 15, which was highest when disregarding rLM altogether (34.5%), intermediate with the ± 0.5 s definition (32.4%) and lowest with the -2 to 10.25 s definition (26.2%), although only the difference between rules 4 and 2 was statistically significant ($p = 0.0235$).

Table 2. Comparison of leg movement parameters for different sets of criteria in participants with $AHI \geq 5$.

Rule No.:	1	2	3	4	
<i>WASM rule set:</i>	2006	2016	2016	2016	
<i>Unilateral LM/CLM:</i>	0.5-10s	0.5-10s	0.5-10s	0.5-10s	
<i>Bilateral LM/CLM:</i>	offset-onset < 0.5 s	offset-onset < 0.5 s			
		max 4 CLM, no LM > 10 s, max total duration \leq 15s			
<i>LM > 10 s:</i>	ignored	nonCLM: end PLM series			
<i>Inter-movement interval (IMI):</i>	5-90 s	10-90 s	10-90 s	10-90 s	
<i>IMI < 5/10s ends PLM series:</i>	no	yes	yes	yes	
<i>rLM definition:</i>	± 0.5 s	± 0.5 s	-2/+10.25 s	-	Between-group
<i>rLM excluded from PLM evaluation:</i>	yes	yes	yes	no	comparison, p^*
LM/CLM, n/hour of sleep	32.1 ± 21.6^a		31.5 ± 21.4^b		< 0.001
unilateral LM/CLM, n/hour of sleep	23.4 ± 16.8^a		22.8 ± 16.7^b		< 0.001
bilateral LM/CLM, n/hour of sleep	8.7 ± 7.8^a		8.7 ± 7.7^b		< 0.001
nonCLM, n/hour of sleep			0.75 ± 0.82		
rLM/rCLM, n/hour of sleep	1.1 ± 1.8^a	1.1 ± 1.9^b	6.0 ± 7.2^c	-	< 0.001
LM/CLM evaluated for periodicity, n/hour of sleep	31.1 ± 20.6^a	30.4 ± 20.4^b	24.8 ± 18.2^c	31.5 ± 21.4^a	< 0.001
PLM, n/hour of sleep	19.3 ± 18.4^a	13.8 ± 15.8^b	10.9 ± 14.6^c	14.6 ± 16.6^d	< 0.001
PI	0.34 ± 0.24^a	0.34 ± 24^b	0.30 ± 0.24^c	0.34 ± 0.24^d	< 0.001
PLM \geq 15/h sleep	157 (46.7%) ^a	109 (32.4%) ^b	88 (26.2%) ^b	116 (34.5%) ^b	< 0.001

* Friedman test or χ^2 test as appropriate; for group means that do not share the same superscript there is a statistically significant difference (paired Wilcoxon test, Bonferroni-corrected). CLM: candidate leg movement; LM: leg movement; nonCLM: non-candidate leg movement; PI: periodicity index; PLM: periodic leg movements; rLM: respiratory event associated leg movement

Determinants and features of respiratory event associated leg movements

To describe determinants and features of rLM, we selected 172 participants with a minimum number of respiratory events, i.e. an AHI equal or above 10 and an RDI equal or above 15. In these, rLM were identified according to the WASM 2016 rules.¹⁴

Concerning the features of rLM, we found that rLM were more often bilateral LM (in 31.0% of cases, 95% confidence interval (CI): 28.6 – 33.6%) when compared to all other (23.5%, 21.5 – 25.6%) or separately to periodic (21.3%, 19.4 – 23.4%) and isolated LM during sleep (24.6%, 22.5 – 26.7%, all p s < 0.001, post-hoc Tukey tests). Similarly, rLM were slightly but significantly longer (2.26 s, CI: 2.19 – 2.34) compared to all other (1.99, 1.92 – 2.07) or periodic (1.99, 1.91 – 2.06) or isolated LM (2.00, 1.93 – 2.07, all p s < 0.001, post-hoc Tukey tests)

