Cardiac Autonomic Regulation During Sleep in Idiopathic REM Sleep Behavior Disorder

Paola A. Lanfranchi, MD, MSc1,2; Lorraine Fradette, BS3; Jean-François Gagnon, PhD4; Roberto Colombo, BEng5; Jacques Montplaisir, MD, PhD2

1Department of Medicine, Cardiology Division, Hôpital du Sacré-Coeur de Montréal, Montréal, Canada; 2Centre d’étude du sommeil et des rythmes biologiques, Hôpital du Sacré-Coeur de Montréal, Montréal, Canada; 3Bioengineering Department, Salvatore Maugeri Foundation, Veruno, Italy

Objective: To assess cardiac autonomic and respiratory changes from stage 2 non-rapid eye movement sleep (NREM) to rapid eye movement (REM) sleep in subjects with idiopathic REM sleep behavior disorder (RBD) and controls. We tested the hypothesis that REM-related cardiorespiratory activation is altered in subjects with RBD.

Design: Retrospective case-control study.

Setting: University hospital-based sleep research laboratory.

Patients: Ten subjects with idiopathic RBD (2 women, mean age 63.4 ± 6.2 years) and 10 sex- and age-matched controls (mean age 63.9 ± 6.3 years).

Intervention: One-night polysomnography was used to assess R-R variability during NREM and REM sleep.

Measurements and Results: Spectral analysis of R-R interval and respiration were performed. Mean R-R interval, low-frequency (LF) and high-frequency (HF) components in both absolute and normalized units (LFnu and HFnu), and the LF/HF ratio were obtained from 5-minute electrocardiogram segments selected during NREM and REM sleep under stable conditions (stable breathing pattern, no microarousals or leg movements). Respiratory frequency was also assessed. Values obtained were then averaged for each stage and analyzed by 2 × 2 analysis of variance with group (RBD subjects and controls) as factor and state (NREM and REM) as repeated measures. RR interval, HF, and HFnu components decreased from NREM to REM in controls but did not change in RBD subjects (interaction P < 0.05). LFnu (interaction P < 0.001), LF/HF (interaction P < 0.001), and respiratory frequency (interaction P < 0.05) increased from NREM to REM sleep in controls but remained stable in RBD subjects.

Conclusion: REM-related cardiac and respiratory responses are absent in subjects with idiopathic RBD.

Keywords: REM sleep behavior disorder, autonomic nervous system, heart rate variability.

Citation: Lanfranchi PA; Fradette L; Gagnon JF; Colombo R; Montplaisir J. Cardiac autonomic regulation during sleep in idiopathic REM sleep behavior disorder. SLEEP 2007;30(8):1019-1025.

IN HEALTHY SUBJECTS, AUTONOMIC CARDIOVASCULAR REGULATION VARIES CONSIDERABLY WITH SLEEP STAGE. NON-RAPID EYE MOVEMENT (NREM) SLEEP is characterized by relative autonomic stability, a dominance of parasympathetic influences to the heart, and a reduction in sympathetic efferent vasomotor tone, all of which translate into a stable low heart rate and low blood pressure.1,2 In contrast, rapid eye movement (REM) sleep is a state of autonomic instability, dominated by remarkable fluctuations between parasympathetic and sympathetic influences, which produce marked sudden changes in heart rate and blood pressure.1,3 In addition, respiration becomes shallower and more frequent in response to REM sleep.4,5

Spectral analysis of RR variability has consistently revealed that, in normal subjects, different rhythms dominate in NREM and REM sleep: a shift toward the respiratory-mediated high-frequency components (HF, ~0.25 Hz) of R-R variability characterizes NREM sleep, whereas the cardiovascular excitation and instability of REM sleep is reflected by a significant increase of the low-frequency components (LF, ~0.1 Hz).6,7 REM sleep behavior disorder (RBD) is a parasomnia occurring during REM sleep only, characterized by a loss of the characteristic skeletal muscle atonia and the presence of complex motor activity in association with dream mentation.8,9 Patients with RBD frequently evolve toward neurodegenerative disorders, especially Parkinson disease and dementia with Lewy bodies,8,10 both known to be associated with dysautonomia.11,12 Preliminary studies have revealed a blunted heart rate response associated with body movements during sleep in idiopathic RBD.13,14

The objective of this study was to assess autonomic cardiac regulation and respiratory responses during sleep in subjects with idiopathic RBD, compared with controls, using spectral analysis of R-R variability and respiration variability. We tested the hypothesis that REM sleep-related cardiac and respiratory responses are altered in subjects with idiopathic RBD.

