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The Effect of Nocturnal Nasal Continuous Positive Airway Pressure Therapy on Obstructive Sleep Apnoea-Hypopnoea Syndrome and Brain Natriuretic Peptide-Biomarker for Cardiac Failure

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Abstract: ***Background: Obstructive sleep apnoea hypopnoea syndrome (OSAHS) is characterized by repetitive apnoea and hypopnoea, excessive daytime sleepiness, fatigue, raised levels of brain natriuretic peptide (BNP) and higher incidence of cardiovascular morbidity. Objectives: Evaluation of nocturnal nasal continuous positive airway pressure (nCPAP) therapy and BNP levels in OSAHS. Materials and Methods: Twenty OSAHS patients-ten with and ten without overt heart failure (HF)-underwent baseline clinical assessment, overnight polysomnography and blood BNP assay. HF patients were treated medically for two weeks followed by nCPAP therapy for two weeks; non-HF patients were only given 4-week nCPAP therapy. BNP assay was repeated after medical and nCPAP therapies. Results: nCPAP therapy produced statistically significant improvement of symptoms and improved Epworth sleepiness score in both groups of patients. Baseline median BNP values were significantly raised in both, more so in the HF group (160.92 vs 678.55 pg / ml; normal ≤ 100pg / ml). In the HF group, while medical treatment did not produce a significant decrease in BNP values, nCPAP therapy produced a statistically significant decrease in BNP values. In the non-HF group also, nCPAP therapy produced statistically significant decrease in BNP values. Post-nCPAP therapy, BNP values were normalized in both groups (HF-93.49; non-HF-58.02 pg / ml; p- <0.05). Conclusions: OSAHS patients may have cardiac involvement even in absence of overt HF. They should be treated with nocturnal nCPAP for 4-6 hr daily. with monitoring of BNP levels.***

Keywords: Obstructive sleep apnoea, OSA, brain natriuretic peptide, CPAP

1. Introduction

The hallmark of obstructive sleep apnoea (OSA) hypopnoea syndrome (OSAHS) is recurrent occlusion of upper airway at the pharyngeal level during sleep.[1, 2] Next to asthma and chronic obstructive pulmonary disease (COPD), this is believed to be the most common chronic respiratory disorder. Approximately 3-7% adult males and 2-5% adult females in western countries and Asia are reported to suffer from OSAHS. [3] In India too, OSA is a significant public health problem. In a hospital- based study of adult men from the city of Mumbai, 7.5% were reported to have OSAHS. [4] In a population- based study from Delhi, Sharma et al. [5] reported prevalence rates of 13.7 % OSA and 3.75 % OSAHS in habitual and non-habitual snorers respectively. In a cross-sectional community- based study from south Delhi, Reddy et al. [6] estimated population prevalence of OSA (9.3%) and OSAHS (2.8%)

The clinical spectrum of OSAHS has snoring, apnea and hypopnea and nocturnal hypoxemia at the one end, and a series of morbidities at the other end. The latter comprise systemic hypertension; [7] myocardial ischemia; [8, 9] stroke; [10] diabetes, metabolic syndrome; [11] increased cardiovascular morbidity and mortality; [12] and higher risk of automobile and work place accidents.[13] In recent years assessment of cardiovascular morbidity in OSAHS has assumed great importance.[14-16] For example, in a group of male patients with systolic heart failure, 49% were reported to suffer from sleep apnoea.[17, 18] The cardiovascular effects are believed to be the result of a series of mechanical, haemodynamic, chemical, neural and inflammatory responses triggered by OSA.[19- 23]

Nocturnal nasal CPAP (nCPAP) therapy even on short term basis has been shown to produce 9% increase in left ventricular ejection fraction along with significant reduction in blood pressure. [24] In another study, CPAP administered for ≥ 4 hr each night for two months in patients with severe OSAHS produced reductions of oxidative stress, blood pressure, cholesterol level, insulin resistance and improvement of insulin sensitivity; which may be responsible for improvement of symotoms [25]

