Autonomic Activity Difference during Continuous Positive Airway Pressure Titration in Patients with Obstructive Sleep Apnea/Hypopnea Syndrome with or without Hypertension

Jen-Hao Cheng, MD; Chung-Ching Hua, MD; Ning-Hung Chen', MD; Yu-Chih Liu, PhD; Chung-Chieh Yu, MD

Background: Current evidence suggests that obstructive sleep apnea-hypopnea syndrome (OSAHS) is an independent risk factor for systemic hypertension. The mechanisms linking OSAHS to hypertension remain unclear. However, recent studies have indicated that abnormal autonomic control may be an important factor. Our study aims to evaluate differences in autonomic activity between hypertensive and normotensive OSAHS patients before and during continuous positive airway pressure (CPAP) therapy.

Methods: Fifty-three OSAHS patients were analyzed in this study. Patients were divided into 2 groups, one group comprising patients with hypertension and the other of patients without hypertension. Heart rate variability (HRV) was assessed by polysomnography, before patients received CPAP titration and during CPAP titration. Then, HRV was compared between the hypertensive and normotensive groups. Multivariate analyses were used to evaluate the influence of clinical variables on autonomic activity.

Results: Although HRV before CPAP titration was not statistically different between the 2 groups, low frequency variability was significantly lower in hypertensive subjects who received CPAP titration compared with normotensive subjects. Multivariate analysis revealed that hypertension is a determinant factor of autonomic change during CPAP use.

Conclusions: Our findings demonstrate that CPAP therapy results in a greater and immediate change in autonomic activity in hypertensive OSAHS patients compared with normotensive OSAHS patients. This suggests that CPAP lowers blood pressure by decreasing the patient’s autonomic activity.

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Key words: continuous positive airway pressure, hypertension, heart rate variability, obstructive sleep apnea/hypopnea syndrome, autonomic activity
risk factor for systemic hypertension. The mechanisms that link OSAHS to hypertension remain unclear, but recent studies have suggested that abnormal autonomic control may be an important contributing factor. For instance, studies using peroneal microneurography or testing of plasma catecholamines have shown that sympathetic activity is substantially elevated in subjects with OSAHS. Some reports support the theory that the autonomic nervous system is involved in the development of hypertension.

Continuous positive airway pressure (CPAP) therapy is the standard treatment for patients with OSAHS. It has been shown to reduce muscle sympathetic nerve activity and plasma norepinephrine levels. Long-term CPAP therapy can improve vagal heart rate control. Recently, numerous studies have been conducted using spectral analysis of heart rate variability (HRV) as a tool for the noninvasive assessment of the autonomic nervous system. An increasing number of studies have been performed on OSAHS patients using HRV to evaluate autonomic function both before and after treatment. It has been well documented that CPAP treatment can reduce cardiovascular consequences. Clinically, OSAHS patients with hypertension benefit from more blood pressure reduction in CPAP treatment than normotensive patients. We hypothesize that there is a greater difference in autonomic activity in hypertensive OSAHS patients than normotensive patients after CPAP therapy.

METHODS

Study subjects

We retrospectively collected the polysomnographic variables of patients with OSAHS data before and during CPAP therapy from February 2007 to October 2007. OSAHS was confirmed by an apnea-hypopnea index (AHI) of > 5/h in an initial diagnostic polysomnography (PSG). Initially, 77 patients were involved in the study, but 24 patients with central sleep apnea, significant cardiac arrhythmias, congestive heart failure, diabetes mellitus, coronary artery disease, stroke, use of beta-blockers, or chronic lung disease on medical records were excluded from the study. Hypertensive patients who took other kinds of hypertensive drugs were allowed into the study, because there was not enough evidence proving these drugs alter HRV. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital. The confidentiality of each patient was well maintained.

Study design

The subjects were divided into 2 groups. One group was comprised of hypertensive patients (n = 19) and the other of normotensive patients (n = 34). We defined patients as having hypertension if they had more than one recorded systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg, or were using antihypertensive agents. All of the hypertensive patients continued to take their regular hypertensive medication during the study. We evaluated the HRV obtained from PSG data before and during CPAP titration to study its effects on sympathetic activity.

