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BRIEF COMMUNICATION

Greatest rapid eye movement sleep atonia loss in men and older age

Stuart J. McCarter[1], Erik K. St. Louis[1,2,3,4], Bradley F. Boeve[1,2,4], David J. Sandness[1] & Michael H. Silber[1,2,4]

[1]Mayo Center for Sleep Medicine, Mayo Clinic and Foundation, Rochester, Minnesota
[2]Mayo Clinic College of Medicine, Mayo Clinic and Foundation, Rochester, Minnesota
[3]Mayo Clinic Department of Medicine, Mayo Clinic and Foundation, Rochester, Minnesota
[4]Mayo Clinic Department of Neurology, Mayo Clinic and Foundation, Rochester, Minnesota

Correspondence
Erik K. St. Louis, Mayo Center for Sleep Medicine, Departments of Medicine and Neurology, Mayo Clinic College of Medicine, 200 First Street Southwest, Rochester, MN 55905.
Tel: (507) 266-7456;
Fax: (507) 266-7772;
E-mail: stlouis.erik@mayo.edu

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Abstract

To determine quantitative REM sleep muscle tone in men and women without REM sleep behavior disorder, we quantitatively analyzed REM sleep phasic and tonic muscle activity, phasic muscle burst duration, and automated REM atonia index in submentalis and anterior tibialis muscles in 25 men and 25 women without REM sleep behavior disorder. Men showed significantly higher anterior tibialis phasic muscle activity. Higher phasic muscle activity was independently associated with male sex and older age in multivariate analysis. Men and the elderly may be biologically predisposed to altered REM sleep muscle atonia control, and/or some may have occult neurodegenerative disease, possibly underlying the predominance of older men with REM sleep behavior disorder.

Introduction

REM sleep without atonia (RSWA), the loss of normal REM sleep skeletal muscle atonia, is the physiologic substrate of REM sleep behavior disorder (RBD).[1,2] RBD most commonly affects older men, with over 80% of RBD patients over 50 years old being men.[3] However, possible mechanisms underlying the predominance of RBD in men of older age and factors predisposing individuals for development of RBD remain unknown.[4]

To our knowledge, only a single previous study focused on quantitative RSWA analysis in neurologically normal individuals without a history of dream enactment, which used the automated REM atonia index (RAI) of submentalis (SM) muscle activity, showing that REM muscle atonia peaked in early adulthood and decreased with older age.[5] However, this study did not compare RAI differences between men and women. We aimed to determine whether sex and age impacted RSWA muscle activity in adults without a history of dream

enactment behaviors seen in our clinical sleep medicine practice.

Methods

A total of 50 consecutive patients (25 men and 25 women) without a history of dream enactment or nocturnal behaviors seen from 2010 to 2012 were identified for retrospective analysis of RSWA from the polysomnographic (PSG) database at the Mayo Clinic Center for Sleep Medicine. Thirty-eight patients presented with a chief complaint of snoring or suspected sleep-disordered breathing, while 12 patients presented due to sleepiness, fatigue, or insomnia. Patients were excluded from analysis if PSG revealed an apnea hypopnea index (AHI) of >15, a REM AHI of >10, a total REM time of <5 min, or a periodic limb movement index (PLMI) of >50 per hour. Patients on central nervous system active drugs or with psychiatric or neurodegenerative disorders were also excluded from analysis. The Mayo Clinic Institutional Review Board approved this study and oversaw its activities.

Manual analysis of phasic muscle activity was performed for both individual SM and anterior tibialis (AT) muscles similar to previously published methods utilizing Hypnolab sleep scoring software (ATES Medica Labs, Verona, Italy).[6,7] SM and AT phasic muscle activity was also combined to determine overall phasic muscle activity. Phasic muscle burst durations lasting from 0.1 to 14.9 sec and exceeding four times background electromyogram (EMG) were also calculated for SM and AT muscles.[7] Each 30-sec epoch was broken down into 3-sec mini-epochs for analysis of phasic muscle activity, with any 3-sec mini-epoch containing a phasic muscle burst scored as positive.[6,7] Tonic muscle activity was defined as sustained increased voltage EMG activity lasting longer than 15 sec, with an amplitude twice the background EMG.[6,7] Tonic muscle activity was calculated as the number of 30-sec epochs with tonic muscle activity divided by the total number of 30-sec REM epochs.[6,7] The automated SM RAI was also calculated using Hypnolab sleep scoring software with a value of <0.9 indicating the presence of RSWA.[5,8]

