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ORIGINAL RESEARCH

Mood Disorders are Correlated with Autonomic Nervous Function in Chronic Insomnia Patients with OSA

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Purpose: To evaluate the correlation between sleep microstructure, autonomic nervous system activity, and neuropsychological characteristics in chronic insomnia (CI) patients with obstructive sleep apnea (OSA).

Patients and Methods: Forty-five CI-OSA patients, forty-six CI patients and twenty-two matched healthy control subjects (HCs) were enrolled. CI-OSA patients were then divided into two groups: mild OSA and moderate-to-severe OSA. All participants completed neuropsychological tests, which included the Hamilton Depression and Anxiety Scales (HAMD and HAMA), the Pittsburgh Sleep Quality Index (PSQI), the Insomnia Severity Index (ISI), the Epworth Sleepiness Scale (ESS), and the Mini-mental State Examination (MMSE). The autonomic nervous system activity and sleep microstructure were examined by the PSM-100A.

Results: The CI-OSA patients exhibited higher scores on the PSQI, ESS, ISI, HAMA, and HAMD than HCs and CI patients (all $p < 0.01$). The CI-OSA patients had a lower proportion of stable sleep, REM sleep and a higher proportion of unstable sleep ratio (all $p < 0.01$) than HCs and CI patients (all $p < 0.01$). The CI-OSA patients had higher ratios of LF and LF/HF, and lower ratios of HF and Pnn50% (all $p < 0.01$) than HCs and CI patients (all $p < 0.01$). Compared to CI-mild OSA patients, the CI-moderate-to-severe OSA patients presented with a higher ESS scores, higher ratios of LF and LF/HF, and lower ratios of HF (all $p < 0.05$). In CI-OSA patients, higher HAMD scores were correlated with decreased MMSE scores ($r=-0.678$, $p < 0.01$). A higher LF ratio was correlated with higher HAMD and HAMA scores ($r=0.321$, $p=0.031$, $r =0.449$, $p =0.002$), and a higher HF ratio was correlated with lower HAMD and HAMA scores ($r=-0.321$, $P =0.031$, $r =-0.449$, $p =0.002$).

Conclusion: OSA exacerbates the abnormalities of sleep microstructure and the autonomic nervous dysfunction in CI patients. Dysfunction of the autonomic nervous system could contribute to mood deterioration in CI with OSA patients.

Keywords: chronic insomnia, obstructive sleep apnea, OSA, depression, sleep microstructure, autonomic function

Introduction

Chronic insomnia and obstructive sleep apnea (OSA) are two of the most common sleep disorders. The conventional description of a typical OSA patient has primarily focused on symptoms relating to increased daytime sleepiness; however, recent research demonstrated that insomnia in OSA patients could be associated with a particular phenotype.[1] More and more clinical observational studies have suggested that 39–58% of patients with OSA report insomnia symptoms, higher than in the general population, and the proportion of patients with chronic insomnia who co-develop OSA is 29%-67%.[2–4] Comorbidity not only increases the incidence of both diseases but also increases the severity of diseases. It has also been found that patients with moderate and severe OSA have a lower incidence of insomnia compared with those with mild OSA or those without OSA.[5]

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Long-term sleep deprivation can lead to mood disorders and somatization diseases, and cognitive impairment is a common complication of insomnia patients.[6–8] In patients with OSA, intermittent nocturnal hypoxia and apnea disrupt deep sleep and REM sleep, resulting in sleep structure disorders such as increased N1 sleep, total sleep time, decreased N3 sleep, and frequent awakenings.[9] During the day, symptoms such as drowsiness, decreased social work ability, inattention, cognitive decline, anxiety, or depression may occur.

There are growing evidences that insomnia is associated with altered autonomous function and impaired heart rate variability.[10–12] Previous studies indicated that insomnia patients had significantly blunted sympathetic baroreflex sensitivity[10] and an impaired heart rate variability during sleep.[11] The hyperarousal state caused by chronic insomnia can also cause hyperactivation of the sympathetic nervous system.[13] Researches also have reported elevated heart rate, increased metabolic rate, increased cortisol and norepinephrine concentrations, and elevated body temperature in patients with chronic insomnia.[14,15] Obstructive events during sleep can result in intermittent hypoxia, large intra-thoracic pressure swings, and activation of the sympathetic autonomic nervous system (ANS).[16,17] Research has also found that patients with anxiety and depression have an imbalance of autonomic nervous function compared with healthy individuals,[18,19] suggesting that there is a significant correlation between the autonomic nervous system and anxiety and depression. Autonomic function can be assessed by heart rate variability (HRV), baroreceptor function, catecholamines, microneurography, blood pressure variability (BPV), pupillometry, myocardial sympathetic function, and cardiography. HRV is an alternative noninvasive method for assessing autonomic control.[20]