Initial diagnostic polysomnography

An initial diagnostic PSG, was conducted using a computerized system (Embla N7000, Somnologica, Broomfield, U.S.A.), which included the monitoring of the electroencephalogram, submental and anterior tibial electromyograms, electrooculogram, oxygen saturation, electrocardiogram, inductance plethysmographs of the chest wall and abdomen, nasal pressure, and oronasal thermister. Respiratory events and sleep stages were manually scored following the criteria of Rechtschaffen and Kales. Hypopnea was defined as a ≥ 50% reduction in airflow from the baseline value lasting ≥ 10 s and associated with 3% desaturation or an arousal. Apnea was defined as the absence of airflow on the nasal cannula lasting > 10 s. The AHI was established as the ratio of the number of episodes of apnea and hypopnea per hour of sleep.

Polysomnography under CPAP

The auto-adjusting CPAP system (ResMed, Sydney, Australia) is a computer-based device that performs automatic pressure titration. It automatically increases or decreases the mask pressure in response to snoring, specific changes in inspiratory airflow contour morphology, or the presence of apnea or hypopnea, thus acting to restore airway patency completely. Auto-adjusting CPAP is recommended by the American Academy of Sleep Medicine as an alternative method to attended CPAP.
titration. In the process, a technician supervises and corrects the initial mask position and fitting. An initial CPAP of 4 cm H2O is applied to patients and the automatic titration of pressure begins when the patients fall asleep.

Heart rate variability analysis

The whole-night PSG electrocardiogram was recorded whether the patient was awake or asleep. The mean with standard deviation of the R-R intervals (SDNN) was analyzed. HRV was calculated by a fast-Fourier transform spectral analysis algorithm (Somnologica version 3 software) with a frequency resolution of 0.0005 Hz and a range of 0–0.4 Hz. The spectral powers of the following frequency-domains were obtained: (1) high frequency (HF: approximately 0.15–0.4 Hz) which is synchronized to the respiratory rhythm and primarily modulated by cardiac parasympathetic innervation, (2) low frequency (LF: approximately 0.04–0.15 Hz) which is sensitive to changes in cardiac sympathetic nerve activity and is modulated by both the sympathetic and parasympathetic nervous systems, and (3) the ratio of the spectral power amplitude of LF to that of HF (LH/HF) which is generally considered to provide a good index of sympathetic modulation.

Statistics

Data were presented as mean ± standard deviation (SD). Statistical evaluation was performed by computer analysis with SPSS software version 16.0 (SPSS Inc., Chicago, IL, U.S.A.). The spectral powers of the diagnostic PSG and CPAP titration recordings in the same individual were compared with the Wilcoxon test. The differences in spectral powers between the normotensive and hypertensive groups were analyzed with the Mann-Whitney U test. A multivariate general linear model was used to evaluate the main effects of HRV. A p value < 0.05 was considered statistically significant.

RESULTS

There were 53 patients with OSAHS whose HRV were analyzed. Table 1 shows the characteristics of the normotensive and hypertensive subjects. The gender, total sleep time, sleep efficiency, mean SpO2, and Epworth Sleepiness Scale were not different between the 2 groups. However, the body mass index (BMI) and AHI were higher in the hypertensive subjects. Three hypertensive subjects were newly diagnosed and were not receiving antihypertensive agents. The other hypertensive subjects were regularly taking antihypertensive agents during the study period. The difference in the HRV between the initial diagnostic PSG and the second PSG during CPAP titration in the normotensive and hypertensive patients is shown in Table 2. The SDNN was significantly decreased during CPAP titration in both normotensive and hypertensive patients (p < 0.001; Table 2). Table 3 shows a further comparison of the differences in the HRV between the normotensive and hypertensive groups before and during CPAP titration. All parameters of HRV were not different between groups prior to CPAP administration. LF was significantly lowered in the hypertensive subjects while they received CPAP titration in comparison with the normotensive group (p = 0.04; Table 3). The Figure shows the LF changes after CPAP use in both groups. The reduction in low frequency (ΔLF) was significant in the hypertensive group (p = 0.02; Table 3) but not in the normotensive patients.