Scorers were blinded to the gender of each patient and had high inter-rater reliability with a κ coefficient of 0.88. Clinical and demographic data were presented as means, standard-deviations, and ranges. Chi-square tests were used to compare categorical variables while nonparametric Wilcoxon rank-sum tests were used for comparison of quantitative variables. Relationships between clinical variables and phasic, tonic, RAI, and phasic muscle burst durations were analyzed using multivariate regression models. To correct for multiple comparisons, an experiment-wise Bonferroni correction factor was applied for the main RSWA measure comparisons, setting significance at an alpha of $P < 0.01$. Alpha was set at $P < 0.05$ for exploratory analyses comparing the subgroups of younger and older men and women.

Results

Clinical, demographic, and PSG data did not differ between groups (Table 1). The average age and age range

Table 1. Demographics, polysomnographic, and RSWA characteristics of the sample.

	Men	Women	*P*-value
Demographics			
Age	49.5 ± 18.2	53.3 ± 16.8	0.36
ESS	8.47 ± 5.2	10.5 ± 5.1	0.25
Beta-blocker use, *n* (%)	6 (24)	4 (16)	0.73
Reason for visit			
Snoring/SDB, *n* (%)	21 (84)	17 (68)	0.32
Insomnia/EDS, *n* (%)	4 (16)	8 (32)	0.32
PSG variables			
AHI	3.6 ± 4.0	2.2 ± 2.9	0.34
REM AHI	3.1 ± 2.9	3.2 ± 3.4	0.81
REM time (min)	62.2 ± 20.4	60.1 ± 22.0	0.79
% ME excluded	6.3 ± 4.0	6.8 ± 4.4	0.67
No. ME analyzed	1170.8 ± 396	1118.1 ± 410	0.55
Hypoxic time (min)	2.7 ± 7.5	3.1 ± 9.3	0.16
SE (%)	77.5 ± 12.7	63.1 ± 30.9	0.17
TST (min)	313.7 ± 87.5	307.2 ± 123.2	0.75
ISL (min)	17.9 ± 12.2	32.2 ± 36.6	0.32
IRL (min)	82.7 ± 50.2	117 ± 61.8	0.02
Wake after sleep onset (min)	62.6 ± 50.2	69.0 ± 46.7	0.52
REM %	17.9 ± 6.0	19.3 ± 6.2	0.60
N1%	8.9 ± 4.6	8.3 ± 4.4	0.62
N2%	51.7 ± 9.1	51.4 ± 12.3	0.59
N3%	21.5 ± 10.7	21.0 ± 9.2	0.62
PLMI	10.0 ± 11.9	11.2 ± 14.3	0.73
PLMAI	2.7 ± 3.7	2.7 ± 4.7	0.69
RDI	5.6 ± 4.9	3.6 ± 2.8	0.26
Muscle combination			
SM + AT phasic %	17.2 ± 7.7	12.1 ± 8.2	0.002*
Single muscles			
SM phasic %	4.1 ± 2.4	6.4 ± 4.3	0.04
AT phasic %	14.5 ± 8.1	6.2 ± 6.9	<0.0001*
SM tonic %	0.06 ± 0.19	0	0.15
RAI	0.96 ± 0.02	0.94 ± 0.04	0.31
SM duration (sec)	0.51 ± 0.23	0.41 ± 0.10	0.11
AT duration (sec)	0.50 ± 0.28	0.49 ± 0.28	0.71

