

## Changes in heart rate related to rhythmic masticatory muscle activities and limb movements in patients with sleep bruxism

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*Published in:*  
Journal of Oral Rehabilitation

*DOI (link to publication from Publisher):*  
[10.1111/joor.12900](https://doi.org/10.1111/joor.12900)

*Publication date:*  
2020

*Document Version*  
Accepted author manuscript, peer reviewed version

[Link to publication from Aalborg University](#)

*Citation for published version (APA):*  
Zhong, Z., Xu, M., Zou, X., Ouyang, Q., Zhang, L., Yu, B., Wang, K., & Yao, D. (2020). Changes in heart rate related to rhythmic masticatory muscle activities and limb movements in patients with sleep bruxism. *Journal of Oral Rehabilitation*, 47(2), 170-179. <https://doi.org/10.1111/joor.12900>

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Article type : Original Article

## **Rhythmic masticatory muscle activities and limb movements related heart rate changes in patients with sleep bruxism**

**Running title:** Heart Rate Changes in Patients with Sleep Bruxism

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/JOOR.12900](#)

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### **Acknowledgments:**

The authors thank all the volunteers for participating in the study. This study was funded by Provincial Natural Science Foundation of Jiangxi for Young Scholars (2014BAB215070), Provincial Natural Science Foundation of Jiangxi (S2017ZRMSB2145), Natural Science Foundation of China (81760202), and Jiangxi Provincial People's Hospital (2019-009).

### **Abstract**

**Background:** Most sleep bruxism (SB) episodes are accompanied by an increase in sympathetic tone and heart rate (HR).

**Objectives:** To characterize heart rate (HR) changes in relation to rhythmic masticatory muscle activities (RMMAs) in SB patients.

**Methods:** Polysomnographic recordings were performed on 10 SB patients and 11 normal controls. The duration of movement events, amplitude and duration of HR increases, and time to reach HR peak associated with RMMAs and limb movements (LMs) were determined and the relationships of the parameters of HR increases with types of movements and RMMAs were analyzed.

**Results:** All of the parameters of HR increases associated with the three types of movements (RMMAs, RMMAs + LMs and LMs) and masseter activities (phasic, tonic and mixed) were significantly different (Two way ANOVA,  $P < 0.001$  for all) in both SB patients and controls. The duration of RMMAs/LMs was positively correlated with the parameters (SB patients:



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$R^2=0.24-0.85$ ,  $P<0.0001$ ; Controls:  $R^2=0.23-0.68$ ,  $P<0.0001$ ). The amplitude of HR increases was also positively correlated with respiration changes in the SB patients ( $R^2=0.3258$ ,  $P<0.0001$ ) and controls ( $R^2=0.09469$ ,  $P<0.05$ ). The proportions of phasic RMMAs associated with awakenings, microarousals and no cortical arousals were significantly different and so were the proportions of tonic and mixed RMMAs (Friedman's tests,  $P<0.05-0.001$ ).

**Conclusions:** The HR increases associated with RMMAs may be intrinsic to the cortical arousal response and autonomic activation, and differences in HR increases associated with different types of movements and RMMAs might be related to the changes in respiration and differences in cortical arousal levels.

**Keywords:** sleep bruxism; rhythmic masticatory muscle activities; limb movements; cortical arousal; heart rate; respiration

## Introduction

Sleep bruxism, a masticatory muscle activity during sleep, is characterized by rhythmic (phasic) or non-rhythmic (tonic) and not a movement disorder or sleep disorder in otherwise healthy individuals<sup>1</sup>. SB prevalence rate has been reported about 14-20%<sup>2</sup> in children and 8-12% in adolescents and adults with a decrease with age<sup>3</sup>. Most SB patients complain of tooth wear, locked jaw, temporomandibular pain and temporal headache. Previous studies showed psychological (e.g. stress and anxiety) and genetic factors as well as smoking, esophageal reflux, drugs (such as selective serotonin reuptake inhibitors) might induce occurrence of SB<sup>4</sup> but the etiology of SB is not fully clear. Although there are several types of treatments for SB patients<sup>5</sup>, most of them are only used to prevent the teeth and associated structures from being further damaged and none of them could effectively decrease the occurrence of SB without causing severe side effects. Therefore, more research is required to explore pathophysiologic mechanisms of SB.

SB episodes have been shown to be associated with changes in electroencephalographic (EEG) activities, sympathetic tone, heart rate (HR), blood pressure<sup>6,7</sup>. Several studies have showed that urinary catecholamine levels in SB patients were significantly higher than those in normal

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controls<sup>8,9</sup>, which is similar to with previous findings that higher levels of catecholamines in patients with hypertension or CHF<sup>10-12</sup>. It raises the possibility that SB might be associated with cardiovascular diseases. Indeed, a recent study even suggested a close relationship between SB and cardiovascular diseases by showing a higher occurrence of SB in cardiopathic patients than in non-cardiopathic patients<sup>13</sup>. However, the pathophysiological mechanisms underlying the SB are largely unknown.

Increased sympathetic activity was reported to start before SB onset, followed by an increase in EEG activities and HR/arterial blood pressure<sup>6,7</sup>. This highlights association of change in the sympathetic activity and HR increases associated with SB episodes or rhythmic masticatory muscle activities (RMMAs). In addition, rhythmic masticatory muscle activities (RMMAs) /SB episodes are often accompanied by limb movements (LMs)<sup>14,15</sup> and most of the LMs occur before the onset SB episodes<sup>15</sup>. Moreover, previous studies demonstrated<sup>14,16,17</sup> that the increase in HR started several tens of seconds before or after the onset of periodic leg movements (PLMS)<sup>16,18</sup>. These previous findings suggest that HR increases may be associated with LMs in addition to RMMAs/SB episodes. Indeed, recent study from our laboratory showed the HR increases occurred with RMMAs and LMs<sup>19</sup>. Given above, it would be interesting to know whether there were any differences between HR increases associated with isolated RMMAs, RMMAs accompanied with LMs (RMMAs + LMs) and LMs, between HR increases associated with different types of RMMAs. Therefore, the aim of this study was to examine HR changes in relation to different types of movements (isolated RMMAs, RMMAs +LMs, isolated LMs) and different types of RMMAs/SB episodes in patients with SB.