The BMI and AHI differed between the hypertensive and normotensive groups. Therefore, multi-

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Normotensive (n: 34)</th>
<th>Hypertensive (n: 19)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46.9 ± 10.4</td>
<td>51.9 ± 9.7</td>
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<tr>
<td>Male/Female</td>
<td>31/3</td>
<td>18/1</td>
<td>0.62</td>
</tr>
<tr>
<td>BMI</td>
<td>27.9 ± 4.7</td>
<td>30.3 ± 3.1</td>
<td>0.04</td>
</tr>
<tr>
<td>ESS</td>
<td>11.2 ± 5.2</td>
<td>12.7 ± 4.2</td>
<td>0.25</td>
</tr>
<tr>
<td>AHI (times/h) before CPAP</td>
<td>61.2 ± 26.6</td>
<td>76.2 ± 21.1</td>
<td>0.03</td>
</tr>
<tr>
<td>TST (min)</td>
<td>306.6 ± 62.1</td>
<td>88.7 ± 62.1</td>
<td>0.34</td>
</tr>
<tr>
<td>SE (%)</td>
<td>85.1 ± 15.5</td>
<td>81.6 ± 15.2</td>
<td>0.48</td>
</tr>
<tr>
<td>Mean SpO2 (%)</td>
<td>93.3 ± 3.9</td>
<td>90.9 ± 3.9</td>
<td>0.07</td>
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<tr>
<td>AHI (times/h) with CPAP</td>
<td>5.2 ± 5.9</td>
<td>8.6 ± 8.1</td>
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<tr>
<td>TST (min) with CPAP</td>
<td>313.9 ± 66.9</td>
<td>306.6 ± 61.8</td>
<td>0.71</td>
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<tr>
<td>SE (min) with CPAP</td>
<td>88.5 ± 14.2</td>
<td>89.5 ± 6.6</td>
<td>0.68</td>
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<tr>
<td>Mean SpO2(%) with CPAP</td>
<td>96.9 ± 1.5</td>
<td>96.1 ± 1.4</td>
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</tbody>
</table>

Abbreviations: BMI: body mass index; ESS: Epworth Sleepiness Scale; AHI: apnea hypopnea index; TST: total sleep time; SE: sleep efficiency; SpO2: O2 saturation; CPAP: continuous positive airway pressure.

Data presented as mean ± SD or Number.
Table 2. Time-dependent and Spectral Analysis of HRV in Normotensive and Hypertensive OSAHS Patients before and with CPAP Therapy

<table>
<thead>
<tr>
<th></th>
<th>Normotensive OSAHS patients</th>
<th>Hypertensive OSAHS patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before CPAP (mean ± SD)</td>
<td>With CPAP (mean ± SD)</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>93.3 ± 36.9</td>
<td>72.4 ± 30.7</td>
</tr>
<tr>
<td>LF (ms²)</td>
<td>16157.9 ± 7165.9</td>
<td>17241.8 ± 10222.6</td>
</tr>
<tr>
<td>HF (ms²)</td>
<td>7749.4 ± 3017.7</td>
<td>6750.5 ± 3335.1</td>
</tr>
<tr>
<td>LF/HF</td>
<td>2.4 ± 1.3</td>
<td>2.9 ± 2.1</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>&lt; 0.001</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Abbreviations: HRV: heart rate variability; CPAP: continuous positive airway pressure; SDNN: standard deviation of all RR intervals on electrocardiography; LF: Low frequency; HF: High frequency; LF/HF: ratio between low frequency and high frequency spectral power.

Data presented as mean ± SD.

Table 3. Time-dependent and Spectral Analysis of HRV between Normotensive and Hypertensive Patients

<table>
<thead>
<tr>
<th></th>
<th>Normotensive</th>
<th>Hypertensive</th>
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<tbody>
<tr>
<td>SDNN (ms)</td>
<td>93.3 ± 36.9</td>
<td>94.6 ± 49.5</td>
<td>0.68</td>
</tr>
<tr>
<td>LF (ms²)</td>
<td>16157.9 ± 7165.9</td>
<td>15913.2 ± 12737.9</td>
<td>0.35</td>
</tr>
<tr>
<td>HF (ms²)</td>
<td>7749.4 ± 3017.7</td>
<td>7307.6 ± 6937.4</td>
<td>0.09</td>
</tr>
<tr>
<td>LF/HF</td>
<td>2.4 ± 1.3</td>
<td>2.8 ± 1.7</td>
<td>0.34</td>
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HRV with CPAP

