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Original Article

Physiology Section

Effect of Short Term CPAP Therapy in Obstructive Sleep Apnea Patients with Metabolic Syndrome

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ABSTRACT

Background: Patients of obstructive sleep apnea (OSA) with metabolic syndrome (MetS) are at increased risk of cardiovascular morbidity and mortality. The role of oxidative stress in pathogenesis of OSA and MetS has been widely reported. Continuous positive airway pressure (CPAP) therapy remains the first-line of treatment in OSA. The beneficial effect of long term CPAP therapy in OSA is well-known. However, the effect of short term CPAP on the components of MetS and oxidative stress-antioxidant levels is still unclear.

Aim: The present study explored the effects of one night of CPAP therapy on the oxidant-antioxidant status and components of MetS in patients of OSA with MetS.

Materials and Methods: Twenty adult males and postmenopausal females with MetS and symptoms suggestive of OSA were enrolled in the study. None of the subjects were smoker or alcoholic. They did not consume any drugs that would alter their antioxidant levels. Overnight polysomnography was done to confirm diagnosis and assess CPAP pressure. Following which they spent one night in the sleep lab for CPAP therapy. Blood pressure data and blood samples were collected at baseline and after CPAP. Collected samples were transferred immediately to the laboratory for analysis of serum thiol, lipid peroxidation, insulin resistance (HOMA-IR) and lipid profile.

Results: Paired t-test with two-tail significance was used to compare the changes in study parameters in the same patient before and after treatment. The antioxidant level increased and oxidative stress decreased as evidenced by serum thiol concentration (204.2±65.7 vs 254.9±72 µmol/L, p<0.001) and lipid peroxidation levels (13.1±6.2 vs 8.4±3.1 µmol/L, p<0.01). There was a significant decrease in both systolic (132.1±16.1 vs 127.2±14.3 mmHg, p<0.01) and diastolic blood pressure (86.4±9.4 vs 81.2±9.8 mmHg, p<0.01) after one night of CPAP. However, there was no change in lipid parameters and the reduction seen in insulin resistance was not statistically significant.

Conclusion: One night of CPAP therapy seems to be helpful in reducing oxidative stress, improving antioxidant levels and decreasing the severity of various components of MetS.

Keywords: Blood pressure, Insulin resistance, Lipid profile, Oxidative stress

INTRODUCTION

Obstructive sleep apnea (OSA) is a clinical disorder characterized by repetitive episodes of upper airway collapse during sleep. Patients with OSA frequently exhibit metabolic abnormalities like obesity, insulin resistance, hypertension, and dyslipidemia, collectively known as the "metabolic syndrome". In a community based study it has been observed that OSA patients have a fivefold increased risk of having metabolic syndrome [1]. In India the prevalence of OSA is estimated to be 13.7% [2] and the prevalence of metabolic syndrome in OSA patients ranges from 4.5% in population-based study [3] to 79% among patients with OSA in hospital-based study [4]. There is cumulative evidence suggesting the presence of increased oxidative stress in OSA patients [5]. In our previously published study we have demonstrated an increased lipid peroxidation and decreased total reduced glutathione levels indicating an imbalance between reactive oxygen species (ROS) and antioxidant capacity [6]. Chronic nocturnal intermittent hypoxia occurring in OSA leads to low grade systemic inflammation [7]. Thus the oxidative stress, metabolic abnormalities and low grade inflammation seem to be the key factors initiating the various cardiovascular morbidity and mortality occurring in these patients. Nasal continuous positive airway pressure (nCPAP) therapy remains the first line of treatment in confirmed cases of OSA. It appears to be beneficial in improving the cardiovascular and metabolic outcomes in such patients [8]. Many studies have shown a reduction in blood pressure with CPAP treatment [9] whereas there are conflicting results on the effect of CPAP on other components of metabolic syndrome like insulin resistance [10] and lipid profile [11]. Thus, the effect of CPAP on the components of metabolic syndrome in OSA still remains ambiguous. The presence of both OSA and metabolic syndrome in the same patient act synergistically, increasing their cardiovascular risk. Thus, identifying and treating such high risk population may prove to be highly beneficial. We conducted the present study to explore the effects of one night of CPAP therapy on the metabolic parameters in OSA patients with metabolic syndrome.

MATERIALS AND METHODS

The study was conducted in the Department of Physiology, in conjunction with Department of Respiratory Medicine, at Vallabhbhai Patel Chest Institute (VPCI), Delhi for a period of 15 months from January 2009-March 2010. We recruited 20 adult males and postmenopausal females (M=13, F=7) aged 50-60 years, attending the outpatient department of VPCI with symptoms suggestive of OSA. We included postmenopausal women as the incidence rates of OSA are similar in men and in women after menopause. This is due to the fact that after menopause women do not have the protective effect of oestrogen. Patients were interviewed about their sleep habits and symptoms, demographics and detailed clinical data was collected. All subjects completed the Epworth sleepiness scale (ESS) questionnaire. A score of greater than 10 on ESS was taken as evidence for excessive daytime sleepiness [12].