PSG is still recommended for the diagnosis of OSA, but PSG is expensive, technically complex to perform, time consuming, and the first-night phenomenon. Portable sleep monitoring (PSM) has been utilized as an alternative diagnostic test for OSA based in part on the premise that they can be used at home, are less expensive, quicker to deploy and more accessible compared to in-laboratory PSG. The American Academy of Sleep Medicine (AASM) has approved the use of PSMs as an alternative to PSG in certain situations.[21–23] PSM-100A device is a new type of portable sleep monitor. Based on dual-source cardiopulmonary coupling (CPC), ECG signals can obtain the sleep spectral characteristic map.[22,24,25] Meanwhile, the bioimpedance method, a new technology, can be used to measure the degree of respiratory movement by adding respiration movement electrodes. In this way, information related to the respiratory rhythm is extracted to calculate the respiratory time sequence, and the characteristic relationship between the two time sequences is calculated by the cross-spectrum method to more accurately detect changes in the sleep cycle. In addition, the blood oxygen finger sleeve, nasal and oral airflow, and snoring monitoring equipment are added. Studies have shown that PSM-100A has the highest positive predictive value (PPV) of OSA and insomnia.[25–28]

Both insomnia and OSA are associated with disrupted sleep structure, autonomic nervous dysfunction, anxiety, and depression. There is a strong consensus that altered autonomic function and elevated sympathetic activity are pivotal to the pathogenesis of hypertension. Additionally, there is a significant correlation between the autonomic nervous system and anxiety and depression. Base on the previous researches, we found that the effect of OSA on neuropsychological characteristics, sleep microstructure and ANS in insomnia patients remains poorly understood. Therefore, the present study aims to evaluate effects of OSA on sleep microstructure, neuropsychological characteristics and autonomic nervous function in chronic insomnia patients and further explore the correlation between sleep microstructure, autonomic nervous function, and neuropsychological characteristics.

Materials and Methods

Subjects

Participants were recruited from Tianjin Medical University General Hospital from October 2019 to June 2021. Inclusion criteria were as following: (1) patients who met the diagnostic criteria of chronic insomnia in International Classification of Sleep Disorders (ICSD-3). These criteria include a chronic difficulty in initiating or maintaining sleep causing impaired daytime function, such as fatigue, decreased attention and memory, mood disorders, decreased ability to work or learn, impulsive behavior, etc. These symptoms occur at least 3 times a week for at least 3 months and cannot be explained solely by inappropriate sleep environment and other types of sleep disorders. (2) ages between 18 and 75 years.(3) patients had to present with a worse subjective sleep quality assessed by the Pittsburgh Sleep Quality Index (PSQI≥7).

Exclusion criteria were as following: (1) hearing loss, parachromatism, illiteracy, and the inability to complete the required tests; (2) a history of psychiatric diseases such as depressive disorder and schizophrenia; (3) diabetic patients who have any type of neuropathy or cardiac autonomic dysfunction; cardiac diseases such as arrhythmia, coronary heart disease, cardiac insufficiency, or after pacemaker implantation, or taking drugs that affect heart rate variability such as βblockers; hyperthyroidism, tumor, anemia, infection and other diseases that significantly influence heart rate; (4) patients with severe organ dysfunction, history of asthma, chronic obstructive pulmonary disease, pulmonary heart disease and other respiratory diseases (5) neurological conditions, a history of head trauma or any other sleep disorder such as parasomnia or REM sleep behavior disorder; (6) those with drug or alcohol abuse or dependence. Ninety-one individuals with chronic insomnia and 22 age-, sex-, and education-matched healthy controls were enrolled. All patients completed the PSM-100A examination. According to the AHI, the chronic insomnia patients were divided into the chronic insomnia group (AHI<5) and chronic insomnia with the OSA group (AHI≥5). Furthermore, chronic insomnia in the OSA group was divided into the CI-mild OSA group (AHI<15) and the CI- moderate-to-severe OSA group (AHI ≥15).

This study was an observational study and was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human participants were approved by the Tianjin Medical University General Hospital Review Board and Ethics Committee. All participants were informed about the purpose of the study and signed the informed consent forms.

Subjective Sleep and Neuropsychological Evaluations

Subjective sleep and neuropsychological evaluations were performed by a trained doctor in an evaluator-blinded fashion. The sleep evaluation included the following: (a) subjective sleep quality was evaluated with the Pittsburgh Sleep Quality Index (PSQI);[29] (b) severity of insomnia was evaluated with the Insomnia Severity Index (ISI);[30] (c) daily sleepiness was evaluated with the Epworth Sleepiness Scale (ESS);[31] (d) severity of depressive and anxious symptoms was evaluated with the HAMD and HAMA[32,33] and (e) evaluation of cognitive function was conducted using the Chinese version of the Mini-mental State Examination (MMSE) test.[34]

All the subjective sleep and neuropsychological evaluations were performed by the same physician.