## **Materials and methods**

### **Subjects**

Twenty-one volunteers from Nanchang University, including 10 SB patients [4 males and 6 females with ages of 18–24 years] and 11 normal controls [5 males and 6 females with ages of 20–

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25 years] without any family history of cardiovascular diseases before 65 years old were recruited for the study. Every subject had a full dentition and no one had any psychiatric, medical (e.g. temporomandibular disorder) or sleep disorders such as sleep insomnia, sleep apnea and periodic leg movements. In the past six months, no one has used any alcohol, cigarettes, coffee, drugs or psychostimulants. All SB subjects were chosen based on the following criteria: 1) tooth grinding more than three days per week during the last six months, 2) complaints of facial muscle pain and morning headache, 3) masseter and/or temporalis muscle hypertrophy diagnosed by clinical examination, directed interview, and muscle palpation<sup>20</sup> as well as presence of tooth wear (flattened occlusal and incisal surfaces without any sign of erosion)<sup>21, 22,23</sup>, and 4) two or more episodes of grinding with noise per night as well as presence of at least four RMMA episodes and 25 bursts of masseter electromyographic (EMG) activities per hour of sleep during polysomnographic examination<sup>22,24</sup>. All subjects were provided with informed consent and they were free to withdraw any time.

### **Polysomnographic sleep recording**

All polysomnographic recordings were carried out at the Sleep Center of the Jiangxi Metal Hospital. The first night was used for subjects to adapt to the laboratory environment, confirm SB and exclude sleep or sleep-related disorders such as periodic leg movements, sleep apnea, and rapid eye movement (REM) sleep behavioral disorders. The data from the polysomnographic recordings in the second night were used for further confirmation of SB and data analysis described below. Polysomnographic recordings of EEG (F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, O2-A1), electrocardiographic (ECG) and electrooculographic (EOG) activities as well as thoracic and abdominal respiration, nasal air flow, body posture, and capillary oxygen saturation (SpO<sub>2</sub>) in index finger or thumb were performed<sup>15,19,25</sup>. In addition, EMG activities from mylohyoid, bilateral masseter and limb muscles (bilateral gastrocnemius and tibialis anterior muscle, and bilateral flexor and extensor carpi radialis) were also recorded. Infrared cameras and video recorders were used to monitor the movements in orofacial area, limbs and other parts of the body

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to exclude non-specific oral activities such as lip sucking and swallowing, and to confirm the presence of tooth grinding and limb movements during data analysis.

### **Data Analysis and Statistics**

All the data were initially analyzed with the Pro Fusion PSG 3 Software (Compumedics Limited, Abbotsford, Australia) and then with Spike 2 (Version 8.07, CED, Cambridge, UK) based on the criteria established by the American Association of Sleep Medicine (AASM) <sup>22</sup>. SB-related masseter EMG activities were defined as masseter EMG activities that were two times above the background and SB episodes were classified as phasic (at least three consecutive 0.25 to 2.0 s long masseter EMG bursts), tonic (masseter EMG burst lasting longer than 2.0 s) and mixed type (a mixture of two types of masseter muscle activities). EMG activities in limb muscles were considered to LM-related when they were 8  $\mu$ V higher than the background with duration longer than 0.5s. LMs and RMMAs were considered to be related each other only if a time overlap existed between them. Transient cortical arousals (at least 3 s) were scored as previously described<sup>26</sup> and divided into microarousals (mAR, 3–15 s) and awakenings (AW, longer than 15 s, but less than 60 s) <sup>27,28</sup>. When any RMMAs/LMs occurred during wakefulness or started in sleep but ended in wakefulness, the data were excluded. If cortical arousal lasted shorter than 3 s, it was considered as no cortical arousal (NA).

RMMAs/LMs related HR increases were defined as the HR that increased above two standard deviations (SD) of the baseline HR (Fig. 1) and there was a time overlap between RMMAs/LMs and HR increases. Since the onset of HR increases occurred less than 10 s before the SB episodes<sup>15</sup>, a period of 10 s stable HR (10-20 s before the onset of RMMAs/LMs) was used to calculate mean baseline value and SD as previously described<sup>19</sup>. The onset and offset of the HR increases were defined as the time points when HR increased above and fell below the mean plus 2 times SD, respectively. Then, duration of HR increases (i.e. duration between the onset and offset of HR increases) was determined. The amplitude of HR increases [peak HR value -

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(baseline mean +2SD)] and time to reach peak HR (interval between the onset of HR increases and time point of peak HR) were calculated as previously described<sup>19</sup>.

The change in respiratory amplitude was calculated by the amplitude of respiration during RMMAs/LMs (difference between the highest and lowest points of nasal airflow pressure) minus the average amplitude of the five breathing cycles before the onset of the respiratory change.

The statistical analyses were performed by using Graph Pad Prism (Version 7, San Diego, California, USA), SPSS (Version 22, Armonk, NY, USA) and Sigmaplot (Version 14.0, San Jose, California, USA). The differences between SB patients and controls were assessed by  $\chi^2$  test, t-test or Wilcoxon rank-sum test wherever appropriate. Two way analysis of variance (ANOVA) with post hoc Holm-Sidak tests were used to analyze HR increases associated with different types of movements and RMMAs in both SB patients and controls. The relationships between the parameters of HR increases (i.e. duration, amplitude and time to reach peak HR) and duration of the movement events of RMMAs/LMs, and between HR increases and respiration changes were analyzed by using liner correlation analyses. Association of different types of RMMAs with arousal levels was analyzed by Friedman's tests with post hoc Wilcoxon rank-sum tests with Bonferroni corrections. All data were expressed as mean  $\pm$  standard error of mean (SEM) unless indicated otherwise and  $P < 0.05$  was considered to be statistically significant.

