EXPERIMENTAL STUDY

The Impact of Respiratory Events on the Autonomic Nervous System during Sleep

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Summary

Sleep apnea hypopnea syndrome (SAHS) is an independent risk factor for cardiovascular diseases. However, the pathophysiology between them is not yet clear. This paper seeks to understand how respiratory events impact the cardiovascular system by heart rate variability. We compared the differences between successional pathological respiratory events (PR) and pure normal respiration (NR) during sleep. The transitions between normal and pathological respiration (TR) were also analyzed. Thirteen patients who suffered moderate or severe SAHS were enrolled in this study. The results demonstrate that the beat-to-beat interval (RR interval) mean value and sample entropy are significantly lower during PR than during NR. RR interval standard deviation, the power of very low frequency (VLF) and low frequency (LF), total power, and the low frequency/high frequency (LF/HF) ratio were significantly larger during PR than during NR. However, the high frequency (HF) power was not significantly different between normal and pathological respiration. Additionally, the trends during TR also supported these significant differences. The results indicate that during pathological respiration, as the heart rate and its volatility increase, the complexity of its rhythm decreases. We conclude that the energy of the autonomic nervous system rapidly increases during pathological respiration, especially at the beginning. The HF power does not significantly change to modulate the heart rhythm, but the activity of the sympathetic nervous system will significantly increase, resulting in the imbalance of the LF/HF ratio. In addition to these findings, this paper discusses the influence of arousal on these indices during TR.

Key words: Pathological respiration, Heart rate variability, Sleep apnea hypopnea syndrome

Sleep apnea hypopnea syndrome (SAHS) is classified as a sleep-disordered breathing (SDB) disease. It is defined by repeated apnea or hypopnea of at least 10 seconds each time, for at least five times each hour during sleep.1-3 The typical clinical symptoms of this chronic disease include intermittent hypoxemia, insomnia, type 2 diabetes, and metabolic dysfunction.4 Additionally, there is a high prevalence of SAHS patients with a number of clinical symptoms of cardiovascular diseases (CVD), including systemic hypertension, arrhythmia, heart failure, myocardial infarction, coronary artery disease, and stroke.5-7

It is known that heart rhythms are modulated by the autonomic nervous system (ANS). ANS activity has been widely evaluated by heart rate variability (HRV).5,9 For HRV analysis, low frequency (LF, 0.04-0.15 Hz) power reflects the combination of the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) influences, mainly modulated by SNS activity.10-12 High frequency (HF, 0.15-0.4 Hz) power reflects PNS activity. The detailed physiological adaptations of HRV indices used in this paper are listed in section 2.4 (Table I). The differences in overnight HRV between SAHS patients and healthy individuals have been analyzed. In recent years, a number of studies have examined HRV in CVD and SAHS using time, frequency domain, and non-linear analysis.13-16 Previous HRV studies suggest that LF power increases in SAHS patients, but HF power results have been controversial.17-20

The overnight HRV analysis for SAHS patients can study the long-term trend. However, compared to the long-term trend, the purpose of this study is to analyze the whole night short term and respiratory events related HRV and thus further analyze the HRV before, during, and after respiratory events. Besides, the different result on HF power from the previous studies, we wish to deter-
Electrocardiogram (ECG) signals were recorded by Philips-Respironics Alice® device. These signals were exported via Philips-Respironics Alice® Diagnostics Sleep System (Philips-Respironics, Amsterdam, Netherlands). The recommended derivations of the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events were adopted. The ECG sampling rate was predetermined as 500 Hz. The cut-off frequency of the low-pass filter was 70 Hz, and the high-pass filter was 0.3 Hz. Additionally, other physiological signals, such as oral and nasal airflow, electromyogram, electrooculogram, electroencephalogram, thoracic and abdominal motions, and fingertip pulse oxygen saturation were also recorded by the above-mentioned device. These signals were exported via Philips-Respironics Alice® Sleepware.

### Methods

**Participants:** Thirteen patients diagnosed with SAHS were recruited to participate in this study between April 2014 and August 2015. Patient demographics and general health parameters are listed in Table II. Measurements were nocturnally recorded by polysomnography (PSG) in the Sleep-Disordered Breathing Center of the 6th Affiliated Hospital of Sun Yat-Sen University. All patients were diagnosed as free from cardiac or vascular diseases and had been instructed not to consume any alcohol or drugs prior to PSG recording. This study was approved by the ethics committee of the above-mentioned hospital.