The overall probability for one or more rLM within -2 s to +10.25 s at the end of respiratory events was 29.2% (95% CI: 26.1 - 32.6%, derived from the logistic mixed model). Univariate analyses showed that rLM-probability was lower during REM sleep (24.8%) than both N1 (32.1%) and N2 (30.4%, post-hoc Tukey tests p < 0.001) disregarding the rare respiratory events during N3 (3.7%±6.4%). The rLM-probability was higher for obstructive apneas (31.6%) compared to both hypopneas (25.9%, post-hoc Tukey tests p < 0.001) and RERAs (25.9%, p < 0.001), which did not differ from each other (disregarding the infrequent mixed (2:2 ± 4:2%) and central apneas (5:3 ± 8:0%) as well as unclassified apneas (<1%)). Probability of an rLM was significantly increased when there was an arousal at the end of the respiratory event (52.9% vs. 22.7%, $\chi^2 = 1407$, p < 0.001), and it was also higher when an oxygen desaturation was associated with the event (30.8% vs. 26.3%, $\chi^2 = 41$, p < 0.001). Overall, rLM probability increased with the duration of the respiratory event ($\chi^2 = 201$, p < 0.001) and decreased over the course of the night ($\chi^2 = 6$, $p = 0.017$).

About 24% ($n = 42$) of the participants had a non-respiratory (nr) PLMS index above 15 according to the WASM 2016 rules (rule no. 3 in table 2) and in these participants rLM-

probability was significantly higher (43.8% vs. 25.4%, $\chi^2 = 22$, $p < 0.001$,). Apnea-hypopnea frequency had no influence on rLM probability neither as a categorical variable with three (AHI 10-20 vs. 20-30 vs. ≥ 30 ; $\chi^2 = 0.3$, $p = 0.842$) or four categories (AHI: 10-20; 20-30; 30-40; ≥ 40 , $\chi^2 = 0.4$, $p = 0.947$) nor as a linear variable ($\chi^2 = 0.6$, $p = 0.448$).

In the multivariate analysis that included all significant univariate effects and explored their possible interaction with PLMS status, all effects remained significant, but for several, the effect was different for participants with high vs. low nrPLMS frequency (Figure 1). Only the presence of an arousal or an oxygen desaturation at the end of the respiratory event had a uniform large (arousal, $\chi^2 = 1203$, $p < 0.001$) or small (oxygen desaturation, $\chi^2 = 8$, $p = 0.005$) effect on rLM probability in all participants. There was a significant interaction between sleep stage and PLMS status ($\chi^2 = 23$, $p < 0.001$) with the reduced rLM probability during REM sleep being more pronounced in participants with nrPLMS (Figure 1). In addition, rLM probability decreased over the course of the night in PLMS subjects while it increased in nonPLMS subjects ($\chi^2 = 88$, $p < 0.001$). On the other hand, rLM probability increased with the duration of the respiratory event to a larger extent in nonPLMS subjects ($\chi^2 = 12$, $p < 0.001$) and also the increase in rLM probability with obstructive apneas vs. hypopneas or RERAs was only seen in the nonPLMS group ($\chi^2 = 25$, $p < 0.001$).

