Clinical Research

Continuous Positive Airway Pressure Therapy Lowers Vagal Tone in Patients with Obstructive Sleep Apnoea-Hypopnoea Syndrome

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Introduction: Sleep apnoea, which constitutes a major social problem because of its high prevalence and its emerging association with cardiovascular morbidity and mortality, is known to affect autonomic nervous system activity. We assessed the hypothesis that treatment of sleep apnoea patients with continuous positive airway pressure (CPAP) alters the indices of heart rate variability (HRV) that reflect sympathetic and parasympathetic autonomic nervous system activity.

Methods: We studied 26 patients (18 men, aged 49.2 ± 7.6 years) with obstructive sleep apnoea-hypopnoea syndrome. In all patients, a 24-hour Holter recording was obtained one week before initiation of CPAP treatment and another one two months later. From these recordings we assessed the time domain indices of HRV (pNN50, rMSSD, SDNN, SDANN, SD) during the day (08:00-23:00) and during the night hours (23:00-08:00) as well as their post-treatment changes. The same HRV indices were also assessed in a group of 19 age and sex matched controls, without sleep apnoea.

Results: No significant differences in the HRV indices were observed during the daytime hours, while during the night both pNN50 and rMSSD were significantly higher in patients compared to controls (19.5 ± 12.5 vs. 13.8 ± 9.7, p=0.001, for pNN50 and 54.7 ± 23.1 vs. 44.0 ± 15.9, p=0.001, for rMSSD, for patients and controls respectively). No such differences were observed in any of the monitored indices following CPAP treatment.

Conclusions: The indices that reflect parasympathetic activity are increased during the night in patients with obstructive sleep apnoea syndrome. CPAP treatment reduces the night time vagal indices of HRV to resemble those of normal controls. The reduction of parasympathetic activity may be one of the mechanisms responsible for the alleviation of bradyarrhythmic episodes following the initiation of CPAP therapy.

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Sleep apnoea-hypopnoea syndrome, a frequently observed breathing disorder, affects 4% of men and 2% of women aged 30 to 60 years old.[1] The syndrome is characterised by repeated breathing cessations during sleep –with concomitant haemoglobin desaturation– and arousals, which result in sleep fragmentation. Its clinical presentation is associated with impaired cognitive function and daytime somnolence, frequently resulting in costly labour and traffic accidents, thus constituting a major social problem. Moreover, there is increasing evidence associating the syndrome with the initiation and progression of arterial and pulmonary hypertension, heart failure, myocardial ischaemia, myocardial infarction, stroke and vascular complications.[2-4] Existing studies have shown that patients with the apnoea-hypopnoea syndrome exhibit an increased sympathetic drive, which in turn has been implicated in the pathogenesis of the aforementioned diseases. Furthermore, cardiac

rhythm disturbances –sinus pauses, sinoatrial and atrioventricular block, ventricular and supraventricular arrhythmias– have all been reported as being syndrome-related.

A recent study making use of advanced monitoring with implantable loop recorders demonstrated that obstructive sleep apnoea patients primarily exhibit bradyarrhythmias, such as atrioventricular block and sinus pauses, while supraventricular or ventricular tachyarrhythmias were less frequently observed. The researchers demonstrated that comprehensive treatment with continuous positive airway pressure eradicates these arrhythmias over a relatively short period of time.[5]

Previous studies have suggested that a reflex increase in vagal tone, triggered by a combination of hypopnoea and hypoxia, rather than structural abnormalities of the conduction system, plays a pathogenetic role in the appearance of these arrhythmias. This study was designed to examine the autonomic nervous system activity during sleep and daytime in patients with obstructive sleep apnoea-hypopnoea syndrome, and to investigate possible alterations of this activity following continuous positive airway pressure therapy (CPAP).