**Experimental device and setting:** Electrocardiogram (ECG) signals were recorded by Philips-Respironics Alice®5 Diagnostics Sleep System (Philips-Respironics, Amsterdam, Netherlands). The recommended derivations of the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events were adopted. The ECG sampling rate was predetermined as 500 Hz. The cut-off frequency of the low-pass filter was 70 Hz, and the high-pass filter was 0.3 Hz. Additionally, other physiological signals, such as oral and nasal airflow, electromyogram, electrooculogram, electroencephalogram, thoracic and abdominal motions, and fingertip pulse oxygen saturation were also recorded by the above-mentioned device. These signals were exported via Philips-Respironics Alice® Sleepware.

### Classification of respiratory patterns: Three respiratory patterns were selected from the PSG record: pure NR, successional pathological respiratory events (PR), and the TR. PR status is defined as continuous pathological respiration, including obstructive sleep apnea (OSA), central sleep apnea (CSA), and hypopnea. The definition of NR is the complete opposite of PR and does not include any pathological respiratory events. The TR status includes the process of normal to continuous pathological respiration (TR-NP), pathological to normal respiration (TR-PN), and quick succession of normal to pathological and back to normal respiration (TR-NPN, < 1 minute). The above classifications are demonstrated in Figure 1. An entire night’s PSG record was divided into 60-second epochs; NR and PR recordings were randomly selected from the PSG record for analysis, and all of the TR recordings were analyzed.

### Extraction of HRV features: The original RR interval sequences were extracted from the ECG signal. Next, a spectral transform was applied to the sequence. The VLF, LF, and HF band features of the HRV were extracted, and the LF/HF ratio was also calculated. Figure 2 shows the flowchart of this process.

After we divided the entire night’s ECG signal into continuous 60-second epochs, we performed a continuous 1-D Mexican hat wavelet transform on each epoch. Next, the baseline drift was removed, and the ECG complex wave which represents the simultaneous activation of the right and left ventricles (QRS) was detected. The continuous wavelet transform can be expressed as follows:

$$CWT_x(a,b) = \frac{1}{\sqrt{a}} R_x^b \int f(x) \psi \left(\frac{x-b}{a}\right) dx$$

where $a$ and $b$ represent the scaling factor and the shift factor, respectively. In the present paper, we used predetermined values of $a = 6$ and $b = 0$.

The continuous 1-D Mexican hat wavelet can be expressed as:
Figure 1. A: Pure normal respiration (NR); B: Successional pathological respiratory events (PR); C: The process of normal to continuous pathological respiration (TR-NP); D: Normal to pathological and back to normal respiration (TR-NPN); and E: Pathological to normal respiration (TR-PN).

After the baseline drift was removed, the QRS complex can be distinguished. We adopted a difference threshold algorithm to detect the R peaks from the ECG wave and removed the interfaces of the P peaks according to the minimum heartbeat intervals to determine the times of occurrences of the R peaks in each ECG cycle. Next, the RR interval sequences were obtained.

A spectral transform was used to obtain the frequency domain features of the HRV based on RR interval sequence. We adopted the autoregressive (AR) model and Burg algorithm to estimate the power spectral density (PSD) of the RR interval in each epoch. The procedure was as follows:

First, according to the AR power spectrum density calculation formula:

$$ P_{AR}(f) = \frac{\sigma^2}{1 + |a_k|} $$

where $\sigma^2$ is the noise variance of the input signal, $p$ is the order of the autoregressive model, and $a_k$ is the autoregression coefficient, which can be calculated from the Levinson-Durbin recursive algorithm:

$$ a_k(i) = a_{k-1}(i) - \rho_k a_k(k - i); \quad i = 1, 2, \ldots, k - 1 $$

where $\rho_k$ can be calculated from the minimum error criterion of the Burg algorithm, which predicts the minimum
error of the average power spectrum in the forward and backward directions:

$$\rho_k = \frac{2 \sum_{n=1}^{N-k} e^f_k(n) e^b_{k-1}(n-1)}{\sum_{n=1}^{N-k} [e^f_k(n)]^2 + [e^b_{k-1}(n-1)]^2}$$

(5)

where $e^f$ represents the errors of forward predicting, and $e^b$ represents the errors of back predicting. The recursion formula and initial conditions were as follows:

$$\begin{align*}
e^f_k(n) &= e^f_{k-1}(n) - \rho_k e^b_{k-1}(n-1) \\
e^b_k(n) &= e^b_{k-1}(n-1) - \rho_k e^f_{k-1}(n) \\
e^b_0(n) &= x(n); 0 \leq n \leq N - 1
\end{align*}$$

(6)

We obtained the differential of the HRV power spectrum density estimation and calculated the integrals of the VLF (0.0033-0.04 Hz), LF (0.04-0.15 Hz), HF (0.15-0.4 Hz), and TP (0.0033-0.4 Hz), which resulted in the powers of the different frequency bands of the HRV and LF/HF ratio.