Metabolic syndrome was diagnosed according to the National Cholesterol Education Program (NCEP) guidelines [13]. Patients had metabolic syndrome if they had three or more of the following risk factors: abdominal obesity of 90 cm for men and 80 cm for women, as recommended by the World Health Organization guidelines for South Asians [14]. Triglycerides≥150 mg/dl, HDL cholesterol<40 mg/dL (male), < 50 mg/dL (female), blood pressure ≥ 130/85 mmHg (or treated for hypertension), and fasting glucose ≥ 110 mg/dl. All subjects were newly diagnosed cases of metabolic

syndrome, who were not under any treatment. Subjects with history of smoking, alcohol consumption, unstable angina, myocardial infarction, stroke, transient ischemic attacks, neuromuscular diseases, chronic respiratory diseases, acute or chronic infection, patients receiving lipid-lowering drugs, antioxidants, psychotrophic agents and patients already being treated for sleep apnea were excluded from the study even before recruitment.

The purpose of the study and the procedures involved were explained to the subjects and written consent was obtained from all of them. After getting the institutional ethical clearance, the study was conducted in accordance with the ethical guidelines for biomedical research on human subjects by Central Ethics Committee on Human Research (CECHR), Indian Council of Medical Research (ICMR)-2000 and those as contained in "Declaration of Helsinky".

PLAN OF STUDY

Patients with metabolic syndrome and symptoms suggestive of OSA based on sleep questionnaire and those who agreed for the study spent a total of 3 nights in the sleep lab. First night prior to sleep study for acclimatization to the new environment and baseline blood sampling and blood pressure measurement (7 am), following which the next night a split night sleep study was done(diagnostic + titration done on the same night). After confirmation of diagnosis and identification of CPAP pressure, the subjects were given CPAP therapy on the third night at prescribed pressure for 6-8 h. The next morning (7 am) blood pressure measurement and fasting venous blood sample was collected and sent for various biochemical investigations immediately.

POLYSOMNOGRAPHY

Polysomnography (PSG) was done (RemlogicTM version 1.1, Embla N7000, Medcare, Netherland) with a standard montage of electroencephalogram (EEG), electro-oculogram (EOG) and electromyogram (EMG) signals, pulse oximetry, respiratory impedance, nasal airflow measurements, thoracoabdominal movements, limb movements, body position and electrocardiogram (ECG). Sleep studies were analysed by a sleep technician using computer software. Apnoea was defined as a cessation of airflow for at least 10 sec accompanied by ≥4% desaturation in the following 30 sec. Hypopnoea was defined as 50% reduction in airflow accompanied by ≥4% desaturation and a reduction in chest wall movement. Apnoea-hypopnoea index (AHI) was calculated for each patient using the following formula [15], AHI= Number of apnoeas + Number of hypopnoeas /Total sleep time. Sleep efficiency was calculated as total sleep time/time in bed×100. Snoring period was detected when a minimum of three snores were present. Snoring periods were merged into one when the interval between them was less than 10 seconds. CPAP titration was done using a mask and apparatus (Respironics, PA). Optimal pressure was obtained when the patient slept in supine position with stable REM sleep, saturation maintained, snoring vanished, no heart rate variability and no arousals. Entire analysis was done according to the American Academy of Sleep Medicine (AASM) guidelines [16].

ANTHROPOMETRY

Height and weight were measured using standard methods [17], and the body mass index (BMI) was calculated using the following formula- weight in kg/ (height in m)^2. The circumference of the neck was measured at the cricothyroid membrane level. All the measurements were performed by the same observer.

COMPONENTS OF METABOLIC SYNDROME

Blood Pressure

Blood pressure was measured in accordance with the British hypertension society guidelines [18]. It was recorded as a mean of three readings taken at 2 min interval using a periodically calibrated mercury sphygmomanometer.

Lipid Profile

Lipid profile (serum total cholesterol, triglyceride and HDL cholesterol) was measured using standardized commercially available SIEMENS kit [19]. Serum LDL and VLDL were calculated from the estimated values of cholesterol, triglyceride and HDL, using Frieldwald's equation [20].

Insulin Resistance

Serum fasting glucose was measured by colorimetric method using glucose oxidase [21]. Quantitative measurement of fasting levels of serum insulin was done using commercially available insulin ELISA kits [22]. Insulin resistance was calculated via Homeostasis model assessment (HOMA) [23].

