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Original Article

Estimation of parasympathetic nerve function during sleep in patients with obstructive sleep apnea by instantaneous time–frequency analysis

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ABSTRACT

Background and objectives: The pathophysiologic aspects of parasympathetic nerve (PN) function during sleep in patients with obstructive sleep apnea (OSA) studied by classical power spectrum analysis on heart rate variability (HRV) are highly controversial. The controversy is attributed to methodologic concerns, such as poor time resolution involved in power spectrum analysis. We aimed to establish the appropriate method for the investigation of PN function in OSA patients with apneas and hypopneas using instantaneous time–frequency analysis with complex demodulation (CD) and sufficient time resolution.
Methods: A total of 30 patients with PSG-confirmed mild to severe OSA were recruited for the analysis of frequency spectra contained in R-R intervals (RRI) of overnight electrocardiograph (ECG) tracings. High-frequency (HF) domains ranging between 0.15 and 0.40 Hz were selected for analysis. Among these domains, the HF domain with the maximum instantaneous amplitude was defined as the main HF peak and was used as the surrogate marker of PN discharge. Based on density spectrum array (DSA) map for main HF peak constructed with a time scale of 1 s and a frequency resolution of 0.002 Hz (HF-DSA map), the shift in central frequency (CF) of main HF peak over time was continuously monitored. When the main HF peak with the same CF lasted for more than 20 s or 5 min on HF-DSA map, the PN function was considered to be stable or very stable. The measurements were then repeated after continuous positive airway pressure (CPAP) treatment.
Results: The extent of PN-evoked modulation of RRI was enhanced in nonrapid eye movement (NREM) sleep, though the stability was reduced in both NREM and rapid eye movement (REM) sleep. These peculiar behaviors of PN function were reversed by CPAP treatment.
Conclusion: We found that instantaneous time–frequency analysis allowed estimation of transitional changes in PN function during sleep in OSA patients.

1. Introduction

The autonomic nerve dysfunction in patients with obstructive sleep apnea (OSA) has been shown to be closely implicated in the pathogenesis of a variety of comorbidities, including systemic hypertension, heart failure, myocardial infarction, and stroke [1,2]. A classical study performed by Somers et al. [3], who measured the sympathetic nerve activity using direct intraneural recordings of efferent sympathetic discharges to muscle blood vessels (microneurography), demonstrated that sympathetic burst frequency was significantly augmented in both nonrapid eye movement (NREM) sleep and rapid eye movement (REM) sleep during the nighttime in OSA patients. This finding has been confirmed by measurements of plasma and urine norepinephrine levels [2] and power spectrum analysis on heart rate variability (HRV) [4,5]. However, the results, which are based on the power spectrum analysis on HRV reported for the efferent parasympathetic nerve (PN) discharges traveling to the cardiac sinus node in OSA patients, have been considerably inconsistent.

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Khoo et al. [6] showed that the extent of PN-evoked modulation on HRV was inhibited in OSA patients, while Gula et al. [7] reported its enhancement in OSA patients. Vanninen et al. [8] concluded that the parasympathetic modulation on HRV was unchanged during the night in OSA patients. The inconsistent findings obtained from the power spectrum analysis of PN function in OSA patients may be attributed to methodologic concerns. The time resolution of the classical power spectrum analysis on HRV, including the fast Fourier transform (FFT) algorithm or the autoregressive approach (AR), is low and requires at least 100 heat beats (corresponding to approximately 2 min) to obtain the data necessary for a definitive analysis of the frequency domains contained in the R-R intervals of heart beats (RRI), which is representative of HRV [9,10]. Within 2 min, a subject with severe apneic episodes (apneas and hypopneas) sometimes experiences difficulties with respiration influencing PN function, which is no longer monitored using classical methods. In addition, the classical methods calculate the power (ms^2) by integrating the area beneath each frequency component (FFT) or by summing the square of each amplitude (AR), within a certain range of frequency. Thus the change in PN function related to the complicated distortion of respiratory states around the time points of apneic events often may be missed when using the classical methods. Therefore, it is expected that it is difficult to apply the classical power spectrum analysis to the examination of PN discharge during sleep in subjects with significant apneas and hypopneas.

On the other hand, the complex demodulation (CD) method [11,12] enables us to measure a transitional change in instantaneous amplitude (in ms) of a target frequency domain from a short-time tracing of an electrocardiograph (ECG) recorded for at least 6.7 s, corresponding to approximately 7 heart beats. This measure indicates that the CD method can differentiate the quantitative change in PN discharge during a morbid apnea and hypopnea episode lasting 10 s or longer. To differentiate between the classical power spectrum procedure and the CD method, we refer to the latter as the instantaneous time–frequency analysis.

