Sleep Medicine 17 (2016) 138–143

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Inter-movement interval as a primary stable measure of periodic limb movements of sleep

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ARTICLE INFO

Article history:
Received 28 July 2015
Received in revised form 26 September 2015
Accepted 7 October 2015
Available online 11 November 2015

ABSTRACT

Aim: Periodic leg movements in sleep (PLMS) are generally evaluated by the number of events per hour during sleep, but this is an unstable measure with marked nightly variability and also fails to assess the basic periodicity that essentially characterizes these movements. The inter-movement interval (IMI) evaluates a putative biological process producing the period of PLMS. By contrast, the actual number of PLMS reflects the expression of this biological process that would likely be affected by multiple factors, particularly those disrupting sleep. Thus, this study tests the hypothesis that measurement of IMI duration should be more stable over nights in comparison to any measure based on counting the number of movements. IMI approximates a log-normal distribution. This study, therefore, tests the hypothesis that the means of the log IMI are more stable from night 1 (N1) to night 2 (N2) sleep recordings compared with measures of the number of PLMS.

Methods: PLMS/h and IMI were measured for two consecutive nights of full sleep recordings for 29 restless legs syndrome (RLS) patients not being treated and 22 healthy controls without RLS. N1–N2 difference between nights was measured as percent of average for the nights.

Results: Mean log IMI showed little nightly variability (mean ± SD for RLS: 3.6% ± 3.7, controls: 7.1% ± 7.0) significantly less $p < 0.001$) in comparison to PLMS/h (mean ± SD for RLS: 43.2 ± 37.1, controls: 63.7 ± 40.8). The IMI nightly variability was also significantly better than that for the periodicity index. IMI also varied considerably between individuals.

Conclusion: Mean log IMI is a remarkably stable measure across nights within a subject and shows differences between subjects that may have clinical and biological significance. Because of this consistency, the mean log IMI should be considered as one standard measure of PLMS alongside the PLMS index.

1. Introduction

Periodic leg movements in sleep (PLMS) are a consistently observed phenomenon in restless legs syndrome (RLS) [1] that also occur in adults with increasing age [2] and for some other disorders, for example, narcolepsy [3]. The customary primary measure of PLMS is the number of periodic leg movements (PLM) per hour of sleep (PLMS/h), often referred to as PLMS index (PLMSI). The periodic limb movements (PLM) during wake are also often reported as number per hour of wake time (PLMW/h) during the recording period. Large variability in these measures within patients and between nights, however, significantly compromises clinical utility of these measures [4], particularly in patients with RLS [5]. Thus, the PLMSI from a sleep study cannot be considered a reliable measure, particularly if it is taken from the first night's recording, as is commonly done in clinical practice.

The search for better and more stable measurements of PLMS has been greatly advanced by Ferri's work emphasizing the time between onsets of consecutive movements referred to as the inter-movement interval (IMI). He introduced the periodicity index (PI) as the proportion of all IMI that are periodic, that is, three or more consecutive IMI that are each ≥10 and ≤90 s [6]. By shifting focus away from number of movements, he has reframed the measurement of PLMS in terms of the periodicity of the events, and suggested that, in order to understand the biology of PLMS, research should focus on accurately identifying true PLMS and assessing their periodicity and occurrence relative to other leg movements.

IMI is itself of particular interest for measuring PLMS because it represents the inherent period of an underlying biology producing these repetitive movements. The PLMS biology producing these often remarkably patterned movements presumably differs between individuals possibly reflecting disease state but would likely be relatively stable over short periods of time when there are no significant

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http://dx.doi.org/10.1016/j.sleep.2015.10.004
1389-9457/

biological changes. IMI may, therefore, reflect a significant property of a putatively stable biological process producing the PLMS, while the actual number of PLM, in contrast, may reflect factors that affect expression of this underlying biological process. If IMI reveals the inherent periodicity of a biological process, then it should be reasonably stable over several nights while, in contrast, any measure based on counting the *number* of PLM (eg, PLMS/h) or IMI (eg, PI) may vary considerably depending on factors affecting expression of these periodic events, for example, noise or novel environment disrupting sleep. As IMI of PLMS (defined to range from 5 to 90 s) shows a unimodal strongly right-skewed distribution approximating a lognormal [7], the central tendency and variance would be best measured by the mean and standard deviation of the log IMI (see Fig. 1).

The two aims of this study were (1) to test the hypothesis that average variability from the first to the second night would be significantly less for mean log IMI in comparison to either PLMS/h or PI, and (2) to explore the first to second night variability of IMI compared with another commonly reported feature of PLM, that is, duration of PLMS.

