ORIGINAL ARTICLE

Prevalence and profile of sleep disordered breathing amongst patients with congestive heart failure

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Abstract

Introduction: It has been observed that since heart failure is highly prevalent and central sleep apnea (CSA) is common in patients with a failing heart, heart failure is the commonest cause of CSA in the general population.

Aims & Objectives: The present study was undertaken with the purpose of finding prevalence of sleep disordered breathing (SDB) in patients of heart failure and also to find the association of severity of SDB with severity of heart failure.

Material & Methods: Forty patients suffering from systolic heart failure were selected on random basis. All these patients underwent complete evaluation of history, physical examination and overnight polysomnography. The patients were divided into two groups, namely group 1 and group 2, on the basis of polysomnography. Group 1 consisted of 17 patients who did not have sleep disordered breathing i.e. AHI (central or obstructive) < 5. Group 2 consisted of 23 patients who had sleep disordered breathing i.e. AHI (central or obstructive) > 5. Comparison of biochemical profile and sleep parameters was made between group 1 and group 2 and results analyzed.

Observations: Aetiology of heart failure was ischemic heart disease in 34 patients, viral myocarditis in 3 patients and postpartum cardiomyopathy in 3 patients. Total prevalence of CSA in heart failure was 57.5%.Prevelance in males and females was 47.6% and 68.42% respectively. There was a significant difference in O2 desaturation index, minimum O2, arousal index, total sleep time, AHI (central), sleep efficiency and wake O2 amongst the two groups. A negative correlation was observed between ejection fraction and O2 desaturation index, AHI (central), and arousal index. A positive correlation was found between ejection fraction and wake O2.

Conclusions: A fairly high prevalence of sleep-disordered breathing (57.5%) was found in patients of heart failure in the present study. With increasing severity of HF a significant worsening of CSA-CSR was observed. The treatment of CSA-CSR may prevent the worsening status of HF. Hence long term randomized and controlled interventions are required to further substantiate these fact.

Keywords: sleep disordered breathing, central sleep apnea, Cheyne-Stokes respiration, congestive heart failure

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Introduction

Central sleep apnea (CSA) is characterized by a loss of ventilator effort lasting for 10 seconds or more, caused by a temporary failure in the pontomedullary pacemaker that generates the breathing rhythm.(24) Poly- somnographically, there is cessation of airflow at mouth as well as absence of thoraco-abdominal excursions. There are several physiological and pathological conditions associated with the occurrence of CSA. Physiologic conditions encountered are sleep onset, post-arousal/ post-sigh phase and phasic REM sleep. The various pathologic states include non-hypercapneic CSA (systolic heart failure, post-stroke and high altitude), hypercapneic CSA (primary and congenital hypoventilation syndromes, brainstem and spinal cord disorders like encephalitis, tumors, infarcts, amyotrophic lateral sclerosis, muscular disorders and Guillain-Barre syndrome), endocrinopathies (like acromegaly and hypothyroidism) and upper airway disorders. CSA has also been described to occur in cases of obstructive sleep apnea (OSA), particularly when the latter is treated with CPAP, when it is termed as complex sleep apnea. By and large, it has been observed that since heart failure is highly prevalent and CSA is common in patients with a failing heart, heart failure is the commonest cause of CSA in the general population. (24)

Congestive heart failure (CHF) is a clinical syndrome that occurs in patients who, because of an inherited or acquired abnormality of cardiac structure and /or function, develop a constellation of clinical symptoms (dyspnoea and fatigue) and signs (oedema and rales) that lead to frequent hospitalizations, poor quality of life, and shortened life expectancy.(1) Conventionally, heart failure has been known to be associated with sleep disordered breathing (SDB)(19).CHF may occur due to valvular disease, cardiac arrhythmias or cardiac muscle pump failure. Cardiac muscle pump failure or cardiomyopathy is due to systolic or diastolic dysfunction. The former occurs as a result of impaired left ventricular contractility (left ventricular ejection fraction<40% or impaired left ventricular shortening<28%), usually secondary to ischemic heart disease, longstanding hypertension or unknown causes (idiopathic). Diastolic dysfunction, also known as heart failure with normal systolic function (HFNSF), occurs due to stiff ventricular walls due to hypoxia, tachycardia, hypertension, and rarely following constrictive pericarditis, pericardial effusion and myocardial infiltrative disorders.(2,3) HFNSF is responsible for CHF in 13 to 74% of patients.(4) According to a recent report, in a combined group of 1250 consecutive patients with systolic heart failure, using apnea-hypopnea index (AHI) of 15 as the threshold, 52% of the patients were found to have moderate to severe sleep apnea, 31% had central sleep apnea, and 21% had obstructive sleep apnea.(24)