PSM-100A Examination

PSM-100A sleep respiration monitoring device (Silan Technology Chengdu Co., LTD.) was used to monitor the objective sleep status of the enrolled subjects. The recording only requires a single-lead electrocardiogram or photoplethysmography and use the patented algorithm (20,162,210145) approved by China's Food and Drug Administration (CFDA). The sleep data were collected by a novel ECG-based home sleep monitoring device (AECG-600D), which collected ECG, actigraphy, and body position data at a sampling rate of 128 Hz. It relies on cardiopulmonary coupling (CPC) technology that establishes sleep quality from the analysis of the coupling between heart rate variability and respiratory volume variability. It also consisted a nasal cannula pressure transducer to measure airflow and a finger pulse oximetry sensor to measure oxygen saturation and heart rate. Once acquired, the data were stored in the Alibaba cloud system (Alibaba Cloud Computing Co. Ltd.). The PSM data were downloaded and analyzed using the software and again analyzed by an experienced sleep specialist. The detailed original methodology of the CPC algorithm has been published.[24] The sleep process can be divided into the awake period, non-rapid eye movement (NREM), and REM. NREM includes Stage 1–4. Stages 1 and 2 are combined to represent"light sleep" or "unstable sleep". Stages 3 and 4 are combined to represent "deep sleep" or "stable sleep" where the brain almost exclusively produces delta waves. Apneas were defined as ≥90% drop in airflow, lasting 10s or longer. Hypopneas were defined using ≥30% drop of airflow lasting at 10s followed by a ≥3% oxygen saturation drop.

Participants were taught how to use the PSM-100A at home and instructed to attach the device when they were ready to go to sleep. To wear the PSM-100A: a) stick two electrodes, respectively, at the 3rd intercostal space of the right midclavicular line and the V5 point on the left anterior axillary line; b) place the PSM on the left anterior axillary line close to the left clavicle; c) press the power button for 3 seconds to start recording; d) press power button for 3 seconds again to stop recording. All manually scored PSM studies were reviewed by the same sleep specialist.

Autonomic Nervous System Activity Measurements

Heart rate variability (HRV) was measured as a function of the autonomic nervous system (ANS). After reimporting raw PSM-100A data, the CPC algorithm (The Sleep Quality Assessment System of CPC, V2.0) uses continuous ECG data and extracts heart rate variability and EDR activity from the ECG signal. The analysis of HRV involved the ECG sampling frequency setting, RR interval sequence editing, and time and frequency domain analysis methods, following the standard published by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[35]

Time domain analysis. Five time domain indices were derived: the mean of RR intervals (RR mean), the standard deviation of RR intervals (SDNN), the root mean square of successive RR interval differences (RMSSD), and the percentage of successive RR intervals that differed by >50 ms (pNN50).

Frequency domain analysis. First, the original RR interval was interpolated at 4 Hz, and then the HRV spectrum was calculated with a fast Fourier transform using a Hamming window. The power density was calculated by integrating the power spectral density into the LFC (0.04–0.15Hz) and HFC (0.15–0.40Hz) components. The ratio of LF-to-HF power (LF/HF) was also calculated.

Statistical Analysis

The results are expressed as the mean ± standard deviation (SD) for continuous variables and as the probability (percent) for categorical variables. Differences in the demographic, clinical, and sleep characteristics among the three groups were descriptively compared using chi-square tests for categorical measures, using one-way ANOVA tests for data that were normally distributed and which homoscedasticity was respected, using nonparametric Kruskal–Wallis or Mann–Whitney *U*-tests for variables that were not distributed normally or for which homoscedasticity was not respected. The associations between scores of subjective sleep scales and autonomic function and severity of depressive and anxious symptoms were evaluated by means of Pearson correlation coefficient and linear regression. Statistical significance was defined as $p < 0.05$. Statistical analyses were performed using the SPSS software (Inc. Chicago, IL, USA).

Results

Demographics of the Participants and Neuropsychological Evaluations of the Participants

The demographic and clinical characteristics are reported in Table 1. This study included 91 chronic insomnia patients and 22 healthy control subjects, and no differences were found in age, gender, education, smoke consumption, BMI, hypertension, diabetes, and hyperlipemia among the three groups (Table 1). There were no differences in age, gender, education, smoke consumption, BMI, hypertension, diabetes, and hyperlipemia between the CI-mild OSA patients (AHI<15) and CI- moderate-to-severe OSA patients (AHI ≥15) (Table 2).

Compared with the HC subjects and CI patients, the CI-OSA patients exhibited more severe symptoms of depression and anxiety (all $p < 0.01$) and worse cognition ($p< 0.01$) (Table 1). In the CI-moderate-to-severe OSA patients, the symptoms of depression and anxiety were more obvious than in the CI-mild OSA patients ($p< 0.05$) (Table 2).

Sleep Microstructure and Subjective Sleep Characteristics of the Participants

The stable sleep ratio in the CI patients was significantly lower than in the HC subjects and the unstable sleep ratio in the CI patients was significantly higher than in the HC subjects (all $p <0.01$). No differences were found in AHI index between the CI patients and HC subjects.