RSWA, REM sleep without atonia; ESS, Epworth Sleepiness Scale score; SDB, sleep-disordered breathing; EDS, excessive daytime sleepiness; AHI, apnea-hypopnea index; ME, 3-sec mini-epochs; hypoxic time, mins spent O_2 saturation <90%; SE, sleep efficiency; TST, total sleep time; ISL, initial sleep latency; IRL, initial REM latency; PLMI, periodic limb movement index; PLMAI, periodic limb movement arousal index; RDI, respiratory disturbance index; SM, submentalis muscle; AT, anterior tibialis muscle; RAI, REM atonia index.
*Indicates statistically significant at $P < 0.01$.

was similar in men (24–78 years) and women (24–80 years). Suspected sleep-disordered breathing or snoring (76%), and sleepiness or insomnia (24%) were the most common reasons for PSG. None of the patients had narcolepsy.

The key RSWA comparisons between men and women are shown in Figure 1. Men had higher overall phasic muscle activity compared to women (17.2 ± 7.7 vs. 12.1 ± 8.2, $P < 0.002$). Male sex and older age were associated with higher phasic muscle activity, adjusting for REM time, REM AHI, and PLMI ($P = 0.006$). SM phasic muscle activity (4.1 ± 2.4 vs. 6.4 ± 4.3, $P = 0.04$) and RAI (0.96 ± 0.02 vs. 0.94 ± 0.04, $P = 0.31$) did not differ significantly between groups, and there was no association between SM phasic muscle activity or RAI with group or age. AT phasic muscle activity was significantly higher in men than women (14.5 ± 8.1 vs. 6.2 ± 6.9, $P < 0.0001$), and increased AT phasic muscle activity was associated with both male sex and older age after adjusting for REM AHI, REM time, and PLMI ($P < 0.0001$). Neither SM or AT phasic muscle burst duration differed between groups (Table 2).

Subdividing groups into younger controls aged 24–49 years (14M, 14F) and older controls aged 50–80 years (11M, 11F) demonstrated higher AT muscle activity in older than younger subjects, higher in older men than women (19.8 ± 8.1 vs. 9.8 ± 9.3, $P = 0.015$). Young men had significantly higher overall (14.3 ± 5.7 vs. 9.4 ± 5.6, $P = 0.008$) and leg (10.2 ± 5.0 vs. 3.5 ± 1.8, $P < 0.0001$) phasic muscle activity than young women. Older men had higher AT phasic muscle activity than younger men (19.8 ± 8.1 vs. 10.2 ± 5.0, $P = 0.004$). Overall (14.3 ± 5.7 vs. 15.7 ± 9.9, $P = 0.85$) and leg (10.2 ± 5.0 vs. 9.8 ± 9.3, $P = 0.29$) phasic muscle activity were similar between younger men and older women.

Discussion

Our results suggest that there may be biological sex and age-related differences in the amount and location of REM sleep muscle tone between men and women without complaints of dream enactment. RBD primarily affects older men; however, the reason for this sex discrepancy is unknown.[3,4,9] The findings in this study suggest that men may be biologically predisposed to higher amounts of phasic muscle tone during REM sleep, possibly due to altered control of REM sleep muscle atonia, especially in the AT, as they age. Interestingly, these findings are similar to a previous small study that compared RSWA in RBD between men and women. This study found that men with RBD had a significantly higher degree of RSWA in the leg compared to women, whereas women had