OXIDANT-ANTIOXIDANT STATUS ASSESSMENT

Lipid Peroxide Assay

The level of thiobarbituric acid reactive substances (p-TBARS) in serum is an indicator of lipid peroxidation and oxidative stress. This assay was carried out in serum by precipitation of lipid peroxides in phosphotungstic acid-sulfuric acid system, MDA levels were determined by reaction with thiobarbituric acid (TBA). The assay mixture contained 200µL of distilled water, 200µL of serum, 50µL of butylated hydroxyl toluene (BHT) (11mg/10ml ethanol) and 400µL of orthophosphoric acid (OPA) (1.115 OPA upto 50ml distilled water). To the assay mixture, 50µL of TBA (160mg/10ml of 0.1M NaOH) was added and incubated in boiling water bath for 45 minutes. The eppendorfs were ice cooled and colour was extracted with 1000µL of butanol. After centrifugation at 10000 rpm for 5 min, absorption of the supernatant was read at 535nm [24].

Serum thiol Assay

Thiols are extraordinarily efficient antioxidants protecting cells against consequences of damage induced by free radicals. Total serum thiol concentrations were measured using the method originally described by Ellman [25] and modified by Hu [26]. The reaction mixture contained 900ml 0.2M $NaHPO_4$ containing 2mM Na_2 EDTA, 100 µl serum, 20 ml 10mM DTNB in 0.2M $NaHPO_4$. Absorbance taken at 412 nm 37°C for 5 min and max absorbance was noted. Similarly absorbance of sample blank and reagent blank were measured. Absorbance of sample blank and reagent blank was subtracted from plasma absorbance values to obtain corrected values. The concentration of thiol was calculated using standard curve obtained using glutathione dissolved in phosphate buffer saline.

STATISTICAL ANALYSIS

The results are expressed as mean±SD (standard deviation). Comparison between the study parameters in the same patient before and after CPAP therapy was done using paired Students t-test with two-tail significance. The p-value less than 0.05 was considered to be significant.

RESULTS

The mean age, BMI, neck circumference, Epworth sleepiness score, apnea-hypopnea index, sleep efficiency, oxygen desaturation events and average snore episode duration are given in [Table/Fig-1]. From the above table we can note that all our subjects were obese and had severe sleep apnea with increased daytime sleepiness. [Table/Fig-2], demonstrates the comparison of components of metabolic syndrome like systolic and diastolic blood pressure, insulin resistance and lipid profile before and after CPAP treatment. There was a significant decrease in both systolic and diastolic blood pressure. However, there was no change in lipid parameters and the reduction seen in insulin resistance was not statistically significant after CPAP treatment. The oxidant-antioxidant status as evidenced

SUBJECTS (n=20)	Mean±SD
Age (yrs)	54.6±19.2
Sex	M=13, F=7
BMI(kg/m^2)	33.8±10.2
Neck circumference (cms)	39±4.5
Waist circumference (cms)	111.5±3.2
ESS	13±3.1
AHI (/hr)	45.6±36.2
Sleep efficiency (%)	90.4±6.3
Oxygen desaturation events (/hr)	44.6±36.2
Average snore episode duration(sec)	0.4±0.3

[Table/Fig-1]: Demographic and Polysomnoraphy parameters
BMI- Body mass index, ESS- Epworth Sleepiness Score, AHI- Apnea-hypopnea index

	Before CPAP	After CPAP
Systolic Blood Pressure (mmHg)	132.1±16.1	127.2±14.3*
Diastolic Blood Pressure(mmHg)	86.4±9.4	81.2±9.8*
Fasting blood glucose (mg/dl)	119.5±31.9	116.5±32.5
Fasting serum insulin (µU/mL)	27.5±6.25	26.6±6.5
Insulin resistance (HOMA-IR)	7.7±4.9	7.3±4.5
Lipid profile		
Triglycerides (mg/dl)	161.1±22.8	159.3±16.1
Total cholesterol (mg/dl)	327±25.9	336.3±36.2
HDL(mg/dl)	34.5±54.1	34.1±50.1
LDL(mg/dl)	111.1±33.9	113±41.1

[Table/Fig-2]: Comparison of components of metabolic syndrome before and after CPAP therapy, CPAP- Continuous Positive Airway Pressure. *p<0.01- significant

	Before CPAP	After CPAP
Serum Thiol (µmol/L)	204.2±65.7	254.9±72**
Lipid Peroxidation (µmol/L)	13.1±6.2	8.4±3.1*

[Table/Fig-3]: Comparison of Oxidant-Antioxidant status before and after CPAP therapy, CPAP- Continuous Positive Airway Pressure. *p<0.01, **p<0.001-significant

by serum thiol and lipid peroxidation is given in [Table/Fig-3]. There is a marked increase in the antioxidant status and significant decrease in pro-oxidant levels.