### **Ethical approval:**

The research protocol was reviewed and approved by the local Ethical Review Board at Jiangxi Mental Hospital (2017007) in accordance with the ethical standards of the Declaration of Helsinki. Prior to participation, informed consent was obtained from each subject.

## **Results**

### **General sleep characteristics of the SB patients and the controls**

All general sleep variables from 10 SB patients and 11 controls were shown in Table 1. The total sleep time and the proportions of sleep time spent in different sleep stages in the SB patients were not significantly different from those in the controls (t-test,  $P>0.05$ ). In addition, there was no significant difference in sleep efficiency between SB patients and controls (t-test,  $P>0.05$ ). Nevertheless, the SB index for the SB patients was significantly higher (t-test,  $P<0.001$ ) than that for the controls, and the microarousal and arousal indexes for the SB patients were significantly higher (Wilcoxon rank-sum test,  $P<0.01$ ) than those for the controls, respectively. However, there were no significant differences in the apnea-hypopnea index (AHI), and periodic leg movement index (PLMI) between SB patients and controls (Wilcoxon rank-sum test,  $P>0.05$ ).

#### **Differences in HR increases associated with isolated RMMAs, RMMAs + LMs, and isolated LMs**

The mean duration of HR increases per night in the SB patients ( $17.45 \pm 2.37$  min) was significantly longer (t-test,  $P<0.05$ ) than that in the controls ( $11.10 \pm 1.03$  min). A total of 1027 events (617 in the SB patients and 410 in the Controls) of HR increases associated with isolated RMMAs (43 and 23), RMMAs with a companion of LMs (RMMAs + LMs, 446 and 285), and isolated LMs (128 and 102) were analyzed. Two way ANOVA analyses showed that the amplitude and duration of HR increases, time to reach HR peak, and duration of movement events from the onset of RMMAs or LMs (whatever appeared first) to the offset of RMMAs or LMs (whatever ended last) were significantly different between types of movements [ $F(2, 1021)=114.46, 116.64, 95.3$  and  $113.59$ , respectively.  $P<0.001$  for all]. There were no significant differences between subjects [ $F(1, 1021)=0.22, 0.03, 0.16$  and  $0.24$ , respectively.  $P>0.05$  for all] and mixed statistical results for their interactions [ $F(2, 1021)=4.22, 1.20, 1.59$  and  $0.44$ , respectively.  $P>0.05$  for all except for amplitude of HR increases ( $P<0.05$ )].

Post hoc Holm-Sidak tests showed that the durations of movement events and HR increases, and time to reach HR peak associated with RMMAs + LMs were significantly longer than those

associated with isolated RMMAs ( $P<0.001$ ) or isolated LMs ( $P<0.001$ ) in both SB patients and controls (Fig. 2b-2d). In addition, in the controls, the amplitude of HR increases associated with RMMAs + LMs was significantly higher than that associated with isolated RMMAs ( $P<0.001$ ) or isolated LMs ( $P<0.001$ ), but there was no significant difference between the amplitudes of HR increases associated with isolated RMMAs and isolated LMs ( $P>0.05$ ) (Fig. 2a). In contrast, in the SB patients, the amplitude of HR increases associated with RMMAs + LMs, and isolated RMMAs were both significantly higher than that associated with isolated LMs ( $P<0.001$ ,  $P<0.01$ ) and the amplitudes of HR increases associated with RMMAs + LMs were significantly higher ( $P<0.01$ ) than those associated with isolated RMMAs (Fig. 2a).

Compared with the controls, time to reach HR peak and amplitude associated with RMMAs + LMs were significantly shorter ( $P<0.001$ ) (Fig. 2c) and lower ( $P<0.001$ ) (Fig. 2a) in the SB patients. There were not any other significant differences in the duration, amplitude and time to reach HR peak and duration of movement events associated with 3 different types of movements between SB patients and controls.

### **Correlation of the HR increases with duration of the events of RMMAs/LMs**

There were significantly positive correlations between the duration of the events of RMMAs/LMs and the amplitude of HR increases, between the duration of the events of RMMAs/LMs and the duration of HR increases, and between the duration of the events of RMMAs/LMs and the time to reach peak HR in both SB patients ( $R^2=0.2361$ ,  $0.8464$ , and  $0.5286$ , respectively,  $P<0.0001$ ) and controls ( $R^2=0.2265$ ,  $0.6807$ , and  $0.5415$ , respectively,  $P<0.0001$ ).

### **HR increases associated with different types of RMMAs**

A total of 489 events of HR increases associated with RMMAs (phasic: 248, tonic: 85, and mixed: 156) in the SB patients and 308 (phasic: 115, tonic: 68, and mixed: 125) in the controls were analyzed (Fig. 3).  $\chi^2$  test showed the percentage of three types of RMMAs was significantly

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different ( $P=0.001$ ) in the SB patients from that in the controls. The percentage of mixed type of RMMAs was significantly smaller ( $P=0.015$ ) in the SB patients than that in the controls.

Two way ANOVA analyses showed significant differences in the amplitude and duration of HR increases, time to reach HR peak, and duration of movement events between types of masseter muscle activities [ $F(2, 791)= 41.33, 36.18, 27.70$  and  $28.06$ , respectively.  $P<0.001$ ], and mixed statistical results between subjects [ $F(1, 791) =12.95, 2.21, 4.68$  and  $0.434$ , respectively.  $P<0.001$ ,  $P<0.05$  for amplitude and time to reach HR peak, respectively;  $P> 0.05$  for the others] and for their interactions [ $F(2, 791)=2.796, 3.19, 1.21$  and  $2.77$ , respectively.  $P>0.05$  for all except for the duration of HR increases ( $P<0.05$ )].

