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Original Research Article

Remodeling of Heart and Pulmonary Vasculature in Severe Obstructive Sleep Apnea Patients

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ABSTRACT

Background: Obstructive sleep apnea (OSA) is known to induce to cardio vascular remodeling. These change lead to the adverse consequences. This study was planned to compare the pulmonary artery pressure and morphological parameters of left sided chambers of the heart between subjects with severe and control group.
Methods: 30 consecutive subjects with severe OSA and 30 consecutive without OSA were recruited in this study. Informed consent was taken and they were screened for exclusion criteria. Their medical history and anthropometric parameters were recorded. They underwent whole night video-synchronized attended Polysomnography. Manual scoring was done according to AASM criteria. 2 D Echo following standard guidelines was done by a cardiologist, who was blind regarding the diagnosis. Statistical analysis was done using SPSS software (17.0).
Result: In this study, both the group were comparable with regards to age (52.2±10.1 years cases; 54.5±12.1 years control; t=-0.78; P=0.43). As expected, cases had a higher BMI (25.2+ 3.3 controls vs. 32 ± 4.1 cases; t=6.97; P<0.001) and larger neck circumferences (42 ± 3cm. in cases vs 35.9 ± 2.5 cm in controls; t=8.9; P<0.001). 40% cases and 7% controls had history of systemic hypertension (X2=9.31; P=0.002). 50% of OSA patients had mild to moderate tricuspid regurgitation while none among the controls. None of the subjects in either group ever had myocardial infarction). OSA subjects had higher systolic pulmonary artery pressure as compared to control (19.5 ± 7.8 in OSA vs 14.7 ± 3.5 mmHg in controls; t=3.03; P=0.004). Left atrial diameter was larger in OSA subjects (3.6+ 0.4 cms in OSA vs 3.1 ± 0.4 cm in controls; t=4.35; P<0.001), so was the left ventricular end systolic volume (53.1 ± 16.6 in OSA vs 36.9 ± 9.3 in control; t=4.65; P<0.001 left ventricular posterior wall was thicker in OSA subjects as compared to control (1.2 ± 0.13 cm vs 0.65 ± 0.2 cm in control; t =11.5; P<0.001). Among these variable, Left ventricular end systolic volume remained significantly higher even after controlling for body surface area.
Conclusion: Severe OSA lead to the remodeling of pulmonary vasculature and left sided chamber of the heart.

Key words: Obstructive sleep apnea (OSA), remodeling of pulmonary vasculature, Heart.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common sleep disorder sleep disorder of the middle aged obese population. [1] It has been suggested that obesity increase the amount of adipose tissue in parapharyngeal pads of fat and thus reduces the caliber of upper airway. [2] Thus, obesity leads to mechanical compromise. During sleep, the tone of pharyngeal muscles drops, tongue fall back

in oropharynx due to effect of gravity, the upper airway caliber gets compromised and obstructive sleep apnea develop in obese subjects with already compromised airway. [1] However, reduction of airway caliber goes beyond the mechanical effect of obesity. Obesity also reduces the activity of CRH neurons in hypothalamus, which in turn lead to compromise of ventilation and thus OSA, develop. [3]

Besides OSA, Obesity is also a known factor for the development of metabolic syndrome and cardio-vascular problems. [1] In such cases it is difficult to ascertain whether the cardio vascular problems are caused by obesity or OSA. Our present understanding suggests that OSA is associated with recurrent hypoxemia and consequent mechano-chemical changes that include but not limited to, increased intra-thoracic negative pressure, release of neuro-inflammatory marker, metabolic syndrome and changes in mechanics of cardio- respiratory apparatus. [4] On the contrary, Vgontzas et al [1] suggested that OSA, excessive daytime sleepiness, cytokine release and insulin resistance all can be manifestation of metabolic syndrome. Further, these factor act in synergistic manner to increase each other, which finally leads to the cardio-vascular illness. [1] However, this hypothesis still needs to be confirmed.