<table>
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<th>Normotensive</th>
<th>Hypertensive</th>
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<tbody>
<tr>
<td>SDNN (ms)</td>
<td>72.4 ± 30.7</td>
<td>63.7 ± 14.4</td>
<td>0.38</td>
</tr>
<tr>
<td>LF (ms²)</td>
<td>17241.8 ± 10222.6</td>
<td>11558.6 ± 7685.6</td>
<td>0.04</td>
</tr>
<tr>
<td>HF (ms²)</td>
<td>6750.4 ± 3335.1</td>
<td>5428.5 ± 2788.8</td>
<td>0.12</td>
</tr>
<tr>
<td>LF/HF</td>
<td>2.9 ± 2.1</td>
<td>2.3 ± 0.9</td>
<td>0.39</td>
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</tbody>
</table>

HRV difference before and with CPAP

<table>
<thead>
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<th>Normotensive</th>
<th>Hypertensive</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>ΔSDNN (ms)</td>
<td>20.9 ± 22.5</td>
<td>30.8 ± 47.9</td>
<td>0.94</td>
</tr>
<tr>
<td>ΔLF (ms²)</td>
<td>-1083.9 ± 7214.9</td>
<td>4354.6 ± 8552.5</td>
<td>0.02</td>
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<tr>
<td>ΔHF (ms²)</td>
<td>998.9 ± 3363.4</td>
<td>1683.7 ± 7540.4</td>
<td>0.71</td>
</tr>
<tr>
<td>ΔLF/HF</td>
<td>-0.6 ± 1.9</td>
<td>0.6 ± 1.7</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Abbreviations: HRV: heart rate variability; CPAP: continuous positive airway pressure; Δ: the difference in values before and with continuous positive airway pressure; SDNN: standard deviation of all RR intervals on electrocardiography; LF: low frequency; HF: high frequency; LF/HF: ratio between low frequency and high frequency spectral power.

Data presented as mean ± SD.

Fig. 1 (A) The low frequency of heart rate variability (LF) of normotensive subjects before and with continuous positive airway pressure (CPAP). (B) The LF of hypertensive subjects before and with CPAP.
variate analysis was further performed to clarify the determinant factors of the ΔLF/HF and ΔLF ratio. Analyses of the ΔLF/HF with BMI, AHI, and hypertension showed all these factors had no significant effects. Also, analyses of the ΔLF revealed that hypertension (95% CI, 820.45 to 10320.51; \( p = 0.022 \)) was a determinant factor, but not BMI (95% CI, –757.55 to 405.16; \( p = 0.545 \)) or AHI (95% CI, –65.92 to 131.29; \( p = 0.508 \)).

**DISCUSSION**

Our data revealed no differences in HRV between the hypertensive and normotensive groups before CPAP titration. The SDNN was decreased by CPAP in both groups. During CPAP titration, the HRV showed a significant change in the hypertensive group compared with normotensive subjects. The major HRV change was found in the LF, revealing that the hypertensive subjects have a marked LF decline during CPAP titration.

SDNN refers to the standard deviation of all R-R intervals, which is all intervals between adjacent QRS complexes resulting from sinus node depolarization. Roche et al found that the SDNN is higher in OSAHS patients when they are asleep and it has been suggested as an inexpensive tool in screening for OSAHS. We found that the SDNN is reduced when CPAP titration is being administered to eliminate respiratory events; this also confirmed that respiratory events could alter the SDNN. HRV is mediated by three primary mechanisms: (1) vagal feedback from pulmonary stretch receptors; (2) central medullary coupling respiratory and cardiovagal neurons; and (3) the arterial baroreflex. HRV has several components; HF and LF are the two most important components representing autonomic activity. Efferent vagal activity is a major contributor to the HF component and the LF component is modulated by cardiac sympathetic effects. In OSAHS patients, the baroreflex and central respiratory-cardiovascular neuron activity are impaired. The LF and LF/HF values of OSAHS patients are significantly higher than those in healthy groups, but their HF values are lower. On the other hand, CPAP therapy can reverse this condition and thus help restore the autonomic defects in OSAHS patients.