Methods

Thirty-one patients with documented moderate or severe sleep apnoea-hypopnoea syndrome constituted our study population and were recruited consecutively from our Sleep Disorders Unit. The diagnosis was based on both polysomnographic recordings and sleep history. After diagnosis was made and before inclusion in the study, all patients underwent a diagnostic workup that included medical history, physical examination, routine laboratory investigation, echocardiographic evaluation and a Tl^{201} scintigraphic exercise test for the assessment of myocardial perfusion. Additionally, the sinus node and atrioventricular node function was assessed with an invasive electrophysiology study. Blood gases and lung function tests were also evaluated in each patient.

Exclusion criteria

Patients with co-morbidities known to affect heart rate variability were excluded from the study. Thus, hypertension, diabetes mellitus, sinus node disease or atrioventricular conduction abnormalities, indications of coronary artery disease, dilated or hypertrophic cardiomyopathy, valvular heart disease, respiratory failure, and lung disease that might have led to structural or functional pulmonary dysfunction, comprised the exclusion criteria. We also excluded patients currently on medication with cardioactive drugs (affecting the heart rate), hypnotics or drugs affecting sleep.

Control group

A selection of 19 healthy individuals who had also been examined in the Sleep Disorders Unit constituted our control group. All of them had a 24-hour Holter electrocardiogram, echocardiogram and exercise test and they all satisfied the same exclusion criteria as did our patient group.

The hospital's Ethical Committee approved the study, while both oral and written informed consent were obtained from every patient and control subject.

Sleep study and polysomnography scoring

All participants underwent a full night of polysomnography in the sleep laboratory. A sleep history was also taken and daytime sleepiness was evaluated using the Epworth Sleepiness Scale (ESS).[6] In addition spirometry was performed and arterial blood gases were measured.

Monitoring started at 10:30 pm and ended at 06:30 am. Recordings were made with an Alice-4 18 channel polygraph (Alice-4 Respironics, Pittsburgh, Pennsylvania, USA) and included monitoring of electroencephalogram (C3/A2, C4/A1 and Cz/Oz), electro-oculogram, genioglossus and anterior tibialis electromyograms, oxygen saturation, nasal thermistors and nasal canula pressure transducer, thoracic and abdominal bands, microphone for snoring and body position electrode (all according to the 10-20 international electrode placement system.[7]

Sleep staging was scored visually according to the criteria of Rechtschaffen and Kales[7] and micro-arousals were defined according to the criteria of Bonnet et al.[8] Respiratory event analysis and apnoea-hypopnoea index were scored visually and calculated according to international criteria, with hypopnoea manifesting as an adverse of thoracoabdominal effort of at least 50% with an associated oxygen desaturation of at least 4%, and apnoea as a cessation of airflow at the nose and mouth lasting at least 10 s. Episodes were classified as obstructive or central, on the basis of the presence of paradoxical movements of the rib cage and of the abdomen. Obstructive sleep apnoea-hypopnoea syndrome was defined as mild, moderate or severe depending on whether

Table 1. Basic characteristics of our study population

	Patients	Controls	p value
Age (years)	49.2 ± 7.6	51.6 ± 9.6	0.35
Sex (male/female)	18/8	11/8	0.43
Systolic BP (mmHg)	128 ± 12	122 ± 11	0.07
Diastolic BP (mmHg)	79 ± 7	76 ± 7	0.16
FEV_1 (% predicted)	98 ± 21	101 ± 14	0.57
FVC (% predicted)	97 ± 18	100 ± 11	0.53
BMI (kg/m^2)	36 ± 5	23 ± 4	<0.0001
AHI (per hour)	58 ± 24	4 ± 3	<0.0001
Moderate OSAHS	5 (19%)		
Severe OSAHS	21 (81%)		

AHI – apnoea-hypopnoea index; BMI – body mass index; BP – blood pressure; FEV_1 – forced expiratory volume in one second; FVC – forced vital capacity; OSAHS – obstructive sleep apnoea-hypopnoea syndrome.

the apnoea-hypopnoea index was between 5 and 15, 15 and 30, or greater than 30, respectively.[9]

Before the CPAP titration study, all eligible patients were given an educational explanation of obstructive sleep apnoea-hypopnoea syndrome and CPAP treatment by medical staff at the Sleep Disorders Unit and by specialised CPAP nurses. They were also shown an educational video. All patients underwent mask fitting from a wide range of mask types and spent 30 minutes becoming acclimatised to CPAP on a bed during the day. At monthly follow-up the mean nightly run time for each patient's CPAP machine was calculated from the time clock reading to ensure proper usage.

