

Cardiovascular morbidity in subjects with Obstructive sleep apnea and Its correlation with the severity of disease

Sudip S Sachdev, J C Suri, A K Jain, Anita Khalid, H S Isser, M K Mittal

Departments of Internal Medicine, Pulmonary Medicine, Cardiology and Radiology, Safdarjung Hospital and Associated Vardhman Mahavir Medical College, New Delhi

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Abstract

There is paucity of Indian data evaluating the relationship of hypertension, ventricular dysfunction and carotid artery intima media thickness with Obstructive sleep apnea hypopnea syndrome (OSAHS) and its severity. This observational study compared these outcomes amongst subjects with and without OSAHS. Subjects categorized as 'High Risk' on Berlin's questionnaire underwent polysomnography. The outcomes were evaluated by history, examination, electrocardiography, echocardiography and carotid artery ultrasonography. There were 48 cases (polysomnography confirmed OSAHS) and 44 controls (without OSAHS). Of the 48 cases, 28 (58%) were classified as severe and 20 (42%) non-severe (mild and moderate). A significant association independent of confounders was documented between OSAHS and: (i) blood pressure and hypertension; (ii) previous myocardial infarction, diastolic dysfunction, left ventricular hypertrophy, pulmonary hypertension and arrhythmias; and (iii) carotid artery plaques and intima-media thickness. However, there was no significant impairment of ejection fraction or systolic dysfunction. No statistically significant "dose response" relationship was evident on comparing subjects with severe and non-severe OSAHS.

Keywords: Carotid intimal media thickness, Hypertension, Obstructive Sleep Apnea Hypopnea Syndrome, Ventricular dysfunction.

Introduction

In western populations, Obstructive sleep apnea hypopnea syndrome (OSAHS) is frequently associated with increased cardiovascular morbidity and mortality from both ischemic heart disease (interquartile risk ratio of 1.3) and stroke (1.2). OSAHS is also commonly associated with systemic hypertension independent of age, obesity or

Address for correspondence

Dr J C Suri

Senior Chest Physician & Head-Department of Pulmonary, Critical Care & Sleep Medicine, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi. E-mail: jcsuri@rediffmail.com

other confounding factors (3-5). Nocturnal disturbances of cardiac rhythm have also been reported (2). Epidemiological data also suggest an association with congestive cardiac failure (CCF) (2). About half of a small sample of patients with diastolic dysfunction had an apnea hypopnea index >10 (6). Mild daytime pulmonary hypertension is a common complication in patients with OSAHS with a prevalence of approximately 20% (7). Stroke has been linked to OSAHS in both cross sectional and case control studies and sleep apnea is highly prevalent in patients with stroke (2,8,9).

It is primarily over the past two to three decades that implications of OSAHS on cardiovascular diseases have been recognized from data in developed countries. Despite this, even in the west the general cardiovascular community has

been slow in assimilating OSAHS into the cardiovascular diagnostic and therapeutic paradigms (2). South Asian countries are currently witnessing a rapid escalation of cardiovascular morbidity including ischemic heart disease and hypertension (10). The role of traditional risk factors in cardiovascular morbidity have been extensively evaluated in our setting including obesity, diet, physical inactivity, smoking, alcohol intake, diabetes, and metabolic syndrome. However, there is a paucity of information regarding the relationship of OSAHS with cardiovascular morbidity in Indian adults. In view of the rapid escalation of cardiovascular morbidity in India, it would be important to evaluate its association with OSAHS. The present study was therefore designed to evaluate cardiovascular morbidity in subjects with OSAHS and to correlate the severity of cardiovascular morbidity with the severity of OSAHS.

Subjects and Methods

The subjects were screened and recruited from the Medicine Outpatient Department, Respiratory Clinic and Internal Medicine wards of Safdarjung Hospital and associated Vardhman Mahavir Medical College, New Delhi. The Postgraduate thesis committee of the institution had approved the study and an informed written consent was taken from the participants.

The pre-specified inclusion criteria for eligibility for the study were: (i) either gender; (ii) age between 30 to 69 years; and (iii) treatment naïve for OSAHS. Subjects with the following conditions were excluded: (i) life threatening illnesses; (ii) pregnancy; (iii) psychosis; (iv) malignancy; (v) end stage renal disease; and (vi) cirrhosis and fulminant hepatic failure. Screening for obstructive sleep apnea hypopnea syndrome was done with the Berlin's questionnaire (11). Subjects categorized as 'High Risk' on the Berlin's questionnaire were requested to undergo sleep studies by polysomnography. There were 48 cases in which OSAHS was diagnosed by polysomnography and 44 controls that were not diagnosed to have OSAHS by Berlin's questionnaire and/or polysomnography.

A detailed history, especially of snoring, excessive daytime somnolence, nocturia, witnessed apneas, choking, waking up unrefreshed in the morning and personality changes were recorded. A thorough general physical and systemic examination was performed. Anthropometry recordings included: (i) weight in kg on a spring balance calibrated daily; (ii) height in cm on a stadiometer; (iii) body mass index calculated as weight in kg divided by height in meters square;

(iv) waist and hip circumferences in cm by fiberglass tape using standard techniques. Mean of three readings of blood pressure were recorded by a calibrated mercury sphygmomanometer in consonance with recommendations (12). Laboratory investigations performed included hemogram, plasma glucose, serum sodium and potassium, lipid profile and arterial blood gas analysis, if required (Eishweiler System).