When compared to the CI patients, the stable sleep ratio and REM sleep ratio in the CI-OSA patients was lower than in the CI patients ($p <0.05$) and the unstable sleep ratio in the CI-OSA patients was significantly higher than in the CI patients ($p < 0.01$). CI-OSA patients had higher AHI index than CI patients ($p <0.01$).

The CI and CI-OSA patients suffered from poorer subjective sleep quality and more severe insomnia (all $p < 0.01$) in the subjective sleep evaluations than the HCs. The CI-OSA patients suffered from severe daytime sleepiness more than the CI patients ($p < 0.01$). The details of sleep characteristics are summarized in Table 3.

Table 1 Demographics of the Participants and Neuropsychological Evaluations of Three Group Patients

	HCs Group (n=22) (A)	CI Group (n=46) (B)	CI with OSA Group (n=45) (C)	*p*
Age, year	51.78±11.80	54.65±11.43	57.09±7.25	NS
Male, n (%)	7 (31.8%)	21 (45.7%)	19 (42.2%)	NS
Education, year	13.96±2.01	12.87±3.32	12.58±3.46	NS
Smoke, n (%)	3 (13.6%)	6 (13.0%)	11 (24.4%)	NS
BMI, kg/m2	23.01±1.96	23.43±2.46	24.58±3.83	NS
Hypertension, n (%)	3 (13.6%)	8 (17.4%)	15 (33.3%)	NS
Diabetes, n (%)	1 (4.5%)	7 (15.2%)	7 (15.6%)	NS
Hyperlipemia, n (%)	4 (18.2%)	3 (6.5%)	6 (13.3%)	NS
HAMA	3.82±2.44	9.15±3.82	11.91±2.75	A<B**, A<C**, B<C**
HAMD	3.73±2.35	8.98±2.95	11.56±2.88	A<B**, A<C**, B<C**
MMSE	29.73±0.63	28.31±1.64	27.35±1.38	A<B**, A<C**, B<C**

Notes: Plus-minus values are means ± SD. **$p < 0.01$.
Abbreviations: HCs, healthy control subjects; CI, chronic insomnia; CI-OSA, chronic insomnia patients with OSA; HAMD, Hamilton Depression Scales; HAMA, Hamilton Anxiety Scales; MMSE, Mini-Mental State Examination.

Table 2 Demographics of the Participants and Neuropsychological Evaluations of the CI-Mild OSA Patients and CI- Moderate-to-Severe OSA Patients

	CI-Mild OSA Group (AHI<15, n=27)	CI-Moderate to Severe OSA Group (AHI≥15, n=18)	*P*
Age, year	57.70±6.91	56.17±7.84	0.492
Male, n (%)	10 (37.0%)	9 (50.0%)	0.388
Education, year	12.33±3.59	12.94±3.32	0.568
Smoke, n (%)	6 (22.2%)	5 (27.8%)	0.671
BMI, kg/m2	23.97±3.51	25.50±4.19	0.191
Hypertension, n (%)	7 (25.9%)	8 (44.4%)	0.197
Diabetes, n (%)	6 (22.2%)	1 (5.6%)	0.131
Hyperlipemia, n (%)	5 (18.5%)	1 (5.6%)	0.210
HAMA	11.11±2.47	13.11±2.78	0.015
HAMD	10.67±2.35	12.89±3.14	0.010
MMSE	27.52±1.45	27.11±2.27	0.466

Note: Plus-minus values are means ± SD.
Abbreviations: HCs, healthy control subjects; CI, chronic insomnia; CI-OSA, chronic insomnia patients with OSA; HAMD, Hamilton Depression Scales; HAMA, Hamilton Anxiety Scales; MMSE, Mini-Mental State Examination.

In addition, we evaluated the sleep microstructure and subjective sleep characteristics between the CI-mild OSA patients and CI- moderate-to-severe OSA patients. As demonstrated in Table 4, the results showed that the stable sleep ratio and REM sleep ratio of the CI- moderate-to-severe OSA patients were lower than CI-mild OSA patients (all $p < 0.05$), the unstable sleep ratio were higher than CI-mild OSA patients (all $p < 0.05$). The CI- moderate-to-severe OSA patients

Table 3 Objective and Subjective Sleep Characteristics of the Three Groups Patient

	HCs Group (n=22) (A)	CI Group (n=46) (B)	CI with OSA Group (n=45) (C)	*P*
Objective evaluation				
Unstable sleep,%	43.64±13.30	55.23±13.03	62.62±11.05	A<B**, A<C**, B<C*
Stable sleep,%	32.06±12.89	21.86±12.80	15.95±10.48	A>B**, A>C**, B>C*
REM sleep,%	24.31±2.22	22.91±2.74	21.43±2.35	A>C**, B>C*
AHI	1.92±1.56	1.94±1.31	15.01±13.33	A<C**, B<C**
Mean oxygen saturation	96.77±0.53	96.02±0.58	94.80±0.89	A>C**, B>C*
PSQI	4.00±1.95	12.72±3.62	12.13±3.27	A<B**, A<C**
ESS	0.32±0.95	0.61±1.29	2.58±3.03	A<C**, B<C**
ISI	2.05±2.66	13.04±5.00	12.91±4.61	A<B**, A<C**

Notes: Plus-minus values are means ± SD. *$p < 0.05$; **$p < 0.01$.
Abbreviations: REM, rapid eye movement; AHI, apnea-hypopnea index; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index.

