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Research Article

Relationship of Obstructive Sleep Apnoea Severity, Disease Severity Indices with Attributable Morbidities especially Cardiovascular Events.

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Abstract

Background: *Cardiovascular Events (CVE) is one of the major clinical manifestations of obstructive Sleep Apnoea (OSA). Polysomnography (PSG) is the gold standard in diagnosis and severity assessment.*

Objective:*To assess correlation between severity of OSA, disease severity indices and attributable morbidities. To compare various severity indices to find better predictor for attributable morbidities.*

Methods: *Prospective observational study included adult OSA patients after undergoing PSG. These patients underwent various relevant biochemical tests, pulmonary function test (PFT), Electrocardiogram (ECG), Echocardiography (ECHO). Appropriate statistical tests were applied and statistical significance was documented at* $p \leq 0.05$.

Results: *A total 100 OSA patients (75-Male, 25-Female) were evaluated. Average age was 53 years. Mean BMI and neck circumference was 33.12kg/m2 and 44.33cm respectively. Morbidities found were: uncontrolled systemic hypertension-68%, pulmonary hypertension-16%, uncontrolled diabetes-57%, dyslipidemia-32%, psychiatric disorders-7% and gastroesophageal reflux disease-13%. 43% had at least one CVEs. 51% had severe, 22% had moderate and 27% had mild OSA. Moderate and severe OSA groups had significantly higher number of patients with uncontrolled hypertension as compared to mild OSA group (p=0.034). Individually none of these indices had significant predictive association with the attributable morbidities and none was superior over the other.*

Conclusion: *Increasing severity of OSA is associated with increased prevalence of uncontrolled systemic hypertension. Patients with coexistent chronic obstructive pulmonary disease (COPD) and OSA are more prone for developing pulmonary hypertension and left ventricular hypertrophy.*

Keywords*: Obstructive sleep apnoea (OSA); Cardiovascular events (CVE); Polysomnography (PSG), Apnoea-Hypopnoea index (AHI), Pulmonary function test (PFT).*

Introduction

The field of sleep medicine has undergone a great change in the last few years. In particular, significant advances have been made in the diagnosis, and management of sleep apnoea.

The clinical expressions of sleep disordered breathing are many. Cardiovascular system has huge immediate and long-term consequences, because of which the general medical community has become increasingly interested in sleep related breathing disorders. Greater public and medical attention to sleep disorders have resulted in a 12-fold increase in the volume of referrals for sleep studies over the last decade.

The diagnosis of sleep-disordered breathing is contingent upon the history and the measurement of ventilation during sleep. Standardized tests and questionnaires have become increasingly important as objective measures of daytime sleepiness. These tests aim at better characterization and evaluation of the complexity of clinical symptoms. Polysomnography (PSG) remains the gold standard approach to clearly define sleep apnoea, to differentiate it from other sleep disorders, to introduce and supervise optimal therapy. The apnoea-hypopnoea index (AHI) is widely used for the diagnosis and the assessment of the severity of obstructive sleep apnoea (OSA).

Many indices and variables are assessed during PSG and their importance in connection to predict cardiovascular events (CVE) is not clear. While many of them have been individually assessed in different studies, but the results are equivocal. AHI is well established as an index to define the severity of OSA; however, it remains questionable whether AHI is the optimal index to estimate cardiovascular risks, particularly in mild to moderate OSA patients. In the clinical setting, some patients with mild to moderate OSA defined by AHI, already had severe cardiovascular events (CVE). Therefore, in this study, we correlate various severity indices measured by PSG with attributable morbidities and compare among them to find the better predictor of CVEs.

Aims

1. To assess correlation between severity of OSA, disease severity indices and attributable morbidities.
2. To compare various severity indices and find the better predictor for attributable morbidities.

Materials & Method

This is a prospective, observational study which included 100 consecutive adult patients (≥ 18 years) diagnosed with OSA by split night PSG (AHI ≥5).