METHODS

Population

Ethical standards were used in our research. We retrospectively examined clinical data and polysomnographic recordings of all consecutive patients diagnosed with idiopathic RBD at our sleep clinic between January 1996 and June 2006. RBD diagnosis was based on the criteria of the second edition of the International Classification of Sleep Disorders,15 i.e., presence of excessive muscular activity during REM sleep with either a history of...
motor manifestations during sleep or presence of motor behaviors recorded by polysomnography. Subjects were excluded if they were older than 75 years of age; had concomitant diabetes, cardiovascular, lung, kidney, neurologic, or psychiatric conditions; had other sleep disorders such as restless legs syndrome, sleep apnea, or narcolepsy; or if they were taking medications known to affect sleep or the autonomic nervous system. Additional entry criteria included adequate electrocardiogram signals to allow R wave detection and the potential for at least 5 segments of 5 minutes during NREM sleep and 3 segments during REM sleep, in the absence of EEG arousal, periodic leg movements during sleep, or respiratory changes (see below).

Of the original population of 94 subjects diagnosed with idiopathic RBD, 84 subjects were excluded for concomitant cardiovascular disease (n = 21), diabetes (n = 4), obstructive sleep apnea (n = 15), poor electromyogram recording quality (n = 24), or excessive number of periodic limb movements during sleep, which would preclude R-R variability analysis (n = 20). A final population of 10 subjects with idiopathic RBD (2 women; mean age 63.4 ± 6.2 years) was considered for analysis. Data from 10 age- and sex-matched healthy subjects (mean age 63.9 ± 6.3 years), from our sleep disorders center databank, were also included as controls.

Data collection and Analysis

All subjects had 1 night of polysomnography in the sleep laboratory, using the Harmony acquisition system (Stellate Systems, Montreal, Canada). Polysomnography was performed according to a standard clinical protocol, with electroencephalographic recording (C3-A2, O2/A1), submental and anterior tibialis electromyography, electrooculography, oronasal airflow (thermocouples), thoracic and abdominal strain gauges, oxygen finger probe, and 1-lead electrocardiography (Lead I).

Sleep stages 1 to 4 were scored according to a modified version of the standard method, using 20-second epochs. REM sleep was scored based on electroencephalogram and electrooculogram only, according to a method developed for RBD. Microarousals and respiratory events were scored according to standard methods. Periodic limb movements of sleep were scored according to Coleman’s criteria. Polysomnography variables examined included sleep latency (time elapsed between lights off and sleep onset), sleep efficiency (total sleep time/total sleep period from sleep onset to the last awakening), percentage of each sleep stage, microarousal index (index: number per hours of sleep), apnea-hypopnea index, and periodic leg movement index.

The electrocardiographic signal was processed for R-wave detection and arrhythmia and artifact identification and removal. Five-minute R-R and respiration segments were selected from stage 2 NREM and REM sleep during the night. Segments included stationary signals (without microarousals, periodic leg movements, complex movements during REM sleep, or apneas) and apart from sleep-state changes. R-R variability was analyzed in time and frequency domains using Cardiolab software (Fondazione S. Maugeri, Italy). Time-domain variables included mean R-R interval, standard deviation of the RR intervals (sdRR), and percentage of 50-ms or greater differences between adjacent R-R intervals (pNN50), a measure in time domain of parasympathetic influence. Spectral components were quantified by an autoregressive decomposition algorithm to compute spectral peak powers and their central frequencies and classify them into LF (0.04-0.15 Hz) and HF (0.15-0.4 Hz) bands (Figure 1). LF and HF R-R variability components were considered in both absolute values and normalized units (LFnu and HFnu), which were obtained by dividing the power of each component by total variance, from which the very low frequencies (< 0.04 Hz) and DC components (0 Hz) had been subtracted, and multiplying them by 100.