OSA is also associated with systemic hypertension and it has been found that a number of subjects with resistant hypertension have OSA. [4] Besides, causing hypertension through a variety of mechanisms that include atherosclerosis and persistent activation of sympathetic system, OSA is also associated with re-modeling of the cardiac chambers and pulmonary vasculature. [5-7] These changes induce a verity of the effect e.g., right ventricular dysfunction, pulmonary artery hypertension (PAH), increase of left atrial volume index (LAVI) and left ventricular diastolic dysfunction. [5-7] However, OSA is often missed by the physicians owing to lack of knowledge when they are working with these kinds of problems. [4]

Previous studies that had assessed the cardiovascular remodeling in OSA patients adopted a variety of approaches. There were inconsistencies with regards to the inclusion Criteria, number of subjects in each group, selection of control group and nonhomogeneous OSA subjects. [7,8] Hence, the outcome cannot be generalized across studies. The present study was planned to study the remodeling of pulmonary vasculature and left sided chambers of the heart on severe OSA patients. We compared the pulmonary artery pressure, left atrial end diastolic size index, left ventricular end systolic size index and post wall thickness of left ventricular between subjects with severe OSA and control group.

MATERIALS AND METHODS

This study was conducted in the sleep clinic of a teaching institute after obtaining permission from institutional ethics committee. All the subjects were explained regarding the rationale and objective of the study and informed consent was obtained.

All the subjects who attended sleep clinic between April 2012 to June 2013 were requested to participate in this study. They were screened for the presence of OSA with the help of a validated questionnaire -STOP Bang. [9] However, according to Indian studies we have taken BMI of 25 as a cut off. [10] They were divided into two groups-“high risk for OSA” and “low risk for OSA” based upon the score of screening questionnaire. A score of 3 was taken as the cut off. Subjects in the former group fell in the category of ‘cases’ while the subjects in the latter group were considered as ‘controls’.

However, subjects with any of the following condition were excluded from the study: those not willing to participate in the study; already using CPAP for any reason; children below 18 years; pregnant females; those with congestive heart failure; uncontrolled hypertension; uncontrolled

hypothyroidism; cardiac arrhythmias; those with cerebrovascular accidents; subjects abusing alcohol or opioid; subjects with chronic obstructive pulmonary disease or interstitial lung disease; with neuro degenerative disorder; those with conspicuous craniofacial deformity or naso-pharyngeal pathology (spur of nasal septum, intranasal polyp, enlarged tonsils etc.) and those with advanced age (>70 years). (Fig 1)

30 consecutive subjects with "low risk for OSA" constituted the control group. Owing to financial constraints, they did not undergo Polysomnography. Subjects with "high risk for OSA" were requested to undergo whole night attended video Polysomnography (Cadwell Inc., USA) to ascertain the diagnosis and severity of OSA. 30 subjects with severe OSA (AHI > 30) were included in this study as cases and rest excluded (Fig 1).

Demographic data and anthropometric measurement of all the subjects included in this study were recorded. Body surface area was calculated using Boyd's formula. [11] Their medical history was also recorded. Hypertension was defined as three recording above 140/90 mmHg taken at different times, or when the subject was already on anti-hypertensive medications. Diabetes was defined as fasting blood sugar higher than 120 mg%. Subjects who have been taking oral hypoglycemic agents or insulin at the time of presenting to us were also considered as having diabetes mellitus.

Polysomnography

Whole night attended video Polysomnography was done (Cadwell Inc, USA). Six channels of electro-encephalogram (frontal, central and occipital of both sides) with referenced to the opposite mastoid electrode (M1 and M2) were used to record electro-encephalogram. Two channels of electro-oculogram (PG1 and PG2) were record for tracing eye movements. Submentalis electromyogram was recorded. Lead I of electro-cardiogram was also recorded. Movements were judged by right and left anterior tibialis myograms. Nasal airflow was recorded using thermistors and pressure transducer. Chest and abdominal movements were recorded simultaneously. Continuous pulse oximetery was also recorded. AASM guidelines were followed for the placement of electrodes and scoring of data. [12] Scoring of the data was done manually by a certified sleep physician (RG) after dividing the data into 30 seconds epochs for sleep staging and 120 seconds epochs for assessment of apneas and hypopnea. Hypopnea was defined as 30% or more reduction in the pressure transducer airflow signals for continuous 10 second along with 4% oxygen desaturation or an arousal. Obstructive apnea was defined as cessation of airflow in nasal airflow channels (thermistors and pressure transducer) in the presence of thoracic and abdominal movements.