Sleep disordered breathing represents a spectrum of abnormalities that range from mild (simple snoring) to severe (hypoventilation and sleep apnoea-hypopnoea) forms. SDB can manifest as obstructive sleep apnoea (OSA) and central sleep apnoea (CSA). In patients with heart failure, Cheyne - Stokes respiration (CSR), a periodic form of crescendo-decrescendo breathing, is synonymous with CSA (5, 18).

Aims & objectives

The present study was undertaken in the Department of Pulmonary, Critical Care and Sleep Medicine, Safdarjung Hospital, New Delhi with the purpose of finding prevalence of sleep disordered breathing (SDB) in patients of heart failure and also to find the association of severity of SDB with severity of heart failure. Not much is known about the prevalence of sleep disordered breathing in patients of heart failure in India.

Material & Methods

In this study 40 patients suffering from systolic heart failure were selected on random basis. Patient enrolment was independent of the presence of sleep-related symptoms (*i.e.* snoring, witnessed apnoeas, excessive daytime sleepiness) although detailed history of all these symptoms was sought. All these patients underwent complete evaluation of history, physical examination and overnight polysomnography. The patients were divided into two groups, namely group 1 and group 2, on the basis of polysomnography. Group 1 consisted of 17 patients who did not have sleep disordered breathing i.e. AHI (central or obstructive) < 5. Group 2 consisted of 23 patients who had sleep disordered breathing i.e. AHI (central or obstructive) $\geq$ 5. Comparison of biochemical profile and sleep parameters was made between group 1 and group 2 and results analyzed. As all the patients were dyspneic (either NYHA class 2 or NYHA class 3), these two groups of patients were compared for their sleep parameters. Further sub-grouping of patients was done into four subgroups according to number of drugs (beta blocker, ACE inhibitor, nitrates, diuretics or digoxin) being taken by the patient. Group A consisting of patients taking one drug, group B consisting of patients on two drugs, group C

consisting of patients on three drugs and group D consisting of patient on four drugs. No patient was on all five drugs. An attempt was made to establish the correlation between the number of drugs being taken by the patient and the various sleep parameters.

Diagnosis of OSA and CSA

The diagnosis was made in accordance with the guidelines of AASM Manual for scoring sleep, 2007 as following.(4) Accordingly the various events were defined as follows.

Apnea: Apnea was scored when all of the following criteria were met (a) drop in peak thermal sensor excursion by >=90% of the baseline, (b) duration of event lasts for at least 10 seconds, and (c) at least 90% of the event's duration meets the amplitude reduction criteria for apnea.

Obstuctive apnea: Apnea was classified as obstructive if it was associated with increased or continued effort throughout the entire period of absent airflow.

Central apnea: Apnea was classified as central if it was associated with absent inspiratory effort throughout the entire period of absent airflow. The patient reports at least one of the following (a) excessive daytime sleepiness, (b) frequent arousals and awakenings during sleep or insomnia complaints, and (c) awakening with shortness of breath. Polysomnography shows five or more central apneas per hour of sleep. The disorder is not better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder. (23)

Cheyne Stokes breathing pattern: Polysomnography shows at least 10 central apneas and hypopneas per hour of sleep in which the hypopnea has a crescendo-decrescendo pattern of tidal volume accompanied by frequent arousals from sleep and derangement of sleep structure. Although symptoms are not mandatory to make this diagnosis, patients often report excessive daytime sleepiness, frequent arousals and awakenings during sleep, insomnia complaints, or awakening with shortness of breath. The breathing disorder occurs in association with a serious medical illness, such as heart failure, stroke, or renal failure. The disorder is not better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder. (23)

Mixed apnea: Apnea was scored mixed apnea if it met apnea criteria and was associated with absent inspiratory effort in the initial portion of the event, followed by resumption of inspiratory effort in the second portion of the event.

Hypopnea: hypopnea was scored if ALL of the following criteria were met: (a) the nasal pressure signal excursions (or alternative hypopnea sensor) drop by >30% of baseline, (b) the duration lasted at least 10 seconds, (c) less than 4% desaturation from pre-event baseline, and (d) at least 90% of the event's duration must meet the amplitude reduction of criteria for hypopnea.

