Preliminary Report

Recovery of Heart Rate Variability in Patients with Moderate to Severe Obstructive Sleep Apnea after 6-Month Continuous Positive Airway Pressure Treatment

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Objective: *To evaluate the effect of long-term treatment with continuous positive airway pressure (CPAP) on the heart rate variability (HRV) of obstructive sleep apnea (OSA) patients.*
Material and Method: *Patients with moderate to severe OSA who had never used CPAP treatment were enrolled. Short recording HRV analysis was performed at baseline then at one, three, and six months after CPAP treatment. The measurement included low frequency HRV (LF), high frequency HRV (HF), low frequency to high frequency ratio (LHR), and standard deviation of R-R intervals (SDNN). All domains were measured both during spontaneous and deep breathing.*
Results: *There were 10 patients in the present study, all were men with the mean age of 45 years, mean body mass index 29.3 kg/m^2, mean apnea-hypopnea index 60.9 events/hour, and mean average CPAP usage 4.8 hours/night. The HRV showed no significant change after one and three months of CPAP treatment. At 6 months, the only significant change was the SDNN measured after deep breathing (28.80 $\pm$ 9.83 vs. 34.43 $\pm$ 14.23 millisecond, p = 0.032).*
Conclusion: *One aspect of heart rate variability in moderate to severe obstructive sleep apnea patients was improved after six month's continuous positive airway pressure treatment.*

Keywords: *Obstructive sleep apnea, Continuous positive airway pressure, Heart rate variability*

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Heart rate variability (HRV) is a marker used to evaluate the autonomic nervous system (ANS); this marker has been used for many years due to the significant relationship between the ANS and cardiovascular mortality. HRV is defined as the fluctuation in heart rate, as assessed by evaluation of consecutive cardiac cycles[1]. It is a useful tool to assess pathological conditions resulting in alterations of the ANS such as hypertension, congestive heart failure, amyloidosis, and obstructive sleep apnea (OSA)[2-5].

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During inspiration, heart rate increases causing a decrease in R-R interval and vice versa during expiration. This variation is referred to as respiratory arrhythmia, which is often observed to be higher in children, decreasing with age. Time domain refers to the following measurements: mean R-R interval, standard deviation of R-R intervals (SDNN), and the percent of R-R interval that differ from the adjacent interval exceeding 50 millisecond. The frequency domain is expressed in normalized units (nu), which means powers at frequencies of interest, low frequency HRV (LF) and high frequency HRV (HF), divided by total power minus power at very low frequencies (VLF). LF reflects cardiac response to sympathetic and parasympathetic

impulse, meanwhile HF reflects only cardiac response to parasympathetic impulse. Conventionally, 24-hour period was used for HRV recording, but the reproducibility of short-sampling period of HRV has been recently demonstrated[6]. A large body of evidence indicated that the sympathetic nervous system promotes unwanted cardiac arrhythmias, such as ventricular tachycardia and ventricular fibrillation. In the contrary, parasympathetic nervous system plays a protective role, decreasing the likelihood of these malignant ventricular arrhythmias. Reduced HRV has been shown to reflect an increased risk for the incidence of cardiac events or even cardiac mortality[7].

OSA is a serious disorder caused by repetitive obstructions of the upper airway during sleep. If left untreated, both OSA patients with and without verified coronary disease were more prone to develop cardiovascular diseases[8,9]. Underlying mechanisms of this association are not known, however sympathetic drive is increased in OSA patients[10-12]. Sympathetic nerve response to continuous positive airway pressure (CPAP) treatment seems to depend on the duration of therapy[13-15]. Treatment of OSA in coronary artery disease patients has been shown to be associated with a decrease in the occurrence of new cardiovascular events[16].

The presented study aims to demonstrate the effect of long-term treatment with CPAP on the ANS activities of moderate to severe OSA patients as assessed by short recording HRV analysis.

Material and Method

From September 2004 to September 2006, 10 voluntary patients newly diagnosed with moderate to severe OSA from Siriraj Sleep Clinic were enrolled after informed consent. None of them had any underlying disease that was causing autonomic dysfunction and cardiac arrhythmia, no evidence of chronic lung disease, or any beta-blocker or anti-arrhythmic drugs used. The study protocol was approved by the Siriraj Ethics Committee.