2D Echocardiography

Their echocardiography was done to assess the pulmonary arterial hypertension (PAH), left atrial (LA) size, left ventricular end systolic volume (LVESV), left ventricular end diastolic volume (LVEDV) and posterior wall thickness of left ventricle (PWT). All images were acquired using a commercially available ultrasound machine (Philips HD11XE) with a MHZphased array probe. According to American society of echocardiography guideline, a standard M-mode, 2-dimensional, Doppler echocardiographic study was performed. [14] Parameters were measured from >3 cardiac cycles. All studies were performed by one investigator who was blinded to whether or not subjects had OSA (AR).

The left atrium size was measured using M mode between the anterior and posterior wall of the left atrium (LA) at the end of systole.

Two - dimensional echocardiography has the capability of obtaining multiple slices through the left ventricle and Simpson's rule is a good method for measuring ventricular volume. This method was used to measure left ventricular end systolic volume (LVESV) and left ventricular end diastolic volume (LVEDV).

The left ventricular posterior wall thickness (PWT) was measured using M mode in the parasternal long axis view and LV ejection fraction was calculated by the modified biplane Simpson method.

Pulmonary artery systolic pressure was diagnosed using the Doppler echocardiography. A quantitative, although estimated, assessment of pulmonary artery pressure was done. Systolic pulmonary artery pressure (SPAP) was considered equal to the right ventricular systolic pressure in the absences of obstruction to right sided flow. An estimation of right ventricular systolic pressure was generated using Doppler echocardiography by calculating the right ventricular to right atrial pressure (RAP) gradient during systole using modified Bernoulli equation as $4v^2$, in which V is the velocity of the tricuspid jet in meters per second. Right ventricular systolic pressure (RVSP) was calculated by adding the estimation of right atrial pressure to the gradient ($RVSP=4V^2$ +RAP). The RAP used was either a standardized number for same centers or based on the echocardiography characteristic of the inferior vena cava. It must be noted that the definition of PAH is based on right heart cauterization data (mean PAP> 25 mmHg). The Doppler definition of PAH is based on tricuspid regurgitation jet is >2.8 ml second utilizing RAP estimation of 5 to 15 mmHg (most commonly used measurements depending on the characteristics of IVC); this equals SPAP of 36 mmHg to 46 mmHg.

Statistical analysis

Statistical analysis was done using SPSS v 17.0 (USA). Descriptive statistics was calculated. Chi-square test used to compare categorical variables. Independent sample t test was used to compare means between severe OSA and control groups.

RESULTS

In this study, both the group were comparable with regard to age (52.2 ± 10.1 years cases; 54.5 ± 12.1 years controls; t =-0.78; P=0.43). Preponderance of male was seen in OSA group (83% males in cases vs. 63% in controls; X2 = 3.06; P=0.08). Similarly, cases had a higher BMI (25.2 ± 3.3 controls vs. 32 ± 4.1 cases; t=6.97; P=<0.001) and larger neck circumference (42.2 ± 3 cm. in cases vs 35.9 ± 2.5 cm in controls; t=8.9; P=<0.001). Snoring was reported by all the cases and majority of the subjects (77%) in the control group also (X2 = 7.92; P=0.005). Daytime tiredness was reported by 93% cases and 20% of the controls (X2 = 32.8; P<0.001); observed pauses in breath were reported by 96% cases and 20% controls (X2 = 36.2; P<0.001); 40% cases and 7% controls had history of systemic hypertension (X2 = 9.31; P=0.002). 50% of OSA patients had mild to moderate tricuspid regurgitation while none among the controls.

Table 1: Comparison of size of the left sided chambers controlled for body surface area.