The purpose of our study was to determine if the instantaneous time–frequency analysis as the basis of the CD method adequately detected the efferent PN discharge transmitted to the cardiac sinus node during apneic episodes. When applying the CD method, we measured transitional changes in instantaneous amplitudes of varied frequency spectra involved in the RRI data during sleep in patients with OSA. The same measurements were repeated after introducing continuous positive airway pressure (CPAP) treatment, enabling us to assess if CPAP treatment notably improved the PN dysfunction during sleep in OSA patients.

2. Methods and materials

2.1. Study population

Thirty subjects with PSG-certified OSA (28 men, 2 women) were enrolled in our study. Among them, one man with mild OSA (subject A; AHI, 14.9 events/h) and one man with severe OSA (subject B; AHI, 57.3 events/h), underwent detailed instantaneous time–frequency analysis with the CD method. The data obtained from both subjects were used for the electrophysiologic interpretation of RRI-associated frequency domains during sleep with repeated apneic episodes. The remaining 28 subjects (26 men, 2 women) with moderate to severe OSA were recruited for the quantitative determination of PN function during sleep in subjects with OSA pathology (Table 1). The age distribution of these subjects ranged from the ages of 45 to 80 years, and their body mass indices ranged from 20.2 to 30.3 kg/m^2. Each subject was required to complete the questionnaire covering age, height, body weight, lifelong cigarette use, drinking, snoring, nocturnal urination, Epworth Sleepiness Scale (ESS) scores, symptoms of restless legs syndrome, gastroesophageal reflux, nasal congestion, and medical history on comorbidities and medication use.

Table 1
Basic characteristics of obstructive sleep apnea patients.

Age (years)	62.1 ± 10.1
Men:women	26:2
Height (m)	1.68 ± 0.06
Body weight (kg)	72.1 ± 10.0
Body mass index (kg/m^2)	25.4 ± 2.8
Cigarette consumption (pack-years)	21.6 ± 22.5
ESS	8.3 ± 4.5
Frequency of nocturnal urination (times/night)	1.4 ± 1.2

Abbreviation: ESS, Epworth Sleepiness Scale.

Based on the information recorded in the questionnaire and the results of physical examinations, chest X-rays, ECGs, and blood examinations, the enrolled subjects were confirmed to have no comorbidities, including malignancy in any organ, severe hypertension, severe diabetes mellitus, conspicuous heart failure, heart or cerebral attack, renal failure, or impaired cognitive function. In addition, the subjects who were taking β agonists, β antagonists, or anticholinergic agents, as well as those with atrial fibrillation or artificial cardiac rhythm generated by a pacemaker, were excluded from the analysis. All subjects provided informed consent specifying that their clinical data would be used for clinical research; they also agreed to the inclusion of their data in the database for various research programs. Our research protocol was approved by the Human Ethics Committee of Tokyo Women's Medical University.

2.2. Polysomnography examination

Overnight full-laboratory polysomnography (PSG) examination was conducted on each subject (EEG-9200 Neurofax, Nihon Kohden; Tokyo, Japan). Sleep state was determined from the data on electroencephalography, electrooculography, and submental electromyography, which were analyzed using the available software (POLYSMITH/QP-260A, Neurotronics; Gainesville, FL, USA). Percutaneous oxyhemoglobin saturation (SpO_2) was measured with a pulse oximeter (JL-951T3, Nihon Kohden; Tokyo, Japan). Apneas and hypopneas were assessed using oral and nasal airflow based on thermocouples, nasal air pressure, and thoracic and abdominal motions recorded by piezoelectric belt sensors. Simultaneously, bipolar ECG was recorded at a sampling frequency of 200 Hz to obtain the RRI data during sleep. Sleep stages and disturbed respiratory events were scored by a trained sleep technician according to the recommendations by the American Academy of Sleep Medicine [13]. The PSG examination was repeated on each subject before and after the CPAP treatment. CPAP generally was initiated 4 weeks after the definite diagnosis of OSA was confirmed by the first PSG examination.

2.3. Instantaneous time–frequency analysis of the RRI using the CD method: basic considerations

The frequency spectra in the RRI data were estimated for the range between zero and 0.40 Hz and were divided into 3 components depending on their central frequencies, i.e., the spectral domain with the central frequency (CF) of less than 0.04 Hz, between 0.04 and 0.15 Hz, and of more than 0.15 Hz but less than 0.40 Hz. These domains were labeled as the bands with very low frequency (VLF), low frequency (LF), and high frequency (HF), respectively [14,15]. In the classical power spectrum analysis, VLF is used as a parameter representing a direct current compo-