![Figure 1](image-url)
LF/HF ratio was also calculated as an estimate of sympathovagal balance. Dominant respiration frequency was measured and defined as the central frequency of the dominant peak of respiration variability. When respiration included more than 1 frequency component, central frequency was calculated as a weighted average. Cross-analysis between respiration and RR signals was also performed to identify coherent peaks for RR and respiration variability. Segments containing coherent RR and respiration spectrum components in the LF band were excluded from the analysis. Cardiorespiratory variables for all NREM and REM sleep segments across the night were averaged for each subject.

**Statistical Analysis**

Sleep measures were compared between RBD subjects and controls by unpaired t test. The effect of sleep on cardiorespiratory variables was compared between groups using $2 \times 2$ analysis of variance with 1 independent factor (group: RBD and controls) and 1 repeated measure (state: NREM and REM sleep). Planned comparisons were performed in the presence of significant interaction. All $P$ values $\leq 0.05$ were considered statistically significant.

Figure 2—Mean R-R interval, high-frequency components in normalized units (HFnu), low-frequency to high-frequency ratio (LF/HF) and respiration frequency changes during sleep in subjects with REM (rapid eye movement) sleep behavior disorder (RBD) and controls ($2 \times 2$ analysis of variance). R-R interval decreased slightly in controls but did not change in subjects with RBD from non-rapid eye movement (NREM) sleep to REM sleep (Interaction: $F = 4.1, P = 0.058$). HFnu decreased significantly during REM sleep in controls only, whereas it remained unchanged in subjects with RBD (Interaction: $F = 11.4, P < 0.01$). LF/HF ratio increased from NREM to REM sleep in controls only and did not change in subjects with RBD (Interaction: $F = 15.9, P < 0.001$). Finally, respiration frequency increased from NREM to REM sleep in controls, but no change was seen between the 2 conditions in subjects with RBD (Interaction: $F = 4.6, P < 0.05$).
RESULTS

Comparisons of sleep measures between the 2 groups are reported in Table 1. No differences were observed between the 2 groups in any of the sleep variables considered.

Sleep-related changes of autonomic and respiratory variables in both groups of RBD patients and controls (2 × 2 analysis of variance) are reported in Table 2 and Figure 2. The R-R interval decreased slightly in controls and did not change in RBD subjects from NREM sleep to REM sleep (Group × state interaction: $F = 4.1, P = 0.058$) (Table 2). In addition, pNN50 decreased from NREM to REM sleep in controls (~2.4%) but less so in RBD subjects (~0.3%) (State effect: $F = 5.1, P < 0.05$; interaction: $F = 2.9, P = 0.1$).

Total power of R-R variability did not change significantly from NREM to REM sleep in either group (Table 2). The HF measured

<table>
<thead>
<tr>
<th>Table 1—Sleep Characteristics in Subjects with RBD and Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep measures</strong></td>
</tr>
<tr>
<td>Sleep latency, min</td>
</tr>
<tr>
<td>Total sleep time, min</td>
</tr>
<tr>
<td>Wake time after sleep onset, min</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
</tr>
<tr>
<td>Stage 1, %</td>
</tr>
<tr>
<td>Stage 2, %</td>
</tr>
<tr>
<td>Stage 3, %</td>
</tr>
<tr>
<td>Stage 4, %</td>
</tr>
<tr>
<td>REM sleep, %</td>
</tr>
<tr>
<td>Microarousal index, no./h</td>
</tr>
<tr>
<td>Apnea-hypopnea index, no./h</td>
</tr>
<tr>
<td>Periodic leg movement index, no./h</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, with P values derived from unpaired t tests. RBD refers to REM (rapid eye movement) sleep behavior disorder.

