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AN OBSERVATIONAL STUDY OF CLINICAL, ANTHROPOMETRIC AND LAB PARAMETERS ASSOCIATED WITH SLEEP APNEA IN STABLE PATIENTS OF HEART FAILURE

Cardiology

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KEYWORDS

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INTRODUCTION

Cardiovascular diseases are the leading cause of mortality and morbidity in both developed and developing countries. While the incidence of ischemic heart disease (IHD) has shown an impressive reduction in developed nations, increasing life expectancy and better chronic care have caused heart failure (HF) to be a major public health issue, especially in older adults. HF is likely to be an important contributor to death and disability in developing countries as well because of increasing vascular disease as well as the persistence of pretransitional diseases such as rheumatic heart disease (RHD) and infectious cardiomyopathies. The estimated prevalence of HF in India is about 1% of the population or about 8–10 million individuals. The estimated mortality attributable to HF is about 0.1–0.16 million individuals per year. [1]

Sleep-disordered breathing (SDB) is common and under-diagnosed in patients with heart failure across a range of ejection fractions and New York Heart Association (NYHA) classes. The most common forms of SDB in patients are obstructive sleep apnoea and central sleep apnoea with Cheyne-Stokes breathing. SDB is important to recognize because it is associated with adverse cardiovascular outcomes and mortality, and because accumulating evidence suggests that treatment of SDB can improve heart failure-related outcomes and quality of life.

OBSTRUCTIVE VERSUS CENTRAL SLEEP APNEA

Two types of SDB are common among patients with heart failure: obstructive sleep apnoea (OSA) and central sleep apnoea with Cheyne-Stokes breathing (CSA-CSB):

1. OSA is characterized by reductions or cessations of airflow during sleep, despite ongoing respiratory effort. It is due to upper airway obstruction.
2. CSB is characterized by cyclic crescendo-decrescendo respiratory effort and airflow during wakefulness or sleep, without upper airway obstruction. When the decrescendo effort is accompanied by apnoea during sleep, it is considered a type of central sleep apnoea syndrome.

Due to similarities in the pathophysiology of sleep-disordered breathing (SDB) and chronic heart failure (CHF), there is an emerging interest in the link between these two conditions. While OSA seems to be a cardiovascular risk factor per se [2], CSA appears to be a marker of CHF severity. [3] However, both OSA and CSA interfere with neuro-humoral systems and thus may worsen heart failure, e.g. by increasing sympathetic and renin–angiotensin– aldosterone activity, both targets of state-of-the-art heart failure therapy. Several studies have demonstrated an increased mortality in CHF patients suffering from SDB in contrast to those without SDB. [2,4]

Patients with systolic heart failure have a high prevalence of sleep apnoea predominantly central sleep apnoea (CSA). [5] Studies suggest that during the night the proportion of CSA goes on increasing, from the first to the last quarter. [5] It is estimated that about one-third of patients with HF have OSA and a similar amount have CSR-CSA. [6] This compares with the general population in whom similar numbers have OSA, [7] whereas 0.1–3% have CSA, a prevalence which appears to increase with age in males.

Heart failure predisposes to OSA by increased soft tissue oedema, increased airway collapsibility and prolonged circulation times. Cardiac function is deranged in OSA due to hypoxia, increased peripheral resistance (due to respiratory efforts), oxidative stress, increased atherosclerosis, and risk of arrhythmias. Thus, OSA in the backdrop of heart failure requires aggressive treatment. [8]

MATERIALS & METHODS

Study design:

This study is a Non- randomized, consecutive, observational study conducted in the Department of Cardiology at Army Hospital (Research & Referral).

Study population:

The representative population for the study included serving and retired defense personals and their families irrespective of race, ethnicity and location, who were referred to or first diagnosed at Army Hospital (R&R), from both rural as well as urban background, including both inpatients and outpatients who consented to be part of the study with a signed informed consent.

Study Duration:

The study was conducted over 18 months from Nov 15 to May 17. Follow up of patients & data collection was carried on till March 2018.

