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Autonomic dysfunction in isolated rapid eye movement sleep without atonia

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HIGHLIGHTS

- Isolated REM sleep without atonia (RSWA) is of unclear clinical significance.
- We demonstrate a significant reduction in several parameters of HRV in isolated RSWA.
- This is the first report of possible autonomic dysfunction in isolated RSWA.

ABSTRACT

Objectives: Autonomic dysfunction has been demonstrated in patients with rapid eye movement sleep behavior disorder utilizing heart rate variability parameters. We hypothesized that isolated rapid eye movement sleep without atonia is similarly associated with autonomic dysfunction as demonstrated by a reduction in heart rate variability.

Methods: An evaluation of 120 records demonstrating rapid eye movement sleep without atonia during polysomnography was performed. Many ($n = 99$) were discarded owing to factors potentially affecting heart rate variability. The remaining 21 records were matched with 21 records of patients demonstrating normal REM atonia, and subjected to electrocardiogram analysis. The parameters measured included R to R interval (RR) length, RR standard deviation, heart rate variability power, and very low frequency, low frequency, and high frequency bands.

Results: Autonomic dysfunction was seen in patients with isolated rapid eye movement sleep without atonia as denoted by a reduction in heart rate variability compared to those with normal REM atonia. Significant differences between the groups were demonstrated in RR standard deviation (mean difference = 0.1502 ± 0.317, 95% confidence interval [95% *CI*]=0.006, 0.295, $p = 0.042$), heart rate variability power (mean difference = 0.3005 ± 0.635, 95% *CI* = 0.011, 0.589, $p = 0.042$), and the low frequency band (mean difference = 0.3166 ± 0.616 ms^2, 95% *CI* = 0.036, 0.597, $p = 0.029$), and a borderline significant reduction in the high frequency band (mean difference = 0.3121 ± 0.686 ms^2, 95% *CI* = 0.000, 0.624, $p = 0.050$).

Conclusions: Our data confirms the hypothesis that heart rate variability is reduced in patients with isolated rapid eye movement sleep without atonia. The values obtained are consistent with previous findings in rapid eye movement behavior sleep disorder patients.

Significance: This is the first report of autonomic dysfunction in isolated rapid eye movement sleep without atonia, revealing the need for further evaluation of the clinical significance and potential implications of this finding.

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1. Introduction

Formally characterized in 1986 (Schenck et al., 1986), rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia consisting of REM sleep without atonia (RSWA) in combination with a history of recurrent nocturnal dream enactment behavior (DEB) (Olson et al., 2000; Schenck and Mahowald, 2002; Arnulf, 2012). During normal REM sleep, there is active inhibition of electromyogram (EMG) activity leading to complete or near complete atonia; RSWA represents the polysomnogram (PSG) finding of abnormally increased EMG tone based on American Academy of Sleep Medicine scoring manual standards (Berry et al., 2012). Multiple neurotransmitter systems are responsible for regulating postural muscle tone during REM sleep (Boeve et al., 2007; Luppi et al., 2012); specifically, inputs from REM atonia circuits activate glycinergic and GABAergic premotor neurons that inhibit motor neurons (Ramaligam et al., 2013). The perilocus coeruleus, located in the rostral pons, exerts an excitatory influence on the medullary reticular formation through the lateral tegmentoreticular tract. These neuronal groups then hyperpolarize the spinal motor neuron postsynaptic membranes through the ventrolateral reticulospinal tract. In RBD, the brainstem mechanisms generating the muscle atonia normally seen in REM sleep may be disrupted (Kryger and Avidan, 2010).

According to the International Classification of Sleep Disorders, 2nd edition (ICSD-2), the clinical diagnosis of RBD requires: the presence of RSWA on overnight PSG and either sleep-related injurious, potentially injurious, or disruptive behaviors by history, and/or abnormal REM sleep behavior documented during PSG monitoring. Additionally, there must be an absence of epileptiform activity on electroencephalography during REM sleep, and the sleep disorder cannot be better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder (American Academy of Sleep Medicine, 2005).