A total 142 patients with high index of suspicion of OSA were first enrolled for the split-night PSG. Subsequently 100 of them, found to have OSA (AHI ≥ 5), were labelled as (population A) and which was then divided into 3 subgroups like OSA with COPD (population B, n=27), OSA with Hypothyroidism (population C, n=6), and only OSA (population D, n=55). They were also divided into 3 severity subclasses based on AHI – mild (5-15), moderate (16-30) and severe (>30). 4 patients of OSA had both COPD and Hypothyroidism; hence were not considered while defining the population groups B and C. Out of total 100 patients, 8 patients lost to follow-up after the PSG; rest 92 patients underwent detailed assessment of disease severity indices with regards to the attributable morbidities and cardiovascular events.

Data was collected for the personal habits, morbidity profile and medications using a preformed questionnaire. Grading of daytime sleepiness was done by the standard questionnaire- Epworth sleepiness scale (EPSS). Clinical assessment is done for blood pressure measurement, calculation of body mass index (BMI) and neck circumference, documentation of systemic findings. Data recorded from split-night polysomnography (PSG) included -Total sleep time (TST), arousal index (AI), apnoea hypopnea index (AHI), number of desaturations in TST, oxygen desaturation index (ODI), lowest O2 saturation, mean duration of desaturation and mean heart rate. A relatively new index integrated area of desaturation (IAD) was calculated. Biochemical assessment included measurement of the plasma levels of glucose (fasting and postprandial), HbA1C, lipids and thyroid profile. Diagnostic investigations - ECG, 2D ECHO, 24 hour holter monitoring and pulmonary function test (PFT) are performed to define the morbidities (systemic hypertension, pulmonary hypertension, diabetes mellitus, dyslipidemia, chronic obstructive pulmonary disease (COPD), hypothyroidism, psychiatric disorders, gastroesophageal reflux disease (GERD) and CVEs - left ventricular hypertrophy (LVH), heart failure, arrhythmias, ischemic heart disease (IHD), cerebrovascular accident (CVA).

The statistical analysis was carried out using the SPSS-PC+ computer program (Version 11.0; SPSS, Chicago, Ill., USA). Mean, standard deviation (SD), median, and mode were calculated as suitable for all parametric data. Correlation of severity of OSA and severity indices namely AI, AHI, ODI, IAD with the attributable morbidities was assessed using chi square test and t-test for equality of means respectively. Comparison for superiority among the severity indices namely AI, AHI, ODI, IAD with regards to attributable morbidities, was done by multiple logistic regression analysis. The severity indices AHI and IAD were correlated with CVEs using analysis of variance (ANOVA). Assessment of the better predictor for CVEs between AHI and IAD within the severity strata, was done using pearson's correlation. The correlation coefficient was

considered significant at p<0.01. The clinical profile, relevant morbidities and disease severity indices of patients with OSA and COPD (population B), OSA and hypothyroidism (population C) and only OSA (population D) were compared using chi square test and ANOVA. Side by side non-parametric tests like Kruskal-Wallis Test, Mann-Whitney tests were also performed. Statistical significance is documented at p<0.05.

Results

Baseline characteristics of the study population and PSG parameters were recorded in table 1. Details of attributable morbidities & CVEs were mentioned in table 2.

Table 1. Baseline characteristics of total population

Gender	M-75, F-25
Physical Examination	**Mean ± SD**
Age (years)	53.90 ± 12.52
BMI (kg/m2)	31.12 ± 5.56
Neck circumference (cm)	44.33 ± 5.04
EPSS	12.49 ± 4.52
PSG Parameters	
TST (hrs)	4.41 ± 1.80
AI (/hr)	33.40 ± 27.49
AHI (/hr)	35.67 ± 25.05
Number of desaturations in TST	65.29 ± 68.71
ODI (/hr)	18.11 ± 20.67
Mean duration of desaturation (sec)	43.84 ± 73.43
IAD	11.29 ± 13.80
Lowest O_2 saturation	75.85 ± 12.62
Mean heart rate	70.73 ± 10.77