Table 4 Objective and Subjective Sleep Characteristics of the CI-Mild OSA Patients and CI- Moderate-to-Severe OSA Patients

	CI-Mild OSA Group (AHI<15, n=27)	CI-Moderate to Severe OSA Group (AHI≥15, n=18)	*P*
Objective evaluation			
Unstable sleep,%	59.45±10.21	67.38±10.80	0.017
Stable sleep,%	18.52±9.55	12.10±10.90	0.043
REM sleep,%	22.03±2.04	20.52±2.55	0.033
AHI	8.40 (5.50, 11.90)	15.85 (15.18, 27.83)	<0.001
Mean oxygen saturation	95.19±0.74	94.22±0.81	<0.001
PSQI score	12.85±3.58	11.06±2.44	0.052
ESS score	1.22±1.97	4.61±3.24	0.001
ISI score	13.89±5.32	11.44±2.81	0.052

Note: Plus-minus values are means ± SD.
Abbreviations: REM, rapid eye movement; AHI, apnea-hypopnea index; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index.

presented more severe daytime sleepiness than the CI-mild OSA patients ($p < 0.01$). No differences were found in the subjective sleep quality and insomnia severity in the subjective sleep evaluations.

Autonomic Nervous System of the Participants

The analysis of HRV includes time domain parameters and frequency domain parameters. The time domain parameters include SDNN, RMSSD, and Pnn50%. The frequency domain parameters include LF, HF, and LF/HF.

SDNN and RMSSD showed no significant difference between the HC subjects, CI patients, and CI-OSA patients (Table 5). The LF ratio, LF/HF ratio, and Pnn50% in CI-OSA patients were higher than in HC subjects and CI patients ($p < 0.01$), while the HF ratio was lower than that of the HC subjects and CI patients ($p < 0.01$).

Table 5 Autonomic Nervous Function of the Three Groups Patients

	HCs Group (n=22) (A)	CI Group (n=46) (B)	CI with OSA Group (n=45) (C)	*p*
HR	63.05±7.54	63.59±8.57	65.47±8.58	NS
LF	54.45±11.66	64.06±13.53	69.81±9.94	A<B**, A<C**, B<C*
HF	45.55±11.65	35.94±13.53	30.19±9.94	A>B**, A>C**, B>C*
LF/HF	1.33±0.55	2.18±1.20	2.67±1.19	A<B**, A<C**, B<C*
SDNN	78.28±1955	74.50±25.38	72.92±21.16	NS
RMSSD	33.25 (26.68, 44.78)	28.25 (22.15, 40.61)	27.00 (23.60, 33.75)	NS
Pnn 50%	11.18 (5.51, 23.09)	5.67 (3.39, 14.06)	3.90 (1.87, 7.53)	A<B*, A<C**

Notes: Plus-minus values are means ± SD. *$p < 0.05$; **$p < 0.01$.
Abbreviations: LF, low-frequency coupling; HF, high-frequency coupling; SDNN, standard deviation of NN intervals; RMSSD, square root of the mean squared differences of successive NN intervals; Pnn50%, the percentage of NN intervals>50ms different from preceding interval.

Further analysis revealed that, compared to the CI-mild OSA patients, the CI- moderate-to-severe OSA patients had a higher ratio of LF and LF/HF, and lower ratios of HF (all $P < 0.05$). No differences were found in SDNN, RMSSD, and Pnn50%. Summarizing values are displayed in Table 6.

Association Between Autonomic Nervous System and Severity of Depression and Anxiety in the CI-OSA Group

The MMSE scores showed a negative correlation with HAMD scores ($r=-0.678$, $p < 0.01$). The HAMD and HAMA scores showed a positive correlation with the LF ratio ($r=0.321$, $p =0.031$; $r =0.449$, $p =0.002$) and a negative correlation with the HF ratio ($r=-0.321$, $p =0.031$; $r =-0.449$, $p =0.002$). The HAMA scores showed a positive correlation with the LF/HF ratio ($r=0.434$, $p =0.003$) (Figure 1).

Linear regression analysis was further used to examine the predicting effect of the two potential predictor-LF and HF identified in correlation analysis. The model test results had significant ($F = 25.80$, $p < 0.0001$). The analysis found that increased LF ratio and decreased HF ratio in the CI-OSA patients were independently associated with HAMD and HAMA scores. The R^2 was 0.3750 and 0.4594 (Figure 2).