Several previous studies have established that hypertensive subjects have different autonomic trends compared with healthy normotensive ones. The LF is greater in hypertensive patients compared with normotensive patients and this suggests enhanced sympathetic activity in hypertension. All of these results indicate dysfunction of cardiac autonomic activity in patients with OSAHS and hypertension. Khoo et al and Guo et al demonstrated that OSAHS patients have higher LF levels than those without OSAHS and they speculated that AHI severity has a positive correlation with the LF level. In addition, the studies also confirm that the LF of patients with severe OSAHS is decreased during CPAP therapy. Heitmann et al revealed that nasal CPAP could reduce the blood pressure and noradrenaline plasma levels in hypertensive patients with OSAHS, whereas this effect was small in normotensive patients. Our results revealing that autonomic activity variation had a greater change during CPAP therapy in hypertensive patients than in normotensive subjects were similar to those in the Heitmann study. Schmid et al’s study found obesity influences autonomic activity. Obesity was associated with a shift from sympathovagal balance trending towards sympathetic dominance. Paschoalet al’s study demonstrated that obese subjects have higher LF levels than non-obese subjects. Increased AHI and BMI are associated with increased LF levels. In our study, the two groups had different AHI and BMI, so these confounding factors may have altered our results. Therefore, multivariate analysis was performed to find the real determinant factors which may influence reduction of the LF. The analysis revealed that hypertension is still the most important factor.

Recent studies indicate that OSAHS is an independent risk factor for systemic hypertension. Sympathetic overactivity remains widely accepted as the mechanism leading to systemic hypertension in OSAHS. Hypoxia, hypercapnia, and negative pressure against a closed airway may lead to chemoreceptor activation and increased sympathetic activity. Evidence has suggested that OSAHS is accompanied by increased chemoreflex sensitivity and depressed baroreflex sensitivity. The chemoreflex is a known autonomic response to hypoxia and hypercapnia that causes sympathetic activation in OSAHS patients. In contrast, the baroreflex is a parasympathetic response that exerts an inhibitory influence on the chemoreflex response to suppress sympathetic
activity. The elimination of respiratory events with the aid of CPAP reduces chemoreflex stimulation, diminishes the demands of the baroreflex response, and improves baroreflex sensitivity. Therefore, we presume that hypertensive patients with OSAHS have higher chemoreflex sensitivity and more depressed baroreflex sensitivity, contributing to a greater reduction in LF when respiratory events are eliminated using CPAP.

Our study could not show the autonomic activity spanning an entire day and at present, there are no long-term follow up results. Our study revealed that changes in the autonomic activity are immediate responses during the sleep period. However, previous studies have reported that long-term use of CPAP could cause a decline in autonomic activity variation and reverse depressed baroreflex sensitivity. This effect is reportedly present both in the daytime and during sleep.

In conclusion, OSAHS patients with hypertension show a greater change in autonomic activity, in terms of LF, than normotensive patients when receiving CPAP therapy. Some studies have shown hypertension as one of the indicators for the treatment of patients with OSAHS. Our study furnishes an explanation why hypertensive OSAHS patients could receive greater benefits from CPAP therapy.

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REFERENCES


心律變異度在有高血壓或正常血壓的睡眠呼吸中止症病患接受連續性正壓呼吸滴定時的變化

鄭人豪 花仲湜 陳淳宏' 劉育志 于鍾傑

背 景：目前的證據顯示阻塞型睡眠呼吸中止症對高血壓來說是個獨立的危險因子，阻塞型睡眠呼吸中止症和高血壓相互連結的機轉目前仍不清楚，但是最近有些報告指出異常的自律神經調節可能是在這兩者扮演重要因素，我們這個研究是為了觀察高血壓或正常血壓的睡眠呼吸中止症的病人經連續性正壓呼吸治療前後的自律神經活性的變異。

方 法：有 53 個阻塞型睡眠呼吸中止症的病人被納入，病人分成有高血壓和無高血壓兩組，我們藉由第一次多項睡眠生理檢查以及第二次正壓呼吸治療滴定時所獲得的心律變異度 (Heart rate variability)，去比較血壓和正常血壓這兩組病人的自律神經變異度，最後再利用多變項分析來檢測自律神經活性的變異影響。

結 果：未經連續性正壓呼吸治療前，這兩組病患的心律變異度沒有統計學上的意義，但在接受連續性正壓呼吸治療後，高血壓這組的病人在低頻 (Low frequency) 變異度有明顯下降。多變項分析顯示本研究中影響自律神經活性的變異最主要的因子為高血壓。

結 論：我們發現阻塞型睡眠呼吸中止症合併高血壓的病人比沒有合併高血壓的病人接受連續性正壓呼吸治療時，其自律神經活性有較顯著的變化。

(長庚醫誌 2011;34:410-7)

關鍵詞：連續性正壓呼吸、高血壓、心跳變異性、阻塞型睡眠呼吸中止症、自律神經活性