Recently, cardiac neurohormone B-type natriuretic peptide (BNP) assay has been evaluated to diagnose CHF. Three well designed studies found BNP cut-off level of 80 pg / ml to have sensitivities ranging from 93% to 98% in diagnosing heart failure in symptomatic patients, and negative predictive values ranging from 92% to 98%, to rule out congestive heart failure. [26-28] BNP has been reported to be the single best marker of left ventricular hypertrophy and systolic and diastolic dysfunction.[29]

In India, OSAHS remains under diagnosed mainly due to lack of awareness, as typical symptoms of habitual snoring and excessive daytime sleepiness (EDS) are often ignored by the patient as well as the treating physician. Moreover, the diagnostic facility of polysomnography (PSG) is either not

available, or can not be easily accessed. This prospective study was designed with the twin objective of clinical assessment of patients with OSAHS, including BNP assay as a biomarker for cardiac failure; and evaluate the results of short term nocturnal nCPAP therapy clinically and effect on BNP levels.

2. Materials and Methods

This is a prospective; double group, random sampling experimental out-patient based study conducted on twenty PSG diagnosed OSAHS patients with AHI ≥15 per hour. The method of random selection of patients is depicted in Fig. 1

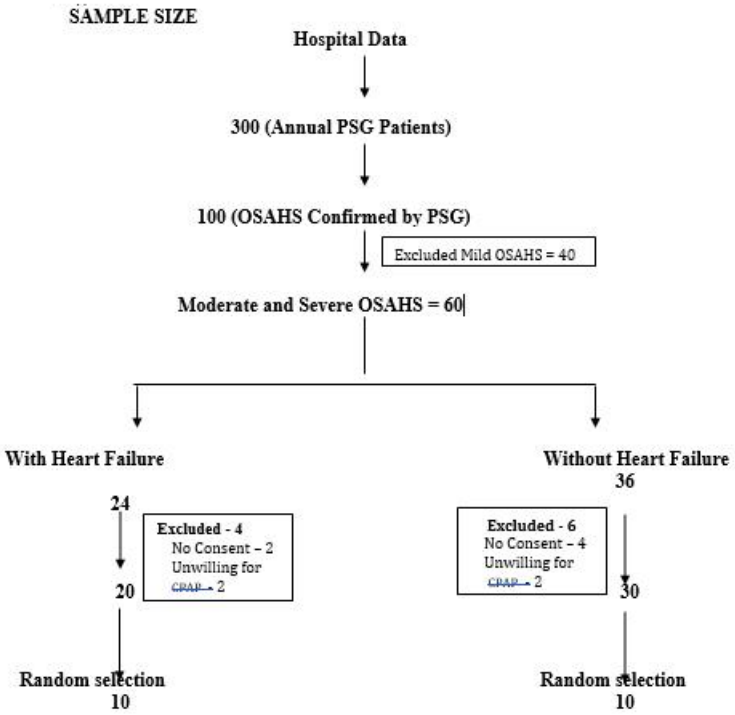

Figure 1: Flow chart for patient selection

The inclusion criteria comprised of: age ≥40 years; loud habitual snorer; BMI≥ 25 kg / m^2; EDS with Epworth sleepiness score of ≥10; and committed cooperation in the study including CPAP treatment. The exclusion criteria were: daytime hypoxemia; history of primary valvular heart disease; implanted cardiac pacemaker; unstable angina; myocardial infarction; significant cardiac arrhythmias; stroke; chronic renal failure; and chronic alcohol / substance abuse. As per the hospital practice, informed consent of the patient was taken in writing.