Group	Mean	Std. Deviation	't'	P
LA index				
case	1.92	0.22		
Control	1.93	0.29	-0.13	0.89
LVESVI				
Case	28.08	8.34		
Control	22.56	5.90	2.95	0.005
LVEDVI				
Case	36.71	18.65		
Control	36.63	8.33	0.02	0.98

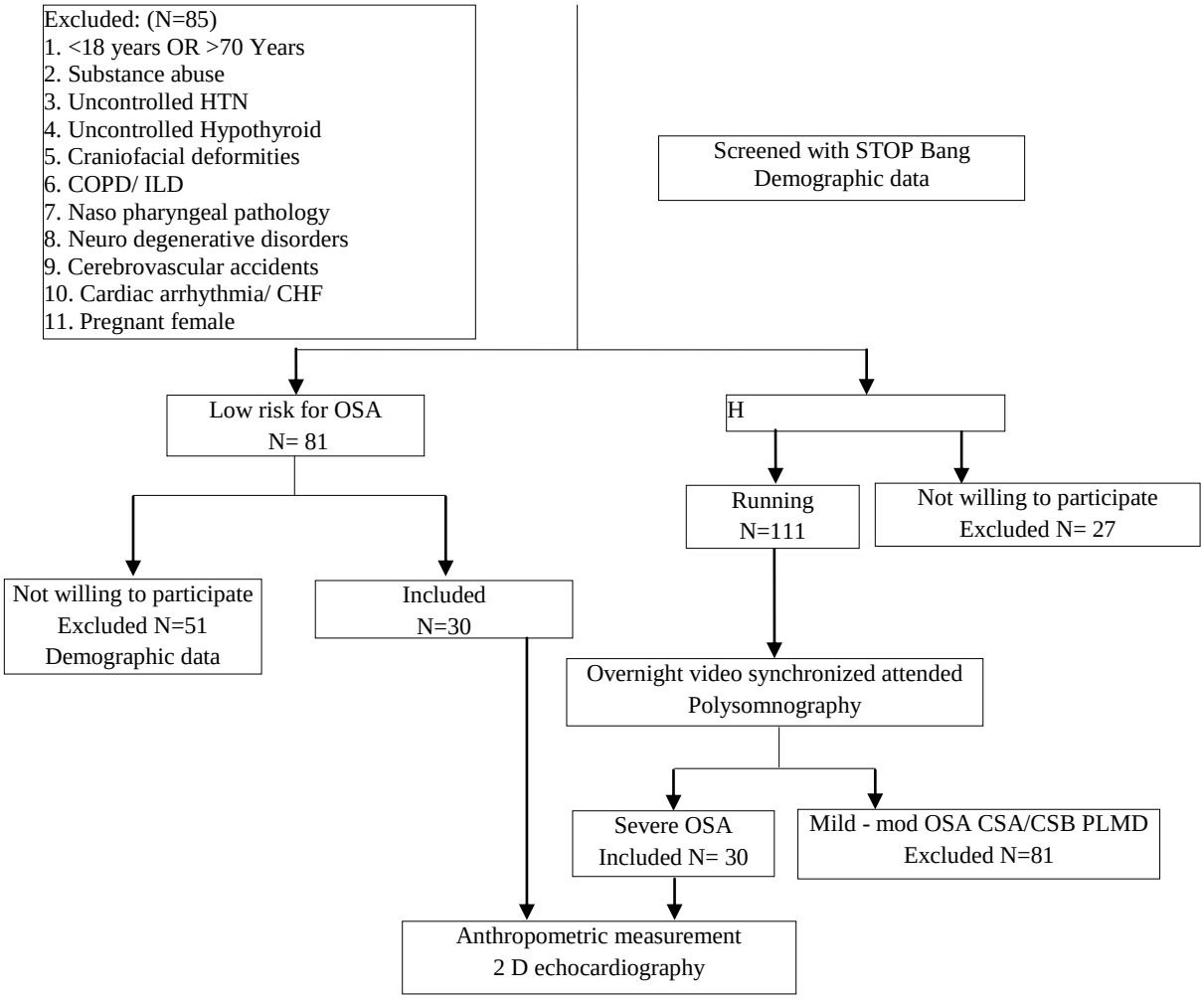
LVESVI: Left ventricular end systolic volume index; LVEDVI: Left ventricular end diastolic volume index.