The patients were evaluated for ANS activities between 9 to 12 AM for avoiding circadian variation of HRV parameters. Studies were conducted in quiet room with control temperature between 24-27□C. Subjects were asked to avoid a heavy meal, vigorous exercise, caffeine containing beverages, alcohol consumption, and smoking on the day of the present study. At the beginning of each trial, patients were rested for at least 10 minutes in supine position before a three-lead ECG was recorded in the same position. After connected with lead II ECG, the recordings were performed during approximately 6 minutes of supine controlled breathing at 10 breaths per minute by using stopwatch to minimize the effect of respiration. The ECG was sampled with the PowerLab□ acquisition system (AD Instruments Pty Ltd, Castle Hill, Australia) installed on a personal computer. The accuracy of measurements was 1 millisecond. The first minute of each ECG recording was disregarded to allow for stabilization of the data prior to analysis. All recordings were visually examined and manually overread to verify beat classification. Abnormal beats and areas of artifact were automatically and manually identified and excluded from the analysis. Each HRV analysis was performed at baseline, then at one, three, and six months after CPAP treatment.

All patients used the same model of CPAP machine and the same interface. Measurement of CPAP compliance was monitored by self-reported use and CPAP usage hours from the machine. The LF and HF spectral components of R-R interval were expressed in nu, LF to HF ratio (LHR), and SDNN were measured. Recovery of ANS activities was defined as either increase in SDNN, decrease in LHR, decrease in LF nu, or increase in HF nu after CPAP treatment.

Demographic, polysomnographic, and HRV data were expressed as mean $\pm$ SD (range). Statistical analyses were performed by SPSS software version 13.0 for window (SPSS Inc., Chicago, USA). Data were analyzed using student paired *t*-test, a p-value of < 0.05 was considered significant.

Results

Six patients had severe OSA (mean AHI 80.9 events/hour), four had moderate OSA (mean AHI 20.9 events/hour), all were men, and the mean body weight was stable during the study period. Compliance with the prescribed CPAP varied widely among individual patients, with average nightly use ranging from 2.27 to 5.15 hours at one month and 1.10-5.12 hours at six months. The demographic and polysomnographic characteristics are summarized in Table 1.

After CPAP treatment for one, three, and six months, time domains of HRV were compared with baseline. The data are summarized in Table 2-5.

Only the SDNN during deep breathing was significantly improved (increased SDNN) after treatment for 6 months (p 0.032). Seven patients had an increase in SDNN (responsive group) and three patients had a decreased SDNN (non-responsive group). The details of SDNN changes were presented in Table 6. Two patients in the non-responsive group

Table 1. Demographic and polysomnographic data

Parameter	Mean ± SD	Range
Age (y)	45.2 ± 5.1	36.0-50.0
Body mass index (kg/m^2)	29.3 ± 2.8	26.8-34.5
Apnea hypopnea index (events/hour)	60.9 ± 31.7	18.2-87.8
Sleep efficiency (%)	86.7 ± 5.3	80.0-95.0
Lowest SpO_2 (%)	73.2 ± 11.0	58.0-86.0
Average SpO_2 (%)	88.5 ± 3.9	83.0-94.0
CPAP pressure (cmH_2O)	10.3 ± 3.9	6.0-16.0

Table 2. Comparison of LF(nu) before and after CPAP treatment

LF	Mean ± SD	Range	p-value
SB baseline	57.74 ± 13.61	41.95-78.23	
SB 1 month	65.69 ± 13.98	30.85-84.57	0.072
SB 3 months	58.62 ± 17.55	24.38-84.54	0.899
SB 6 months	56.03 ± 17.13	27.72-77.58	0.815
DB baseline	39.96 ± 26.10	12.92-87.81	
DB 1 month	46.10 ± 23.10	17.30-83.00	0.396
DB 3 months	40.21 ± 29.50	15.10-96.18	0.960
DB 6 months	51.04 ± 19.43	23.82-90.87	0.159

Abbreviation: LF, low frequency HRV; SB, spontaneous breathing; DB, deep breathing

Table 3. Comparison of HF(nu) before and after CPAP treatment

HF	Mean ± SD	Range	p-value
SB baseline	37.14 ± 11.65	19.35-56.44	
SB 1 month	30.92 ± 14.05	14.07-67.45	0.091
SB 3 months	36.20 ± 16.75	13.92-69.16	0.883
SB 6 months	33.44 ± 12.48	15.14-77.58	0.240
DB baseline	57.21 ± 24.72	11.55-83.69	
DB 1 month	51.07 ± 21.84	15.86-74.94	0.392
DB 3 months	56.85 ± 28.41	3.29-79.80	0.946
DB 6 months	46.21 ± 18.45	8.95-72.11	0.155

Abbreviation: HF, high frequency HRV

had nightly CPAP compliance of < 2 hours.