A detailed clinical history and findings on physical examination related to OSAHS were recorded. These included Epworth sleepiness score (ESS), OSAHS symptoms; upper and lower respiratory tract abnormalities; cardiovascular system evaluation and level of physical activity. [30, 31] Special investigations included chest radiograph; computed tomography of thorax and para-nasal sinuses; 12-lead ECG, and 2-D & M-mode echocardiography; thyroid, lipid and renal profiles; arterial blood gases and pH; and spirometry before and after inhaled salbutamol. The diagnosis of congestive heart failure was made as per the European Society of Cardiology criteria. [32]

Measurement and interpretation of BNP assay. Five ml of venous blood was collected in tubes containing potassium EDTA. B-type natriuretic peptide was measured in plasma with the use of rapid florescence immunoassay (The Triage BNP Test Biosite, USA) with a measurable range of 5 to 5000 pg / ml. Values >100 pg / ml were considered abnormal, suggestive of CHF. [27 -29] BNP measurements were made: i) in the HF group-at baseline; after two weeks of medical therapy; and on conclusion of two weeks nCPAP therapy; ii) in the without heart failure group-at baseline and on conclusion of 4-week nCPAP therapy.

Polysomnography (PSG). Overnight attended PSG (split-night study: 4-hr PSG + 4-hr titration) was performed in sleep laboratory, with 32 channel polysomnograph (Medcare Embla S7000 with Video), following standard international methodology. [33]

The PSG data were scored as per standard international practice [33, 34] for sleep variables such as apnea-hypopnea index (AHI), respiratory disturbance index (RDI), oxygen desaturation events per hour, and sleep efficiency (% total sleep time divided by total bed time). Video attachment helped visualizing the patient, especially at arousal.

Overnight nCPAP titration was done with Resmed Autoset Clinical III Machine; ensuring minimum oxygen saturation > 90%, minimal leak, and AHI below 5 per hr. The median and highest pressures were recorded, and the data were analyzed.

The patients without cardiac failure, after baseline BNP measurement, were given nCPAP therapy for 4 to 6 hr daily for four weeks. Those with overt cardiac failure-after BNP

assay-on the other hand, were first given medical therapy for two weeks, BNP assay was repeated, and put on nCPAP therapy for a further two weeks. All patients were fully trained in using the CPAP machine. The built-in timer automatically recorded the time for which the machine was used.

Statistical analyses of data

This is a prospective, double group, random sampling, pre-test post-test experimental study on patients with OSAHS. The data were expressed in mean ± SD and percentage representation of total sample size. Paired t-test was used to compare the values before and after intervention to the patient population of the two groups (OSAHS with and without heart failure respectively) for samples with parametric measurement and normal distribution; whereas Wilcoxon Signed ranked test was used for measurements without normal distribution. Similarly, independent t-test was used for the between group analyses for parametric distribution and normal distribution, and Mann Whitney U test was used for measurements without normal distribution. The level of significance was taken at $p \leq 0.05$.

3. Results

The results of analysis of clinical, PSG, sleep and BNP assay data of twenty patients with moderate to severe OSAHS-before and after nCPAP therapy-are presented in Tables 1 to 6.

Table 1: Demographic characteristics of study group patients

Parameter	Male (n= 14)	Female (n= 6)
Age (years)	53.36±8.08	55.67±11.7
BMI (kg/m^2)	28.55±3.9	32.76±3.84
Hip: waist ratio	1.014 ± 0.059	1.035 ± 0.039
Smoker (n)	12 (86%)	0 (0%)

The demographic characteristics of all patients are shown in Table-1. It can be seen that mean BMI was ≥30 in all the six women patients; they also had a slightly higher waist: hip ratio than men.

General Clinical Assessment

Only four (20%) of the twenty patients were free from any clinical symptoms or signs pertaining to upper / lower respiratory tracts. Clinical and imaging evaluation revealed the following abnormalities in the remaining 16 patients: nasal symptoms (6); headache (14); cough with or without expectoration (15); wheeze (10); and dyspnea on MRC scale (II-4, III-10, IV- 2). Abnormal radiological and C-T findings showed: deviated nasal septum (3); pan-rhino-sinusitis (2); turbinate hypertrophy (1); bilateral lung hyperinflation (3); prominent bronchovascular markings (4) blunting of costo-phrenic angle (2); opacities / infiltrates in lungs (5); and reticulo-nodular opacities in lungs (1). FEV_1 was normal in 7 (28%), moderately impaired in 4 (20%), and severely impaired in 9 (36%) patients.