In the SB patients, as illustrated in Fig. 3, post hoc Holm-Sidak tests showed that the movement events associated with tonic RMMAs had a significantly shorter duration ( $P<0.01$ ;  $P<0.001$ ) and their related HR increases had a significantly shorter duration ( $P<0.01$ ;  $P<0.001$ ), shorter time to reach peak HR ( $P<0.05$ ;  $P<0.001$ ), and lower amplitude ( $P<0.01$ ;  $P<0.001$ ) compared with those associated with phasic and mixed RMMAs. Moreover, the duration of movement events, the amplitude and duration of HR increases, as well as the time to reach HR peak associated with mixed RMMAs were significantly longer ( $P<0.01$ ), higher ( $P<0.001$ ), longer ( $P<0.01$ ) and longer ( $P<0.01$ ), respectively, than those associated with phasic RMMAs.

In the controls, the movement events associated with mixed RMMAs had a significantly longer duration ( $P<0.001$ ;  $P<0.001$ ) (Fig. 3d) and their related HR increases had a significantly a longer duration ( $P<0.001$ ;  $P<0.001$ ) (Fig. 3b), longer time to reach HR peak ( $P<0.001$ ;  $P<0.001$ ) (Fig. 3c), and a higher amplitude ( $P<0.001$ ;  $P<0.001$ ) (Fig. 3a) compared with those associated with phasic and tonic RMMAs, respectively.

Compared with the controls, HR increases associated with mixed RMMAs in the SB patients had a significantly shorter duration ( $P<0.05$ ) (Fig. 3b), lower amplitude ( $P<0.001$ ) (Fig. 3a) and shorter time to reach HR peak ( $P<0.01$ ) (Fig. 3c). There were not any other significant differences in the above parameters between SB patients and controls ( $P>0.05$ ).



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### Association of different types of RMMAs with cortical arousal levels

In the SB patients, 36.94% (0-75%) (median, minimum-maximum), 50.48% (25-88%), and 4.38% (0-22.22%) of phasic RMMAs and in the controls, 28.57% (0-75%), 71.43% (25-100%), and 0% (0-11.11%) of phasic RMMAs were associated with AW, mAR, and NA, respectively (Fig. 4). Friedman's test showed a significant difference in proportion of phasic RMMAs associated with AW, mAR and NA ( $P<0.001$  for both) in both SB patients and controls. Post hoc Wilcoxon rank-sum tests with Bonferroni corrections (the level of significance at 0.017) showed the proportions of phasic RMMAs associated with AW and mAR were significantly larger than those associated with NA in both SB patients ( $P=0.013$  and  $P=0.005$ , respectively) and controls ( $P=0.008$  and  $P=0.003$ , respectively).

In contrast, 2.27% (0-50%), 73.33% (33.33-100%), and 7.27% (0-44.44%) of tonic RMMAs in the SB patients and 33.33% (0-54.55%), 57.14% (0-75%) and 0% (0-100%) of the tonic RMMAs in the controls were associated with AW, mAR, and NA, respectively (Fig. 4). Friedman's test showed a significant difference in the proportions of tonic RMMAs associated with AW, mAR and NA ( $P<0.01$ ;  $P<0.05$ ) in both SB patients and controls. Post hoc Wilcoxon rank-sum tests with Bonferroni corrections showed the proportions of tonic RMMAs associated with mAR were significantly larger ( $P=0.007$  and  $P=0.007$ , respectively) than those associated with NA and AW in the SB patients and no significant difference in the proportions of tonic RMMAs associated with different cortical arousal levels in the controls. However, there was a trend of higher percentage of tonic RMMAs associated with mAR than that associated with AW in the controls although the difference did not reach a statistical significance (the level of significance at 0.017,  $P=0.028$ ).

However, 45% (0-71.43%), 47.92% (28.57-100%), and 1.06% (0-25%) of the mixed RMMAs in the SB patients and 61.54% (50-100%), 38.46% (0-50%) and 0% (0-0%) of the mixed RMMAs in the controls were associated with AW, mAR, and NA, respectively (Fig. 4).

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Friedman's test showed significant differences in proportions of mixed RMMAs associated with AW, mAR and NA ( $P<0.01$ ,  $P<0.001$ ) in both SB patients and controls. Post hoc Wilcoxon rank-sum tests with Bonferroni corrections showed the proportions of mixed RMMAs associated with AW and mAR were significantly larger than those associated with NA in both SB patients ( $P=0.015$  and  $P=0.005$ , respectively) and controls ( $P=0.003$  and  $P=0.008$ , respectively). In addition, the proportions of mixed RMMAs associated with AW were significantly larger ( $P=0.008$ ) than those associated with mAR in the controls.

The mixed RMMAs in the controls were more (Wilcoxon rank-sum test,  $P=0.013$ ) frequently associated with AW and less ( $P<0.05$ ) frequently associated with mAR than those in the SB patients. However, no significant difference ( $P>0.05$ ) was found in the proportion of the phasic and tonic RMMAs associated with AW and mAR between SB patients and controls. Nevertheless, the phasic and mixed, not tonic RMMAs, in the SB patients were more ( $P<0.01$  and  $P<0.05$ , respectively) frequently associated with NA than those in the controls.