Table 6 Autonomic Nervous Function of the CI-Mild OSA Patients and CI- Moderate-to-Severe OSA Patients

	CI-Mild OSA Group (AHI<15, n=27)	CI-Moderate to Severe OSA Group (AHI≥15, n=18)	*p*
HR	63.41±8.68	68.56±7.65	0.047
LF	67.31±10.61	73.55±7.67	0.038
HF	32.69±10.61	26.45±7.67	0.038
LF/HF	2.39±1.16	3.07±1.13	0.059
SDNN	73.89±22.11	71.48±20.21	0.714
RMSSD	27.00 (24.30, 30.00)	27.50 (22.98, 38.00)	0.487
Pnn 50%	4.53 (1.81, 7.68)	3.74 (2.40, 5.37)	0.711

Note: Plus-minus values are means ± SD.
Abbreviations: LF, low-frequency coupling; HF, high-frequency coupling; SDNN, standard deviation of NN intervals; RMSSD, square root of the mean squared differences of successive NN intervals; Pnn50%, the percentage of NN intervals>50ms different from preceding interval.

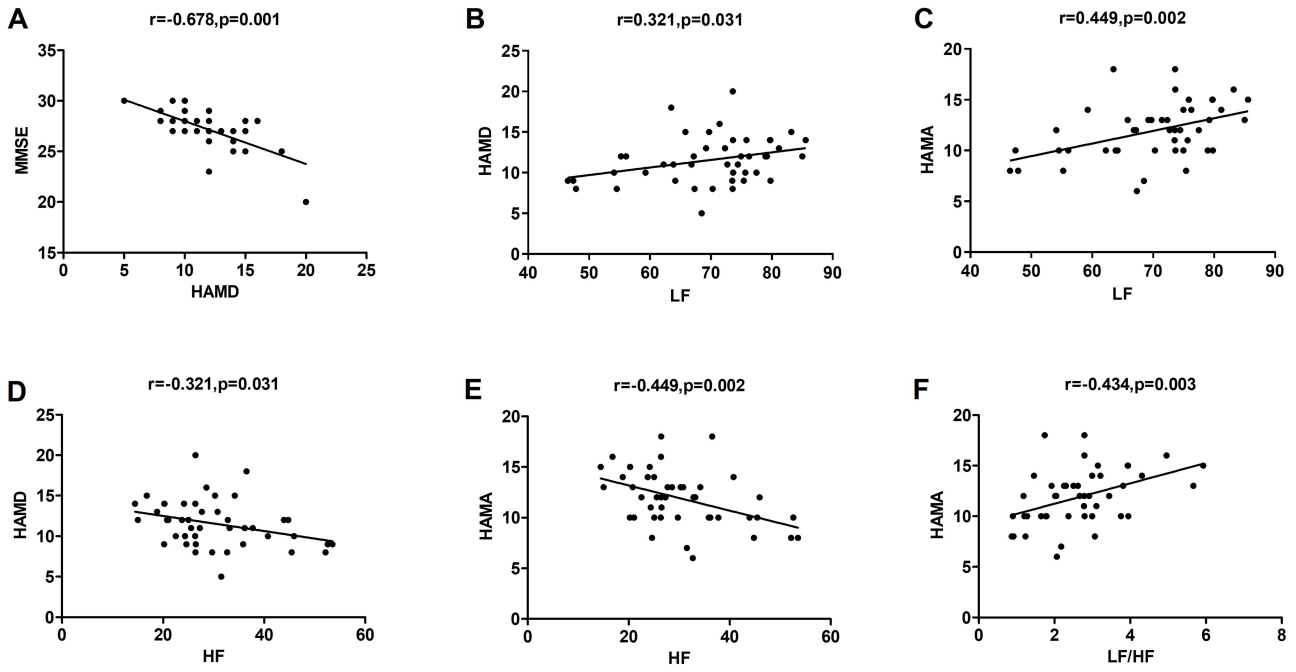

Figure 1 Correlation between autonomic nervous function and severity of depressive and anxiety in the CI-OSA group. The MMSE scores showed a negative correlation HAMD scores (r=−0.678, p < 0.01) (**A**). The HAMD and HAMA scores showed a positive correlation with LF ratio (r=0.321, p =0.031; r =0.449, p =0.002) (**B** and **C**) and a negative correlation with HF ratio (r=−0.321, p =0.031; r =−0.449, p =0.002) (**D** and **E**). And the HAMA scores showed a positive correlation with LF/HF ratio (r=0.434, P =0.003) (**F**).