Nine (45%) of the 20 patients had hypertension-stabilized on medical treatment. Four (20%) patients were on treatment for diabetes; 9 (45%) patients had dyslipidemia. Ten (50%) patients had overt heart failure, which was medically treated before giving nCPAP therapy. The baseline mean values of heart rate and blood pressure in the study group patients were 90.1 ± 18.69 beats per minute and 100.1 ± 10.5 mmHg respectively. After CPAP therapy mean values of blood pressure did not show any significant change, but heart rate showed a small but significant reduction.

Table 2: Polysomnographic (PSG) data in twenty OSAHS patients

PSG variables	Mean ± SD	Range
Sleep efficiency %	68.26 ± 13.81	41.1-94
AHI (per hour)	48.63 ± 27.01	17-90.4
Oxygen desaturation events	190.5 ± 157.47	29-483
Lowest O_2 saturation (%)	68.8 ± 13.8	50-80%

AHI-apnoea hypopnoea index

PSG data in Table-2 show wide variations of sleep efficiency, AHI, oxygen desaturation events in individual patients. Six (male-3; female-3) of 20 patients had AHI of 15 to 30 events per hr; the remaining 14 (male-11; female-3) had AHI ≥ 30 events per hr.

Clinical Evaluation of nCPAP Therapy

Table-3 shows that all symptoms related to OSAHS, based on self reporting, were significantly relieved after nCPAP therapy. A significant reduction of Epworth sleepiness score (ESS) from 18.45 ± 4.18 to 5.45 ± 2.28 indicates relief from the disabling symptom of excessive daytime sleepiness.

Table 3: Comparative evaluation of nCPAP on severity of OSAHS, based on self- reported symptoms

Symptom	Pre- CPAP	Post- CPAP	p- value
*Stoppage of breathing	4.5±1.00	1.05±0.22	0.0001
*Breathlessness on awakening	4.05±1.58	1.16±0.36	0.0001
*Sweating	1.60±1.50	0.90±0.45	0.031
*RERA	4.50±1.15	1.05±0.22	0.0001
**Morning headache	0.55±0.51	0.15±0.37	0.002
**Difficulty getting back to sleep	0.40±0.50	0.05±0.22	0.005
**Memory lapse	0.35±0.49	0.15±0.37	0.042
**Episodes of choking	0.75±0.44	0.05±0.22	0.0001
**Mood swings	0.35±0.49	0.15±0.37	0.042
**ESS	18.45±4.18	5.45±2.28	0.001

Key:*= 1-never; 2-less than once per week; 3-once or twice per week; 4-3 to 4 times per week; 5-almost daily. **= mean prevalence. ESS = Epworth sleepiness scale.
RERA = respiratory effort related arousal event. P-value ≤ 0.05 = statistically significant.

ECG and Echocardiography Findings

ECG changes were detected in 4 (20%) patients: left ventricular hypertrophy with left axis deviation in two (10%), and sinus tachycardia with left ventricular hypertrophy in two (10%). No further changes were detected after nCPAP therapy. The left ventricular ejection fraction (LVEF) in each of the ten patients without heart failure was 60%; remained unaffected after nCPAP therapy. The LVEF in patients with heart failure ranged from 20 to 45 percent. After nCPAP therapy, it increased from 26 to 28% in one patient; in the remaining 9 patients it showed no change.

Table-4 shows comparative analyses (before and after nCPAP) of sleep, cardiovascular and spirometry data of the heart failure and without heart failure group patients. It can

be seen that the heart failure group patients had lower values of BMI, LVEF and H^+ concentration (suggestive of hyperventilation due to congested lungs) than the without HF group patients; the difference is statistically significant. Interestingly, they also show more favorable mean values for sleep efficiency, AHI, oxygen desaturation events / hr- although the difference is statistically not significant.