The HRV features and other heart rate indices used in this study are listed in Table I, and the relationship between HRV features and SNS and PNS activity are also listed.24-27)

Table III. Transition Process Sample Numbers

| Process | Total sample | With micro-arousal | Without micro-arousal |
|---------|--------------|--------------------|-----------------------|
| TR-NP   | 112          | 88                 | 24                    |
| TR-NPN  | 47           | 25                 | 22                    |
| TR-PN   | 100          | 63                 | 37                    |

Statistical analyses of the heart rate variability features: The HRV features during PR and NR were comparatively analyzed. Each HRV feature was normalized from 0 to 1 for each patient. The Mann-Whitney U Test, which is a nonparametric test, was performed to identify significant differences in each HRV feature between these two respiratory patterns, and the values of $P < 0.05$ (two-tailed test) were defined as statistically significant. The above-mentioned analyses were performed with the IBM SPSS Statistics software (Version 22.0, SPSS Inc.; New York, USA).

Trend analyses during normal and pathological respiration transition: To study the ANS activity during TR, the trends of the HRV indices during these processes were analyzed. The process was classified into three patterns: TR-NP, TR-PN, and TR-NPN. In each classification, a total 4 minutes of ECG signal was analyzed. As shown in Figure 3, these 4-minute epochs have been divided into seven windows: window size = 1 minute; slide window size = 30 seconds; overlap window size = 30 seconds.

Pathological respiratory events commonly occurred during window 3 to window 5. Additionally, the transition processes with micro-arousal and without micro-arousal were also separately analyzed, and the sample numbers in these processes are listed in Table III. For each transition process, each feature was normalized from 0 to 1, and the mean value of each feature for the same chronological order window was calculated.

Results

Comparison of normal and pathological respiration: A typical PSD of HRV from NR and PR is shown in Figure 4. From these results, we observed that during NR, the HF band peak was significantly larger than the LF and VLF peaks. However, during PR, the VLF and LF peaks were greater than the HF band peak. These results are significantly different, as measured by the Rank Sum Test (Mann-Whitney U) between NR and PR and are shown in Figure 5. From these data, we found that the RR interval mean (RRM) and sample entropy (SE) during NR were significantly greater than during PR but that the RR interval standard deviation (RRSD), VLF power (VLFP), LF power (LFP), total power (TP), and the LF/HF ratio during NR were all significantly lower than during PR. In addition, the HF power (HFP) was not significantly different.
between NR and PR.

**The transition between normal and pathological respiration:** From a typical PSD TR-NP, shown in Figure 6, we observed that the main peak for normal respiration was located in the HF band but that during the transition from normal respiration to pathological respiration, this peak moved to the VLF or LF bands.

As shown in Figures 7, 8, during TR-NP, RRSD, VLFP, LFP, TP, and the LF/HF ratio were stable and relatively low from window 1 to window 3 (the normal respiratory period), rapidly increased from window 3 to window 5 (the pathological respiratory period), and exhibited a minor fallback from window 5 to window 7 (the sustained pathological respiratory period). During TR-NPN, these trends exhibited a relatively sharp fall back from window 5 to window 7. In addition, the trends seen in TR-PN were the opposite of those seen in TR-NP. However, the SE demonstrated opposite trends during these three processes.

Comparison between with- and without micro-arousal transitions showed a large difference in fluctuation for HF power between with- and without micro-arousal during these three processes. In the post-period of TR-NP (sustained pathological respiration) and the entire periods for both TR-NPN and TR-PN, opposite trends were observed. This may contribute to the results of no significant difference in HF power in Section 3.1. For RRSD, LFP, TP, and the LF/HF ratio, these features exhibited a sharper decrease in the periods without micro-arousal when compared to periods with micro-arousal. For the RRM, the periods with and without micro-arousal exhibited similar fluctuations during TR-NP and TR-PN. However, without micro-arousal, the valley appeared faster during TR-NPN and exhibited a faster fallback after pathological respiration. In addition, the SE exhibited similar trends regardless of micro-arousal.

**Discussion**

It is well known that RRM directly reflects heart rate alteration. A statistically significant difference ($P < 0.01$) in RRM was found between normal respiration and pathological respiration (Figure 5). During TR, the RRM showed a consistent and significant decreasing tendency at the beginning of pathological respiration both with and without micro-arousal. This decrease may reflect overactivity of the SNS or underactivity of the PNS. However, after pathological respiration, these trends were unstable...
between with- and without micro-arousal situations (Figure 7). Our results suggest that heart rate increases at the beginning of a pathological respiratory event. The heart rate dynamic during respiratory events supported the results of the previous study. The study of Lusina, et al.\textsuperscript{28} demonstrated that the heart rate and systolic blood pressure significantly increased during hypoxia event, and it would fall back to the baseline after normal ventilation.