Respiratory effort related arousal: Respiratory effort-related arousal (RERA) was scored if there was a sequence of breaths lasting at least 10 seconds characterized by increasing respiratory effort or flattening of the nasal pressure waveform leading to an arousal from sleep when the sequence of breaths does not meet criteria for an apnea or hypopnea.

Arousals: Arousal was scored during any stage of sleep if there was an abrupt shift of EEG frequency including alpha, theta, and/or frequencies > 16 Hz (but not spindles) that lasts at least 3 seconds, with at least 10 seconds of stable sleep preceding the change. The number of arousals per hour is taken as the arousal index (AI).

Desaturations: Desaturation is defined as a fall >3% in saturation from baseline following a respiratory event. The number of such episodes per hour is taken as desaturation index.(DI).

Apnea Hypopnea Index (AHI): The AHI was defined as the number of apneic and hypopneic episodes per hour of sleep.

Diagnosis of OSA was based on polysomnography with an AHI (obstructive) of > 5 per hour. Diagnosis of CSA was based on polysomnography with an AHI (central) of > 5 per hour.

Diagnosis of *systolic heart failure* was made by 2 D echocardiography. Patients with left ventricular ejection fraction < 40% were included in study. Patients with congenital heart diseases, unstable angina, acute pulmonary edema, intrinsic liver and renal diseases, kyphoscoliosis, intrinsic pulmonary diseases, patients on theophylline and morphine and its derivatives were excluded from the study. All subjects underwent detailed history taking, clinical examination, examination of previous medical records and relevant laboratory investigations.

A whole night fully supervised, manually validated level–1 polysomnography was conducted. It included electro-encephalography, electro-oculography, chin electro-myography, oro-nasal airflow (by nasal thermistors and nasal pressure transducer), rib cage and abdominal movements, arterial oxygen saturation monitored via a finger probe, electrocardiography and body position. An

Alice 5 Healthdyne polysomnography system (Respironics, USA) was used. Sleep staging was performed using the criteria of AASM manual for scoring sleep 2007 as described above. A trained physician manually validated all the sleep studies. The minimum arterial blood oxygen saturation attained during sleep was also recorded. Categorization of severity of CSA is done according to AHI (central) value into three groups; mild (5-15), moderate (16-30) and severe (>30).

Statistical Methods

The observed data for the various biochemical parameters was presented in terms of mean± standard deviation (S.D.) for a descriptive analysis. Further analysis of the data for categorical variables was done using the Chi-square test. Logistic regression was applied for BMI adjustment. The level of statistical significance was taken as P d" 0.05. The data was analyzed by using the SPSS statistical software, version 15.0.

Observations & Results

Forty patients of heart failure with ejection fraction <40% were studied. Out of 40 patients 15 patients were on nitrates, 14 patients were on digoxin, 26 patients were on ace inhibitors, 23 on diuretics and 30 patients were on beta blockers. Aetiology of heart failure was ischemic heart disease in 34 patients, viral myocarditis in 3 patients and postpartum cardiomyopathy in 3 patients (Table 3). Total prevalence of CSA in heart failure was 57.5%.Prevelance in males and females was 47.6% and 68.42% respectively. (Table 1)

The prevalence of OSA was found to be 12.5% (Table 2)

There was significant difference (p Value = .006) in ejection fraction in group1 (29.96 ± 4.9%) and group 2 (35.82 ± 3.5). In addition there was also a significant difference in SBP (p Value = 0.042). SBP being 117.53 ± 9.23 in group 1 compared to 124.52 ± 11.7 in Group 2. (Table 4)

There was a significant difference in symptoms, O2 desaturation index, minimum O2, arousal index, total sleep time, AHI (central), sleep efficiency and wake O2 as indicated by p values (Tables 5 & 6)

A negative correlation was observed between ejection fraction and O2 desaturation index, AHI (central), and arousal index. A positive correlation was found between

Table 1: Total prevalence of central sleep apnea in the cases

	HF with CSA	HF without CSA	Total Patients of HF	Percentage of HF with CSA
Male	10	11	21	47.6%
Female	13	6	19	68.42%
Total	23	17	40	57.5%

(HF = Heart failure; CSA = Central Sleep apnea)