Twenty four-hour ambulatory Holter monitoring

Continuous ambulatory Holter recorders were connected to the patients using standard procedures, following the manufacturer's instructions (ELA Medical, Paris, France). Two 24-hour Holter recordings were obtained from every patient: the first one week before and the second two months after CPAP commencement. Data analysis was performed using the ELATEC analyser V3-03 software (ELA Medical, Paris, France).

Each QRS complex was automatically detected and labelled by the analysing program. This procedure was followed by careful manual review to limit any potential artefacts. Beats preceding or following an ectopic (ventricular or supraventricular) beat were excluded. RR intervals greater than 5 seconds were also excluded.

We derived six time domain indexes of heart rate variability (HRV): i) NN (in ms), the mean of all coupling intervals between normal beats, represents the simplest index with the smallest prognostic value; ii) SDNN (in ms), the standard deviation about the mean of all coupling intervals between normal beats, is an index with a proven prognostic value in post-infarction patients;[10,11] iii) SD (in ms), the mean of all 5-minute standard deviations of NNs, tends to eliminate the effect of circadian variation on heart rate; iv) pNN50 (%), the proportion of adjacent normal RR intervals differing by >50 ms, represents the respiratory effect on heart rate variability and thus constitutes an indirect index of vagal tone; v) rMSSD (in ms), the root-mean-square of the difference between successive RRs, is also used as an estimate of vagal activity;[10] vi) SDANN (in ms), the standard deviation of 5-minute mean NN intervals, is an index representing deviations from the mean heart rate and especially differences observed during wakefulness and sleep. These indices were calculated for the whole 24-hour recording and thereinafter for both daytime (08:00-23:00) and night hours (23:00-08:00). Changes observed pre and post CPAP therapy were carefully evaluated.

Results

Twenty-six (18 men, 49.2 ± 7.6 years old) of 31 consecutively screened patients, who met the inclusion criteria, were included in the study. Five initially screened patients were excluded because of coronary artery disease (n=2), obstructive pulmonary disease (n=2) or sinus node dysfunction (n=1).

The basic clinical and anthropometric characteristics of our population are presented in Table 1. Severe obstructive sleep apnoea-hypopnoea syndrome

Table 2. Heart rate variability indices in patients prior to and following the application of CPAP therapy compared to controls.

HRV Index	Pre-CPAP		Post-CPAP		p	Controls	
	Mean	Standard deviation	Mean	Standard deviation		Mean	Standard deviation
24 hour							
HR (bpm)	73.8	9.0	75.0	8.3	0.50	73.4	6.1
pNN50 (%)	10.9	8.9	10.0	7.4	0.40	10.9	8.0
rMSSD (ms)	45.2	20.0	41.0	15.6	0.13	42.0	18.1
SDNN (ms)	57.6	15.6	58.6	15.3	0.64	58.3	16.9
SDANN (ms)	111.7	31.7	112.3	30.8	0.92	108.3	36.6
SD (ms)	130.2	30.0	122.4	29.8	0.19	124.5	37.2
Daytime							
HR (bpm)	80.7	8.1	81.3	9.7	0.77	79.9	7.4
pNN50 (%)	5.3	7.3	6.5	7.4	0.42	7.6	5.4
rMSSD (ms)	32.0	17.6	35.8	19.6	0.09	38.4	16.0
SDNN (ms)	45.4	12.3	47.1	13.7	0.48	55.6	14.8
SDANN (ms)	79.2	22.6	82.1	18.2	0.52	76.4	20.3
SD (ms)	87.3	21.6	92.0	22.8	0.27	98.0	18.2
Night							
HR (bpm)	66.7	8.5	66.6	8.6	0.96	66.2	7.1
pNN50 (%)	19.5*	12.5	16.1	10.7	0.001	13.8*	9.7
rMSSD (ms)	54.7*	23.1	47.3	18.4	0.001	44.0*	15.9
SDNN (ms)	67.5	27.3	64.9	24.8	0.21	54.8	13.9
SDANN (ms)	65.8	23.0	67.0	20.9	0.53	65.9	19.3
SD (ms)	102.6	38.0	99.3	30.7	0.21	93.0	28.1