Sample Size and sampling procedure:

Sample size: 50

Sampling Procedure: This was a consecutive and observational study. After doing a pilot study, it was observed that, on an average, about 10 to 12 patients visiting Cardiology OPD (thrice per week) fulfilled the inclusion criteria of the study were subjected to STOP-BANG question. A sample size of 50 was decided due to logistic reason as polysomnograhy (PSG) Lab was available only once a week for the study. Eligible subjects were informed about the study and a number was assigned to each subject. A cardiology consultant was asked to draw a chit from all eligible patients of a week. The patient whose chit number was drawn was contacted on telephone and asked to come for sleep study that week. In case the patient was not available it was decided that the next chronological number would be requested to participate in the study. If the patient consented, he was selected for overnight PSG that week. The data collection was done using a pretested & validated [9] questionnaire and study performa for recording patient particulars, examination findings and lab investigation reports.

Inclusion criteria:

- Sex: Male
- Age: 40-75 yrs.
- Patients diagnosed with Stable Heart Failure based on history, clinical examination and 2D-ECHO by the cardiologist
- Functional class: NYHA I
- LVEF: < 45%
- Intermediate to high risk of OSA as per the Questionnaire

Exclusion criteria:

- Unstable heart failure
- Primary valve disease

- Congenital heart disease
- Acute coronary syndrome
- Acute pulmonary oedema
- Intrinsic liver or renal disorders
- Intrinsic pulmonary disease
- Obstructive lung disease
- Interstitial lung disease
- Female patients*

* - Female patients were excluded as overnight stay in the hospital for sleep study for OPD patients was cumbersome.

Details about clinical parameters:
This domain included the symptomatology and the general and systemic examination findings of the recruited subjects. The purpose of collecting details on these variables (Smoking status, BMI, Waist-Hip ratio, BP) was to study the distribution of OSA in each age group.

Details about lab parameters:
This domain included complete hemogram, liver function tests, renal function tests, blood sugar, lipid profile, 2D ECHO findings (in LVEF) and PSG findings (in AHI). The purpose of collecting details on these variables (Fasting blood sugar, LDL-cholesterol, LVEF) was to study the distribution of OSA in each age group.

Compilation of data:
Data so collected was entered simultaneously into Microsoft excel worksheets designed and coded appropriately.

Analysis of data:
Continuous variables are presented with mean and standard deviation (SD) and categorical variables are presented with the number and percentages. Statistical significance of differences is analyzed using one-way ANOVA for continuous variables and the chi-square for categorical variables. Statistical analysis is computed using SPSS 17.0 (SPSS Inc, Chicago, IL). All the statistical tests were two-sided and considered statistically significant if $P < 0.05$ and highly significant if $P < 0.001$.

Instruments used:
A study performa was prepared under the guidance of experts in the field. Based on inputs derived from the findings, the data was tabulated and analyzed. Left ventricular ejection fraction (in %) as measured on 2DECHO by the cardiologist was recorded. It was classified as mild (LVEF >35%) and severe (LVEF ≤35%)

RESULTS:

OSA and Age group
Mean age of study population, i.e. those having intermediate to high risk of OSA as per the STOP Bang criteria was 55.96 yrs. After the PSG, the mean age for those with mild OSA was 55.57±6.44, moderate OSA was 57.17±7.36 and severe OSA 54.22±7.06.

Smoking and OSA
There were 22 non-smokers and 28 smokers. Out of those who smoked, 7.1% did not have OSA, 25% had mild OSA, 39.3% had moderate OSA and 28.6% had severe OSA as compared to the non-smokers amongst whom, 36% did not have OSA, 31.8% mild, 27.3% moderate and only 4.5% severe OSA[Bar 2]. Smokers had a significantly higher severity of OSA (P 0.019) when compared to non-smokers

BMI and OSA
10 subjects were in normal BMI group (18.5-23 Kg/m2), 40 were equally divided into overweight (BMI 23-27.5 Kg/m2) and obese group (BMI ≥27.5 Kg/m2). [Table 3] In the normal BMI group, 50% did not have OSA, 40 % had mild OSA, 10 % had moderate and none had severe OSA. Among overweight group, 20% had no OSA, 50% had mild, 30% moderate and none had severe OSA. In the obese group, only 5% had no OSA, none had mild OSA, 50% had moderate and 45% had severe OSA. [Table 1] The mean BMI in normal subjects was 23.23(±2.96) Kg/m2, in mild OSA was 24.13(±1.93) Kg/m2, moderate OSA 27.76(±2.60) Kg/m2 and severe OSA was 32.55(±1.60) Kg/m2. [Table 6] The difference was statistically highly significant (P <0.001).