Table 2: Prevalence of obstructive sleep apnea in the cases

Total HF Cases	HF without OSA	HF with OSA	Percentage
40	35	5	12.5%

Table 3: Etiology of heart failure among patients

Etiology	Number of Patients
Ischemic Cardiomyopathy	34
Post Partum Cardiomyopathy	3
Viral Myocarditis	3

Table 4: Comparison of demographic characteristics between patients without CSA (Group 1) and patients with CSA (Group 2)

Characteristics	Group 1	Group 2	P value
Age (years)	44.76±13.46	52.39±9.8	0.058
Height (cm)	163.59±7.45	159.78±8.22	0.135
Weight (Kgs)	62.65±7.5	62±10.2	0.819
BMI	23.1±1.59	24.2±3.0	0.165
Duration of heart failure (months)	18.53±15.4	15.7±13.6	0.552
Ejection fraction%	35.82±3.5	29.96±4.9	0.006
SBP (mm of Hg)	117.53±9.23	124.52±11.7	0.042
DBP (mm of Hg)	76.35±5.6	81.13±9.3	0.053
Hemoglobin Gram%	12.6±1.73	13.56±1.2	0.06
Platelets (in Lakhs per cu mm)	2.54±0.67	2.46 ± 0.57	0.67
TLC (per cu mm)	6652.94± 1597.6	6434.78± 1273.3	0.646
Blood urea (mg per dl)	25.82±10.6	27.04±9.2	0.701
S. creatinine (mg per dl)	1.2±2.5	1.843±0.199	0.701
Random blood sugar (mg per dl)	140±14	142±15.5	0.61

ejection fraction and wake O2. (Figure 1)

Table 5: Comparison of symptoms of SDB between Group 1 and Group 2

Symptom	Percentage of patients in Group 1	Percentage of patients in Group 2
Excessive daytime sleepiness	14	26
Witnessed apneas	12	25
Daytime fatigue	15	23

Table 6: Comparison of sleep parameters between Group 1 and Group 2

Characteristics	Group 1	Group 2	p value
O2 desaturation index	4.86 ± 3.8	30.62 ± 23.4	<0.01
Minimum O2%	90.8 ± 3.7	75.3 ± 19.4	0.03
Arousal index	12.41 ± 5.6	22.6 ± 12.7	0.002
Time in bed (in minutes)	392 ± 25	400 ± 19	0.594
Total sleep time (in minutes)	300 ± 64	277 ± 49	<0.05
Sleep efficiency (total sleep time/time in bed %)	76.5 ± 15	69 ± 13	<0.05
AHI (central) wake O2%	2.08 ± 1.5 94.8 ± 2.84	28.15 ± 20.9 90.6 ± 3.0	<0.01 <0.01

Significant difference was observed in various sleep parameters in group A, B, C and D as indicated by the p values. (Table 7)

Discussion

Prevalence of SDB in heart failure

In our study we found the prevalence of sleep disordered breathing in patients of heart failure to be 57.5% i.e. 23 out of 40 patients. All the 23 patients had CSA. There was no significant gender difference in the prevalence of SDB amongst the patients. Out of 23 patients who had CSA 5 (12.5%) patients were also found to have OSA (Table-2). The prevalence of SDB in the study conducted by Jawaheri et al on 81 ambulatory male patients of heart failure was 51% (40% had CSA and 11% had OSA) (6). In another study conducted by Schulz et al, the prevalence was found to be 43% and 28% for OSA and CSA respectively in patients of heart failure (7). The prevalence of SDB in the study conducted by Sonia Ancoli - Israel was 53% in patients of heart failure.(8) The mean AHI (central) in our present study was 28.15 ± 20.9 while that in study conducted by Schulz, Jawaheri and Sonia Ancoli was 35 ± 3, 44 ± 19 and 30 ± 5 respectively(6,7). The prevalence of SDB in our CHF