DISCUSSION

The key findings of the present study are that when patients of obstructive sleep apnea with metabolic syndrome are treated with CPAP therapy at prescribed pressures for duration of 6-8 h it produced significant improvements in blood pressure and oxidant-antioxidant status. Patients of OSA exhibit various cardiovascular abnormalities like atherosclerosis, systemic hypertension, ischemic heart disease and stroke [27]. Though the cause for such abnormalities in OSA is not clear, oxidative stress has been proposed to be one of the important factors in the pathogenesis of these metabolic abnormalities. The chronic nocturnal intermittent hypoxia occurring in OSA mimics ischemia- reperfusion injury that has been associated with increased production of vascular ROS which promotes oxidative stress [5]. We also found a significant reduction of lipid peroxidation after one night of CPAP treatment [Table/Fig-3]. Evaluation of antioxidant status by serum thiol concentration showed a significant increase in serum thiol levels after one night of CPAP treatment [Table/Fig-3]. This is in agreement with a study done by Alzoghaibi et al., [28] where one night of CPAP treatment in OSA hypertensives resulted in significant reduction in lipid peroxidation, however in their study they could not demonstrate an increase in antioxidant defense. To the best of our knowledge this is the first study showing an immediate increase in antioxidant defense after one night of CPAP therapy. This could be due to the fact that application of CPAP improves the oxygenation status throughout the night by reducing the apneic episodes thus diminishing the hypoxia/reoxygenation phenomenon and minimizing the oxidative stress. There by decreasing the consumption of antioxidant and increasing their concentration. Such a decrease in oxidative stress and increase in antioxidant levels with just one night of CPAP treatment shows the potential beneficial effect of CPAP in avoiding the various cardiovascular complications in OSA patients with metabolic syndrome.

Not only did CPAP improve the antioxidant status it also significantly decreased the systolic as well as diastolic blood pressure [Table/Fig-2]. Research has shown that hypertension is the factor most closely associated with the presence of metabolic syndrome in a patient with OSA [29]. The nocturnal apneic episodes produce surges in systolic and diastolic blood pressure that remain elevated even during daytime. The reason behind development of such a phenomenon is due to the increased sympathetic nerve activity and vascular endothelial dysfunction caused by oxidative stress and reduced nitric oxide (NO) production [30]. Probably CPAP therapy for one night decreased blood pressure by reducing the acute hemodynamic changes associated with reduced NO production. In addition to restoring the normal nocturnal “dipping” pattern CPAP treatment has also reduced daytime blood pressure in a few studies [9]. Since even small decrease in arterial pressure can contribute to reducing cardiovascular disease risk in such patients. CPAP treatment again proves to be very effective in OSA patients with metabolic abnormalities.

Insulin resistance is a precursor state of diabetes mellitus. Several studies have reported an association between OSA and insulin resistance [31]. There are conflicting results on effect of CPAP treatment on insulin resistance. West et al., [32] showed no change in insulin sensitivity in diabetic men with OSA after 3 months of CPAP treatment compared with sham CPAP. Similarly in a crossover study by Sharma et al., [33] in nondiabetic OSA men, it has been reported that there is no change in insulin resistance after 6 wk of CPAP treatment. Similar to the observation of West and Sharma in our study also we found that OSAS patients had insulin resistance. After one night of CPAP treatment there was no change in the insulin resistance.

Chronic intermittent hypoxia (CIH) that is characteristic of OSA induces hypercholesterolaemia by increasing lipoprotein secretion by up regulation of a key hepatic enzyme, stearoyl-coenzyme A desaturase-1(SCD-1) [34]. Metabolic and atherosclerotic changes have been well established in mice with CIH [35]. Still an association between OSA and lipid profile is unclear. Many studies support the notion that OSA is independently associated with lipid abnormalities, while others show that dyslipidaemia occurring in OSA is related to obesity and not directly to OSA [36]. In the present study we did not observe any change in lipid profile after one night of CPAP therapy which is similar to the findings of our previous study [6] where two nights of CPAP treatment did not show changes in lipid profile. One reason for no changes in lipid profile could be very short duration of time for which the subjects were treated. However, Drager et al., [37] could not demonstrate any change in lipid profile even after 4 months of treatment with CPAP. Whereas in a recent double-blind, placebo-controlled trial Sharma et al., [38] evidenced a significant improvement in the lipid profile after 3 months of treatment with CPAP in subjects of OSA with metabolic syndrome. Thus, the reason for such conflicting results observed by different examiners needs to be elucidated further.

LIMITATIONS

The changes in oxidant-antioxidant status and various components of metabolic syndrome were assessed after one night of CPAP therapy. Longer use of CPAP might have resulted in significant improvements in insulin resistance and lipid profile. Also the small sample size limit the conclusion of the study, hence larger randomized controlled trials are needed to extrapolate the results.

CONCLUSION

In summary, the present study supports the notion that the even one night of CPAP therapy significantly reduces the oxidative stress and improves metabolic parameters like blood pressure in patients of obstructive sleep apnea with metabolic syndrome.

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