CPAP – continuous positive airway pressure; HR – heart rate; pNN50 – proportion of adjacent normal RR intervals differing by >50 ms; rMSSD – root mean square difference between successive RRs; SD – the mean of all 5-minute standard deviations of NNs; SDANN – standard deviation of 5-minute mean NN intervals; SDNN – standard deviation about the mean of all coupling intervals between normal beats.

*Statistically significant difference ($p<0.05$) between patients prior to CPAP therapy and controls.

was identified in 21 patients (constituting 81% of our study population), while 5 patients (19% of our population) demonstrated a moderate form of the syndrome. The prevalence of smoking in those patients was 31%.

The ejection fraction, end-systolic and end-diastolic diameters, as assessed by echo-Doppler studies before and two months after CPAP initiation, did not differ significantly ($p=0.24$, 0.83 and 0.09, respectively). In addition, body weight and smoking status did not change before and after treatment ($p=0.41$ and 0.95 respectively).

The control group consisted of 11 men and 8 women (mean age 51.6 ± 9.6 years). Their anthropometric and clinical characteristics are given in Table 1 for comparison with the patients' data. Controls were similar to the patients in terms of age and sex, while other variables such as blood pressure, left ventricular systolic and diastolic function, forced expiratory volume in one second and forced vital capacity did not differ significantly either. On the other hand, controls had significantly lower body mass index and, by definition, significantly fewer apnoeic-hypopnoeic episodes per hour of sleep compared to the patients.

Twenty-four hour HRV indices did not differ significantly between patients and controls. As shown in Table 2, CPAP therapy did not significantly alter the HRV indices in the patient group during the 24-hour or the daytime Holter monitoring ($p=NS$). Night monitoring, however, revealed a statistically significant reduction in the pNN50 and rMSSD indices in the patient group following treatment (Figure 1). Note that both pNN50 and rMSSD values were significantly higher in the patients than in controls prior to CPAP