None of the subjects in either group ever had myocardial infarction. Diabetes was reported by 3 subjects in control group and 2 subjects in OSA group. Two OSA patients were hypothyroid that was clinically and biochemically controlled.

OSA subjects had higher systolic pulmonary artery pressure as compared to control (19.5 ± 7.8 in OSA vs 14.7 ± 3.5 mmHg in controls; t = 3.03; P= 0.004). Left atrial diameter was larger in OSA vs 14.7 ± 3.5 mmHg in controls; t= 3.03; P=0.004). Left atrial diameter was larger in OSA subjects (3.6 ± 0.4 cms in OSA vs 3.1 ± 0.4 cm in controls; t=4.35; P<0.001)' so was the left ventricular end systolic volume (53.1 ± 16.6 in OSA vs 36.9 ± 9.3 in controls; t= 4.65; p<0.001). Left ventricular end diastolic volume was also higher in OSA patients, however it did not reach statistical

significance (68 ± 30.4 vs 59.7 ± 12.6; t= 1.37; P=0.17). Left ventricular posterior wall was thicker in OSA subjects as compared to control (1.2 ± 0.13 cm vs 0.65 ± 0.2 cm in controls; t= 11.5; P=<0.001). OSA subjects had higher ratio of left ventricular wall thickness to left ventricular end diastolic volume (0.02 ± 0.006 in cases vs 0.01 ± 0.006 in controls; t=5.94; P= <0.001). Ejection fraction was compared between both group (cases= 59.3 ± 1.7; controls = 59.6 ± 0.7, t= -0.94, P=0.3). Cardiac data after controlling for the body surface area is shown in Table 1.

Fig 1: Working with the subjects included in the study 284 subjects in sleep clinic



DISCUSSION

This study had shown that subjects with OSA had re-modeling of the left sided chamber of the heart, which was characterized by larger left atrium, larger size of left ventricle at the end of the systole and thickened posterior left ventricular wall. These subjects had higher systolic pulmonary artery pressure and higher ratio of posterior left ventricular wall to left ventricular end diastolic volume. These findings were seen even when all the subjects were free of pulmonary, valvular or systemic pathology and less than half of the cases were having systolic hypertension.

Higher pulmonary artery pressure was observed in the OSA patients. In this sample, nearly 34% subjects had mild PAH (>20 mmHg). PAH has been reported in earlier studies as well, though the proportion varied across studies and it ranged from 20% to 86%. [14-17] Among these studies, O'Hearn et al [15] had a sampling bias that resulted in an unusually high frequency (86%) of PAH. While measuring the PAH, they included only those subjects that had

pretibial edema, which has been reported as a reliable clinical indicator of PAH in OSA patients. [15] Thus we can say that PAH is seen in approximately 40% of the OSA patients. This must be remembered that PAH is common in OSA patients even in absence of pulmonary pathologies and previous studies have excluded subjects with significant pulmonary pathology. [14-16] In present study also, none of the subjects had pulmonary disorder, yet PAH was seen.

Though the OSA related hypoxia can induce pulmonary vaso-constriction and thus increase pulmonary artery pressure during apneic spells, it has been found insufficient to induce daytime PAH in one study. [7] Feng et al [18] reported that apnea hypopnea index was not associated with the PAH. However when we consider the subjects with congestive heart failure (CHF), both central and obstructive apnea have been found to have an association with PAH in a small sample of six patients. On the other hand, studies that have included subjects without CHF reported that daytime hypoxemia and hypercapnia must be present to develop PAH. [7,16,18] In present study, none of the subject in either group had daytime hypoxemia, hypercapnia or CHF yet PAH was present. This suggested that OSA itself can lead to pulmonary hypertension. Other factors that have been found to correlate with PAH are higher BMI and advancing age. [16,18] In the present study all the cases were obese and were middle aged. BMI is one of the factors that predispose a person to OSA. Thus, BMI could be associated with PAH through OSA. Further evidence also suggests that OSA could be directly linked to the PAH. In the past, PAH reversal has been shown by the CPAP THERAPY. [14,16] The CPAP has been found to improve PAH even in a case of very high pulmonary artery pressure (more than 70 mmHg). [19]