Analysis of blood pressure data shows: **HF-group.** n = 10; SBP Mean ± SEM = 135.2± 5.02; DBP Mean ± SEM = 84.4 ± 3.98. **Non-HF group. n =** 10; SBP = 132.4 ± 3.12; DBP = 82.2 ± 2.39. There was no statistically significant difference between SBP (0.642) and DBP (0.641) between the two groups.

Table 4: Sleep, cardiovascular and respiratory data in OSAHS patients with heart failure (HF) compared with patients without HF

	With HF (n = 10)	Without HF (n =10)	p-value
Parameter	Mean ± SEM	Mean ± SEM	
Age (years)	56.8±2.075	55.5±3.557	0.76
BMI (kg/m^2)	27.976±1.276	31.65±1.214	0.05*
Sleep efficiency (%)	85.37±18.93	70.46±4.757	0.45
AHI per hour	45.14±7.378	52.25±8.922	0.55
O_2 desaturation per hour	154.80±47.37	208.86±48.12	0.43
Lowest O_2 saturation	72.5±4.854	66.6±3.781	0.35
Snoring (pre -n CPAP)	5.0±0.0	5.0±0.0	1.00
Snoring (post-nCPAP)	1.0±0.0	1.0±0.0	1.00
PaO_2 (mm Hg)	79.43±2.979	81.15±3.704	0.72
$PaCO_2$ (mm Hg)	37.99±2.784	43.18±6.568	0.47
Ph	7.455±0.013	7.391±0.024	0.03*
Systolic blood pressure (mm Hg)	135.2±5.02	132.4±3.12	0.642
Diastolic blood pressure (mm Hg)	84.4±3.98	82.2±2.39	0.641
Mean blood pressure (mm Hg)	101.29±4.04	98.89±2.56	0.62
Heart rate per min	93.6±7.45	86.6±3.95	0.42
FEV_1 (% predicted)	58.62±6.87	56.12±6.79	0.79
FEV_1/ FVC %	68.44±5.65	69.64±4.8	0.87
Left ventricular ejection fraction (LVEF %)	38.1±4.65	60.0±0.00	0.01*

*-statistically significant

Table-5 shows between-group analysis of BNP assay data. It can be seen that although both groups of patients showed considerably raised base line BNP values, these are significantly more raised in the heart failure group (p-0.023) compared with the without heart failure group. After nCPAP therapy, BNP values decreased close to normal in both groups, with no statistically significant difference between them (p-0.618). There was no statistically significant difference in median BNP values between normotensive subjects (n = 9; 305 pg /ml) and hypertensive subjects (n =11; BNP = 200 pg /ml; p- 0.79) BNP levels with respect to smoker and non-smoker were not found significantly different in our study. Median BNP values (pg / ml) were: smokers-n = 12; BNP = 352.5 pg / ml; non-smokers-n = 8; BNP = 190.52 pg / ml; p-0.165 (Mann-Whitney Test).

Table 5.1: BNP assay values in OSAHS patients with heart failure (HF) compared with patients without HF: base line and post-CPAP therapy

Status	BNP (pg / ml) Median		p-value
	With heart failure (n= 10)	Without heart failure (n=10)	
Base line	678.55	160.92	0.023*
Post-CPAP	93.49	58.02	0.618

Statistical analyses of data, using Mann-Whitney U test, *-statistically significant

Table-5.2 shows within-group analysis of BNP assay data. It can be seen that the heart failure group patients who were medically treated did show some decrease of BNP values, but the change was not statistically significant (p- 0.112). However, a statistically significant decrease in BNP values occurred on conclusion of nCPAP therapy (p-0.001); and came close to normal. Without heart failure group patients (not given medical therapy) also showed a statistically significant decrease in BNP values after the CPAP treatment, and which also came close to normal (p- 0.009).