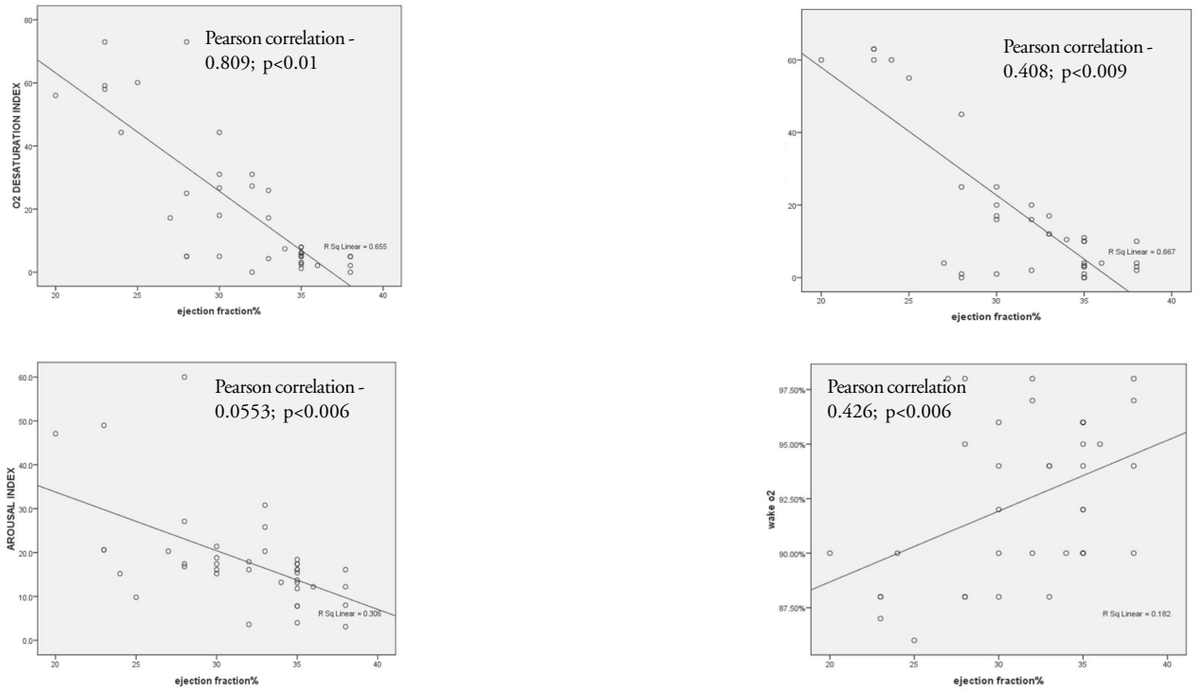

Figure 1: Correlation of ejection fraction and O2 desturation index, AHI (central), arousal index and wake O2.

Table 7: Comparison of various sleep parameters in Group A, B, C and D

Sleep parameter	Group A	Group B	Group C	Group D	P Value
O2 deaturation index	14.19 ± 26.0	8.55 ± 8.5	26.49 ± 23.9	27.68 ± 23.4	0.12
Arousal index	13.8 ± 7.3	15.4 ± 6.4	19.3 ± 10.8	23.7 ± 17.5	0.28
Apnea hypopnea index (central)	11.7 ± 15.2	8.49 ± 6.9	20.3 ± 23.8	27.1 ± 26.2	0.17
Minimum O2	76 ± 16	78 ± 20.8	70.5 ± 22.7	82 ± 18.9	0.34
Sleep quality	87.1 ± 6.3	79.9 ± 17.8	87.2 ± 7.5	85.9 ± 5.7	0.31
Wake O2	91.7 ± 2.8	94.0 ± 3.3	92.4 ± 4.1	91.1 ± 3.4	0.34

patients was higher. However, it is difficult to compare the results of the present study to those obtained in earlier studies for several reasons. Various studies have employed different scoring criteria for SDB; the sleep recordings from the different studies have been scored by different investigators, thus introducing inter-rater variability. There have been differences in monitoring techniques of sleep and breathing between various studies. For example, in contrast to the our study and that conducted by Jawaheri et al which mainly employed in-hospital polysomnography, Schulz used a portable device which may underestimate the prevalence and severity of the disease. (7) The criteria for defining the heart failure also vary in different studies, for example, we selected patients with ejection fraction less than 40% while Jawaheri et al had enrolled patients with ejection fraction less than 45%. Moreover, the profile of the population studied and the number of patients were also different in different studies. Furthermore, the mean age of patients in different studies was also different. It may be appreciated that the various studies were performed in different regions of the world and ethnicity may influence the occurrence of SDB due to differences in respiratory chemosensitivity, craniofacial morphology and the level of obesity.