Waist-hip ratio and OSA
24 subjects had waist hip ratio ≤ 0.9 (described normal for males) and 26 subjects had waist hip ratio >0.9 (obese). 29.2% subjects with normal WHR had no OSA, 50% mild, 20.8% moderate and none had severe OSA. While in those having WHR >0.9, it was observed that 11.5% had no OSA, 7.7% had mild, 46.2% moderate and 34.6% had severe OSA. The mean Waist-hip ratio in normal subjects was 0.81(±0.08), in mild OSA was 0.79(±0.07), moderate OSA 0.94(±0.13) and severe OSA was 1.11(±0.10). The difference was statistically highly significant (P <0.001).

Neck circumference and OSA
We observed that 23 subjects had neck circumference ≤37 cm while 27 had neck circumference >37 cm. The mean neck circumference in normal subjects (AHI <5) was 33.7 (±2.35) cm, mild OSA 34.29 (±2.40) cm, moderate OSA 37.21 (±3.04) cm and severe OSA was 40.94 (±1.81) cm. The difference was statistically highly significant (P <0.001)

Blood pressure and OSA
50% subjects had SBP ≤ 140 mm Hg while 50% >140 mm Hg. The mean SBP in normal subjects was 135.6 (±6.78), mild OSA was 135.50 (±11.68), moderate OSA 140.94 (±10.77) and for severe OSA was 152.44 (±11.17) mm Hg. The difference was statistically significant (P 0.002). Similarly, 28 subjects had DBP ≤90 mm Hg while 22 had DBP >90 mm Hg (hypertension).The mean DBP in normal subjects was 83.20 (±6.74), mild OSA was 82.14 (±8.64), moderate OSA 85.411 (±9.55) and for severe OSA was 91.77 (±7.17) mm Hg. The difference was however statistically not significant (P 0.060).

Blood sugar and OSA
Fasting blood sugar was <126 mg/dl in 26 subjects (52%) and ≥126 mg/dl in 24 subjects (48%). Mean fasting blood sugar in normal subjects was 121(±20.63) mg/dl, in those with mild OSA was 122.5(±25.01) mg/dl, moderate OSA was 132.47(±23.32) mg/dl and severe OSA was 125.44(±19.33) mg/dl.The difference was statistically not significant (P 0.536). This may be because many of the subjects were already taking antidiabetic medications and also because there were much more subjects with mild -moderate OSA than those with severe OSA.

Lipid profile and OSA
Mean LDL cholesterol in normal subjects was 122(±21.98) mg/dl, mild OSA was 124.78(±9.34) mm Hg, moderate OSA was 150(±23.9) mg/dl and those with severe OSA was 188(±16.94) mg/dl. The difference was statistically highly significant (P <0.001).

STOP-Bang score and OSA
The mean STOP Bang score in our study for normal subjects was 3.5(±.70), mild OSA was 3.50(0.65), moderate OSA 4.82(1.015) and severe OSA was 6.78(0.66). [Bar 1] The difference was statistically highly significant (P <0.001).

LVEF and OSA
32 subjects had mild HF (LVEF >35%) and 18 had severe HF (LVEF ≤35%). The mean LVEF in normal subjects was 42.00(±4.21), mild OSA group was 40.35(±4.98), moderate OSA was 38.82(±4.85) and in severe OSA was 36.11(±6.00). [Bar 3] The difference was statistically not Significant (P .076).

DISCUSSION

OSA is a sleep disorder characterized by intermittent complete and partial airway collapse, resulting in frequent episodes of apnea and hypopnea. The breathing pauses cause acute adverse effects, including hemoglobin desaturation, fluctuations in blood pressure and heartrate, increased sympathetic activity, cortical arousal, and sleep fragmentation.