### **HR increases during RMMAs/LMs in relation with changes of respiration**

Although HR increases could occur before, during or after the onset of RMMA/LMs, they always occurred after the onset of respiratory changes ( $2.9293\pm0.2410$  s and  $2.6922\pm0.1837$  s after the onset of the changes in respiration in the SB patients and controls, respectively). In addition, the amplitudes of HR increases and respiration changes were significantly correlated in both SB patients ( $R^2=0.3258$ ,  $P<0.0001$ ) and controls ( $R^2=0.09469$ ,  $P<0.05$ ). However, the time intervals between the onset of HR increases and changes in respirations were not significantly different between SB patients and controls (t-test,  $P>0.05$ ). No apnea or hypopnea (decreases in SpO<sub>2</sub>  $\geq 3\%$ ) was observed during RMMAs/LMs.

### **Discussion**

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SB, a rhythmic (phasic) or non-rhythmic (tonic) masticatory muscle activity during sleep<sup>1</sup> affects a large proportion of population especially children <sup>2,3</sup>. In the study, we have systemically investigated the relationships of different types of movements (i.e. isolated RMMAs, RMMAs + LMs and isolated LMs) and RMMAs with associated HR increases during sleep and found significant differences in the parameters of HR increases associated with different types of movements and RMMAs (Fig. 2 and 3). These findings might contribute to a better understanding of pathophysiology of SB.

The occurrence of RMMAs/SB has been shown to be related to activation of central and autonomic nervous systems. The transient cortical arousals and increased sympathetic activity contribute to the increase in cortical excitatory input to the central pattern generator (CPG) through the cortico-bulbar projection and occurrence of RMMAs/SB episodes<sup>29</sup>. Indeed, the increase in sympathetic activity was reported to start prior to the onset of SB episodes, followed by an increase in cortical alpha and theta wave electroencephalographic (EEG) activities, heart rate, and arterial blood pressure<sup>6,7</sup>. In addition, most of episodes of RMMAs/SB were shown to be associated with transient cortical arousals, and when transient cortical arousals appeared, episodes of RMMAs/SB more likely occurred with a companion with LMs in the previous studies<sup>15,30,31</sup>.

In the SB patients and normal subjects, some common features existed in HR increases associated with RMMAs/SB episodes. First, the durations of increased sympathetic activity and transient cortical arousals in association with RMMAs accompanied with LMs in the SB patients and normal controls may last longer than those related to isolated RMMAs or isolated LMs since the durations of RMMAs accompanied with LMs and the related HR increases were significantly longer than durations of isolated RMMAs and isolated LMs and their related increases in HR, respectively (Fig. 2). Also, all other parameters of HR increases associated with RMMAs + LMs were also significantly different from those associated with isolated RMMAs or isolated LMs. This might be due to a higher percentage of RMMAs + LMs associated with longer cortical arousals (e.g. AW) than isolated RMMAs or isolated LMs<sup>15</sup>. Second, the duration of movement events might be associated with duration and amplitude of HR increases<sup>19</sup>. Third, duration of

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movement events and parameters of HR increases associated with mixed RMMAs were significantly different from those associated with phasic and tonic RMMAs, which might be due to a significantly higher proportion of mixed RMMAs associated with AW and longer duration of mixed RMMAs than that of tonic and phasic RMMAs, which was correlated with the parameters of HR increases associated with RMMAs<sup>19</sup>. Although previous studies have reported that the amplitude and frequency of RMMAs in SB patients were significantly higher than those in normal subjects<sup>32</sup>, there were no significant differences in the HR increases associated with the three different types of RMMAs between SB patients and controls. This might be due to the HR increases associated with RMMAs were correlated with the duration of RMMAs<sup>19</sup>. These similar findings in both SB patients and controls suggest genesis of RMMAs and increases in HR associated with RMMAs with or without a companion of LMs in both SB patients and normal controls might involve some common mechanisms.

Although HR increases associated with RMMAs in the controls followed the similar pattern as in the SB patients, some distinct differences existed between HR increases associated with RMMAs in the SB patients and controls. First, HR increases associated with RMMAs accompanied with LMs in the controls were higher and lasted longer than those in the SB (Fig. 2). This might be due to stronger and longer stimulation was needed to activate the central nervous system to generate RMMAs accompanied with LMs in the controls than in the SB patients. Indeed, previous study reported that a much lower percentage of RMMAs could be evoked by peripheral stimulation in normal subjects than in SB patients although a similar percentage of transient cortical arousals could be evoked in both normal subjects and SB patients<sup>19</sup> which suggests stronger and longer peripheral stimulation is needed to evoke occurrence of RMMAs in normal subjects (e.g. AW) so longer cortical arousals (e.g. AW) would be more likely to occur and the resulting cortical excitation would be more likely to spread to more areas of the CNS, which might include the part controls LMs. This is supported by our recent findings that there was a lower frequency of RMMAs and a higher percentage of RMMAs accompanied with LMs in the normal subjects than in the SB patients<sup>25</sup> and that there was a higher proportion of RMMAs with a companion of LMs associated with AW in the normal subjects<sup>19</sup> than in the SB patients. Second,

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the parameters of HR increases associated with mixed RMMAs, but not with phasic and tonic RMMAs, in the SB patients were significantly different from those in the controls, which may be due to a lower (Wilcoxon rank sum test,  $P=0.013$ ) proportion of mixed RMMAs associated with AW and a significantly higher ( $P<0.05$  for both) proportion of mixed RMMAs associated with mAR and NA in the SB patients than those in the controls, and no significant difference ( $P>0.05$ ) in the phasic and tonic RMMAs associated with AW between SB patients and controls.

As HR increases, respiration changes occurring with RMMAs, might be a part of responses to changes in the cortical arousal levels associated with RMMAs<sup>19</sup>. However, SpO<sub>2</sub> was slightly decreased (less than <3%) during RMMAs/LMs as the SB patients recruited for the study were otherwise healthy (e.g. without concomitant obstructive sleep apnea). As shown in the previous study<sup>19</sup>, the onset of HR increases in relation to the onset of RMMAs can be variable, which might be due to respiration changes associated with RMMAs. It has been shown HR increases associated with RMMAs/LMs always occurred after the onset of the changes in respiration and the parameters (e.g. amplitude) of HR increases was significantly correlated with the changes in respiration in the previous<sup>19</sup> and current studies, which suggests HR increases associated with RMMAs were closely related to respiration changes.