Discussion

OSA impairs breathing during sleep and leads to repetitive hypoxia and arousals. It has been shown to be associated with many diseases and conditions such as hypertension, heart failure, and arrhythmia[5]. Patients with OSA have alterations in autonomic nervous system function such as increased sympathetic nerve firing, elevated in plasma norepinephrine, diminished beta-adrenergic receptor sensitivity, and altered HRV[11-14].

In one study, 41 patients with OSA were randomly assigned to receive effective treatment with CPAP usage 4-8 hours/night or placebo with an ineffective level of CPAP. The cardiac sympathetic measures were significantly lower in the CPAP-treated subjects after 11 days of treatment but not on the first

Table 4. Comparison of LHR before and after CPAP treatment

LHR	Mean ± SD	Range	p-value
SB baseline	1.86 ± 1.51	0.74-4.04	
SB 1 month	2.61 ± 1.44	0.46-3.60	0.133
SB 3 months	2.23 ± 1.68	0.35-6.07	0.566
SB 6 months	1.96 ± 1.01	0.75-3.61	0.801
DB baseline	1.53 ± 2.39	0.18-7.6	
DB 1 month	1.49 ± 1.66	0.23-5.23	0.941
DB 3 months	4.37 ± 9.36	0.19-29.20	0.293
DB 6 months	1.96 ± 2.92	0.34-10.16	0.332

Abbreviation: LHR, low frequency to high frequency ratio

Table 5. Comparison of SDNN (millisecond) before and after CPAP treatment

SDNN	Mean ± SD	Range	p-value
SB baseline	42.23 ± 14.60	22.74-65.82	
SB 1 month	43.55 ± 14.77	20.87-64.32	0.632
SB 3 months	47.31 ± 18.15	25.48-79.38	0.345
SB 6 months	44.06 ± 18.09	23.03-82.85	0.693
DB baseline	28.80 ± 9.83	14.76-47.16	
DB 1 month	30.20 ± 10.35	18.31-46.25	0.554
DB 3 months	31.02 ± 10.78	16.83-50.04	0.336
DB 6 months	34.43 ± 14.23	20.91-61.59	0.032*

Abbreviation: SDNN, standard deviation of R-R intervals

Table 6. Comparison of SDNN (millisecond) at baseline and after 6 months of CPAP treatment in each subject

Case No.	Baseline	At 6 months
1	38.70	55.08
2	25.86	20.91*
3	47.16	61.59
4	14.76	20.57
5	31.81	39.51
6	37.74	34.92*
7	22.73	22.58*
8	24.75	31.41
9	21.22	24.11
10	23.30	33.71

* = Decrease in SDNN

day[17]. Roche et al studied 14 patients with OSA after 3 months of CPAP treatment, continuous synchronized electrocardiographic and polysomnographic monitoring showed significant decreases in LF, HF, and LHR when the patients were asleep and a decrease in LHR was prolonged into the daytime[15]. From this body of evidence, effect of CPAP on ANS activity seems to depend on duration of treatment.

Most studies of HRV have used 24-hour Holter recorded electrocardiograms. The reproducibility of short-sampling periods of resting HRV was assessed and found no significant differences between the time domain and the frequency domain between the days[6]. There was evidence to suggest that time and frequency domain analyses on continuous 5-minute recording HRV in both spontaneous and controlled breathing were stable over months in a healthy person[18]. In the present study, evaluation of HRV by 5-minute recording, only the time domain of HRV (SDNN) during deep breathing was affected at six months, but the frequency domain (LF, HF, and LHR) were not significantly changed.

Two out of three non-responsive patients with no recovery of SDNN had poor compliance for CPAP treatment (< 2 hours/night). From a previous study, the sympathetic activity significantly decreased in those with effective CPAP usage of 4-8 hours/night[17].

