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Original Article

# Enhanced cardiorespiratory coupling in patients with obstructive sleep apnea following continuous positive airway pressure treatment

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ABSTRACT

*Background:* Weak cardiorespiratory coupling (CRC) has been suggested in patients with obstructive sleep apnea (OSA), but the effects of continuous positive airway pressure (CPAP) on CRC remain unclear. We investigated the effects of CPAP treatment on CRC in patients with severe OSA to examine possible reversibility of altered CRC.

*Methods:* High-resolution electrocardiograms (ECGs) and respiratory signals were simultaneously recorded for 13 never-treated OSA patients at baseline and after CPAP treatment. The analyses were performed on a 15-min daytime recording of ECG and respiration. Heart rate variability (HRV) indices were extracted from ECGs. After computing the sample entropy (SampEn) to quantify the regularity of both heart rate ($SampEn_{RR}$) and respiration rhythm ($SampEn_{resp}$), cross-sample entropy (cross-SampEn) was calculated to measure the interaction between the two signals. Cross-SampEn denotes asynchrony between heart rate and respiration, and thus negatively correlates with CRC.

*Results:* Lower $SampEn_{RR}$ and higher cross-SampEn as well as a shift toward sympathetic dominance were found in OSA patients compared with age- and gender-matched controls. CPAP treatment was associated with improved sympathovagal balance, increased $SampEn_{RR}$, and enhanced CRC, corresponding to a decrease in the cross-SampEn value from 0.71 ± 0.08 to 0.49 ± 0.06 ($P < .001$). The effect sizes for the CPAP-induced changes in sympathovagal balance, $SampEn_{RR}$, and cross-SampEn were medium to large (0.54–0.90).

*Conclusions:* The findings of our study indicate reduced CRC in untreated OSA patients and suggest that CPAP treatment may reverse this abnormality.



## 1. Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder that is characterized by repetitive partial or complete closure of the upper airways during sleep, which leads to nocturnal hypoxia and daytime sleepiness. Chronic hypoxia secondary to OSA leads to an increase in inflammatory cytokines, sympathetic predominance, endothelial dysfunction, and cardiovascular mortality [1,2]. Animal models of OSA also support the detrimental effects of OSA on cardiovascular regulation [3]. Although biologic mechanisms linking OSA to cardiovascular alterations remain unclear, central autonomic dysregulation has been suggested to increase the risk for cardiovascular events in OSA patients [4]. Autonomic regulation in subjects with OSA has been studied using numerous indices of heart rate variability (HRV), which are based on variations in beat-to-beat intervals (RR intervals) on digital electrocardiograms (ECGs) [5]. Previous studies suggest that diminished HRV in OSA patients may be indicative of cardiac autonomic dysregulation and may increase the risk for cardiovascular events [6].

The parameters of cardiorespiratory coupling (CRC) have been developed to link HRV to the respiratory rate [7–9] and to quantify the strength of the association between the two physiologic systems (i.e., the cardiac and respiratory systems) under central autonomic control [10]. The level of CRC is highly associated with the vagal output from the central autonomic network [11]. By integrating HRV with the respiratory rhythm, CRC can enhance the signal-to-noise ratio [8] and can be used to evaluate the complex interactions between brainstem regions and higher regulatory centers [11,12]. Thus diverse indices of CRC may present different aspects of the cardiorespiratory interaction from the HRV [13]. Thomas et al. [8] proposed an automated ECG-based CRC algorithm and suggested that CRC may be associated with sleep quality in patients with OSA [14]. A recent study using cardiorespiratory phase

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locking reported decreased CRC in patients with OSA [15]. Therefore, reduced CRC may reflect altered autonomic regulation in patients with OSA.

Continuous positive airway pressure (CPAP) is the first-line treatment for symptomatic OSA. Several studies suggest that CPAP therapy may exert beneficial effects on HRV parameters in patients with OSA [16,17]. However, the effect of CPAP on CRC remains unclear. In our study, we hypothesized that untreated patients with severe OSA would exhibit reduced CRC, indicating the central autonomic dysregulation, and that this abnormality would be reversed after CPAP treatment. We computed cross-sample entropy (cross-SampEn) to assess the nonlinear coupling of the heart rate and respiration [18,19]. Increased cross-SampEn indicates weakened CRC, suggesting disturbances in the central autonomic regulation [20].