Sleep studies were performed on Alice 5 Healthdyne Polysomnography System (Respironics, USA). A whole night fully supervised, manually validated, level 1 complete polysomnography was conducted. Sleep staging was performed using the criteria of Rechtschaffen and Kales (13). Apnea was defined as the cessation of airflow for 10 seconds or longer. Hypopnea was defined as a recognizable transient reduction (but not complete cessation) of breathing for 10 seconds or longer, a decrease of greater than 50% in the amplitude of validated measures of breath reduction or decrease of <50% associated with oxygen desaturation of 3% or more (14). Flow limitation was defined as any series of 2 or more breaths, lasting greater than 10 seconds that have flattened or non-sinusoidal appearance on the inspiratory nasal cannula flow signal and end abruptly with a return to breaths with sinusoidal shape. Desaturation was defined as fall of >3% in saturation from the baseline following an obstructive event. The number of such episodes per hour was taken as desaturation index (DI). Respiratory distress index (RDI) was calculated as a sum of apnea, hypopnea and flow limitation. Arousal was defined as EEG alpha bursts exceeding 3 seconds during non rapid eye movement (NREM) sleep and bursts with increased chin muscle tone during rapid eye movement (REM) sleep. All non-respiratory arousals were eliminated. The number of arousals per hour was taken as the arousal index (AI). The minimum arterial blood oxygen saturation attained during sleep was also recorded. Categorization of severity of OSAHS was done according to RDI value into three groups: mild (RDI = 5-19), moderate (RDI = 20-39), and severe (RDI ≥ 40).

Either overnight (cases) or daytime (controls) electrocardiographic recording was done to document arrhythmias. Nighttime recording was done via polysomnographic machine and the daytime recording of ECG with long Lead II.

High resolution ultrasonography by Philips HDI 4000 machine was performed to determine the presence of carotid artery plaques and intima-media thickness, which is considered to be an early marker of progression of

atherosclerosis. The intima-media thickness (IMT) and lumen diameter measurements were performed 1 to 2 cm proximal to the carotid bifurcation. The sound beam was adjusted perpendicular to the far wall of the vessel, thereby obtaining two parallel echogenic lines corresponding to lumen intima-media and media-adventitia interfaces. These two parallel line echoes were separated by a small echo free space. The intima-media thickness (IMT) was measured between these two leading edges corresponding to the far wall of the common carotid artery (CCA). At each longitudinal projection, the IMT was measured in three segments of the common carotid artery on each side at the point of greatest thickness and at two points 1.0 cm upstream and 1.0 cm downstream from the point of greatest thickness (depending on individual variation in vessel wall, tortuosity and habitus). The mean of 6 IMT measurements (3 from left and 3 from right common carotid artery) was used as representative value for each subject (15,16). An artery was classified as being affected by a plaque if there was a localized thickening of >1.5 mm that did not uniformly involve the whole left or right carotid artery with or without flow disturbance (17). Echocardiography was performed on (Philips Sonos 5500 USA) machine. Special efforts were made to document the following parameters: ejection fraction, diastolic dysfunction, systolic dysfunction, hypertrophy of ventricles and pulmonary artery pressure.

Data was entered and analyzed in EPI-INFO and SPSS (Version 13) statistical softwares. The primary outcomes of interest in relation to cardiovascular morbidities were hypertension, ventricular dysfunction and carotid artery intima-media thickness. These and other outcome variables were compared amongst subjects with OSAHS and controls and amongst severe and non-severe categories of OSAHS. The relationship of various outcome variables with group (case or control) and severity of OSAHS was analyzed with and without adjustment for confounding factors (age, gender and body mass index). The statistical tests employed included Chi-square test, Fischer exact test, Student 't' test, Pearson's correlation coefficient, univariate and multiple regression analysis and univariate and multiple logistic regression analysis. A two-tailed P value below 0.05 was considered to denote statistical significance.

Results

Of the 48 cases, 10 (21%) were classified as mild, 10 (21%) as moderate and 28 (58%) as severe OSAHS. The disease

duration was 1-3 years in 20 (42%), 4-6 years in 20 (42%) and above 6 years in 8 (16%) cases.

Comparison of Cases and Controls

Amongst the compared characteristics (Table 1), the cases were older (7 years; $P < 0.001$), smoked more often and had less positive family history of hypertension, coronary artery disease and diabetes. Subjects with OSAHS were significantly heavier with a greater body mass index, waist to hip circumference and neck circumference. Cases had significantly lower total serum cholesterol, high-density lipoprotein, and low-density lipoprotein. OSAHS was associated with significantly greater C-Reactive Protein levels and non-outcome morbidities including overweight or obesity, diabetes, dyslipidemia and metabolic syndrome.

In view of significant differences between cases and controls for age and body mass index, further comparative analysis for outcome measures of interest also used adjustment for these variables. Three analytic strategies were utilized for comparisons (Table 2): (i) unadjusted, (ii) adjusted for age and gender, and (iii) additional adjustment for body mass index, a close correlate of OSAHS.

Unadjusted and adjusted (age and sex) systolic and diastolic blood pressures were significantly higher amongst subjects with OSAHS (Table 2). However, on additional adjustment for BMI, the differences were not statistically significant. The risk of being hypertensive was significantly higher in cases (Odds Ratio 6.42; 95% Confidence Interval 2.59 to 15.92; $P < 0.001$) even after adjustment for age and gender (OR 6.22; 95% CI 2.24 to 17.28; $P < 0.001$). However, on additional adjustment for BMI, the risk of being hypertensive was not statistically significant ($P = 0.15$). The blood pressure readings had been taken while the subjects were consuming prescribed anti-hypertensive drugs. An additional comparison was therefore done for current hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) despite being on anti-hypertensive medication. None of the controls receiving anti-hypertensive drugs had current hypertension. Thus the odds ratio for hypertension despite medication was not measurable. However, on evaluating the Omnibus tests of model coefficients by introducing adjustment variables in a graded manner (analogous to Fischer exact test), there was a significantly higher risk of being currently hypertensive despite being on anti-hypertensive drugs (≥ 1 or ≥ 2). These differences remained highly significant despite adjustment for age and gender, and also additionally for BMI. Only