Similar to the study conducted by Jawaheri we also found in our study a higher prevalence of CSA as compared to OSA in contrast to the study done by Schulz which found more prevalence of OSA as compared to CSA. It is speculated that the optimization in pharmacotherapy in the form of beta blocker led to the disappearance of CSR in a subset of patients leading to decreased prevalence of CSA as compared to OSA in study conducted by Schulz. It is worth noting that, in the study conducted by Jawaheri, none of the patients was on beta blockers while percentage of patients on bêta blockers in study by Schulz was 90%. The proportion of patients on beta blockers in our study was 45%. Beta blockers might suppress CSR not only by decreasing circulation times and pulmonary venous congestion but also by altering chemo-reflex regulation of ventilatory control. It is worth noting that this assumption is supported by two recent studies showing that CHF patients taking â-blockers have a lower prevalence and severity of CSR than those who do not (9-11). No significant difference was found in sleep characteristics of the patients on different drugs although 18 out of 40 patients i.e. 45% of our patients were on beta blocker.

Correlation of polysomnographic parameters with severity of heart failure

In our study we found significant negative correlation between EF and AHI (central) (Pearson correlation -0.408, p value = 0.009). This implies that the severity of CSA increases with the decrease in ejection fraction i.e. severity of CSA increases with severity of heart failure. Ejection fraction correlated negatively with both arousal index and desaturation index. Similar results were found in other studies (6,12), which also concluded that central sleep apnea can be considered as a marker of severity of heart failure. (21) When we compared the sleep characteristics of patients of NYHA class 2 and NYHA class 3, we found a significant difference in sleep characteristics of the two groups. Values of AHI (central), O2 desaturation index and arousal index were significantly more in NYHA class 3 as compared to NYHA class 2. Due to frequent arousals, as can be expected, sleep efficiency was lower in NYHA class 3 compared to NYHA class 2. Similarly minimum O2 saturation achieved was significantly lower in NYHA class 3 compared to NYHA class 2. The reason for the negative correlation of the ejection fraction and AHI (central) lies in fact that HF causes prolonged circulation time. Prolonged circulatory time, plays a critical role in development of CSR (13,14). The circulatory time in heart failure is prolonged as a result of reduced cardiac output and increased blood volume. This prolonged circulatory time has the potential to create cascades of changes in ventliatory control mechanism that result in development and or maintenance of CSR (15,16).

Normally, the arterial blood gas changes that occur in pulmonary circulation reach carotid and central chemoceptors promptly, typically within seven seconds.(20) A prolonged circulation time delays this transfer of information by as much as twenty seconds or more. As a result what is usually a negative feedback is transformed into positive feedback system. In this scenario, the arterial blood gas changes that occur during apneic phase may reach the chemoreceptors after apnea phase has terminated, thereby triggering ventilator overshoot during hyperapnea. Arousal associated with CSR may play a role in the pathogenesis of CSR, i.e. the arousal may increase the magnitude of ventilator overshoot during hyperapnea with a subsequent undershoot during hypoventilation.

Our study also showed that patients with heart failure slept significantly less as evidenced by the sleep efficiency. These abnormalities may result in daytime fatigue and sleepiness when measured quantitatively. (17) We found a tendency for greater prevalence of subjective excessive daytime sleepiness and fatigue in patients with sleep disordered breathing. CSA-CSR also resulted in severe arterial oxyhemoglobin desaturation as seen in our study. Periodic breathing also resulted in excessive number of arousals in patients with sleep apnea. Recurrent episodes of nocturnal oxyhemoglobin desaturations and arousals due to periodic breathing, while asleep, could adversely affect the cardiac function by a variety of mechanisms eventually resulting in imbalance between myocardial oxygen delivery and consumption. This study has conclusively found a definite correlation between increasing severity of HF with increasing severity of CSA.

In patients with heart failure, comorbid sleep apnea is most often not tested and consequently subjects are underdiagnosed and not treated.(22) Clearly there is a need for further research, using well designed studies and long term follow up, to fully demonstrate an association of SDB with progression of severity of heart failure. Also large-scale, carefully executed therapeutic studies are needed to determine if the treatment of sleep-related breathing disorders changes the natural history of left ventricular failure. A better understanding of relationship between SDB and heart failure may have important public health implications.

Conclusions

A fairly high prevalence of sleep-disordered breathing (57.5%) was found in patients of heart failure in the present study. With increasing severity of HF a significant worsening of CSA-CSR was observed. The severity of SDB was thus observed to be a surrogate marker of severity of heart failure. The sympathetic activation during multiple arousals and desaturation may be associated with further worsening of HF. The treatment of CSA-CSR may prevent the worsening status of HF. Hence long term randomized and controlled interventions are required to further substantiate these facts.

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