Determinants of respiratory event associated LM

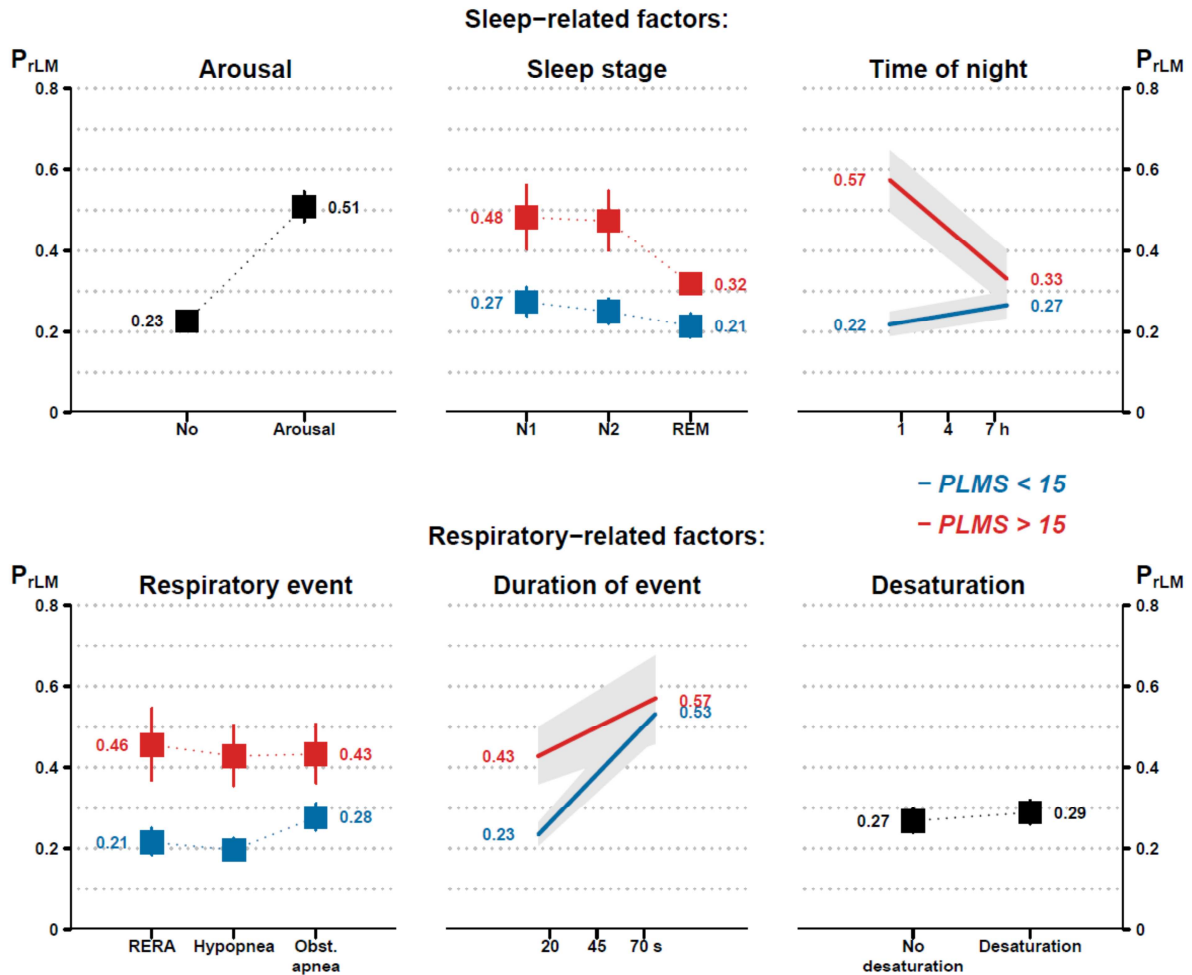


Figure 1. Effects display of the determinants of respiratory event associated leg movements (rLMs) derived from logistic mixed regression (see Methods). The main outcome PrLM refers to the probability to have one or more rLMs at the end of the respiratory event (- 2s to +10.25 s). Points and vertical lines are predicted probabilities with 95% confidence intervals derived for the different values for each explanatory variable while keeping values of the other explanatory variables constant at their mean value. Blue symbols/lines depict participants with PLMS < 15/h, red symbols/lines denote participants with PLMS > 15/h. (PLMS: periodic leg movements during sleep; RERA: respiratory effort related arousals)

Sleep-related leg movements and new cardiovascular events

During the follow-up period, 14 participants had one or more new cardiovascular events. There were no statistically significant differences between participants with or without ($n = 158$) a new cardiovascular event in demographics, sleep, leg, or respiratory parameters (all $ps > 0.15$, Table S1). With only 14 participants, there were obvious concerns regarding statistical power and we therefore also calculated effect sizes, which were Cohen's d for continuous variables and odds ratios for categorical variables. There were no effect sizes larger than 0.4 or with odds ratios above 1.2, supporting the absence of significant differences between groups.

Sleep-related leg movements and CPAP adherence

CPAP treatment had been offered to 101 participants and at follow-up, 74% ($n = 75$) reported to use CPAP for 4 hours or longer per night and on 5 or more days per week and this was classified as "good adherence". In contrast, 26 (26%) participants either did no longer use CPAP or used it less than 4 hours/nights or less than 5 days/week, which was denoted as "no/poor adherence".

In the group of patients with no/poor adherence, there was a higher prevalence of diabetes mellitus (33.3%) compared to patients with good adherence (7.4%, $p = 0.005$). No other significant differences were found in demographic, sleep, leg, or respiratory parameters (Table S2).