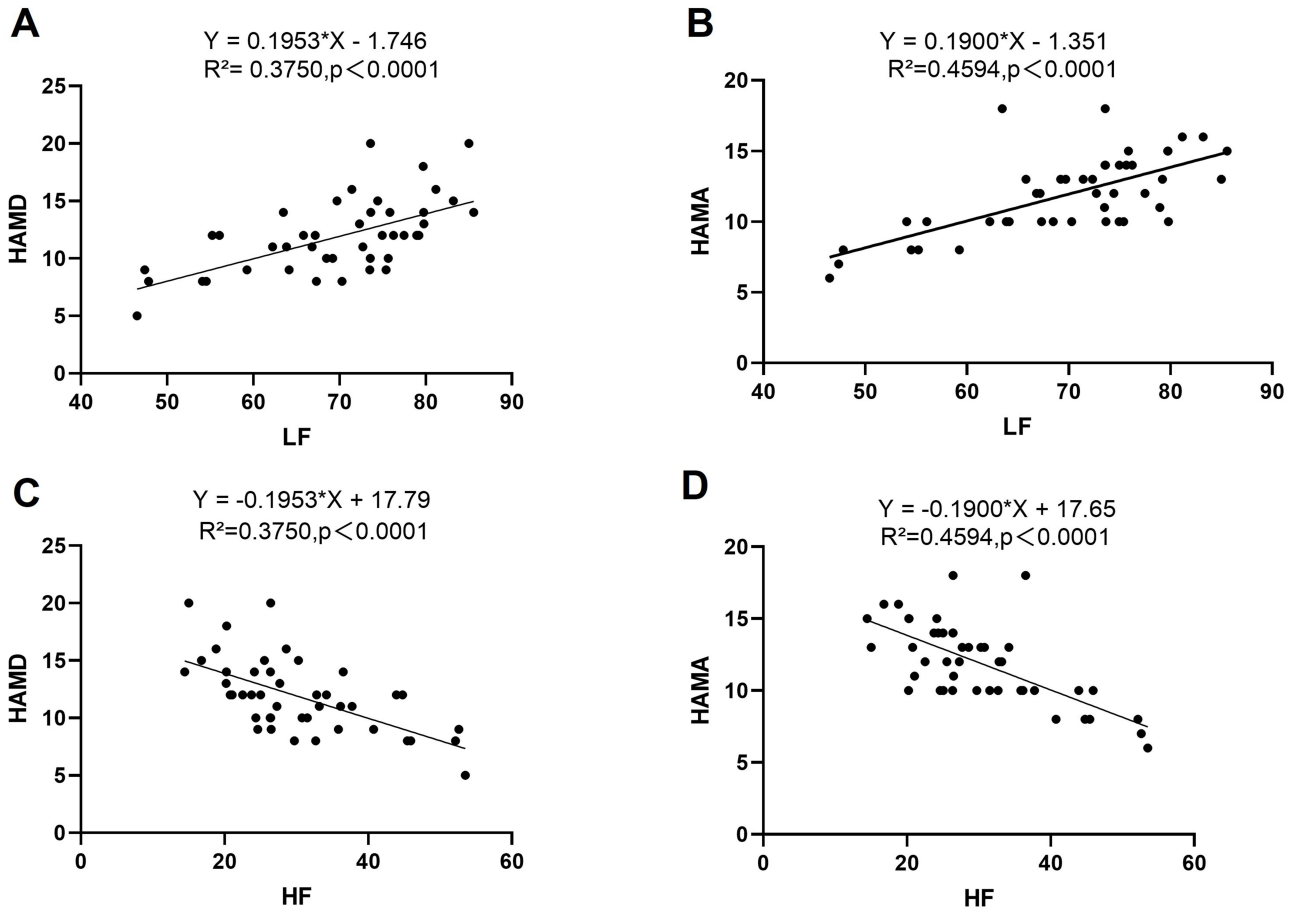

Figure 2 Linear regression of autonomic nervous function and severity of depressive and anxiety in the CI-OSA group. (**A** and **C**) Increased LF ratio and decreased HF ratio in the CI-OSA patients were independently associated with HAMD scores (R^2=0.3750, p<0.0001); (**B** and **D**) Increased LF ratio and decreased HF ratio in the CI-OSA patients were independently associated with HAMA scores (R^2=0.4594, p<0.0001).

Discussion

In our study, the key findings are as follows: (a) compared with CI patients, CI-OSA patients showed a lower REM sleep ratio, a lower stable sleep ratio, a higher unstable sleep ratio, and more severe symptoms of depression and anxiety; (b) sympathetic activity increased in CI-OSA patients compared with CI patients, including higher ratios of LF and LF/HF, lower ratios of HF, and Pnn50%. As the severity of OSA increased, the autonomic nervous dysfunction was aggravated; (c) poor cognition was associated with more severe symptoms of depression, and more severe symptoms of depression and anxiety were associated with an increased LF ratio and a decreased HF ratio measured in the CI-OSA group.

Previous researches based on PSG found that insomnia patients with OSA showed a decreased actual total sleep time, N3 sleep time, and frequent awakening, compared with insomnia patients and OSA patients,[36] and the N1 sleep and arousal index showed a linear upward trend as the severity of OSA increased, while N3 and REM sleep showed a downward trend with OSA severity.[9] In our study, chronic insomnia with OSA patients had more serious sleep structure disorders in a PSM-100A examination. This finding was consistent with previous findings that manifested as decreases in REM sleep, and stable sleep, increases in unstable sleep. Furthermore, a significant statistical difference in sleep microstructure was observed across the groups with different AHI levels.