2. Methods

2.1. Subjects

Data from two consecutive nights of standard polysomnogram (PSG) recordings conducted on 37 RLS and 30 control subjects, who were participating in an ongoing RLS study, that had been approved by the Hopkins Institutional Review Board for research involving human subjects, were available for analysis. The PSG recordings and sleep stage scoring followed the standards set by the American Academy of Sleep Medicine with bilateral anterior tibialis muscle electromyogram (EMG) recordings on a separate channel for each leg [8]. Full respiratory measures including oximetry, nasal and oral air pressure, and thoracic and abdominal respiratory effort were obtained on the first night recording only. Subjects who had apnea/hypopneas with desaturations ≥4% on the first night of PSG occurring more often than 15/h during sleep, were excluded. Using the clinical version of the validated Hopkins Telephone Diagnostic Interview for RLS, an RLS expert diagnosed the subjects as having RLS or non-RLS through a clinical interview [9]. All RLS subjects who were on medications for their disease stopped RLS medications for at least 12 days before the first night sleep study. RLS patients had been screened to include only those with an average PLMS index >15/h over five days of home recording with the PAM-RL activity meter [10]. Conversely, control subjects were included only if they had an average PLMS index <10/h for five consecutive days, recorded the same as the RLS subjects. Besides RLS, both control and RLS subjects were clinically screened to exclude those with significant mental health or sleep disorders.

Subjects were excluded by visual analyses of the PSG if the data from any time during either N1 or N2 from either leg showed high levels of EMG noise or unstable thresholds clearly indicating loss of recording integrity. Subjects were excluded prior to the data analyses for this study, thus excluding eight RLS patients and eight controls leaving 51 (29 RLS, 22 control) subjects included in this study.

2.2. Scoring of PLM

PSG data were extracted from REMLOGIC European data format into MATLAB data structure, to be scored by the validated MATPLM1 auto-detection program (sensitivity: 95.3%, specificity: 91.7%) [11]. MATPLM1 strictly applies World Association of Sleep Medicine (WASM) criteria in order to score periodic leg movements (PLMs). The automatic scoring was visually inspected and records with significant recording problems, for example, noise, electrocardiogram (EKG) artifact, were rejected before data analyses.

2.3. PLMS features and variability measures

The MATPLM1 program was used to calculate PLM index, IMI, and PLM durations for all of sleep and separately for each sleep stage using the WASM criteria [11]. PI is defined for IMI in sleep as the number in a series of at least 3 with IMI ≥10 and ≤90 s divided by the total number of IMI in sleep. For the results in the body of this paper, PLMS must have an IMI ≥5 s and ≤90 s, but recent research has indicated that PLMS may be better characterized by an IMI minimum of 10 s [6], and so results from PLMS so calculated are included in supplementary tables (Tables S1 and S2 available online). Except for the PI, the PLMS sequences are defined ignoring IMI <minimum.

N1–N2 variability for each measure was calculated for each subject by dividing the absolute N1–N2 difference by the mean of the two nights and multiplying this number by 100 to return a percentage.

2.4. Statistics

Variability of the different measures was compared using a two-sided Wilcoxon signed-rank test. To test the primary hypothesis, the percentage variability for mean log IMI was compared with PLMS/h and PI. Hierarchical testing was used. The statistical tests of the percentage variability were made in the following order: mean log IMI versus PLMS/h, mean log IMI versus PI. Statistical significance was set at $p < 0.05$ for each step in the evaluation. Testing continued in this order until statistical significance was not established or all tests had been used. Controls and RLS patients were tested separately.

3. Results

3.1. Subjects

Data were analyzed for 29 RLS (average age: 58.8 ± 9.4, 59% female) and 22 control (average age: 59.5 ± 8.9, 64% female) subjects. The average (±SD) severity of RLS as measured by the International RLS Severity Scale [12], when patients were off treatment for at least 11 days, was 25.8 ± 5.6 (range 16–39).

3.2. PLMS features and N1–N2 variability

The N2 average values of PLMS features for RLS patients and controls are presented in Table 1 to describe the PLM features of these subjects for sleep, wake during sleep period, and each sleep stage. Table 2 similarly presents the average percentage N1–N2 error for the PLM features for sleep, wake, and each sleep stage.

Table 3 displays the average values for Night 2, the N1–N2 percent error, and the results of the Wilcoxon test comparing each metric's error to that of the log IMI. Each step of the hierarchical testing was statistically significant, revealing that mean log IMI varies significantly less than PLMS index and PI. Fig. 2 illustrates the relatively high N1–N2 variability for PLMS index and PI compared with log IMI.

Exploratory analyses revealed several potentially relevant differences. N1–N2 variability for all types of sleep for RLS patients and controls showed overall least variability for both mean log IMI (4.1% and 8.8%, respectively), standard deviation of log IMI (12.1% and 13.5%), and mean linear IMI (12.7 and 21.6%). Duration variability can be compared with linear IMI for all sleep and across all sleep stages (Wilcoxon tests show no statistically significant