The condition has received increasing attention during the past 3 decades. Until 1981, the only effective treatment for OSA was tracheostomy. The advent of continuous positive air pressure (CPAP) therapy, an effective non-invasive treatment, was a turning point, and clinical interest began to increase in tandem with the accumulation of research linking OSA to cognitive, behavioural, cardiovascular, and cerebrovascular morbidities.

Findings from large population studies in different countries during the last decade have contributed to a better understanding of the epidemiology of OSA. In most population studies, OSA status has been indicated by the frequency of apnea and hypopnea events per hour of sleep (apnea-hypopnea index AHI) as determined by PSG (a

continuous overnight recording of sleep, breathing, and cardiac parameters). The apnea-hypopnea index cut points of 5, 15, and 30 (with or without daytime sleepiness) are commonly used to indicate mild, moderate, and severe OSA respectively. These studies have demonstrated that OSA is highly prevalent in adults.

Associations of OSA with serious morbidity have raised concern that untreated OSA is a substantial but underappreciated public health threat. Primary care physicians are currently being encouraged to be alert to OSA symptoms of disruptive snoring, breathing pauses, and excessive daytime sleepiness in their patients. It is important that physicians also recognize that not all OSA patients are "Pickwickian" (ie, male, obese, sleepy, snoring, and middle-aged), a stereotype that emerged from clinical observations of the highly selective patient populations observed in earlier years.

Although OSA and cardiovascular disease have common risk factors, epidemiologic studies show that sleep apnea increases risks for cardiovascular disease independently of individuals' demographic characteristics (i.e., age, sex, and race) or risk markers (i.e., smoking, alcohol, obesity, diabetes, dyslipidemia, atrial fibrillation, and hypertension). Individuals with severe sleep apnea are at increased risk for coronary artery disease, CHF, and stroke.

The underlying mechanisms explaining associations between OSA and cardiovascular disease are not entirely delineated. Several intermediary mechanisms might be involved including sustained sympathetic activation, intrathoracic pressure changes, and oxidative stress. Other abnormalities such as disorders in coagulation factors, endothelial damage, platelet activation, and increased inflammatory mediators might also play a role in the pathogenesis of cardiovascular disease.

Patients with systolic HF have a high prevalence of sleep apnea. HF predisposes to OSA by increased soft tissue edema, increased airway collapsibility and prolonged circulation times. Cardiac function is deranged in OSA due to hypoxia, increased peripheral resistance, oxidative stress, increased atherosclerosis, and risk of arrhythmias. Treatment with CPAP therapy has been shown to increase stroke volume and improve functional status in patients with HF. Thus, OSA in the backdrop of HF requires aggressive treatment.

Linkage between OSA and cardiovascular disease is corroborated by evidence that treatment of sleep apnea with CPAP reduces systolic blood pressure, improves left ventricular systolic function, and diminishes platelet activation. Data from observational studies strongly suggest relationships between sleep apnea including both OSA and CSA, and cardiovascular morbidity and mortality. Although most of the data are not supported by randomized or long-term trials, treatment of sleep apnea may have beneficial effects on long-term cardiovascular outcomes in patients with HF.

This study was carried out in stable hf patients who were on standard therapy, with no change in signs or symptoms of HF within the previous 4 weeks. The relationships between OSA, CSR-CSA and HF have attracted considerable interest in the past few decades. This is in part due to a greater understanding of the bidirectional pathophysiological relationship between HF and these sleep-related breathing disorders, and to a greater understanding of the effects that therapies of one condition can have upon the other. Importantly, in epidemiological studies within an ambulant community, untreated OSA increases the prevalence of HF symptoms [10] and incidence of physician-diagnosed HF, whereas the identification of CSR-CSA appears to predict a greater incidence of admissions to hospital with HF. [11]

This observational study helped us to make some salient observations and conclusions which are listed below: -

1. In our study population of 50 subjects, who were at intermediate to high risk of having OSA, 10 actually did not have OSA, 14 had mild, 17 had moderate and 9 had severe OSA. So, it can be concluded that STOP-Bang questionnaire is about 80% sensitive in picking up OSA in patients with stable heart failure.
2. The mean age for patients with HF, who are at risk for having OSA was 55.96 years.
3. Smoking predisposes to a higher severity of OSA.
4. BMI, Waist-hip ratio and neck circumference are strongly associated with the severity of OSA.
5. Blood pressure was not directly associated with OSA. However, since most of our subjects were already on anti-hypertensive medications, a clear-cut association is not feasible.
6. Similarly, no statistically significant relationship could be established between fasting blood sugar and OSA. This could be explained as most of our subjects were already on anti-diabetic medications.
7. It was found that serum LDL-cholesterol level strongly co-related to severity of OSA.
8. Severity of HF measured as LVEF (in %) did not have a direct bearing on the severity of OSA.