DISCUSSION

This study has generated three main results: first, we have shown that the application of the new WASM 2016 scoring rules¹⁴ substantially impacts the classification of sleep-related leg movements in OSA patients. This is due to both the newly introduced periodicity criteria and the change in the definition of rLM. Second, RERAs are just as likely as hypopneas to be accompanied by an rLM and both are less likely than obstructive sleep apneas, a finding not previously reported. In addition, rLM are more frequent in participants with OSA and frequent non-respiratory PLMS and in these participants behave more PLMS-like. In fact, both sleep-related and respiratory-related parameters influence rLM probability but these have partly different and/or opposing effects in participants with compared to without nrPLMS. These findings are an important replication and extension of previous results.¹⁹ Third, we have not been able to relate sleep leg movement parameters to the occurrence of new cardiovascular events or to CPAP adherence, likely due to methodological shortcomings.

The new WASM 2016 rules reduce periodic leg movements in people with OSA

The new WASM 2016 rules¹⁴ have modified several criteria and introduced new criteria, based on empirical evidence^{18,31-35}, with the aim to better distinguish between true periodic LM and unspecific increased leg movement activity.³⁶ Importantly, these rule changes have only minor effect on the classification of true periodic LM, such as in patients with RLS^{16,17}. However, besides the periodicity criteria also the criteria to define rLM have been changed, and it was unknown whether the two major modifications would have additive and/or synergistic effects in people with OSA. We find that the new periodicity criteria substantially reduce PLMS frequency, even when respiratory criteria are unchanged or even ignored. In participants with OSA, therefore, a non-negligible proportion of LM does not fulfil stricter periodicity criteria. Changing the respiratory criteria further reduces PLMS, but to a lesser extent. As in previous studies,^{18,19,37,38} around half of the participants with OSA (47%) had a PLMS index above 15,

when using the WASM 2006 rules¹⁵. This proportion is nearly halved (26 %) when considering the strictest definition, the WASM 2016 with the revised respiratory criterion. It is also important to note the difference in rLM frequency when changing the rLM criterion from ± 0.5 s to -2 to 10.25 s (definitions 2 vs. 3 in Table 2) which again shows the presence of a significant number of LM in this interval in agreement with previous studies.^{18,19} Together these findings support the notion that the frequency of PLMS has been overestimated in people with OSA and that the group of people with OSA and frequent PLMS is smaller than previously reported. This had been reported first by Manconi et al.¹⁸ and our results replicate their findings and extend it to the case where leg movements are scored by the newest WASM 2016 rules¹⁴. In particular, it implies that previous studies on the role of PLMS in people with OSA have included both participants with true PLMS as well as participants with frequent periodic appearing rLM in the group of OSA with PLMS. It is therefore promising – possibly even mandatory - to revisit both significant³⁸⁻⁴⁴ as well as non-significant effects^{37,45,46} that had been ascribed to PLMS in populations with significant OSA.

Respiratory event related LM at the end of respiratory effort related arousals and the role of arousals

In the present study we have for the first time also included RERAs and showed that rLM probability at the end of RERA's equals those of hypopneas. This result is remarkable since - by definition - there is an arousal at the end of the event and independent of the type of respiratory event and the by far strongest effect on rLM probability in both this and a previous study¹⁹ was the presence of an arousal at the end of the respiratory event. Indeed, in the study of Fulda and colleagues¹⁹, the presence of an arousal at the end of a respiratory event increased rLM probability from 26% to 64%. In the present study, arousals increased rLM probability from 23% to 51%, a particularly large effect. Yet, despite the arousals being necessarily present with RERAs, they were not more likely to be accompanied by rLM. This was also the case, when only

considering the univariate analysis where arousal occurrence was not controlled for. This could suggest that the presence of arousals at the end of apneas and hypopneas act as a possibly multidimensional marker for different respiratory features, any of which increases arousal probability. In this sense, arousal presence would signal a particularly long event or an apnea rather than a hypopnea or the presence of an oxygen desaturation and could represent a final common feature of different features. In line with this, previous studies have found no consistent respiratory event features that reliably differ between events that end with an arousal compared to those that do not.⁴⁷⁻⁴⁹

It must be noted, however, that arousals were detected automatically^{25,26} in the present study. We cannot fully exclude that a manual arousal detection would have detected more arousals. This, however, does not pertain to RERAs, which by definition have an arousal at the end of the event and which therefore can be considered as manually scored. Therefore the univariate comparison, i.e. the lower rLM probability at the end of RERAs and hypopneas compared to obstructive apneas – independent of arousal presence – can still be a meaningful comparison.