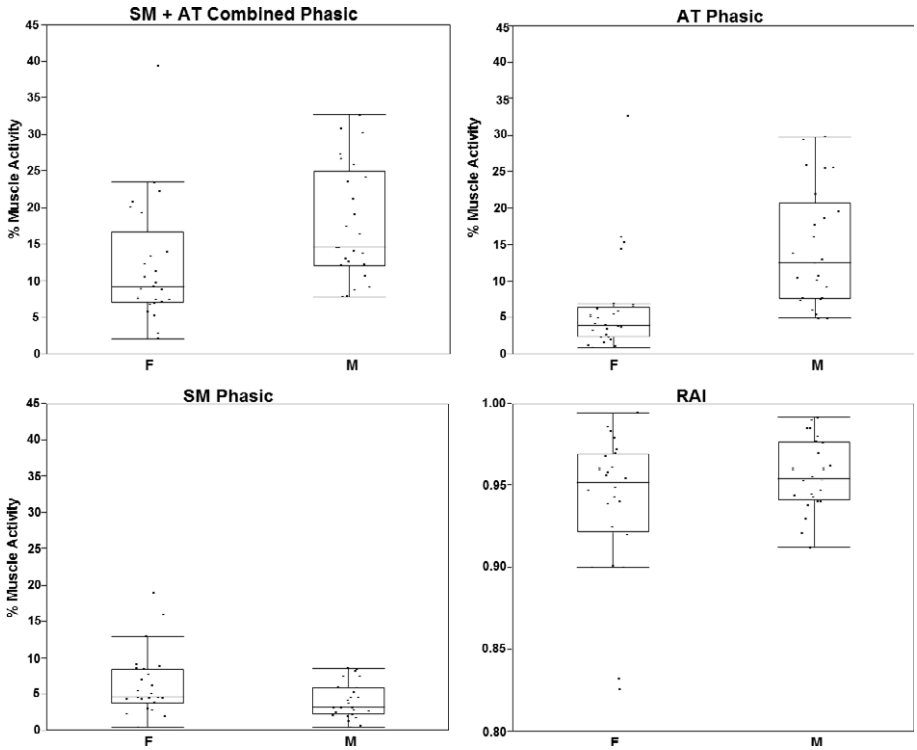

Figure 1. Phasic and tonic muscle activity, phasic muscle burst durations, and REM sleep atonia index in men and women.

Table 2. RSWA comparisons between male and female subgroups.

	Young men[a] (24–49 years)	Young women[b] (24–49 years)	Old men[c] (50–78 years)	Old women[d] (50–80 years)	*P*-value <0.05
Number	14	14	11	11	
SM + AT phasic %	14.3 ± 5.7	9.4 ± 5.6	22.4 ± 7.9	15.7 ± 9.9	a > b, c > a, c > d, c > b
SM phasic %	4.7 ± 2.5	6.2 ± 5.2	3.4 ± 2.3	6.4 ± 3.0	
AT phasic %	10.2 ± 5.0	3.5 ± 1.8	19.8 ± 8.1	9.8 ± 9.3	a > b, c > a, c > b, d > b
SM tonic %	0.1 ± 0.3	0	0	0	
RAI	0.95 ± 0.02	0.93 ± 0.05	0.96 ± 0.03	0.95 ± 0.02	
SM duration (sec)	0.51 ± 0.16	0.41 ± 0.1	0.52 ± 0.31	0.40 ± 0.09	
AT duration	0.54 ± 0.19	0.50 ± 0.33	0.42 ± 0.21	0.48 ± 0.21	

RSWA, REM sleep without atonia; SM, submentalis muscle; AT, anterior tibialis muscle; RAI, REM atonia index.

significantly more muscle tone in the arm than men.[10] Unfortunately, arm EMG was not recorded in our patients. However, we observed a similar pattern of significantly higher phasic muscle tone in the leg than chin in men, while women had a nonsignificant trend toward higher phasic muscle tone in the chin than leg, suggesting that different somatotopic control regions within the pontomedullary region governing REM sleep muscle atonia may be preferentially affected between the sexes. However, animal research and additional prospective human studies will be necessary to determine whether differential somatotopic control mechanisms for REM sleep atonia exist, and whether such mechanisms could explain our observed differences in RSWA between men and women.