Table 1: Comparison of characteristics amongst cases & controls

Characteristic	Cases	Controls	P value
Number	48	44	NA
Gender: [No. (%)]			
Male	39 (81)	29 (66)	
Female	9 (19)	15 (34)	0.09
Age (yrs) [Mean \pm SD]	50.3 \pm 7.4	43.5 \pm 8.0	<0.001
Lifestyle: [No. (%)]			
Sedentary	30 (63)	28 (64)	
Non-sedentary	18 (37)	16 (36)	0.91
Alcohol intake: [No. (%)]	19 (40)	15 (34)	0.59
Alcohol consumers: [Mean \pm SD]			
Duration (yrs)	16.6 \pm 7.4	13.8 \pm 2.0	0.16
Volume (ml/day)	39.9 \pm 48.7	47.3 \pm 71.4	0.72
Drug addiction: [No. (%)]	1 (2.1)	2 (4.5)	0.61*
Smoking: [No. (%)]	19 (40)	6 (14)	0.005
Smokers: [Mean \pm SD]			
Duration (yrs)	22.6 \pm 10.3	13.0 \pm 2.3	0.030
Number per day	13.2 \pm 12.4	33.2 \pm 33.9	0.037
Dietary habits: [No. (%)]			
Vegetarian	17 (36)	17 (39)	
Eggetarian	5 (10)	2 (4)	
Non-vegetarian	26 (54)	25 (57)	0.57
Family history: [No. (%)]			
Hypertension	12 (25)	28 (64)	<0.001
CAD or MI	2 (4)	18 (41)	<0.001*
Stroke	0 (0)	1 (2)	0.48*
Diabetes	3 (6)	22 (50)	<0.001*
Anthropometry: [Mean \pm SD]			
Weight (kg)	83.5 \pm 12.6	60.8 \pm 9.9	<0.001
Height (cm)	165.8 \pm 8.4	164.7 \pm 9.4	0.56
Body mass index (kg/m ²)#	30.1 \pm 1.2	22.2 \pm 1.1	<0.001
Waist to hip circumference	0.99 \pm 0.1	0.90 \pm 0.1	<0.001
Neck circumference (cm)	41.1 \pm 2.8	35.5 \pm 2.4	<0.001
Investigations: [Mean \pm SD]			
Hemoglobin (gram/dl)	13.4 \pm 1.5	13.9 \pm 2.1	0.15
Serum CRP (mg/ dl)	4.0 \pm 5.4	2.1 \pm 2.6	0.037
Blood sugar fasting (mg/dl)	110.8 \pm 29.5	107.1 \pm 42.3	0.63
Blood sugar post prandial (mg/dl)	149.9 \pm 56.5	130.2 \pm 80.2	0.17
Serum lipid profile: [Mean \pm SD]			
Total cholesterol (mg/dl)#	177.6 \pm 1.2	202.2 \pm 1.2	0.001
High density lipoprotein (mg/dl)#	42.9 \pm 1.2	48.1 \pm 1.3	0.012
Low density lipoprotein (mg/dl)#	100.5 \pm 1.4	121.4 \pm 1.3	0.002
Very low density lipoprotein (mg/dl)#	29.5 \pm 1.4	27.3 \pm 1.6	0.38
Triglycerides (mg/dl)#	147.6 \pm 1.4	136.4 \pm 1.6	0.38
HDL: LDL ratio	0.51 \pm 0.34	0.43 \pm 0.18	0.17
Co-morbidities (non-outcome) [No. (%)]			
Past stroke	2 (4)	0 (0)	0.27*
Past diabetes	18 (38)	1 (2)	<0.001*
Current diabetes	21 (44)	6 (14)	0.002
Current dyslipidemia	39 (81)	23 (52)	0.003
Overweight or obese (BMI \geq 25)	40 (83)	0 (0)	<0.001*
Overweight or obese (Asian; BMI \geq 23)	45 (94)	22 (50)	<0.001
Metabolic syndrome (IDF Asian defin)	37 (77)	10 (23)	<0.001

CAD – Coronary artery disease;

MI – Myocardial infarction;

NA – Not applicable;

RDI – Respiratory distress index

Values depict either mean \pm SD (standard deviation), # geometric mean \pm SD or number (percentage). P value refers to two tailed comparison between the cases and controls with Student 't' test for means and chi-square or Fischer exact test* for numbers.

Current diabetes defined as person with known diabetes or fasting blood sugar \geq 126 mg/dl or post prandial blood sugar \geq 200 mg/dl. Current dyslipidemia defined as a person on treatment for dyslipidemia or serum cholesterol \geq 240 mg/dl or serum LDL \geq 160 mg/dl or serum HDL <40 mg/dl for men and < 50 mg/dl for women or serum triglyceride \geq 150 mg/dl.

Metabolic syndrome was defined as per the International Diabetes Federation definition for South Asians: waist circumference \geq 90 cm (men) or \geq 80 cm (women) plus two or more of the following: a) fasting serum triglyceride > 150 mg/dl; b) HDL-cholesterol < 40 mg/dl (men) or < 50 mg/dl (women); c) hypertension defined as on treatment for hypertension or systolic blood pressure \geq 130 mmHg or diastolic pressure \geq 85 mmHg and d) known diabetes or fasting plasma glucose \geq 100 mg/dl (18).