Patients with OSA and HF have less subjective daytime sleepiness despite less sleep time, and the Epworth Sleepiness Scale is unhelpful in predicting OSA in this population.[12] The STOP-Bang questionnaire is an effective screening tool to pick-up cases of OSA among patients with HF and can be conveniently applied in patients with stable heart failure so that, they can be timely offered lifestyle modification, CPAP, pharmacotherapy and optimized HF medications to improve their cardiac function, blood pressure, exercise capacity, and quality of life. Recent studies have shown nocturnal CPAP significantly improves the daytime left ventricular systolic function of patients with HF and coexisting OSA whose condition is stable.[13]

Since this study was conducted in a tertiary care hospital on male patients exclusively, who had stable HF, results cannot be extrapolated on general population. Since, in this study, no distinction was made between CSA and OSA, further studies can be done to find if any significant co-relation between the selected parameters and the two different types of SDB in stable heart failure patients exists. Furthermore, number of studies on Indian sub-population is also limited.

Several large-scale systematic studies are necessary to explicate complex associations between OSA and cardiovascular disease, which may be compounded by the involvement of diseases comprising the metabolic syndrome (i.e., central obesity, hypertension, diabetes, and dyslipidemia).
The questions remain, which HF patients need a screening sleep study, uncertainty about whether and how to treat OSA in this population and the need for treatment goals in absence of guidelines.

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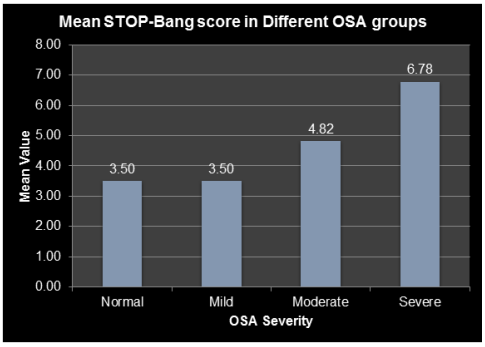
Table 1 : BMI distribution between OSA groups: -

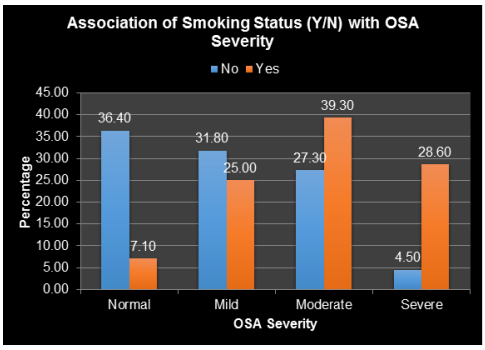
Group (OSA severity)	(n)	BMI (Kg/m2) Mean	± SD	P value
Normal	10	23.2339	2.96512	<0.001**
Mild	14	24.1392	1.93784	
Moderate	17	27.7615	2.60087	
Severe	9	32.5521	1.60472	

NS: p > 0.05; Not significant; *p<0.05; Significant; **p<0.001; Highly significant

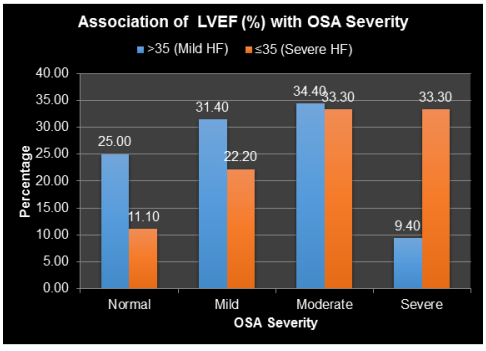
BAR GRAPH 1



BAR GRAPH 2



BAR GRAPH 3



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