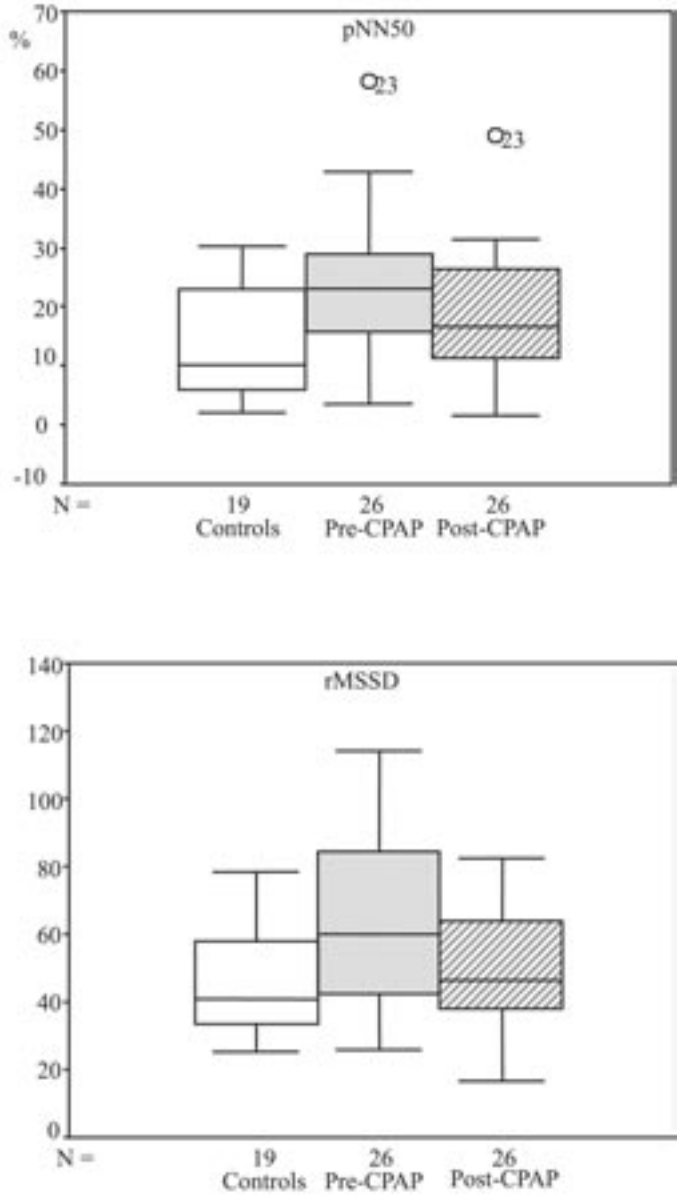

Figure 1: The pNN50 and rMSSD variables represented graphically in patients pre and post CPAP therapy, compared to controls.

therapy. Appropriate treatment eliminated those differences between patients and controls (note the values in the post-CPAP and controls columns).

Discussion

In this study we demonstrate that patients with severe or moderate obstructive sleep apnoea-hypopnoea syndrome show elevated parasympathetic tone during the night, as expressed by the higher values of pNN50 and rMSSD compared to controls. What is more, our study suggests that appropriate treatment with CPAP therapy restores normal autonomic nervous system activity.

Although many of the previous studies of autonomic nervous system function in sleep apnoea-hypopnoea syndrome have reported inconsistent or conflicting results in relation to our findings, it should be noted that most of those studies used a different methodology and included patients who had other concomitant diseases and/or were under pharmaceutical therapy. In addition, in certain studies, the HRV calculations were conducted simultaneously with other tests (polysomnographic recordings, muscle sympathetic nerve activity measurements) under conditions that may have influenced the balance of the autonomic nervous system.

Narkiewicz et al[12] used spectral analysis of HRV to assess the autonomic indices of neural cardiac control noninvasively. They showed that the subgroup of patients with moderate to severe obstructive sleep apnoea (15 patients) had an increased normalised low frequency variability of the RR interval (representing mainly the sympathetic drive of the autonomic nervous system) while the high frequency component (reflecting vagal tone) was decreased. However, those patients were evaluated during arousal while other measurements were being performed at the same time to evaluate the muscle sympathetic nerve activity.

The same researcher went on to show that extended CPAP therapy in patients with obstructive sleep apnoea and no other concomitant disease decreases sympathetic drive, as expressed by a reduced muscle sympathetic nerve activity.[13]

Standard spectral analysis of HRV, such as the ratio of low to high frequency power and normalised high-frequency power, can be confounded by the abnormal breathing patterns that occur during sleep. Using a slightly modified model of HRV analysis, Khoo et al[14] managed to circumvent this limitation. He also reported a decreased vagal activity in patients with obstructive sleep apnoea, which was significantly improved by CPAP therapy. In a subsequent study[15] the same author showed that restoration of normal cardiac autonomic function is closely related to long term compliance with CPAP therapy. It should be mentioned, however, that all of the measurements were performed while the patients were awake and that 5 out of 13 patients examined were hypertensive on treatment.

Wiklund et al[16] found a significant decrease in indices reflecting vagal drive, thus indicating decreased parasympathetic activity, in sleep apnoea patients compared to controls. No relation between apnoea-hypopnoea index and indices of vagal modulation was shown. Nevertheless, the study was again conducted on awakened patients in the supine position, under controlled breathing and tilting, using frequency domain analysis of HRV. Patients with diseases other than obstructive sleep apnoea were not excluded. It is clear that the population evaluated and the methodology used were not similar to ours; thus, the findings are not comparable. These results rather reflect the sympathovagal status under the specific conditions tested.