Table 2: Comparison of outcome measures amongst cases and controls

Characteristic	Controls	Cases	Mean difference or OR (95% CI)	P value
Number	44	48	NA	NA
Blood pressure				
Systolic blood pressure (mm Hg) [Mean \pm SD]	124.6 \pm 14.7	134.0 \pm 15.5		0.004
Unadjusted			9.3 (3.1, 15.5)	0.004
Adjusted (age, sex)			9.8 (3.0, 16.5)	0.006
Adjusted (age, sex, BMI)			2.2 (-7.0, 11.3)	0.64
Diastolic blood pressure (mm Hg) [Mean \pm SD]	78.8 \pm 11.9	84.7 \pm 11.6		0.017
Unadjusted			5.9 (1.1, 10.7)	0.017
Adjusted (age, sex)			8.0 (2.9, 13.1)	0.003
Adjusted (age, sex, BMI)			5.1 (-1.9, 12.1)	0.16
Hypertensive* [No. (%)]	13 (30)	35 (73)		<0.001
Unadjusted			6.42 (2.59, 15.92)	<0.001
Adjusted (age, sex)			6.22 (2.24, 17.28)	<0.001
Adjusted (age, sex, BMI)			2.76 (0.69, 11.02)	0.150
Current hypertension on ≥ 1 antihypertensive drugs # [No. (%)]	0 (0)	19 (40)		<0.001**
Unadjusted			NE	<0.001**
Adjusted (age, sex)			NE	<0.001**
Adjusted (age, sex, BMI)			NE	<0.001**
Current hypertension on ≥ 2 antihypertensive drugs ## [No. (%)]	0 (0)	12 (25)		<0.001**
Unadjusted			NE	<0.001**
Adjusted (age, sex)			NE	<0.001**
Adjusted (age, sex, BMI)			NE	<0.009**
Current hypertension on 3 antihypertensive drugs ### [No. (%)]	0 (0)	2 (4)		0.27**
Echocardiography and Electrocardiography				
Previous myocardial infarction [No. (%)]	0 (0)	8 (17)		0.006 **
Unadjusted			NE	0.001**
Adjusted (age, sex)			NE	0.002**
Adjusted (age, sex, BMI)			NE	0.006**
Ejection fraction (%) [Mean \pm SD]	71.9 \pm 5.1	67.4 \pm 11.1		0.017
Unadjusted			-4.5 (-7.2, -0.9)	0.017
Adjusted (age, sex)			-3.7 (-7.7, 0.3)	0.072
Adjusted (age, sex, BMI)			0.2 (-5.3, 5.6)	0.951
Systolic dysfunction [No. (%)]	0 (0)	3 (6)		0.24**
Unadjusted			NE	0.046**
Adjusted (age, sex)			NE	0.079**
Adjusted (age, sex, BMI)			NE	0.59**
Diastolic dysfunction [No. (%)]	9 (21)	33 (69)		<0.001
Unadjusted			8.56 (3.30, 22.20)	<0.001
Adjusted (age, sex)			6.82 (2.43, 19.12)	<0.001
Adjusted (age, sex, BMI)			3.0 (0.73, 12.28)	0.13
Pulmonary artery hypertension [No. (%)]	0 (0)	10 (21)		0.001**
Unadjusted			NE	<0.001**
Adjusted (age, sex)			NE	0.003
Adjusted (age, sex, BMI)			NE	0.019
Left ventricular hypertrophy [No. (%)]	5 (11)	27 (56)		<0.001
Unadjusted			10.03 (3.34, 29.88)	<0.001
Adjusted (age, sex)			8.48 (2.61, 27.63)	<0.001
Adjusted (age, sex, BMI)			7.49 (1.65, 33.92)	0.009
Arrhythmias [No. (%)]	0 (0)	8 (17)		0.006**
Unadjusted			NE	0.001**
Adjusted (age, sex)			NE	0.002**
Adjusted (age, sex, BMI)			NE	0.006**
Carotid artery ultrasound				
Previous stroke [No. (%)]	0 (0)	2 (4)		0.50**
Plaque [No. (%)]	3 (7)	13 (27)		0.013**
Unadjusted			5.08 (1.33, 19.27)	0.017
Adjusted (age, sex)			4.40 (0.99, 19.52)	0.051
Adjusted (age, sex, BMI)			11.42 (1.41, 92.87)	0.023
Intima media thickness (mm) [Mean \pm SD]	0.85 \pm 0.12	1.09 \pm 0.18		<0.001
Unadjusted			0.25 (0.18, 0.31)	<0.001
Adjusted (age, sex)			0.22 (0.15, 0.29)	<0.001
Adjusted (age, sex, BMI)			0.21 (0.11, 0.31)	<0.001

NA – not applicable; NE – Not estimable

* Defined as physician diagnosed hypertension or on any anti-hypertensive drug medication or systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg.

Defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg despite ≥ 1 anti-hypertensive drugs. ## Defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg despite ≥ 2 anti-hypertensive drugs. ### Defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg despite 3 anti-hypertensive drugs.

** Fischer exact test or Omnibus tests of model coefficients.

None of the case or control subjects had right ventricular hypertrophy.

Amongst arrhythmias 4 subjects had ventricular ectopics, 3 had sinus tachycardia and 1 had sinus bradycardia.

two cases with OSAHS had current hypertension despite being on three anti-hypertensive drugs. Thus, subjects with OSAHS had significantly greater severity of hypertension even after adjustment for age, gender and BMI.

Eight cases had a history of previous myocardial infarction in comparison to none, among controls ($P=0.001$; age and gender adjusted $P=0.002$; age, gender and BMI adjusted $P=0.006$). The unadjusted ejection fraction was significantly ($P=0.017$) lower in subjects with OSAHS (67.4% vs 71.9%) (Table 2). However these differences did not retain significance on adjustment for age and gender, and additionally for BMI. There were no significant differences between cases and controls for systolic dysfunction for the unadjusted and adjusted estimates. The risk of diastolic dysfunction was significantly ($P<0.001$) greater in subjects with OSAHS (OR 8.56; 95% CI 3.3 to 22.2) even after adjustment for age and gender (OR 6.82; 95% CI 2.43 to 19.12; $P<0.001$). On additional adjustment for BMI the difference was not statistically significant ($P=0.13$). Ten cases had pulmonary artery hypertension in comparison to none, among controls ($P<0.001$); the statistical significance persisted after adjustment for age and gender ($P=0.003$) and additionally for BMI ($P=0.019$). The unadjusted risk for left ventricular hypertrophy was significantly ($P<0.001$) greater in subjects with OSAHS (OR 10.03; 95% CI 3.34 to 29.88). This significant risk persisted even after adjustment for age and gender (OR 8.48; 95% CI 2.61 to 27.63; $P<0.001$), and additionally for BMI (OR 7.49; 95% CI 1.65 to 33.92; $P=0.009$). In comparison to none, among controls eight cases had documented arrhythmias (four had ventricular ectopics, three had sinus tachycardia and 1 had sinus bradycardia) ($P=0.001$). This statistical significance persisted after adjustment for age and gender ($P=0.002$), and additionally for BMI ($P=0.006$).