OSA patients often complain about sleepiness or insomnia-like symptoms. Studies have found that OSA patients with chronic insomnia are more likely to have emotional disorders, cognitive decline, and obvious somatization symptoms than insomnia or OSA patients.[37] In this study, we also found that insomnia with OSA patients had poorer sleep quality and cognition, more sleepiness, depression, and anxiety than healthy subjects and insomnia patients; as AHI increased, these symptoms became more severe. Sleep fragmentation in OSA patients causes dysregulation of the level of 5-hydroxytryptamine (5-HT) neurotransmitters,[38,39] which is the main cause of anxiety and depression. Functional imaging studies have found that in OSA patients, the prefrontal cortex function declined,[40,41] and inhibition of the prefrontal cortex, the amygdala's connection to related emotional regions, is reduced. The excessive activation of brain emotional regions, such as the amygdala, hippocampus, striatum, island cortex, and cingulate cortex amplifies the emotional response.[42] Hypoxia leads to frequent arousal, which activates the HPA axis, increases sympathetic excitability, disorders, or even destruction of autonomic nervous function, promotes the release of cortisol and norepinephrine, and increases susceptibility to anxiety and depression.[13,43] Recent studies have found that hypoxia time is positively correlated with the degree of depression.[44,45]

HRV is an alternative noninvasive method for the assessment of autonomic control. In our study, HRV was used to quantitatively analyze changes in autonomic nervous function during sleep based on PSM-100A. The time domain parameters mainly include SDNN, RMSSD, and PNN50%, reflecting parasympathetic nerve activity. The frequency domain parameters include LF, HF, and LF/HF. LF represents sympathetic nerve activity, HF represents parasympathetic nerve activity, and LF/HF reflects the equilibrium between sympathetic and parasympathetic nerves. Our PSM-100A recordings found that the LF and LF/HF ratios increased and the HF ratios and Pnn50% decreased in chronic insomnia with OSA patients, which indicated activation of the sympathetic nerve and inhibition of the parasympathetic nerve. As the severity of OSA increased, the autonomic nervous dysfunction was aggravated.

The ANS enables fine-tuning of physiological states via the sympathetic and parasympathetic branches of the ANS. Sympathetic nerve activity is closely coupled to circadian rhythms, and parasympathetic nerve activity increases, and sympathetic nerve activity decreased during slow wave sleep.[46] Additionally, CO2 retention caused by apnea in OSA patients stimulates chemoreceptors to activate parasympathetic nerves, and the body remains in a state of hypoxia after respiratory recovery, which induces the activation of sympathetic nerve activity.[47–49] The frequent awakening of OSA patients at night causes activates the arousal mechanism of the cerebral cortex and leads to a high state of physiological arousal and activates the sympathetic nerves.[50]

Autonomic nerve function can be used as an evaluation index for emotional symptoms. The increased sympathetic tone manifests as emotional fluctuations, irritability, and fatigue, while the increased parasympathetic tone manifests as a more peaceful state of mind.[51] Consistent with previous researches, we found that the symptoms of anxiety and depression in the chronic insomnia with OSA patients were positively correlated with the frequency domain indicators of HRV, LF, and LF/HF, and negatively correlated with HF. LF mainly evaluated sympathetic tone, while HF was used to evaluate parasympathetic tone. LF/HF was used to evaluate the balance state of tension between the two, which also indicates that the autonomic

nervous imbalance of patients with comorbidities is related to their emotional state. The excessive hyperactivity of sympathetic nerves can cause anxiety and depression, which further exacerbate autonomic nervous function disorders.

We acknowledge the following limitations to our study. First, the sample size of the study was small and it is necessary to verify these findings in a larger sample. More patients must be recruited in the future to continue the subgroup analysis. Second, PSG was not performed to determine the accurate proportions of sleep stages and their association with sleep parameters. Third, the dynamic changes of HRV and daytime HRV in each sleep stage must be analyzed in future studies to more comprehensively assess changes in autonomic nerve function in insomnia patients with OSA.

Conclusion

In conclusion, OSA exacerbates the abnormalities of sleep microstructure and the autonomic nervous dysfunction in CI patients. Dysfunction of the autonomic nervous system could contribute to mood deterioration in CI with OSA patients. Professionals should enhance the awareness of OSA in chronic insomnia patients with the aim of improving the mood and the autonomic nervous function.

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Author Contributions

Yahui Wan designed the experiment, acquired and analyzed the data, and drafted the manuscript; Mengdi Li acquired and analyzed the data; Kaili Zhou, Zheng Li and Xueyun Du participated in data acquisition; Wei Wu and Rong Xue revised the manuscript, formulated the study concept, designed the study, and acquired funding for the study.

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Disclosure

The authors declare that they have no competing interests.

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