There have been numerous recent reports suggesting that autonomic function is impaired in RBD. Patients with idiopathic RBD have a higher frequency of constipation, erectile dysfunction, and orthostatic blood pressure changes compared with controls (Postuma et al., 2006, 2009). Studies of RBD patients using cardiac metaiodobenzylguanidine scintigraphy have demonstrated postganglionic degeneration of cardiac sympathetic neurons (Miyamoto et al., 2006), and that the presence of RBD in Parkinson's disease may reflect profound synuclein pathology (Nomura et al., 2010). Prior studies have demonstrated abnormal beat-to-beat variability in idiopathic RBD (Ferini-Strambi et al., 1996), as well as an absence of REM-related cardiac and respiratory responses (Lanfranchi et al., 2007). The pattern of autonomic dysfunction in idiopathic RBD is similar to that reported in idiopathic Parkinson's disease (Haapaniemi et al., 2001). The pathophysiological mechanisms of RBD are not fully understood, but neuropathological and imaging studies performed in RBD patients have demonstrated abnormalities in several brainstem areas (Gagnon et al., 2006), and it is possible that brainstem structures contributing to the central autonomic network are also affected by this neuronal damage (Lanfranchi et al., 2007).

In 2010, Postuma et al. demonstrated that RBD is associated with autonomic dysfunction as measured by a reduction in heart rate variability (HRV), irrespective of whether the patient develops synucleopathy (Postuma et al., 2010). In their study, an analysis of HRV was performed on the electrocardiogram (ECG) portion of 5-min epochs representing continuous wake for both RBD subjects and controls (Postuma et al., 2010). Our study was designed to test the hypothesis that isolated RSWA (without DEB, from the history and video recording of PSG) is associated with autonomic dysfunction as measured by HRV.

2. Methods

This study was approved by the institutional review board at Weill Cornell Medical College. All PSG records and clinical data from adult patients (ages 18–80) diagnosed with RSWA and recorded at the Weill Cornell Center for Sleep Medicine from July 2010 to June 2013 were analyzed. All patients underwent PSG testing as part of the clinical evaluation of sleep disorders including snoring, obstructive sleep apnea, insomnia, hypersomnia. The scoring of RSWA was performed by registered technologists, according to the AASM scoring manual guidelines (Berry et al., 2012), which includes either sustained muscle activity (tonic activity) of the chin EMG or excessive transient muscle activity (phasic activity) of the chin or limb EMG during REM sleep. The EMG technical specifications were as follows: sampling rate of 200 Hz, low frequency filter of 10 Hz, high frequency filter of 100 Hz, maximum electrode impedance of 5 KΩ, and digital resolution was 16 bits per sample.

For tonic activity, an epoch of REM sleep with at least 50% of the duration of the epoch having chin EMG amplitude greater than the minimum amplitude demonstrated in NREM sleep was considered RSWA. For phasic activity, a 30-s epoch of REM sleep was divided into 10 sequential, 3-s mini-epochs, and RSWA was scored if at least 5 (50%) of the mini-epochs contained bursts of transient muscle activity in the chin or limb EMG. Excessive transient muscle activity bursts were defined as 0.1–5.0 s in duration and at least 4 times as high in amplitude as the background EMG activity (Berry et al., 2012).

A total of 120 records demonstrated RSWA, and patients with potential confounding factors that could affect HRV analyses were excluded ($n = 99$) based on the following criteria: clinical diagnosis of RBD with a history of DEB or a history of conditions associated with RBD (synucleopathies such as Parkinson's disease), respiratory disturbance index (RDI)>15/h (in order to exclude pseudo-RBD) (Iranzo and Santamaria, 2005) and to be consistent with other work (Montplaisir et al., 2010; Postuma et al., 2010), seizure activity on PSG, use of medications associated with RSWA (e.g. antidepressants) (Hoque and Chesson, 2010), diagnosis of narcolepsy (Dauvilliers et al., 2012), alcohol intake (night of the study and/or a history of abuse) (Nardone et al., 2013), history of cardiac arrhythmias, and use of medications affecting the heart rate (particularly beta blockers, calcium channel blockers, and amphetamines) (See Fig. 1).

Twenty-one patients remained for analysis, and were age- and sex-matched with 21 patients taken from a pool of polysomographic studies during the same time frame, and meeting the same exclusionary criteria, save for the fact that they exhibited normal REM atonia. These polysomnograms were performed as part of an evaluation of the various sleep disorders mentioned previously.

Demographic data and multiple facets of PSG data were compiled for both groups. The determination of HRV was based on 5-min epochs of ECG data during continuous wakefulness taken from full-night PSGs, consistent with previous studies (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Postuma et al., 2010). The data were then analyzed in the time- and frequency-domains using the SuperECG Package software (Mortara Instrument, Inc., Milwaukee, WI) (Penn State University College of Medicine, 2008; Liao et al., 2010; Rodriguez-Colon et al., 2010; He et al., 2011). Time-domain variables included mean RR interval (conventionally labeled "NN" to indicate "normal beats") and standard deviation of the RR intervals (conventionally labeled "SDNN") (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Frequency-domain variables included components of RR variability quantified by an autoregressive decomposition algorithm to compute spectral peak powers