Gula et al[17] examined a small group of patients with obstructive sleep apnoea and concomitant diseases under medication, and by using frequency domain analysis they came to the conclusion that there is an increased sympathetic tone in patients with moderate sleep apnoea, which is blunted in severely ill patients. Moreover, their data suggest that CPAP therapy in the latter group may restore the autonomic system status to that of moderately ill patients. These authors recognised important limitations in their study, mainly the small sample of patients (8 with severe and 5 with moderate obstructive sleep apnoea, while CPAP was applied in only 5 patients) and other confounding factors such as co-morbidities and medication. However, they described a significant increase in the high frequency component of HRV, representing enhanced parasympathetic activity, in severely ill patients, as were most of the patients in our study.

In an interesting study, Roche et al[18] hypothesised that time-domain analysis of HRV would yield more pertinent diagnostic information about autonomous nervous system activity and could be used as an accurate and inexpensive massive screening test for diagnosing obstructive sleep apnoea-hypopnoea syndrome. In accordance with our own data, they also showed that mean night SDNN and rMSSD, and therefore parasympathetic nervous system activity, are higher in these patients compared to controls. A possible pathophysiological explanation of the observed abnormalities lies in the following schematic approach: upper airway obstruction → parasympathetic activation → hypoxia → abrupt sympathetic activation. At night, the successive alternating strong parasympathetic and sympathetic drives dramatically enhance RR variability; this enhanced HRV however, does not correspond to an isolated increase in parasympathetic activity as in healthy subjects. On the other hand, diurnal HRV is known to be reduced in patients with obstructive sleep apnoea syndrome, reflecting an enhanced sympathetic nerve activity. It is very likely that differences in time domain HRV values between day and night result mainly from the combination of these two phenomena.

The results of our study are not indicative of any significant alterations in the sympathetic nervous system activity of sleep apnoea patients before and after CPAP therapy, or when compared to normal controls. The same is true for parasympathetic nervous system activity during the daytime. However, there are certain methodological issues, regarding the way our study was planned, that should be mentioned. The patients enrolled were carefully screened and selected to exclude individuals with any other concomitant disease, especially hypertension, which is known to affect the tone of the autonomic nervous system by in-

creasing sympathetic nervous system activity. Frequency domain analysis of HRV, a rather common practice in the literature, is used to assess autonomic nervous system balance and activity over short periods of time, mainly 2-5 minutes. Estimates for longer periods, using mean values of successive 5 minute intervals, poses a significant issue of validity. On the other hand, HRV analysis using time domain indices seems capable of yielding more pertinent information and a better assessment of autonomic nervous system activity.[19] In support of this, Salo et al[20] showed in their study that time domain measures of HRV demonstrate better reproducibility than frequency domain measures in hypertensive patients with sleep apnoea syndrome. Moreover, the authors indicated that the reproducibility of frequency domain measures is closely related to the conditions under which the analyses are performed.

According to our inclusion criteria, our patients could have moderate or severe obstructive sleep apnoea-hypopnoea syndrome. However, only 5 patients were found to demonstrate a moderate severity profile: the remainder were considered severely ill with an increased apnoea-hypopnoea index during their sleep (Table 1). The consequent frequent and exaggerated Mueller manoeuvres in such an advanced disease status could partly explain the increased vagal tone we observed. On the other hand, episodes of apnoea are associated with hypoxaemia, carbon dioxide retention, bradycardia and a decrease in blood pressure that is, in turn, associated with an increased vagal tone leading to periodic variations in heart rate.[21,22] What we have shown in our study is that CPAP therapy improves the indices reflecting vagal activity to such a degree that they do not differ from those of normal individuals of similar age and sex. Our findings seem complementary to those we have previously published in a recent study[5] and explain the severe bradyarrhythmic episodes recorded during the night, as well as their disappearance following successful treatment with CPAP devices.

Study limitations

The patients in our study differed significantly from the controls in terms of body mass index. It is well known, however, that any HRV alterations observed in obese individuals mainly reflect increased sympathetic activity. It is therefore highly unlikely that any of the differences in vagal tone activity we observed were related to this discrepancy in body mass index.

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