Our results showed that men and women had inherently different quantitative REM sleep muscle activity, especially in older age, suggesting different potential biological predispositions to loss of REM muscle atonia and development of RBD. Estrogen has been shown to influence concentrations of serotonin, norepinephrine (NE), and dopamine, which all play a potentially stabilizing role in the regulation of REM sleep muscle control.[11] In particular, estrogen may decrease noradrenergic secretion in the locus coeruleus (LC) of rats.[12] NE potentially amplifies glutamatergic muscle excitation during REM sleep. A speculative mechanism for lower REM phasic muscle activity in women could be that their higher endogenous estrogen might lead to a lower level of central nervous system (CNS) NE neurotransmission, thereby reducing the quantity of rapid eye movement (REM) phasic muscle bursts.[13] The average age of menopause in the US is 51, so that decreased levels of estrogen could also have contributed to increased amounts of RSWA in our older women (age >50) as compared to younger women.[14] However, prospective clinical and basic research studies correlating estrogen levels and RSWA are necessary to elucidate whether estrogen could play a role in our observed gender and age-related differences in REM sleep muscle atonia quantities.[11,15]

Another potential explanation for our findings relates to the existence of incidental Lewy body disease (iLBD) in the population. iLBD refers to the presence of Lewy bodies and Lewy neurites in the nervous system of older individuals at autopsy who otherwise exhibited no antemortem features of cognitive impairment, Parkinsonism, or autonomic dysfunction.[16–18] While the prevalence of iLBD in the population is not known, growing evidence suggests that it is not rare and tends to be more common in men than women.[17] Some patients with PSG-proven RBD have been found to have iLBD at autopsy.[19,20] Therefore, our findings could be explained, at least in part, due to the presence of underlying iLBD in some of our subjects. Our findings suggest that a future study should be conducted to determine whether RSWA may be a useful biomarker for identifying subjects with iLBD in the general population for possible participation in future neuroprotective medication trials.

This study has several limitations. As a retrospective study of patients seen in a sleep center, we were unable to control for several potential confounding biases, such as presenting sleep complaints or medical comorbidities. However, we excluded patients with known neurological or psychiatric disorders and those receiving centrally active medications such as antidepressants that are known to impact REM sleep muscle tone[1]; and beta-blocker use, sleep-disordered breathing or sleepiness were not associated with REM sleep muscle activity. In addition, periodic limb movements of sleep (PLMS) did not appear to be responsible for the difference between men and women in REM sleep muscle tone in the AT muscle, given that PLMI was not associated with REM sleep muscle activity. Our median PLMI was 3.2 for women and 3.3 for men, similar to a recently published study in healthy volunteers that found PLMI was similar between men and women with a median PLMI of 2.9.[21] Fragmentary myoclonus, defined as a muscle burst of <150 msec, is more frequent in older men than women and may have influenced our results; however, AT average phasic muscle burst duration

was significantly longer than 150 msec in both men and women,[21] making it unlikely that fragmentary myoclonus explained the findings in our subjects. Future prospective studies should recruit healthy community male and female controls without sleep complaints or medication use throughout the lifespan to better determine whether differences in REM sleep muscle activity differ by age and sex, and to establish normative quantitative RSWA metrics throughout the lifespan.

Conclusions

REM sleep muscle activity appears to be higher in men than women without RBD, especially in the AT. Young men have higher muscle activity compared to younger women but similar to those of older women. These results suggest that the difference seen in RBD between the sexes could be a result of a biological predisposition to altered REM sleep muscle atonia control in men, the presence of an underlying neurodegenerative disorder such as Lewy body disease, or both factors. Further prospective basic and clinical research of quantitative REM sleep muscle tone is necessary to confirm these findings and elucidate mechanisms for differences in REM sleep muscle tone due to age and sex.

Author Contributions

Stuart J. McCarter – Study design, primary data analysis, drafting and critical revision of the manuscript. Erik K. St. Louis – Study design, assistance with data analysis, drafting and critical revision of the manuscript. Bradley F. Boeve – Critical revision of the manuscript. David J. Sandness – Critical revision of the manuscript. Michael H. Silber – Critical revision of the manuscript.

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Conflict of Interest

Dr. St. Louis reports grants from Mayo Clinic CTSA, grant from Mayo Clinic Alzheimer's Diseases Research Center, during the conduct of the study; other than Inspire, Inc., outside the submitted work. Dr. Boeve reports other from Cephalon, Inc., other from Allon Pharmaceutical, grants and other from GE Healthcare, personal fees from Cambrige Medicine, personal fees from American Academy of Neurology, personal fees and other from Tau Consortium, outside the submitted work.

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