Table 2: Summary of attributable morbidities and CVEs

Co-morbidities	**Mean ± SD**
Uncontrolled hypertension	68 %
Pulmonary hypertension	16 %
Uncontrolled diabetes mellitus	57 %
Dyslipidaemia	32 %
COPD	31 %
Hypothyroidism	10 %
GERD	13 %
Psychiatric Illness	7 %
Cardiovascular Events	
LVH	25 %
IHD	30 %
Heart failure	16 %
Arrhythmias	9 %
CVA	4 %

Of the total 100 OSA patients, 51% had severe OSA, 22% had moderate and 27% had mild OSA. The comparison of the severity groups (mild, moderate, severe) with regards to attributable morbidities and CVEs revealed that moderate and severe OSA groups had significantly higher number of patients with uncontrolled hypertension as compared to mild OSA group ($p=0.034$). No correlation was found between the severity of OSA and other morbidities and CVEs ($p>0.05$). Individually, none of the indices have significance in predicting attributable morbidities. Subsequently on multiple logistic regression, none of them was found superior to the other.

On comparison of 3 different population groups, presence of COPD or hypothyroidism in OSA patients, did not show significant difference in clinical profile, severity of OSA, various severity indices and attributable morbidities. Population B and C had significantly a greater number of patients with LVH ($p=0.04$) and trend

towards having pulmonary hypertension (p=0.07). This indicates that presence of COPD or hypothyroidism in OSA patients significantly increases their chances of having LVH & pulmonary hypertension.

Discussion

In this prospective, observational study, a total of 142 patients with suspected OSA were received over a period of 2 years. Following polysomnography, 100 of them were found to have OSA (AHI ≥5). They subsequently underwent detailed evaluation for attributable morbidities. Total population (A) was then divided into 3 subgroups - population 'B' having COPD with OSA, population 'C' having hypothyroidism with OSA and population 'D' having only OSA. Four patients had both COPD and hypothyroidism. Eight patients lost to the follow up and were not considered during data analysis.

Estimations of prevalence of OSA in the general population is variable and depend on the population studied, methods used to measure sleep and threshold employed to define normal from abnormal. Data from the Wisconsin sleep cohort study, suggested that the prevalence of OSA was high in men 4% as compared to 2% in women. [1] In our study of 100 patients also, males were more commonly affected, thrice as compared to females (75% and 25%) respectively and similar distribution is found in different population groups B, C and D (p=0.002). The reason appears to be related to hormonal influence and body fat distribution.

The effect of age is complex. Average age of OSA patients in our study is 53.93 years, similar to the population studies which illustrate higher prevalence of OSA with increasing age, peaking in the fifties and sixties. The syndrome also occurs in childhood and elderly although less frequently, but in this study only adults (age >18yrs) are included, so occurrence in children cannot be commented. Older individuals have lower rates of apnoea and snoring. Reduced recognition of sleep problems by the elderly and a survivor effect are potential reconciling explanations for this paradox. Referral populations of OSA patients represent only the tip of the iceberg of OSA prevalence. So, the current actual prevalence may be substantially higher.

Obesity is a well-established risk predictor for OSA. The BMI is a reliable measure of body fat and body fat mass. Obesity can affect the structure and function of the upper airway. An increase in weight has also been shown to worsen OSA. Peppard and colleagues [2] conducted a population based, prospective cohort study from 1989 to 2000 and measured the independent association between weight change and change in the AHI. They found that a 10% weight gain predicted about a 32% increase in the AHI and a sixfold increase in the risk for developing moderate to severe OSA.

Clinical observations and population studies throughout the United States, Europe, Asia and Australia have consistently shown a graded increase in the prevalence of sleep disordered breathing (SDB) as body mass index, neck circumference or other measures of body habitus increases.