There were no significant differences between the two groups for a previous episode of stroke but only two subjects reported this history (Table 2). Subjects with OSAHS had significantly greater carotid artery plaques (OR 5.08; 95% CI 1.33 to 19.27; $P=0.017$). The greater risk for plaques was evident even after adjustment for age and gender (OR 4.40; $P=0.051$) and additionally for BMI (OR 11.42; $P=0.023$). The unadjusted carotid intima media thickness was significantly greater (0.25 mm, $P<0.001$) in cases. These significant differences persisted even after adjustment for age and gender (0.22 mm; $P<0.001$), and additionally for BMI (0.21 mm; $P<0.001$ mm).

Comparison of severe and non-severe cases

The 28 severe cases were compared with the 20 non-severe (mild and moderate) cases. The two groups (non-severe and severe cases) were largely comparable with respect to the various historical, examination and investigative features, and non-outcome co-morbidities (Table 3). The duration of OSAHS was also comparable in the two groups. However, in severe cases neck circumference was significantly ($P=0.003$) greater and metabolic syndrome documented more frequently ($P=0.034$).

The unadjusted and adjusted estimates of blood pressure, hypertension and current hypertension on anti-hypertensive drugs were statistically comparable in the two groups, namely, non-severe OSAHS and severe OSAHS (Table 4).

Both groups were comparable with regards to previous history of myocardial infarction (Table 4). The unadjusted and adjusted estimates of various echocardiographic parameters were also statistically comparable between the non-severe and severe cases of OSAHS. These parameters included ejection fraction, systolic and diastolic dysfunction, pulmonary artery hypertension, and left ventricular hypertrophy. Arrhythmias were documented more frequently (21% vs 10%) in severe cases but the differences were not statistically significant.

Previous stroke and plaques were documented in a comparable proportion of subjects in the two groups (Table 4). The carotid intima media thickness was also statistically comparable amongst subjects with non-severe and severe OSAHS.

Discussion

The findings from the current study in Indian adults suggest a significant association independent of confounders between obstructive sleep apnea hypopnea syndrome (OSAHS) and the following evaluated cardiovascular morbidities: (i) blood pressure and hypertension; (ii) previous myocardial infarction, diastolic dysfunction, left ventricular hypertrophy, pulmonary hypertension and arrhythmias; and (iii) carotid artery plaques and intima-media thickness. These data are in conformity with the earlier epidemiologic evidence and suggest that OSAHS is a significant risk factor for cardiovascular morbidity. However, unlike some earlier studies no significant impairment of ejection fraction or systolic dysfunction could

Table 3 : Comparison of characteristics amongst non-severe and severe OSAHS

Characteristic	Non-severe	Severe	P value
Number	20	28	NA
Duration of OSAHS (yrs): [No. (%)]			
1 - 3	8 (40)	12 (43)	
4 - 6	9 (45)	11 (39)	
≥ 7	3 (15)	5 (18)	0.92
Men: [No. (%)]	17 (85)	22 (79)	0.43
Age (yrs) [Mean ± SD]	49.3 ± 7.2	51.1 ± 7.6	0.40
Sedentary lifestyle: [No. (%)]	13 (65)	17 (61)	0.76
Alcohol intake: [No. (%)]	13 (65)	16 (57)	0.58
Alcohol consumers: [Mean ± SD]			
Duration (yrs)	17.9 ± 6.3	15.9 ± 8.1	0.60
Volume (ml/day)	52.0 ± 65.0	32.8 ± 37.9	0.42
Drug addiction: [No. (%)]	1 (5)	0 (0)	0.42*
Smoking: [No. (%)]	7 (35)	12 (43)	0.58
Smokers: [Mean ± SD]			
Duration (yrs)	22.7 ± 12.6	22.6 ± 9.3	0.98
Number per day	13.7 ± 9.1	12.9 ± 14.4	0.90
Dietary habits: [No. (%)]			
Vegetarian	9 (45)	8 (28)	
Eggetarian	0 (0)	5 (18)	
Non-vegetarian	11 (55)	15 (54)	0.11*
Family history: [No. (%)]			
Hypertension	5 (25)	7 (25)	1.0
CAD or MI	2 (10)	0 (0)	0.17*
Stroke	0 (0)	0 (0)	NA
Diabetes	1 (5)	2 (7)	0.63*
Anthropometry: [Mean ± SD]			
Weight (kg)	81.4 ± 12.8	85.0 ± 12.4	0.33
Height (cm)	166.9 ± 7.5	164.9 ± 9.0	0.43
Body mass index (kg/m ²)#	28.9 ± 1.2	31.0 ± 1.2	0.18
Waist to hip circumference	0.99 ± 0.1	1.0 ± 0.1	0.65
Neck circumference (cm)	39.7 ± 2.4	42.1 ± 2.7	0.003
Investigations: [Mean ± SD]			
Hemoglobin (gram/dl)	13.1 ± 1.7	13.6 ± 1.3	0.25
Serum CRP (mg/ dl)	3.1 ± 3.7	4.7 ± 6.3	0.33
Blood sugar fasting (mg/dl)	104.8 ± 25.3	115.1 ± 32.0	0.24
Blood sugar post prandial (mg/dl)	141.4 ± 58.7	156.0 ± 55.2	0.38
Serum lipid profile: [Mean ± SD]			
Total cholesterol (mg/dl)#	181.2 ± 1.2	175.1 ± 1.2	0.54
High density lipoprotein (mg/dl)#	45.4 ± 1.2	41.2 ± 1.2	0.08
Low density lipoprotein (mg/dl)#	100.3 ± 1.4	100.7 ± 1.4	0.97
Very low density lipoprotein (mg/dl)#	29.7 ± 1.4	29.4 ± 1.4	0.94
Triglycerides (mg/dl)#	148.3 ± 1.4	147.1 ± 1.4	0.94
HDL: LDL ratio	0.51 ± 0.32	0.43 ± 0.16	0.28
Co-morbidities (non outcome) [No. (%)]			
Past stroke	1 (5)	1 (4)	0.27*
Past diabetes	6 (30)	12 (43)	0.36
Current diabetes	6 (30)	15 (54)	0.11
Current dyslipidemia	14 (70)	25 (89)	0.09
Overweight or obese (BMI ≥ 25)	16 (80)	24 (86)	0.60
Overweight or obese (Asian; BMI ≥ 23)	18 (90)	27 (96)	0.36
Metabolic syndrome (IDF Asian defin)	12 (60)	25 (89)	0.034