<table>
<thead>
<tr>
<th>Table 2—NREM-to-REM Sleep Changes in R-R Variability and Respiration in Patients with RBD and Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with RBD</strong></td>
</tr>
<tr>
<td><strong>R-R interval, ms</strong></td>
</tr>
<tr>
<td>1000 ± 48</td>
</tr>
<tr>
<td>2.2 ± 0.9</td>
</tr>
<tr>
<td>788 ± 197</td>
</tr>
<tr>
<td>449 ± 170</td>
</tr>
<tr>
<td>59.8 ± 5.7</td>
</tr>
<tr>
<td>134 ± 30</td>
</tr>
<tr>
<td>31.1 ± 5.3</td>
</tr>
<tr>
<td>5.0 ± 2.0</td>
</tr>
</tbody>
</table>

Planned comparison: *$P < 0.05$; **$P < 0.001$; ***$P < 0.0001$ in controls derived from 2 × 2 analysis of variance

Data are presented as mean ± SD. NREM refers to non-rapid eye movement sleep; RBD, REM (rapid eye movement) sleep behavior disorder; pNN50, the percentage of 50-ms or greater differences between adjacent R-R intervals; LF, low frequency; HF, high frequency; nu, normalized units.
in both absolute and normalized units decreased significantly during REM sleep in controls but remained unchanged in RBD subjects (Interaction: for HF, $F = 6.8$, $P < 0.05$; planned comparisons: $P < 0.001$ in controls, $P = ns$ in RBD; for HFnu, $F = 11.4$, $P < 0.01$; planned comparison: $P < 0.0001$ in controls, $P = NS$ in RBD). LFnu increased from NREM to REM sleep in controls but did not change in RBD subjects (Interaction, $F = 4.7$, $P < 0.05$; planned comparison $P < 0.05$ in controls only). Hence, LF/HF ratio increased from NREM to REM sleep in controls but not in RBD subjects (Interaction: $F = 15.9$, $P < 0.001$; planned comparison $P < 0.0001$, in controls only) (Table 2 and Figure 2). When looking at individual changes in the LF/HF ratio, 8 of 10 subjects with RBD and 1 of 10 controls showed either no change or a reduction (1 RBD subject) in the LF/HF ratio from NREM to REM sleep ($\chi^2 9.9$, $P = 0.001$). Figure 3 shows the power spectra of RR variability during NREM and REM sleep in 2 subjects with RBD who had different profiles of sympathovagal balance during NREM sleep. No changes in the individual sympathovagal balance were observed in either subject during REM sleep.

Finally, respiration frequency was higher during REM compared with NREM sleep in control subjects, but no change was seen between the 2 conditions in subjects with RBD (Interaction: $F = 4.6$, $P < 0.05$; planned comparison: $P < 0.05$ in controls, $P = NS$ in RBD).

Note that all cardiac variables and respiratory frequency during stage 2 NREM sleep were similar between the 2 groups (Table 2 and Figure 2).

**DISCUSSION**

This study shows that normally observed NREM-to-REM-sleep cardiac excitatory response and parasympathetic withdrawal are absent in patients with idiopathic RBD. The lack of changes in mean RR and spectral components of RR variability was striking in these subjects (Figures 2 and 3). We also observed that respiration frequency, which, as expected,13 was higher in controls during REM than during NREM sleep, remained unchanged between the 2 sleep stages in patients with RBD. These results indicate the presence of a deregulation of autonomic and respiratory responses during REM sleep with this condition. Such deregulation could

---

**Figure 3**—Power spectra of RR variability during non-rapid eye movement (NREM) and rapid eye movement sleep (REM) in 2 subjects with REM sleep behavior disorder. Note the stability of the individual profiles and the striking similarity of the low-frequency to high-frequency ratio (LF/HF) between NREM and REM sleep in both subjects.
reflect a primary alteration of the REM sleep processes, implicating the autonomic and respiratory mechanisms as well, or it could be part of a more generalized autonomic dysfunction.