Terry Young and colleagues [3] in a study among adults aged 30-69 years estimated that 17% of adults have mild SDB (AHI ≥ 5) and 41% of these adults have SDB attributable to a body mass index ≥25 kg/m^2. Similarly, 5.7% of adults have moderate SDB (AHI ≥ 15) and 58% of these adults have SDB attributable to excess weight. Imaging studies have also demonstrated that the total volume of fat surrounding the airway is greater in apnoeic than in BMI matched normal subjects, suggesting that fat deposition in the neck plays a role in the pathogenesis of OSA. Indeed, neck size is the strongest of the obesity predictors for OSA and it correlates with increased dimensions of parapharyngeal fat pads. [4] Neck circumference of 17 and 15 inches in males and females respectively is considered as risk factor of OSA. [5] OSA also occurs in nonobese subjects. In nonobese patients, craniofacial morphology's contribution to apnoea risk is supported by observations in Asian patients. [6]

In our study, mean BMI and neck circumference of all OSA patients was found to be 33.12kg/m2 and 44.33cm (17.7 inches) respectively, which matches with the previous studies predicting OSA risk. These parameters were comparable in different population groups (B, C, D) and in different severity classes of OSA. This indicate that BMI and neck circumference have no association with coexistent COPD or hypothyroidism in OSA patients and individually, they are poor predictors of OSA severity.

Epworth Sleepiness Scale (EPSS) is a standard useful questionnaire with high sensitivity of around 80% to assess the degree of self-rated sleepiness. The total score ranges from 0 to 24, with a score <7 is considered normal and a score >9 suggestive of sleep-disordered breathing. In our study the average EPSS of all OSA patients was 12.49 indicating their high risk for OSA. A few OSA patients in our study have EPSS <9 with minimum being 4. This difference could be because it is a subjective tool. When EPSS of the population groups (B, C, D) and different severity groups is compared, no significant variation was noted ($p>0.05$), suggesting that overlapping COPD or Hypothyroidism in OSA does not affect the degree of day time sleepiness and also severity of OSA does not correlate with the EPSS.

OSA has been proposed as an independent risk factor for the development of essential hypertension because it can precede and predict the onset of hypertension. 50% of OSA patients are hypertensive and almost 30% of hypertensive patients also have OSA often undiagnosed. [7] This has been demonstrated by the Wisconsin sleep cohort study, which noted a consistent OSA-BP dose response relationship, even after controlling for

age, sex, BMI and antihypertensive medications. [8] In our study, 68% had uncontrolled systemic hypertension similar to the population studies.

In a series of 220 consecutive patients with OSA and an AHI >20, pulmonary arterial hypertension (mean pressure >20 mm Hg) was found in 17% of patients, which was mild (<35 mm Hg) in severity. [9] In our study 16% of OSA patients had pulmonary hypertension similar to the above study.

In our study, 57%, 32%, 7%, 13% patients had uncontrolled diabetes, dyslipidemia, psychiatric disorder and GERD, respectively. Higher nocturnal BP in hypertensive patients with OSA than in those without OSA may place such individuals at greater risk in the long term for left ventricular hypertrophy. [10] LVH was reported in 25% of patients in our study.

The prevalence of SDB in coronary artery disease patients has been 2fold greater than in subjects without coronary artery disease. Hanly et al [11] noted that ST depression occurred in about a third of patients with severe OSA. ST depression was markedly attenuated during nasal CPAP. In our study also 30% OSA patients had IHD.

The prevalence of OSA in heart failure was greater in men than women (38% vs 31%). [12] Observational data suggest that the presence of untreated OSA (AHI >15) in patients with heart failure is associated with an increased risk of death compared with patients with an AHI <15, independent of confounding factors. [13] In our study 16% of OSA patients had heart failure. Cardiac arrhythmias are reportedly more frequent in persons with OSA and increase with the number of apnoeic episodes and the severity of the associated hypoxemia. [14] In a retrospective cohort study of >3500 adults without past or current atrial fibrillation who underwent complete overnight polysomnography, both obesity and nocturnal oxygen desaturation were independent predictors of incident atrial fibrillation, in subjects <65 years of age. [15] In our study, arrhythmia was reported in 9% of OSA patients which could not be compared with above studies as control subjects were not available and we used split night PSG in our study.