Clinically, pretibial edema is a useful sign of the PAH and OSA. O'Hearn et al [15] included the subjects with OSA and found that pretibial edema was a good marker of PAH. On the contrary, other study that inducted subjects with pretibial edema and normal echocardiogram showed that a number of subjects had OSA. [20] Thus, all the OSA subjects must be looked for pretibial edema since it Depicts presence of PAH and the need for quick intervention. At the same time, subjects with pretibial edema must also be screened for OSA. In present study, we found that atrial diameter was higher among the OSA patients as compared to control group. Similar finding has been reported earlier. [8,21,22] However, none of these studies have controlled the left atrial diameter for body surface area. Left atrial diameter is related to the body surface area, and if it is not controlled for it, it can provide misleading information. [23] When we indexed the left atrial diameter for the body surface area, the left atrium diameter index was comparable across groups. This shows that OSA was not related to the increased diameter of left atrium in this group. A number of factors affect the remodeling of the left atrium. These include left ventricular diastolic dysfunction (LVDD). [6,24] arterial stiffness, [22] apnea hypopnea index, [6] severity of OSA, [8] diastolic blood pressure and use of CPAP. [25] In OSA patients, LA enlargement was related mainly to the diastolic dysfunction even when the hypertension, BMI, gender and diabetes were controlled. [26] Theoretically, enlargement of LA also depends upon the length of time, that the LA is exposed to LVDD. LA size has been reported to correlate well with the LVDD and left ventricular posterior wall thickness. [27] Though, we did not assess the LVDD and this was a cross sectional study, yet indirect evidences cannot rule out the presence of LVDD in the cases of our study.

In the present study, OSA subjects had higher left ventricular end systolic volume (LVSEV). It remained significant even after controlling for the body surface area. Increment in LVESVI has been found to be associated with an increase in the proportion of male subjects and in those with history of myocardial infarction even in non obese subjects. [27] In present study,

none of the subjects ever had myocardial infarction. Thus higher LVSEV could be related to mechanical effect of the OSA that lead to dilatation of hearts. [28]

In this study, we found that left ventricular posterior wall thickness was higher in the OSA group as compared to control group. This has been reported earlier also. [29,30] Left ventricular hypertrophy, which is not uncommon in patients with systemic hypertension, was seen in absence of systemic hypertension in OSA patients (Drager et al, 2007). [31] However, when both of them co-exit is additive (Drager et al, 2007). [31]

Thus, this study showed significant remodeling of cardio-pulmonary vascular and chambers in adult subjects with OSA, these effects are not limited to the adult, but they are also seen among children with OSA (Amin et al, 2002). [32] On the other hand, treatment of OSA is able to reverse these abnormalities (Shivalkar et al, 2006). [33] Hence, all obese subjects, people with metabolic syndrome and cardio-vascular problems must be screened for OSA.

This study had some methodological limitation First, the sample size was small. Second, Polysomnography data was not recorded from the control group. This was not possible due to financial constrains. Moreover, the STOP-Bang questionnaire is a reliable instrument. [34] A cut off score of 3 that we have used in this study, has the sensitivity of 90% and positive predictive value of 85%.34 Thirdly, duration of OSA was not determined, which could have an effect on all cardio vascular remodeling. This was not possible due to cross sectional design of the study. In future, we propose that longitudinal prospective studies should be conducted with methodological improvement so that further information regarding the mechanism and incidence of cardio vascular effect of OSA can be gathered. Fourth, a number of exclusion criteria, while on one hand improve the methodological power of this study; on the other hand, they interfere with the generalization of results of this study.

CONCLUSION

Remodeling of cardio- pulmonary vasculature and left sided chambers of heart is not uncommon in OSA patients. Hence, all the obese subjects and subjects with cardio-vascular morbidities must be screened for OSA and vice versa. If OSA is found on the attended Polysomnography, they should be offered management for the same.

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