Respiratory event related LM are more frequent in participants with frequent PLMS and resemble periodic leg movements

The conditional frequency of rLM is determined by sleep-related - arousal, NREM vs. REM sleep stage, time of the night - and respiratory-related factors – type of respiratory events, duration of event, oxygen desaturations - that act differently in participants with OSA that have frequent PLMS compared to participants without PLMS. Independent of PLMS status, the presence of arousals strongly increases rLM probability; the presence of an oxygen desaturation also increases rLM probability but has only a comparatively minor effect. For all other sleep- or respiratory-related factors, the effect on rLM probability depends on PLMS status. In participants with frequent PLMS, rLM behave more PLMS-like, i.e. their frequency is more suppressed

during REM sleep and they strongly decrease over the course of the night. Moreover, they are less affected by respiratory-related factors such as the difference between apneas and hypopneas or the duration of the respiratory event. In contrast, in patients without PLMS, rLM probability strongly increases with the duration of the respiratory event and is also significantly higher at the end of obstructive apneas compared to hypopneas or RERAs.

Importantly, these results replicate and extend results of the study of Fulda and colleagues¹⁹ who showed for the first time that OSA patients with PLMS have a more frequent rLM, which behaved more PLMS-like. Both the increased frequency, the decrease of rLM probability over the course of the night and the relative insensitivity to respiratory features in OSA patients with PLMS mirrors the present findings. It is noteworthy that the present study replicated these previous results¹⁹ despite considerable differences in methodology and in particular the fact that both LM²⁷ and arousal^{25,26} were automatically detected in the present study, while they were manually scored in the study of Fulda et al.¹⁹ This suggests that the effects reported here are rather robust.

Besides these similarities, there are also differences: we do no longer find an interaction between the presence of oxygen desaturations and PLMS status, but only a main effect, and we find a new interaction between respiratory event type and PLMS status where the previous study has found a main effect only. In both studies, however, the presence of an oxygen desaturation and an obstructive apnea (vs. hypopneas, RERAs) increased rLM probability. These two new findings and in particular, the finding that the difference between obstructive sleep apneas and hypopneas and RERAs are more pronounced in participants without PLMS, are in line with and further support the notion that in non-PLMS participants, respiratory factors – the type of event, the event duration – are the major determinants of rLM occurrence. On the other hand, in PLMS participants, rLM behave more PLMS-like and are less or even not at all influenced by respiratory factors. As such, the present study replicates the overall conceptual finding of the Fulda et al. study¹⁹, if not every single result.

Together, the results of the two studies point to new and testable hypotheses. The results suggest that there are two types of respiratory event related LM: “true” periodic ones in people with frequent non-respiratory PLMS where periodic LM are displaced or paced by the respiratory events and where rLM behave plms-like, and “pure” respiratory related LM that are foremost driven by respiratory event features, such as the duration and type of the respiratory event. So far, this distinction is apparent on the level of the individual, i.e. in people with frequent nrPLMS, most rLM behave like PLMS, while in people without nrPLMS most rLM are respiratory driven.

If this assumption is correct, then the presence of non-respiratory PLMS could be a promising stratification factor that might contribute to the so far unpredictable evolution of PLMS with CPAP treatment. So far, any possible pattern has been observed: PLMS that decrease with CPAP treatment, PLMS that are unaffected with treatment, and even the new appearance of PLMS with CPAP^{20,50–53} without any consistent factor that is able to distinguish these possibilities. Our results suggest that the group of patients with OSA and PLMS identified in these studies did include both patients with true PLMS and patients with periodic appearing but respiratory driven LM. The obvious hypothesis would be that CPAP treatment will reduce the latter – periodic appearing but respiratory driven LM – but not the true PLMS and that stratifying the group by non-respiratory PLMS frequency will demonstrate a reduction of PLMS in only the group without non-respiratory PLMS.

A further implication of our results is that in participants without PLMS, rLM are mostly driven by respiratory factors and could therefore act as a marker for a more severe form of OSA. A remarkable finding in this and previous studies^{18,19} is that rLM probability is completely independent from apnea-hypopnea frequency, the AHI. Of course, apnea-hypopnea frequency is the limiting factor for absolute rLM frequency – there cannot be more rLMs than there are respiratory events – but the percentage of respiratory events that have one or more rLM is

independent of AHI and varies widely. Two participants can therefore have the same AHI but very different rLM probabilities. Our results suggests that in such a case, two participants with the same AHI but different rLM probabilities, the subject with the higher rLM probability will have more arousals, more obstructive apneas vs. hypopneas, and that these are likely to be longer and more often followed by an oxygen desaturation. The presence of rLM then, signals any of these conditions and could act as a unifying, sensitive, and AHI-independent marker. In the ongoing search for outcomes beyond the AHI⁵⁴, rLM probability could be a promising candidate.