## 2. Methods

### 2.1. Participants

Thirteen middle-aged untreated men with severe OSA and 13 healthy age- and gender-matched controls participated in our study. Table 1 depicts the demographic and polysomnographic characteristics of the two groups. The patients were recruited from the Sleep Laboratory at Seoul National University Bundang Hospital, Seongnam, Republic of Korea. Complete medical and neurologic or psychiatric histories of the patients were available through medical records. A community-based control group was recruited through advertisements. All of the participants underwent in-laboratory polysomnography (Embla TMN 7000, Embla, Reykjavik, Iceland). For OSA patients, a second-night polysomnography was performed for CPAP titration. Apnea was defined as complete cessation of airflow for at least 10 s, and hypopnea was defined as a substantial reduction in airflow (>50%) for at least 10 s or a moderate reduction in airflow for at least 10 s associated with electroencephalographic arousal or oxygen desaturation ($\geqslant$4%) [21]. All of the patients had severe OSA (apnea–hypopnea index [AHI] > 30), whereas all of the healthy controls showed an AHI < 5. The exclusion criteria were clinical diagnosis or history of respiratory disease, cerebrovascular or coronary heart disease, endocrinologic diseases (e.g., diabetes mellitus, thyroid diseases), neurologic conditions (e.g., neurodegenerative diseases, epilepsy, head injury), psychiatric disorders (e.g., recurrent depression, psychotic disorders, substance-related disorders), or current intake of psychotropic medications. Cardiologists examined routine ECGs of all the participants and confirmed that there were no considerable abnormalities. The Institutional Review Board approved the study protocol, and we obtained written informed consent from each participant. All of the procedures that were used in our study were in accordance with the Good Clinical Practices guidelines and the most recent version of the Declaration of Helsinki.

### 2.2. Procedure

A high-resolution (1000 Hz) ECG was recorded for 15 min using a Synamps two amplifier (Compumedics, Melbourne, Australia) in a dimly lit, sound-attenuated, and temperature-controlled room between 10:00 am and 2:00 pm. ECG signals were recorded using two sintered Ag/AgCl electrodes placed on the left and right supraclavicular areas. The respiratory signals were simultaneously obtained using a thoracic belt (Summit IP Inductive Respiratory Effort Kit, Compumedics, Melbourne, Australia), which continually tracked each breath at a sampling rate of 1000 Hz. After a 10-min test session to stabilize the signal, we recorded the resting state for 15 min. Before the optimal signal detection period, we adjusted the sensitivity of the signals during a 10-min test session with the aid of a visual screen. The participants refrained from consuming caffeine and nicotine for 2 h before testing and alcohol for 12 h before testing. The participants were seated in recliners with instructions to limit their movement, and the recordings were made while the participants breathed normally with their eyes closed. The participants also completed questionnaires, which included the Epworth Sleepiness Scale (ESS) for daytime sleepiness, the Beck Depression Inventory for depressive mood, and the Pittsburg Sleep Quality Index for subjective sleep disturbances. In the patients with OSA, electrophysiologic and clinical assessments were repeated after 3 months of CPAP treatment. Data for CPAP usage and the mean AHI during the CPAP treatment were collected from the data cards inside the CPAP machine. CPAP compliance was defined as days of

**Table 1**
Clinical and demographic characteristics of the study sample.

| | Control group | OSA group ($n$ = 13) | |
|---|---|---|---|
| | ($n$ = 13) | Pre-CPAP | Post-CPAP |
| Age, mean (SD), y | 46.0 (9.4) | 49.8 (7.0) | |
| Education, mean (SD), y | 16.1 (2.7) | 15.1 (3.0) | |
| MMSE score, mean (SD) | 29.3 (0.8) | 29.3 (1.2) | |
| BMI, mean (SD), kg/m[2a] | 23.7 (1.9) | 30.6 (4.6) | 30.1 (4.4) |
| AHI, mean (SD), n/h[a,b] | 4.1 (3.7) | 60.3 (21.2) | 3.8 (2.2) |
| ODI, mean (SD), n/h[a] | 1.6 (1.3) | 54.6 (23.0) | – |
| Time with $SpO_2$ < 90%[a] | 0.01 (0.02) | 22.8 (24.4) | – |
| Inspiration, mean (SD), ms | 1521.9 (197.6) | 1520.9 (151.5) | 1531.5 (99.7) |
| Expiration, mean (SD), ms | 2243.3 (243.7) | 2219.6 (164.7) | 2201.5 (127.4) |
| Duty cycle, mean (SD), % | 40.9 (5.7) | 40.7 (3.8) | 41.0 (2.8) |
| PSQI score, mean (SD)[b] | 5.8 (2.1) | 6.4 (3.1) | 3.7 (1.8) |
| ESS score, mean (SD)[b] | 9.8 (5.4) | 12.3 (5.7) | 6.7 (5.3) |
| BDI score, mean (SD)[b] | 3.2 (3.6) | 6.7 (5.5) | 3.7 (2.8) |
| CPAP pressure, mean (SD), mm $H_2O$ | – | 11.2 (2.1) | |
| CPAP duration, mean (SD), d | – | 93.8 (19.8) | |
| CPAP compliance, mean (SD),% | – | 78.9 (14.5) | |

*Abbreviations*: OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure; SD, standard deviation; y, years; MMSE, Mini-Mental State Examination (a measure of general cognition); BMI, body mass index; AHI, apnea–hypopnea index; n/h, number per hour; ODI, oxygen desaturation index; $SpO_2$, oxygen saturation; Duty cycle, percent inspiratory time; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; BDI, Beck Depression Inventory; mm $H_2O$, millimeters of water; d, days.

[a] Control vs OSA before CPAP, $P < .05$; $P$ values were computed from independent $t$ tests.

[b] OSA pre-CPAP vs post-CPAP, $P < .05$; $P$ values were computed from dependent $t$ tests.