Table 5.2: Within group analysis of BNP assay values in OSAHS patients: heart failure group and without heart failure group

Status	Heart failure (n= 10) BNP (pg / ml)		Without heart failure (n= 10) BNP (pg /ml)	
Baseline	678.55		160.92	
	Median	p-value	Median	p-value
Post-medical therapy	250.00	0.112	No medical therapy given	
Post-nCPAP	93.49	0.001*	58.02	0.009*

*- statistically significant

4. Discussion

The present study clearly demonstrates that even a short term nCPAP therapy-4 to 6 hr daily-for 2 to 4-weeks significantly relieved symptoms of obstructive sleep apnea-hypopnea syndrome and also resulted in improved quality of life. Furthermore, normalization of BNP assay values after nCPAP therapy is strongly suggestive of improvement in cardiovascular function, whether or not there was clinical evidence of congestive heart failure. CPAP administered for ≥ 4 hr daily for 2 months in severe OSAHS is known to reduce oxidative stress, insulin resistance, blood pressure and serum cholesterol. [25] The findings strongly suggest that in the present series even the non-heart failure group patients actually had cardiac involvement, but this had not

progressed to clinically detectable cardiac failure. As pointed out in the Introduction, cardiovascular effects are believed to be the result of a series of mechanical, haemodynamic, chemical, neural and inflammatory responses triggered by OSA. [19-23]

The clinical profile of OSAHS patients complicated with CHF was found to be somewhat less characteristic than patients with OSAHS alone, in that the incidence of obesity was lower and majority of them did not complain of excessive daytime sleepiness. Similar findings have been reported by other investigators [17, 35]

A diagnosis of overt heart failure as per the criteria of the European Society of Cardiology [32] was made in 10 of the 20 patients included in the present study. This group of patients showed the following clinical characteristics which contrasted with the group without overt heart failure: i) lower mean LVEF (38.1± 4.65%) in contrast with normal 60% in the non-heart failure group; ii) significantly lower BMI values; iii) a lower mean value of $PaCO_2$ and a higher mean value of arterial pH suggesting that the patients were hyperventilating apparently due to congested lungs; iv) more favorable mean values of sleep efficiency, AHI /hr, nocturnal desaturation events / hr, and lowest nocturnal oxygen-although the difference was not found statistically significant. It is possible that age and other life style related factors potentiate the effects of OSA and lead to development of congestive heart failure which OSA alone would not have done. [17, 18]

As stated earlier, the increased cardiovascular morbidity and mortality in OSAHS have assumed great importance. [15-17] Some times, it is difficult to establish diagnosis of cardiovascular morbidity-especially of heart failure-on clinical ground alone. [36] Dyspnea-the most important differentiating symptom-may be related to obesity and lung function impairment on account of COPD co-existing with OSAHS in the present study. The facility of a more reliable diagnostic echocardiography may not always be accessible. Even experienced physicians often disagree on diagnosis in individual cases, especially in patients with mild heart failure. [37]

Several studies have found strong evidence that BNP level is both sensitive as well as specific for heart failure. [26-28] BNP assay level of more than 100 pG /ml was considered suggestive of cardiac involvement. [27-29] It also serves as a reliable prognostic cardiac biomarker. In the present study, both groups of OSAHS patients, with and without overt heart failure respectively, showed significantly raised BNP values-much more so in the heart failure group. In the latter group, BNP values showed reduction after medical treatment of heart failure but these still remained significantly raised. After CPAP therapy for four weeks in the non-heart failure group and for two weeks in the heart failure group, BNP values almost decreased to normal level in both groups of patients-the change was statistically significant. The findings can be explained on the basis of nCPAP related improvement in cardiovascular function in both groups of patients.

The results of the present study also confirm the reports in literature that OSAHS carries a high risk for cardiovascular morbidity. This should be kept in mind by the treating physician even if there are no overt clinical signs of cardiac failure. All patients diagnosed with stroke, hypertension or CAD should be interrogated for co-existing OSAHS and on the slightest suspicion should be subjected to overnight PSG to confirm diagnosis.

5. Conclusions

All patients with OSAHS must be treated for at least 4-6 hr each night with nasal CPAP, not only to ameliorate OSA symptoms, but also to prevent and / or treat cardiovascular complications. Regular monitoring of BNP levels would be the best way for early detection, prognostification, and evaluating therapy of cardiovascular complications.

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