The concept of OSA as a risk factor for primary ischemic stroke is mostly inferential and derives from evidence implicating sleep apnoea in hypertension and heart disease, both of which are risk factors for stroke. Bassetti and Aldrich [16] found an AHI ≥10 in 62% of transient ischemic attack patients compared with 12% of control subjects, suggesting that SDB may precede the onset of stroke. A cross-sectional analysis of >6000 subjects from the sleep heart health study, [17] showed that the prevalence of stroke was modestly greater (OR-1.58) among those subjects with OSA and AHI >11. In our study 4% of OSA patients had stroke. This could be because PSG is performed only on referred subjects with high index of suspicion, which is not representing the total OSA population.

51% of our patients had severe OSA, while 22% had moderate and 27% had mild OSA. The reason for this could be because PSG is performed in symptomatic patients referred with high index of suspicion. However, prevalence of mild to moderate OSA in asymptomatic patients is underestimated. The comparison of the severity groups (mild, moderate, severe) with regards to attributable morbidities and CVEs revealed that moderate and severe OSA groups had significantly higher number of patients with uncontrolled hypertension as compared to mild OSA group (p=0.034). However, no significant correlation was noted between severity of OSA and other morbidities or CVEs (p>0.05).

Correlation of the severity indices with the attributable morbidities revealed that, individually none of these indices had significant predictive association with the attributable morbidities (p>0.05). Further comparison of these indices by multiple logistic regression, did not reveal any one of them to be a better predictor of attributable morbidities over the other (p>0.05).

AHI is well established index to define the severity of OSA. However, it remains questionable whether AHI is the optimal index to estimate cardiovascular risks, particularly in mild to moderate OSA patients. In the clinical setting, some patients with mild to moderate OSA defined by AHI have already had severe CVEs.

Therefore, a relatively new index, the integrated area of desaturation (IAD), considering factors such as the duration and degree of hypoxia during sleep to estimate the risk of CVEs for patients with mild to moderate OSA was developed by analysis of polysomnography (PSG). Kihiro Asano et al [18] in his study for validity of this index concluded that in the mild to moderate OSA patients, the mean IAD of the CVEs group was significantly higher than that of the non-CVE group (94.4±82.7 vs. 62.3 ±50.8, p = 0.001), whereas mean AHI and 3% oxygen desaturation index were similar in both groups. Multivariate analysis demonstrated that the IAD was an independent variable for CVEs (OR 1.006, 95%CI 1.001–1.012, p=0.031). There was no significant difference in AHI, IAD or other polysomnographic parameters in the severe OSA patients. Thus, IAD might be superior to AHI alone in the evaluation of the history of CVEs in mild to moderate OSA patients, and it deserves attention as a possible predictor of future CVEs.

In our study, the correlation of the severity indices AHI and IAD with cardiovascular events (LVH, heart failure, arrhythmias, IHD and CVA) did not reveal a significant predictive association. Further comparison between AHI and IAD was then performed within their respective severity strata with regards to prediction of the cardiovascular events which also did not demonstrate any difference.

Later on, analysis of severity distribution of OSA in population groups B, C and D indicated that presence of COPD or hypothyroidism in OSA, neither affect the severity of OSA (p=0.153) nor alter the severity indices significantly (p>0.05). Further comparison of the population groups B, C and D for the occurrence of

morbidities and CVEs revealed that presence of COPD in OSA patients, significantly increases their chances of having LVH (p=0.04) and showed trend towards increased susceptibility to pulmonary hypertension (p=0.07). The occurrence of other morbidities and cardiovascular events was not significantly altered by coexistent COPD or hypothyroidism in OSA (p>0.05). There was significant disparity in sample size which limits the extrapolation of these results to larger population in general.

Conclusion

Increasing severity of OSA is associated with increased prevalence of uncontrolled systemic hypertension. Individually none of the disease severity indices are reliable in predicting attributable co-morbidities and none of them is superior to the other. Coexistent COPD or hypothyroidism in OSA patients neither affect severity of the disease and nor alter the severity indices. Patients with coexistent COPD and OSA are more prone for developing LVH and pulmonary hypertension.

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