The hypothesis that subjects with idiopathic RBD have autonomic dysfunction was previously proposed by Mahowald and Schenck, who noted a lack of heart rate changes in association with the vigorous REM sleep behaviors shown by these patients. This hypothesis was supported by 2 studies reporting an attenuation of the cardiac response to motor activity during both NREM and REM sleep in subjects with RBD, compared with both controls and subjects with restless leg syndrome. More recently, Postuma et al noted that symptoms of clinical dysautonomia (constipation, urinary symptoms, and erectile dysfunction) were more frequent in subjects with idiopathic RBD, as compared with age-matched controls. Clinical and subclinical signs of autonomic dysfunction, along with early appearance of olfactory disturbances and electroencephalographic changes, have been interpreted as early signs of neurodegeneration in subjects with RBD. Indeed, 40% to 65% of patients with idiopathic RBD eventually develop a neurodegenerative disease, mainly Parkinson disease or dementia with Lewy bodies. Preclinical signs of autonomic dysfunction have been reported in patients with Parkinson disease. Unmedicated patients with newly diagnosed Parkinson disease show an overall reduction in the sympathetic cardiac influence during wakefulness, with reduced R-R variability and impaired LF components and LF/HF ratio, along with decreased sympathetic vasomotor and cardiac adrenergic activity. In this study, we did not measure cardiac autonomic function during wakefulness. However, the autonomic cardiac modulation during stage 2 NREM sleep was highly similar between controls and subjects with RBD, differing profoundly between the 2 groups only during REM sleep. These results suggest that the autonomic regulation of the heart is still preserved in steady NREM sleep in these subjects (Table 2) and becomes evident only during situations of sympathetic excitation. It may be possible that an alteration in the autonomic cardiac control would become evident in NREM sleep as well but only in cases in which the evolution is toward neurodegenerative disease, such as Parkinson disease or dementia with Lewy bodies. Follow-up studies examining RR variability during sleep in subjects with RBD to measure autonomic changes could potentially predict the evolution of RBD toward a neurodegenerative disease. Also, studies exploring the cardiovascular and neurohumoral response to sympathetic stimulation in subjects with RBD during wakefulness would help clarify whether the dysautonomia is a distinct feature of subjects with RBD or only an expression of altered REM sleep processes.

The common denominator of RBD and cardiac autonomic dysfunction is yet to be determined. Although the pathophysiological mechanisms of RBD are not fully understood, neuropsychological and imaging studies performed in patients with RBD have reported abnormalities in several brainstem areas. It is highly possible that brainstem structures contributing to the central autonomic network are also affected by this neuronal damage. For instance, the locus coeruleus-subcoeruleus complex was found to show histopathological abnormalities in patients with RBD. This structure is known to be implicated in REM sleep generation, and it also known to provide extensive noradrenergic innervation to all areas of the central nervous system involved in the integration of sensory and motor responses to arousals and stressful situations. Hence, neuronal damage in this area could be a factor implicated in both blunted and absent cardiac response in association with motor activity and during REM sleep. However, a recent study by Miyamoto et al reported a reduced cardiac uptake of (123)I-MIBG (a noradrenaline analog) in subjects with idiopathic RBD, consistent with loss of sympathetic heart innervation. Hence, it appears that a diffuse alteration of the noradrenergic system (likely implicating central nuclei as well as peripheral postganglionic neurons directed to the target organs) occurs in RBD, which would explain the lack of cardiac response to sympathetic stimuli documented in these patients.

ACKNOWLEDGMENTS

The study was conducted at the Centre d’étude du sommeil et des rythmes biologiques, Hôpital du Sacré-Coeur de Montréal. The authors were supported by the Fonds de Recherche en Santé du Québec (scholarship, Dr. Lanfranchi); the Fondation J.A. de Sève (studentship, Lorraine Fradette); the Canadian Institutes of Health Research (postdoctoral scholarship, Dr. Gagnon, and operating grants, Dr. Lanfranchi and Dr. Montplaisir); and the Heart and Stroke Foundation of Québec (operating grant, Dr. Lanfranchi). Dr. Montplaisir holds a Canadian Government Chair on Sleep Disorders.

The authors are grateful to Margaret McKyes for linguistic revision.

REFERENCES


27. Schenck CH, Bundlie SR, Mahowald MW. REM behavior disorder (RBD): delayed emergence of parkinsonism and/or dementia in 65% of older men initially diagnosed with idiopathic RBD, and an analysis of the minimum & maximum tonic and/or phasic electromyographic abnormalities found during REM sleep. Sleep 2003;26:A316.