Compliance with CPAP treatment has been demonstrated to be an important factor determining the survival of OSA patients[19]. In the case-control study of 124 OSA patients who died with 123 matched control OSA subjects, 57% of the deceased patients used CPAP for $\geq$ 5 hours/night while 77% of the control subjects had this level of compliance[20].

Due to the small sample size in this pilot study, it is difficult to draw definitive implications. Further investigation with more patients and more accuracy of measurement methods, may enhance the insight in the beneficial of CPAP treatment in these patients with high-risk for cardiovascular events.

In conclusion, one aspect of autonomic nervous system activity in moderate to severe OSA patients, was improved after 6 months CPAP treatment by short recording of heart rate variability.

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การฟื้นตัวของความผันแปรในอัตราการเต้นของหัวใจในผู้ป่วยที่มีภาวะหยุดหายใจจากการอุดกั้นระหว่างนอนหลับระดับปานกลางถึงรุนแรงภายหลังการรักษาด้วยเครื่องสร้างแรงดันบวก

พิมพร ลิ้มพันธ์อุดม, นิธิพัฒน์ เจียรกุล, ณรงค์ศักดิ์ ภิญโญภัทรกุล, อรรถ นานา, ชนะ นฤมาน, สุวัฒน์ ตั้งจิตยงสิวะ, วัฒนา วัฒนาภา, อโนรัตน์ เจนวิถีสุข

วัตถุประสงค์: *เพื่อศึกษาผลของการรักษาด้วยเครื่องสร้างแรงดันบวกในระยะยาว ต่อการเปลี่ยนแปลงของ ความผันแปรในอัตราการเต้นของหัวใจในผู้ป่วยที่มีภาวะการหยุดหายใจจากการอุดกั้นขณะนอนหลับ*

วัสดุและวิธีการ: *ทำการศึกษาในผู้ป่วยที่มีภาวะการหยุดหายใจจากการอุดกั้นขณะนอนหลับระดับปานกลางถึงรุนแรงที่ไม่เคยได้รับการรักษาด้วยเครื่องสร้างแรงดันบวกมาก่อน วิเคราะห์ ความผันแปรในอัตราการเต้นของหัวใจแบบย่อก่อนเริ่มการรักษาและหลังจากรักษาไปแล้ว 1, 3, และ 6 เดือน โดยวัดค่าความผันแปรในอัตราการเต้นของหัวใจความถี่ต่ำ ความผันแปรในอัตราการเต้นของหัวใจความถี่สูง สัดส่วนของค่าความถี่ต่ำต่อความถี่สูง และ ค่าเบี่ยงเบนมาตรฐานของ ระยะอาร์-อาร์ การวัดค่าต่าง ๆ ทำทั้งขณะหายใจตามปกติและขณะหายใจลึก*

ผลการศึกษา: *มีผู้ป่วยเข้าร่วมการศึกษาจำนวน 10 ราย ทั้งหมดเป็นเพศชาย อายุเฉลี่ย 45 ปี ค่าเฉลี่ยดัชนีมวลกาย 29.3 กก./ม.^{2} โดยมีดัชนีการหยุดหายใจและหายใจน้อยเฉลี่ย 60.9 ครั้ง/ชั่วโมง และค่าเฉลี่ยการใช้เครื่องสร้างแรงดันบวก 4.8 ชั่วโมง/คืน ค่าความผันแปรในอัตราการเต้นของหัวใจไม่มีการเปลี่ยนแปลงภายหลังการรักษา 1 และ 3 เดือน แต่ที่ 6 เดือนมีการเปลี่ยนแปลงของค่าเบี่ยงเบนมาตรฐานของระยะอาร์-อาร์ที่วัดขณะหายใจลึกเป็น 28.80 $\pm$ 9.83 เทียบกับ 34.43 $\pm$ 14.23 มิลลิวินาที*

สรุป: *ภายหลังการรักษาด้วยเครื่องสร้างแรงดันบวกในผู้ป่วยที่มีภาวะการหยุดหายใจจากการอุดกั้นขณะนอนหลับระดับรุนแรงปานกลางถึงมากเป็นเวลานาน 6 เดือน มีการเปลี่ยนแปลงในทางที่ดีขึ้นของตัวแปรหนึ่งในค่าความผันแปรในอัตราการเต้นของหัวใจ*