In SB patients, sympathetic cardiac activity associated with RMMAs was significantly higher than that in normal controls although resting HR in SB patients was not higher than that in the normal controls<sup>33</sup>. In SB patients, RMMAs and their associated with HR increases occurred more often than those in normal controls (Table 1). In addition, the mean duration of HR increases in SB patients was significantly longer ( $P<0.05$ ) than that in the control. The movements and their associated HR increases in SB patients may be related to an increase in stress. SB patients tend to feel more stressful at work and in their daily life<sup>34</sup> and have an increase in oxidative stress and anxiety<sup>35</sup>, salivary cortisol<sup>36</sup> and urinary catecholamines<sup>8,9</sup>. Stress or emotional responses might increase jaw movements as neurons in forebrain limbic nuclei including amygdala, in which some of neurons are innervated by corticotrophin-releasing factor immunopositive fibers, project to the mesencephalic nucleus, the trigeminal motor nucleus or to reticular regions around the motor

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nucleus. Forebrain nuclei related to stress responses and autonomic control might influence the trigeminal motor neurons and consequently play a role in the pathophysiology of SB<sup>37</sup>. Indeed, psychological counseling<sup>38</sup> and relaxation therapies<sup>39</sup> that could reduce exaggerated responsiveness to emotional or physical stress<sup>40</sup> might be used in treatment of SB.

Previous<sup>6,41</sup> and current studies have shown close relationships between occurrence of RMMAs/SB and sympathetic activation, so any approaches that can decrease sympathetic activity per se and reduce any stimulation that causes sympathetic excitation might be used to treat SB. For example, orthopedic appliances<sup>24</sup> and occlusal adjustments<sup>42</sup>, which can reduce sympathetic activity related to oral somatosensory stimulation, and  $\alpha_2$  receptor agonists (such as clonidine), which reduce sympathetic activity<sup>43-45</sup>, have been reported for treatment of SB. Clonidine (an  $\alpha_2$  receptor agonist) has been shown to reduce SB index in SB patients by 61% even though it is not currently used for treatment of SB due to its blood pressure lowering effects<sup>44</sup>. However, cause versus effect relationship between sympathetic excitation and occurrence of RMMAs cannot be established in the current study. A previous study showed there was a close relationship between SB and cardiovascular diseases<sup>13</sup>. However, it is unclear whether frequent movements associated with HR increases and arousals in SB patients during sleep increase cardiovascular vulnerability. Further studies of pathophysiological mechanisms of SB and possible influences of RMMAs/SB on cardiovascular vulnerability are needed.

In short, we have studied HR increases in relation to different types of movements and RMMAs in the SB patients and normal controls. These data suggest the HR increases associated with RMMAs may be intrinsic to the cortical arousal response and autonomic activation, and difference in HR increases associated with different types of movements and RMMAs might be related to the changes in respiration and difference in cortical arousal levels associated with RMMAs. Inhibition of sympathetic activity or removal/reduction of any stimulation that causes sympathetic excitation might contribute to treatment effects in some therapies for SB.

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## Conclusions

These data suggest the HR increases associated with RMMAs may be intrinsic to the cortical arousal response and autonomic activation, and differences in HR increases associated with different types of movements and RMMAs might be related to the changes in respiration and differences in cortical arousal levels.

## Limitations of the study

The number of subjects used in the current study was relatively small, the ratios of male to female subjects in the groups of the SB patients and controls were not the same, and the age range was narrow. Further studies are required to examine larger groups of the SB patients and controls with equal ratios of female to male subjects in a wider age range. Since calculation of respiration was based on an indirect measure of air flow and estimation of nasal pressure from the PSG recordings, data interpretation should be made with caution.

## Conflict of Interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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**Table 1.** Demographic and general sleep data of the study population

	<b>SB patients</b>	<b>Controls</b>	<b><i>P</i>*</b>
Sex			
Male	4	5	
Female	6	6	
Age, yr	21.3±0.63	22.55±0.45	0.122
Sleep variables			
Total sleep time, min	422.55±15.04	443.86±13.61	0.305
Sleep efficacy, %	91.33±2.08	91.20±1.25	0.957
Microarousal index, events/h	5.95 (3.31-16.36)	3.45 (1.92-6.45)	0.005
Arousal index, events/h	8.55 (6.40-18.10)	5.13 (2.85-8.30)	0.001
AHI, events/h	0.55 (0.30-4.97)	0.70 (0.21-4.80)	0.557
SB index, events/h	8.35±0.83	3.77±0.38	<0.001
PLMI, events/h	2.25 (0.45-8.50)	0.80 (0.00-4.41)	0.468
Sleep stage (%)			
N1	6.98±1.20	8.23±0.90	0.410
N2	35.18±3.65	41.99±1.35	0.132
N3	31.89±2.30	26.58±2.17	0.110
REM	25.71±2.45	23.20±1.30	0.364

Values are expressed as mean ± standard error of mean (SEM) for variables with a normal distribution and median (minimum-maximum) for variables with a non-normal distribution. AHI: apnea-hypopnea index. N1-N3: non-rapid eye movement sleep stage 1-3. PLMI: periodic leg movements index. REM: rapid eye movement. SB: sleep bruxism.

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\* t-test or Wilcoxon rank-sum test.