CAD – Coronary artery disease;
MI – Myocardial infarction;
NA – Not applicable;
RDI – Respiratory distress index

Values depict either mean ± SD (standard deviation), # geometric mean ± SD or number (percentage). P value refers to two tailed comparison between the cases and controls with Student 't' test for means and chi-square or Fischer exact test* for numbers.

Current diabetes defined as person with known diabetes or fasting blood sugar ≥ 126 mg/dl or post prandial blood sugar ≥ 200 mg/dl. Current dyslipidemia defined as a person on treatment for dyslipidemia or serum cholesterol ≥ 240 mg/dl or serum LDL ≥ 160 mg/dl or serum HDL < 40 mg/dl for men and < 50 mg/dl for women or serum triglyceride ≥ 150 mg/dl.

Metabolic syndrome was defined as per the International Diabetes Federation definition for South Asians: waist circumference ≥ 90 cm (men) or ≥ 80 cm (women) plus two or more of the following: a) fasting serum triglyceride > 150 mg/dl; b) HDL-cholesterol < 40 mg/dl (men) or < 50 mg/dl (women); c) hypertension defined as on treatment for hypertension or systolic blood pressure ≥ 130 mmHg or diastolic pressure ≥ 85 mmHg and d) known diabetes or fasting plasma glucose ≥ 100 mg/dl (18).

Table 4: Comparison of outcome measures amongst non-severe and severe OSAHS.

Characteristic	Non-severe	Severe	Mean difference or OR (95% CI)	P value
Number	20	28	NA	NA
Blood pressure				
Systolic blood pressure (mm Hg) [Mean \pm SD]	135.3 \pm 15.6	133.0 \pm 15.7		0.62
Unadjusted				
Adjusted (age, sex)			-2.3 (-11.3, 6.7)	0.62
Adjusted (age, sex, BMI)			-2.1 (-11.4, 7.1)	0.65
			-3.0 (-12.4, 6.4)	0.54
Diastolic blood pressure (mm Hg) [Mean \pm SD]	86.1 \pm 12.0	83.7 \pm 11.5		0.49
Unadjusted				
Adjusted (age, sex)			-2.4 (-9.1, 4.3)	0.49
Adjusted (age, sex, BMI)			-1.6 (-8.3, 5.1)	0.64
			-1.7 (-8.6, 5.2)	0.64
Hypertensive* [No. (%)]	14 (70)	21 (75)		0.70
Unadjusted			1.29 (0.36, 4.64)	0.70
Adjusted (age, sex)			1.12 (0.30, 4.24)	0.86
Adjusted (age, sex, BMI)			0.97 (0.24, 3.85)	0.96
Current hypertension on ≥ 1 antihypertensive drugs # [No. (%)]	8 (40)	11 (39)		0.96
Unadjusted				
Adjusted (age, sex)			0.97 (0.30, 3.14)	0.96
Adjusted (age, sex, BMI)			1.01 (0.31, 3.36)	0.98
			0.87 (0.25, 3.02)	0.83
Current hypertension on ≥ 2 antihypertensive drugs ## [No. (%)]	5 (25)	7 (25)		1.00
Unadjusted				
Adjusted (age, sex)			1.00 (0.27, 3.76)	1.00
Adjusted (age, sex, BMI)			1.00 (0.26, 3.81)	1.00
			0.88 (0.22, 3.48)	0.85
Current hypertension on 3 antihypertensive drugs ### [No. (%)]	1 (5)	1 (4)		1.00**
Echocardiography and Electrocardiography				
Previous myocardial infarction [No. (%)]	4 (20)	4 (14)		0.70**
Unadjusted			0.67 (0.15, 3.06)	0.60**
Adjusted (age, sex)			0.64 (0.14, 2.98)	0.57**
Adjusted (age, sex, BMI)			0.66 (0.14, 3.15)	0.60**
Ejection fraction (%) [Mean \pm SD]	68.8 \pm 10.9	66.5 \pm 11.4		0.49
Unadjusted				
Adjusted (age, sex)			-2.28 (-8.7, 4.13)	0.49
Adjusted (age, sex, BMI)			-1.28 (-7.45, 4.90)	0.69
			-0.75 (-7.04, 5.53)	0.82
Systolic dysfunction [No. (%)]	1 (5)	2 (7.1)		1.00**
Unadjusted			1.46 (0.12, 17.32)	0.76
Adjusted (age, sex)			1.20 (0.08, 19.14)	0.90
Adjusted (age, sex, BMI)			1.50 (0.07, 31.43)	0.80
Diastolic dysfunction [No. (%)]	11 (55)	22 (78)		0.08
Unadjusted			3.00 (0.85, 10.59)	0.09
Adjusted (age, sex)			2.93 (0.80, 10.73)	0.10
Adjusted (age, sex, BMI)			2.74 (0.74, 10.20)	0.13
Pulmonary artery hypertension [No. (%)]	2 (10)	8 (28.6)		0.16
Unadjusted			0.28 (0.05, 1.48)	0.13
Adjusted (age, sex)			0.25 (0.05, 1.43)	0.12
Adjusted (age, sex, BMI)			0.26 (0.04, 1.56)	0.14
Left ventricular hypertrophy [No. (%)]	6 (30)	15 (54)		0.11
Unadjusted			0.37 (0.11, 1.25)	0.11
Adjusted (age, sex)			0.35 (0.10, 1.19)	0.09
Adjusted (age, sex, BMI)			0.33 (0.09, 1.17)	0.09
Arrhythmias [No. (%)]	2 (10)	6 (21)		0.44**
Unadjusted			2.46 (0.44, 13.67)	0.31
Adjusted (age, sex)			2.23 (0.39, 12.95)	0.37
Adjusted (age, sex, BMI)			2.39 (0.41, 14.04)	0.34
Carotid ultrasound				
Previous stroke [No. (%)]	1 (5)	1 (4)	NE	1.00
Plaque [No. (%)]	6 (30)	7 (25)		0.70
Unadjusted			0.78 (0.22, 2.81)	0.70
Adjusted (age, sex)			0.57 (0.14, 2.33)	0.43
Adjusted (age, sex, BMI)			0.60 (0.14, 2.50)	0.48
Intima media thickness (mm) [Mean \pm SD]	1.09 \pm 0.20	1.10 \pm 0.18		0.89
Unadjusted				
Adjusted (age, sex)			0.01 (-0.10, 0.11)	0.89
Adjusted (age, sex, BMI)			-0.01 (-0.11, 0.10)	0.92
			-0.01 (-0.11, 0.10)	0.91