LM parameters, cardiovascular events and CPAP compliance

A further aim of the present study was the attempt to relate LM parameters to clinically meaningful consequences – new cardiovascular events and CPAP compliance – and in both cases we failed to find such a relationship.

There are several possible reasons for this, but in the case of new cardiovascular events, the most obvious one is the low number of participants with a first-ever cardiovascular event during the 5-year follow up interval. With only 14 participants in this group, our analysis was definitely underpowered to find any but extremely large and systematic effects.

We also failed to find any difference between participants with good CPAP adherence compared to those with poor or no adherence. Our hypothesis was that non-respiratory PLMS would not decrease with CPAP treatment and could therefore contribute to poor adherence because of persistent sleep disturbances. This hypothesis was not confirmed and the likely explanation is that CPAP adherence is a multifactorial process that is influenced by multiple factors, with LM parameter playing only a minor role if at all. Indeed, psychological measures, such as self-efficacy and other, have emerged as the most consistent predictors of CPAP adherence.⁵⁵

Limitations and future research

The present study has several limitations that need to be taken into account when interpreting the results. For one, LM²⁷ and arousal^{25,26} were automatically detected while sleep and respiratory event scoring had been done in a clinical context and records had not been re-scored for research. While it is encouraging that, despite these differences, we could replicate key findings in the literature,¹⁹ which argues for the robustness of the findings, we cannot fully exclude that the automatic analyses introduced systematic bias or was overly sensitive to noise and artifacts. We tried to address this possibility in an indirect way by excluding recordings with an outlying high number of LM, but can of course not be completely sure. Nevertheless, our results warrant some optimism concerning the application of automatic scoring procedures for large scale data.

A further limitation is the quality of the patient data. Although the study was prospective in the sense that all patients were contacted with a questionnaire, the analyses in the present study relied foremost on data available and recorded at the time of diagnosis, 5 years before the prospective part of the study. As such the confidence in the completeness of the information is moderate. In particular, we have no reliable information about RLS status of the participants, information of obvious relevance when addressing PLMS. Based on the few studies available,⁵⁶⁻⁵⁹ it must be suspected that around 10% of participants with OSA also had RLS and this, in turn, could have influenced PLMS probability. It must be said, however, that our results largely replicate those of the study of Fulda et al.¹⁹ where all OSA patients denied symptoms of RLS. Nevertheless, it is a still open question, whether our results also extend to people comorbid for OSA and RLS.

As is customary in studies addressing sleep-related leg movements, it must be acknowledged that there is considerably inter-night variability^{60,61} and that ideally, more than one recording night should have been available. All the more so, since also sleep apnea severity has high night-to-night variability.⁶²⁻⁶⁵ Considering that our results suggest that rLM behavior has

trait-like aspects – PLMS-like in some, respiratory driven in other participants – the registration of multiple nights in the same subjects, would be a critical test for this assumption.

A further limitation was that CPAP adherence relied on self-report only and might have been overestimated.^{66,67} It would have been a critical addition to record sleep and LM also with CPAP treatment, preferably even at multiple times. As discussed above, we hypothesize that stratification by non-respiratory PLMS frequency could be systematically related to the evaluation of PLMS with CPAP treatment.

In summary, we show that the classification of PLMS in people with OSA strongly depends on the rule set used and that previous rules likely overestimated PLMS in this population, confounding true periodic LM with periodic appearing rLM. We confirm that rLM are more frequent in participants with frequent non-respiratory PLMS and in these behave PLMS-like. On the contrary, in participants without PLMS, rLM are mostly driven by respiratory factors, which positions rLM frequency as a possible AHI-independent severity marker in this population.

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- Applying the WASM 2016 criteria changes the LM in OSA patients
- Frequency of PLMS in OSA patients has been overestimated
- Respiratory event related LM were more frequent and behaved more like PLMS in participants with PLMS
- In people without PLMS, respiratory event related LM are driven by respiratory factors
- Non-respiratory PLMS frequency and rLM probability are promising clinical stratification factors in OSA.

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