### Figure legends

**Fig. 1.** The raw data recorded from SB patients showing SB/RMMAs (a: Phasic, b: Tonic and c: Mixed type), LMs and their associated HR changes. SB: sleep bruxism; RMMAs: rhythmic masticatory muscle activities; LMs: limb movements; HR: heart rate; MASS: masseter muscle; MH: mylohyoid muscle; LUE: extensor carpi radialis of left forearm; LUF: flexor carpi radialis of left forearm; RUE: extensor carpi radialis of right forearm; RUF: flexor carpi radialis of right forearm; LLE: tibialis anterior muscle of left leg; LLF: gastrocnemius of left leg; RLE: tibialis anterior muscle of right leg; RLF: gastrocnemius of right leg. Horizontal bar: 10 s; Vertical bar: 20 bpm for HR, 1 mV for electrocardiographic activities and 100  $\mu$ V for all electromyographic traces.

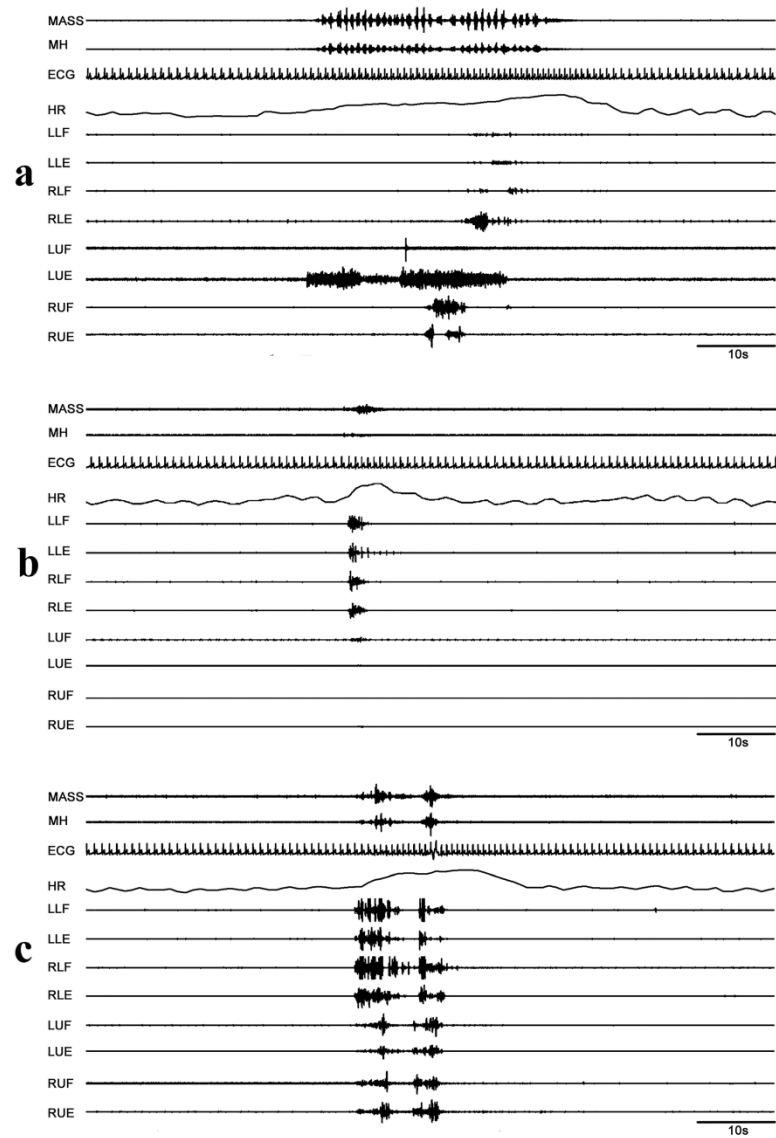
**Fig. 2.** Differences in the amplitude (a), duration (b) of HR increase, time to reach HR peak (c) and duration of movement events (d) associated with RMMAs, RMMA+LMs and LMs in the SB patients and the controls. \* $P<0.05$ , \*\* $P<0.01$  and \*\*\* $P<0.001$ , post hoc Holm-Sidak tests. Errors represent one SEM. HR: heart rate; SB: sleep bruxism; RMMAs: rhythmic masticatory muscle activities; LMs: limb movements; SEM: standard error of mean.

**Fig. 3.** Differences in the amplitude (a), duration (b) of HR increases, time to reach HR peak (c) and duration of movement events (d) associated with phasic, tonic and mixed RMMAs in the SB patients and the controls. \* $P<0.05$ , \*\* $P<0.01$  and \*\*\* $P<0.001$ , post hoc Holm-Sidak tests. Error bars represent one SEM. HR: heart rate; SB: sleep bruxism; RMMAs: rhythmic masticatory muscle activities; SEM: standard error of mean.