NA – not applicable;

NE – Not estimable

* Defined as physician diagnosed hypertension or on any anti-hypertensive drug medication or systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg.

Defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg despite ≥ 1 anti-hypertensive drugs. ## Defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg despite ≥ 2 anti-hypertensive drugs. ### Defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure > 90 mm Hg despite 3 anti-hypertensive drugs.

** Fischer exact test or Omnibus tests of model coefficients.

None of the case or control subjects had right ventricular hypertrophy. Amongst arrhythmias in non-severe OSAHS, 1 subject had ventricular ectopics and 1 had sinus tachycardia. Amongst severe OSAHS 3 had ventricular ectopics, 2 had sinus tachycardia and 1 had sinus bradycardia.

be documented probably due to lower sample size. The lack of a statistically significant “dose response” relationship on comparing subjects with severe and non-severe OSAHS is probably a reflection of the smaller sample size and non-comparison of the extreme tails of the disease spectrum.

Comparison of confounders and non-outcome co-morbidities

Subjects with OSAHS were significantly older, heavier and more obese and had greater associated co-morbidities including diabetes, dyslipidemia and metabolic syndrome. All these variables are well-documented correlates of cardiovascular morbidities including hypertension, ventricular dysfunction and carotid vascular health (2,19-22). These variations partially stem from the study design including its setting in a tertiary care hospital of an urban metro. In any study of this magnitude and nature, it would be virtually impossible to balance all known confounders and co-morbidities across the two arms. Potential controls matched for age and body mass index, either failed to clear the screening criteria of Berlin's questionnaire or declined consent. The older and obese potential controls usually declined consent because of their preoccupation with the primary morbidity necessitating the hospital visit or refusal by younger relatives to accompany them for participation in a study.

The clustering of co-morbidities including obesity, diabetes, dyslipidemia and metabolic syndrome in subjects with OSAHS is not unexpected. There is abundant epidemiological evidence documenting the co-existence of OSAHS and these morbidities (2,19,20). This has led some workers to propose that OSAHS is a manifestation of the metabolic syndrome (23,24). The proposed clinical entity “Syndrome Z” includes the combination of metabolic syndrome and OSAHS (25,26).

A simple comparison of outcomes (cardiovascular morbidities) amongst subjects with and without OSAHS will obviously confuse the interpretation. It was therefore important to adjust for differences by multiple regression analysis with due cognizance to the available sample sizes. Two types of adjustments were utilized: (i) gender and age; (ii) gender, age and BMI. In the latter adjustment, BMI was a good surrogate for most of the co-morbidities (diabetes, dyslipidemia and metabolic syndrome). Addition of all confounders and co-morbidities as adjustment co-variables would not have been feasible with the available sample size and would have caused collinearity with BMI, which was highly correlated with other co-morbidities.

Blood pressure and hypertension

The unadjusted, age and gender adjusted estimates of systolic and diastolic blood pressure and hypertension were significantly greater in subjects with OSAHS. This is in conformity with earlier evidence from the literature, which is largely from the western world (2,3,5,19,20). However, on additional adjustment for BMI, these differences did not retain statistical significance. This observation is at variance with the earlier data, which documented a significantly greater risk of elevated blood pressure and hypertension after adjustment for several potential confounders including BMI (2,3,5,19,20). The possible explanations for this are: (i) The available sample size did not have adequate power to detect such differences as the variation increased with additional adjustment. The documented odds ratio of 2.76 after adjustment for BMI is within the reported adjusted range (1.37 to 2.89) from the literature (2,19,20); however the 95% confidence intervals are relatively wide (0.69 to 11.02) indicating wider variability. (ii) The blood pressure readings were recorded and hypertension was defined with subjects on anti-hypertensive drugs. As a greater proportion of the cases were consuming anti-hypertensive drugs (34/48 or 71% vs 2/44 or 5%; $P < 0.001$), there was a bias for lowering the actual differences amongst the two groups, which could result in false negative statistical significance; (iii) BMI may represent the common pathway in subjects with OSAHS for elevation of blood pressure; for example it has been proposed that OSAHS may be added as a feature of metabolic syndrome (23-26) and obesity is an essential component of this malady. Control for BMI could thus conceivably represent an over adjustment leading to loss of statistical significance; and (iv) The remote possibility of misclassification of subjects with mild OSAHS as controls could not be excluded with certainty.