Significant differences ($P < 0.01$) were also found in RRSD and SE between normal respiration and pathological respiration (Figure 5). During TR, the RRSD showed a consistent and significant increasing tendency during pathological respiration both with and without micro-arousal (Figure 7). Next, RRSD reached a relative plateau if there were other successional pathological respiratory events. Otherwise, RRSD significantly decreased to a stable level. This indicates that heart rate significantly fluctuates during pathological respiration compared with normal respiration. Additionally, compared with RRSD, the SE demonstrates opposite trends, indicating that heart rate complexity decreases during pathological respiration.

To reveal the impact of respiratory events on the ANS during sleep, HRV analysis was used. We first analyzed the HRV indices between NR and PR. Then, we focused on HRV indices during TR in detail. As shown in Figures 4, 6, the HF peak was greater than the LF peak during normal respiration, but the opposite result was found during pathological respiration. In addition, during the transition from normal to pathological respiration, the peak of HRV power spectrum moved from the left to the right. This suggests that the SNS plays a main role during pathological respiration. And this suggests that during normal respiration, the PNS’s main function is to maintain resting status.

Our statistical results demonstrate that there are significant differences in VLFP, LFP, TP, and the LF/HF ratio between NR and PR, and these features significantly increased at the beginning of a pathological respiratory event. However, the HFP demonstrated no significant difference. The LF’s results indicate that the SNS’s dynamic will significantly enhance during pathological respiration, especially at the beginning. However, the HF’s performance indicates that the PNS’s function does not significantly alter during this process. In addition, the results of the LF/HF ratio indicate that the ANS’s balance will be broken and will fluctuate with the SNS during pathological respiration. Furthermore, the TP results indicate that the ANS’s energy rapidly increases during pathological respiration, especially at the beginning.

We observed a large difference in the fluctuation of HF power between with- and without micro-arousal conditions during TR. In the post-period of TR-NP (sustained pathological respiration) and in the entire periods for both TR-NPN and TR-PN, opposite trends were observed. These results imply that HFP is impacted by many factors, such as respiration and micro-arousal. Sleep stage\textsuperscript{29} and age\textsuperscript{30} also impact HFP. These factors may act together to impact HFP, which may explain why we observed no significant difference on HF power, and this may also be the reason why no uniform conclusion on HF power has been reached.\textsuperscript{17-20}

The probable physiological relation between respira-
Figure 7. The trends of the HRV time domain and non-linear features including RR interval mean (RRM), RR interval standard deviation (RRSD), and sample entropy (SE) during the transition between normal and pathological respiration (TR). The red line indicates pure respiration (without micro-arousal) during the process; the blue line indicates micro-arousal during the process; the black line indicates mixed (with and without) micro-arousal.

Respiratory events and cardiovascular system was shown in Figure 9. Because of the intermittent hypoxia caused by sleep apnea or hypopnea, the oxygen partial pressure \((PO_2)\) decreased and the carbon dioxide partial pressure \((PCO_2)\) increased, which evoked a central chemoreflex response. The SNS would be innerved. Thus, heart rate (HR) and blood pressure (BP) would increase to make a short-term oxygen supplementation. The PNS maintained the previous level and the ANS lost balance for a short while. For a normal ANS response process, the PNS would also excite after a short period to ensure the balance of ANS, which decreased the HR and BP. Our results demonstrated that without micro-arousal it would follow the above-mentioned mechanism generally. But with the impact of micro-arousal, the mechanism we discussed does not match well. It may reveal that the sleep fragmentation caused by micro-arousal affected the modulation of ANS, and their mechanisms need further research.

In this paper, we focused on the impact of respiratory events on the ANS in individual. We will study more probable impact factors on the ANS, including age, gender, BMI, and sleep stage. In addition, other assessment methods of ANS, such as muscle sympathetic nerve activity and frequency analysis for BP, will be enrolled in the further study.

Conclusion

In summary, during pathological respiration, the HR accelerates, the HR fluctuation increases, and the complexity of heart rhythm decreases. Additionally, the HF, which reflects the PNS’s activity, does not significantly modulate heart rhythm, whereas the LF, which reflects the SNS’s activity, does significantly increase. The LF/HF ratio, which reflects the balance of the ANS with the SNS, loses balance with the fluctuation of the SNS. In addition, the TP, which reflects the ANS’s energy, rapidly increases during pathological respiration, especially at the beginning of the respiratory event. During TR, the VLF, LF, TP, and the LF/HF ratio show similar trends both with and without micro-arousal; however, HF power exhibits different
Figure 8. The trends of the HRV frequency domain features including VLF power, LF power, HF power, total power (TP), and the LF/HF ratio during the transition between normal and pathological respiration (TR). The red line indicates pure respiration (without micro-arousal) during the process; the blue line indicates micro-arousal during the process; the black line indicates mixed (with and without) micro-arousal.
trends across these two situations.

Disclosures

Conflicts of interest: None.

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