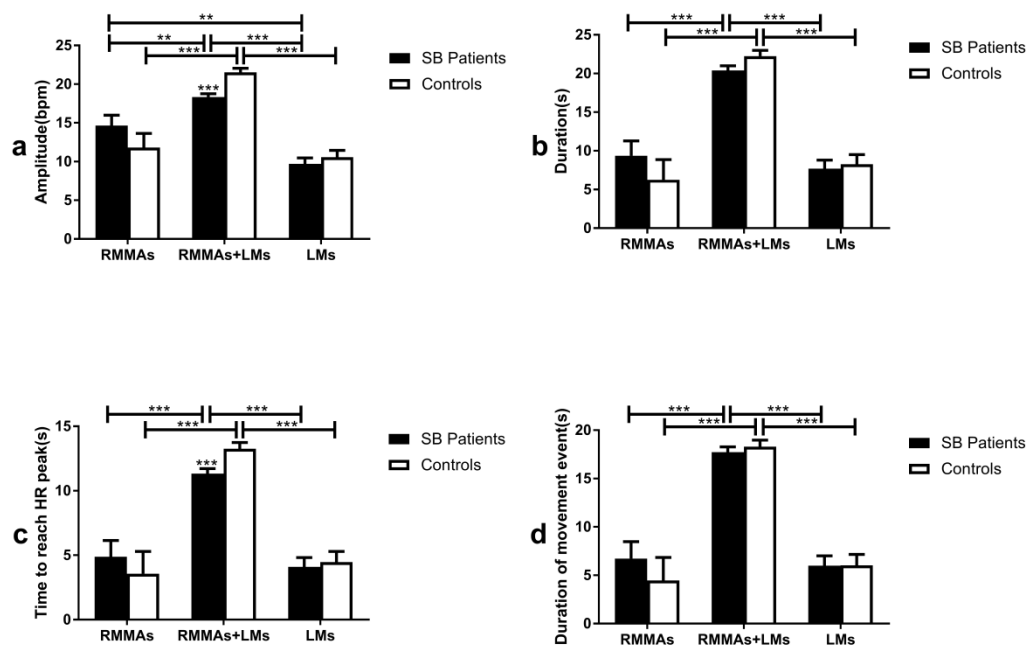
**Fig. 4.** Association of different types of RMMAs with changes in arousal levels. AW: awakenings; mAR: microarousal; NA: no arousal.  $n=10$  for the SB patients and  $n=11$  for the controls. The data

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were expressed as median (minimum-maximum). \* $P<0.017$ , \*\* $P<0.003$ , post hoc Wilcoxon rank-sum tests with Bonferroni corrections. SB: sleep bruxism; RMMAs: rhythmic masticatory muscle activities; SEM: standard error of mean.

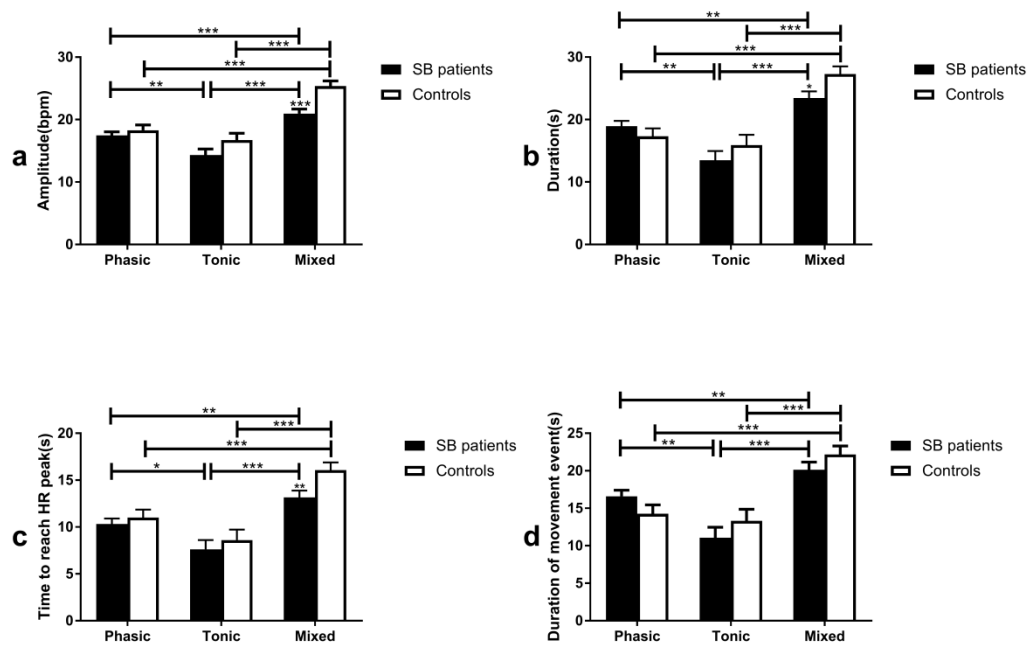


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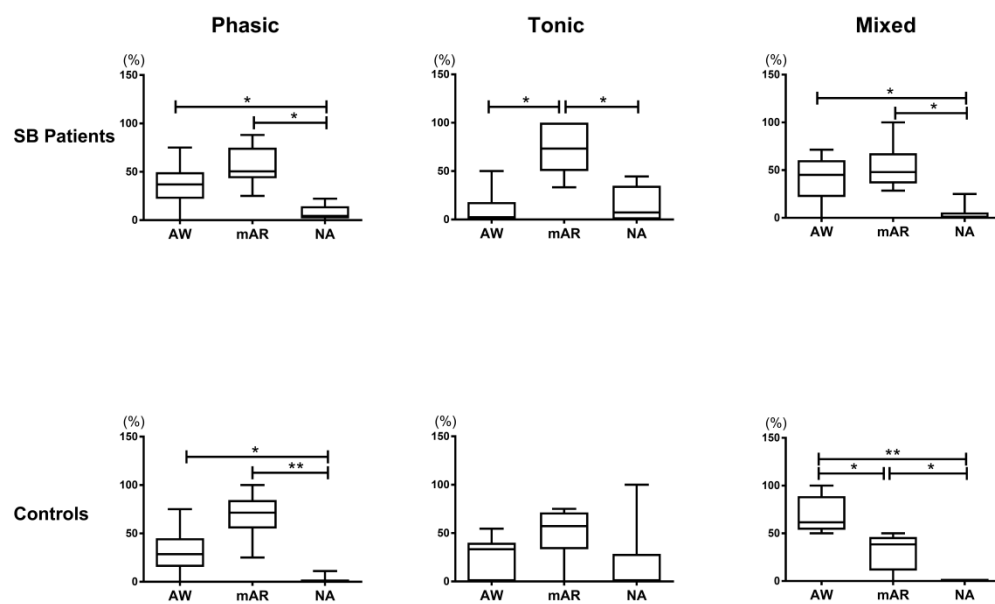


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