Nevertheless, even after adjustment for BMI (good surrogate for other confounders), the risk for severer forms of hypertension was significantly greater in subjects with OSAHS. This is in conformity with earlier evidence (2,19,20).

On comparing subjects with severe and non severe OSAHS, no significant differences were observed for the unadjusted and adjusted estimates of blood pressure, hypertension and current hypertension on anti-hypertensive medication. This finding is at variance with some earlier evidence, which indicates a “dose response” relationship (2,19,20). The possible reasons for not demonstrating statistical significance in the current study could be the relatively small sample sizes for comparison in the two groups

(28 and 20 subjects in the two arms). *Post-hoc* power calculations from the current study suggest that 150 subjects each would be required with severe and non-severe OSAHS to detect with 80% power and 95% confidence: (i) a difference of 5 mm in systolic blood pressure; or (ii) an odds ratio of 2 for hypertension. Also the contrast did not relate to the extreme ends of the spectrum of severe and mild disease.

Echocardiography, Ventricular dysfunction and Arrhythmias

There was a significant ($P \leq 0.006$) association of unadjusted and adjusted (including BMI) estimates of previous myocardial infarction in subjects with OSAHS. This observation is in conformity with the earlier literature documenting an increased cardiovascular morbidity and mortality from ischemic heart disease (1,2,20).

The unadjusted ejection fraction was significantly lower (4.5%; $P=0.017$) amongst subjects with OSAHS. However these differences did not retain statistical significance on adjustment for age, sex and additionally for BMI. There were no statistical differences for the unadjusted and adjusted estimates for systolic dysfunction; this condition was however documented infrequently (3 cases versus no controls). These findings are slightly at variance with earlier studies, which documented an increased risk of heart failure also after adjustment for several potential confounders (1,2,19,20). This is probably a reflection of the available sample size.

There was a significantly greater association of OSAHS with diastolic dysfunction and left ventricular hypertrophy for the unadjusted, age and gender adjusted, and age, gender and BMI adjusted (for left ventricular hypertrophy only) estimates. Earlier studies have documented that chronically OSAHS is associated with hypertension and increased left ventricular wall thickness, which may lead to diastolic dysfunction (27,28) and its reversibility with therapy (27,28). On adding systolic blood pressure and drug intake for hypertension in the regression model, systolic blood pressure emerged a significant predictor of left ventricular hypertrophy (OR 1.06, 95% CI 1.02 to 1.11; $P=0.008$), suggesting its contribution to the observed left ventricular hypertrophy.

Subjects with OSAHS had a significantly greater prevalence of pulmonary artery hypertension even after adjustment for age, gender and BMI. Mild pulmonary artery hypertension is a common complication in patients

with OSAHS with a prevalence of approximately 20% (7).

There was a significantly greater association of OSAHS with arrhythmias even for BMI adjusted estimates ($P=0.006$). This finding is in conformity with earlier studies which also documented an increased confounder adjusted risk of arrhythmias, particularly atrial fibrillation and ventricular ectopics (2,19,20,29,30). However some observational trials could not document an increased risk of bradyarrhythmias (29,31).

On comparing subjects with severe and non-severe OSAHS, no significant differences were observed for the unadjusted and adjusted estimates of previous myocardial infarction, ejection fraction, systolic and diastolic dysfunction, pulmonary artery hypertension, left ventricular hypertrophy and arrhythmias. This finding is at variance with some earlier evidence, which indicates a "dose response" relationship (2,19,20,27,28). This could be due to relatively small sample sizes and non-comparison of the extreme tails of the spectrum.

Carotid artery ultrasound

Subjects with OSAHS had a significantly greater risk of carotid artery plaques even after adjustment for age, gender and BMI. This observation is in conformity with the earlier literature documenting an increased occurrence of atherosclerotic plaques in the carotid arteries of OSAHS patients, independent of hypertension (32,33). In the current study also, the greater risk of carotid artery plaques was borderline significant after additional adjustment for hypertension ($P=0.054$). However, a few earlier studies with relatively small sample sizes have failed to document a significant increase in the prevalence of plaques in OSAHS (34,35).

The mean carotid intima media thickness was significantly greater in subjects with OSAHS even after adjustment for age, gender and BMI. Earlier studies have documented similar findings without (34-38) and with (32,33,39,40) adjustment for confounders including hypertension. In the current study also, the intima media thickness was significantly greater with additional adjustment for hypertension ($P<0.001$).

On comparing subjects with severe and non-severe OSAHS, no significant differences were observed for the unadjusted and adjusted estimates of any of the above evaluated carotid ultrasound parameters. However, a significant association of severe OSAHS with carotid intimal thickness has been reported in unadjusted (34,37,38) and

adjusted (35,39,40) analyses. The lack of a statistically significant “dose response” relationship is probably a reflection of the smaller sample size and non-comparison of the extreme tails of the spectrum.

In summary, the findings from the current study in Indian adults are in conformity with the earlier epidemiologic evidence and suggest that OSAHS is a significant risk factor for cardiovascular morbidity.

Implications for practice

It would be prudent to periodically screen subjects diagnosed as OSAHS for various cardiovascular morbidities through echocardiography and carotid ultrasound, if possible. This will result in early identification and therapy of co-existent cardiovascular morbidities, which may improve the prognosis. Conversely, subjects with cardiovascular morbidities, especially refractory hypertension should be screened through questionnaire and treated for OSAHS (if detected), which may prove helpful in alleviating the primary condition.

Implications for future research

In the Indian setting, larger epidemiological studies will help to clarify the independent relationship between OSAHS and its severity with the various cardiovascular morbidities. There is thus a need for performing multi-centric studies to achieve the requisite sample size, and also for initiating intervention trials.

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